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Synthesis of halogenated bicyclic molecules involving Prins cyclization from aldehydes and non-conjugated diene alcohol

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Abstract

The reactions of aldehydes and a non-conjugated alcohol, (*E*)-octa-3,7-dien-1-ol, in the presence of halogen-containing reagents afforded the corresponding halogenated bicyclic molecules in good yields. The optimization, scope and limitations of the reactions as well as scale-up reactions have been examined. Quantum chemical

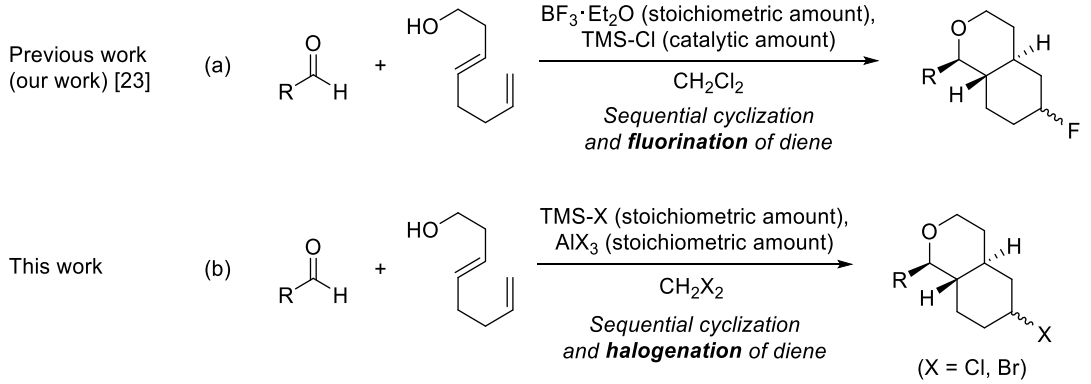
calculations helped clarify the microscopic mechanism of a key reaction process, the introduction of a Cl atom to a bicyclic carbocation.

Keywords

Prins Cyclization; C－C Bond Formation; Bicyclic Molecules; Sequential Reactions

Introduction

Prins cyclization and related chemistry have attracted much attention, because the simple operation using aldehydes and homo allylic alcohols with some kinds of chemical reagents produces various tetrahydropyran rings [1-3]. The reactions often play an important role in the field of the total synthesis of natural products [4-8]. Among them, the integrated Prins cyclization [9-10], in which the Prins cyclization and another type of reactions have been combined, is one of the most widely explored transformations in organic synthesis [11-14]. For instance, Reddy and co-workers have extensively studied the tandem cyclization involving Prins cyclization so far [15-22].



Scheme 1. Prins cyclization followed by (a) the fluorination (our work) [23] and (b) the halogenation such as chlorination and bromination (this work). TMS = trimethylsilyl

Recently, we have reported the integrated Prins cyclization using various aldehydes and a non-conjugated diene alcohol, (*E*)-octa-3,7-dien-1-ol. In the presence of $BF_3 \cdot Et_2O$ and a catalytic amount of TMSCl, the cyclization gave the corresponding bicyclic compounds in good yields (Scheme 1 (a)) [23]. A single fluorine atom was contained in the cyclized products. If we succeed in combining other halogenation reactions, such as chlorination and bromination, with the bicyclization, it would greatly increase the value of our reaction because the halogen group introduced is useful for subsequent derivatization processes [24-32]. In this work, we have studied the possibility of the introduction of Cl and Br atoms in the termination of the integrated Prins cyclization using (*E*)-octa-3,7-dien-1-ol (Scheme 1(b)). The simple and accessible syntheses of the halogenated bicyclic compounds have been attained. In addition, we have theoretically investigated the key mechanism of the chlorination of a bicyclic carbocation, which leads to the formation of the end products.

Results and Discussion

Table 1 shows the results of the reaction optimization. The non-conjugated diene alcohol, (*E*)-octa-3,7-dien-1-ol (**2**), was synthesized according to our previous report [23]. We employed the basic reaction condition of reagents and halide source reported by Liu et al [26]. The reaction of *n*-octanal (**1a**, 0.25 mmol) and **2** (0.25 mmol) in the presence of TMSCl (2 eq) and $AlCl_3$ (0.05 eq) in CH_2Cl_2 (2 mL) at −40 °C did not give the desired product **3aCl** at all (entry 1). Likewise, the increased amount of **1a** such as 0.50 mmol (2 eq) with $AlCl_3$ (0.05 eq) or without $AlCl_3$ did not yield **3aCl** (entries 2-3). However, the reaction using $AlCl_3$ (1 eq) at −40 °C gave the corresponding product **3aCl** in 89% yield (entry 4). As for the reaction temperature, the condition of −5 °C was also examined, and the results are summarized in entries 5 to 8. The reaction in the

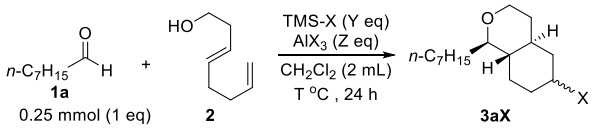
absence of $AlCl_3$ afforded **3aCl** in 20% yield (entry 5). The combination of TMSCl (2 eq) and $AlCl_3$ (0.05 eq) gave **3aCl** in 12% yield (entry 6). Interestingly, the combination of TMSCl (2 eq) and $AlCl_3$ (1 eq) gave **3aCl** in 87% yield (entry 7), in which the ratio of diastereomers associated with the Cl position was 1.2:1. The ^1H NMR analysis clarified that the major diastereomer has the Cl group on the axial position. In addition, the use of $AlCl_3$ (2 eq) in the absence of TMSCl also produced **3aCl** in 90% yield (entry 8). These results highlight the importance of a sufficient amount of $AlCl_3$ for a better yield, although entry 5 evidently shows that TMSCl can act as a chloride source. Based on the above investigations, the conditions of entries 4, 7 and 8 can be regarded as optimized parameters. Here, given the good performance reported by Liu et al [26] and a high yield of **3aCl**, we adopted the condition of entry 7, in which the combined use of TMSCl (2 eq) and $AlCl_3$ (1 eq) would facilitate the Cl introduction to various cyclized carbocation intermediates. We adopted −5 ^oC rather than −40 ^oC for easy handling.

As for the introduction of a Br atom into the cyclized compounds, we employed a condition similar to entry 7. The use of TMSBr (2 eq) and $AlBr_3$ (1 eq) in CH_2Cl_2 surprisingly produced a mixture of **3aBr** and **3aCl** in a total yield of 86% yield (entry 9). This indicates that Cl^- or its equivalent originating from CH_2Cl_2 might also attack an intermediate of a cyclized carbocation. To avoid the contamination of **3aBr** and **3aCl**, we used the CH_2Br_2 as a solvent, which actually gave **3aBr** in 91% yield (entry 10).

Because it turns out that the reaction optimization was achieved, we now discuss the scope and limitations of the bicyclization reactions accompanied by the Cl introduction (Table 2). The reaction of benzaldehyde (**1b**) using the optimized condition produced the desired product **3bCl** bearing a Cl moiety in 87% yield (entry 1). The aromatic aldehyde derivatives such as 4-methylbenzaldehyde (**1c**), 3-methylbenzaldehyde (**1d**), 4-chlorobenzaldehyde (**1e**), 3-chlorobenzaldehyde (**1f**), 4-nitrobenzaldehyde (**1g**), and 3-nitrobenzaldehyde (**1h**) were also promising starting

substrates, leading to the corresponding cyclized and chlorinated compounds in good yields (entries 2-7). In the case of 2-nitrobenzaldehyde (**1i**), three diastereomers were formed in good yield of **3iCl**, in which diastereomer ratio was 1.2:1:1 (entry 8). The ^{1}H NMR analysis of **3iCl** indicated that the 2-nitrobenzene ring in any of the three diastereomers was located in the equatorial position, the Cl atom in two of the three was located in the axial position, and the Cl atom in the remaining one was located in the equatorial position. This result suggested that one of the three diastereomers might have a *cis* condensed ring, although the detailed structural analysis was difficult because of the overlapping of ^{1}H NMR spectrum. The NO_2 group in **1i** might intramolecularly stabilize the intermediate from **D** by using NO_2 participation, although the detail is not clarified as yet. (*vide infra*, Scheme 3).

Table 1. Reaction optimization.[a]



Entry	**1a** (mmol)	TMS-X (Y eq)	AlX_3 (Z eq)	T (°C)		% Yield[b]
1	0.25	TMSCl (2 eq)	$AlCl_3$ (0.05 eq)	-40	**3aCl**	n.d.[c]
2	0.50	TMSCl (2 eq)	$AlCl_3$ (0.05 eq)	-40	**3aCl**	n.d.[c]
3	0.50	TMSCl (2 eq)	—	-40	**3aCl**	n.d.[c]
4	0.50	TMSCl (2 eq)	$AlCl_3$ (1 eq)	-40	**3aCl**	89 (1.1:1)[d]
5	0.50	TMSCl (2 eq)	—	-5	**3aCl**	20 (1:1.1)[d]
6	0.50	TMSCl (2 eq)	$AlCl_3$ (0.05 eq)	-5	**3aCl**	12 (3.6:1)[d]
7	0.50	TMSCl (2 eq)	$AlCl_3$ (1 eq)	-5	**3aCl**	87 (1.2:1)[d]
8	0.50	—	$AlCl_3$ (2 eq)	-5	**3aCl**	90 (1.2:1)[d]
9	0.50	TMSBr (2 eq)	$AlBr_3$ (1 eq)	-5	**3aBr**/ **3aCl**	86[e]
10[f]	0.50	TMSBr (2 eq)	$AlBr_3$ (1 eq)	-5	**3aBr**	91 (1.4:1)[d]

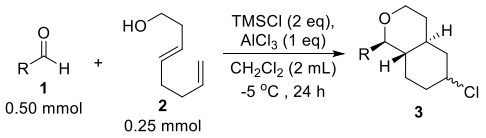
[a]The reaction was carried out using **1a** (0.25 mmol or 0.50 mmol) and **2** (0.25 mmol) with chemical reagents in CH_2Cl_2 (2 mL) at T ^oC for 24 h; [b]Isolated yields after the preparative GPC separation of crude materials; [c]n.d. = no detection; [d]Diastereomer ratio was determined using ^1H NMR spectra, which were derived from isolated and purified products. The ratio of diastereomers is given in the order of major diastereomer of **3** : minor diastereomer of **3**, shown in Scheme 3. In most entries, the ^1H NMR spectra imply a small amount of third diastereomer contamination, which has not been unambiguously confirmed yet; [e]**3aBr** and **3aCl** were obtained as a mixture. The isolated yield was calculated using the average molecular weight of **3aBr** and **3aCl** and the **3aBr** and **3aCl** contributions to ^{13}C NMR spectra, instead of the strongly overlapping ^1H NMR spectra. The ratio of **3aBr**/**3aCl** was 1.1:1. For both of **3aBr** and **3aCl**, diastereomer ratio was 1.6:1; [f]CH_2Br_2 (2 mL) was used instead of CH_2Cl_2 in order to avoid the formation of **3aCl**.

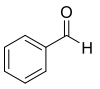
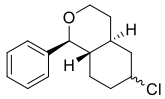
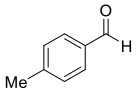
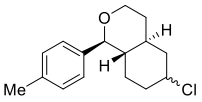
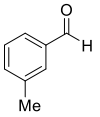
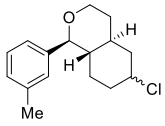
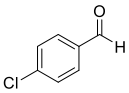
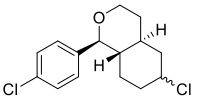
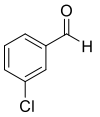
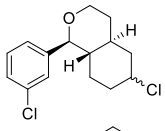
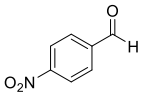
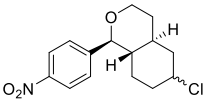
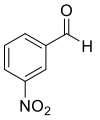
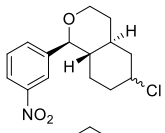
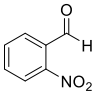
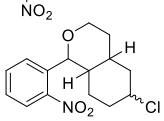
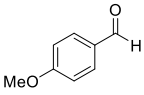
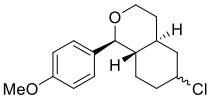
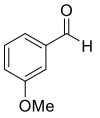
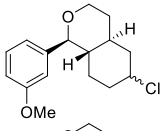
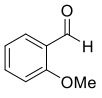
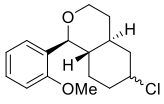
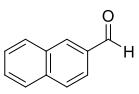
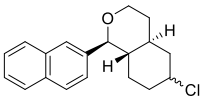
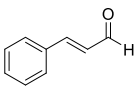
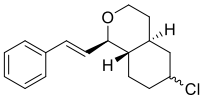
In the cases of 4-methoxybenzaldehyde (**1j**), 3-methoxybenzaldehyde (**1k**) and 2-methoxybenzaldehyde (**1l**), the reactions smoothly proceeded to give the products of **3jCl**, **3kCl** and **3lCl** in 85%, 80%, and 79% yields, respectively (entries 9-11). The stereo-selectivity of **3lCl** is less obvious in entry 11, compared with the other entries in Table2, which might be attributed to the substituent at the *ortho* postion in the aromatic ring. In addition, the reaction of 2-naphthaldehyde (**1m**) and **2** led to the formation of the corresponding **3mCl** in <91% yield (entry 12). It is worth noting that cinnamaldehyde (**1n**) was tolerant, despite of the presence of a carbon-carbon double bond, enough to afford bicyclic molecule **3nCl** in 76% yield (entry 13).

We could clarify the detailed structure of the minor diastereomer of **3cCl** (*vide supra*) by using X-ray analysis (Figure 1). Both of 4-MeC_6H_4 and the Cl atom in the minor diastereomer of **3cCl** were located in the equatorial position. This is consistent with the

above-mentioned fact that the major diastereomer of **3aCl** has the Cl atom on the axial position (Table 1, entry 7).

Table 2. Scope and limitations.[a]



Entry	Aldehyde		Product		% Yield[b]
1		**1b**		**3bCl**	87 (2.3:1)[c]
2		**1c**		**3cCl**	90 (2.1:1)[c]
3		**1d**		**3dCl**	87 (2.1:1)[c]
4		**1e**		**3eCl**	88 (2.9:1)[c]
5		**1f**		**3fCl**	90 (2.7:1)[c]
6		**1g**		**3gCl**	< 77 (3.0:1)[c]
7		**1h**		**3hCl**	< 85 (3.1:1)[c]
8		**1i**		**3iCl**	< 85 (1.2:1:1)[c]
9		**1j**		**3jCl**	85 (1.8:1)[c]
10		**1k**		**3kCl**	80 (2.1:1)[c]
11		**1l**		**3lCl**	79 (1.1:1)[c]
12		**1m**		**3mCl**	< 91 (2.3:1)[c]
13		**1n**		**3nCl**	76 (2.1:1)[c]

[a]The reaction was carried out using **1** (0.50 mmol) and **2** (0.25 mmol) with TMSCl (2 eq) and $AlCl_3$ (1 eq) in CH_2Cl_2 (2 mL) at −5 °C for 24 h; [b]Isolated yields after the preparative GPC separation of crude materials; [c]Diastereomer ratio was approximately determined by ^{13}C NMR spectra, which were derived from isolated and purified products. Diastereomer ratio could not be calculated by ^{1}H NMR spectra, because of the overlapping. In most entries, the ^{1}H NMR spectra suggest that a small amount of third diastereomer seems to be contained.

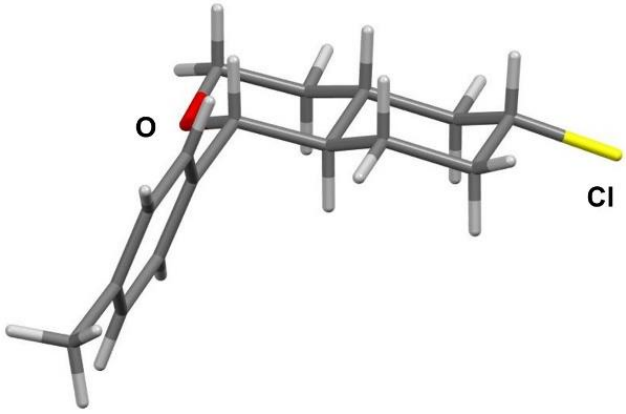
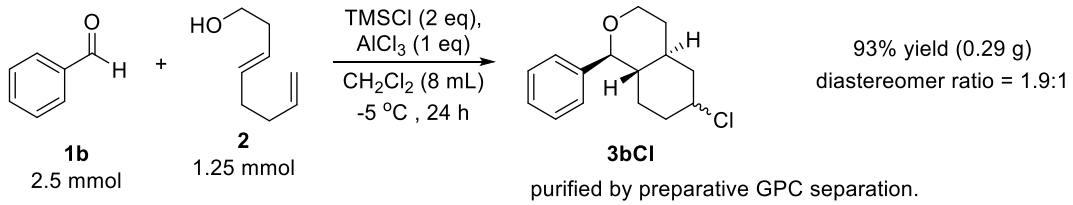


Figure 1. X-ray structure of the minor diastereomer of **3cCl** (CCDC: 2070265).

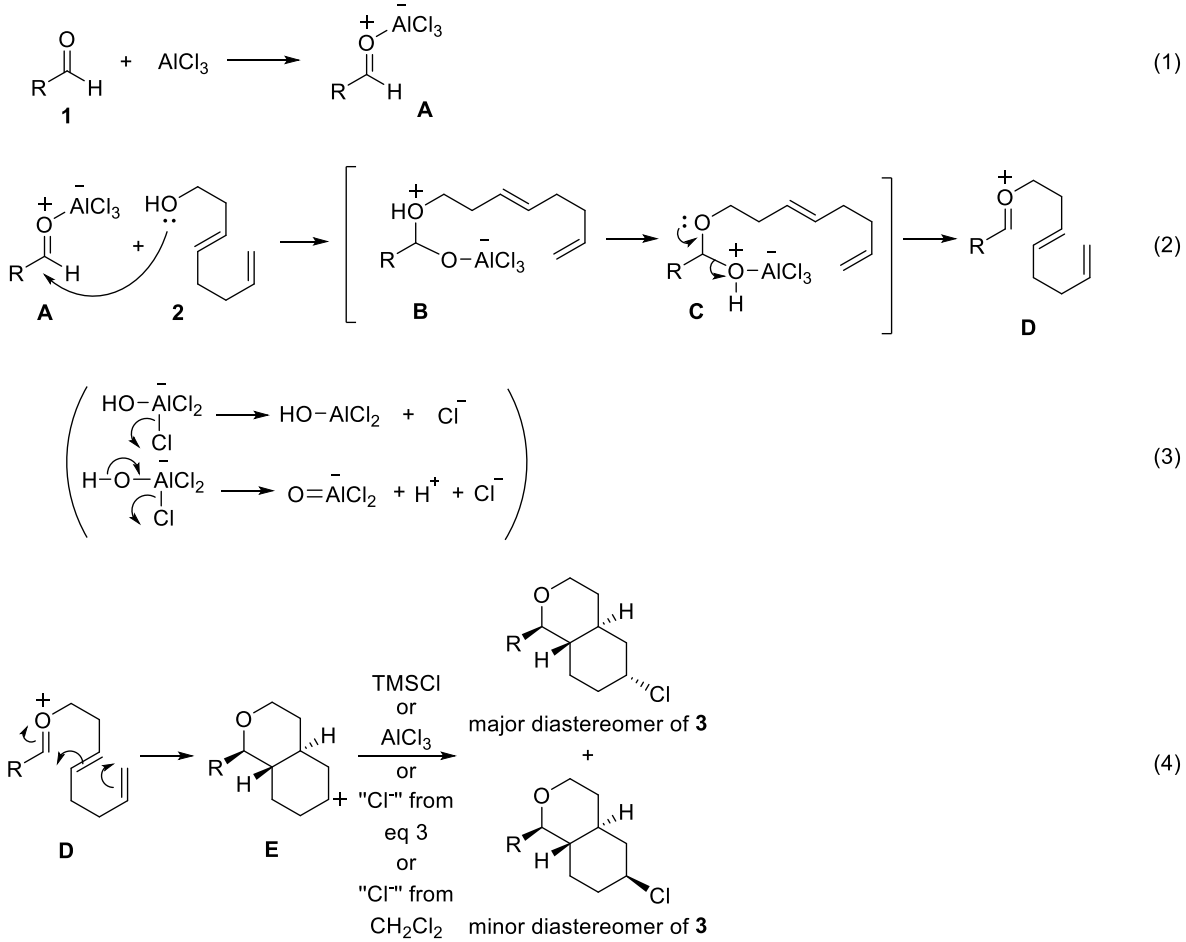
Taking a typical example, we assessed the applicability of the reaction to a scale-up condition (Scheme 2). That is, **1b** (2.5 mmol) and **2** (1.25 mmol) were reacted in the presence of TMSCl (2 eq) and $AlCl_3$ (1 eq) in CH_2Cl_2 (8 mL) at −5 °C for 24 h. The reaction gave the corresponding product **3bCl** in 93% yield (0.29 g), which was purified by the preparative GPC separation using the recycle HPLC. The result indicates that the scale-up condition does not notably affect the chemical yield of this reaction.



Scheme 2. Scale-up synthesis of **3bCl**.

The plausible reaction path is shown in Scheme 3, although the detailed reaction mechanism for the generation of alkoxycarbenium ion intermediate **D** [33-34] using stoichiometric amounts of $AlCl_3$ and TMSCl is not crystal clear now. The reaction of aldehyde **1** and $AlCl_3$ might form the activated aldehyde **A** (Scheme 3 (1)). **A** might be attacked by alcohol **2** to produce the adduct **B**, leading to the formation of **C** via the intramolecular transfer of H^+ (Scheme 3 (2)). **C** might release $[HOAlCl_3]^-$, generating alkoxycarbenium ion intermediate **D**. At this stage, $[HOAlCl_3]^-$ might generate Cl^-, shown in Scheme 3 (3). Another possibility that the generation of intermediate **D** might be achieved by the combination of $AlCl_3$ and TMSCl can not be ruled out.

After the formation of the intermediate **D**, the sequential bicyclization affords the carbocation **E**, which is terminated by a halide ion (Cl^- or Br^-) to give the final product **3** (Scheme 3 (4)). The same process is described in a previous report [23]. As for the final step of halogenation of **E**, such as chlorination, there is the possibility that Cl^- derived from TMSCl, $AlCl_3$, $[HOAlCl_3]^-$, and/or CH_2Cl_2 solvent would react with **E** to form **3**. In the literature of Liu et al. [26], TMSCl played a critical role as a primary chloride source. This is consistent with entry 5 in Table 1. In addition, entries 8 and 9 of Table 1 showed that $AlCl_3$ and CH_2Cl_2 could also serve as chloride sources. Therefore, the clear identification of a single Cl^- source seems to be difficult in the current reactions.



Scheme 3. Plausible reaction path for the generation of alkoxycarbenium ion intermediate **D**, followed by the cyclization and chlorination leading to **3**.

Focusing on the synthesis of **3cCl** (Table 2, entry 2) whose structure is well characterized, we theoretically studied the process of Cl^- introduction to the carbocation **E** (Scheme 3 (4), R = 4-MeC_6H_4 group). By referring to the previous study conducted by Liu et al. [26], we assumed that TMSCl is the chloride source in the theoretical calculations. As shown in Scheme 3 (4), we obtained two diastereomers as end products. The major diastereomer, denoted by **3cCl** (major), has the Cl group on the axial position. The minor diastereomer, denoted by **3cCl** (minor), has the Cl group on the equatorial position, as is shown in the X-ray crystal structure (Figure 1). The experimental yield of **3cCl** (major) and that of **3cCl** (minor) are 60% and 30% yields, respectively. Figure 2 displays the enthalpy diagram together with the equilibrium

geometries, which were obtained by using the density functional theory (DFT) calculations incorporating the solvation effects of CH_2Cl_2. Note that we discuss the enthalpy change rather than the Gibbs free energy change because the calculated entropies and, thus, the Gibbs energies were not reliable due to low-frequency normal modes. The energy scale of Figure 2 is relative to the total enthalpy of **E** and TMSCl at infinite separation. The equilibrium geometry of **E**, shown in Figure 2, exhibits sp^2 hybridization on the cationic C atom, to which only one H atom is attached. In fact, this C atom has a positive natural atomic charge (+0.33 *e*), and **E** exhibits an almost planar structure around the C atom. When the Cl atom of TMSCl approaches the cationic C atom in the out-of-sp^2-plane direction, there occurs Cl^- addition to **E**. Depending on from which side the Cl atom approaches the cationic C atom on the sp^2 plane, the addition can yield different diastereomers, **3cCl** (major) and **3cCl** (minor). To the Cl atom of each of the diastereomers, TMS^+ is bound by the electrostatic attraction (Si-Cl length ~ 2.33 Å). As shown in Figure 2, the enthalpy of **3cCl** (major)-TMS^+ cluster and also that of **3cCl** (minor)-TMS^+ cluster are more stable than the total enthalpy of **E** and TMSCl at infinite separation (-4.81, -4.79 kcal/mol, respectively). Although the enthalpy of **3cCl** (major)-TMS^+ cluster is more stable than that of **3cCl** (minor)-TMS^+ cluster, the difference is almost negligible (0.02 kcal/mol). This small enthalpy difference is attributed presumably to the weak steric repulsion in the clusters, regardless of the different configurations (Figure 2). Even after TMS^+ is eliminated, the enthalpy difference between **3cCl** (major) and **3cCl** (minor) remains very small (0.48 kcal/mol). This TMS^+ elimination requires overcoming enthalpy destabilization (Figure 2) for breaking the electrostatic attraction between TMS^+ and Cl. The destabilization is somewhat large, that is, 16.17 kcal/mol for **3cCl** (major) and 15.67 kcal/mol for **3cCl** (minor). We added water, a highly polar solvent, for quenching the reaction, which reduces the enthalpy destabilization of TMS^+ elimination; in water, the corresponding

destabilization is 14.82 kcal/mol for **3cCl** (major) and 14.29 kcal/mol for **3cCl** (minor). It turns out that there are, on the whole, only subtle differences between the reaction leading to **3cCl** (major) and that leading to **3cCl** (minor) in terms of the enthalpy diagram in Figure 2. This is consistent with the limited stereo-selectivity of **3cCl**. Transition states can play a crucial role in kinetically controlled reactions. To locate the transition states for Cl^- addition and TMS^+ elimination, we manually changed a key bond length (i.e., C-Cl length for Cl^- addition and Si-Cl length for TMS^+ elimination) and performed computational optimization of all geometrical parameters, except for the key bond length. In the potential energy curves obtained, however, there are no transition states, or activation energy barriers, for both processes; the potential energy profile for Cl^- addition is purely downhill (Figure 3 (a)) and the profile for TMS^+ elimination is purely uphill (Figure 3 (b)). In addition, the potential energy profile for the path to **3cCl** (major) is very similar to that for the path to **3cCl** (minor). All of these observations demonstrate that TMSCl can actually act as a chloride source and the chlorination can readily form both of the two bicyclic diastereomers. In the future, we plan to experimentally and theoretically clarify the overall reaction mechanism in greater detail.

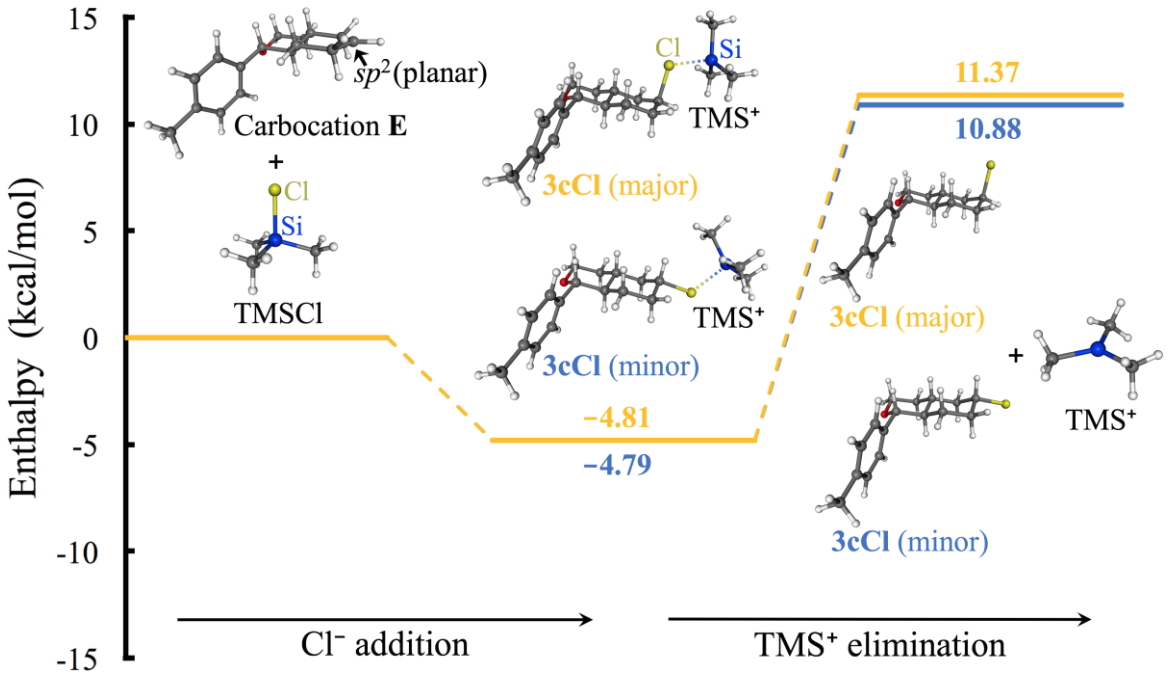
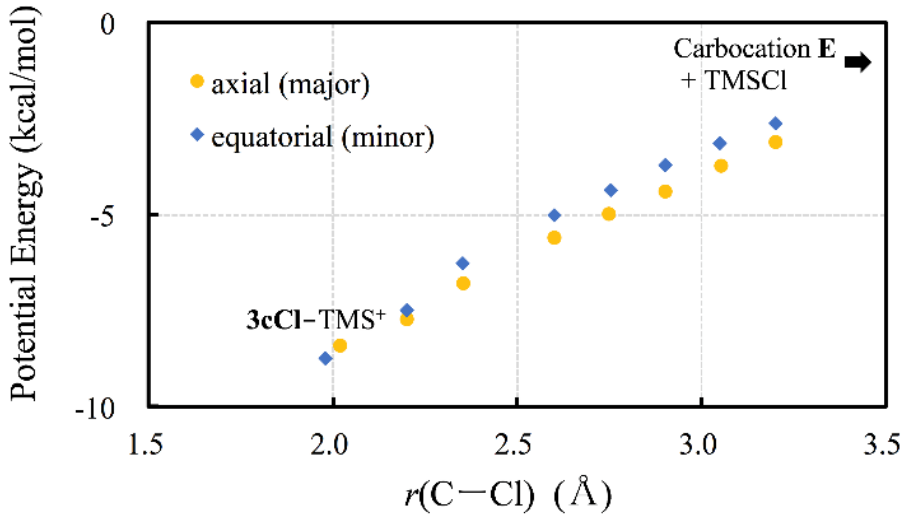
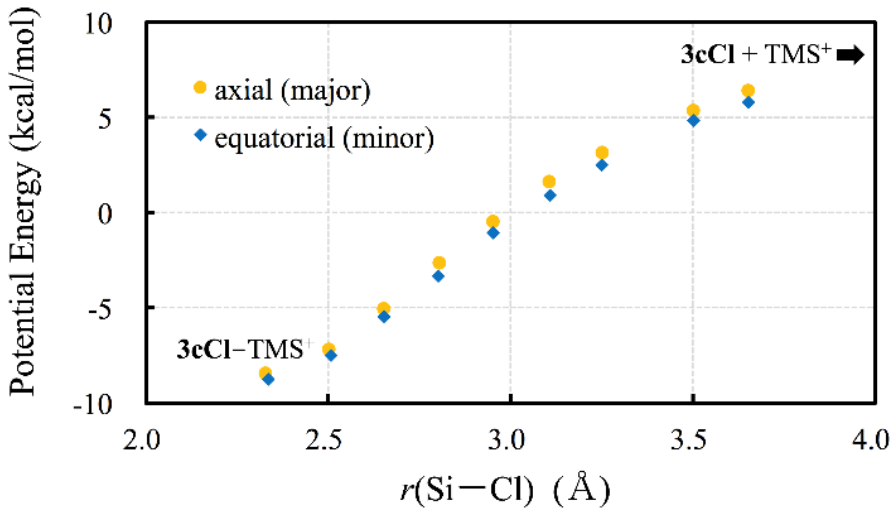


Figure 2. Enthalpy diagram for Cl^- introduction to **E** in the syntheses of **3cCl** (major) and **3cCl** (minor). The reaction is decomposed into two elementary processes, that is, Cl^- addition and TMS^+ elimination. The corresponding equilibrium geometries are also displayed.



(a) Cl^- addition



(b) TMS^+ elimination

Figure 3. Potential energy curves for (a) Cl^- addition and (b) TMS^+ elimination in the syntheses of **3cCl** (major) and **3cCl** (minor). To evaluate the energy curves for Cl^- addition, we gradually shortened the distance between the cationic C atom of **E** and the Cl atom of TMSCl, *r*(C-Cl). To evaluate the energy curves for TMS^+ elimination, we gradually lengthened the distance between the Cl atom of **3cCl** and the Si atom of TMS^+, *r*(Si-Cl).

Conclusion

In summary, we have successfully constructed the halogenated bicyclic molecules bearing Cl and Br via Prins cyclization using (*E*)-octa-3,7-dien-1-ol. Focusing on the bicyclization accompanied by chlorination, we showed that the present reaction can be applicable for various aldehydes such as aliphatic and aromatic substituents as well as cinnamaldehyde. The reaction efficiently took place under a scale-up condition. The reaction optimization helped the achievement of a good yield and revealed that TMSCl, $AlCl_3$, and/or CH_2Cl_2 can be chloride sources in our reaction. We theoretically investigated the chlorination of a typical bicyclic carbocation, thereby confirming that TMSCl can act as a chloride source. There are no transition states for the chlorination, resulting in the formation of the two bicyclic diastereomers. We plan to deepen the understanding of the reaction mechanism, including the role of $AlCl_3$. Further synthetic application is currently underway.

Experimental

General Remarks. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-ECS 400 (^1H, 400 MHz; ^{13}C, 100 MHz) and a MERCURY 300 (^1H, 300 MHz; ^{13}C, 75 MHz) spectrometer. The chemical shifts of ^1H NMR are reported using 0.00 ppm of tetramethylsilane (TMS) or 7.26 ppm from the residual $CHCl_3$ in case of $CDCl_3$. The chemical shifts of ^{13}C NMR are reported using 77.0 ppm in case of $CDCl_3$. Mass spectra (HRMS) were measured by a Thermo Fisher Scientific EXACTIVE Plus. Merck pre-coated silica gel F_{254} plates (thickness 0.25 mm) were used for thin-layer chromatography (TLC) analysis. A silica gel column (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40-100 μm) was used for the flash chromatography by using an air pump. Preparative GPC separation was carried out by using a Japan Analytical

Industry LC-9201, LC-9210 NEXT, or LC-9110 NEXT equipped with JAIGEL-1H-20 and JAIGEL-2H-20, or JAIGEL-1H-40 and JAIGEL-2H-40, in which $CHCl_3$ was used. All reactions were carried out under N_2 atmosphere, unless mentioned.

Quantum chemical calculations. We employed Gaussian 09 program [35]. Using B3LYP functional [36-38] and cc-pVDZ basis set [39-40], we performed the DFT optimization. After obtaining the optimized geometries, we verified, by means of the frequency analysis, that they are indeed equilibrium geometries. For all of the equilibrium geometries, we performed self-consistent-field stability analysis (i.e., instability check) to assess the reliability of the electronic structures. The solvation effects of CH_2Cl_2 were incorporated by employing the polarizable continuum model [41]. The thermochemistry analysis was performed at −5 ^oC.

X-ray Crystal Structure Determinations. The measurement of compound **3cCl** was made on a Rigaku XtaLAB-PRO MM007-PILATUS-200 diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71075 Å). The diffraction data were collected at 100(2) K by the ω scan mode. Data were collected and processed using the CrysAlisPro (Rigaku Oxford Diffraction). The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods (SHELXTL 2018/2) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically (SHELXL 2018/3). All hydrogen atoms were refined using the AFIX command. All calculations were performed using Crystal Structure (ver. 4.3.2). Crystal data and detailed structure determinations are summarized in Table S1. Selected bond lengths and bond angles are listed in Table S2. CCDC: 2070265 (**3cCl**).

Materials. Dry CH_2Cl_2 was prepared as follows. CH_2Cl_2 was washed with distilled water by several times to remove a trace amount of MeOH. P_2O_5 was added and dried overnight. Then, CH_2Cl_2 was distilled. The reflux of CH_2Cl_2 in the presence of dried

K_2CO_3, and CH_2Cl_2 was directly redistilled. Finally, activated molecular sieves 4A were added to CH_2Cl_2 for the storage.

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. The alcohol **2** was prepared according to the previous literature [23].

Typical procedure for synthesis of halogenated bicyclic molecules (Table 1, entry 7). To the solution of CH_2Cl_2 (2.0 mL) containing $AlCl_3$ (33.7 mg, 0.253 mmol) and TMSCl (63 μL, *d* = 0.86 g/mL, ca. 54.2 mg, 0.499 mmol) at −5 °C, octanal (**1a**, 64.3 mg, 0.501 mmol) and (*E*)-octa-3,7-dien-1-ol (**2**, 32.0 mg, 0.254 mmol) were added. The solution was stirred at the same temperature for 24 h. The reaction was quenched by H_2O (10 mL). The organic phase was extracted by CH_2Cl_2 (10 mL x 3), and the combined organic phase was washed by bine (50 mL x 1). The organic phase was dried over $MgSO_4$, and filtered. The organic solvent was removed under vacuum to give the crude material, which was purified by the preparative GPC separation to give the 6-chloro-1-heptyloctahydro-1*H*-isochromene (**3aCl**, 60.5 mg, 87% yield).

6-Chloro-1-heptyloctahydro-1*H*-isochromene (3aCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82-2.32 (m, 25H, major and minor diastereomers), 2.87-2.94 (m, 1H, minor diastereomer, C<u>H</u>-*n*-C_7H_{15}, 1H of axial position), 2.99-3.08 (m, 1H, major diastereomer, C<u>H</u>-*n*-C_7H_{15}, 1H of axial position), 3.43 (td, *J* = 11.2, 2.8 Hz, 1H, minor diastereomer, -O-CH_2-, 1H of axial position), 3.52 (td, *J* = 12.0, 2.8 Hz, 1H, major diastereomer, -O-CH_2-, 1H of axial position), 3.86 (tt, *J* = 11.6, 4.4 Hz, CH-Cl, 1H of axial position), 3.96-4.04 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.52 (quintet, *J* = 3.2 Hz, major diastereomer, CH-Cl, 1H of equatorial position) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.4 and 22.6, 25.1 and 25.2, 27.8, 29.3 and 29.8, 31.8, 32.6 and 32.8, 33.0 and 33.2, 33.8 and 33.9, 36.9, 40.4 and 40.7, 43.6 and 44.9,

46.1, 58.6 and 59.4, 67.8 and 68.0, 81.0 and 81.2 ppm; HRMS (ESI, positive) calcd for $C_{16}H_{29}ClO$ ($[M]^+$): 272.1901, found: 272.1906.

Bromo-1-heptyloctahydro-1*H*-isochromene (3aBr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-2.42 (m, 25H, major and minor diastereomers), 2.84-3.10 (m, 1H, major and minor diastereomers, *n*-C_7H_{15}-CH, 1H of axial position), 3.37-3.58 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.95-4.10 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position, and m, 1H, minor diastereomer, CH-Br, 1H of axial position), 4.72 (quintet, *J* = 2.8 Hz, 1H, major and minor diastereomers, CH-Br, 1H of equatorial position) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 14.1, 22.2, 22.7, 25.2, 29.32, 29.82, 31.9, 32.6, 32.8, 34.6, 34.8, 41.1, 46.2, 54.2, 68.0, 81.0 ppm, and minor diastereomer (selected) δ 25.1, 28.9, 29.29, 29.79, 32.8, 33.2, 37.9, 41.9, 44.5, 44.9, 50.6, 67.8, 81.2 ppm; HRMS (ESI, positive) calcd for $C_{16}H_{29}BrONa$ ($[M+Na]^+$): 339.1294, found: 339.1275.

6-Chloro-1-phenyloctahydro-1*H*-isochromene (3bCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89-2.30 (m, 10H, major and minor diastereomers), 3.58-3.67 (m, 1H, minor diastereomer, -O-CH_2-, 1H of axial position), 3.67-3.77 (m, 1H, major diastereomer, -O-CH_2-, 1H of axial position), 3.81-3.96 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 3.87 (d, *J* = 9.2 Hz, 1H, minor diastereomer, CH-Ph, 1H of axial position), 4.00 (d, *J* = 9.2 Hz, 1H, major, CH-Ph, 1H of axial position), 4.10-4.18 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.51 (quintet, *J* = 2.8 Hz, 1H, major, CH-Cl, 1H of equatorial position), 7.24-7.37 (m, 5H, major and minor diastereomers) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer: δ 21.6, 32.7, 33.6, 34.2, 40.3, 47.6, 59.4, 68.5, 84.9, 127.2, 127.8, 128.2, 140.7 ppm, and minor diastereomer: δ 28.0, 33.0, 36.7, 40.8, 43.5, 46.5, 58.5, 68.3, 85.0, 127.0, 127.9, 128.3, 140.5 ppm; HRMS (ESI, positive) calcd for $C_{15}H_{19}ClONa$ ($[M+Na]^+$): 273.1017, found: 273.1015.

6-Chloro-1-(4-tolyl)octahydro-1*H*-isochromene (3cCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86-1.05 (m, 1H, major and minor diastereomers), 1.20-2.26 (m, 9H, major and minor diastereomers), 2.33 (s, 3H, major and minor diastereomers, -C_6H_4-C$\underline{H}_3$), 3.56-3.77 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.83 (d, *J* = 9.6 Hz, 1H, minor diastereomer, CH-Ar, 1H of axial position), 3.85-3.92 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 3.97 (d, *J* = 9.6 Hz, 1H, major, CH-Ar, 1H of axial position), 4.08-4.17 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.51 (quintet, *J* = 2.8 Hz, major diastereomer, CH-Cl, 1H of equatorial position), 7.10-7.24 (m, 4H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.1, 21.6, 32.7, 33.6, 34.3, 40.3, 47.6, 59.5, 68.5, 84.7, 127.1, 128.9, 137.5, 137.8 ppm, and minor diastereomer (selected) δ 28.0, 33.1, 36.8, 40.9, 43.5, 46.5, 58.5, 68.3, 84.8, 127.0, 129.0, 137.66, 137.7 ppm; HRMS (ESI, positive) calcd for $C_{16}H_{21}ClONa$ ($[M+Na]^+$): 287.1173, found: 287.1171.

6-Chloro-1-(3-tolyl)octahydro-1*H*-isochromene (3dCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87-2.25 (m, 10H, major and minor diastereomers), 2.34 (s, 3H, major and minor diastereomers, CH_3), 3.56-3.77 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.83 (d, *J* = 9.2 Hz, 1H, minor diastereomer, CH-Ar, 1H of axial position), 3.85-3.92 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 3.97 (d, *J* = 9.6 Hz, major diastereomer, CH-Ar, 1H of axial position), 4.09-4.17 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.51 (quintet, *J* = 2.8 Hz, 1H, major diastereomers, CH-Cl, 1H of equatorial position), 7.02-7.24 (m, 4H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.4, 21.6, 32.7, 33.6, 34.3, 40.3, 47.5, 59.4, 68.5, 85.0, 124.4, 127.7, 128.0, 128.5, 137.9, 140.5 ppm, and minor diastereomer (selected) δ 28.0, 33.0, 36.7, 40.9, 43.5, 46.4, 58.5, 68.3, 85.1, 124.3, 127.6, 128.1, 128.6 ppm; HRMS (ESI, positive) calcd for $C_{16}H_{21}ClONa$ ($[M+Na]^+$): 287.1173, found: 287.1172.

6-Chloro-1-(4-chlorophenyl)octahydro-1*H*-isochromene (3eCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89-2.30 (m, 10H, major and minor diastereomers), in which especially 0.92-1.02 (m, 1H, major), 1.16-1.29 (m, 1H, major and minor diastereomers), 1.37-1.70 (m, major and minor diastereomers, lefts of all of H in major and minor diastereomers), 1.90-2.06 (m, 2H, major and minor diastereomers), and 2.10-2.27 (m, 1H, major diastereomer) were analyzed. 3.56-3.75 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.85 (d, *J* = 9.6 Hz, 1H, minor diastereomer, CH-Ar, 1H of axial position), 3.79-3.94 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 3.98 (d, *J* = 9.6 Hz, 1H, major diastereomer, CH-Ar, 1H of equatorial position), 4.08-4.17 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.51 (quintet, *J* = 2.8 Hz, major diastereomer, CH-Cl, 1H of equatorial position), 7.20-7.34 (m, 4H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.5, 32.6, 33.5, 34.2, 40.2, 47.7, 59.2, 68.5, 84.1, 128.4, 128.6, 133.4, 139.3 ppm, and minor diastereomer δ 27.8, 32.9, 36.6, 40.7, 43.4, 46.6, 58.3, 68.3, 84.2, 128.5, 133.5, 138.7, 139.1 ppm; HRMS (ESI, positive) calcd for $C_{15}H_{18}Cl_2ONa$ ($[M+Na]^+$): 307.0627, found: 307.0626.

6-Chloro-1-(3-chlorophenyl)octahydro-1*H*-isochromene (3fCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-2.30 (m, 10H, major and minor diastereomers), 3.56-3.77 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.85 (d, *J* = 9.6 Hz, 1H, minor diastereomer, CH-Ar, 1H of axial position), 3.84-3.94 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 3.98 (d, *J* = 9.6 Hz, 1H, major diastereomer , CH-Ar, 1H of axial position), 4.09-4.17 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.51 (quintet, *J* = 2.8 Hz, 1H, major diastereomer, 1H of equatorial position), 7.11-7.38 (m, 4H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.4, 32.6, 33.4, 34.1, 40.2, 47.6, 59.2, 68.5, 84.2, 125.6, 127.2, 127.9, 129.4, 134.19, 142.7 ppm, and minor diastereomer (selected) δ

27.8, 32.9, 36.6, 40.7, 43.3, 46.5, 58.3, 68.3, 84.3, 125.4, 128.0, 129.5, 134.22, 142.6 ppm; HRMS (ESI, positive) calcd for $C_{15}H_{19}Cl_2O$ ($[M+H]^+$): 285.0807, found: 285.0801.

6-Chloro-1-(4-nitrophenyl)octahydro-1*H*-isochromene (3gCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-2.30 (m, 10H, major and minor diastereomers), 3.57-3.80 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.83-3.95 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 4.00 (d, *J* = 9.6 Hz, 1H, minor diastereomer, CH-Ar, 1H of axial position), 4.01-4.09 (m, 1H, minor diastereomer, -O-CH_2-, 1H of equatorial position), 4.13 (d, *J* = 9.6 Hz, 1H, major diastereomer, CH-Ar, 1H of axial position), 4.10-4.20 (m, 1H, major diastereomer, -O-CH_2-, 1H of equatorial position), 4.49-4.55 (m, 1H, major diastereomer, CH-Cl, 1H of equatorial position), 7.43-7.56 (m, 2H, major and minor diastereomers), 8.16-8.25 (m, 2H, major and minor diastereomers) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.4, 32.5, 33.4, 34.1, 40.2, 47.9, 59.0, 68.5, 83.8, 123.5, 128.1, 147.5, 148.1 ppm, and minor diastereomer δ 27.7, 32.8, 36.5, 40.6, 43.3, 46.8, 58.0, 68.3, 83.9, 123.5, 128.0, 147.5, 147.9 ppm; HRMS (ESI, positive) calcd for $C_{15}H_{18}ClNO_3Na$ ($[M+Na]^+$): 318.0867, found: 318.0866.

6-Chloro-1-(3-nitrophenyl)octahydro-1*H*-isochromene (3hCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-2.30 (m, 10H, major and minor diastereomers), 3.60-3.80 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.83-3.95 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 4.01 (d, *J* = 10.0 Hz, minor diastereomer, CH-Ar, 1H of axial position), 4.14 (d, *J* = 9.6 Hz, minor diastereomer, CH-Ar, 1H of axial position), 4.11-4.21 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position, a part of some signals was overlapped with other signals), 4.50-4.55 (m 1H, major diastereomer, CH-Cl, 1H of equatorial position), 7.47-7.70 (m, 2H, major and minor diastereomers, Ar), 8.12-8.25 (m, 2H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.4, 32.4, 33.3, 34.0, 40.1,

47.7, 59.0, 68.5, 83.7, 122.1, 122.7, 129.1, 133.5, 142.9, 148.2 ppm, and minor diastereomer (selected) δ 27.7, 32.8, 36.4, 40.6, 43.2, 46.7, 58.0, 68.3, 83.8, 122.9, 129.2, 133.3, 142.8, 148.1 ppm; HRMS (ESI, positive) calcd for $C_{15}H_{18}ClNO_3Na$ [$(M+Na)^+$]: 318.0867, found: 318.0859.

6-Chloro-1-(2-nitrophenyl)octahydro-1*H*-isochromene (3iCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-2.28 (m, 10H, all diastereomers), 3.57-3.76 (m, 1H, all diastereomers, -O-CH_2-, 1H of axial position), 3.84-3.94 (m, 1H, one diastereomer, CH-Cl, 1H of axial position), 4.06-4.15 (m, 1H, all diastereomers, -O-CH_2-, 1H of equatorial position), 4.44-4.52 (m, 1H, two diastereomers, CH-Cl, 1H of equatorial position), 4.60-4.76 (m, 1H, all diastereomers, CH-Ar, 1H of axial position), 7.37-7.45 (m, 1H, all diastereomers, Ar), 7.56-7.80 (m, 3H, all diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 and 26.7 and 27.2, 32.4 and 32.8 and 32.9, 33.3 and 33.5 and 34.0, 34.8 and 36.7 and 40.29, 40.35 and 40.5 and 42.2, 43.4 and 47.5 and 48.3, 58.0 and 58.8 and 59.3, 68.3 and 68.6 and 68.7, 77.6 and 77.9 and 78.1, 123.5 and 123.6, 128.3 and 128.4, 128.9 and 129.0, 132.7 and 133.0 and 133.2, 135.0 and 135.1 and 135.2, 149.2 and 149.4 and 149.5 ppm; HRMS (ESI, positive) calcd for $C_{15}H_{18}ClNO_3Na$ ($[M+Na]^+$): 318.0867, found: 318.0866.

6-Chloro-1-(4-methoxyphenyl)octahydro-1*H*-isochromene (3jCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-2.26 (m, 10H, major and minor diastereomers), 3.56-3.73 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.79 (s, 3H, major and minor diastereomers, -OCH_3), 3.82 (d, *J* = 10.0 Hz, minor diastereomer, CH-Ar, 1H of axial position), 3.84-3.91 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 3.96 (d, *J* = 9.2 Hz, 1H, major diastereomer, CH-Ar, 1H of axial position), 4.07-4.16 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.51 (quintet, *J* = 2.8 Hz, major diastereomer, CH-Cl, 1H of axial position), 6.83-6.90 (m, 2H, major and minor diastereomers, Ar), 7.18-7.27 (m, 2H, major and minor diastereomers, Ar) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.6, 32.7, 33.6, 34.3, 40.3, 47.6, 55.2, 59.4, 68.5, 84.4, 113.6, 128.3, 132.9, 159.1 ppm, and minor diastereomer (selected) δ 28.0, 33.0, 36.8, 40.9, 43.5, 46.5, 58.5, 68.3, 84.5, 113.7, 128.2, 132.8, 159.2 ppm; HRMS (ESI, positive) calcd for $C_{16}H_{21}ClO_2Na$ ($[M+Na]^+$): 303.1122, found: 303.1107.

6-Chloro-1-(3-methoxyphenyl)octahydro-1*H*-isochromene (3kCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89-2.26 (m, 10H, major and minor diastereomers), 3.56-3.75 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.80 (s, 3H, major and minor diastereomers, -OCH_3), 3.84 (d, *J* = 9.6 Hz, 1H, minor diastereomer, CH-Ar, 1H of axial position), 3.83-3.93 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 3.98 (d, *J* = 9.6 Hz, 1H, major diastereomer, CH-Cl, 1H of axial position), 4.09-4.17 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.51 (quintet, *J* = 2.8 Hz, 1H, major diastereomer, CH-Cl, 1H of equatorial position), 6.78-6.96 (m, 3H, major and minor diastereomers, Ar), 7.18-7.30 (m, 1H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.6, 32.7, 33.6, 34.2, 40.3, 47.6, 55.2, 59.4, 68.5, 84.9, 112.6, 113.3, 119.7, 129.15, 142.2, 159.6 ppm, and minor diastereomer (selected) δ 27.9, 33.0, 36.7, 40.8, 43.5, 46.5, 58.5, 68.3, 85.0, 119.6, 129.22, 142.1 ppm; HRMS (ESI, positive) calcd for $C_{16}H_{21}ClO_2Na$ ($[M+Na]^+$): 303.1122, found: 303.1106.

6-Chloro-1-(2-methoxyphenyl)octahydro-1*H*-isochromene (3lCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95-2.30 (m, 10H, major and minor diastereomers), 3.58-3.76 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.79 (s, 3H, minor diastereomer, -OCH_3), 3.81 (s, 3H, major diastereomer, -OCH_3), 3.81-3.93 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 4.07-4.16 (m, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.46-4.70 (m, 1H, major and minor diastereomers, CH-Ar, 1H of axial position, and m, 1H, major diastereomer, CH-Cl, 1H

of equatorial position), 6.81-6.88 (m, 1H, major and minor diastereomers, Ar), 6.93-7.01 (m, 1H, major and minor diastereomers, Ar), 7.17-7.27 (m, 1H, major and minor diastereomers, Ar), 7.35-7.47 (m, 1H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer δ 21.0, 27.4, 32.9, 33.8, 36.96, 40.4, 55.4, 59.6, 68.6, 110.2, 120.8, 127.3, 128.4, 129.5, 156.8 ppm, in which other signal was overlapped with $CDCl_3$ around 77 ppm, by the analysis of HMQC, and minor diastereomer (selected) δ 33.2, 34.3, 40.9, 43.6, 58.7, 68.4, 121.0, 128.5, 129.3, 156.6 ppm; HRMS (ESI, positive) calcd for $C_{16}H_{22}ClO_2$ ($[M+H]^+$): 281.1303, found:281.1287.

6-Chloro-1-(naphthalen-2-yl)octahydro-1*H*-isochromene (3mCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-2.30 (m, 10H, major and minor diastereomers), 3.60-3.82 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of axial position), 3.82-3.92 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 4.03 (d, *J* = 9.2 Hz, 1H, minor diastereomer, CH-Ar, 1H of axial position), 4.17 (d, *J* = 9.2 Hz, 1H, major diastereomer, CH-Ar, 1H of axial position), 4.14-4.22 (m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.50 (quintet, *J* = 2.8 Hz, 1H, major diastereomer, CH-Cl, 1H of equatorial position), 7.40-7.50 (m, 3H, major and minor diastereomers, Ar), 7.70-7.86 (m, 4H, major and minor diastereomers, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer (selected) δ 21.6, 32.8, 33.5, 34.3, 40.3, 47.7, 59.4, 68.6, 85.0, 125.0, 125.8, 125.95, 126.4, 127.6, 127.9, 128.0, 133.1, 138.1 ppm; and minor diastereomer (selected) δ 28.0, 33.0, 36.7, 40.8, 43.5, 46.5, 58.5, 68.4, 85.1, 124.8, 125.8, 126.0, 126.3, 128.2, 138.0 ppm; HRMS (ESI, positive) calcd for $C_{19}H_{21}ClONa$ ($[M+Na]^+$): 323.1173, found: 323.1168.

(*E*)-6-Chloro-1-styryloctahydro-1*H*-isochromene (3nCl): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-2.30 (m, 10H, major and minor diastereomers), 3.50-3.75 (m, 2H, major and minor diastereomers, -O-CH_2-, 1H of axial position, and CH-Ar, 1H of axial position), 3.80-3.93 (m, 1H, minor diastereomer, CH-Cl, 1H of axial position), 4.03-4.12

(m, 1H, major and minor diastereomers, -O-CH_2-, 1H of equatorial position), 4.52 (quintet, *J* = 2.8 Hz, 1H, major diastereomer, CH-Cl, 1H of equatorial position), 6.07-6.18 (m, 1H, major and minor diastereomers), 6.53-6.65 (m, 1H, major and minor diastereomers), 7.20-7.42 (m, 5H, major and minor diastereomers, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer (selected) δ 21.7, 32.5, 33.6, 33.8, 40.3, 46.4, 59.4, 67.9, 82.7, 126.4, 128.4, 132.7, 132.8, 136.6 ppm, and minor diastereomer δ 28.0, 32.8, 36.7, 40.4, 43.4, 45.3, 58.4, 67.7, 82.8, 127.6, 127.7, 128.2, 128.4, 133.1, 136.5 ppm; HRMS (ESI, positive) calcd for $C_{17}H_{21}ClONa$ ($[M+Na]^+$): 299.1173, found: 299.1157.

Supporting Information

Supporting Information File 1:

File Name: Supporting Information File 1

File Format: PDF file

Title: X-ray crystal structure determinations for CCDC:2070265 (**3cCl**) and DFT-optimized geometries

Supporting Information File 2:

File Name: Supporting Information File 2

File Format: CIF file

Title: CCDC:2070265 (**3cCl**)

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