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Efficient Rhodium-Catalyzed Conjugate Addition of Arylboronic Acids to Unsaturated Furano Esters for the Highly Stereoselective Synthesis of Four Natural Trisubstituted Furanolignans

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Dedicated to Professor Max Malacria on the occasion of his 60th birthday

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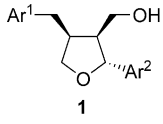
Four natural lignans, (±)-dihydrosesamin (**1a**), (±)-lariciresinol methyl ether (**1b**), (±)-sanshodiol methyl ether (**1c**) and (±)-acuminatin methyl ether (**1d**), were prepared stereoselectively in five steps from a 4-(arylmethylene)-2-methoxytetrahydrofuran derivative obtained by a MCR reaction. The key step of this synthesis is the microwave-assisted stereoselective addition of a boronic acid (Hayashi–Miyaura reaction) to a 4-ethoxycarbonyldihydrofuran, generating three contiguous stereogenic centers with an excellent diastereoselectivity.

Introduction

Lignans are a large family of compounds widely found among natural products.[1] Among them 2,3-*trans*-3,4-*cis*-trisubstituted tetrahydrofuran lignans such as dihydrosesamin (**1a**), lariciresinol methyl ether (**1b**), sanshodiol methyl ether (**1c**) and acuminatin methyl ether (**1d**) (Figure 1) are of great interest due to their biological activities including antitumor, antioxidant, analgesic and antiinflammatory properties.[2]



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1a $Ar^1 = Ar^2$ = 3,4-methylenedioxyphenyl — Dihydrosesamin
1b Ar^1 = 3,4-methylenedioxyphenyl, Ar^2 = 3,4-dimethoxyphenyl — Sanshodiol methyl ether
1c $Ar^1 = Ar^2$ = 3,4-dimethoxyphenyl — Lariciresinol methyl ether
1d Ar^1 = 3,4-dimethoxyphenyl, Ar^2 = 3,4-methylenedioxyphenyl — Acuminatin methyl ether

Figure 1. Four natural 2,3,4-trisubstituted lignans.

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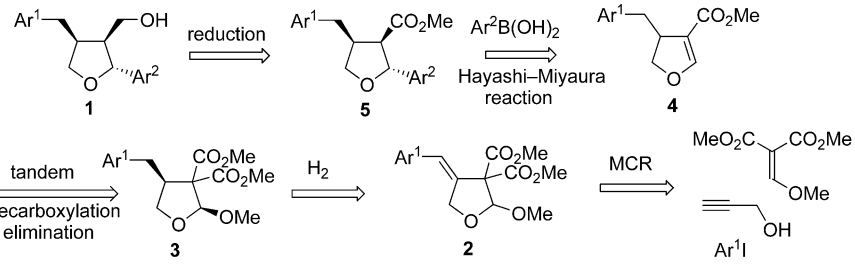
Consequently, significant efforts have been made towards the construction of this challenging class of compounds containing three contiguous stereocenters. However, few methods exist for the preparation of such compounds in a highly stereoselective manner.[3]

We have recently succeeded in the syntheses of disubstituted furanolignans and lactone lignans based on an efficient palladium-catalyzed three-component synthesis of 4-(arylmethylene)-2-methoxytetrahydrofuran derivatives that we developed in our group.[4,5] In a further application of this methodology, we present here a highly stereoselective and efficient new access to 2,3,4-trisubstituted lignans **1a**–**d**.

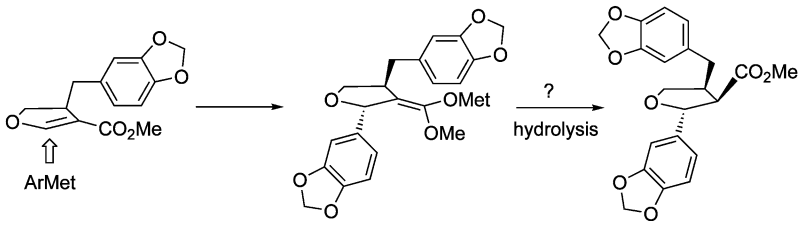
Results and Discussion

Our retrosynthetic strategy, outlined in Scheme 1, involves the conjugate addition of an organometallic aryl species to the α,β-unsaturated ester **4**. The Michael acceptor **4** may, in turn, be obtained by a tandem decarboxylation/elimination performed on the diester **3**, which has been prepared previously in our laboratory.[5]

The key synthetic challenge in our planned approach is the conjugate addition step, since three contiguous stereocenters are generated in the course of the reaction and thus, four possible diastereomeric compounds could be produced. It was anticipated that the desired stereogenic centers C-2 and C-4 would be controlled in this step, since the conjugate addition should occur from the less hindered face of the dihydrofuran (Scheme 2).



Scheme 1. Retrosynthetic analysis.



Scheme 2. Sterically directed conjugate addition of the arylmetal species.

However, whereas the conjugate addition of organometallic reagents to unsaturated carbonyl compounds has been well described,[6] few examples of such reaction on 4-(ethoxycarbonyl)- or 4-carboxy-2,3-dihydrofurans are known, and in this particular case, the 1,4-addition of organometallic species such as Grignard reagents is often followed by a ring opening of the heterocycle.[7] We thought that one possibility of solving this problem was the use of the rhodium-catalysed addition of organoboronic acids pioneered by Hayashi and Miyaura.[8] However, to the best of our knowledge, the Rh-catalyzed conjugate addition to trisubstituted α,β-unsaturated ester derivatives has been relatively unexplored.[9] Consequently, we decided to evaluate the feasibility of this approach, and initial studies were conducted on the readily available unsaturated furano ester **6** as model compound.[10]

We first attempted the conjugate addition of phenylboronic acid using the conditions reported by Miyaura.[11] Thus, treatment of **6** with $PhB(OH)_2$ (2 equiv.) in the presence of KOH as base (2 equiv.) and 5 mol-% of the rhodium catalyst generated from $Rh(acac)(CO)_2$ and dppb in dioxane/H_2O (6:1) led to the formation of the expected addition product **7a**, but in rather low yields – even after heating at 100 °C for 40 h (Table 1, Entry 1). The use of $[RhCl(cod)]_2$/dppb in place of $Rh(acac)(CO)_2$/dppb gave **7a** only in 28% yield after heating at 100 °C for 24 h (Table 1, Entry 2). Increasing of the reaction time to 48 h improved the yield of **7a** up to 62%, and unreacted starting material **6** was recovered in 25% yield (Table 1, Entry 3). Pleasingly, the reaction took place with a high degree of stereoselectivity (*trans*/*cis* = 95:5) according to the analysis of ^1H NMR spectra of the crude reaction mixture.[12] The 2,3-*trans* stereochemistry of the major isomer has been confirmed by X-ray crystallography.[13]

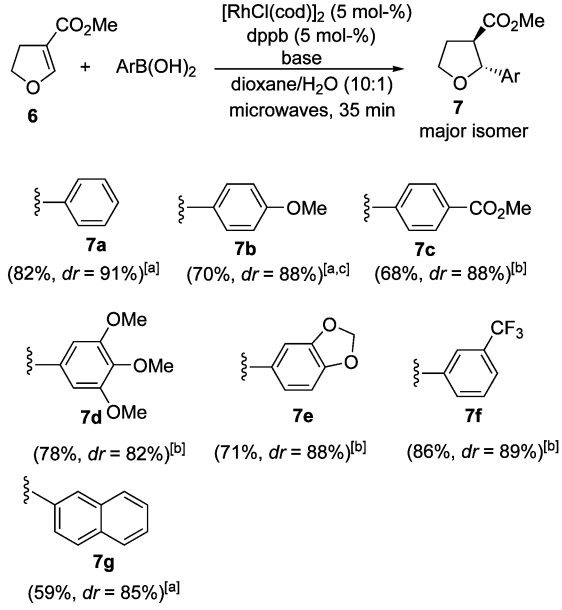
To shorten the long reaction times, the same conjugate addition was performed under microwave irradiation,[14] and the best results (82% yield of the 1,4-addition product) were obtained when the reaction was carried out at 150 °C for 35 min in the presence of 2 equiv. of phenylboronic acid in dioxane/H_2O (10:1) (Table 1, Entry 4). A decrease in the amount of phenylboronic acid affected the yield significantly (Table 1, Entry 5), and the use of phenylpotassium organotrifluoroborate salts as boron component resulted in lower yield[15] (Table 1, Entry 6).

Using the optimized conditions, we further explored the scope of this rhodium-catalyzed conjugate addition with a variety of boronic acids. Some representative results are shown in Scheme 3. The reaction generally proceeded in good yields and with excellent diastereoselectivity with both electron-rich and electron-deficient arylboronic acids. In some cases (**7c**–**f**), the conversion was not satisfactory, and best yields were achieved when using $Ba(OH)_2$ instead of KOH as base.

Table 1. Optimization of the addition reaction of phenylboronic acid to furan **6**.

Entry	ArMet (equiv.)	Heating method, time	Catalyst system	Isolated yield of furan **7a**
1	$PhB(OH)_2$ (2)	thermal (100 °C), 40 h	$Rh(acac)(CO)_2$ (5 mol-%), dppb (5 mol-%), KOH 1 equiv.	9%[a]
2	$PhB(OH)_2$ (2)	thermal (100 °C), 24 h	$[RhCl(cod)]_2$ (5 mol-%), dppb (5 mol-%), KOH (1 equiv.)	28%[a]
3	$PhB(OH)_2$ (2)	thermal (100 °C), 48 h	$[RhCl(cod)]_2$ (5 mol-%), dppb (5 mol-%), KOH (1 equiv.)	62%[a]
4	$PhB(OH)_2$ (2)	microwaves (150 °C), 35 min	$[RhCl(cod)]_2$ (5 mol-%), dppb (5 mol-%), KOH (1 equiv.)	82%[b]
5	$PhB(OH)_2$ (1.5)	microwaves (150 °C), 35 min	$[RhCl(cod)]_2$ (5 mol-%), dppb (5 mol-%), KOH (1 equiv.)	15%[b]
6	$PhBF_3K$ (1.2)	microwaves (150 °C), 35 min	$[RhCl(cod)]_2$ (5 mol-%), dppb (5 mol-%), KOH (1 equiv.)	12%[b]

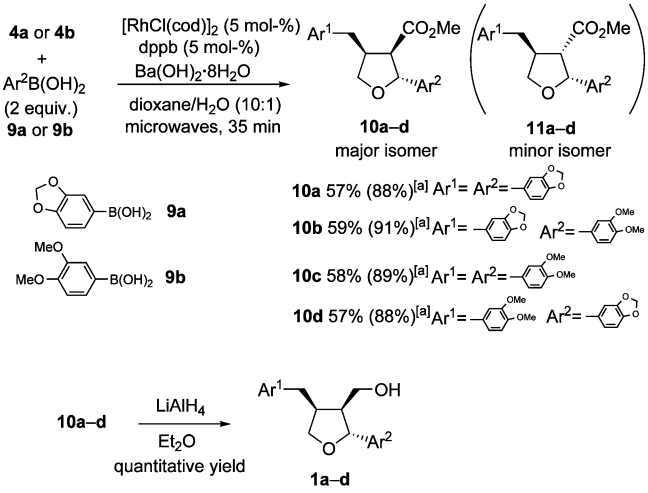
[a] Solvent dioxane/H_2O (6:1). [b] Solvent dioxane/H_2O (10:1).



Scheme 3. Rh-catalyzed 1,4-addition of several boronic acids to unsaturated ester **6**. [a] KOH, 150 °C. [b] $Ba(OH)_2·8H_2O$, 130 °C. [c] 1 h of irradiation.

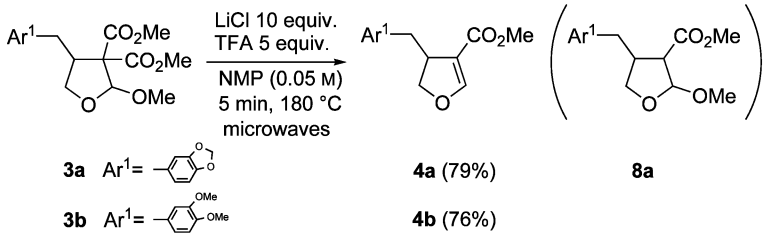
We next turned our attention to the application of this rhodium-catalyzed 1,4-addition to the cyclic unsaturated ester **4a**. The preparation of this product was envisaged by demethoxycarbonylation of the known diester **3a** followed by elimination of the methoxy group. However, initial attempts by using Krapcho's conditions[16] (NaCl, DMSO, 130 °C) afforded a 1:1 mixture of two products in moderate yields, the expected unsaturated ester **4a** and the methoxy ester **8a** resulting from a subsequent conjugate addition of lithium methoxide generated during the reaction.[17] After several unsuccessful attempts to improve the yield of this demethoxycarbonylation reaction including the use of different solvents (DMF, NMP, addition of H_2O), temperature (140–200 °C) and salts (NaCl, NaCN), it was found that addition of TFA[18] avoided the formation of **8a**. Nevertheless, under optimum conditions (5 equiv. of LiCl, 5 equiv. of TFA, DMSO, 130 °C) the yield of the tandem decarboxylation/elimination product did not exceed 50% and was difficult to reproduce. Consequently, we decided to optimize the tandem reaction under microwave conditions, and higher yields (79%) of **4a** were obtained when the reaction was carried out at a 0.05 M concentration in NMP at 180 °C for 5 min in the presence of LiCl (10 equiv.) and TFA (5 equiv.). These conditions were successfully applied to diester **3b** leading to **4b** in 76% yield (Scheme 4).

With these results in hand, we examined the Rh-catalyzed 1,4-addition of arylboronic acids **9a** and **9b** to unsaturated esters **4a** and **4b** under optimum conditions as established above, and the results of this study are listed in Scheme 5. Gratifyingly, all the addition reactions gave rise to only two products **10a**–**d** and **11a**–**d**, epimeric at the C-3 position, together with some recovered starting material, and in excellent diastereoselectivity (diastereomeric ratio > 94:6). The major isomers **10a**–**d** were isolated in comparable yieds 57–59% (88–91% based on recovered starting material **4a** or **4b**) by careful flash chromatography,[19] and the structure assignments were unambiguously secured by subsequent reduction of their ester group with $LiAlH_4$ leading to natural lignans **1a**–**d**, respectively, in high yields (Scheme 5).

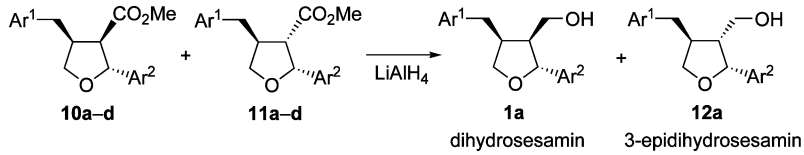


Scheme 5. Stereoselective synthesis of lignans **1a**–**d**. [a] based on recovered **4a** or **4b**.

The 2,3-*cis* stereochemistry of the minor isomeric esters was again established by the chemical shifts of the methyl group in the ^1H NMR spectrum.[12] To further confirm the structure of the minor isomers, a reduction of the crude mixture of esters **10a** and **11a** with $LiAlH_4$ to the corresponding alcohols **1a** and **12a** was carried out (Scheme 6). The NMR spectroscopic data (^1H and ^{13}C) for alcohol **12a** were compared with those of 2,3-*trans*-3,4-*trans* and 2,3-*cis*-3,4-*trans* isomers of dihydrosesamin already reported in the literature[20] and were found to be in accordance with those given for the later 3-epidihydrosesamin.



Scheme 4. Preparation of unsaturated esters **4a**–**b** by tandem decarboxylation/elimination.



Scheme 6. Elucidation of the structure of the minor compound **11a**.

Conclusions

We have described a convergent and efficient total synthesis of four members of a trisubstituted tetrahydrofuran family of lignan natural products exploiting a three-component coupling strategy developed in our group. The key step involves a highly stereoselective rhodium-catalyzed addition leading to the formation of three contiguous stereocenters. Further development will be directed toward the enantioselective synthesis of natural lignans through this strategy.

Experimental Section

General Procedure: 5 mol-% of rhodium complex $[Rh(cod)Cl]_2$ and 5 mol-% of dppb in dioxane (1 mL) were dissolved in a microwave vial. Then, water (0.1 mL), 1 equiv. of base, 1 equiv. of α,β-unsaturated furan **6** and 2 equiv. of boronic acid were added successively. The vial was capped and exposed to microwave heating at 150 °C or 130 °C during the defined time. Time and temperature were depending on the nature of the base: 150 °C for potassium hydroxide and 130 °C for $Ba(OH)_2$. We obtained a mixture of diastereoisomers where the *trans* isomer is the major product. The mixture was washed with water and extracted with dichloromethane. The organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to obtain the desired product **7a**–**g**.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and characterization data for **4a**–**b**, **7a**–**g** and **10a**–**d**, ^1H and ^{13}C NMR spectra for **4a**–**b**, **7a**–**g**, **10a**–**d**, **1c**, and **12a**–**1a**.

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