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Graphical Abstract

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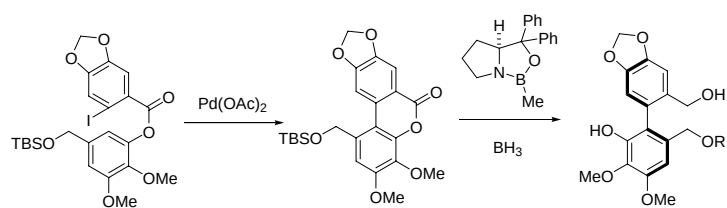
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Abstract - A Pd-mediated intramolecular aryl-aryl coupling reaction of phenyl benzoate derivatives were examined to form benzo[c]chromen-6-ones, and then enantioselective lactone-opening reaction with a borane-oxazaborolidine combination was carried out. The resulting biphenyl was transformed into a key intermediate for the stegane related compounds. The absolute configuration of the biphenyl is also discussed.

Stegane and related compounds are important because of their interesting biological activities such as antileukemic properties.¹ One of the most outstanding features of their chemical structures is an unsymmetrical 2,2'-disubstituted biphenyl moiety with an axial chirality (Figure 1). For the formation of such a biphenyl part in the syntheses of the stegane families, several approaches have been attempted such as photocyclization,² Suzuki coupling,³ oxidative biaryl coupling,⁴ the S_NAr reaction,⁵ Ullmann coupling,⁶

and the [2+2+2] three-component cyclization reaction.⁷

Figure 1

Diastereoselective formation of the chiral 2,2'-disubstituted biaryl has been a general method for the synthesis of the stegane related compounds. On the other hand, the enantioselective synthesis of the biaryl moiety is an unknown route to these targets.

Bringmann has proposed a "lactone strategy" for the enantioselective preparation of biaryl compounds, which is very effective for the syntheses of biaryl-type natural products in the optically active form.⁸ In this report, we extend the Bringmann's "lactone strategy" to the first enantioselective synthesis of the biphenyl moiety of stegane and related compounds.^{9,10}

Initially, we prepared phenyl benzoates **1a**, **1b**, and **1c** through simple esterification between the phenols and the benzoic acid.¹¹ These compounds were investigated for the Pd-mediated biaryl coupling reaction under various conditions. The reaction of **1a** and **1b** with Pd(OAc)₂ proceeded to give lactones **2a** and **2b** in good yields when the reaction was carried out in the presence of both the phosphine ligand and base (Table 1). Contrary to the above results, the methyl ester **1c** did not afford the desired lactone at all in spite of our intensive investigation.

Table 1

Next, we examined the asymmetric lactone-opening reaction of **2a** and **2b** with a chiral oxaborolidine-borane complex, based on dynamic optical resolution. As shown in Table

2, lactone **2a** was reduced to give a lactone-opened product **3a** in an enantioselective manner (run 1). When this reaction was carried out at 0°C, the ee of **3a** was only 47% although the reaction rate was accelerated (run 2). In order to improve the reaction conditions, 50 mol% of the chiral ligand **5** was employed to the same reaction. However, only moderate yield of **3a** was obtained with 68% ee (run 3). Unfortunately, in each case, generation of undesired **4a** could not be avoided (run 1-3). On the other hand, a more efficient result was obtained in the reaction of **2b**, in which a higher yield of **3b** was obtained (run 4). In sharp contrast to the reaction of **2a**, no by-product **4b** was detected under this reaction condition. However, when the same reaction was carried out at higher temperature, undesired **4b** was obtained in 51% yield (run 5). Further attempts to improve these reaction conditions are under investigation in our group.

Table 2

In order to determine the absolute configuration of the obtained alcohol **3b**, a short-step transformation into **6**, which is a known compound, was carried out (Chart 1). The methylation of the phenolic hydroxy group followed by the oxidation with PDC successfully afforded aldehyde **7** without racemization. The reaction with methyl lithium produced two diastereomers which could be easily separated by chromatography to isolate a major diastereoisomer. *O*-Allylation of the resulting secondary alcohol gave **6**, whereas the configuration at the benzylic position was not determined. All spectral data of **6** including the optical rotation agreed with those of a known compound which was reported by Uemura et al.^{3c, 12} Consequently, the absolute configuration of **3b** could be determined as *R*.

Scheme 1

In summary, we succeeded in preparing a key intermediate of the optically active stegane families through the Pd-mediated biaryl coupling reaction of phenyl benzoate followed by the enantioselective lactone-opening reaction.

The synthesis of (-)-steganone from **6** has already been reported.^{3a} Thus, we accomplished the formal total synthesis of (-)-steganone.

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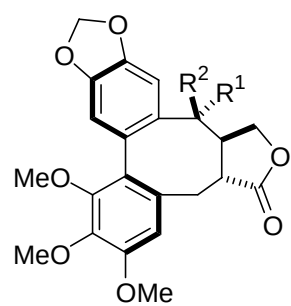
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12. The e.e. of **4** was 80% by HPLC analysis.

Figure 1

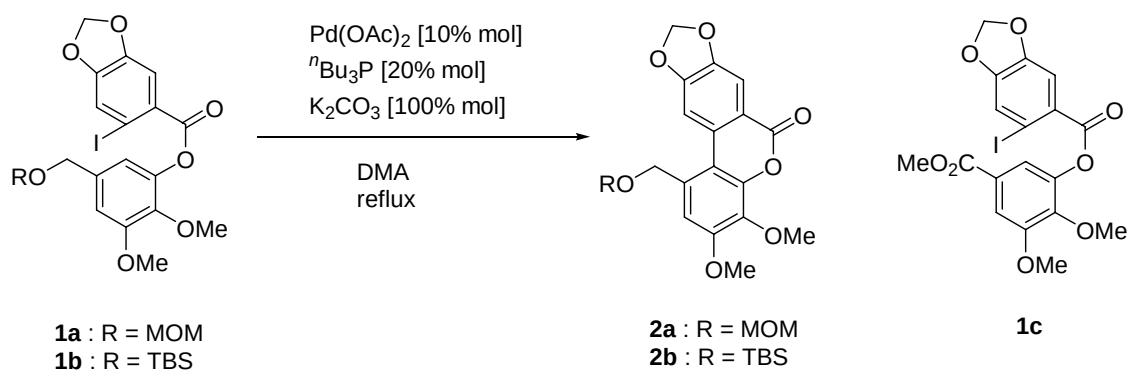


$R^1 = R^2 = H$: (-)-stegane

$R^1, R^2 = O$: (-)-steganone

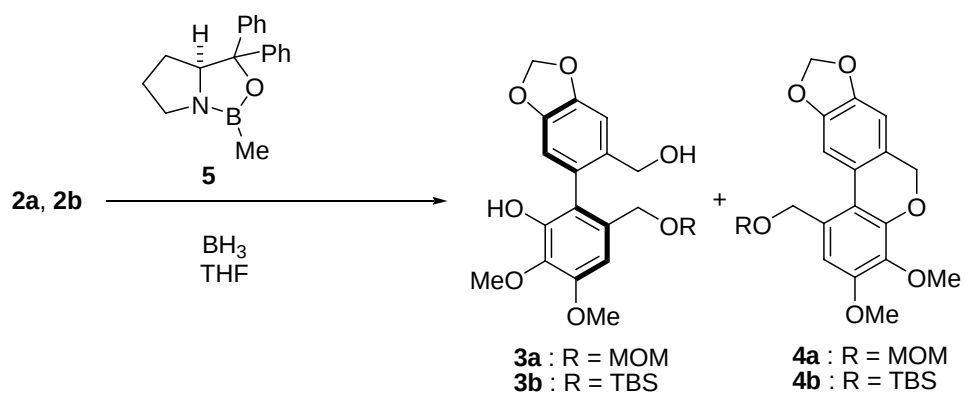
$R^1 = OAc, R^2 = H$: (-)-steganacin

Table 1



Substrate	Time (min)	Product	Yield (%)
1a	30	2a	71
1b	10	2b	63

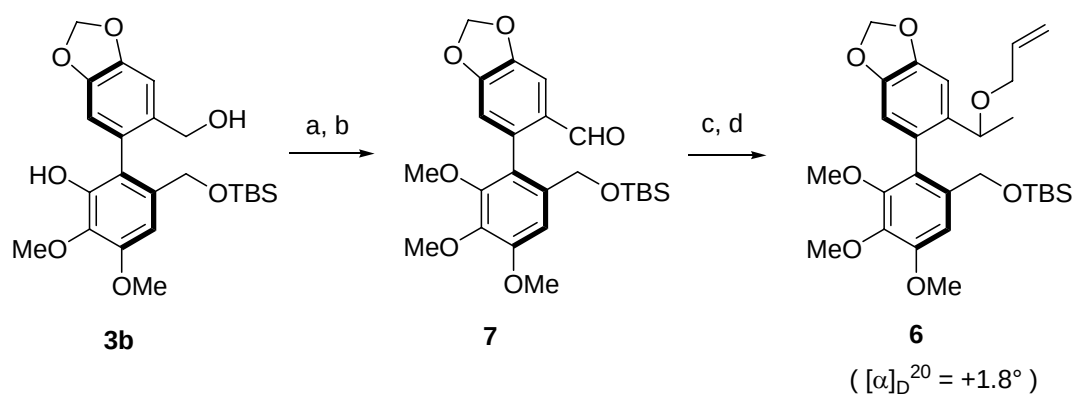
Table 2



Run	Substrate	BH_3 (mol%)	5 (mol%)	Temp (°C)	Time (h)	Yield (%)		E.e. (%) of 3 ^a
						3	4	
1	2a	400	300	-78 to r.t.	8	59	16	86
2		400	300	0	1.5	67	26	47
3		200	50	-40	40	55	11	68
4	2b	400	300	-78 to -40	17	97	-	83
5		400	300	-78 to 0	17	49	51	78

a) Determined by HPLC analysis using CHIRALCEL OD.

Scheme 1



Reagents and conditions: (a) MeI, ^tBuOK, THF, 88%; (b) PDC, CH₂Cl₂, 77%;
 (c) MeLi, THF, 55%; (d) allyl bromide, NaH, DMF, 66%.