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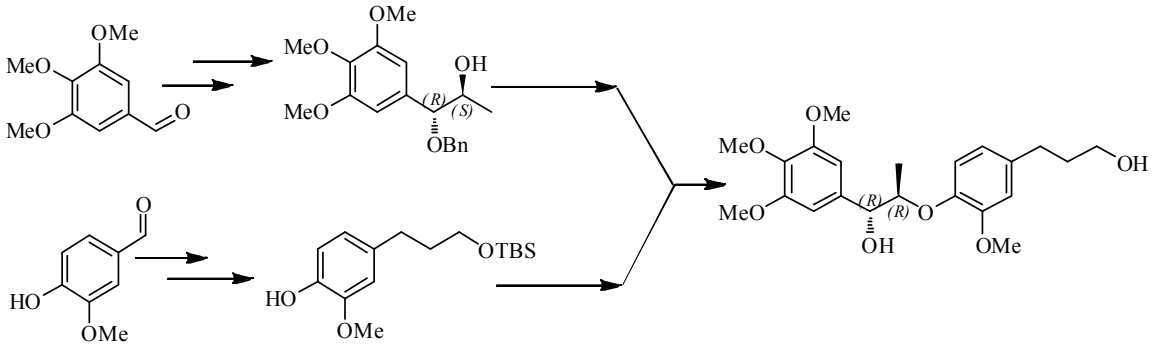
GRAPHICAL ABSTRACT

The first stereoselective total synthesis of a new antitumour and anti-inflammatory neolignan, surinamensinol A

Parigi Raghavendar Reddy and Biswanath Das*



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Communication

The first stereoselective total synthesis of a new antitumour and anti-inflammatory neolignan, surinamensinol A†

Parigi Raghavendar Reddy and Biswanath Das*

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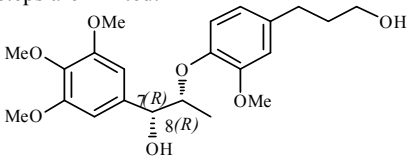
Abstract: The stereoselective total synthesis of an antitumour and anti-inflammatory 8-*O*-4′-neolignan, surinamensinol A has been accomplished starting from two aldehydes, 3,4,5-trimethoxy benzaldehyde and vanillin. The key steps involve the asymmetric reduction using a chiral oxazaborolidine complex, Sharpless asymmetric dihydroxyllation and Mitsunobu reaction. This is the first report of the total synthesis of surinamensinol A.

Introduction

Surinamensinol A (**1**) and B (**2**), two new diastereomeric 8-*O*-4′-neolignans along with several other phenolics have recently been isolated from the rhizomes of the aquatic plant, *Acorus gramineus* (Araceae).[1] The first compound bears (7*R*, 8*R*) configuration while the latter (7*S*, 8*R*). The compound **1** and **2** were found to possess potent cytotoxicity against the A549 cell line and moderate activity against SK-OV-3, SK-MEL-2 and HCT-15 cell lines.[1] Both the compounds **1** and **2** also exhibited impressive anti-inflammatory activity. They significantly inhibited NO levels in LPS-stimulated BV-2 cells.[1] In continuation to our work[2] on the construction of natural products herein we disclose the total synthesis of **1**. This is the first report of the synthesis of this molecule. Synthesis of some 8-*O*-4′-oxyneolignan derivatives have been reported,[3] but earlier synthetic approaches were different compared to our present work. Our current approach involves two non-chiral easily available aldehydes as the starting materials. The reagents are also commercially available and the synthetic steps are limited.



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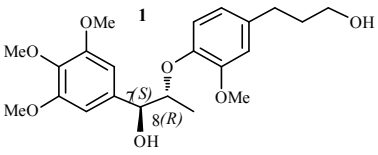

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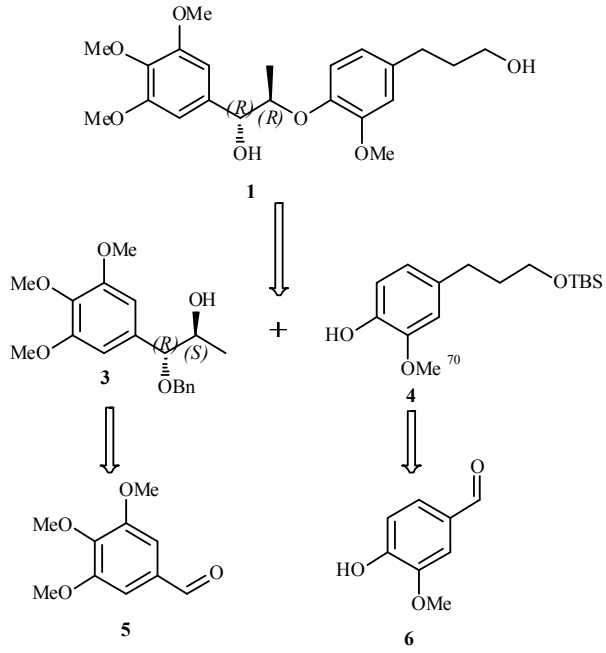
Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 607, India.
Corresponding author: Fax: +91-40-27193198; E-mail: biswanathdas@yahoo.com (B.Das)

†*Electronic supplementary information (ESI) available: Experimental procedures, Copies of ^{1}H and ^{13}C NMR spectrum of products. see DOI: 10.1039/b000000x/*

The retrosynthetic analysis (Scheme 1) indicates that surinamensinol (**1**) can be synthesized from the chiral diol **3** and the TBS ether **4**. Compounds **3** and **4** can, in turn, be obtained from 3,4,5-trimethoxy benzaldehyde (**5**) and vanillin (**6**) respectively.



Scheme 1. Retrosynthetic route for surinamensinol A

For the synthesis of chiral diol **3,** 3,4,5- trimethoxy benzaldehyde (**5**) was treated with vinyl magnesium bromide to produce the alcohol **7** (Scheme 2).[4] The alcohol **7** was oxidized with IBX and the corresponding ketone was subjected to chiral reduction using (*R*)-(+) 2-methyl–CBS-oxazaborolodine and BH_3SMe_2 to furnish the chiral alcohol **8** (*ee* 91%).[5] The free hydroxyl group of **8** was protected as Bn-ether (**9**) by treatment with BnBr and NaH. Compound **9** underwent Sharpless asymmetric dihydroxylation[6] with AD-mix β in *t*-BuOH:H_2O (1:1) to furnish the diol **10** along with its minor diastereomer (diastereomeric ratio 82:18) which was separated out. The primary hydroxyl group of **10** was tosylated with TsCl to form the mono-hydroxy compound **11**. Subsequent reduction of **11** with $LiAlH_4$ afforded the desired fragment **3** in high yield.[7]

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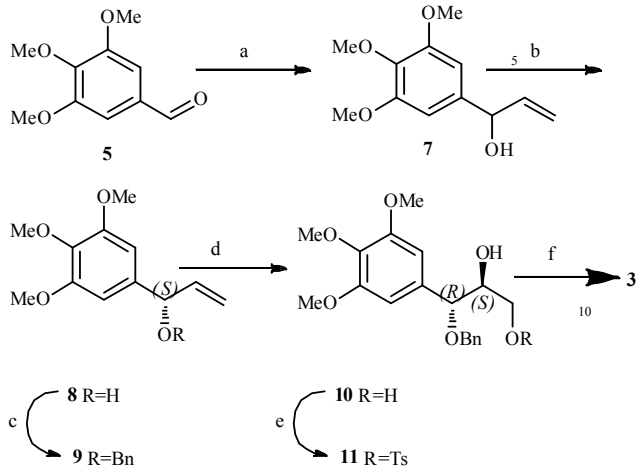
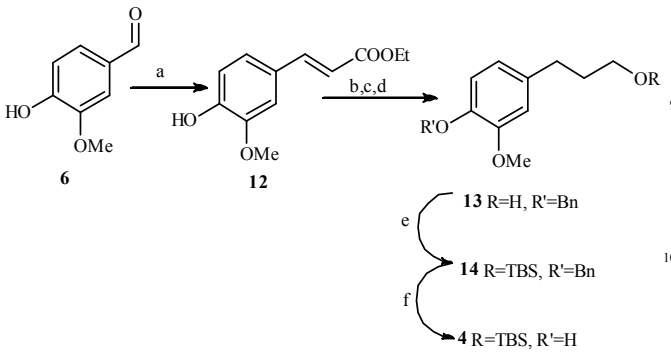


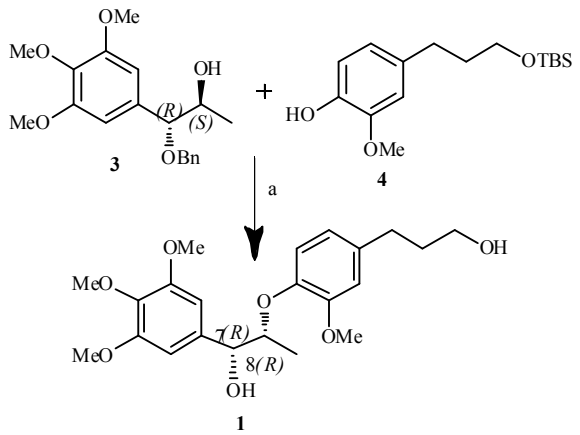
Scheme 2. Reagents and conditions: (a) H_2C=CHMgBr, THF, 0 °C to rt, 85%; (b) (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt; (ii) (*R*)-(+)-2-methyl-CBS-oxazaborolidine, $BH_3.SMe_2$, THF, -40 °C, 65% (*ee* 91%); (c) NaH, BnBr, THF, 0 °C to rt, 83%; (d) AD-mix β, *t*-BuOH:H_2O (1:1), 0 °C, 80% (82:18); (e) TsCl, Et_3N, DCM, DMAP, 0 °C to rt, 76%; (f) $LiAlH_4$, THF, 0 °C to reflux, 89%.

For synthesis of another fragment **4** vanillin (**6**) was subjected to Wittig reaction with $Ph_3PCHCOOEt$ to form the unsaturated ester **12**[8] (Scheme 3) with *E*/*Z* ratio of 92:8. The reduction of **12** with $NaBH_4$ in the presence of $NiCl_2.6H_2O$ followed by protection of the phenolic hydroxyl group by treatment with BnBr and NaH and subsequent reduction with $LiAlH_4$ afforded the saturated alcohol **13**. The hydroxyl group of **13** was protected as TBS ether **(14)** by using TBSCl and imidazole and the compound **14** was then hydrogenated in the presence of 10% Pd-C to produce the fragment **4**.[9]



Scheme 3. Reagents and conditions:(a) Ph_3P=$CHCO_2Et$, benzene, reflux, 81%, (*E*/*Z* ratio 92:8); (b)$NaBH_4$, $NiCl_2.6H_2O$, MeOH, 0 °C to rt; (c) NaH, BnBr, THF 0 °C to rt; (d) LAH, dry THF, reflux, 67% (over 3 steps); (e) TBSCl, imidazole, DCM, 95%; (f) 10% Pd–C, H_2, EtOAc, rt, 91%.

Finally, the coupling of the two fragments **3** and **4** was carried out by Mitsunobu reaction[10] using Ph_3P and DEAD and the resulting product on treatment with *p*-TsOH in MeOH followed by hydrogenation in the presence of 10% Pd-C yielded the target molecule, surinamensinol A (**1**) (Scheme 4) with 90% *ee*. The physical and spectral properties of the compound were compared to those reported for the natural product.[1]



Scheme 4. Reagents and conditions:(a) (i) Ph_3P, DEAD, dry THF, reflux; (ii) *p*-TsOH, MeOH, rt; (iii) 10% Pd–C, H_2, rt, 40%.

In conclusion, we have demonstrated the first stereoselective total synthesis of the bioactive neolignan, surinamensinol A starting from two easily available aldehydes, 3,4,5- trimethoxy benzaldehyde and vanillin. Chiral reduction, asymmetric dihydroxylation and Mitsunobu reaction are the key steps in the present synthesis. The overall yield of **1** starting from **5** is 10% involving sixteen steps.

Acknowledgments

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