TOTAL SYNTHESIS OF (+)-LINOXEPIN

Minami Odagi,* Kota Furukori, Yoshiharu Yamamoto, and Kazuo Nagasawa*

Department of Biotechnology and Life Science, Faculty of Technology, Tokyo University of Agriculture and Technology (TUAT), Koganei, Tokyo 184-8588, Japan: odagi@cc.tuat.ac.jp, knaga@cc.tuat.ac.jp

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 with a wide range of biological activities, including antitumor, anti-inflammatory, antioxidant, antiviral, cardiovascular and immunosuppressive activities, and their synthesis has attracted much interest. Various aryl–dihyronaphthalene-type lignans, represented by 1-6, have been isolated as natural products. Among them, (+)-linoxepin (1) was isolated from the flower of Linum perenne L. by Schmit and co-workers in 2007. It has the characteristic dihyronaphthalene 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, Lautens’ group and our group have independently reported total syntheses of 1. This review describes the methodology used by each group.

2. TIEJZE’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). They subsequently synthesized 1 in optically active form. Their synthetic approach is illustrated in Scheme 1. A palladium-catalyzed domino process involving carhopalladation 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).

Alkylation of benzyl bromide 9 with phenol 10 in the presence of K$_2$CO$_3$ 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 Cul 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$_2$CO$_3$ 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.

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

Scheme 1. Synthetic approach of 1 of Tietze’s group
In the case of (-)-(ipc)BH₂, asymmetric hydroboration reaction proceeded to afford alcohol 14 with 52% ee on treatment with hydroxysilane 13 and TBAF. However, it proved difficult to increase the enantioselectivity, though (-)-(ipc)₂BH and Masamune’s chiral borane²⁷ were examined as alternative reagents. Total synthesis of (+)-linoxepin (1) was achieved from 14 by oxidation of the allylic moiety with MnO₂ followed by oxidation of the resulting aldehyde to the lactone with iodine in the presence of K₂CO₃ 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 carboxypalladation 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)BH₂ 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...
subsequent Mizoroki-Heck-type reaction.\textsuperscript{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 \textit{tert}-butyl acrylate (17) in the presence of a catalytic amount of Pd(OAc)\textsubscript{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\textsubscript{4}-NaIO\textsubscript{4}, the resulting aldehyde 15 was subjected to aldol condensation reaction using TiCl\textsubscript{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\textsubscript{2}-PPh\textsubscript{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 \(\beta\)-substituted tetralone.\textsuperscript{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](image-url)

We have recently developed asymmetric \(\alpha\)-hydroxylation of tetralone-derived \(\beta\)-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 LiAlH₄ 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

<table>
<thead>
<tr>
<th>entry</th>
<th>CHP (X eq)</th>
<th>time (Y h)</th>
<th>(-)-23a yield [%]</th>
<th>ee [%]</th>
<th>(+)-30 yield [%]</th>
<th>ee [%]</th>
<th>s[a]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.75</td>
<td>48</td>
<td>44</td>
<td>76</td>
<td>49</td>
<td>89</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>1.50</td>
<td>48</td>
<td>50</td>
<td>91</td>
<td>34</td>
<td>87</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>72</td>
<td>37</td>
<td>99</td>
<td>52</td>
<td>77</td>
<td>39</td>
</tr>
</tbody>
</table>

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

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(PPh₃)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

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (5 mol%)</th>
<th>base (5 eq)</th>
<th>solvent (0.2 M)</th>
<th>32 [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄</td>
<td>2 M Na₂CO₃ aq</td>
<td>1,4-dioxane</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄</td>
<td>Na₂CO₃ (solid)</td>
<td>1,4-dioxane</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄</td>
<td>2 M Na₂CO₃ aq</td>
<td>toluene</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>2 M Na₂CO₃ aq</td>
<td>1,4-dioxane</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh₃)₄</td>
<td>KOH (solid)</td>
<td>1,4-dioxane</td>
<td>47</td>
</tr>
</tbody>
</table>
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).

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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REFERENCES


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Minami Odagi was born in Ibaraki, Japan, in 1988. He received his PhD in 2015 form Tokyo University of Agriculture and Technology (TUAT) under the supervision of prof. Kazuo Nagasawa. In 2015 he became an Assistant Professor at TUAT. His research interests include the development of organocatalytic asymmetric reaction and the total synthesis of natural products.

Kota Furukori was born in Tokyo in 1990 and graduated from Tokyo University of Agriculture and Technology in 2013. He received his Master degree in 2015 from Tokyo University of Agriculture and Technology under Professor Kazuo Nagasawa.

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).