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# The first regiospecific synthesis of helioxanthin by novel palladium-catalyzed benzannulation reaction of α,β-bisbenzylidene-γ-lactone

Hideya Mizufune,* Minoru Nakamura and Hiroyuki Mitsudera

*Chemical Development Laboratories, Pharmaceutical Production Division, Takeda Chemical Industries, Ltd., Jusohonmachi 2-17-85, Yodogawaku, Osaka 532-8686, Japan*

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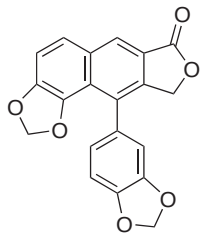
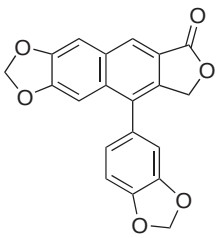
**Abstract**—We achieved the first regiospecific and biomimetic transformation of α,β-bisbenzylidene-γ-lactone to an arylnaphthalene lignan lactone, helioxanthin, using a novel palladium-catalyzed benzannulation reaction. 

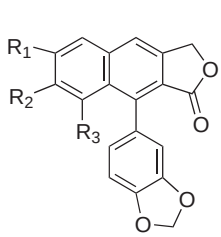
Arylnaphthalene lignan lactones occur widely in nature, and by themselves or their analogues show various biological activities,[1] such as leuckotriene biosynthesis inhibition, hypolipidemic activity and phosphodiesterases inhibition; therefore, this class of compounds has received the wide attention of synthetic chemists. A number of methods have been developed to construct the arylnaphthalene lignan skeleton, for example, classified by the key reaction of the strategy, the intermolecular[2] or the intramolecular Diels–Alder reactions,[3] conjugate addition reactions,[4] biaryl coupling reactions,[5] and a certain benzannulation reaction.[6] These methods are useful for certain types among this class of compounds, but not individually appropriate for regioselective synthesis of various lignan lactones. Particularly, the total synthesis[2b,3b,c] of helioxanthin **1** has suffered from formation of by-products, its regioisomers, such as **2** (justicidine E), **3** (taiwanin C) and **4** (retroherioxanthin).



**1** (Helioxanthin)

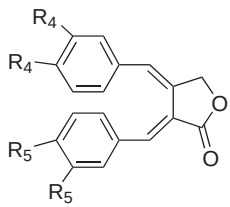


**2** (Justicidine E)



**3** (Taiwanin C)
: $R_1$-$R_2$=$OCH_2O$, $R_3$=H

**4** (Retrohelioxanthin)
: $R_1$=H, $R_2$-$R_3$=$OCH_2O$



**5** (Taiwanin A)
: $R_4$-$R_4$= $R_5$-$R_5$=$OCH_2O$

**6** : $R_4$=OMe, $R_5$=H

**7** : $R_4$=H, $R_5$=OMe

*Keywords*: lignans; palladium and compounds; naphthalenes; biaryls.
* Corresponding author. E-mail: Mizufune_Hideya@takeda.co.jp

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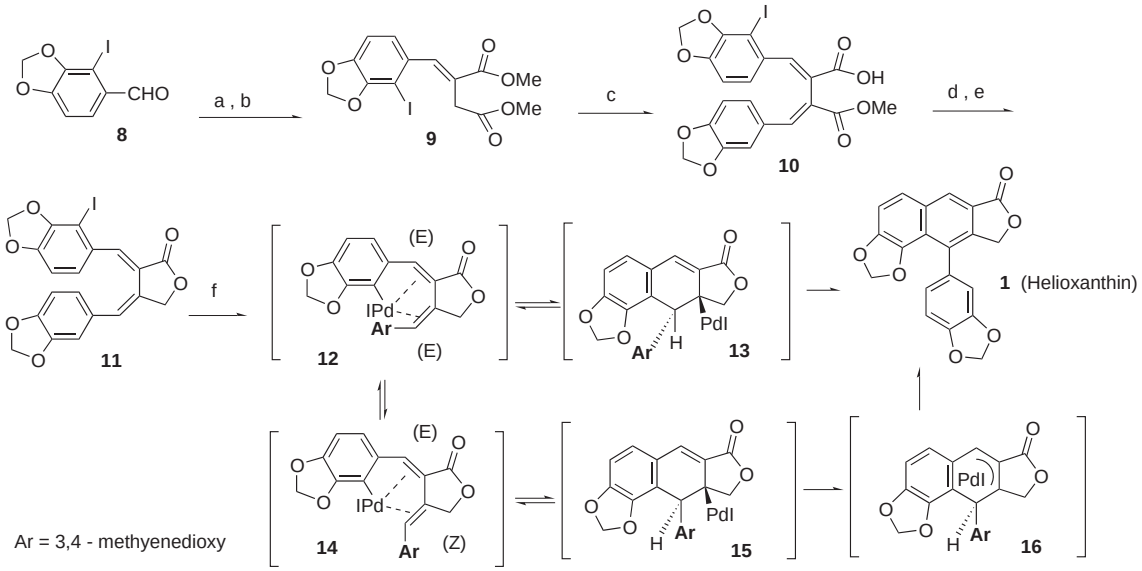


**Scheme 1.** *Reagent and conditions*: (a) $(CH_2COOEt)_2$, NaOMe, MeOH, aq. NaOH, 62%; (b) MeOH, $H_2SO_4$, 84%; (c) piperonal, NaOMe, MeOH, 82%; (d) $LiEt_3BH$, THF, 67%; (e) ClCOOEt, $Et_3N$, THF, 88%; (f) $Pd(OAc)_2$ (0.1 equiv.), $K_2CO_3$ (2.2 equiv.), NMP, 110°C, 50 min, 60%.

Thus, herein, we wish to report the first regiospecific synthesis of **1** (helioxanthin) by a novel palladium-catalyzed benzannulation reaction of α,β-bisbenzylidene-γ-lactone, which may be applicable to a synthetic study of arylnaphthalene lignans and also various biaryl compounds. As shown in Scheme 1, the key intermediate, α,β-bisbenzylidene-γ-lactone **11**, was derived from 2-iodopiperonal **8** by application of the syntheses[7] for the similar (*E*,*E*)-α,β-bisbenzylidene-γ-lactones **5**, **6** and **7**. Namely, the two-stage Stobbe condensation reaction of diethyl succinate with 2-iodopieronal **8**[8a] and the following piperonal provided bisbenzylidene-halfester **10**, in which the ester moiety distant from the reacting carbon was selectively saponified by the typical Stobbe condensation method. The halfester **10** was converted into α,β-bisbenzylidene-γ-lactone **11** by the Super-Hydride reduction[8b] and the following lactonizaion.[8c] The geometrical configuration of α,β-bisbenzylidene-γ-lactone **11** was assigned as (*E*,*E*)-configuration on the basis of the NOESY spectrum which showed the relationship between benzylidene and lactone protone.

Our aim is to achieve the first regiospecific transformation of α,β-bisbenzylidene-γ-lactone **11** to an arylnaphthalene lignan lactone, helioxanthin **1**. It is known[7] that the similar α,β-bisbenzylidene-γ-lactones **5**, **6** and **7**, including the natural lignan **5** (taiwanin A), were converted to a regioisomeric mixture of 1-phenyl-2,3-naphthalide type lignans (e.g. **3** and **4**) via the photo-cyclization process, which is interesting from the viewpoint of biosynthesis. Our efforts were focused on the intramolecular palladium-catalyzed reaction of α,β-bisbenzylidene-γ-lactone **11**. After some screening of the palladium-catalytic systems, we fortunately discovered a novel palladium-catalyzed benzannulation reaction on the $Pd(OAc)_2$ (0.1 equiv.)/$K_2CO_3$/NMP system, by which α,β-bisbenzylidene-γ-lactone **11**[†] was regiospecifically transformed to helioxanthin **1**[‡] (HPLC yield

[†] Identification of α,β-bisbenzylidene-γ-lactone **11**: $^1$H NMR (DMSO-$d_6$, TMS, 300 MHz) $\delta$ (ppm): 5.06 (2H, d, $J=1.5$ Hz), 5.85 (2H, s), 5.98 (1H, d, $J=1.5$ Hz), 6.09 (2H, s), 6.19 (2H, s), 6.41 (1H, d-d, $J=8.0$ and 1.1 Hz), 6.56 (1H, d, $J=8.0$ Hz), 6.66 (1H, brs), 7.38 (1H, d, $J=0.9$ Hz), IR (KBr, cm$^{-1}$): 1743, 1456, 1340, 1244, 1182, 1047, MS (EI, *m*/*z*): 476 ($M^+$). Elemental analysis: calcd for $C_{20}H_{13}O_6I$; C, 50.44; H, 2.75, found for C, 50.51; H, 2.99.

[‡] Synthetic procedure of helioxanthin: to a solution of α,β-bisbenzylidene-γ-lactone **11** (250 mg, 0.525 mmol) in NMP (5 ml), were added $Pd(OAc)_2$ (11.8 mg, 0.0525 mmol) and $K_2CO_3$ (160 mg, 1.16 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h and heated at 110°C for 50 minutes. After cooling, the insoluble matter in the reaction mixture was filtered off and washed with NMP and AcOEt. To the mixture of the filtrate and the washings, aq. $Na_2S_2O_3$ was added and the organic and aqueous layers were separated. The aqueous layer was extracted twice with AcOEt. The combined organic layer was washed (aq. $Na_2S_2O_3$ and brine), dried ($MgSO_4$), decolorized (activated carbon), and concentrated in vacuo. To a solution of the residue in toluene–AcOEt, silica gel was added, stirred for 1 h and filtered off. The filtrate was evaporated, and the solid residue was washed with methanol to give helioxanthin **1** (110 mg, 60%) as pale yellow crystals. $^1$H NMR ($CDCl_3$, TMS, 300 MHz), $\delta$ (ppm): 5.20 (2H, dd, $J=25.0$ and 15.2 Hz), 5.95 (2H, dd, $J=7.0$ and 1.4 Hz), 6.05 (2H, dd, $J=8.6$ and 1.4 Hz), 6.7–6.8 (2H, m), 6.88 (1H, d-d, $J=7.5$ and 0.7 Hz), 7.31 (1H, d, $J=8.7$ Hz), 7.70 (1H, d, $J=8.7$ Hz), 8.42 (1H, s), (DMSO-$d_6$, TMS, 300 MHz) $\delta$ (ppm): 5.30 (2H, s), 6.01 (2H, dd, $J=5.8$ and 0.8 Hz), 6.10 (2H, dd, $J=14.9$ and 0.7 Hz), 6.90 (1H, dd, $J=7.9$ and 1.6 Hz), 6.98 (1H, d, $J=7.9$ Hz), 7.03 (1H, d, $J=1.6$ Hz), 7.52 (1H, d, $J=8.7$ Hz), 7.95 (1H, d, $J=8.8$ Hz), 8.58 (1H, s), IR (KBr, cm$^{-1}$): 1760, 1234, 1072, MS (EI, *m*/*z*): 348 ($M^+$). Elemental analysis: calcd for $C_{20}H_{12}O_6\cdot 0.2H_2O$; C, 68.26; H, 3.55, found for C, 68.39; H, 3.66, mp: 241–243°C (lit.[2b]; 239–242°C, lit[3b]; 243–244°C).

83%, isolated yield 60%). Therefore, this novel benzannulation reaction may be applicable to regiospecific and biomimetic synthesis of other arylnaphthalene lignans (e.g. **2**, **3** and **4**), by using some α,β-bisbenzylidene-γ-lactones derived from various 2-halobenzaldehydes and benzaldehydes.

On the other hand, to our knowledge, a benzene ring formation using the intramolecular Heck reaction of an arylhalide or a vinylhalide to the conjugated 1,3-diene system has not been investigated. A few examples of naphthalene synthesis[9] from 3-allyl-4-bromoindole derivative using the intramolecular Heck reaction are known. Additionally, the palladium-mediated synthesis of the dihydronaphthalene lignan lactone was achieved by Ishibashi et al.,[10] in which method, however, substrates are limited to such as a carbonyl-conjugated olefin and the (*Z*)-olefin configuration isomer.

Thus, it is important to discuss the mechanism of our novel benzannulation reaction of (*E*,*E*)-α,β-bisbenzylidene-γ-lactones **11**. The following reaction mechanism including two conceivable processes is proposed in Scheme 1. In the first process, the oxidative addition of palladium into the C–I bond of substrate **11** generates σ-arylpalladium complex **12** based on the (*E*,*E*)-configuration isomer. Despite steric hindrance of the other aryl group, the stable palladium(II) complex with the 1,3-diene system (square-planar complex) accelerates *syn* insertion of σ-arylpalladium complex **12** to the intramolecular alkene, to give σ-dihydronaphthalene–palladium complex **13**. Then, the palladium(II) species **13** smoothly undergoes *syn* β-hydride elimination to yield the naphthalene product **1**.

In the other process, σ-arylpalladium complex **12** based on the (*E*,*E*)-configuration isomer is isomerized to (*E*,*Z*)-type σ-arylpalladium complex **14** because of the delocalized π-electron system on the 1,3-diene complex with the palladium(II) species. The following *syn* insertion of σ-arylpalladium complex **14** to the intramolecular alkene provides σ-dihydronaphthalene–palladium complex **15** which can undergo the formal *anti* β-hydride elimination via π-allylpalladium complex **16** to yield the naphthalene product.

In both processes, the role of the 1,3-diene system in the proposed reaction mechanism can be responsible for our intramolecular-annulation reaction of the arylhalide to the different configuration alkene with the different substituent ((*E*)-configuration isomer without the conjugated lactone) from Ishibashi's case ((*Z*)-configuration isomer with it).[10] Furthermore, our methodology might be applied to general 1-(*o*-halophenyl)-1,3-butadiene systems bearing various substituents as a substrate.

In conclusion, we have achieved the first regiospecific and biomimetic transformation of bisbenzylidene-γ-lactone **11** to helioxanthin **1** using a novel palladium-catalyzed benzannulation. Now we are investigating the expansion and application of this synthetic method.

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