

A NEW TWO-STEP SYNTHESIS OF 1-ARYLNAPHTHALENE LIGNANS FROM CYANOHYDRINS

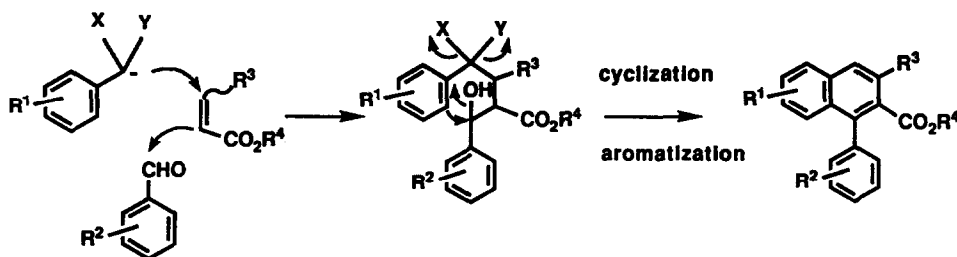
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Abstract: 1-Arylnaphthalene lignans were synthesized in good yields from *O*-*t*-butyldimethylsilylcyanohydrins in two steps based on a new approach involving a tandem conjugate addition-aldol reaction, followed by an acid-catalyzed construction of the naphthalene ring.

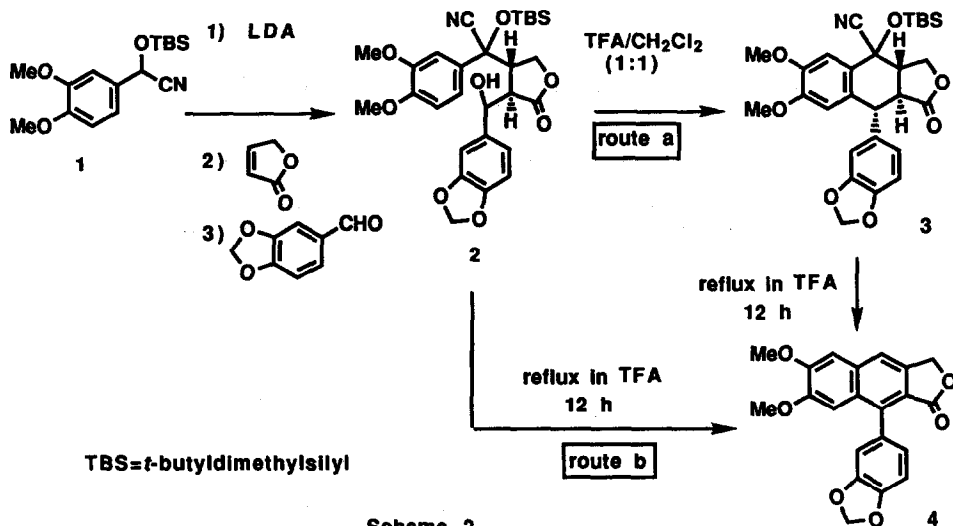
Lignans of the 1-arylnaphthalene series, e.g., taiwanin C and chinensin, have attracted considerable attention recently with the discovery of intriguing biological activities.¹⁾ Current synthetic methods²⁾ of 1-arylnaphthalene lignans include those based on Diels-Alder reaction of 1-arylisobenzofurans,³⁾ cyclization of Stobbe condensation products⁴⁾ and nucleophilic addition of phenyl lithium to naphthyloxazolines.⁵⁾ These methods, however, need a number of steps for construction of the 1-arylnaphthalene skeleton. We now report a two-step synthesis of 1-arylnaphthalene lignans from *O*-*t*-butyldimethylsilylcyanohydrins based on a new approach involving a tandem conjugate addition-aldol reaction, followed by an acid-catalyzed construction of the naphthalene ring.

In Scheme 1 are illustrated the main features of our strategy. The requirements imposed on X and Y groups for this process are threefold as follows. X and Y groups must (1) induce the generation of a soft anion which is capable of undergoing conjugate addition reaction;⁶⁾ (2) remain unchanged under reaction conditions for the cyclization; (3) act effectively as leaving groups after the cyclization, thereby contributing to the construction of the naphthalene ring. We envisioned that *O*-*t*-butyldimethylsilylcyanohydrins, well-known acylanion equivalents,⁷⁾ would meet such requirements.⁸⁾



Scheme 1

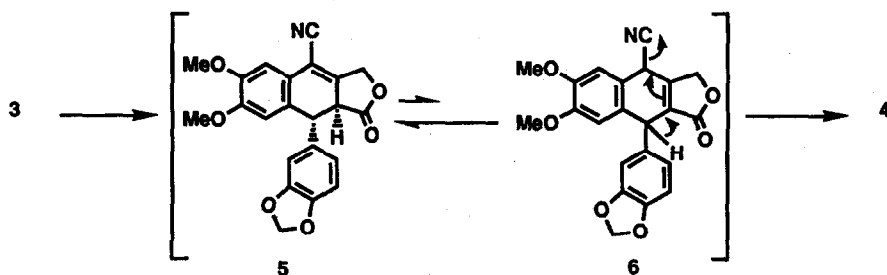
The first successful result was obtained by the reaction using *O*-*t*-butyldimethylsilylcyanohydrin (**1**)⁹⁾ (route a in Scheme 2). Conjugate addition of the anion generated by reaction of **1** with lithium diisopropylamide (LDA) to 2-butenolide cleanly took place in tetrahydrofuran (THF) at -78°C; the result was in marked contrast



Scheme 2

with that using the O-(1-ethoxyethyl)cyanohydrin in which such addition product was not obtained.¹⁰ Without isolation of the addition product, the resulting enolate was subsequently trapped *in situ* with piperonal to afford **2** in 88% yield by purification of the crude product by silica gel chromatography; the 200-MHz ¹H-NMR spectrum of **2** clearly indicated that the α -benzyl group on the lactone ring was *trans* to the β -benzyl group. Treatment of **2** with CF₃CO₂H (TFA)-CH₂Cl₂ (1:1) at room temperature for 30 min afforded **3** in a quantitative yield as a mixture of an almost equal amount of the two diastereoisomers; the diastereoisomers were separated by silica gel chromatography and their structures were unambiguously determined by X-ray crystallographic and/or NMR analyses.¹¹ Refluxing the mixture of the diastereoisomers in TFA for 12 h gave rise to the desired fully aromatized 1-arylnaphthalene lignan (**4**) in 70% yield.¹²

In order to gain an insight into the mechanism of the aromatization, we tried to isolate intermediates. When the aromatization reaction of **3** leading to **4** was quenched after 2 h, the intermediate (**5**)¹³ was isolated in 17% yield together with **3** (33%) and **4** (29%). When the reaction was further continued, it was observed by following the reaction by HPLC that **5** was gradually converted to **4**. Furthermore, refluxing **5** isolated above in TFA afforded **4** in a quantitative yield. Accordingly, the sequence of events in the observed aromatization would be best accounted for by the intervention of the intermediates (**5**, **6**),¹⁴ as shown in Scheme 3.



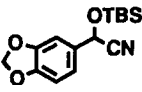

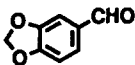
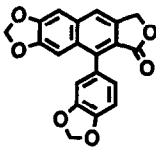
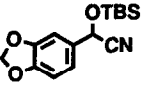

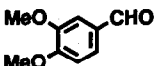
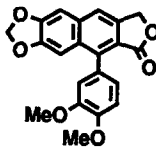
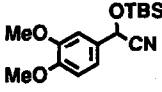

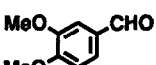
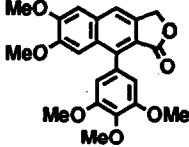
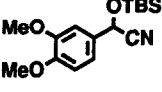

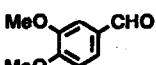
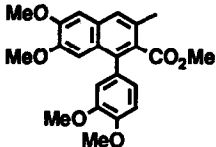
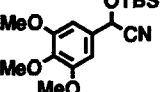

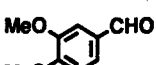
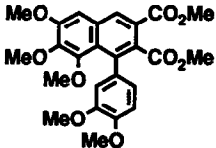
Scheme 3

The above results prompted us to investigate the one-pot conversion of **2** to **4** under TFA-catalyzed conditions (route **b** in Scheme 2). Thus, **2** was treated with refluxing TFA for 12 h to furnish **4** in 66% yield. In this one-pot conversion, **2** needed not be purified but the crude product could be used without any problem.

The following example is representative for the two-step synthesis of **4** from the *O*-*t*-butyldimethylsilylcyanohydrin (**1**).

To a solution of LDA (11mmol) in 50 ml of THF was added **1** (10 mmol in 10 ml of THF) at -78°C under vigorous stirring, followed by successive additions of 2-butenolide (10 mmol in 20 ml of THF) and piperonal (10 mmol in 10 ml of THF) at the same temperature. After 10 min, AcOH (10 ml) was added to quench the reaction. The reaction mixture was poured into a mixture of H_2O and AcOEt. The separated organic layer was

Table 1 Two-step synthesis of 1-arylnaphthalene lignans^{a)}

cyanohydrin deriv.	α,β -unsaturated ester	aromatic aldehyde	product ^{b)}	overall yield ^{c)}
				62%
				71%
				62%
				61%
				78%

a) The reaction was carried out on a 10 mmol scale under the reaction conditions described in the representative example. b) All products were characterized based on $^1\text{H-NMR}$, IR, and mass spectra, and elemental analyses. c) Isolated yield.

dried (MgSO_4) and concentrated. The residue was dissolved in TFA (20 ml) and the solution was refluxed for 12 h. The reaction mixture was evaporated to dryness *in vacuo* and the resulting crystals were recrystallized from MeOH to give **4** in 62% yield.

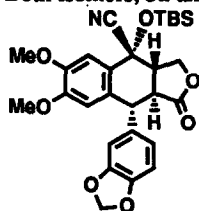
The generality of the two-step synthesis of 1-arylnaphthalene lignans is indicated in Table 1. The α,β -unsaturated esters other than 2-butenolide also worked effectively to afford a variety of 1-arylnaphthalene lignans.

The present methodology should find wide application in the synthesis not only of 1-arylnaphthalene lignans but also of the other naturally occurring carbon aromatics.

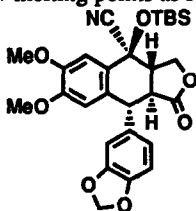
Acknowledgement: The authors thank Dr. Tetsuya Tosa, Director and Dr. Kazuo Matsumoto, Manager of our research laboratory for their encouragement and interest. We are also indebted to Dr. Tadamasu Date and Mr. Kimio Okamura of our company for X-ray crystallographic analyses.

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- Conjugate addition of a thioacetal anion to 2-butenolide has been reported to constitute an efficient method for preparing several types of lignans. See, for example: Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303. However, the thioacetal strategy is not suitable for construction of naturally occurring 1-arylnaphthalene lignans. See, for example: Pelter, A.; Ward, R. S.; Prichard, M. C.; Kay, I. T. *J. Chem. Soc., Perkin Trans. I* **1988**, 1603.
- For a review, see; Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.
- O*-*t*-Butyldimethylsilylcyanohydrins are relatively stable under acidic conditions. See: Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55.
- 1** (mp 46-48°C) was prepared by the reported method. See: Rawal, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275.
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- Both isomers, **3a** and **3b**, show melting points as follows.



3a (mp 188-189°C)



3b (mp 216-218°C)

- The physical constants of **4** were completely consistent with those of justicidin B.
- The structure of **5** (mp 259-261°C) was determined by the two-dimensional $^1\text{H-NMR}$ spectrum.
- The failure to detect **6** may be due to the extremely rapid rate of aromatization leading to **4**.