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# Total synthesis of (+)-virgatusin *via* $AlCl_3$-catalyzed [3+2] cycloaddition†‡

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**The $AlCl_3$-catalyzed cycloaddition of a donor–acceptor (don–acc) cyclopropane and piperonal succinctly provides the core of virgatusin in a selective, high-yielding manner.**

The furanolignan virgatusin was first isolated in 1996 by Chen and co-workers from *Phyllanthus virgatus*.[1] Members of this lignan subgroup display a 2,5-diaryl-3,4-disubstituted tetrahydrofuran skeleton. Virgatusin belongs to the *cis*, *trans*, *trans* diastereoisomeric class of furanolignans which is the largest target for which total syntheses have been reported (Fig. 1). Recent studies have revealed antibacterial and antifungal activity for virgatusin and its derivatives.[2–5]

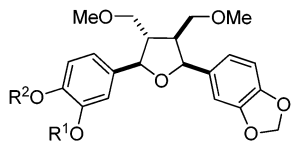
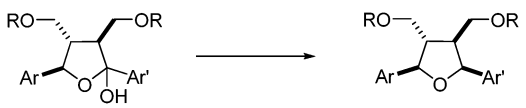



**Fig. 1** Representative *cis*, *trans*, *trans* furanolignans.

The challenge of constructing the virgatusin core containing four contiguous stereocenters has been met by several groups. Yoda *et al.* completed the first synthesis of (−)-virgatusin.[6] The key step of Yoda's synthesis delivered the substituted tetrahydrofuran core *via* diastereoselective reduction of a cyclic hemiacetal intermediate (eqn (1)). Later syntheses by Yamauchi *et al.*[7] and Ghosh and Matcha[8] proceed through selective hydrogenolysis of a similar hemiacetal. Marsden *et al.* took a different approach accessing the tetrahydrofuran core from a condensation of allylsiloxanes with aldehydes.[9] The Brun synthesis is dependent on their Mn(III)-based radical synthesis of 2,3-dihydrofurans.[10] A diastereoselective hydrogenation of the dihydrofuran reveals the virgatusin core and also allows access to (+)-urinaligran.




(1)

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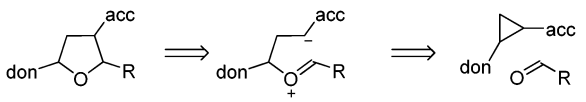
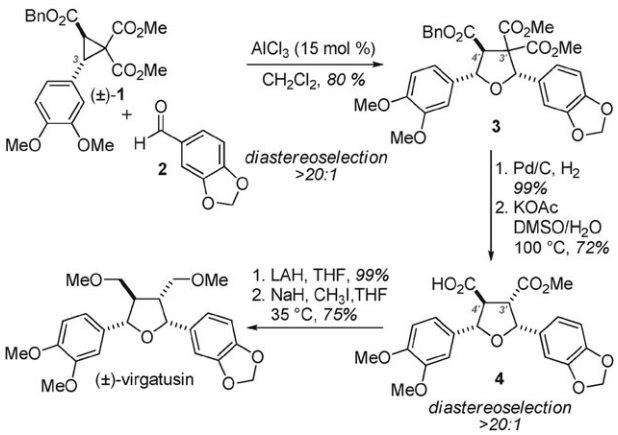
‡ Electronic supplementary information (ESI) available: Experimental details and characterization data for all new compounds. See DOI: 10.1039/b911765b

The concise synthesis of 2,5-*cis*-substituted tetrahydrofurans may be realized *via* the formal [3+2] cycloaddition of donor–acceptor (don–acc) cyclopropanes and aldehydes (eqn (2)). Such reactions are stereospecific at the donor site *via* a substitution reaction that proceeds with inversion and the subsequent ring closure proceeds with high diastereoselectivity.[11–14] We believed this strategy would be applicable to the virgatusin core in a highly selective fashion. This communication reports the results of our studies.




(2)

Scheme 1 details a diastereoselective route to (±)-virgatusin (Scheme 1). The *trans* cyclopropane (±)-**1** was synthesized in two steps from veratraldehyde *via* a Knoevenagel–Corey–Chaykovsky sequence (73% yield).‡ The formal [3+2] cycloaddition of the cyclopropane with piperonal (**2**) was conducted to yield the tetrahydrofuran **3** as one diastereomer in 80% yield. $AlCl_3$ and $Hf(OTf)_4$ were the only Lewis acids in our screen to yield the tetrahydrofuran **3** selectively and in high yield. After the cycloaddition, a Krapcho decarboxylation[15] was attempted, but the diastereoselectivity was low under a variety of conditions. Hydrogenolysis of the benzyl ester followed by decarboxylation furnished the virgatusin core (**4**) in >20 : 1 diastereoselectivity, presumably *via* directed protonation by the carboxylic acid. Subsequent $LiAlH_4$ reduction gave the diol and methylation produced (±)-virgatusin in five steps from **1**. Every stereochemical issue was addressed with >95% selectivity. The strategic application of the benzyl ester was helpful at several stages. First, it simplified the preparation of the cyclopropane. The

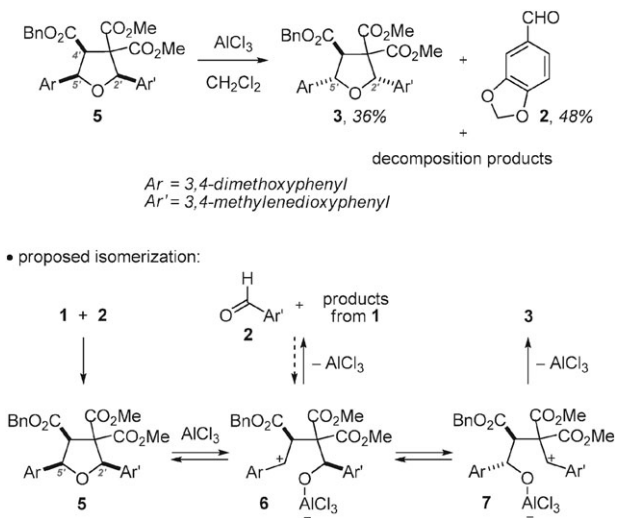



**Scheme 1** Diastereoselective synthesis of (±)-virgatusin.

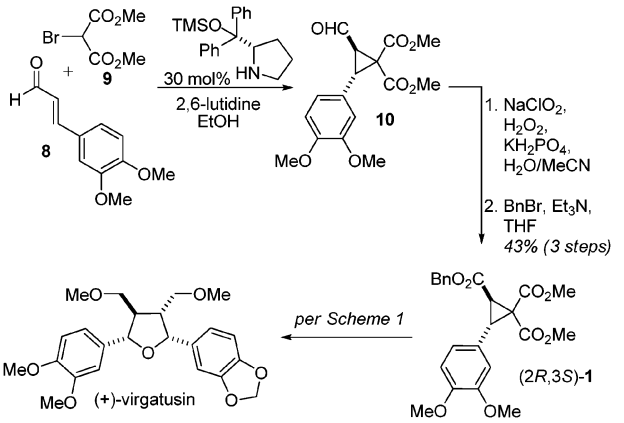
differentiation from the malonate permitted selective acid formation at C4′ in the triester **3**. Ultimately, reduction of the derived C4′ acid could take place concurrently with the C3′ ester in **4**, maximizing overall step efficiency.

Mechanistic studies for the [3 + 2] cycloaddition have provided evidence for a stereospecific nucleophilic substitution mechanism wherein the aldehyde acts as a nucleophile toward a configurationally stable intimate ion pair in a process that proceeds with inversion at the cyclopropane donor site;[13] however, the conversion of **1** → **3** in the present study proceeds with *retention* at C3 of the cyclopropane. How then does **3** arise? To answer this question, we examined the chemistry of tetrahydrofuran **5** which arises from a moderate-yielding [3 + 2] cycloaddition of **1** and **2** using $SnCl_4$ as the Lewis acid. The substituents at C4′ and C5′ of this diastereomer possess the *cis* relationship that would be expected from the nucleophilic substitution mechanism. Upon exposure to $AlCl_3$ in $CH_2Cl_2$, tetrahydrofuran **5** was converted to **3** (C4′/C5′-*trans*) along with piperonal and cyclopropane-derived decomposition products (Scheme 2). If **5** is formed initially in the $AlCl_3$-catalyzed cycloaddition it is conceivable that further association with the $AlCl_3$ isomerizes the product to the observed diastereomer. A possible mechanism involves $AlCl_3$ binding with the ether of the tetrahydrofuran ring causing reversible ring cleavage at both C2′ and C5′. The resultant carbenium ions **6** and **7** are stabilized by the strongly electron releasing aryl groups (Scheme 2) and isomerization of this type is precedented.[9,13,16–19] The appearance of piperonal (**2**) but not veratraldehyde in the reaction of **5** and $AlCl_3$ may be understood in terms of the relative facility of retro-aldolization of intermediates **6** and **7**. It is apparent that C4′ is the only non-epimerizable stereocenter and acts as the keystone that regulates the C2′/C5′ stereochemical outcome *via* what is apparently thermodynamic control. Our data do not exclude pre-cycloaddition isomerization of *trans*-**1** to *cis*-**1** and subsequent stereospecific cycloaddition *via* the established nucleophilic substitution pathway; however, efforts to induce such an isomerization have yielded no evidence of *cis*-**1**.

The stability of the C4′ stereocenter was confirmed in a subsequent asymmetric synthesis of (+)-virgatusin. The




**Scheme 2** Isomerization mechanism.




**Scheme 3** (+)-Virgatusin synthesis.

requisite preparation of enantioenriched cyclopropane **1** is detailed in Scheme 3. An organocatalytic Michael addition–intramolecular alkylation[20] between enal **8** and bromomalonate **9** gave the formyl cyclopropane **10** (er 90 : 10). Oxidation[20] and nucleophilic esterification gave (2*R*,3*S*)-**1**. Cycloaddition with **2** was performed as with the racemate and a single recrystallization gave (2*S*,4*S*,5*S*)-**3** with an er of 99 : 1. The synthesis was completed as detailed for the racemate in Scheme 1 to give (+)-virgatusin.

In conclusion, we have shown that the [3 + 2] cyclopropane–aldehyde cycloaddition previously developed in our laboratory can be used to synthesize more complex tetrahydrofuran derivatives such as virgatusin. This synthesis is straightforward and should be amenable to other members of the furanolignan family of natural products.

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