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Authors  Motoyuki Isoda, Kazuyuki Sato, Kenta Kameda, Kana Wakabayashi, Ryota Sato, Hideki Minami, Yukiko Karuo, Atsushi Tarui, Kentaro Kawai and Masaaki Omote

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ORCID® iDs  Kazuyuki Sato - https://orcid.org/0000-0001-6572-602X; Hideki Minami - https://orcid.org/0000-0002-5926-4356; Kentaro Kawai - https://orcid.org/0000-0002-6291-0558; Masaaki Omote - https://orcid.org/0000-0003-1210-1768
Rhodium-catalyzed intramolecular reductive aldol-type cyclization: Application for the synthesis of a chiral necic acid lactone.

Motoyuki Isoda¹, Kazuyuki Sato*², Kenta Kameda², Kana Wakabayashi², Ryota Sato², Hideki Minami³, Yukiko Karuo², Atsushi Tarui², Kentaro Kawai², Masaaki Omote*²,

Address: ¹School of Pharmacy at Fukuoka, International University of Health and Welfare, 137-1 Enokizu, Okawa, Fukuoka 831-8501, Japan, ²Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan, and ³Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure, Hiroshima 737-0112, Japan

Email: Kazuyuki Sato* - sato@pharm.setsunan.ac.jp, Masaaki Omote* - omote@pharm.setsunan.ac.jp

* Corresponding author

Abstract

Rhodium-catalyzed intramolecular reductive aldol-type cyclization was described to give β-hydroxylactones with high diastereoselectivities. This cyclization gave syn- or anti-form β-hydroxylactones selectively by changing the solvent. Furthermore, the synthesis of a chiral necic acid lactone was also described which is a part of structural
component of pyrrolizidine alkaloid monocrotaline that is used for the preparation of pulmonary hypertension pathological model in rats.

**Keywords**

intramolecular reductive aldol cyclization; β-hydroxy lactone; rhodium catalyst; necic acid lactone

**Introduction**

During the past two decades, numerous numbers of the C–C bond formation reactions have been reported, and aldol reaction is one of the most powerful tools to achieve the reaction.[1] In particular, an intramolecular aldol condensation is an important approach to the formation of ring systems to give cyclic β-hydroxy carbonyl products or cyclic α,β-unsaturated carbonyl products. Therefore, various types of intramolecular aldol-type reaction have been developed and widely applied to the total synthesis of diverse natural products.[2] A reductive aldol-type reaction is also reported by using metal catalysts with hydrosilanes (R₃Si-H) or hydrogen as the reductant, and there are a lot of reports using rhodium catalyst.[3-10] However, there is still room for further investigation in this field, and we have reported reductive α-acylations, reductive aldol-type reactions, and reductive Mannich-type reactions using RhCl(PPh₃)₃ with Et₂Zn.[11] The rhodium-catalyzed reductive aldol reaction of α,β-unsaturated esters with aldehydes or ketones gave aldol-type products in good to excellent yields (Scheme 1).[11c,d] In addition, the reductive aldol-type reaction could also be applied to asymmetric system, although the diastereoselectivity was poor. On the other hand, the reductive Mannich-type reaction was achieved in good to excellent yields with high diastereoselectivity.[11e,f] As part of a wider program of C–C bond formation systems,
we report a rhodium-catalyzed intramolecular reductive aldol-type cyclization using a rhodium catalyst and its application for the synthesis of a chiral necic acid lactone.

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\text{Scheme 1: Previous works and this work.}
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**Results and Discussion**

**Rh catalyzed intramolecular cyclization**

To improve the diastereoselectivity, at first, we optimized the conditions for the reductive aldol-type reaction by intramolecular cyclization of 1 (Table 1). According to the previous condition[11c], the intramolecular reductive aldol-type cyclization of 1a proceeded smoothly and gave the desired product (2a) in a good yield but the diastereomeric ratio was not sufficient as shown in entry 1. After further examination of several rhodium catalysts, we found [RhCl(cod)]_2 was the best result with high diastereoselectivity (entries 1–4). A reduction by rhodium hydride complex was followed by transmetalation towards the corresponding Zn enolate to give the products with high diastereoselectivity in this cyclization. It is known that the formation of reductive enolate to \(\alpha,\beta\)-unsaturated ester using metal hydride is influenced by steric factors around the reaction point. Therefore, it is considered that the use of
[RhCl(cod)]$_2$ having a soft ligand improved the diastereoselectivity as compared with the reaction using RhCl(PPh$_3$)$_3$. The stereochemistry in major product 2a was syn-form between CH$_3$ (C$^\alpha$) and OH (C$^\beta$) moieties and was established from the single-crystal X-ray structure analysis. When THF or DCM was used as the solvent, syn-2a was obtained in good yields with high diastereoselectivity as shown in entries 5–11. Interestingly, using higher coordination solvents, DMF or DMPU, preferentially gave the opposite diastereomer, and the major stereochemistry between CH$_3$ (C$^\alpha$) and OH (C$^\beta$) moieties in 2a was anti-form. A NOESY experiment on the syn-2a showed nOe between the methine proton on C$^\alpha$ and one of the protons of the benzene ring on C$^\beta$, but not anti-2a. The relative configurations of syn-2a and anti-2a were also confirmed by X-ray crystallography.

Next, various substrates were investigated and the results were summarized in Table 2. The synthesis of 2a-c proceeded smoothly to give the corresponding β-
hydroxylactones (2) in moderate to good yields with high diastereoselectivities, although 2d were obtained in low yields. It may suggest that the existence of substituents in γ-position and/or δ-position of 2 become easier to keep the intermediate structure which works in favor of the intramolecular cyclization. β-Substituted substrates on α,β-unsaturated ester moiety of 1 also gave the products (2g and 2h) in low yields, but the formation of 7-membered ring (2f) was not achieved. On the other hand, when the previous condition using RhCl(PPh₃)₃ catalyst was applied to the aldol-type cyclization, 5- and 6-membered products were obtained in good yields (See the yields and dr in parentheses in Table 2). However, the yields were greatly affected by the substituents on β-position of α,β-unsaturated ester moiety, and all diastereomeric ratios were not sufficient results in the case of RhCl(PPh₃)₃ catalyst. The relative configurations of 2b was confirmed by X-ray crystallography, and the relative configurations of 2c, 2g and 2h were confirmed by NOESY experiments.

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\[
\begin{align*}
&\text{1} \quad \text{[RhCl(cod)]}_{2} (2 \text{ mol\%}) \quad \text{EtZn (1.2 equivs.)} \\
&\text{CH}_2\text{Cl}_2, \text{rt} \\
\end{align*}
\]

\[
\begin{array}{c}
\text{1h, 77\%}^{a)} [31:1]^{b)} \\
(64\%)^{a)} [3:1]^{b)}^{c)}^{d)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2b} \quad \text{1h, 59\%}^{a)} \\
(78\%)^{a)}^{d)}^{e)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2c} \quad \text{2h, 80\%}^{a)} \\
(79\%)^{a)}^{d)}^{e)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2d} \quad \text{2h, 27\%}^{a)} [18:1]^{c)} \\
(70\%)^{a)} [4:1]^{b)}^{d)}^{e)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2e} \quad \text{1h, 15\%}^{a)} [2:3]^{c)} \\
(\text{nd})^{a)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2f} \quad \text{13h, nd} \\
(\text{trace})^{a)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2g} \quad \text{1.5h, 31\%}^{a)} \\
(10\%)^{a)} [4:1]^{c)}^{d)}^{e)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2h} \quad \text{3h, 20\%}^{a)} \\
(\text{trace})^{a)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2i} \quad \text{3h, nd} \\
(\text{nd})^{a)} \\
\end{array}
\]

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\(a\) Isolated yield. \(b\) Diastereomeric ratio was determined after purification. \(c\) Diastereomeric ratio was determined by \(^1\)H NMR. \(d\) Diastereomeric mixture. \(e\) The reaction was carried out using RhCl(PPh₃)₃ in THF at rt.
**Table 2:** Scope and limitation of the rhodium-catalyzed reductive aldol-type cyclization.

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**Synthesis for a chiral necic acid lactone of monocrotaline**

There are a lot of reports for the bio-active natural products that have a 3-hydroxy-2-methyllactone scaffold in the molecular. For example, cytospolide K2 [12] containing a 10-membered lactone and feigrisolide [13] containing a 7-membered lactone are known to exhibit cytotoxicity and antimicrobial activity. Moreover, antiviral activity was also confirmed for aggregatin B [14] containing a 7-membered lactone ring, in which the β-position hydroxyl group was dehydrated (Fig. 1). Among them, monocrotaline that is a kind of pyrrolizidine alkaloid was isolated from seeds of *Crotalaria spectabilis* in 1935 and is used for the preparation of pulmonary hypertension pathological model rats.[15] To date, some groups have reported the synthetic method and its synthetic supply will be contributed to hypertension treatment.[16] Although there have been a lot of reports of pyrrolizidine scaffolds or necine base, the synthesis of necic acid lactones such as monocrotalic acid is rare (Fig. 2). Consequently, we attempted to apply the rhodium-catalyzed intramolecular reductive aldol-type reaction to the synthesis of a chiral necic acid lactone that is a part of structural component of monocrotaline.

![cytopsolide K](image1.png) ![feigrisolide A](image2.png) ![aggregatin B](image3.png)

**Fig. 1:** Bio-active natural products bearing 3-hydroxy-2-methyllactone scaffold.
According to the reference, Sharpless dihydroxylation of benzyl tiglate 3 to form a chiral diol 4 was followed by oxidation by Parikh-Doering oxidation to give the corresponding product 5 in 62% (Scheme 2).[17] Subsequent acryloylation in the presence of DMAP and hydroquinone gave the intramolecular cyclization starting material (S)-1j in 61% yield. The application of the compound (R)-1j to rhodium-catalyzed intramolecular reductive aldol-type cyclization was proceeded smoothly and gave a chiral necic acid lactone (2S,3S,4R)-2j in 32% yield (Fig. 3).

**Scheme 2:** Synthetic route for a chiral necic acid lactone ((2S,3S,4R)-2j).
**Fig. 3:** Molecular structure of necic acid lactone ((2S,3S,4R)-2j) in the crystal.

**Conclusion**

In conclusion, we found that using [RhCl(cod)]$_2$ improved the diastereomeric ratios for the application to the intramolecular reductive aldol-type cyclization. It seems that using [RhCl(cod)]$_2$ becomes milder the reaction condition than using RhCl(PPh$_3$)$_3$, and therefore the diastereomeric ratios were greatly improved. In addition, we achieved a new approach to benzyl monocrotalate as the component of monocrotalin. We expect further progress for the study of intramolecular reductive aldol-type reaction.

**Experimental**

See Supporting Information File for full experimental data.
Supporting Information

General procedures and analytical data, including copies of $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR spectra, and X-ray crystallography.

Supporting Information File 1:

References


