



## First Total Synthesis of Tetrasubstituted Tetrahydrofuran Lignan, (-)-Virgatusin

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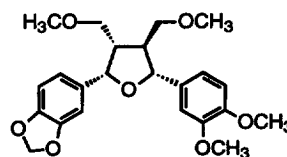
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**Abstract:** The first asymmetric total synthesis of (-)-virgatusin, a new furanolignan, isolated from *phyllanthus virgatus*, was accomplished in a stereoselective manner by nucleophilic addition of organolithium reagent to the functionalized lactone elaborated from dihydroxyacetone dimer followed by asymmetric deoxygenation of the hemiketal intermediate. © 1999 Elsevier Science Ltd. All rights reserved.

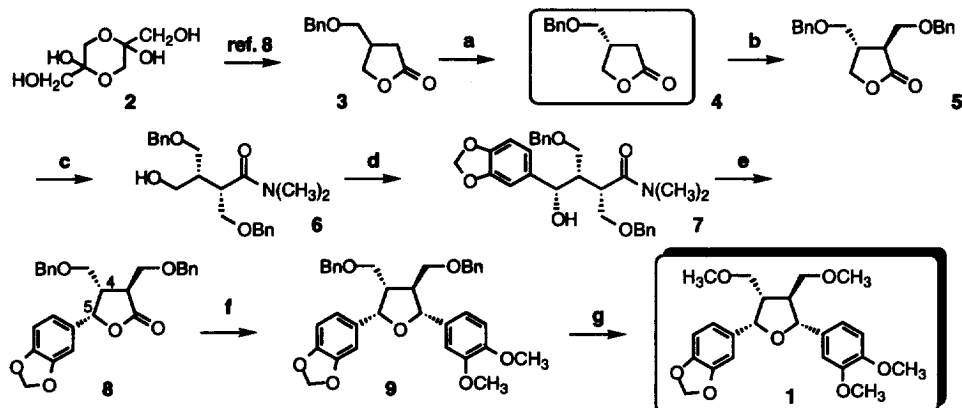
**Keywords:** (-)-Virgatusin, Furanolignan, Trisubstituted Lactone, Deoxygenation, Dihydroxyacetone.

Natural lignans display a wide variety of constitution based on phenolic and *O*-heterocyclic substructures, and an equally wide range of biological activities such as antitumor activity, platelet-activating factor (PAF) antagonists, and inhibitory effects on microsomal monooxygenases in insects.<sup>1</sup> The diverse array of these potentially useful characteristics make them inviting targets for synthesis.<sup>2</sup> In this connection we have also recently reported the total synthesis of two dibenzylbutyrolactone lignans, (-)-hinokinin<sup>3a</sup> and (-)-enterolactone,<sup>3b</sup> employing different synthetic strategies, however, a major sub-group is comprised of tri- and tetrasubstituted tetrahydrofuran groups. Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, very few synthetic strategies for the furanolignans have been reported.<sup>4</sup> Herein we wish to describe the first stereoselective total synthesis of (-)-virgatusin (**1**) based on the asymmetric Lewis acid-promoted deoxygenation. **1** first isolated in 1996 by Chen et al.<sup>5</sup> is a new furanolignan with four substituents in the furan ring and is expected as a herbal drug to inhibit the endogenous DNA polymerase of hepatitis B virus (HBV).<sup>6</sup>



**1:** (-)-Virgatusin

As shown in Scheme 1, the homochiral benzylactone **4**,<sup>7</sup> an important building block for the terpenoid synthesis,<sup>7a</sup> was easily prepared in an enantiomerically pure form starting from dihydroxyacetone dimer **2**<sup>8</sup> through diastereomer separation with (*R*)-(+)- $\alpha$ -methylbenzylamine. Hydroxymethylation of **4** with paraformaldehyde followed by benzylation afforded the dibenzylactone **5** in 96.4% d.e..<sup>9</sup> After aminolysis of **5** with (CH<sub>3</sub>)<sub>2</sub>NH, amide **6**, thus obtained, was successively subjected to Swern oxidation followed by nucleophilic addition of 3,4-(methylenedioxy)phenylmagnesium bromide *in situ*, leading to the amide alcohol **7** predominantly (80:20 isolated diastereomer ratio)<sup>10</sup> explained in terms of the Cram's non-chelation transition model. This was then cyclized under acidic conditions to give the key trisubstituted lactone **8**. Careful treatment of **8** with 3,4-dimethoxyphenyllithium reagent at -78 °C provided the labile hemiketal intermediate, which was readily effected by TiCl<sub>4</sub>-induced deoxygenation with Et<sub>3</sub>SiH<sup>11</sup> at low temperature to lead cleanly to the tetrasubstituted furanolignan derivative **9** as a single stereoisomer in 80% yield from **8** with the desired



**Scheme 1.** Reagents and conditions: (a) 1, (*R*)-(+)- $\alpha$ -methylbenzylamine, MeOH, 60 °C; 2, *p*-TsOH, benzene, 50 °C; 21% (2 steps; diastereomer separation followed by cyclization); (b) 1, LiHMDS, HMPA, (CH<sub>2</sub>O)<sub>n</sub>, THF, -78--20 °C; 35%; 2, Ag<sub>2</sub>O, BnBr, cat. Bu<sub>4</sub>Ni; (c) Me<sub>2</sub>NH, -20--0 °C; 46% (2 steps); (d) 1, (COCl)<sub>2</sub>, DMSO, THF then Et<sub>3</sub>N, -78--45 °C; 2, 3,4-(methylenedioxy)phenylmagnesium bromide, THF, 0 °C; 55% (2 steps); (e) *p*-TsOH, benzene, 50 °C; 87%; (f) 1, 3,4-dimethoxyphenyllithium, Et<sub>2</sub>O, -78 °C; 2, Et<sub>3</sub>SiH, TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; 80% (2 steps); (g) 1, Pd (black), 4.4% HCOOH-MeOH; 93%; 2, NaH, CH<sub>3</sub>I, THF; 80%.

configuration.<sup>12</sup> Accompanying formation of the other stereoisomer was not observed in this reaction. Finally, **9** was methylated effectively with NaH-CH<sub>3</sub>I after deprotection of the benzyl groups to complete the total synthesis of (-)-virgatusin (**1**), [ $\alpha$ ]<sub>D</sub><sup>25</sup>-12.5 (c 0.51, CH<sub>2</sub>Cl<sub>2</sub>) [natural **1**, [ $\alpha$ ]<sub>D</sub><sup>25</sup>-12.7 (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>)<sup>5</sup>]. The spectral data of the synthetically produced **1** (viscous oil) were completely identical with those of the reported natural product.<sup>5</sup>

In summary, this work constitutes the first synthesis of the natural furanolignan, (-)-virgatusin, and verifies the structure proposed in the literature for this compound.

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#### References and notes

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- The d.e. was determined by chiral HPLC using Daicel chiralpak AD after derivatization to the amide **6**.
- Stereochemistry of the new stereocentre was assigned based on our previous results,<sup>8</sup> and observed chemical shift (C<sub>5</sub>-H) and coupling constant ( $J_{4,5} = 8.4$  Hz) after lactonization to **8** according to the following reference; Marino, J. P.; de la Pradilla, R. F. *Tetrahedron Lett.* **1985**, *26*, 5381-5384.
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- The absolute configuration of the generated stereogenic centre was determined unambiguously based on its spectral data of synthetic (-)-**1**.