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TOTAL SYNTHESIS OF (+)-LINOXEPIN

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Dedicated to Professor Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

Abstract – (+)–Linoxepin is a lignan-type natural product with a synthetically challenging fused dihydronaphthalene/dihydrooxepine structure. It also has multiple biological activities, including antitumor, antioxidant, and antiviral activities. Here, we review three recent total syntheses of (+)–linoxepin.

1. INTRODUCTION

Lignans are a family of structurally diverse dimeric phenylpropanoids[1-3] with a wide range of biological activities, including antitumor, anti-inflammatory, antioxidant, antiviral, cardiovascular and immunosuppressive activities,[4-11] and their synthesis has attracted much interest.[2,12,13] Various aryl–dihydronaphthalene-type lignans, represented by **1**-**6**, have been isolated as natural products.[15-21] Among them, (+)–linoxepin (**1**) was isolated from the flower of *Linum perenne* L. by Schmit and co-workers in 2007.[14] It has the characteristic dihydronaphthalene structure, but has a tetra-substituted double bond embedded in a highly strained dihydrooxepine ring system, which presents an interesting synthetic challenge. Recently, Tietze's group,[22,23] Lautens's group[24,25] and our group[26] have independently reported total syntheses of **1**. This review describes the methodology used by each group.

2. TIETZE'S APPROACH TO (+)-1: A PALLADIUM-CATALYZED DOMINO REACTION TO CONSTRUCT THE B, E RINGS OF 1

In 2013, Tietze's group reported the first total synthesis of racemic linoxepin (**1**).[22] They subsequently synthesized **1** in optically active form.[23] Their synthetic approach is illustrated in Scheme 1. A palladium-catalyzed domino process involving carbopalladation and a Mizoroki-Heck-type reaction was

planned to construct the tetracyclic core structure of **1**. The asymmetric center at C8 would be introduced by enantioselective hydroboration reaction (Scheme 1).

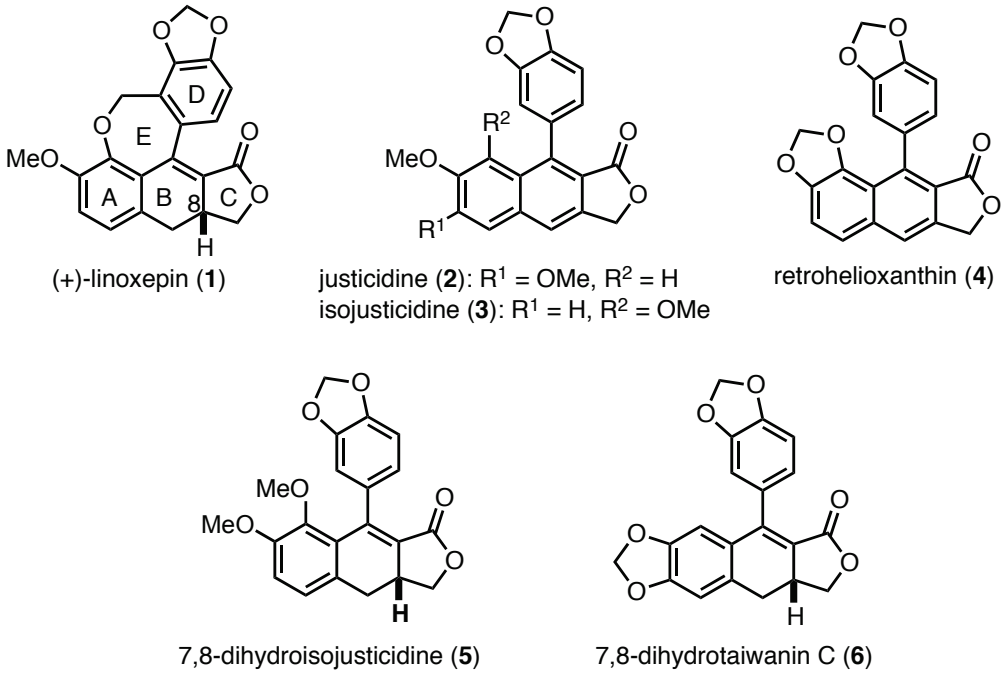
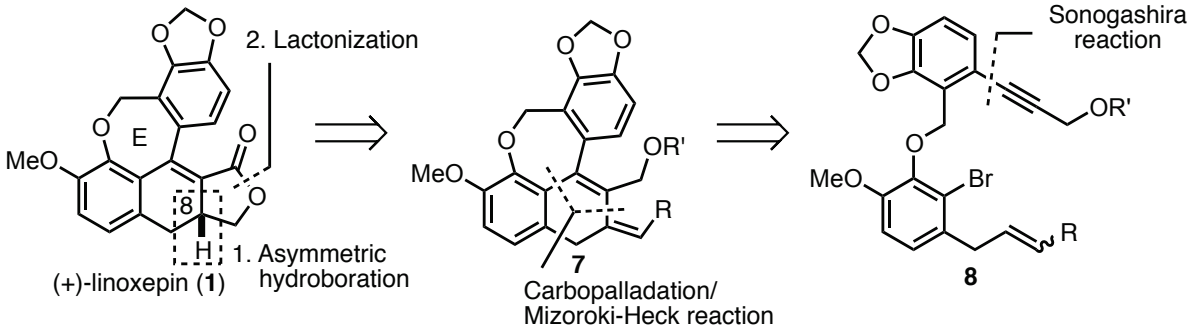


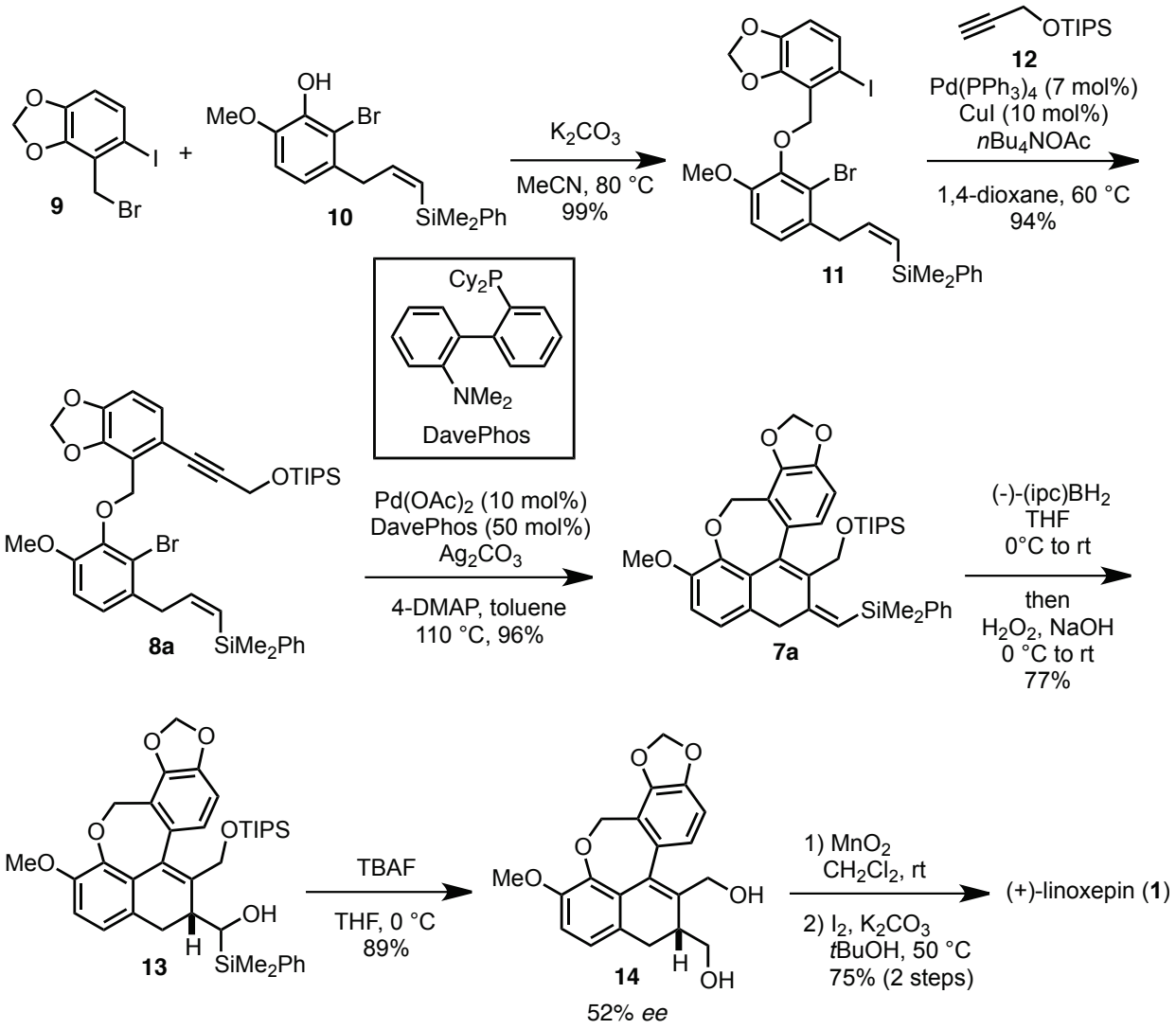
Figure 1. Structures of representative aryl(dihydro)naphthalene lignans, **1**-**6**



Scheme 1. Synthetic approach of **1** of Tietze's group

Alkylation of benzyl bromide **9** with phenol **10** in the presence of K_2CO_3 gave aryl ether **11** in 99% yield. Sonogashira coupling reaction of aryl iodide **11** with TIPS-protected propargylic alcohol **12** was carried out in the presence of $Pd(PPh_3)_4$ and CuI to give **8a**, a domino reaction precursor, in 94% yield. Then, the carbopalladation/Mizoroki-Heck domino reaction was efficiently conducted by treatment of **8a** with a catalytic amount of $Pd(OAc)_2$ and DavePhos as a ligand in the presence of Ag_2CO_3 and DMAP in toluene at 110 °C, affording tetracyclic **7a** in 96% yield. For the enantioselective synthesis of (+)-linoxepin (**1**), they examined asymmetric hydroboration reaction of trisubstituted alkene **7a** with Brown's chiral boranes.

In the case of (-)-(ipc)BH_2, asymmetric hydroboration reaction proceeded to afford alcohol **14** with 52% *ee* on treatment with hydoxysilane **13** and TBAF. However, it proved difficult to increase the enantioselectivity, though (-)-(ipc)$_2$BH and Masamune's chiral borane[27] were examined as alternative reagents. Total synthesis of (+)-linoxepin (**1**) was achieved from **14** by oxidation of the allylic moiety with MnO_2 followed by oxidation of the resulting aldehyde to the lactone with iodine in the presence of K_2CO_3 in 75% yield (Scheme 2).

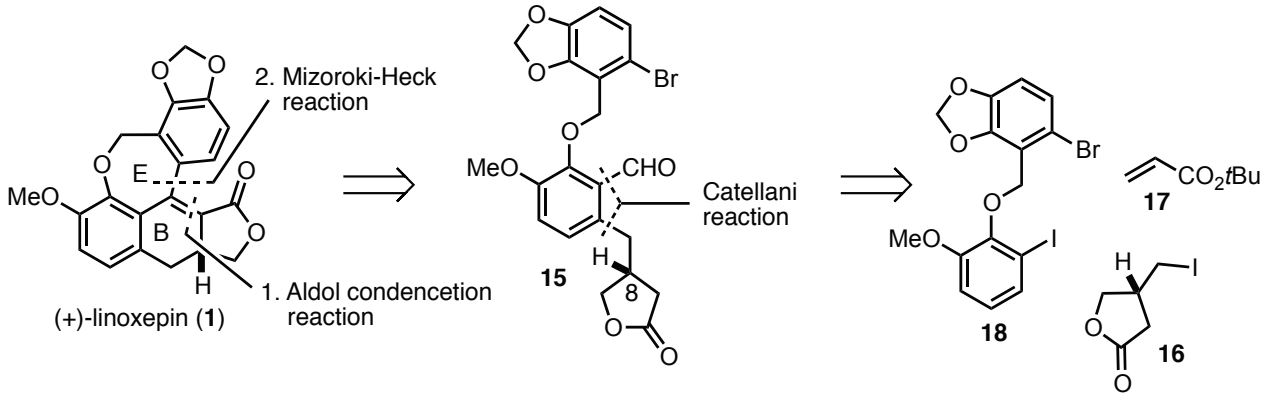


Scheme 2. Synthesis of (+)-linoxepin (**1**) by Tietze's group

The key feature of the above synthesis of (+)-**1** is the palladium-catalyzed domino reaction, involving carbopalladation and Mizoroki-Heck-type reaction of **8a** using DavePhos as a ligand. The stereogenic center at C8 was constructed by asymmetric hydroboration reaction utilizing (-)-(ipc)BH_2 with 52% *ee*.

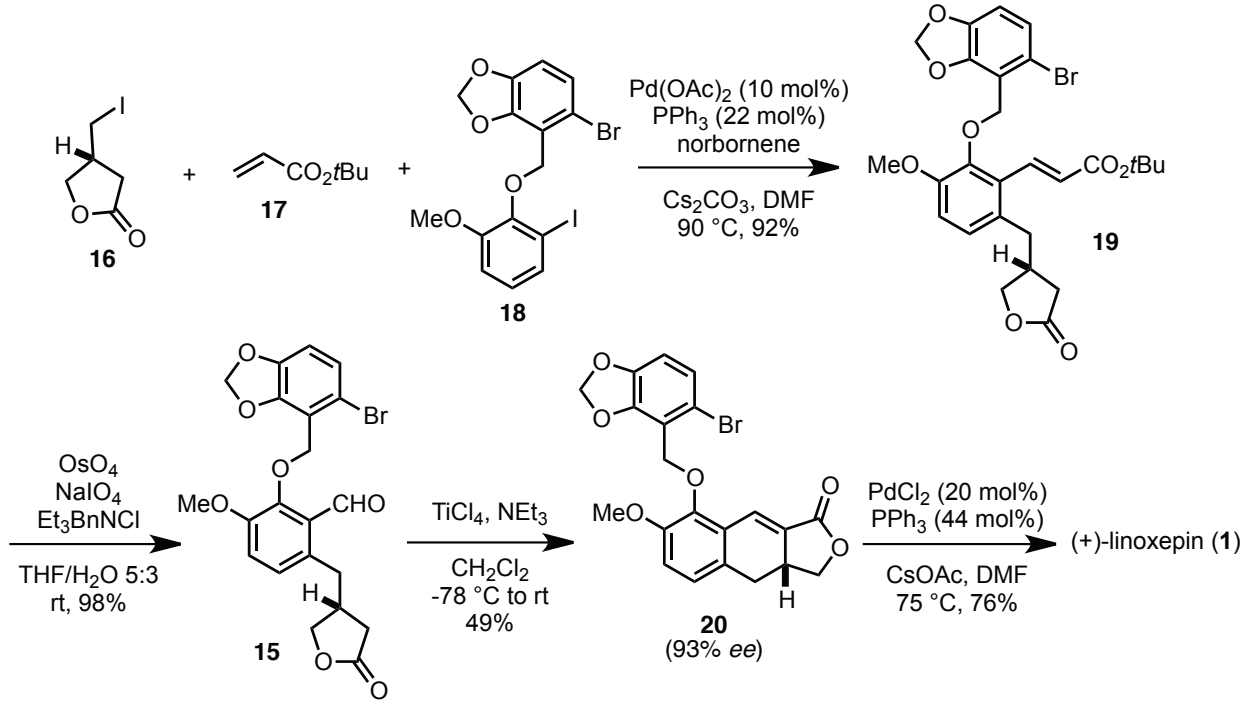
3. LAUTENS'S APPROACH TO (+)-1: CATELLANI REACTION TO CONSTRUCT THE TETRASUBSTITUTED A RING

Lautens's group has reported an enantioselective, protecting-group-free, total synthesis of (+)-linoxepin (**1**) by using palladium-catalyzed Catellani reaction as the key step.[24,25] Their synthetic approach is illustrated in Scheme 3. They planned to obtain **15** by means of Catellani reaction and then to couple it with three other components: optically pure iodolactone **16**, acrylate **17**, and aryl ether **18**. The unsaturated lactone moiety and the E ring in **1** would be obtained by aldol condensation reaction and subsequent intramolecular Mizoroki-Heck reaction.



Scheme 3. Synthetic approach to **1** by Lautens's group

Palladium-catalyzed Catellani reaction, the key reaction in this synthesis, is a powerful carbon-carbon bond-forming reaction, which involves C-H functionalization at the *ortho*-position of aryl iodide and



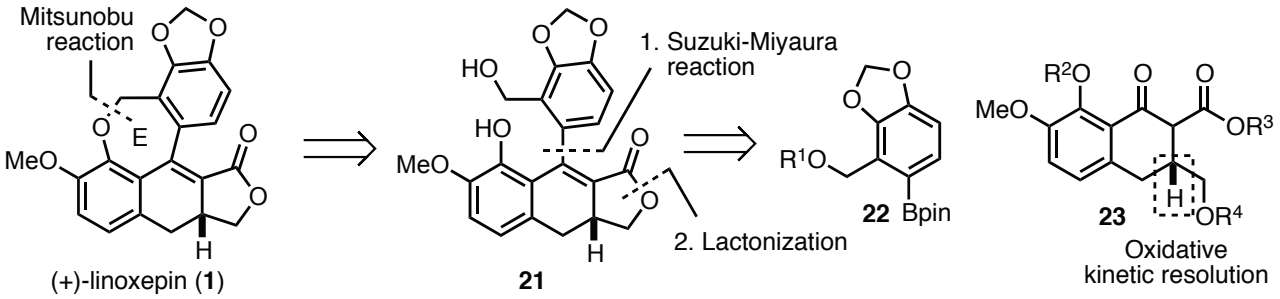
Scheme 4. Lautens's total synthesis of (+)-linoxepin (**1**)

subsequent Mizoroki-Heck-type reaction.[28,29] This enables two adjacent positions on the aromatic ring to be functionalized in one step. Reaction of aryl iodide **18**, optically active lactone **16**, and *tert*-butyl acrylate (**17**) in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol%) and triphenylphosphine (22 mol%) with norbornene and cesium carbonate generated the three-component coupling product **19** in 92% yield. After oxidative cleavage of the unsaturated ester in **19** with OsO_4-$NaIO_4$, the resulting aldehyde **15** was subjected to aldol condensation reaction using $TiCl_4$ to provide unsaturated lactone **20** in 49% yield. Finally total synthesis of (+)–linoxepin (**1**) was achieved by constructing the E ring with intramolecular Mizoroki-Heck reaction in the presence of $PdCl_2$-PPh_3 as a catalyst in 76% yield (Scheme 4).

The key feature of this synthesis is the use of the palladium-catalyzed Catellani reaction to install all of the carbon atoms required for the synthesis of **1**. Moreover, this is the protecting-group-free synthesis in only seven steps from commercially available starting material, and is the first reported application of the Catellani reaction to natural product synthesis.

4. NAGASAWA'S APPROACH TO (+)-1; OXIDATIVE KINETIC RESOLUTION TO CONSTRUCT THE TETRALONE CORE STRUCTURE OF THE AB RING

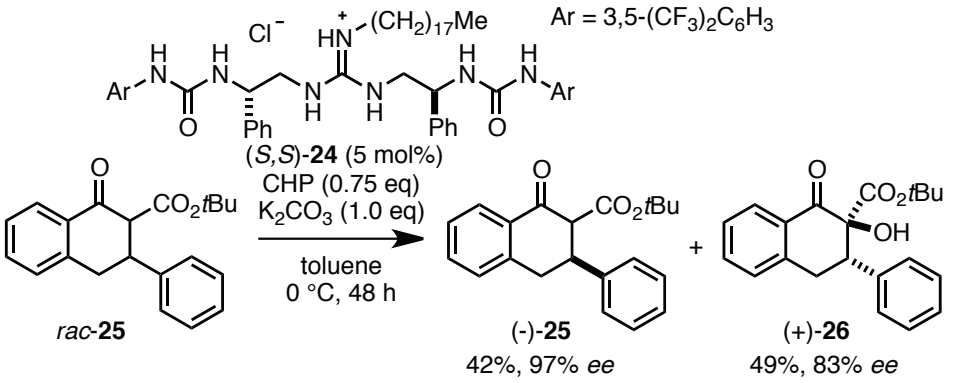
In 2015, our group reported a synthesis of (+)-linoxepin (**1**) based on the organocatalytic oxidative kinetic resolution of β-substituted tetralone.[26] The synthetic approach is illustrated in Scheme 5. In our synthesis, we aimed to obtain optically active tetralone **23** by oxidative kinetic resolution in the presence of a guanidine-bisurea bifunctional organocatalyst. Coupling reaction of the two segments, **22** and **23**, would be done under Suzuki-Miyaura conditions, followed by construction of the E ring by Mitsunobu reaction.



Scheme 5. Synthetic plan for (+)-**1** by Nagasawa's group

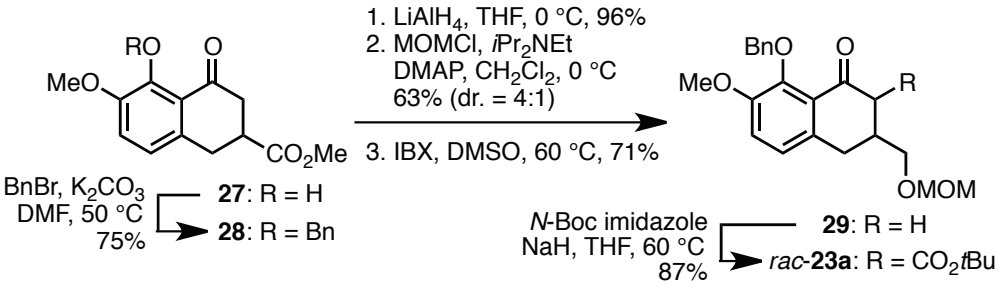
We have recently developed asymmetric α-hydroxylation of tetralone-derived β-ketoesters using guanidine-bisurea bifunctional organocatalyst (*S*,*S*)-**24** in the presence of cumene hydroperoxide (CHP)

as an oxidant. In the case of *rac*-**25** bearing a substituent at the β-position, kinetic resolution afforded (-)-**25** and (+)-**26** in high yield with high *ee* (Scheme 6). Thus, we planned to apply this reaction for the construction of the asymmetric center at C8 in (+)-**1**.



Scheme 6. Oxidative kinetic resolution of *rac*-**25** using (*S*,*S*)-**24**

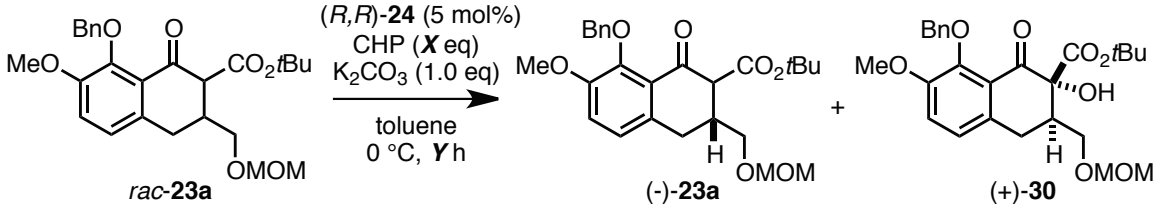
Synthesis of the substrate *rac*-**23a** for the oxidative kinetic resolution reaction is shown in Scheme 7. After protection of the phenolic hydroxyl group in **27** with a benzyl group, ester and ketone in benzyl ether **28** were reduced with $LiAlH_4$ to give the diol. After selective protection of the primary alcohol with a MOM group, the secondary alcohol was oxidized with IBX to give ketone **29**. Then, β-ketoester of *rac*-**23a** was obtained from **29** by reaction with *N*-Boc imidazole in 87% yield.



Scheme 7. Synthesis of β-ketoester *rac*-**23a**

Then, the oxidative kinetic resolution reaction of *rac*-**23a** was investigated (Table 1). Under the previously optimized conditions, i.e., 0.75 equivalent of CHP for 48 hours, the desired (-)-**23a** was obtained in 44% yield with 76% *ee* (entry 1). Enantioselectivity of (-)-**23a** was improved to 99% *ee* by increasing the reaction time to 72 h (entry 3).

Table 1. Investigation of oxidative kinetic resolution of *rac*-**23a**

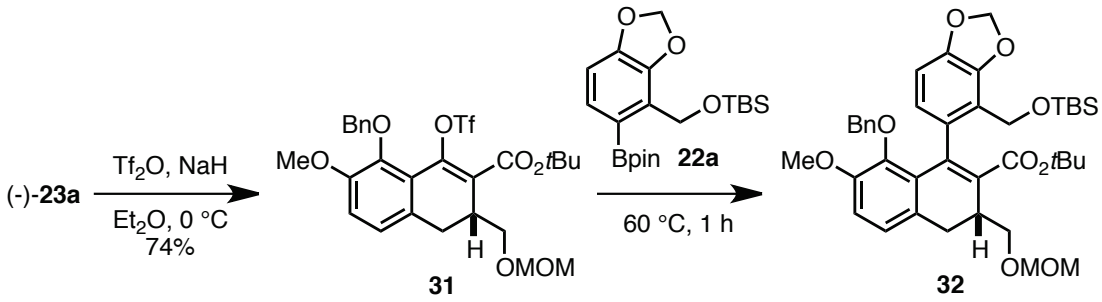


entry	CHP (***X*** eq)	time (***Y*** h)	(-)-**23a**		(+)-**30**		$s^{[a]}$
			yield [%]	*ee* [%]	yield [%]	*ee* [%]	
1	0.75	48	44	76	49	89	39
2	1.50	48	50	91	34	87	45
3	0.75	72	37	99	52	77	39

[a] The selectivity factor (*s*) was calculated as follows. $s = k_{fast}/k_{slow}$ = ln[1-C(1+*ee*(+)-**30**)] / ln[1-C(1-*ee*(+)-**30**)] = ln[(1-C)(1-*ee*(-)-**23a**)] / ln[(1-C)(1+*ee*(-)-**23a**)]; C = *ee*(-)-**23a** / (*ee*(-)-**23a** +*ee*(+)-**30**).

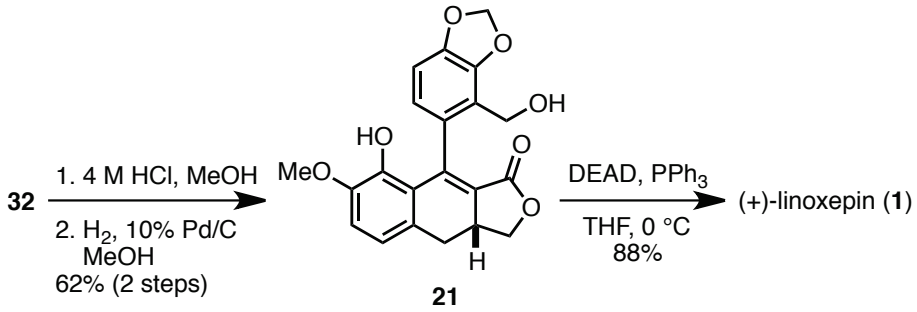
Optically active tetralone (-)-**23a** was then reacted with triflic anhydride in the presence of sodium hydride to give vinyl triflate **31** in 74% yield. Next, coupling reaction of **31** and **22a** was investigated under Suzuki-Miyaura reaction conditions in the presence of palladium catalyst (Table 2). The best result was obtained by utilizing a catalytic amount of $Pd(PPh_3)_4$ (5 mol%) with solid KOH as a base, and **32** was obtained in 47% yield (entry 5).

Table 2. Synthesis of **32** and investigation of Suzuki-Miyaura coupling with **31**



entry	catalyst (5 mol%)	base (5 eq)	solvent (0.2 M)	**32** [%]
1	$Pd(PPh_3)_4$	2 M Na_2CO_3 aq	1,4-dioxane	41
2	$Pd(PPh_3)_4$	Na_2CO_3 (solid)	1,4-dioxane	trace
3	$Pd(PPh_3)_4$	2 M Na_2CO_3 aq	toluene	trace
4	$Pd(OAc)_2$	2 M Na_2CO_3 aq	1,4-dioxane	trace
5	$Pd(PPh_3)_4$	KOH (solid)	1,4-dioxane	47

Total synthesis of (+)-linoxepin (**1**) from **32** was completed as follows. The MOM, TBS, and *tert*-butyl ester groups in **32** were removed under acidic conditions, and then deprotection of Bn ether with hydrogen in the presence of 10% Pd/C provided **21** in 62% yield in two steps. Finally, the E ring was constructed under Mitsunobu reaction conditions by utilizing diethyl azodicarboxylate (DEAD) and triphenylphosphine to give (+)-**1** in 88% yield (Scheme 8).



Scheme 8. Total synthesis of (+)-**1** by Nagasawa and co-workers

Thus, (+)-**1** was synthesized in 11 steps from the known tetralone **27** by utilizing organocatalytic oxidative kinetic resolution of *rac*-**23a**. This approach should be applicable to a variety of natural products containing tetralone structures with asymmetric centers at the β-position.

CONCLUSION

In this article, we have reviewed three recent syntheses of (+)-linoxepin (**1**) via distinct approaches, i.e., palladium-catalyzed domino reaction for the construction of the A,B,D,E ring system, palladium-catalyzed three-component coupling-type Catellani reaction, and oxidative kinetic resolution with an organocatalyst. These three approaches should be applicable to synthesize a range of lignan-type natural products and their derivatives, which should facilitate detailed structure-activity relationship studies of these multi-functional molecules.

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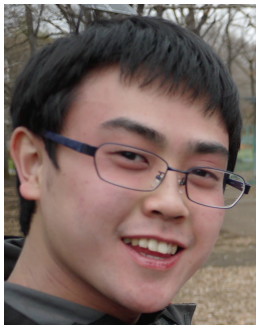

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Yoshiharu Yamamoto was born in Saitama in 1992 and received his baccalaureate degree in 2015 from Tokyo University of Agriculture and Technology. He is currently Master course student in the same University, and interested in the synthesis of amaryllidaceae alkaloids by utilizing organocatalysis.

Kazuo Nagasawa obtained his Ph.D. in 1993 from Waseda University. In 1993, he joined RIKEN (The Institute of Physical and Chemical Research) as a researcher under Professor Tadashi Nakata. From 1997 to 1999, he worked in Kishi's group at Harvard University. He moved to the University of Tokyo (IMCB) in 2001, and to the Tokyo University of Agriculture and Technology in 2004 as an associate professor. In 2009, he was appointed to his current position as a professor. He has received the TORAY Award for Synthetic Organic Chemistry Japan (1999) and Pharmaceutical Society of Japan Award for Young Scientists (2003).