Syntheses of Anolignans A and B Using Ruthenium-Catalyzed Cross-Enyne Metathesis

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Anolignans A and B were synthesized using ruthenium-catalyzed cross-enyne metathesis as the key steps. The 1,3-diene moieties of these natural products were constructed by the introduction of the methylene parts of ethylene into alkyne using Grubbs' catalyst.

Anolignan A and anolignan B are new dibenzylbutadiene lignans isolated from *Anogeissus acuminata*. They were identified as the active HIV-1 reverse transcriptase inhibitory constituents of this plant.[1] A remarkable feature of these compounds is that they have a 1,3-diene moiety in the molecules (Chart 1).

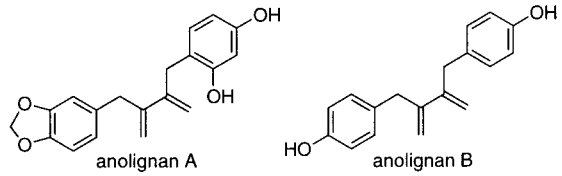
A total synthesis of anolignan A was achieved by Hatakeyama,[2]and he utilized a Lewis acid-catalyzed allenylsilene addition to piperonal.

We have already reported the novel synthesis of 1,3-diene from alkyne and ethylene using ruthenium carbene complex **1a**[3e,f] reported by Grubss.[4a,b] When a CH_2Cl_2 solution of alkyne **2** was stirred in the presence of **1a** at room temperature under an atmosphere of ethylene, 1,3-diene **3** was obtained in high yield. In this reaction, each methylene part of ethylene is introduced onto the two-alkyne carbons, respectively (Scheme 1).

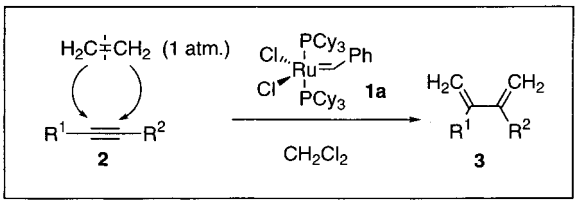
This novel method prompted us to synthesize anolignans. A retrosynthetic analysis of anolignans is shown in Scheme 2. Alkyne **II** would be synthesized by condensation of two aldehydes **IIIa** and **IIIb** with acetylene. Conversion of alkyne **II** into 1,3-diene **I** should proceed using ruthenium carbene complex[4] under ethylene gas. Removal of two acetoxy groups from **I** using palladium catalyst would be achieved, since Hatakeyama successfully removed an acetoxy group in the synthesis of anolignan A.[2]

However, it was previously found that a heteroatom such as a benzoyloxy group or a tosyl amide group at a propargylic position accelerates the reaction rate.[3f] For

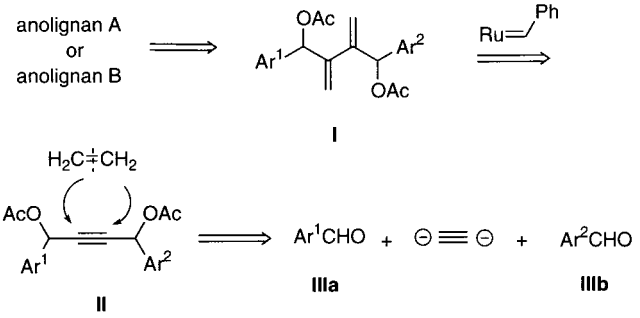
Chart 1



Scheme 1. Novel Synthesis of 1,3-Diene from Alkyne and Ethylene Anolignan A and Anolignan



Scheme 2. Retrosynthetic Analysis of Anolignans



Scheme 3. Problems for Enyne Metathesis

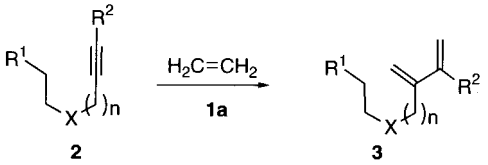


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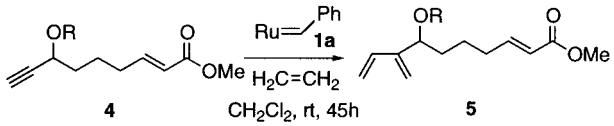
Table 1. Synthesis of 1,3-Diene

run	alkyne	R^1	R^2	X	*n*	yield of **3** (%)
1	**2a**	$CH{=}CHCO_2$Menthyl	H	CH_2	1	10
2	**2b**	$CH{=}CHCO_2Me$	CH_2OBz	CH_2	1	53
3	**2c**	$(CH_2)_3CH_3$	H	NTs	1	81
4	**2d**	$(CH_2)_3CH_3$	H	NTs	2	11

Table 2. Effects of the Protecting Group on the Proporgyl Alcohol



run	R		"Ru" (mol %)		yield (%)	**5** (%)
1	CO_2Me	**4a**	10	**5a**	76	12
2	Bz	**4b**	10	**5b**	77	6
3	Ac	**4c**	5	**5c**	80	16
4	TBDPS	**4d**	5	**5d**	<5	87
5	TBDMS	**4e**	5	**5e**	10	74
6	TMS	**4f**	5	**5f**	8	62
7	MOM	**4g**	5	**5g**	18	64
8	H	**4h**	5	**5h**	<6	<58

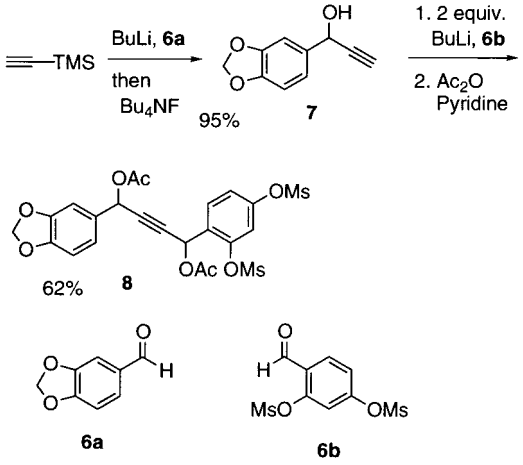
example, when alkyne **2a** was treated with ruthenium carbene complex **1a** under ethylene gas (Scheme 3 and Table 1), 1,3-diene **3a** was obtained in only 10% yield (conversion yield, 58%), while **2b** gave **3b** in 53% yield (conversion yield, 82%). Furthermore, when alkyne **2c** having the tosyl amide group at the propargylic position was treated with ruthenium carbene complex **1a** under ethylene gas, the desired 1,3-diene **3c** was obtained in 81% yield, while alkyne **2d** having the tosyl amide group at the homopropargylic position gave 1,3-diene **3d** in only 11% yield.[3f]

Thus, at first, what protecting group on the hydroxyl group at the propargylic position is suitable was examined. As a model compound, alkyne **4** was chosen (Table 2). Cross-enyne metathesis of alkyne **4** and ethylene was carried out using ruthenium carbene complex **1a**. When a CH_2Cl_2 solution of **4a** and 10 mol % of **1a** was stirred at room temperature under ethylene gas (1 atm) for 45 h, the desired 1,3-diene **5a** was obtained in 76% yield along with the starting material **4a** in 12% yield.

Both alkynes, **4b** and **4c**, having the benzoyl and the acetyl groups, also afforded the desired 1,3-dienes, **5b** and **5c**, in high yields, respectively. However, the silyl and MOM groups did not give good yields of the desired 1,3-dienes **5** (runs 4−7). The alkyne **4h** having no protecting group also did not give a good result (run 8). These results indicated that the MOM group having strong coordination ability to ruthenium or the bulky silyl group[5] decreased the reaction rate. Thus, an acetyl group was chosen as the protecting group.

The starting alkyne **8** was prepared (Scheme 4). To a THF solution of lithium trimethylsilylacetylide was added piperonal **6a** and after a spot of piperonal disappeared on TLC, Bu_4NF was added. After the usual work up, alkyne **7** was obtained in 95% yield. Treatment of **7** with 2 equiv of BuLi and then dimesyloxybenzaldehyde

Scheme 4. Preparation of Substrate for Synthesis of Anolignan A



6b gave diol, whose hydroxy group was protected by the acetyl group.

For the construction of 1,3-diene moiety, a CH_2Cl_2 solution of **8** was stirred in the presence of 10 mol % of **1a** under ethylene gas (1 atm) at room temperature. After 36 h, 1,3-diene **9** was obtained in 65% yield along with the starting material **8** in 15% yield. On the other hand, when a new generation ruthenium carbene complex **1b**[6e] containing *N*-heterocyclic carbene ligand was used for this reaction, the yield increased to 86%. Hydrogenolysis of two acetoxy groups in **9** was successfully achieved by treatment with $Pd_2(dba)_3{\cdot}CHCl_3$ and Bu_3P in the presence of HCO_2H and Et_3N[7] to give **10** (Scheme 5).

Deprotection of **10** with PhLi[8,9] in ether at room temperature proceeded smoothly to give phenolic compound, whose spectral data agree with those of anolignan A reported in the literature.[1] Thus, we succeeded in the total synthesis of anolignan A via six steps in 30% overall yield.

(5) The fact that the silyl groups did not give the good results may be due to the pπ−dπ interaction of the oxygen and the silicon.

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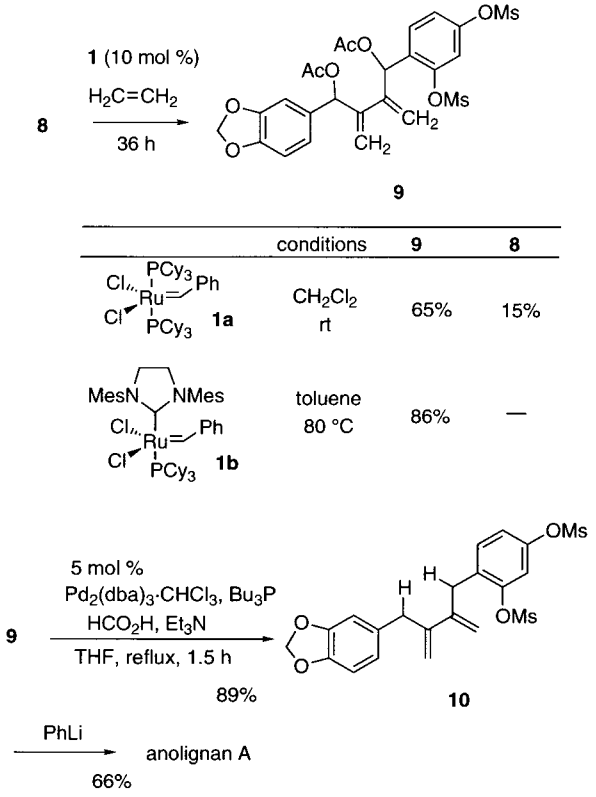
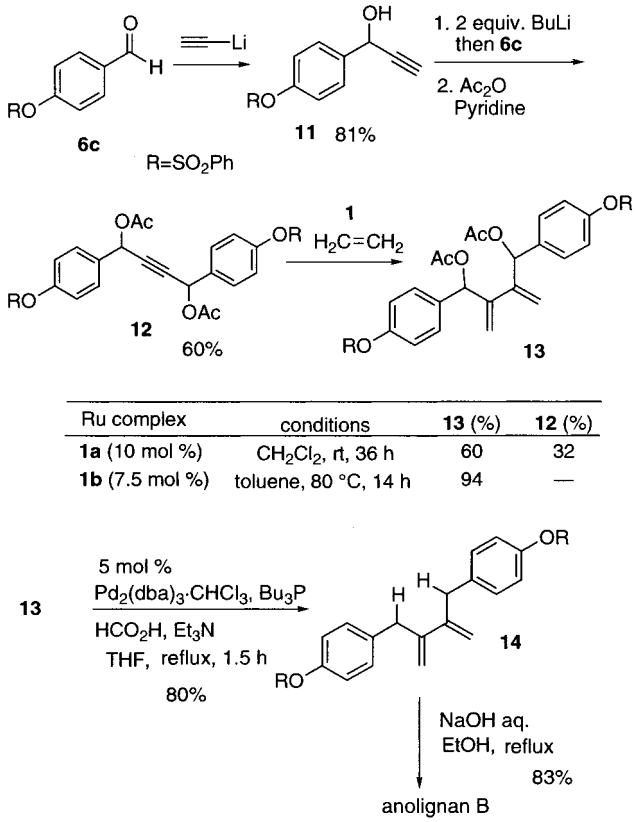
(9) Treatment of **8** with aqueous NaOH in EtOH did not afford anolignan A and two products were formed, but the structures of them could not be determined.

Scheme 5. Synthesis of Anolignan A



Scheme 6. Synthesis of Anolignan B



The synthesis of anolignan B was also achieved from acetylene and 4-benzenesulfonyloxybenzaldehyde **6c** (Scheme 6). Condensation of **6c** with lithium acetylide gave **11**, which was treated with BuLi (2 equiv) and then **6c** followed by acetylation to give alkyne **12**. Reaction of alkyne **12** with ethylene smoothly proceeded using 10 mol % of ruthenium catalyst **1a** to give 1,3-diene **13** in 60% yield along with the starting material **12** in 32% yield. Treatment of **12** with 7.5 mol % of **1b** as a catalyst in toluene at 80 °C for 14 h under ethylene gas gave 1,3-diene **13** in 94% yield. Removal of the two acetoxy groups with a palladium catalyst followed by deprotection of the benzenesulfonyl group with aqueous NaOH gave anolignan B.[10]

Thus, we succeeded in the total syntheses of anolignans A and B using ruthenium-catalyzed cross-enyne metathesis. The remarkable feature of these synthetic procedures is that the 1,3-diene moieties of anolignans are construced by the carbon−carbon bond formation between the alkyne carbon and the methylene carbon of ethylene. This method was very effective for making symmetrical or asymmetrical 1,3-diene.

Experimental Section

General Procedure. CH_2Cl_2 was distilled under an argon atmosphere from CaH_2 and other solvents, and reagents were purified when necessary using standard procedures. All the solvents using the organometallic agents were degassed through a freeze−pump−thaw cycle. Ethylene gas was purified by passing through the aqueous CuCl solution, concentrated H_2SO_4, and a KOH tube.

(10) The spectral data of anolignan B agreed with those reported in the literature.[1]

General Procedure for Cross-Enyne Metathesis. A CH_2Cl_2 or toluene solution of alkyne and ruthenium carbene complex **1** (5−10 mol %) was stirred at room temperature or 80 °C under ethylene gas (1 atm). After the appropriate hours, the solution was allowed to stir under air, and then the solution was concentrated. The residue was purified by column chromatography on silica gel.

Acetic Acid 3-(Acetoxybenzo[1,3]dioxol-5-ylmethyl)-1-(2,4-bismethanesulfonyloxyphenyl)- 2-methylenebut-3-enyl ester (9). According to the general procedure, a solution of **8** (184.4 mg, 0.333 mol) and **1b** (28 mg, 0.033 mmol) in toluene (13.0 mL) was stirred at 80 °C for 36 h under an ethylene. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2/AcOEt, 20:1) to yield **9** (166.3 mg, 86%) as a colorless sticky oil of a mixture of diastereomer. IR (neat): 1737, 1605, 1373, 1262, 1183 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 2.05 (s, 3 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 2.07 (s, 3 H), 3.15 (s, 3 H), 3.17 (s, 3 H), 3.26 (s, 3 H), 3.28 (s, 3 H), 5.17−5.38 (m, 4 H × 2), 5.94 (s, 2 H), 5.95 (s, 2 H), 6.38 (s, 1 H), 6.40 (s, 1 H), 6.60 (s, 1 H), 6.60 (s, 1 H), 6.68−6.87 (m, 4 H • 2), 7.06−7.07 (m, 1 H × 2), 7.33−7.43 (m, 1 H × 2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.84, 21.09, 37.50, 37.57, 38.46, 67.77, 68.07, 74.69, 74.75, 101.12, 107.76, 107.79, 114.35, 115.59, 115.86, 116.05, 116.12, 116.59, 120.36, 120.71, 121.60, 121.78, 122.58, 122.90, 129.41, 129.82, 130.31, 130.36, 130.99, 131.19, 141.73, 142.27, 142.86, 143.41, 146.69, 146.77, 147.39, 147.43, 147.48, 147.55, 148.90, 169.25, 169.32, 169.48. LRMS *m/z*: 605 (M^+ + Na), 463 (M^+ − CH_3CO_2). HRMS *m/z*. Calcd for $C_{25}H_{26}O_{12}NaS_2$ (M^+ + Na): 605.09. Found: 605.0743.

Supporting Information Available: Text describing the experimental procedure and the spectral data of **4c**, **5c**, **6b**,**c**, **7, 8, 10**−**14**, anolignane A, and anolignane B. This material is available free of charge via the Internet at http://pubs.acs.org.

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