Pergamon

Tetrahedron Letters 40 (1999) 4701–4702

TETRAHEDRON LETTERS

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

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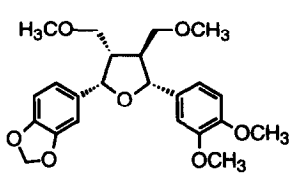
Received 23 March 1999; accepted 23 April 1999

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.

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.[1] The diverse array of these potentially useful characteristics make them inviting targets for synthesis.[2] In this connection we have also recently reported the total synthesis of two dibenzylbutyrolactone lignans, (-)-hinokinin[3a] and (-)-enterolactone,[3b] employing different synthetic strategies, however, a major sub-group is comprized 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.[4] 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.[5] 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).[6]



1: (-)-Virgatusin

As shown in Scheme 1, the homochiral benzyllactone **4**,[7] an important building block for the terpenoid synthesis,[7a] was easily prepared in an enantiomerically pure form starting from dihydroxyacetone dimer **2**[8] through diastereomer separation with (*R*)-(+)-α-methybenzylamine. Hydroxymethylation of **4** with paraformaldehyde followed by benzylation afforded the dibenzyllactone **5** in 96.4% d.e..[9] After aminolysis of **5** with $(CH_3)_2NH$, 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)[10] 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 $TiCl_4$-induced deoxygenation with Et_3SiH[11] at low temperature to lead cleanly to the tetrasubstituted furanolignan derivative **9** as a single stereoisomer in 80% yield from **8** with the desired

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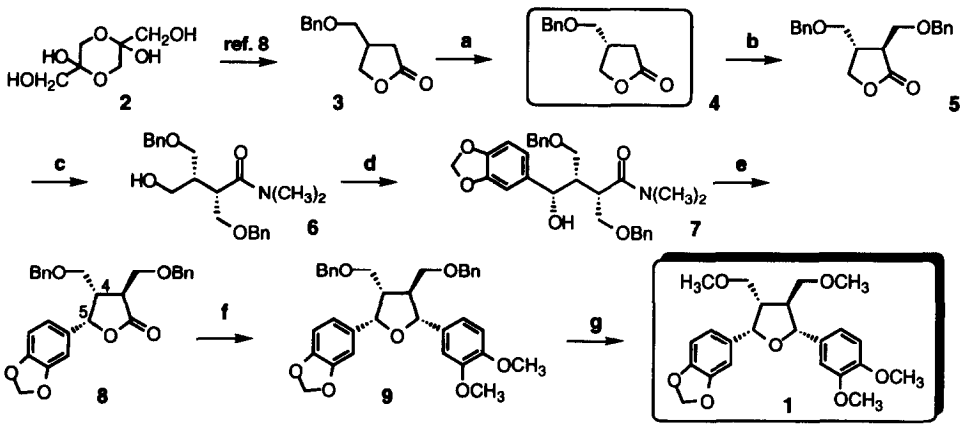
PII: S0040-4039(99)00848-5



Scheme 1. Reagents and conditions: (**a**) **1**, (*R*)-(+)-α-methylbenzylamine, MeOH, 60 °C; **2**, *p*-TsOH, benzene, 50 °C; 21% (2 steps; diastereomer separation followed by cyclization); (**b**) **1**, LiHMDS, HMPA, $(CH_2O)_n$, THF, -78~-20 °C; 35%; **2**, Ag_2O, BnBr, cat. Bu_4NI; (**c**) Me_2NH, -20~0°C; 46% (2 steps); (**d**) **1**, $(COCl)_2$, DMSO, THF then Et_3N, -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_2O, -78 °C; **2**, Et_3SiH, $TiCl_4$, CH_2Cl_2, -78 °C; 80% (2 steps); (**g**) **1**, Pd (black), 4.4% HCOOH-MeOH; 93%; **2**, NaH, CH_3I, THF; 80%.

configuration.[12] Accompanying formation of the other stereoisomer was not observed in this reaction. Finally, **9** was methylated effectively with NaH-CH_3I after deprotection of the benzyl groups to complete the total synthesis of (-)-virgatusin (**1**), $[\alpha]_D^{25}$-12.5 (c 0.51, CH_2Cl_2) [natural **1**, $[\alpha]_D^{25}$-12.7 (c 0.5, CH_2Cl_2)[5]]. The spectral data of the synthetically produced **1** (viscous oil) were completely identical with those of the reported natural product.[5]

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

Acknowledgment:: This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

References and notes

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9. The d.e. was determined by chiral HPLC using Daicel chiralpak AD after derivatization to the amide **6**.
10. Stereochemistry of the new stereocentre was assigned based on our previous results,[8] and observed chemical shift (C_5-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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12. The absolute configuration of the generated stereogenic centre was determined unambiguously based on its spectral data of synthetic (-)-**1**.