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A New Efficient Synthetic Route for the Synthesis of the Antiallergic Drug, Olopatadine Hydrochloride, via Stereospecific Palladium-Catalyzed Reaction

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ABSTRACT: A new practical and efficient synthetic route for the synthesis of olopatadine hydrochloride via the intramolecular stereospecific seven-membered ring cyclization from an alkyne intermediate using palladium catalyst and hydride source was established. Furthermore, the optimization of that key stereospecific reaction was examined by design of experiment (DoE), and the desired *Z*-isomer could be obtained with high yield.

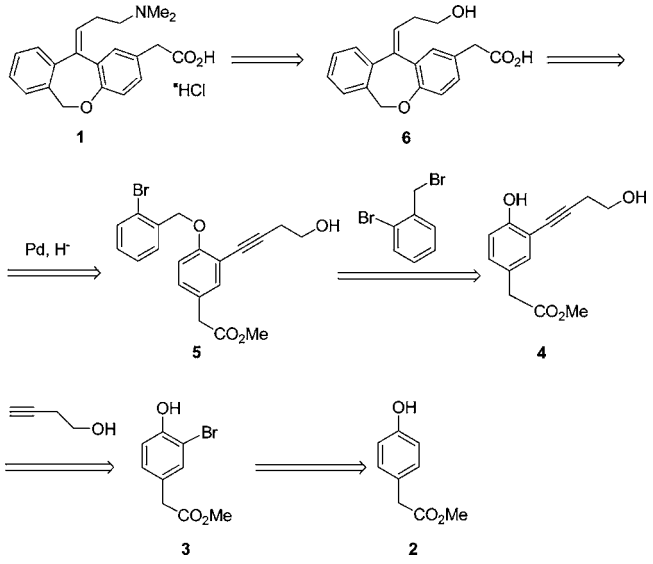
INTRODUCTION

Olopatadine hydrochloride (**1**) is an antiallergic drug which was developed by Kyowa Hakko Kirin Co. Ltd. It is produced for commercial use by the synthesis route using Wittig reaction.[1] Generally, the stereospecific synthesis of the *Z*-isomer is the challenging issue when producing a trisubstituted alkene like olopatadine hydrochloride. However, it was recently reported that **1** could be obtained in high yield from the *E*/*Z* mixture of the *t*-Bu ester derivative of olopatadine by the preferential crystallization with isomerization under acidic condition.[2] On the other hand, an interesting synthetic route of **1** via Mizoroki−Heck reaction using palladium catalyst was reported in a patent.[3] In this synthetic route, stereochemistry of the *Z*-isomer was controlled by the intramolecular cyclization of the *E*-alkene intermediate via Mizoroki−Heck reaction. Herein we describe a new, more efficient, synthetic route of applying the intramolecular cyclization using palladium catalyst and a hydride source for the alkyne intermediate. The retrosynthesis of the new synthetic route is outlined in Scheme 1.

The key reaction of this strategy is the intramolecular stereoselective cyclization from alkyne **5** using palladium catalyst and a hydride source. Such stereospecific ring cyclization is already known.[4] Especially, forming dibenz[*b*,*e*]-oxepine possessing *exo*-olefin was reported by Finch.[5]

The ring cyclization precursor **5** could be introduced from the inexpensive starting material **2** via bromination and Sonogashira coupling with 3-butyn-1-ol. This process could then be continued to the key ring cyclization, and the final product **1** could be synthesized after dimethylamination of terminal alcohol.

Scheme 1. Strategy of the new synthesis route



RESULT AND DISCUSSION

Synthesis of the Seven-Membered Ring Cyclization Precursor 5. The preparation of **3** was performed with quantitative yield via bromination from **2** according to known procedures.[6] Then the protection of hydroxy group in **3** was introduced before the Sonogashira coupling reaction to avoid producing benzofuran as a byproduct.

First, the methoxymethyl group which could be deprotected under a weak acidic condition was introduced to **3**. The protected compound **8** was prepared in moderate yield via the Sonogashira coupling reaction. The deprotection of metoxymethyl group in **8** was carried out using dilute HCl, but the mixture of desired deprotected product **4** and undesired ketone **11** was obtained. It was anticipated that the alkyne group in **4** was easily hydrated to form **11** under acidic conditions.[7]

Next, we tested the deprotection of **10** protected by acetyl group under basic conditions, but the mixture of **4** and benzofuran **12** was obtained. With a very short reaction time, **4** was afforded in 76% yield. However the yield of **4** was greatly decreased, and a lot of benzofuran **12** was afforded with an increase of the reaction scale, since the reaction quenching in very short time was difficult in large-scale production. In the end, the intermediate **4** was very unstable under acidic and basic conditions, and it was proved that this procedure via **4**

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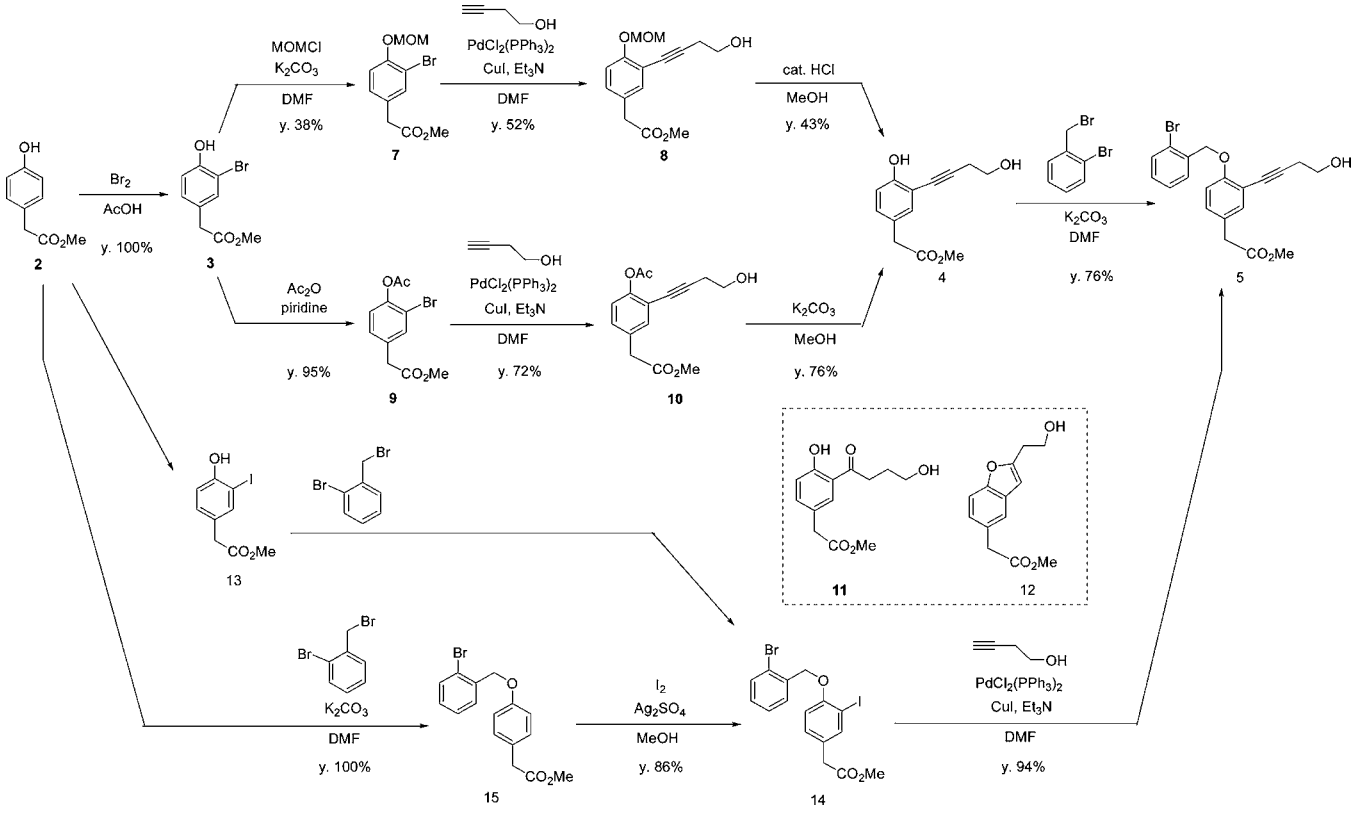
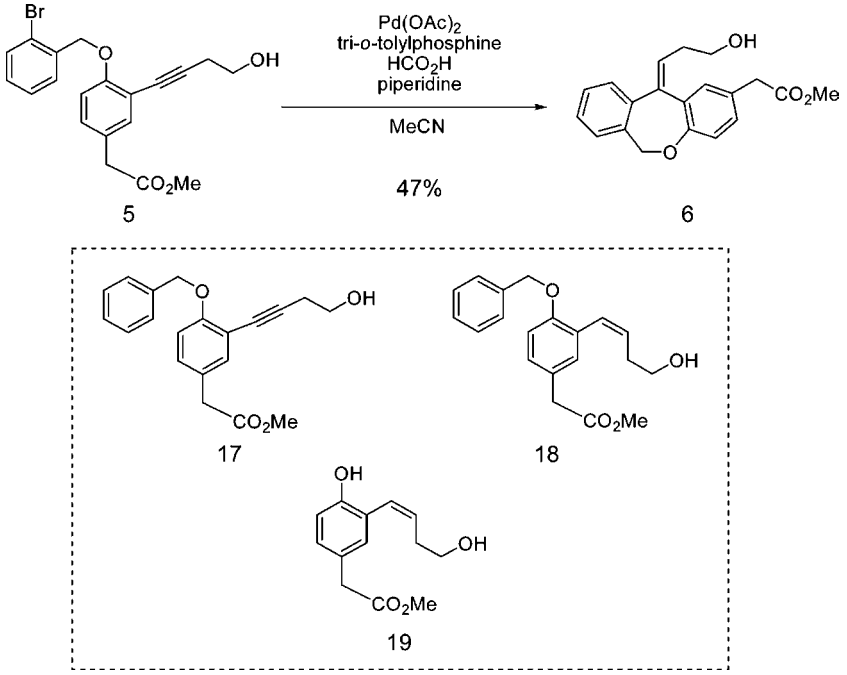
Scheme 2. Synthesis of the seven-membered ring cyclization precursor (5)



Scheme 3. Seven-membered ring cyclization and the synthesis of olopatadine hydrochloride



was not appropriate for a constant production. Therefore, we replanned the synthesis strategy of **5**.

Once the intermediate **14** is obtained, it is expected that the iodine group of **14** would react with 3-butyn-1-ol prior to the bromine group in the Sonogashira coupling. The synthesis of **14** could be performed by *O*-alkylation of monoiodineted compound **13** with 2-bromobenzylbromide. We tried iodination of **2** using inexpensive reagents, I_2 or ICl, but the mixture of monoiodinated compound **13** and diiodinated compound was obtained. It was supposed that the selective monoiodination of **2** was difficult in this reaction condition. We next tried to iodinate **15** after protection of the hydroxy group in **2** with 2-bromobenzyl group. As a result, the product **14** was obtained from **15** in high yield when using Ag_2SO_4 and I_2.[8] Furthermore,

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Sonogashira coupling reaction for **14** with 3-butyn-1-ol proceeded at the iodine position prior to bromine as expected. We could produce the precursor **5** of the seven-membered ring cyclization in the high yield from starting material **2**. (Scheme 2)

The Seven-Membered Ring Cyclization Using Palladium Catalyst. We then performed the seven-membered ring cyclization of **5** using palladium catalyst based on the aforementioned reference.[4] The *Z*-isomer dibenz[*b*,*e*]oxepin **6** could be obtained as a sole product. However the yield of **6** in the key ring cyclization was moderate since considerable amounts of some byproducts —— **17**, **18** and **19** —— were produced. (Scheme 3)

To increase the yield of **6**, screening of phosphine ligands in catalysts and solvents were investigated. As a result, P(*o*-tolyl)$_3$, P(cyclohexyl)$_3$, and dppe were found to be effective (Table 1).

Table 1. Screening of phosphine ligands[a]

		product ratio[b]				
entry	phosphine ligand	**5**	**6**	**17**	**18**	**19**
1	PPh_3	15	24	49	3	<1
2	P(*o*-tolyl)$_3$	1	50 (47)[c]	20	21	3
3	P(*m*-tolyl)$_3$	1	23	61	8	<1
4	P(*p*-tolyl)$_3$	3	24	54	13	<1
5	P(^{t}Bu)$_3$	<1	11	29	41	14
6	P(cyclohexyl)$_3$	16	45	30	4	<1
7	dppe	<1	45	22	24	<1
8	dppp	<1	6	23	58	1
9	dppf	<1	34	36	20	<1

[a]All reactions were carried out on a 100 mg scale in 2 mL of acetonitrile at 60 °C with Pd(OAc)$_2$ (0.10 equiv), phosphine ligand (0.20 equiv), formic acid (3.0 equiv), and piperidine (6.0 equiv). [b]Product ratios were calculated by HPLC peak area. [c]Yield of **6** by HPLC assay

It was clarified that the bulky phosphine ligands were suitable for this type of cyclization, which was already mentioned by Cacch[9]. Then screening for various solvents was carried out, and aprotic solvents such as acetonitrile were effective (Table 2). Consequently, the combination of P(*o*-tolyl)$_3$ and DMF seemed to be suitable taking into account the cost of those reagents. Though acetonitrile may also be appropriate for this reaction, a lot of palladium black stuck to a vessel at the end of the reaction.

Table 2. Screening of solvents[a]

		product ratio (%)[b]				
entry	solvent	**5**	**6**	**17**	**18**	**19**
1	MeCN	1	50 (47)[c]	20	21	3
2	toluene	29	32	10	10	1
3	EtOH	29	23	13	12	1
4	EtOAc	26	40	15	9	1
5	DMF	<1	51	30	16	1
6	DMA	<1	53	32	12	<1
7	DMI	<1	51	36	9	<1
8	NMP	<3	34	23	30	5

[a]All reactions were carried out on a 100 mg scale in 2 mL of solvent at 60 °C with Pd(OAc)$_2$ (0.10 equiv), P(*o*-tolyl)$_3$ (0.20 equiv), formic acid (3.0 equiv), and piperidine (6.0 equiv). [b]Product ratios were calculated by HPLC peak area. [c]Yield of **6** by HPLC assay

Optimization of the Seven-Membered Ring Cyclization by DoE. We next tried to find the optimal conditions of the key reaction to investigate the seven-membered ring cyclization by DoE. Five factors (phosphine ligand, formic acid, piperidine, DMF, temperature) were investigated as a candidate of critical factors. Although Pd(OAc)$_2$ may be a very important factor, we did not investigate it here since it was estimated that the reactivity would increase linearly as the amount of Pd(OAc)$_2$ increased.

Levels of the five factors are shown in Table 3. The 2^{5-1} fractional factorial design with a center point was experimented with using the automatic synthesis machine SK233.

The result of the DoE investigation was evaluated by the product ratio calculated by HPLC area %. The product ratio of each product for 17 runs is shown in Table 4. The HPLC area % of **6** is a convenient response by which to evaluate the yield of **6**, but it cannot evaluate the behavior of byproducts properly. Here the selectivity of **6** was focused on another important response. This shows the ratio of **6** for all known products, which is calculated by following the simple formula: **6**/(**6** + **17** + **18** + **19**). Upon seeing Table 4, we understood that the conditions of run 6 are preferred in both the product ratio and the selectivity of **6**.

The results of Table 4 were analyzed using the statistical analysis software "Design Expert". The half normal plot of HPLC area % and the selectivity of **6** are shown in Figure 1, from which it is possible to estimate the effect of each factor. Temperature was the most critical factor in both responses. This result could be easily understood because of the reactivity generally increasing at higher temperatures. The second critical factor was a little different between the two responses. In the product ratio, the second critical factor was the interaction of formic acid and temperature, but it was greatly lower than that of temperature alone. On the other hand, in the selectivity, the second critical factor was formic acid, the effect of which was as high as the effect of temperature. In the end, it was revealed that formic acid influenced the selectivity. Figure 2 shows the relevancy of temperature and formic acid. These figures indicate that higher temperature and less formic acid were appropriate for affording **6**.

The influence of formic acid for this reaction was explained from the next supposed mechanism (Scheme 4). The byproduct **17** was produced when the intermediate **A** reacted with hydride source before the reaction passed from **A** to **B**. If a lot of formic acid existed in the reaction mixture, the negative pass from **A** to **C** would occur.

Actually, reducing formic acid tends to increase the yield of **6** (Table 5). The highest yield was achieved using 1.1 equiv of formic acid. The yield of **6** could be greatly improved in comparison to that from our initial study.

Next, four other factors in addition to formic acid were optimized. The amount of piperidine was increased to 7.0 equiv because a higher level was appropriate for the selectivity. On the other hand, the amount of solvent could be fixed freely within the examined design space because its effect was marginal. The remaining two factors, phosphine ligand and temperature, were especially important in the palladium-catalyzed reaction. Generally, the ratio of phosphine ligand to palladium often influenced the reactivity of catalytic reaction. Temperature was the most critical factor in this reaction as already mentioned. The best condition for phosphine ligand and temperature was examined using the response surface model (RSM). Figure 3 shows the contour graph of the

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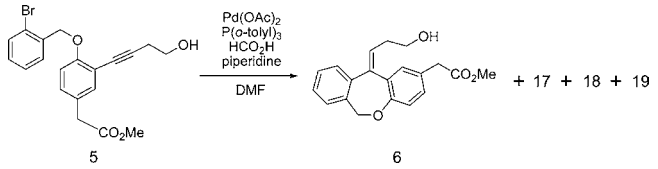
Table 3. Levels of the five factors in the 2^{5-1} fractional factorial design



5 6

factor	low level (−1)	center point (0)	high level (+1)
A: P(*o*-tolyl)$_3$	0.1 equiv	0.2 equiv	0.3 equiv
B: formic acid	2.0 equiv	3.0 equiv	4.0 equiv
C: piperidine	5.0 equiv	6.0 equiv	7.0 equiv
D: DMF	10 v/w	20 v/w	30 v/w
E: temperature	50 °C	70 °C	90 °C

Table 4. Experiment of the 2^{5-1} fractional factorial design[a]

	factor					product ratio (%)[b]					
run	A	B	C	D	E	**5**	**6**	**17**	**18**	**19**	selectivity of **6**[c]
1	−1	−1	−1	−1	+1	0	55	4	34	0	59
2	+1	−1	−1	−1	−1	62	16	14	1	0	53
3	−1	+1	−1	−1	−1	40	15	29	5	0	30
4	+1	+1	−1	−1	+1	0	44	25	26	0	47
5	−1	−1	+1	−1	−1	67	11	13	1	0	46
6	+1	−1	+1	−1	+1	0	66	11	16	0	71
7	−1	+1	+1	−1	+1	0	50	6	37	0	54
8	+1	+1	+1	−1	−1	57	15	16	2	0	46
9	−1	−1	−1	+1	−1	60	16	17	1	0	48
10	+1	−1	−1	+1	+1	0	63	16	15	0	67
11	−1	+1	−1	+1	+1	0	45	12	37	0	48
12	+1	+1	−1	+1	−1	42	19	26	4	0	38
13	−1	−1	+1	+1	+1	0	61	5	28	0	65
14	+1	−1	+1	+1	−1	64	18	11	0	0	60
15	−1	+1	+1	+1	−1	51	17	22	2	0	42
16	+1	+1	+1	+1	+1	0	56	19	19	0	59
17	0	0	0	0	0	2	49	34	10	0	53

[a]All reactions were carried out on a 100 mg scale. [b]Product ratios were calculated by HPLC peak area. [c]Selectivity was calculated by **6**/(**6** + **17** + **18** + **19**).

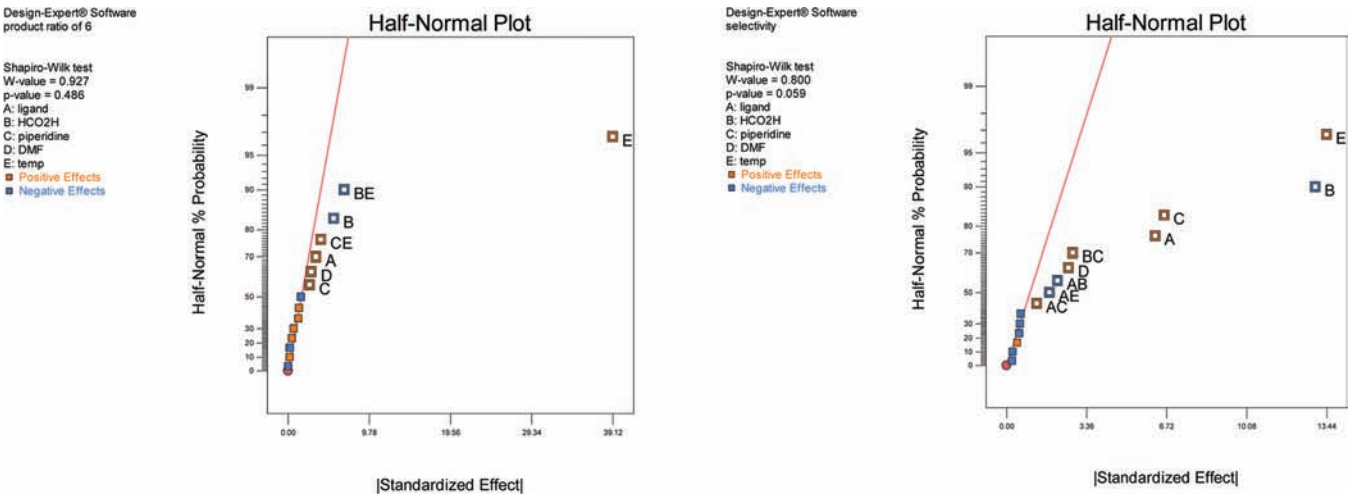


Figure 1. Half normal plot. Product ratio of **6** (left graph), selectivity of **6** (right graph).

estimated value about the yield of **6**. The maximum value, which is indicated by the vertex of the contour, was not more than 80%. It was difficult to achieve a yield higher than 80%. However, when this result was rethought from a different view, we could confirm that conditions around the vertex were robust. Finally we validated the best estimated condition on the vertex point of the contour model. The resulting experimental value approximately matched the estimated value, and the reproducibility for high yield and high selectivity of **6** in this stereospecific palladium-catalyzed reaction was confirmed

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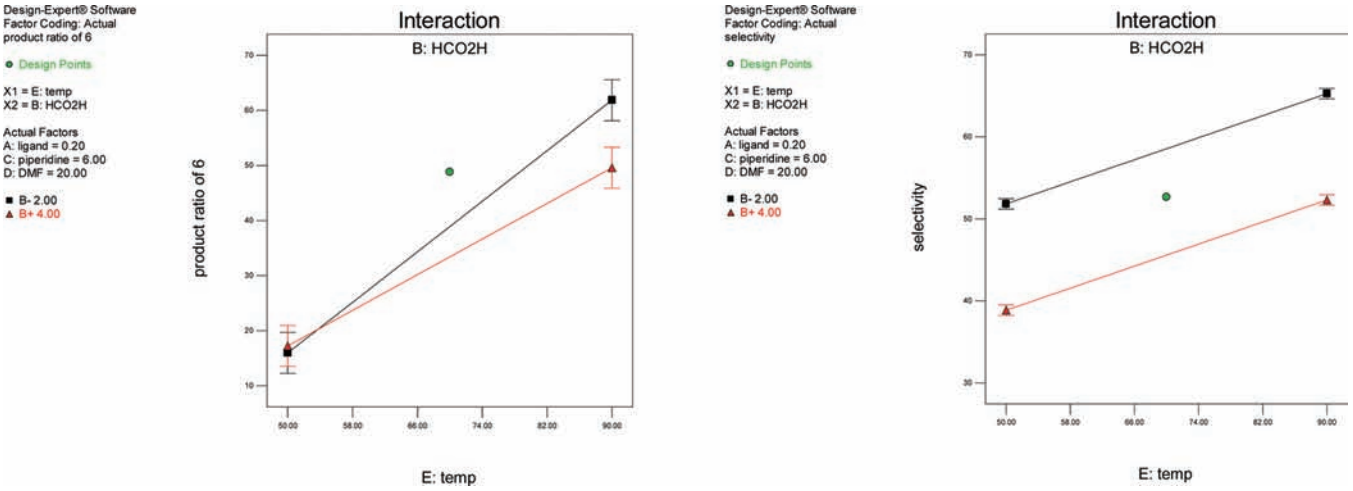

Figure 2. Interaction graph. Product ratio of **6** (left graph), selectivity of **6** (right graph).

Scheme 4. Reaction mechanism of producing byproducts

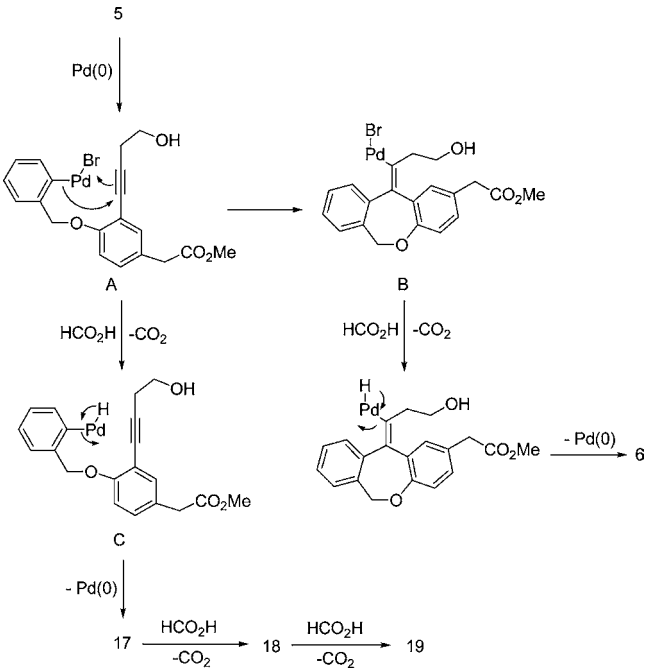

Table 5. Optimizing formic acid[a]

entry	formic acid (equiv)	yield[b] of **6** (%)
1	2.0	59
2	1.6	62
3	1.2	71
4	1.1	80
5	1.0	72

[a]All reactions were carried out on a 100 mg scale in 1 mL of solvent at 90 °C with $Pd(OAc)_2$ (0.10 equiv), P(*o*-tolyl)$_3$ (0.20 equiv), and piperidine (7.0 equiv). [b]HPLC assay.

(Table 6). Though we did not try this reaction in a large-scale production, the reaction conditions would be expected scalable because of a homogeneous reaction. We found the good reaction conditions of the cyclization using Pd catalyst by DoE studies, and the yield of the key intermediate **6** was greatly improved.

The Synthesis of Olopatadine Hydrochloride. The substitution reaction of the mesylate prepared from **6** by a dimethylamine was performed to afford **16**, and olopatadine hydrochloride (**1**) was obtained by hydrolysis of **16** (Scheme 5).[10]

CONCLUSION

We established the new efficient synthetic route of olopatadine hydrochloride (**1**). In the Sonogashira reaction, the alkyne moiety was introduced on iodine of **14** with perfect selectivity. Then, in the seven-membered cyclization of **5**, the 80% yield was achieved by optimization using DoE studies. From **6**, olopatadine hydrochloride could be prepared via mesylation, dimethylamination, and hydrochloridation in high yield. Though this established route was incomplete as a scalable process this time, it is expected that further optimization will make this procedure more practical.

EXPERIMENTAL SECTION

General Information. All reagents and solvents are commercially available (Tokyo Kasei Kogyo Co., Ltd., Sigma-Aldrich Co.) and used without further purification. ^{1}H NMR spectra were obtained on a JEOL JNM-LA300 spectrometer (300 MHz). Chemical shifts (δ) are reported in ppm. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (triplet of doublets), m (multiplet), brs (broad singlet). Proton-decoupled ^{13}C NMR spectra were obtained on a JEOL JNM-LA300 spectrometer (75 MHz). Mass spectra was obtained on a Micromass LCT spectrometer. HPLC analyses were performed on a Hitachi L-7000 system.

HPLC Analyses. The HPLC data in Tables 1, 2, 4, 5, 6 were obtained under the following conditions: detector, ultraviolet absorption photometer (wavelength 254 nm); column, Imtact CD-003; mobile phase, a mixture of 0.05 mol/L KH_2PO_4/CH_3CN (10/17); flow rate, 1.0 mL/min; column temperature, 30 °C; t_R (min) **19** (1.7), **6** (12.4), **17** (13.4), **18** (19.8), **5** (31.2).

Methyl 4-(2-Bromobenzyloxy)phenylacetate (15). To a solution of methyl 4-hydroxyphenylacetate (**2**) (5.00 g, 30.1 mmol) in DMF (50 mL) was added 2-bromobenzylbromide (7.50 g, 1.0 equiv) and K_2CO_3 (6.28 g, 1.5 equiv) at room temperature. The mixture was stirred at 25 °C for 4 h, and then

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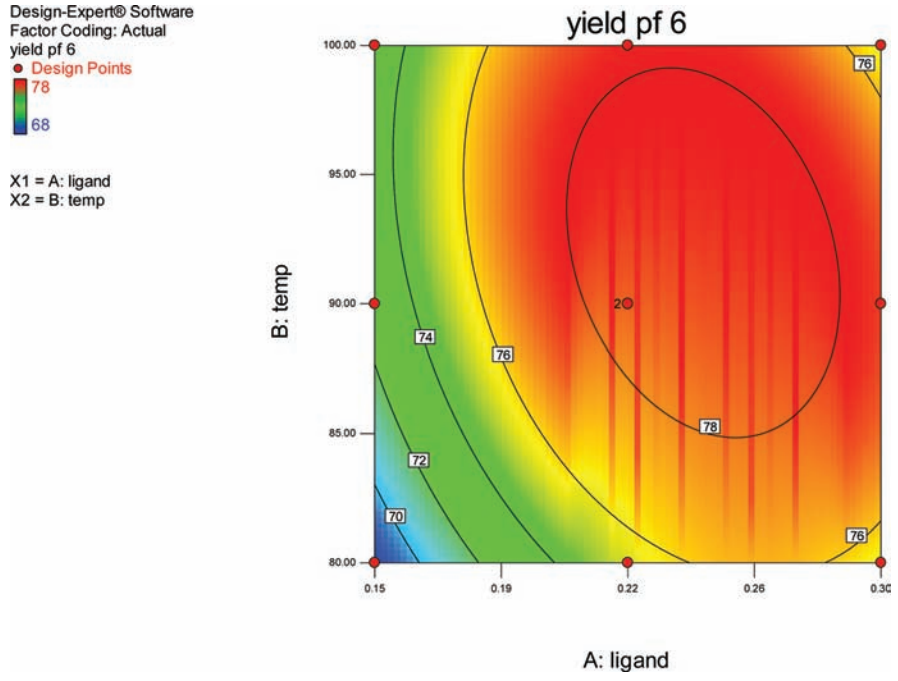


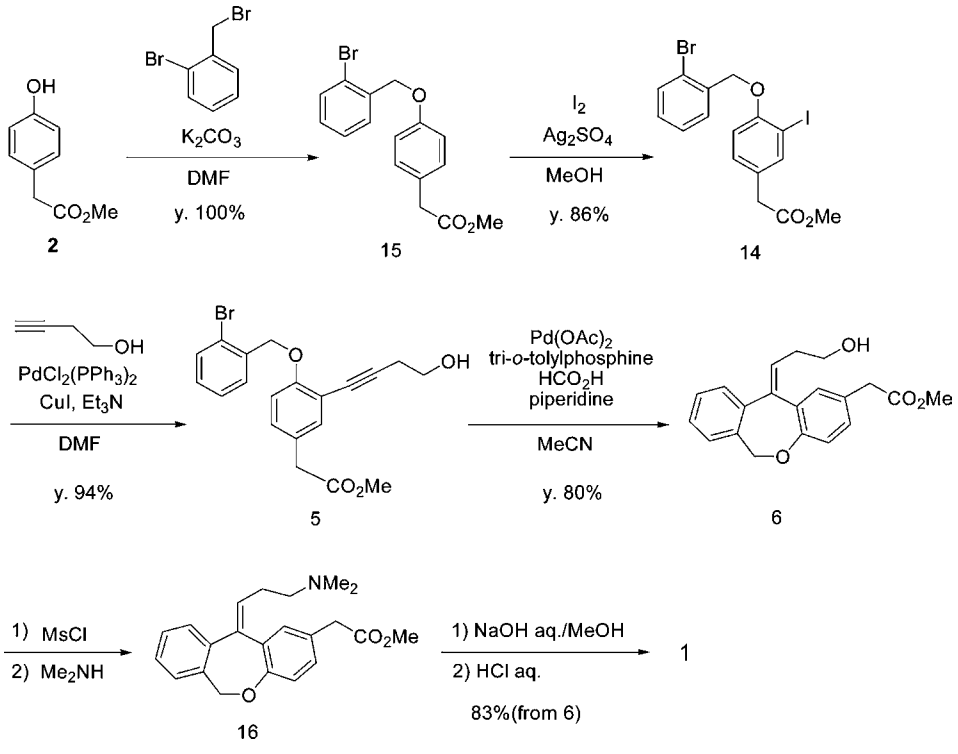
Figure 3. Response surface model (RSM) of the seven-membered ring cyclization.

Table 6. Validation of the estimated value of RSM[a]

	phosphine ligand (equiv)	temp (°C)	product ratio (%)[b]					yield[c] of **6** (%)	selectivity[d] of **6**
			5	**6**	**17**	**18**	**19**		
estimated	0.25	92	2	70	15	4	0	79	80
experimental	0.25	92	4	69	15	3	0	79	79

[a]A reaction was carried out on a 200 mg scale in 2 mL of solvent at the best conditions of RSM. [b]Product ratios were calculated by HPLC peak area. [c] HPLC assay. [d]Selectivity was calculated by **6**/(**6** + **17** + **18** + **19**).

Scheme 5. New synthetic route of olopatadine hydrochloride



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water and EtOAc were added to the mixture. The organic layer was extracted, washed by water, and concentrated at 50 °C to give the title compound **15** (10.25 g, quant.) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (dd, J = 7.7, 1.1 Hz, 1H), 7.53 (dd, J = 7.7, 1.3 Hz, 1H), 7.32 (td, J = 7.7, 1.3 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.17 (td, J = 7.7, 1.1 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 5.17 (s, 2H), 3.68 (s, 3H), 3.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.3, 157.6, 136.3, 132.6, 130.3, 129.2, 128.9, 127.6, 126.7, 122.2, 115.0, 69.5, 52.0, 40.3; MS ESI (+) m/z 337, 335 $[M + H]^+$.

Methyl 4-(2-Bromobenzyloxy)-3-iodophenylacetate (14). Iodine (7.28 g, 1.0 equiv) and $AgSO_4$ (8.71 g, 1.0 equiv) were added to methanol (15 mL), and the mixture was stirred until iodine was dissolved. To the mixture was added a solution of methyl 4-hydroxyphenylacetate (**15**) (9.44 g, 28.1 mmol) in methanol (15 mL) at room temperature. The mixture was stirred at 18 °C for 2 h, then the mixture was filtrated and washed with EtOAc. The filtrate was concentrated at 50 °C to form a yellow solid. The solid was slurried in methanol and corrected by filtration to give the title compound **14** (11.00 g, 86%) as a white colorless crystal; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 7.9, 1.1 Hz, 1H), 7.37 (td, J = 7.9, 1.0 Hz, 1H), 7.25−7.21 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 5.18 (s, 2H), 3.70 (s, 3H,), 3.55 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.7, 156.1, 140.2, 135.8, 132.6, 132.4, 130.4, 129.1, 128.7, 127.7, 121.5, 112.4, 86.5, 70.3, 52.1, 39.6; MS ESI (−) m/z 461, 459 $[M - H]^-$.

Methyl 4-(2-Bromobenzyloxy)-3-(4-hydroxybutynyl)-phenylacetate (5). Under N_2 atmosphere, a solution of methyl 4-(2-bromobenzyloxy)-3-iodophenylacetate (**14**) (5.0 g, 10.8 mmol), $PdCl_2(PPh_3)_2$ (381 mg, 0.05 equiv), CuI (103 mg, 0.1 equiv), 3-butyn-1-ol (1.84 mL, 2.0 equiv). and Et_3N (6.06 mL, 4.0 equiv) in DMF (50 mL) was stirred at 25 °C for 5 h. The mixture was quenched with water and then extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl and filtered to remove Pd residue. Then the organic layer was concentrated and purified by silica gel column chromatography (EtOAc/hexane = 1:1) to afford the title compound **5** (4.34 g, 100%) as an amber oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64 (dd$J$ = 7.7, 1.7 Hz, 1H,), 7.57 (dd, J = 7.7, 1.1 Hz, 1H), 7.34 (td, J = 7.7, 1.1 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.18 (td, J = 7.7, 1.7 Hz, 1H), 7.14 (dd, J = 8.6, 2.2 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 5.18 (s, 2H), 3.80 (t, J = 6.1 Hz, 2H), 3.69 (s, 3H), 3.53 (s, 2H), 2.73 (t, J = 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, 158.1, 136.1, 134.1, 132.5, 130.1, 129.2, 128.6, 127.6, 126.6, 121.8, 113.4, 112.7, 91.0, 78.7, 70.0, 61.1, 52.1, 40.0, 24.2; MS ESI (+) m/z 405, 403 $[M + H]^+$.

Methyl (*Z*)-11-[(3-Hydroxy)propylidene]-6,11-dihydrobenz[*b*,*e*]oxepin-2-acetate (6). Under N_2 atmosphere, a solution of methyl 4-(2-bromobenzyloxy)-3-(4-hydroxybutynyl)-phenylacetate (**5**) (200 mg, 0.496 mmol), $Pd(OAc)_2$ (11.1 mg, 0.1 equiv), tri-*o*-tolylphosphine (37.7 mg, 0.25 equiv), piperidine (344 μL, 7.0 equiv), and formic acid (20.5 μL, 1.1 equiv) in DMF (2.0 mL) was stirred at 92 °C for 3 h. The mixture was quenched with water and then extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl. The organic layer was concentrated, and the obtained oil was purified by silica gel column chromatography (ethyl acetate/hexane = 1:2) to afford the title compound **6** (114 mg, 71%) as a white colorless crystal; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.23 (m, 4H), 7.17 (d, J = 2.2 Hz, 1H), 7.04 (dd, J = 8.4, 2.2 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.74 (t, J = 7.5 Hz, 1H), 5.18 (brs, 2H), 3.80 (t, J = 6.1 Hz, 2H), 3.69 (s, 3H), 3.53 (s, 2H), 2.68 (dt, J = 7.5, 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.4, 154.6, 145.3, 141.4, 133.6, 132.1, 130.0, 129.1, 127.5, 126.2, 125.7, 124.0, 119.7, 70.5, 62.6, 52.1, 40.1, 33.3; MS ESI (+) m/z 325 $[M + H]^+$.

(*Z*)-11-[(3-Dimethylamino)propylidene]-6,11-dihydrobenz[*b*,*e*]oxepin-2-acetic Acid Hydrochloride (1). To methyl (*Z*)-11-[(3-hydroxy)-propyridene]-6,11-dihydrobenz[*b*,*e*]oxepin-2-acetate (**6**) (21.0 g, 64.7 mmol) in pyridine (160 mL) was added methanesulfonyl chloride (28.0 g, 3.8 equiv) gradually at 5 °C. The reaction mixture was heated to room temperature and stirred for 2 h. The mixture was quenched with water and then extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl and concentrated. To a solution of obtained oil in MeOH (400 mL) was add 50% aqueous dimethylamine (120 mL,18.0 equiv). and the mixture was stirred under reflux for 3 h. NaOH solution (2 mol/L, 100 mL) was added to the reaction mixture, then the mixture was stirred under reflux for 2 h. Water and butyl acetate were added to the reaction mixture, and the aqueous layer was adjusted to pH 2 with 2 mol/L HCl. The organic layer was concentrated to afford the title compound **1** (21.4 g, 88.4%).

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