

Comprehensive Synthesis of a Group of Optically Active Caged Hydrocarbon Molecules

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Abbreviations

Ac	Acetyl	Eq.	equation
Å	ångström	Et	ethyl
aq.	aqueous solution	Fig	figure
Ar	aryl	FID	flame ionization detector
Bz	benzoyl	FG	functional group
Bn	benzyl	FGT	functional group transformation
br s	broad singlet (spectra)	g	gram
calcd	calculated	Hz	hertz (s ⁻¹)
cat.	catalyst	HPLC	high performance liquid chromatography
CSB	charge-shift bond	HOMO	highest occupied molecular orbital
δ	chemical shift in parts per million (spectra)	HRMS	highest resolution mass spectrometry
<i>J</i>	coupling constant	h	hour(s)
Cy	cyclohexyl	HAT	hydrogen atom transfer
decomp.	decomposition	<i>i</i> Pr	isopropyl
°	degree	K	Kelvin
°C	degrees Celsius	kcal	kilocalorie(s)
Δ	delta, difference	λ	lambda, wavelength
DFT	density functional theory	LDA	lithium diisopropylamide
DCE	1,2-dichloroethane	LUMO	lowest unoccupied molecular orbital
DCM	dichloromethane	MHz	megahertz
DMAP	4-dimethylaminopyridine	mp.	melting point
DoM	directed <i>ortho</i> -metalation	Mes	mesityl
DG	directing group	Ms	mesyl
d	doublet (spectra)	<i>m</i>	meta
ESI	electro ionization	Mtl	metal
EI	electron ionization	m	meter
eV	electron volt	Me	methyl
EWG	electron withdrawing group		
ECD	electronic circular dichroism		
El	electrophile		

μm	micrometer(s)	TDBMS	tert-butyldimethylsilyl
μmol	micromole(s)	<i>t</i> Bu	tertiary butyl
mg	milligram(s)	THF	tetrahydrofuran
mm	millimeter(s)	TMP	tetramethylpiperidide
mmHg	millimeter of mercury	TLC	thin layer chromatography
mmol	millimole(s)	tol	tolyl
min	minute(s)	Ts	tosyl
M	molar (mol per liter)	TM	transition metal
mol	mole	Tf	triflyl
mol%	mole percent	TMS	trimethylsilyl
m	multiplet (spectra)	t	triplet
nm	nanometer(s)	UV	ultraviolet
<i>n</i>	normal	V	volume
<i>n</i> Bu	normal butyl	wt%	weight percent
NMR	nuclear magnetic resonance		
Nu	nucleophile		
<i>o</i>	ortho		
<i>p</i>	para		
ppm	parts per million (spectra)		
Ph	phenyl		
pin	pinacolato		
PTLC	preparative thin layer chromatography		
quant.	quantitative		
q	quartet (spectra)		
quint	quintet (spectra)		
recov.	recovery		
R _f	retention factor		
rt	room temperature		
sept	septet (spectra)		
sex	sextet (spectra)		
SET	single-electron transfer		
s	singlet (spectra)		

General Introduction

1. Context and Background

Cubane, a saturated hydrocarbon with the molecular formula C_8H_8 , was synthesized by Eaton et al. in 1964. This molecule has a different molecular shape and properties from those of conventional saturated hydrocarbons, which are composed of sp^3 units of a regular tetrahedron.^{1,2} The cubane skeleton is thermally stable despite its large strain, and the strain causes the s -character of the C–H carbons that make up the vertex to be larger than the normal sp^3 , so it is expected that active species such as anions, radicals, and cations will be readily generated. For this reason, it can be applied to a variety of modification reactions, and there is a possibility that it can be incorporated as a partial structure into a number of biologically active molecules.³ When observed from the vertex, cubane is represented as a hexagon that evokes the configuration of benzene. The intermolecular distance between the vertices is nearly identical to that of benzene (approximately 2.7 Å), and the molecular formula $(CH)_n$ aligns, thus classifying cubane as a benzene bioisostere. There have been attempts to substitute the benzene ring of various biologically active molecules with cubane.⁴ The background to the development of such attempts is rooted in the concept of diversity-oriented synthesis (DOS). In the field of pharmaceutical chemistry, the addition of quaternary carbon centres to a molecule increases the steric complexity of the resulting drug candidate. This approach is regarded as an effective method of "Escape from Flatland," as described by Lovering.⁵ In other words, since the substituted cubane contains only eight tertiary or quaternary carbons in the same molecular width as benzene, it can be considered an ideal hydrocarbon unit that can replace benzene. Indeed, the synthesis of novel compounds and drug candidates, including cubane, has emerged as a highly attractive area of research within the field of organic synthetic chemistry.

Furthermore, cubane is not simply a biological analogue of benzene; as a "non-flat" molecule, it has the potential to exhibit chirality. Cubane is a highly cross-linked saturated hydrocarbon with a rigid three-dimensional structure. The introduction of substituents at appropriate vertices in a site-selective manner allows for the creation of a chiral environment in which racemization does not occur (Figure 1, top). The introduction of chirality into cage-like hydrocarbons, such as cubane, and their

utilization as novel molecular scaffolds has been considered a promising avenue of research.^{6,7} Nevertheless, the introduction of site-selective substituents for highly symmetric cubane (O_h symmetry) remains a significant challenge in the field of synthetic chemistry, with no definitive solution yet established.^{3,8} The author then investigated whether there were any other methods of efficient asymmetric expression that were not site-selective substitution reactions. In other words, it is thought that it may be possible to easily construct asymmetric molecules by asymmetrizing the skeleton through cubane skeletal isomerization, rather than through substitution reactions. In 1970, Eaton et al. published a report in which they described the formation of the chiral hexahedral molecule cuneane by the reaction of cubane with Ag(I) and Pd(II).⁹ Nevertheless, the report has not been discussed the chirality. Given that cuneane is a C_{2v} symmetric molecule, it is feasible that it may exhibit chirality even in the mono- and di-substituted forms. In other words, isomerization from cubane to cuneane should be capable of imparting a degree of complexity, such as chirality, to a molecule in a single reaction operation without altering its overall molecular size. Furthermore, the addition of two methylene groups to the eight equivalent bonds of the cubane skeleton results in the formation of a new skeleton, designated bishomocubane. It is possible to impart chirality through asymmetrization via cage expansion.¹⁰ The utilization of molecules such as cuneane and bishomocubane represents a novel strategy for the imparting of chirality through the alteration of molecular shape, as opposed to the “decoration” of the vertices of the cubane skeleton. The author was inspired by the terms “molecular editing”^{11a} and “scaffold hopping”^{11b} and designated this process as “cubane scaffold editing” (Figure 1, bottom).¹²

The author suggests that if it is possible to introduce complexity, such as chirality, into molecules with a highly symmetrical three-dimensional framework, like cubane, by “breaking” the symmetry through scaffold editing, it may become easier to access optically active cage-shaped polyhedral molecules, which have been considered difficult to synthesize. Based on this concept, the author began by synthesizing trisubstituted chiral cubane, and then proceeded to synthesize cage-shaped compounds such as cuneane, semibullvalene, homocubane, bishomocubane, and homocuneane

(Figure 2). The following section is a brief summary of the conventional synthesis methods for each compound before this research.

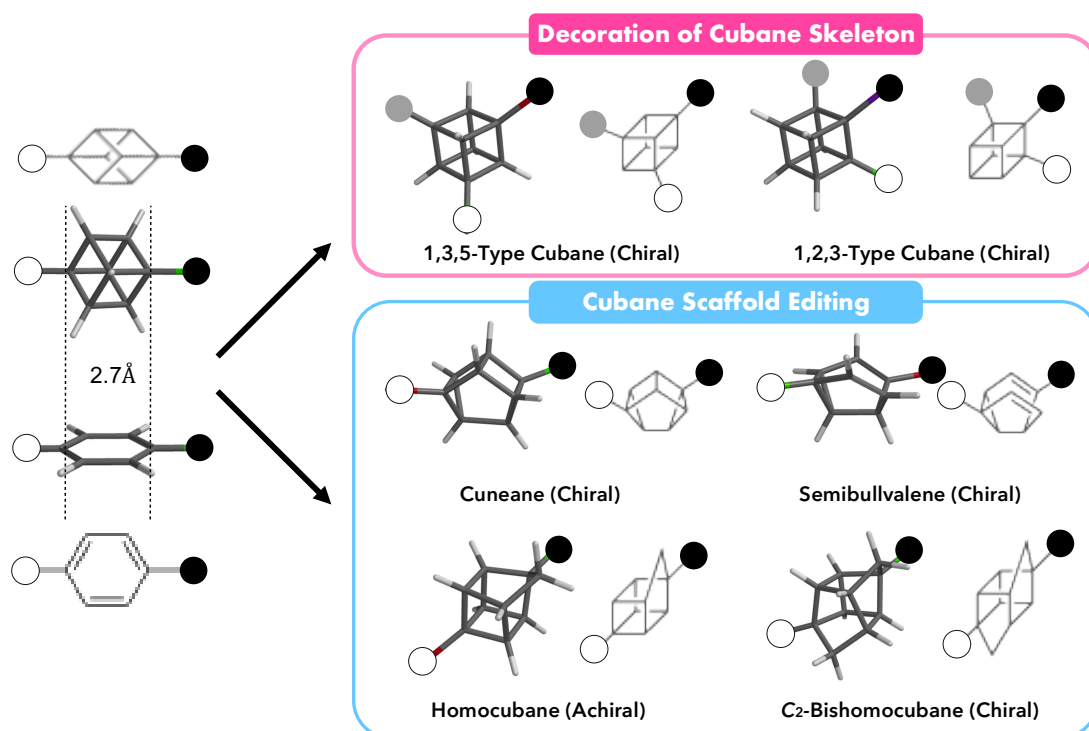


Figure 1. Two approaches to set chirality in cubane derivatives: Decoration of cubane (top) and cubane scaffold editing (bottom).

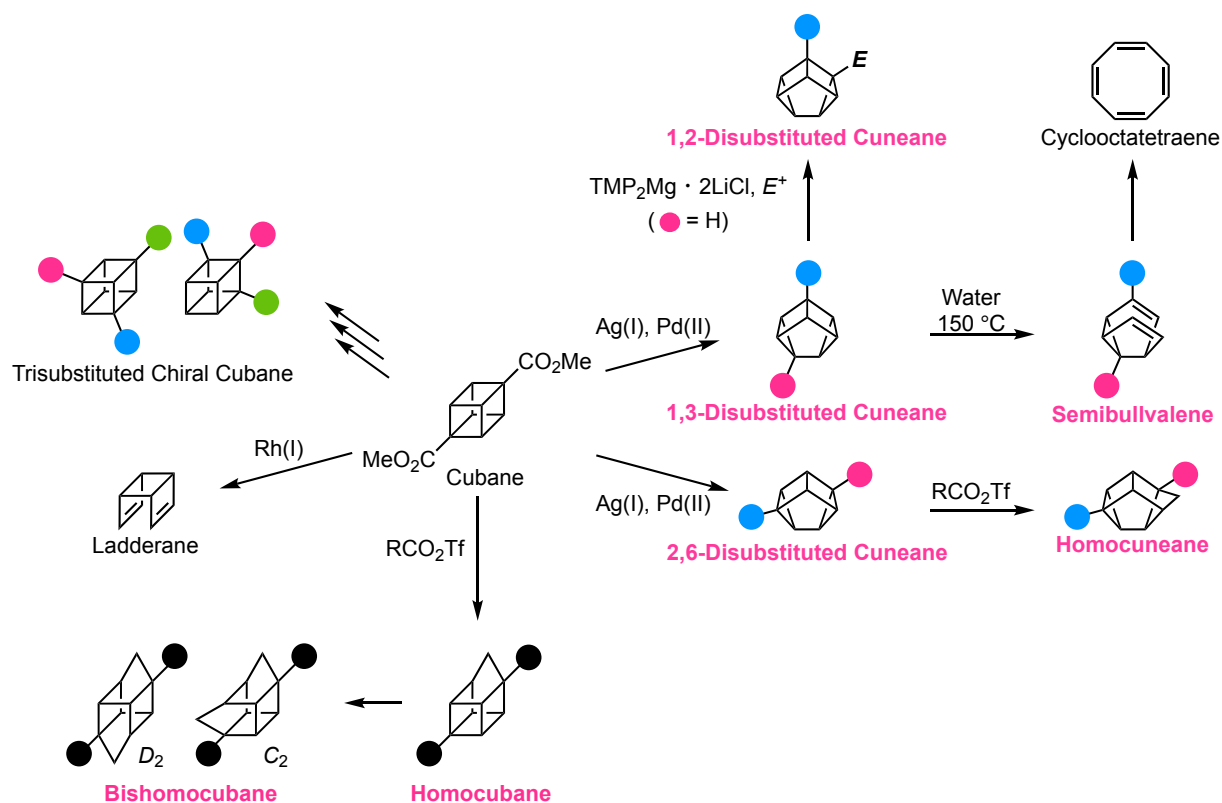


Figure 2. Comprehensive synthesis of a group of optically active caged hydrocarbon molecules.

2. Synthesis of Chiral Caged Hydrocarbon Molecules

2.1 Cubane

Cubane is a hydrocarbon molecule that can have substituents in eight directions, and many researchers have developed various reactions such as the introduction and removal of substituents on the cubane skeleton, and have achieved various multiply substituted derivatives.^{2,3,13} In the case of a trisubstituted derivative, the cubane skeleton itself has the potential to express chirality.^{3,6,7,8}

The chirality of cubane can be readily understood by considering the two regular tetrahedrons (blue and red) that can be formed by connecting four of the eight vertices of cubane (Figure 3).^{6a} To introduce chirality into the cubane framework, it is sufficient to make one of the two regular tetrahedron asymmetric. Given that two substituents are unable to form a regular tetrahedron with an asymmetric structure, it can be concluded that a disubstituted cubane should not possess chiral properties. However, when different substituents are introduced at the three vertices of a regular tetrahedron, it becomes chiral (1,3,5-type: Figure 3, left). The other type is the 1,2,3-trisubstituted compound (Figure 3, right). This is when two different substituents are introduced into one regular tetrahedron, and the third substituent is at position 2 of the other regular tetrahedron. At this time, the substituent at position 2 can be different from or the same as the substituent at position 1 or 3, and the substituent at position 2 makes positions 5 and 7 non-equivalent (1,2,3-type; Type A: $\textcircled{1} \neq \textcircled{2} \neq \textcircled{3}$, Type B: $\textcircled{1} = \textcircled{2} \neq \textcircled{3}$).

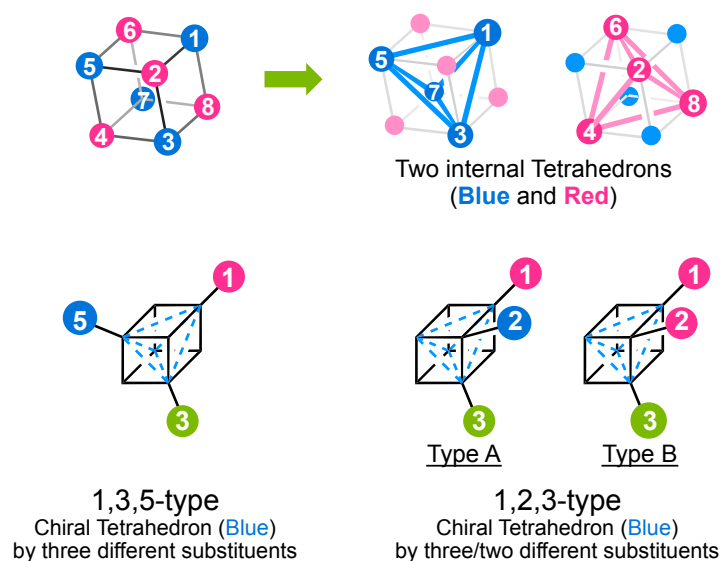


Figure 3. Chirality of trisubstituted cubanes.

Although cubane is often compared to benzene as a fundamental molecular scaffold, the site-selective introduction of substituents into cubane is not as well-established as it is for benzene. In the case of benzene, Friedel-Crafts reactions are commonly used, but for cubane, the cationic equivalent does not undergo direct substitution reactions. Although the fact that the formation of cubyl radicals is more likely than that of phenyl radicals is a distinct advantage in the functionalization of cubane, developing site-selectivity in radical generation reactions is not an easy task. Fortunately, in cubane, *ortho*-metalation can be performed using amides as directing groups (Directed *ortho*-Metalation: DoM). This method has become the most reliable approach for site-selective functionalization in cubane system. Cubene chemistry, which corresponds to benzyne, has long been of interest about CSB, and it is a field expected to develop further in the future. The substitution reactions on the cubane skeleton are summarized in Figure 4.

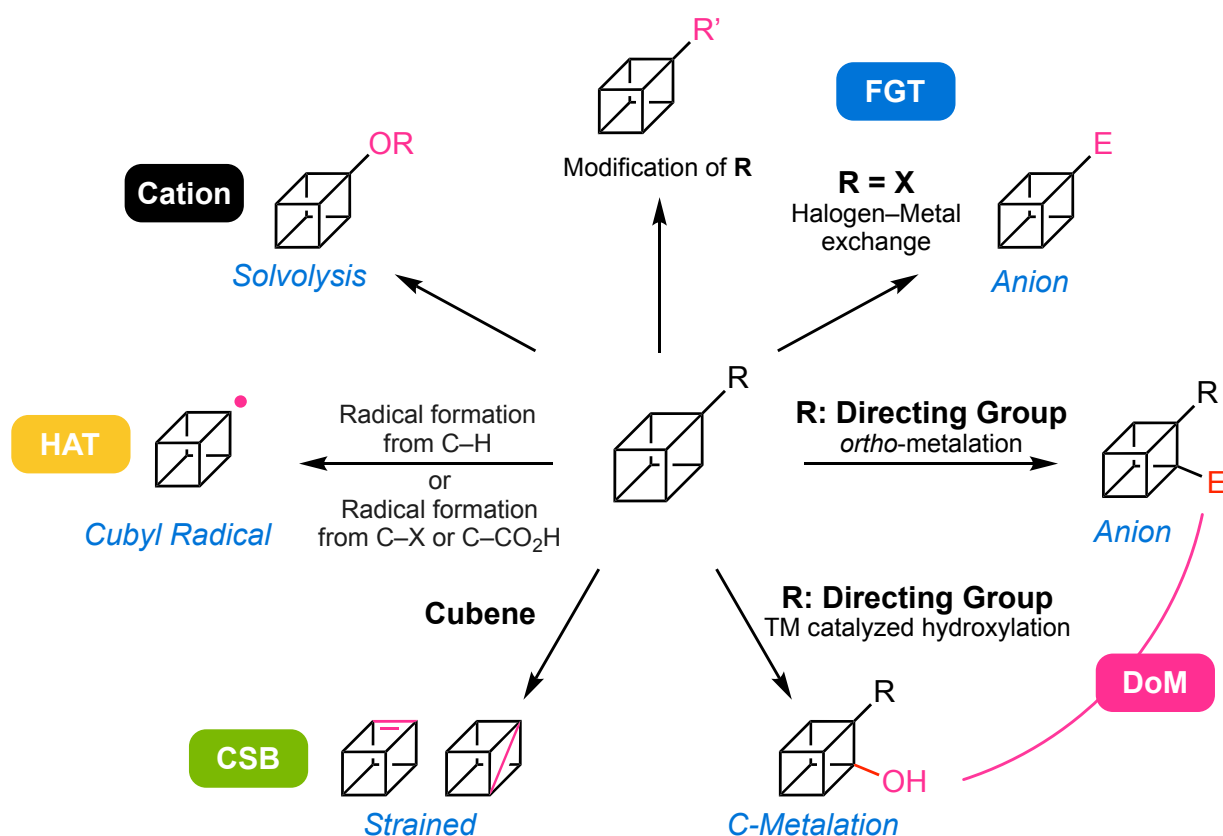
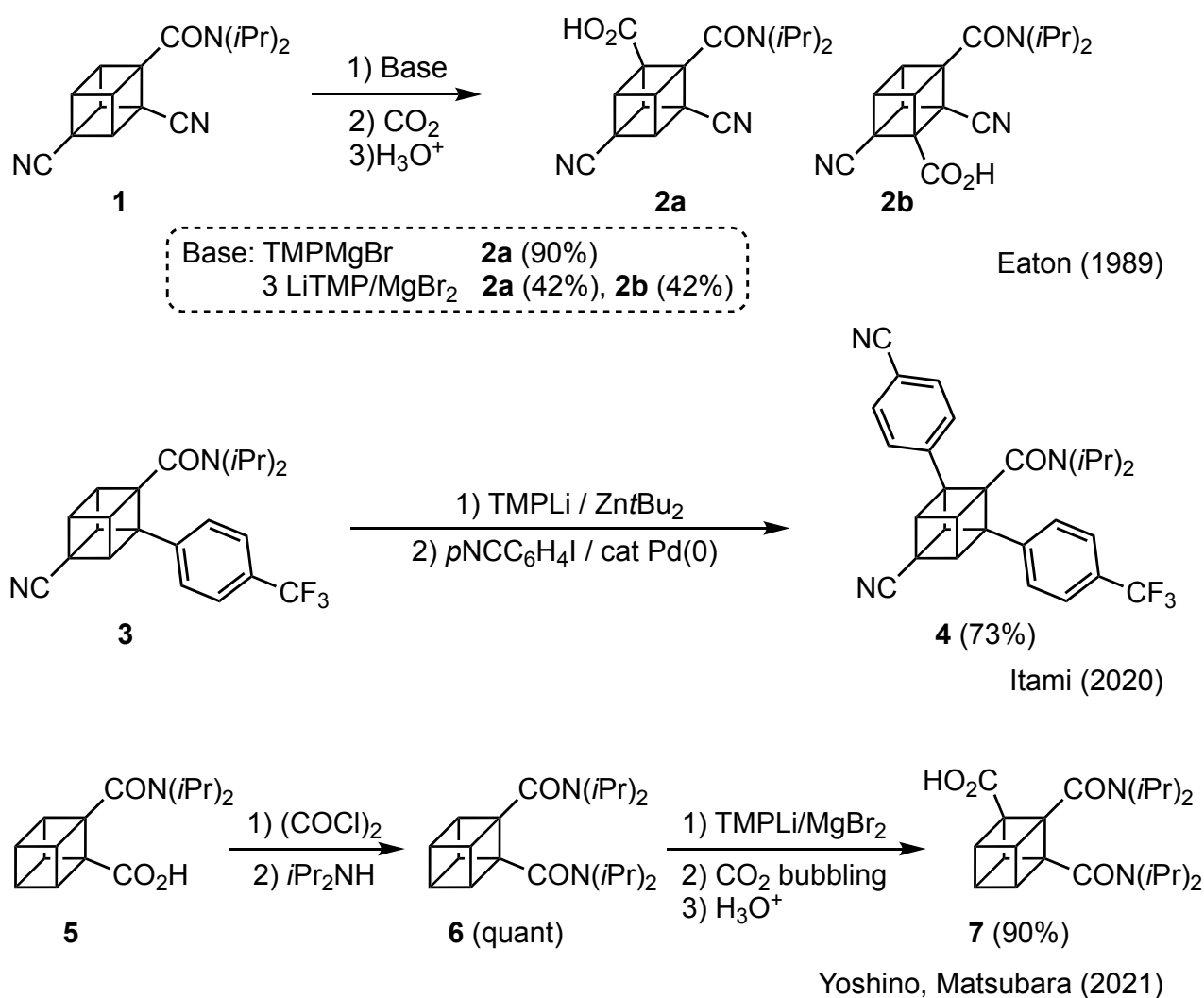


Figure 4. Substituent introduction in cubane skeletons.

2. 1. 1 Synthesis of 1,2,3-Trisubstituted Cubanes

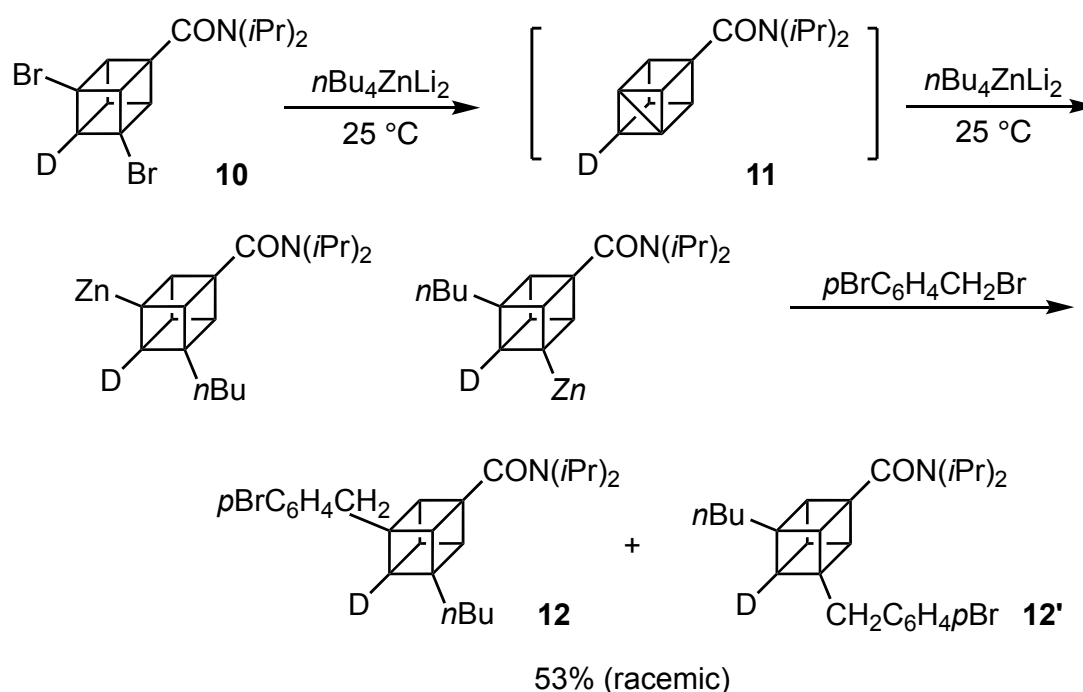
The synthesis of 1,2,3-trisubstituted cubane can be achieved by DoM on two occasions, utilizing the directional group at position 2. As previously stated, 1,2,3-trisubstituted cubane is a chiral molecule. Type A was initially synthesized by Eaton et al. through the implementation of DoM on cubane carboxamide.^{8a} Subsequently, chiral cubane **4** was synthesized using the same DoM method, and it was shown that it could be separated using chPLC.^{8b} In addition, the synthesis of Type B chiral cubane **7** was achieved by Yoshino and Matsubara et al. (Scheme 1).^{6a}



Scheme 1. Preparation of 1,2,3-trisubstituted cubanes.

2. 1. 2. Synthesis of 1,3,5-Trisubstituted Cubanes

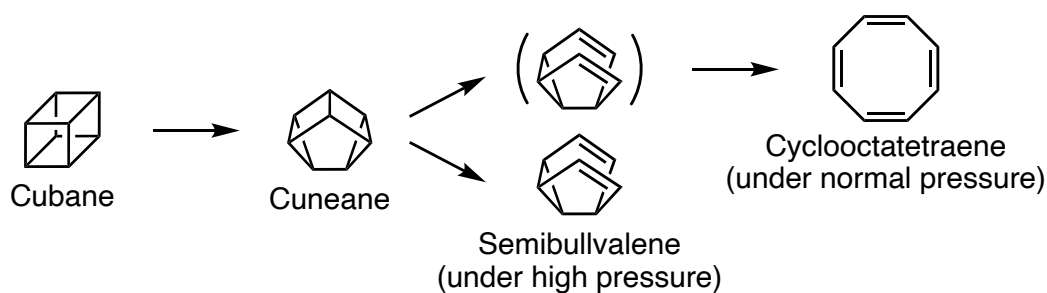
The synthesis of 1,3,5-trisubstituted cubane is even more challenging than that of 1,2,3-trisubstituted cubane, as the direct application of the DoM method is not feasible. In order to synthesize the 1,3,5-trisubstituted compound, it is necessary to repeat the introduction of different substituents to the meta position. Yoshino, Matsubara and co-workers synthesized a chiral 1,3,5-trisubstituted cubane starting from an achiral dibromide **10**, which was synthesized by HAT reaction (Scheme 2). When $n\text{Bu}_4\text{ZnLi}_2$ is reacted with **10**, two bromine atoms are eliminated to form 1,3-cubene **11**, which has a CSB (Charge Shift Bond). This highly reactive bonds reacted with an anionic *n*-butyl group to form an *n*-butylated cubyl metal species, which can be quenched by an electrophile. The 1,3,5-trisubstituted cubane obtained by this method is a racemic mixture, and can be separated into **12** and **12'** by optical resolution using cHPLC. After the resolution by a preparative cHPLC, the obtained both pure enantiomers showed opposite optical rotations, and it was possible to isolate the optically active 1,3,5-trisubstituted cubane for the first time.⁷



Scheme 2. Preparation of the chiral trisubstituted cubane as a racemic mixture (**12** and **12'**).

2. 2. Isomers of Cubane

Thermally stable regular hexahedral cubane begins to decompose when the temperature exceeds 230 °C and undergoes skeletal isomerization and finally becomes cyclooctatetraene. The controlled vapor phase reaction was shown by Walsh (Scheme 3).^{14a} During this decomposition process, cubane is sequentially isomerized into various fused cyclic polyhedral hydrocarbons. The first constitutional isomerized product, cuneane, is a stable and isolable cage-like hexahedral hydrocarbon with 3-membered (×2), 4-membered (×2), and 5-membered rings (×2). On the way to the destitative cyclooctatetraene from cuneane, semibullvalene was also supposed to be formed, these cuneane and semibullvalene are chiral molecule even with monosubstituted case. For example, achiral 1,4-disubstituted cubane can be converted into chiral cuneanes via $\text{Pd}^{2+}/\text{Ag}^+$ catalyzed isomerization. It is also known that when a cation is generated on the carbon next to cubane skeleton, the cage expands by one carbon via Wagner-Meerwein rearrangement and can be converted to homocubane. However, chirality does not occur in the homocubanes obtained in the first rearrangement. Two structural isomers, C_2 and D_2 -type, are possible in bishomocubane produced by two rearrangements at 1 and 4-position of cubane, with chirality occurring in the one with C_2 symmetry.



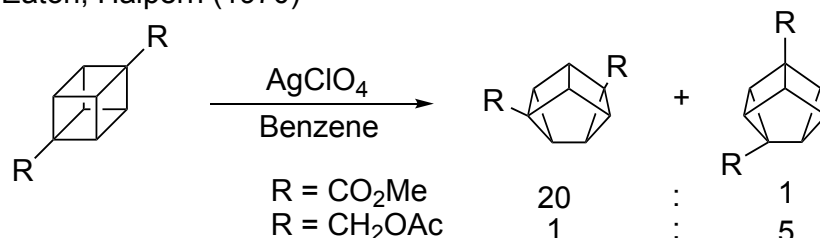
Scheme 3. Thermolysis of cubane in vapor phase.

2. 2. 1 Cuneane

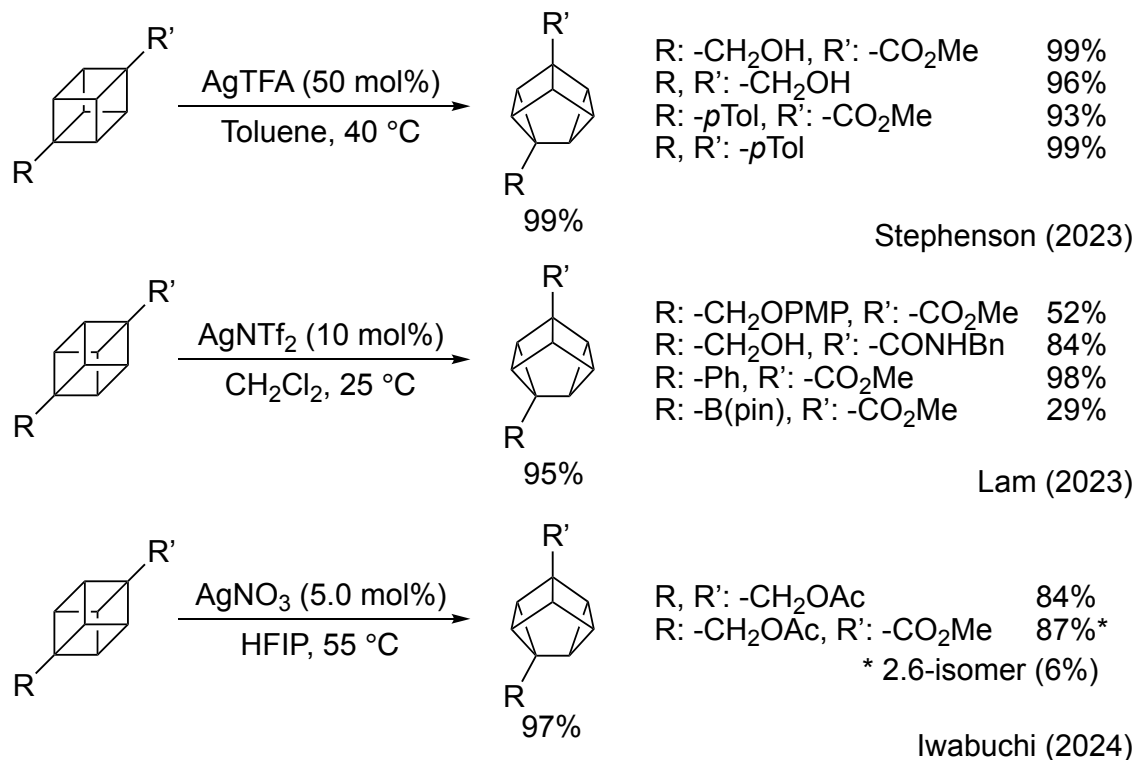
Cuneane (pentacyclo[3.3.0.0^{2,4}.0^{3,7}.0^{6,8}]octane) was first synthesized in 1968 as octamethylcuneane by photoisomerization of the diene octamethylsemibullvalene,¹⁵ and Eaton et al. reported a catalytic isomerization method for cubane in 1970 (Scheme 4a).⁹ In the isomerization of

1,4-disubstituted cubanes to cuneanes, the electronic properties of the substituents have a decisive effect on the selectivity. According to a report by Eaton et al. in 1970,⁹ if one of the 1,4-substituents is an electron-withdrawing group with a carbonyl group, 2,6-disubstituted cuneane is produced, and if not, 1,3-disubstituted cuneane is produced. In fact, it is known that cubane with an ester at the 1,4-position gives 2,6-disubstituted cuneane as the main product, while when the substituent is an acyloxymethyl group or other electron-donating group, 1,3-disubstituted cuneane is the main product (Scheme 4b).¹⁶

a) Eaton, Halpern (1970)



b) Isomerization of cubane to cuneane



Scheme 4. Preparation of cuneanes.

In the isomerization of cubane to cuneane, the cubane of O_h symmetry is isomerized to the cuneane of C_{2v} symmetry while resolving the distortion. By reducing the symmetry to C_{2v} symmetry, cuneane becomes capable of expressing chirality even from a single substitution. As shown in Figure 5, monosubstituted cuneanes with substituents at positions 2, 4, 6 or 8 are chiral, and in the case of disubstituted cuneanes, there are a total of eight types of chiral cuneanes, including 1,3-disubstituted cuneane. However, different substituents are required for 2,4-disubstituted and 2,8-disubstituted cuneanes.

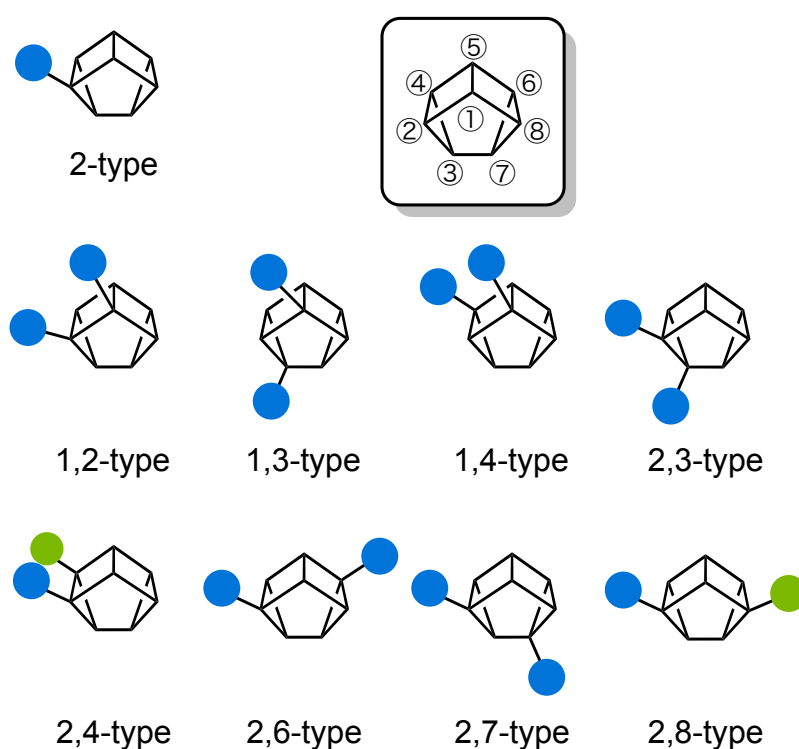
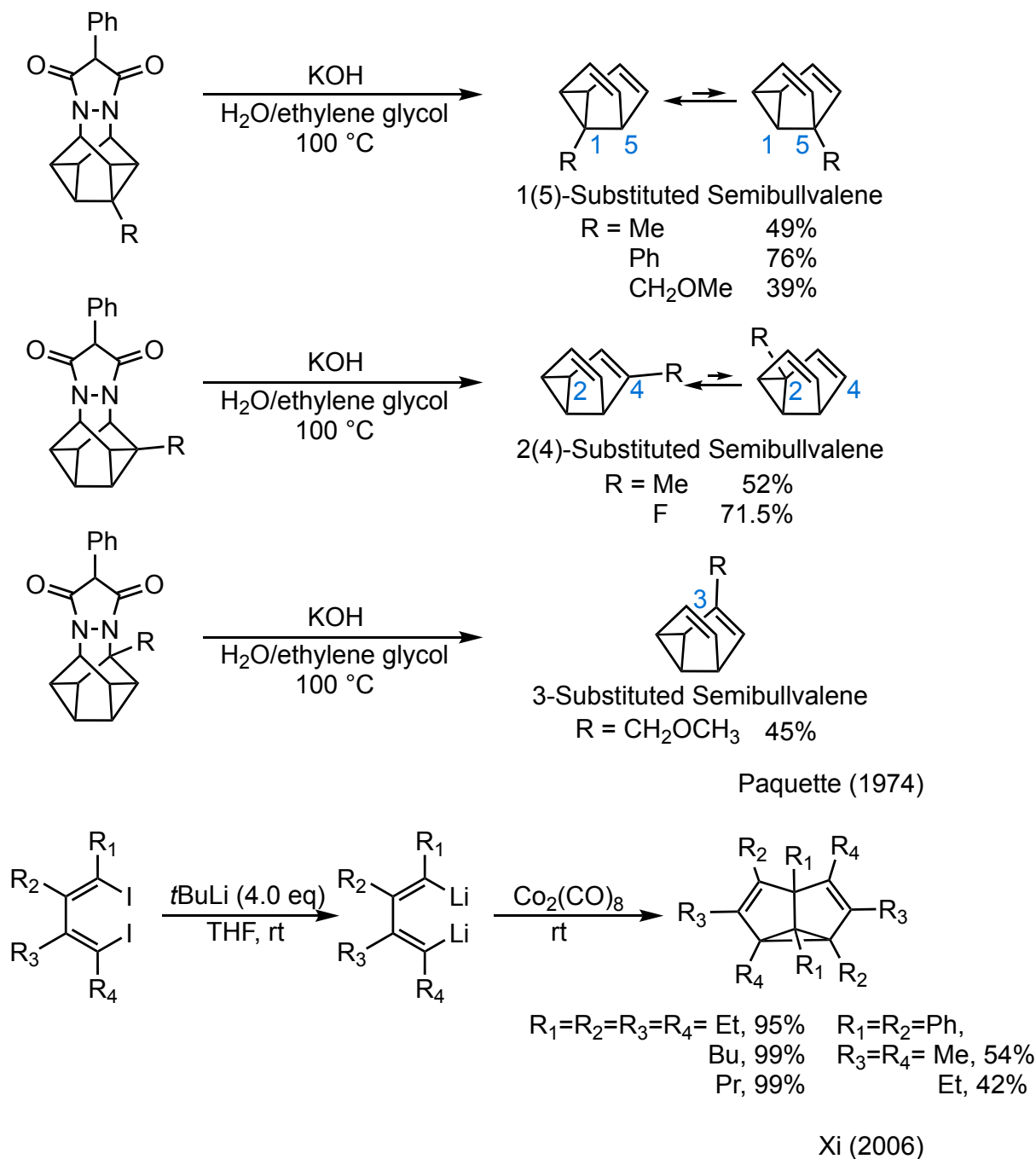


Figure 5. Chiral mono- and di-substituted cuneanes.

2. 2. 2 Semibullvalene

Semibullvalene (tricyclo[3.3.0.0^{2,8}]octa-3,6-diene) was first reported by Zimmerman and Grunewald et al. in 1966.¹⁷ Semibullvalene has attracted attention for its Cope rearrangement and homoaromaticity, and many theoretical and experimental studies have been conducted.¹⁸ The synthesis of semibullvalene consists of a series of classical organic transformations, as shown in Scheme 5, and various semibullvalene derivatives have been reported by Paquette.^{19a} Recently, in 2006, Xi and others

achieved the synthesis of polysubstituted semibullvalenes through a metal-mediated C–C bond formation reaction.^{19b}



Scheme 5. Preparation of semibullvalenes.

2.3 Homocubane, Bishomocubane, and Homocuneane

The polyhedral hydrocarbons obtained by inserting methylene groups into the edges of cubane are classified into homocubane, bishomocubane, and trishomocubane depending on the number of

methylene groups inserted.²⁰ Homocubane (Figure 6, top row) is achiral, but bishomocubane and trishomocubane can exhibit chirality. There are four types of bishomocubane, and only 1,3-bishomocubane (C_2 -bishomocubane), which has C_2 symmetry, is a chiral compound (Figure 6, middle). There are nine possible isomers of trishomocubane, and of these, only four of the chiral structures are shown in the lower part of Figure 6.

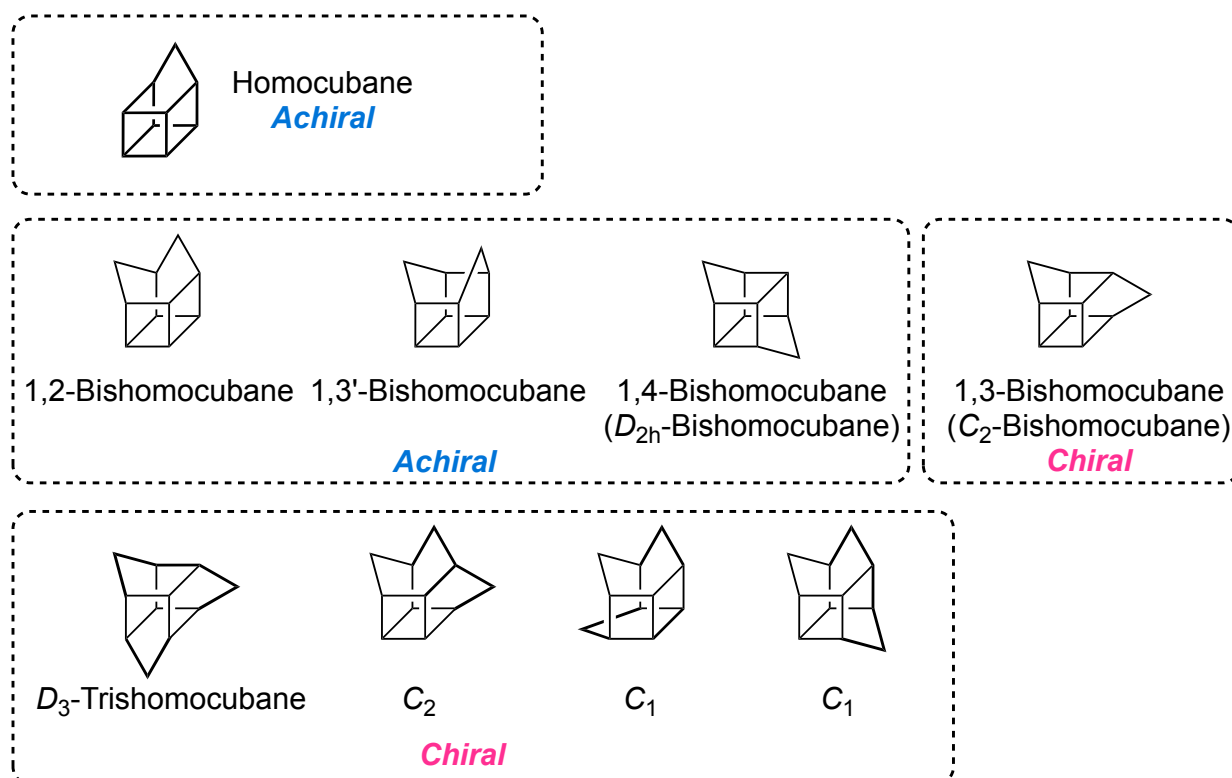


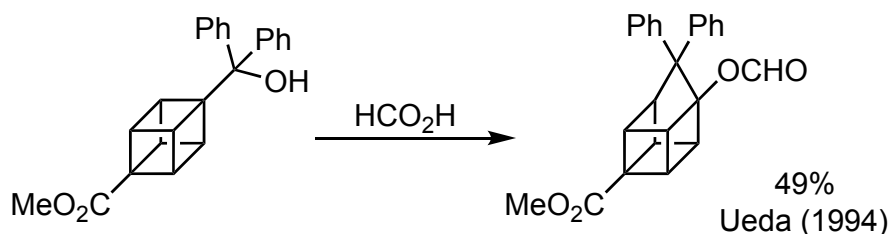
Figure 6. Homocubane, bishomocubane, and trishomocubane.

2.3.1 Homocubane

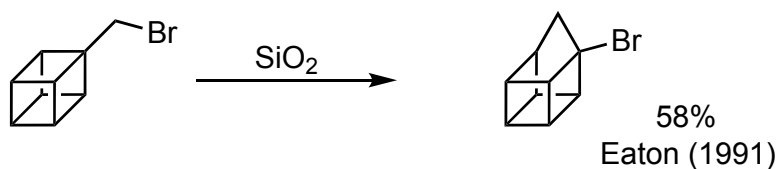
Homocubane (pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane) was reported by Dauben and Whalen in 1966.²¹ When a cation is formed on the carbon adjacent to the cubane, the cubane framework is expected to expand to resolve the distortion. The Wagner-Meerwein rearrangement accompanied by the formation of a stable tertiary cation was reported in 1994 (Scheme 6a).^{10a} However, in order to make wider use of cage-shaped molecules, reactions that contain an equivalent amount of primary cations, which are difficult to produce, are preferable, as unnecessary substituents are not desirable. An example of this is the ring expansion reaction of bromomethyl cubane using SiO₂ reported by Eaton

et al. in 1991 (Scheme 6b).²² Recently, it has also been shown that a similar reaction can also proceed with silver catalysts (Scheme 6c).^{16b}

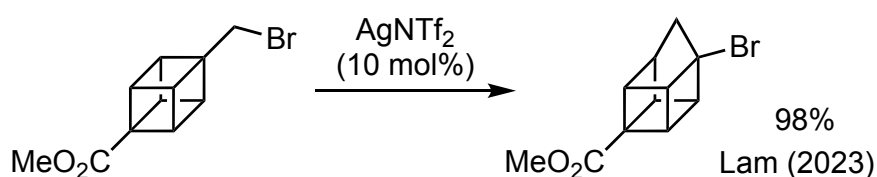
a) Wagner-Meerwein Type Rearrangement



b) Ring Expansion Reaction of Bromomethylcubane with SiO_2



c) Ring Expansion Reaction of Bromomethylcubane with Ag Catalyst



Scheme 6. Preparation of homocubanes.

2. 3. 2 Bishomocubane

Here, the author will describe the chiral C_2 -bishomocubane (1,3-bishomocubane, pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane) among the isomers of bishomocubane. When methylene is inserted into the $\text{C}2\text{--C}3$ and $\text{C}5\text{--C}6$ edges, an *M*-bishomocubane is formed, which is twisted counterclockwise around the $\text{C}1\text{--C}4$ axis. The chirality of C_2 -bishomocubane can be explained by atropisomerism (Figure 7). In the example given by Ueda, it has been demonstrated that the chiral C_2 -bishomocubane was produced as the main product in the sequential ring expansion of 1,4-bis(2-hydroxypropan-2-yl)cubane using the Wagner-Meerwein method (Scheme 7a).^{12a} As shown in Scheme 7b, the synthesis of optically active 1,3-bishomocubane by the build-up method was reported by Nakazaki et al.²³

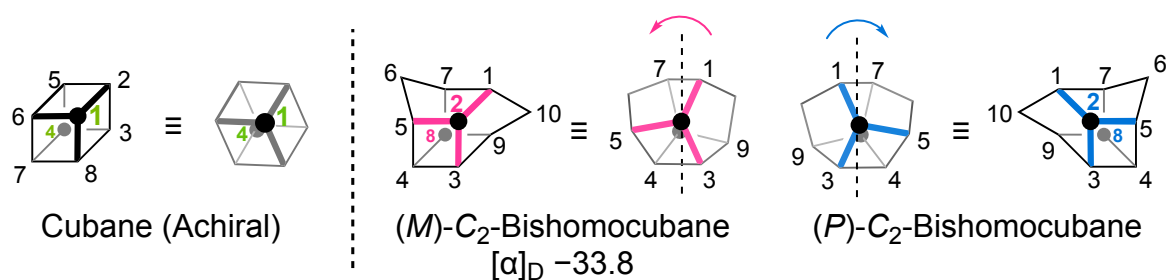
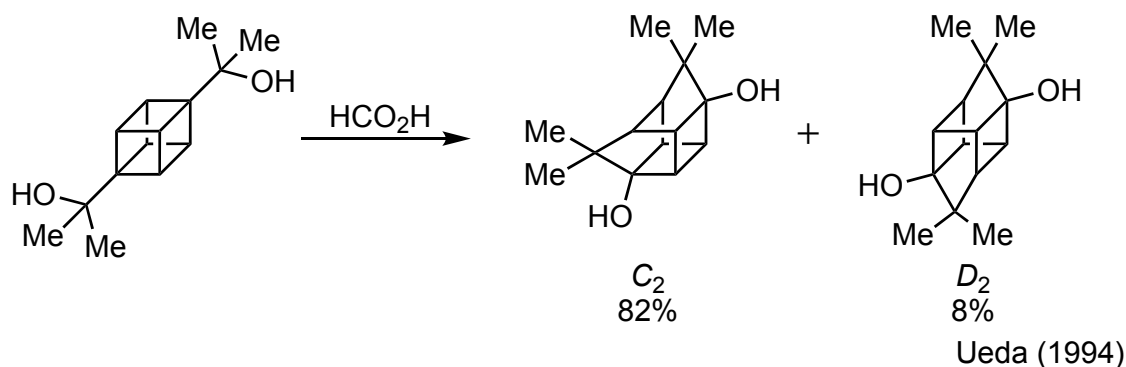
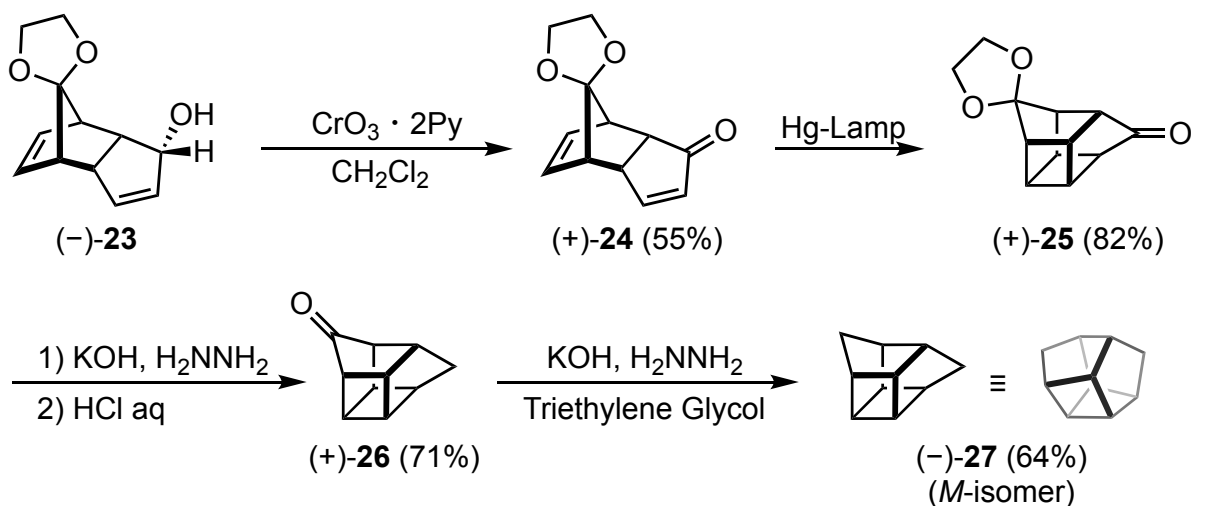


Figure 7. Atropisomerism of C₂-bishomocubane.

a) Acid catalyzed Wagner-Meerwein rearrangement of 1,4-bis(2-hydroxypropan-2-yl)cubane



b) The synthesis of optically active 1,3-bishomocubane

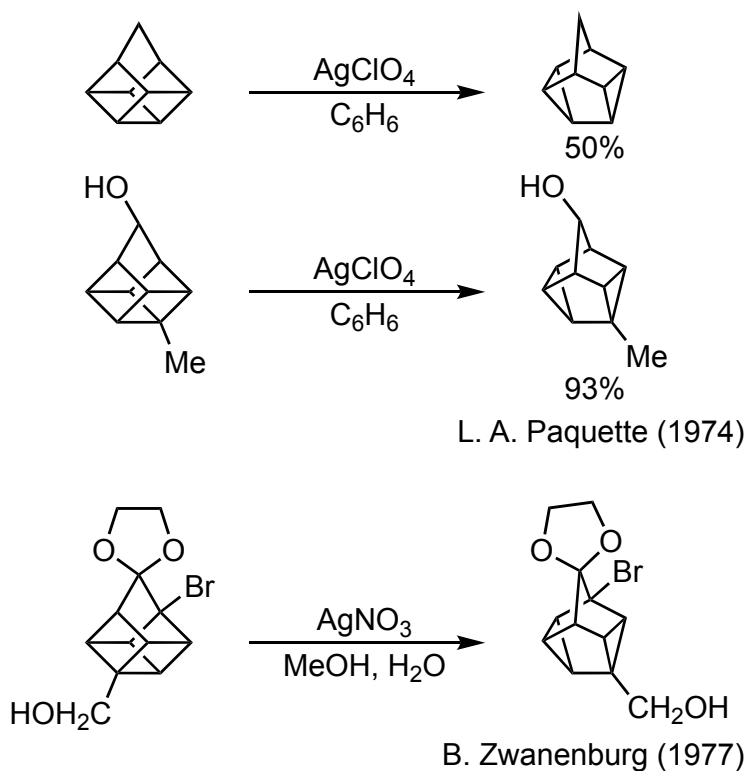


Nakazaki, Naemura (1977)

Scheme 7. Preparation of bishomocubanes.

2. 3. 3 Homocuneane

The isomerization of homocubane has been reported to produce homocuneane (pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane), in which a methylene group is inserted between C1 and C5 of cuneane. When homocubane is isomerized with silver, it becomes homocuneane, with a methylene inserted at the C1–C5 position of cuneane (Scheme 8).²⁴ Whereas cubane consists of eight equivalent C–C bonds, cuneane has four distinct types of C–C bonds. The examples shown in Scheme 8 are isomerized homocubanes. In contrast to these examples, no attempt has been made so far to insert a methylene group directly into cuneane itself. However, considering that cuneane exhibits chirality, it is expected that inserting a methylene group into chiral cuneane would yield a chiral homocuneane in a stereospecific manner.



Scheme 8. Rearrangements of homocubanes to homocuneanes.

3. Overview of this Thesis

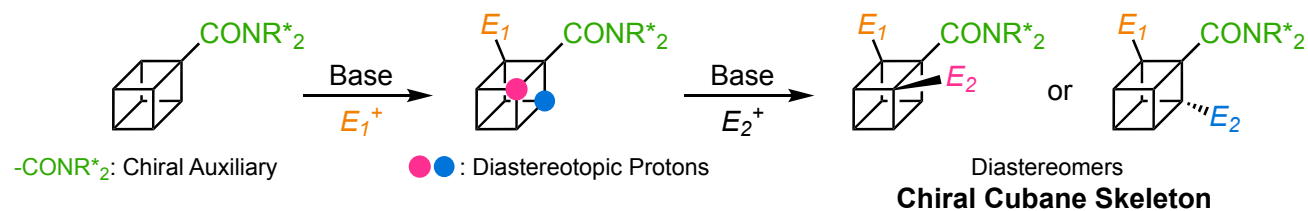
In this thesis, the author focuses on the introduction of chirality by decorating of highly symmetric cubane and by isomerizing of cubane skeleton to polyhedral hydrocarbons with the lower symmetry. In this thesis, the author primarily focuses on introducing chirality through the addition of substituents to the highly symmetric cubane structure. Following this, the work explores the generation of chirality via the isomerization of the cubane skeleton into lower-symmetry polyhedral hydrocarbons, such as cuneane and bishomocubane. Cubane has been attracting attention as a benzene bioisostere since early on. Furthermore, it is also possible to endow chirality by introducing substituents in a site-selective manner. However, the synthesis of chiral cubane is a complex multi-step reaction, and the difficulty of site selectivity has not yet been completely solved. Many cage-type compounds have been synthesized using build-up methods such as cycloaddition and condensation reactions. However, many of these reactions are very complex and do not have functional group tolerance, so it is difficult to introduce them as partial structures of bioactive molecules. Cubanes are very stable and highly symmetrical, and can be introduced as substructures. The method of increasing complexity by introducing chirality through scaffold editing after introducing cubane will be important in the future.

Based on the above, the author explores the possibility of “cubane scaffold editing”, which is the rapid introduction of chirality through structural isomerization of cubane, in addition to the expression of chirality through the “decoration” of cubane, as a method for more efficiently synthesizing chiral cage-type molecular skeletons. The polyhedral molecules that can be accessed by cubane scaffold editing were shown in Figure 2. Below is an overview of each chapter.

Chapter 1: Chiral Auxiliary-Directed Site-Selective Deprotonation of the Cubane Skeleton

The diastereoselective synthesis of trisubstituted cubanes was achieved using a chiral auxiliary. In order to establish chirality within the cubane skeleton, at least three substituents must be introduced at the appropriate positions. Ready conversion of cubane carboxylic acid to a chiral amide,

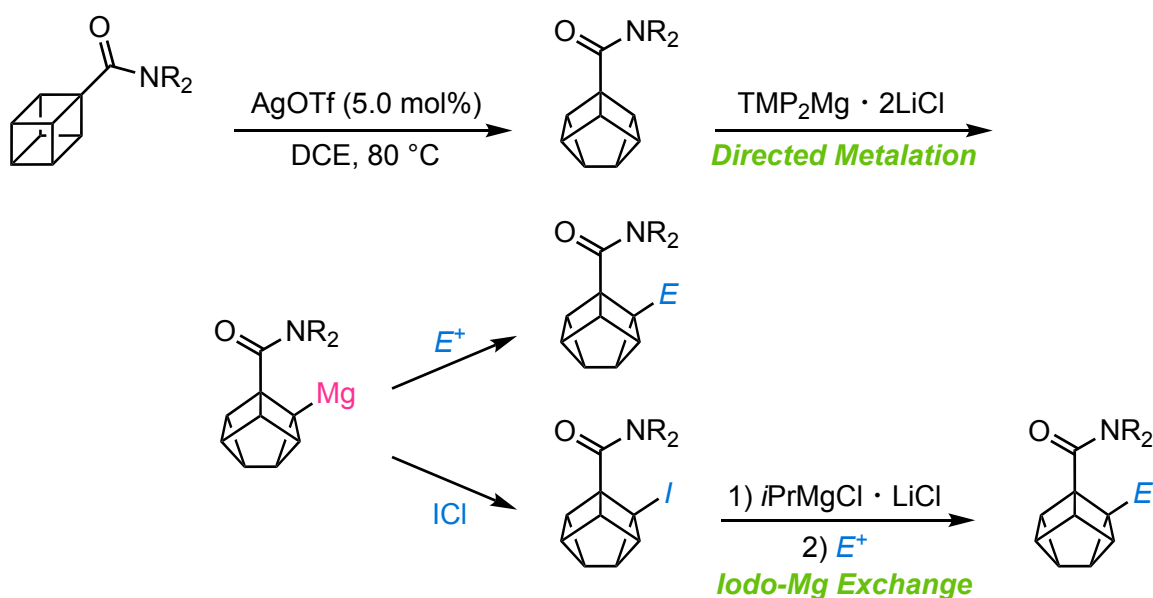
followed by sequential *ortho*-selective deprotonations and electrophilic trapping afforded the corresponding 1,2,3-trisubstituted cubanes in high diastereoselectivity.



Scheme 9. Overview of Chapter 1.

Chapter 2: Directed Metalation of 1-Cuneanecarboxamide: Simple Route to 1,2-Disubstituted Cuneanes

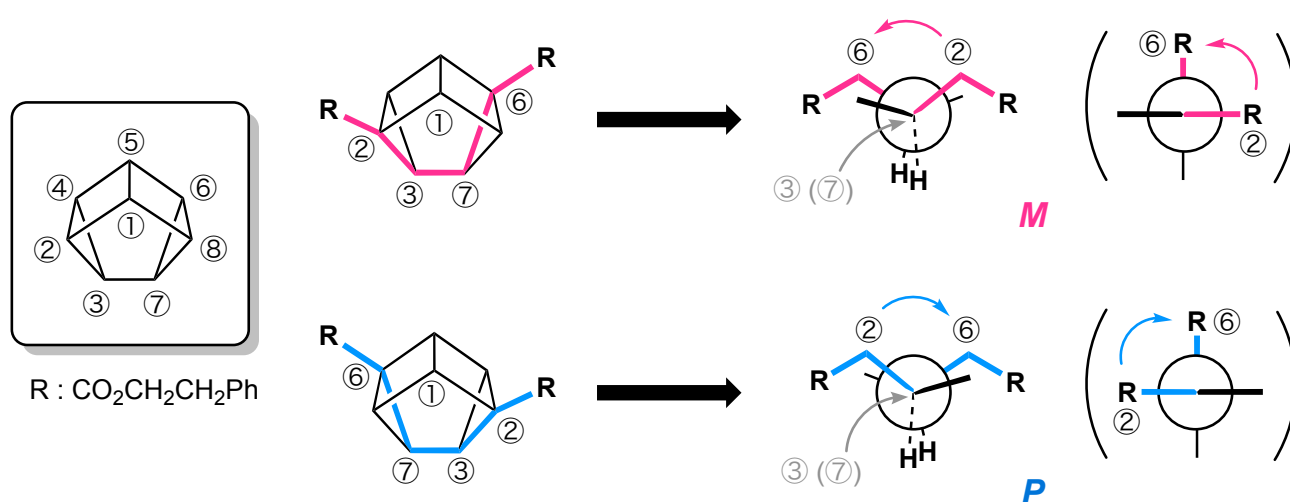
Cuneane is a structural isomer of cubane, and a stable C_{2v} symmetric hexahedron. The introduction of substituents into a cuneane has not been investigated, and the author found that site-selective deprotonation of 1-cuneanecarboxamide proceeds by treatment with $\text{TMP}_2\text{Mg} \cdot 2\text{LiCl}$. The metalated cuneane reacted with various electrophiles to give 2-substituted 1-cuneanecarboxamides, including 2-iodo-1-cuneanecarboxamide. The obtained iodide was converted into 2-metalated 1-cuneanecarboxamide by $i\text{PrMgCl}$, which also reacted with various electrophiles.



Scheme 10. Overview of Chapter 2.

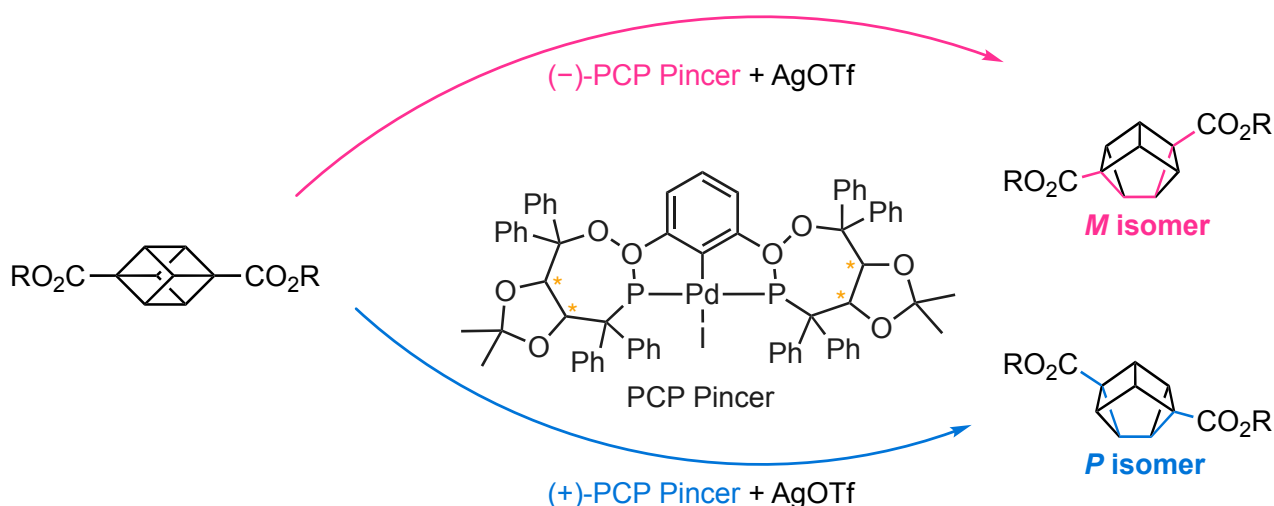
Chapter 3: Studies for Absolute Configuration of Chiral 2,6-Cuneanedicarboxylic Acid Esters

The unique polyfused cyclic hydrocarbon, cuneane, was obtained by structural isomerization of cubane. Eaton has reported that cubane-1,4-dicarboxylic acid ester is selectively isomerized to cubane-2,6-dicarboxylic acid ester catalyzed by silver(I). The cuneane has C_2 symmetry. Chiral resolution of bis(2-phenylethyl) cuneane-2,6-dicarboxylate by chiral HPLC was performed; determination of the absolute configuration of each enantiomer was performed based on ECD spectra and DFT calculation.



Chapter 4: Catalytic Asymmetric Synthesis of 2,6-Disubstituted Cuneanes through Enantioselective Constitutional Isomerization of 1,4-Disubstituted Cubanes

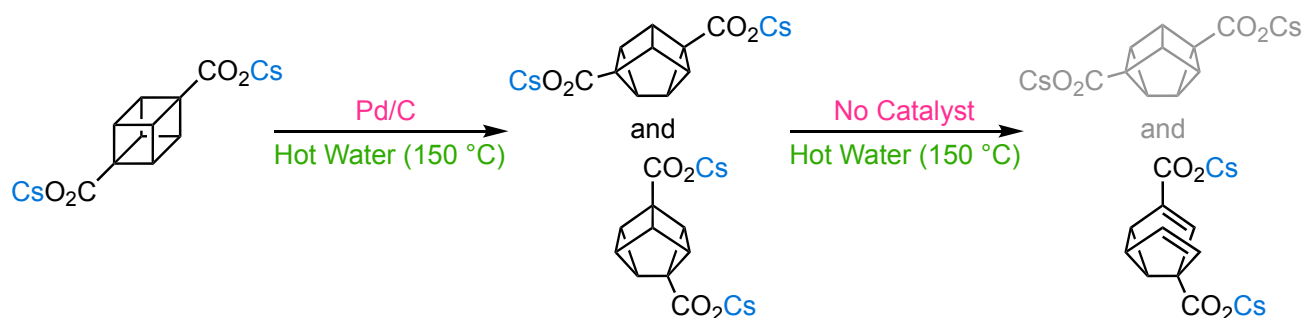
2,6-Disubstituted cuneane has potential as a *p*-substituted benzene bioisostere and a novel chiral scaffold. It is a constitutional isomer of a 1,4-disubstituted cubane obtained via a metal-catalyzed skeletal rearrangement. Unlike the highly symmetrical 1,4-disubstituted cubane, the isomerized 2,6-disubstituted cuneane is a chiral molecule possessing C_2 symmetry. Examining various chiral catalysts revealed that the Pd-pincer catalyst provides a good asymmetric induction.



Scheme 12. Overview of Chapter 4.

Chapter 5: Constitutional Isomerization of Cubane to Semibullvalene via Cuneane in Hot Water

The construction of cage-type hydrocarbon scaffolds, potential bioisosteres for benzene, often involves multiple steps, making their selective syntheses challenging. However, by employing a scaffold editing technique that leverages the isomerization of the highly symmetrical cubane as a precursor, these can be synthesized more efficiently with fewer steps. In this chapter, the author presents a method for the selective synthesis of semibullvalene-1,3-dicarboxylic acid with a good yield, starting from dicesium cubane-1,4-dicarboxylate, using a reaction in hot water.

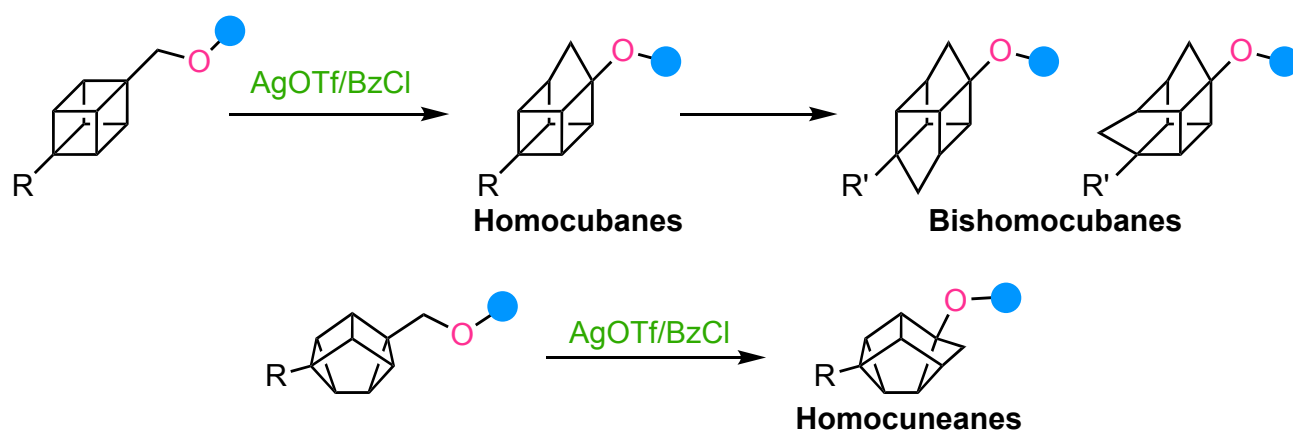


Scheme 13. Overview of Chapter 5.

Chapter 6: Scaffold Editing of Cubanes into Homocubanes, Homocuneanes via Cuneanes

In this chapter, the author identifies a catalyst that facilitates the efficient scaffold isomerization of cubanes into homocubanes. This approach, which involves the direct synthesis of

homocubanol esters, is promising as a novel method for the synthesis of phenoxy bioisosteres. Additionally, the author observed that the isomerization of 1,4-bis(acyloxymethyl)cubane results in the generation of both D_2 - and C_2 -symmetrical bishomocubanes. The same catalyst was also applied to the isomerization of acyloxymethylcuneanes, producing homocuneanol esters.



4. Conclusion

My fascination with the structure of cubane, a perfectly cubic hydrocarbon, led me to embark on this doctoral research. While cubane is often highlighted for its thermodynamic properties as a highly strained molecule, I was drawn to its stereochemical potential as the smallest unit capable of accommodating substituents in eight spatial directions. Approaching this molecule from the perspective of imparting optical activity—a significant challenge in stereochemistry within organic chemistry—posed a particularly ambitious research task.

Initially, I focused on a classical strategy, akin to assembling a molecular model, by introducing three substituents onto the cubic framework, which yielded the results presented in Chapter 1. However, as described from Chapter 2 onwards, I shifted my approach to explore the induction of optical activity through deformation of the cubic structure. This shift in perspective produced unexpected results and led to the conception and validation of the "cubane skeleton editing".

Through this work, I am confident that I have demonstrated a novel synthetic approach for constructing optically active cage-like hydrocarbon frameworks.

5. General remarks compatible to all the experimental parts in the present Thesis

All manipulations of oxygen- and moisture-sensitive materials were conducted under an argon atmosphere.

Nuclear magnetic resonance spectra were taken on Varian UNITY INOVA 500 (^1H , 500 MHz; ^{13}C , 125.7 MHz) spectrometer using chloroform for ^1H NMR as an internal standard ($\delta = 7.26$ ppm), CDCl_3 for ^{13}C NMR as an internal standard ($\delta = 77.0$ ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity, integration, and coupling constants (Hz). High-resolution mass spectra were obtained with a JEOL JMS-700 spectrometer for EI and with a Thermo Fisher SCIENTIFIC EXTRACTIVE spectrometer for ESI and APCI. Infrared (IR) spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Melting points were determined using a YANAKO MP-500D. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence. ECD spectra were recorded with a JASCO J-820 spectrodichrometer. A 1 cm quartz cell was used for these measurements. The magnitude of the ECD signal is expressed in terms of molar circular dichroism $\Delta\epsilon / \text{M}^{-1} \text{cm}^{-1}$. Specific rotations were recorded with a JASCO DIP-1000. The X-ray structural determination was performed on a Rigaku/Saturn724+ CCD diffractometers using graphite-monochromated Mo K α radiation ($\lambda = 0.71075$ Å) at 153 K. TLC analyses were performed by means of Merck Kieselgel 60 F254 (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and a molybdenum blue followed by heating (250 °C). Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–100 μm). PLC purification was performed by means of ANALTRCH UNIPLATE (20 cm x 20 cm x 1 mm). Purification was also performed by YAMAZEN AKROS Smart Flash AI-580S.

Dimethyl cubane-1,4-dicarboxylate was purchased from TCI. Tetrahydrofuran, dehydrated stabilizer free —Super— was purchased from Kanto Chemical Co., stored under argon, and used as it is. Unless otherwise noted, commercially available reagents were used without purification.

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Chapter 1

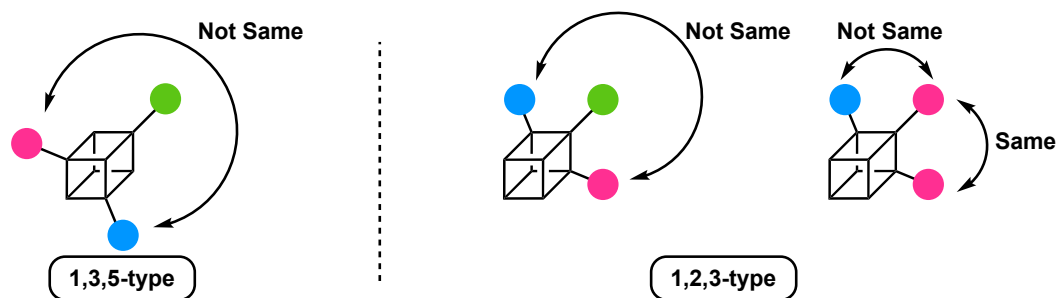
Chiral Auxiliary-Directed Site-Selective Deprotonation of the Cubane Skeleton

The diastereoselective synthesis of trisubstituted cubanes was achieved using a chiral auxiliary. In order to establish chirality within the cubane skeleton, at least three substituents must be introduced at the appropriate positions. Ready conversion of cubane carboxylic acid to a chiral amide, followed by sequential *ortho*-selective deprotonations and electrophilic trapping afforded the corresponding 1,2,3-trisubstituted cubanes in high diastereoselectivity. This route opens new possibilities for the preparation of enantio-enriched cubanes.

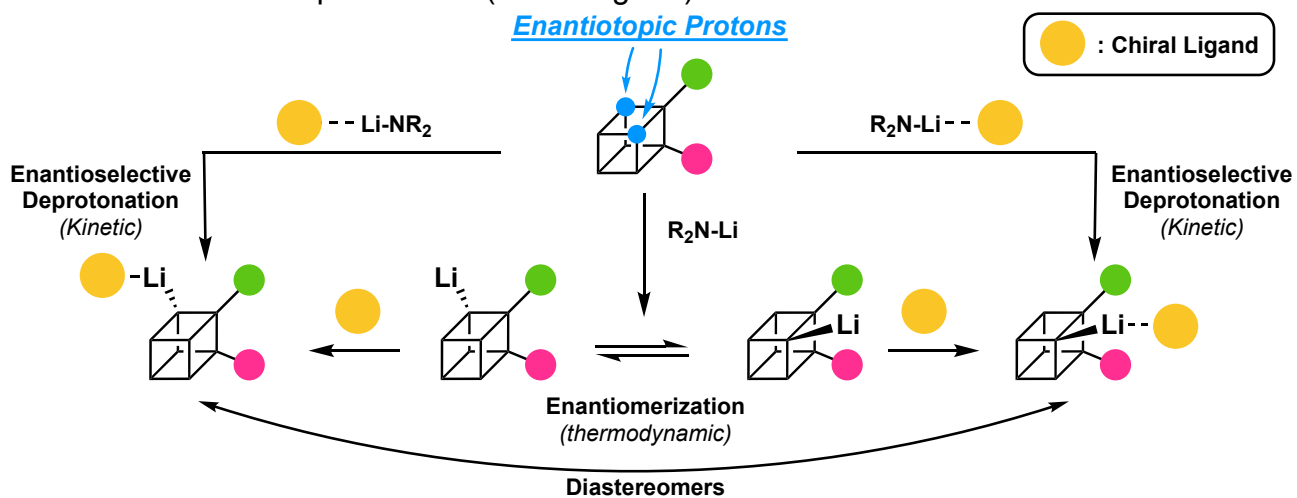
1.1 Introduction

Cubane, the smallest hydrocarbon capable of arranging functional groups in eight ordered spatial directions, has recently been deployed as a scaffold in the design of bioactive molecules since Eaton reported its practical synthesis in 1964.^{1,2} The most notable feature has been its use as a benzene bioisostere due to a number of common molecular similarities.³ Substitution using cubane in conventional bioactive molecules containing benzene rings has been expected to alleviate hydrophobic interactions and increase metabolic resistance.⁴ Previous studies concerning benzene bioisosteres have not considered imparting chirality to the cubane skeleton, as the benzene ring in most situations is not chiral. However, from a chiral scaffold perspective it is an attractive skeleton. As cubane is highly symmetric, access to asymmetric variants can be constructed by introducing at least three substituents site-selectively.⁵ Currently, there are two types of chiral trisubstituted cubane systems known: 1,2,3-substitution^{5,6} and 1,3,5-substitution.⁷ In the former case, in addition to the case where all three substituents are different, those having the same adjacent substituents also have chirality (Figure 1-1a). For 1,3,5-substitution, all substituents must be different. However, there have been no reported attempts to construct chiral 1,3,5-substituted cubanes under asymmetric control. Preparation of racemic 1,2,3-substituted cubanes was reported by Eaton, who showed that sequential *ortho*-metalation can be undertaken using an amide directing group.⁸ In this case, selective deprotonation of 1,2-disubstituted cubanes would be crucial to obtain optically active 1,2,3-trisubstituted cubanes. An approach using enantiotopic deprotonation by *n*BuLi in the presence of sparteine is one possible route (Figure 1-1b).⁹ However, this method often requires epimerization of the organolithium to form a diastereomerically preferred complex with chiral amine ligands under equilibrium, which is not suited to the cubane system. Conversely, introduction of a chiral auxiliary as an amide, would induce diastereoselective deprotonation kinetically, and thus racemization would be unlikely. Anderson et al. recently utilized chiral bis(1-cyclohexylethyl)amine as an asymmetric auxiliary in the deprotonation of bicyclo[1.1.0]pentane amides.¹⁰ Given these observations this chiral auxiliary to attempt the preparation of optically active trisubstituted cubanes as disclosed herein (Figure 1-1c).

a) Trisubstituted Chiral Cubanes



b) Enantioselective Deprotonation (Chiral Ligand)



c) Diastereoselective Deprotonation

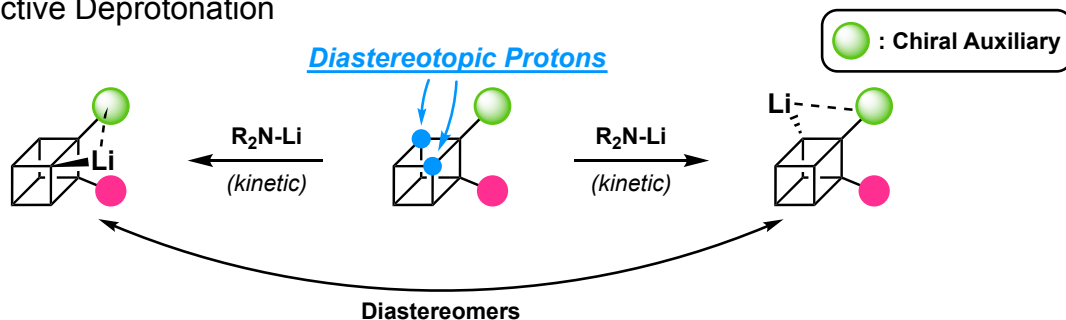
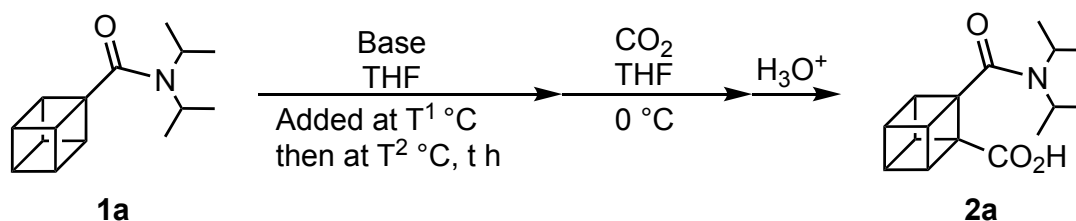


Figure 1-1. (a) Optically active trisubstituted cubanes. (b) Enantioselective deprotonation using a chiral ligand. (c) Diastereoselective deprotonation using a chiral auxiliary.

1.2 Results and Discussion

Firstly, deprotonation followed by treatment with carbon dioxide for *N,N*-diisopropylcubane-1-carboxamide (**1a**) was examined to determine suitable reagents and conditions (Table 1-1). Eaton et al. had previously described *ortho*-metalation of *N,N*-diisopropylcubane-1-carboxamide using 10 equivalent of TMPLi in the presence of 7 equivalent of MgBr₂•OEt₂.^{5,8} The introduction of an electrophile to **1a** under these original conditions gave **2a** in 72% yield (entry 1). Schlosser's mixed base, which was prepared following original procedure,¹¹ was also examined, but gave a complex mixture (entry 2). TMPMgCl•LiCl, which was developed by Knochel et al.,¹² was also pursued, but resulted in low conversion even at 25 °C (entries 3-5). The use of an excess amount of the higher order complex base TMP₂Mg•2LiCl¹³ was found to be effective for *ortho*-metalation, and afforded the desired carboxylic acid **2a** in 80 % yield after treatment with CO₂ gas (entry 7).

Table 1-1. *ortho*-Metalation of **1a** with various bases.^a



entry	base (equiv)	T ¹ (°C)	T ² (°C)	t (h)	yield of 2a (%)	recov. of 1a (%)
1	TMPLi (10)/MgBr ₂ (7.0) ^b	−20	0	16	72	26
2	<i>n</i> BuLi (2.0)/ <i>t</i> BuOK (2.0) ^c	−40	−40	6	<5	20
3	TMPMgCl•LiCl (2.5) ^d	−20	−15	18	<1	98
4	TMPMgCl•LiCl (2.5)	−15	0	18	<1	95
5	TMPMgCl•LiCl (3.0)	−15	25	18	16	79
6	TMP ₂ Mg•2LiCl (1.0) ^e	−15	0	18	9	86
7	TMP ₂ Mg•2LiCl (3.0)	−15	0	18	80	16

^a All reactions were performed using 0.25 mmol of **1a**. ^b See ref 8. ^c See ref 11. ^d See ref 12. ^e See ref 13.

Table 1-2. *ortho*-Metalation of cubane-1-carboxamide with chiral amines.^a

entry	R ₂ NH in 1	yield of 3 (%)	recov. of 1 (%)
1	diisopropylamine (1a)	80 (3a)	<5
2	bis((<i>R</i>)-1-cyclohexylethyl)amine (1b)	95 (3b)	<5
3	(<i>R</i>)-2-(methoxymethyl)pyrrolidine (1c)	– (3c) ^b	<5
4	bis((<i>R</i>)-1-phenylethyl)amine (1d)	18 (3d) ^b	21

diisopropylamine

bis((*R*)-1-cyclohexylethyl)amine

(*R*)-2-(methoxymethyl)pyrrolidine

bis((*R*)-1-phenylethyl)amine

^a All reactions were performed using 0.5 mmol of **1** and 1.5 mmol TMP₂Mg·2LiCl.

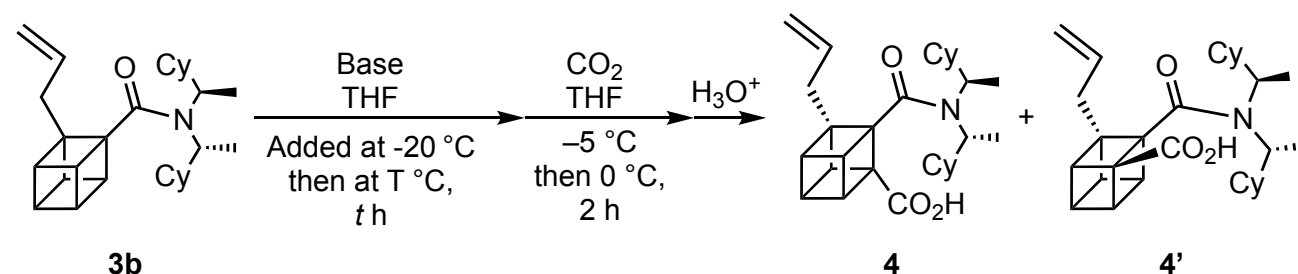
^b A complex mixture was observed.

Using the optimized conditions in Table 1-1, various cubane-1-carboxamides **1a-d** were examined for allylation efficiency; after the deprotonation procedure, the resulting mixture was treated with allyl bromide in the presence of a catalytic amount of CuI. It was already reported that the bulky amine, such as *N,N*-diisopropylamine is necessary for cubanecarboxamide to perform the introduction of electrophiles on the cubane skeleton via directed deprotonation.¹⁴ As shown in Table 1-2, *N,N*-bis((*R*)-1-cyclohexylethyl)cubane-1-carboxamide (**1b**)¹⁰ as well as *N,N*-diisopropylcubane-1-carboxamide (**1a**) gave the corresponding allylated products **3a,b** in good yields. The amides of less-hindered amines such as **1c** gave a complex mixture (entry 3). The corresponding allylated product was obtained in the case of **1d**, but resulted in low yields (18%), although the reaction proceeded in 79% conversion (entry 4). The existence of an acidic and less hindered benzylic proton in **1d** was undesirable for the directed metalation process.

The sequential deprotonation was applied to **3b** to perform the site-selective introduction of an electrophile (Table 1-3). Eaton's procedure using TMPLi and MgBr₂^{6a} followed by treatment with

CO₂ gave the trisubstituted cubane in 31% yield (71/29) (entry 1). The more efficient deprotonation reagent shown in Table 1-1, TMP₂Mg•2LiCl, gave complex reaction mixture when **3b** was treated at 0 °C, although a small amount of the desired product **4** was isolated. The reason for the low yield was likely to be a result of the acidic protons at the allylic position. Hence, a lower reaction temperature for the deprotonation step was examined (entries 3 and 4). At –20 then –15 °C, **4** was obtained in 42% yield with the minor diastereomer **4'** in 8 % yield (84/16).

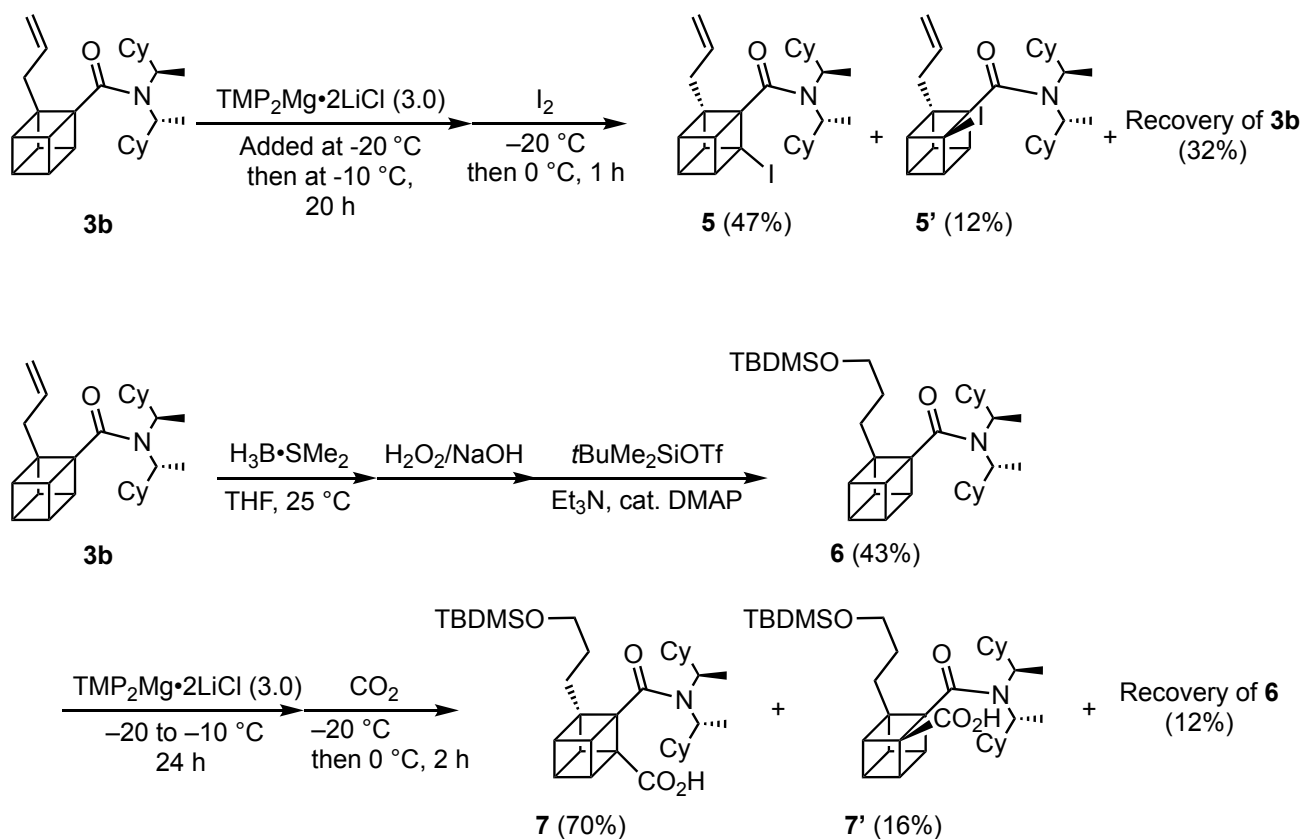
Table 1-3. Site-selective carboxylation via deprotonation of **3b**.^a



entry	base (equiv)	T (°C)	t (h)	yield of 4 (%)	yield of 4' (%)	recov. of 3b (%)
1	TMPLi (10)/MgBr ₂ (7.0)	0	16	22	9	26
2	TMP ₂ Mg•2LiCl (3.0)	0	16	7	—	32
3	TMP ₂ Mg•2LiCl (3.0)	–10	22	33	9	18
4	TMP ₂ Mg•2LiCl (3.0)	–15	30	42	8	16

^a All reactions were performed using 0.5 mmol of **3b**. The yields of **4/4'** was determined by ¹H NMR using CHBr₃ as an internal standard.

Substrates shown in Scheme 1-1 were used for the reaction to investigate the diastereoselectivity change due to the combination of substituents. Use of iodine instead of CO₂ gave a mixture of diastereomers **5** and **5'** in 59% yield with a ratio of 4/1. The 1,2-disubstituted cubane **6**, which was prepared via hydroboration/oxidation of **3b**, was also examined for the chiral auxiliary controlled deprotonation and treated with CO₂ gas. Absence of acidic allylic proton improved the yield of the corresponding carboxylic acid compared to the reaction using **3b**, but the ratio of diastereomers did not change (ca 4.4/1).^{15,16}



Scheme 1-1. Diastereoselectivities with various combination of substituents.

The absolute configuration of **4** was determined by X-ray analysis of a single crystal (Figure 1-2). Successful hydrolysis of the bulky cubanecarboxamide is known to be difficult.^{17,18} Eaton reported a promising protocol that included a reduction-oxidation sequence may remove the auxiliary,¹⁸ but neither this protocol nor a range of other existing methods for the direct hydrolysis of amide worked for **4**.^{19,20}

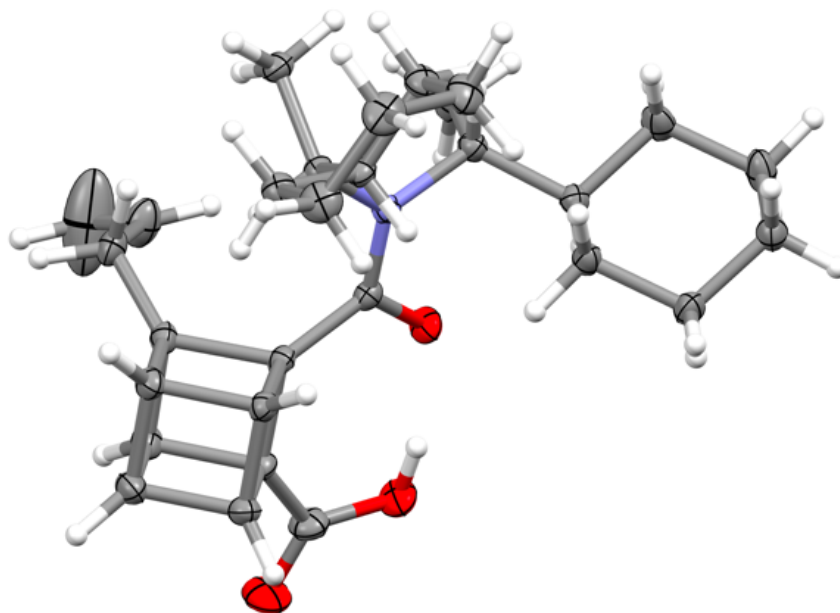
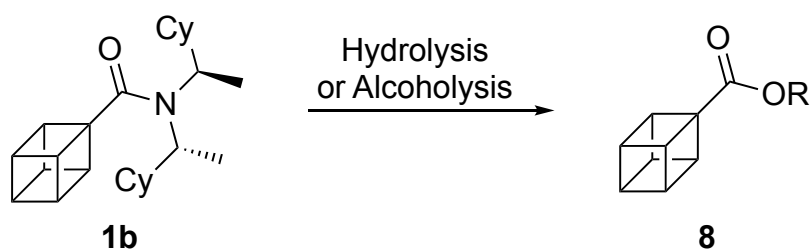


Figure 1-2. X-ray of single crystal **4** with thermal ellipsoid at 50% probability.

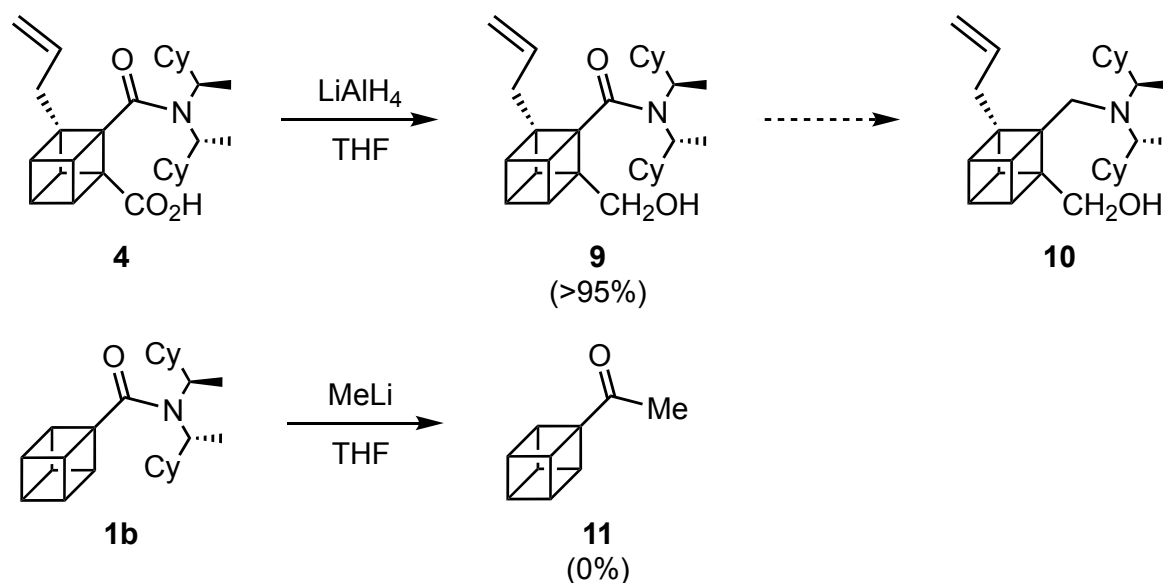
The following methods were explored in attempt to remove the chiral auxiliary in **1b**. In entries 1–4, **1b** was recovered. As shown in entry 5, Garg’s method converted **1b** into the complex mixture completely. It may a result of the reaction of cubane skeleton itself with Ni(0).

Table 1-4. Attempts to remove the chiral auxiliary in **1b**.



entry	condition	results
1	6 M HCl _{aq} EtOH, 50 °C, 10 h (ref 25)	Complete Recovery
2	KOtBu, Water, ether, 50 °C, 10 h (ref 26)	Complete Recovery
3	H ₂ O ₂ /NaOH _{aq} , 35 °C, 10 h (ref 27)	Complete Recovery
4	Tf ₂ O/Pyridine then EtOH (ref 19a)	Complete Recovery
5	Ni(cod) ₂ , SIPr, MeOH (ref 28)	Complex Mixture

The method shown in entry 4, was pursued in an effort to access the proposed imidate intermediate that may be hydrolyzed efficiently by the intramolecular hydroxyl group (Scheme 1-2). Therefore, alcohol **9**, prepared from carboxylic acid **4** and LiAlH_4 , was also examined with the protocol in entry 4, but it resulted in the complete recovery of **9**. Eaton reported a promising protocol that included a reduction-oxidation sequence that removed the auxiliary,⁸ but the LiAlH_4 reduction did not proceed further from **9** to **10** (THF reflux for 12 h). Alkylation of the amide **1b** by MeLi was also examined.²⁹ The reaction resulted in the recovery of **1b**.



Scheme 1-2. Further attempts to remove the chiral auxiliary.

1.3 Conclusion

In conclusion, the author has unearthed a diastereoselective synthesis of 1,2,3-trisubstituted cubane using sequential *ortho*-metalation of a substrate containing a chiral auxiliary. Although the method is of a classical nature, this is the first example of a cubane asymmetric synthesis.

1.4 Experimental Section

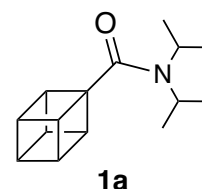
1.4.1 Synthetic Procedure

Preparation of Cubanecarboxamides (1a-d)

Cubane-1-carbonyl chloride (5.0 mmol), prepared following the reported procedure,²¹ was treated with the corresponding amine (6.0 mmol, 1.2 equiv) in the presence of triethylamine (6.0 mmol, 1.2 equiv) and a catalytic amount of DMAP in dichloromethane (30 mL) at 25 °C. After 3 h stirring, the mixture was diluted with chloroform (20 mL) and washed with 1 M HCl aq. The obtained organic solution was dried over Na₂SO₄ and concentrated in *vacuo*. Purification by Silica gel column chromatography (Hexane/AcOEt = 10/1) gave the corresponding amides **1a-d** in 85–96% yields.

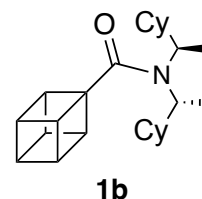
N,N-Diisopropylcubane-1-carboxamide (**1a**)

Isolated as a white solid (1.1 g, 96% yield). ¹H NMR (CDCl₃, 500 MHz): δ 4.19 (m, 3H), 3.97 (m, 4H), 3.53 (sept, 1H, *J* = 6.5 Hz), 3.30 (sept, 1H, *J* = 6.5 Hz), 1.42 (d, 6H, *J* = 6.5 Hz), 1.19 (d, 6H, *J* = 6.5 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 171.2, 59.2, 49.4, 48.1, 46.7, 45.8, 44.2, 21.0, 20.6 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₅H₂₁NONa 254.1526; Found 254.1513; IR (film): 1616, 1447, 1344 cm⁻¹



N,N-Bis((*R*)-1-cyclohexylethyl)cubane-1-carboxamide (**1b**)

Isolated as a white solid (1.65 g, 95% yield). ¹H NMR (CDCl₃, 500 MHz): δ 4.29–4.23 (m, 3H), 3.99–3.90 (m, 4H), 3.04 (dq, 1H, *J* = 8.0, 6.5 Hz), 2.75 (dq, 1H, *J* = 8.0, 6.5 Hz), 2.14–2.06 (m, 1H), 1.93 (t, 2H, *J* = 10 Hz), 1.81–1.60 (m, 9H), 1.45–1.38 (m, 1H), 1.32 (d, 3H, *J* = 6.5 Hz), 1.30–1.00 (m, 5H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.00–0.70 (m, 4H) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 172.1, 59.4, 58.1, 56.9, 49.9, 46.6, 44.1, 42.3, 41.3, 33.2, 31.9, 31.4, 29.9, 26.8, 26.6, 26.5, 26.4, 26.3, 17.6, 17.4 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₂₅H₃₇NONa 390.2766; Found 390.2778; IR (film): 1622, 1446 cm⁻¹; [α]_D²⁰ = –19.4 (*c* 0.51, CH₂Cl₂).



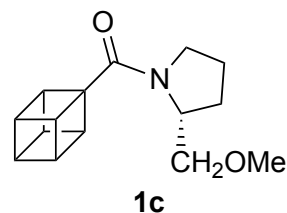
Cuban-1-yl((*R*)-2-(methoxymethyl)pyrrolidin-1-yl)methanone (1c**)**

Isolated as a white solid (1.05 g, 86% yield). ¹H NMR (CDCl₃, 500 MHz):

δ 4.28 (m, 3H), 4.21 (m, 1H), 3.98 (m, 4H), 3.61–3.55 (m, 1H), 3.41–3.31 (m, 3H), 3.34 (s, 3H), 2.05–1.85 (m, 4H) ppm; ¹³C NMR (CDCl₃, 125.7 MHz):

δ 170.4, 72.6, 59.0, 56.6, 48.9, 47.0, 45.4, 44.5, 44.4, 27.2, 24.6 ppm; HRMS (ESI) m/z: [M+Na]⁺

Calcd for C₁₅H₁₉NO₂Na 268.1318; Found 268.1307; IR (film): 1607, 1414, 1114 cm⁻¹.

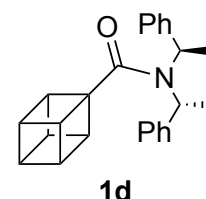
***N,N*-Bis((*R*)-1-phenylethyl)cubane-1-carboxamide (**1d**)**

Isolated as a white solid (1.59 g, 90% yield). ¹H NMR (CDCl₃, 500 MHz): δ 7.37

(bs, 2H), 7.31 (bs, 3H), 7.05 (bs, 3H), 6.84 (bs, 2H), 4.82 (bs, 1H), 4.41 (bs, 3H),

4.18 (bs, 1H), 4.02 (bs, 4H), 1.79 (d, *J* = 7.0 Hz, 3H), 1.76 (d, *J* = 7.0 Hz, 3H) ppm ; ¹³C NMR (CDCl₃, 125.7 MHz): δ 171.3, 141.5, 139.8, 128.4, 128.3, 128.2, 127.9, 127.3, 126.3, 59.8, 55.0, 54.4,

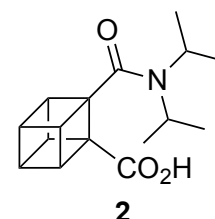
50.1, 46.8, 44.3, 19.2, 18.6 ppm; HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₂₅H₂₅NONa 378.1839; Found 378.1830; IR (film): 1594, 1423, 1359 cm⁻¹.

**Carboxylation via Directed-deprotonation of **1a**; preparation of 2-(diisopropylcarbamoyl)cubane-1-carboxylic acid (**2**, Table 1-1)**

The base was prepared following the reported procedure. TMPLi/MgBr₂ was

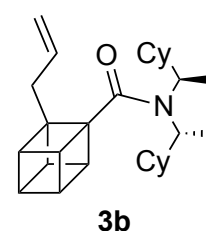
prepared by Eaton's procedure;^{6a} *n*BuLi/*t*BuOK was prepared by Schlosser's procedure;¹¹

TMPMgCl•LiCl and TMP₂Mg•2LiCl were prepared by Knochel's procedure.^{12,13} The representative example (entry 7 in Table 1-1) was as follows. To a solution of TMP₂Mg•2LiCl (0.90 mmol in THF 3 mL, 3.0 equiv.), a solution of **1a** (0.3 mmol) in THF (1.0 mL) was added at -15 °C. The reaction temperature was raised to 0 °C and stirred for 18 h at 0 °C. To a resulting mixture, CO₂ (ca 1 L) gas was bubbled for 5 min and the whole was stirred for 1 h under CO₂ atmosphere. The solvent was removed under reduced pressure. The residue was washed by ether. The washed residue dissolved in 10% HCl_{aq} (15 ml). The aqueous solution was extracted with CHCl₃. The obtained organic solution



was dried over Na_2SO_4 and concentrated in *vacuo*. Purification by a short silica gel chromatography (Hexane/AcOEt = 1/2 as an eluent) gave **2** in 80% yield (66 mg) as a pale-yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 4.31-4.23 (m, 2H), 4.23-4.21 (m, 2H), 4.05-4.02 (m, 2H), 3.56 (sep, 1H, J = 6.5 Hz), 3.42 (sep, 1H, J = 6.5 Hz), 1.80-1.50 (bs, 1H), 1.42 (d, 6H, J = 6.5 Hz), 1.27 (d, 6H, J = 6.5 Hz) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): 173.2, 172.7, 62.0, 58.0, 49.2, 48.6, 47.9, 47.1, 44.7, 44.6, 20.7, 20.1 ppm; HRMS (ESI) m/z : $[\text{M}-\text{H}]^-$ Calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_3$ 274.1449; Found 274.1449; IR (film): 1720, 1553, 1495 cm^{-1} .

Allylation via Directed-deprotonation of 1a-d (Table 2); 2-allyl-*N,N*-bis((*R*)-1-cyclohexylethyl)cubane-1-carboxamide (3b)

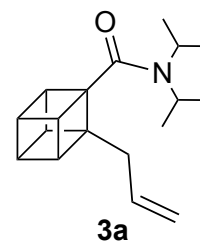


Preparation of **3b** (2-allyl-*N,N*-bis((*R*)-1-cyclohexylethyl)cubane-1-carboxamide)

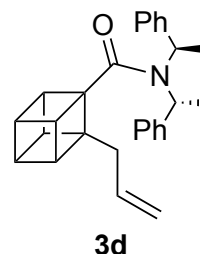
was representative. To a solution of $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (0.90 mmol in THF 3 mL, 3.0 equiv), a solution of **1b** (0.3 mmol) in THF (1.0 mL) was added at -15°C . The reaction temperature was raised to 0°C and stirred for 16 h at 0°C . To a resulting mixture, a mixture of allylbromide (2.4 mmol, 8.0 equiv) and CuI (0.03 mmol, 10 mol%) in THF (1.5 mL) was added dropwise at -15°C . The resulting mixture was stirred for 4 h at 0°C . To a solution, 10% HCl_{aq} (15 ml) was added. The aqueous solution was extracted with CHCl_3 . The obtained organic solution was dried over Na_2SO_4 and concentrated in *vacuo*. Purification by a short silica gel chromatography (Hexane/AcOEt = 5/1 as an eluent) gave **3b** in 95% yield (115 mg) as a colorless oil. ^1H NMR (CDCl_3 , 500 MHz): δ 5.80-5.70 (m, 1H), 5.05-4.95 (m, 2H), 4.15 (m, 1H), 4.11 (m, 1H), 3.95 (m, 1H), 3.57 (m, 3H), 3.16 (dq, 1H, J = 7.0, 5.5 Hz), 2.77 (dq, 1H, J = 9.0, 6.5 Hz), 2.56 (dd, 1H, J = 16.5, 7.0 Hz), 2.54 (dd, 1H, J = 16.5, 7.0 Hz), 2.2-2.1 (m, 1H), 1.96-1.82 (m, 2H), 1.82-1.60 (m, 9H), 1.31 (d, 3H, J = 6.5 Hz), 1.30-0.90 (m, 8H), 1.16 (d, 3H, J = 6.5 Hz), 0.80-0.70 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): 171.5, 133.6, 116.6, 60.5, 60.3, 57.2, 48.3, 47.7, 45.7, 45.3, 44.6, 43.2, 42.5, 41.8, 35.8, 33.0, 32.1, 31.1, 29.4, 26.71, 26.66, 26.6, 26.5, 26.3, 17.9, 16.5 ppm; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{28}\text{H}_{42}\text{NO}$; 408.3272 Found 408.3253; IR (film): 1623, 1333 cm^{-1} ; $[\alpha]_{\text{D}}^{20} = -7.4$ (c 1.23, CH_2Cl_2).

2-Allyl-*N,N*-diisopropylcubane-1-carboxamide (3a)

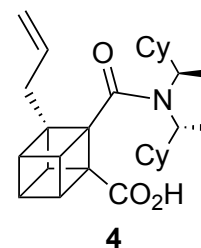
Isolated as a white solid (65 mg, 80% yield). ^1H NMR (CDCl_3 , 500 MHz): δ 5.72 (ddt, 1H, 17.5, 11.0, 6.5 Hz), 5.03 (dd, 1H, 17.5, 1.8 Hz), 5.02 (dd, 1H, 11.0, 1.8 Hz), 4.14–4.08 (m, 2H), 3.95–3.88 (m, 1H), 3.79–3.72 (m, 3H), 3.54 (sept, 1H, J = 6.5 Hz), 3.30 (sept, 1H, J = 6.5 Hz), 2.46 (d, 2H, J = 6.5 Hz), 1.40 (d, 6H, J = 7.0 Hz), 1.21 (d, 6H, J = 6.5 Hz) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 170.5, 132.8, 117.0, 60.5, 60.4, 48.1, 46.8, 45.8, 45.5, 44.7, 43.2, 36.1, 21.5, 20.7 ppm; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{25}\text{NONa}$ 294.1839; Found 294.1830; IR (film): 1622, 1439, 1376 cm^{-1} .

**3a****2-Allyl-*N,N*-bis((*R*)-1-phenylethyl)cubane-1-carboxamide (3d)**

Isolated as a colorless oil (21 mg, 18% yield). ^1H NMR (C_6D_6 , 500 MHz): δ 7.40–6.85 (m, 10H), 5.85–5.70 (m, 1H), 5.10–5.00 (m, 2H), 4.88 (bs, 1H), 4.30 (bs, 2H), 4.22 (m, 1H), 3.96 (bs, 1H), 3.78 (m, 3H), 2.66 (dd, 1H, J = 15, 6.5 Hz), 2.61 (dd, 1H, J = 15, 6.5 Hz), 1.77 (d, 6H, J = 6.5 Hz) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 171.4, 141.9, 140.3, 133.4, 128.5, 128.3, 128.1, 128.0, 127.6, 127.3, 126.3, 125.8, 116.9, 60.6, 60.4, 54.6, 51.3, 48.7, 48.3, 45.7, 45.5, 44.73, 44.70, 43.4, 35.9, 19.4 ppm; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{28}\text{H}_{29}\text{NONa}$; 418.2152; Found 418.2146; IR (Film): 1622, 1307 cm^{-1} .

**3d****Preparation of Chiral Cubane 4 ((2*S*)-3-allyl-2-(bis((*R*)-1-cyclohexylethyl)carbamoyl)cubane-1-carboxylic acid)**

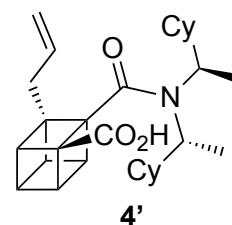
To a solution of $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (1.5 mmol in THF 4 mL, 3.0 equiv), a solution of **3b** (0.5 mmol) in THF (1.5 mL) was added at $-20\text{ }^\circ\text{C}$. The reaction temperature was raised to $-15\text{ }^\circ\text{C}$ and stirred for 30 h at the same temperature. To a resulting mixture, CO_2 (ca 1 L) gas was bubbled for 5 min at $-15\text{ }^\circ\text{C}$ and the whole was stirred for 1 h under CO_2 atmosphere at $0\text{ }^\circ\text{C}$. The solvent was removed under reduced pressure. The residue was washed by ether. The washed residue dissolved in 10% HCl aq (15 ml). The aqueous solution was

**4**

extracted with CHCl_3 . The obtained organic solution was dried over Na_2SO_4 . After passed through a very short silica-gel column (ca 2 cm) to remove magnesium salt, the organic layer was concentrated in *vacuo*. ^1H NMR analysis of crude product using CHBr_3 as an internal standard show the formation of **4** and **4'** in 42% and 8 % yields respectively with a recovery of 16% starting materials. Purification by preparative thin-layer chromatography (Hexane/AcOEt = 1/2) gave **4** in 40% yield (R_f 0.7, 90 mg) as a white solid. The minor product **4'** was isolated in 1% yield as a yellow oil (R_f 0.3, 2.4 mg). Recrystallization of the major product **4** from dichloromethane/hexane gave a colorless prism crystal.; mp. 177.0 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 5.70 (dddd, 1H, 17.5, 9.5, 7.0, 7.0 Hz), 5.13 (dd, 1H, 10.0, 1.5 Hz), 5.09 (dd, 1H, 17.5, 1.5 Hz), 5.0 (bs, 1H), 4.26 (m, 1H), 4.14 (m, 1H), 4.05 (m, 1H), 3.81 (m, 2H), 3.18 (dq, 1H, J = 7.0, 3.5 Hz), 2.95 (dq, 1H, J = 8.5, 6.5 Hz), 2.48 (dd, 1H, J = 15, 6.5 Hz), 2.40 (dd, 1H, J = 15, 6.5 Hz), 2.15-2.05 (m, 1H), 1.91 (t, 2H, J = 15 Hz), 1.85-1.40 (m, 10H), 1.33 (d, 3H, J = 6.5 Hz), 1.26 (d, 3H, J = 6.5 Hz), 1.30-0.90 (m, 8 H), 0.80-0.70 (m, 2H) ppm ; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 173.3, 172.4, 130.7, 118.7, 64.1, 60.3, 58.6, 57.7, 55.6, 49.4, 47.3, 47.1, 46.9, 43.8, 41.2, 41.1, 35.6, 32.2, 32.0, 30.6, 29.7, 28.6, 26.8, 26.6, 26.5, 26.4, 26.2, 26.0, 17.7, 15.2 ppm; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{29}\text{H}_{42}\text{NO}_3$ 452.3170; Found 452.3156; IR (film): 1623, 1560, 1346 cm^{-1} ; $[\alpha]_{\text{D}}^{20} = +72.0$ (c 0.85, CH_2Cl_2).

(2R)-3-Allyl-2-(bis((R)-1-cyclohexylethyl)carbamoyl)cubane-1-carboxylic acid (4')

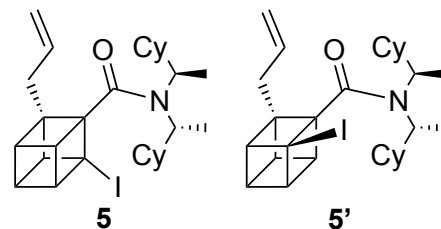
Isolated as a yellow oil (2.4 mg, 1% yield). ^1H NMR (CDCl_3 , 500 MHz): δ 5.75-5.65(m, 1H), 5.15 (dd, 1H, J = 11.5, 6.5 Hz), 5.09 (dd, 1H, J = 17.5, 6.5 Hz), 4.25 (m, 1H), 4.14 (m, 1H), 4.06 (m, 1H), 3.88 (m, 1H), 3.79 (m, 1H), 3.19 (dq, 1H, J = 7.0, 2.0 Hz), 2.99 (dq, 1H, J = 11.5, 6.5 Hz), 2.48 (dd, 1H, J = 14.5, 6.0 Hz), 2.38 (dd, 1H, J = 14.5, 6.5 Hz), 2.10-2.05 (m, 1H), 2.00-1.50 (m, 12H), 1.34 (d, 3H, J = 7.5 Hz), 1.19 (d, 3H, J = 7.5 Hz), 1.40-0.70 (m, 11H) ppm ; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 173.3, 171.9, 130.8, 118.5, 64.5, 59.7, 59.2, 58.6, 55.8, 49.5, 47.2, 46.3, 42.3, 41.4, 41.2, 37.1, 34.9, 33.9, 32.0, 31.1, 29.7, 29.3, 26.6, 26.52, 26.46, 26.4, 26.1, 26.0, 17.7, 15.7 ppm; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for



$C_{29}H_{42}NO_3$ 452.3170; Observed 452.3158; IR (Film): 1623, 1560 cm^{-1} .

(1*R*)-2-Allyl-*N,N*-bis((*R*)-1-cyclohexylethyl)-8-iodocubane-1-carboxamide (5**) and (1*S*)-2-allyl-*N,N*-bis((*R*)-1-cyclohexylethyl)-8-iodocubane-1-carboxamide (**5'**)**

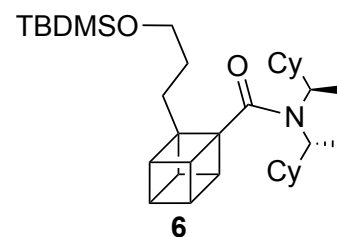
To a solution of $TMP_2Mg \cdot 2LiCl$ (2.1 mmol in THF 5 mL, 3.0 equiv), a solution of **3b** (0.29g, 0.7 mmol) in THF (2.0 mL) was added at $-20\text{ }^{\circ}C$. The reaction temperature was raised to $-15\text{ }^{\circ}C$ and stirred for 24 h at the same temperature. To a resulting



mixture, I_2 (1.43 g, 5.6 mmol, 8.0 equiv) in THF 4 mL was added at $-15\text{ }^{\circ}C$ and the whole was stirred for 2 h at $0\text{ }^{\circ}C$. 1M HCl aqueous solution (5 mL) and EtOAc (30 mL) was added successively. The organic layer was washed with saturated Na_2SO_3 aqueous solution. The obtained organic solution was dried over Na_2SO_4 . After passed through a very short silica-gel column (ca 2 cm) to remove magnesium salt, the organic layer was concentrated in *vacuo*. 1H NMR analysis of crude product using $CHBr_3$ as an internal standard showed the formation of **5** and **5'** in 47% and 12 % yields respectively with a recovery of 32% **3b**. Purification by PTLC (Hexane/AcOEt = 7/1) gave a mixture of **5** and **5'** in 52% yield (R_f 0.7, 194mg) as a pale yellow oil.; 1H NMR ($CDCl_3$, 500 MHz): δ 5.80-5.60 (m, 1H), 5.03 (d, 1H, $J = 17.5$ Hz), 5.02 (d, 1H, $J = 6.0$ Hz) 4.40 (m, 0.8H), 4.34 (m, 0.4 H), 4.29 (m, 0.8 H), 4.05 (m, 0.2 H), 4.02 (m, 0.8 H), 3.95-3.85 (m, 2H), 3.50 (dq, 0.8H, $J = 6.0, 6.0$ Hz), 3.34 (dq, 0.2H, $J = 6.0, 6.0$ Hz), 2.84-2.71 (m, 1H), 2.65 (dd, 1H, $J = 15, 6.5$ Hz), 2.57 (dd, 1H, $J = 15, 6.5$ Hz), 2.30-0.85 (m, 20H), 1.43 (t, 0.6H, $J = 6.5$ Hz), 1.33 (t, 2.4H, $J = 6.5$ Hz), 1.31(t, 0.6H, $J = 6.5$ Hz), 1.14 (t, 2.4H, $J = 6.5$ Hz), 0.81–0.70 (m, 2H) ppm ; ^{13}C NMR for **5** ($CDCl_3$, 125.7 MHz): δ 167.5, 133.0, 117.2, 66.2, 61.7, 57.7, 57.1, 56.6, 54.4, 52.9, 45.1, 44.2, 41.7, 41.6, 38.5, 34.8, 32.8, 32.0, 31.3, 29.5, 26.7, 26.6, 26.6, 26.4, 26.3, 26.2, 17.8, 16.4 ppm; ^{13}C NMR for **5'** ($CDCl_3$, 125.7 MHz): δ 168.6, 133.5, 117.0, 66.0, 61.7, 57.7, 57.4, 56.6, 55.3, 51.6, 45.0, 44.3, 43.4, 41.2, 38.3, 35.1, 32.4, 32.0 30.8, 29.0, 26.7, 26.6, 26.5, 26.4, 26.33, 26.27, 18.8, 16.1 ppm; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_{28}H_{40}NOINa$ 556.2057; Found 556.2046; IR (film): 1616, 1314, 905 cm^{-1} .

2-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-*N,N*-bis((*R*)-1-cyclohexylethyl)cubane-1-carboxamide
(6)

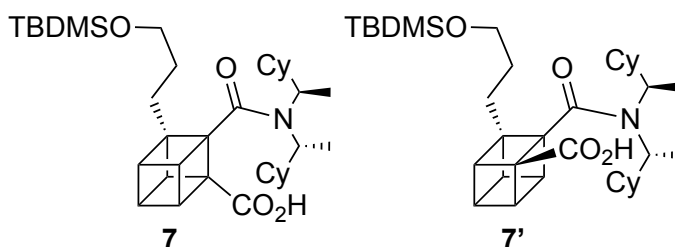
To a solution of **3b** (0.408 g, 1.0 mmol) in THF (5 mL), $\text{H}_3\text{B}\cdot\text{SMe}_2$ (0.22 g, 3.0 mmol) was added at 0 °C. After stirred for 1 h at 25 °C, a mixture of 30% hydrogen peroxide (2.0 mL) and 10 wt% NaOH aqueous solution (2.0 mL) was added carefully at 0 °C. The resulting mixture was stirred



for 60 min at 25 °C. The mixture was diluted with dichloromethane (40 mL) and washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ aqueous solution. The aqueous layer was extracted with chloroform. The combined organic layers were passed through a very short silica gel column (ca 1 cm) to remove boronic acid and dried over Na_2SO_4 . The resulting solution was concentrated under reduced pressure. To the residue, dichloromethane (8 mL), triethylamine (2 mL), 4-*N,N*-dimethylaminopyridine (ca 10 mg), and *t*BuMe₂SiOTf (0.39 g, 1.5 mmol) were added subsequently at 25 °C. The resulting mixture was stirred for 12 h at 25 °C. The solution was diluted with chloroform (20 mL) and washed with 3 wt% HCl aqueous solution. The organic layer was washed with saturated NaHCO_3 aqueous solution. The resulting organic solution was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by a short silica gel chromatography (Hexane/AcOEt = 15/1 as an eluent) gave **6** in 78% yield (421 mg) as a colorless oil.; ¹H NMR (CDCl_3 , 500 MHz): δ 4.18-4.13 (m, 1H), 4.10-4.06 (m, 1H), 3.97-3.92 (m, 1H), 3.78-3.71 (m, 3H), 3.60 (t, 2H, J = 7.0 Hz), 3.17 (dq, 1H, J = 6.5, 6.0 Hz), 2.80 (dq, 1H, J = 6.5, 6.0 Hz), 2.20-2.10 (m, 1H), 1.90 (t, 2H, J = 7.0 Hz), 1.81-1.61 (m, 10H), 1.60-1.40 (m, 4H), 1.32 (d, 3H, J = 6.5 Hz), 1.31-1.20 (m, 4H), 1.16 (d, 3H, J = 6.5 Hz), 1.15-0.95 (m, 4H), 0.88 (s, 9H), 0.89-0.85 (m, 2H), 0.03 (s, 6H) ppm; ¹³C NMR (CDCl_3 , 125.7 MHz): δ 171.5, 63.6, 62.3, 60.4, 57.2, 57.1, 48.0, 46.9, 46.0, 45.3, 44.5, 43.2, 42.9, 41.7, 32.9, 32.1, 31.0, 29.3, 27.7, 27.1, 26.70, 26.67, 26.6, 26.33, 26.30, 26.2, 26.0, 18.4, 17.9, 16.2, -5.25, -5.29 ppm; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{34}\text{H}_{57}\text{NO}_2\text{SiNa}$ 562.4056; Observed 562.4046; IR (Film): 1607, 1103 cm^{-1} .

Carboxylation of Metalated 6: Preparation of (2*S*)-2-(bis((*R*)-1-cyclohexylethyl)carbamoyl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cubane-1-carboxylic acid (7**) and (2*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-(bis((*R*)-1-cyclohexylethyl)carbamoyl)cubane-1-carboxylic acid (**7'**)**

To a solution of $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (2.1 mmol in THF 5 mL, 3.0 equiv), a solution of **6** (0.38g, 0.7 mmol) in THF (3.0 mL) was added at $-20\text{ }^\circ\text{C}$. The reaction temperature was raised to



$-10\text{ }^\circ\text{C}$ and stirred for 18 h at the same temperature. To a resulting mixture, CO_2 (ca 1 L) gas was bubbled for 5 min at $-10\text{ }^\circ\text{C}$ and the whole was stirred for 2 h under CO_2 atmosphere at $0\text{ }^\circ\text{C}$. 10% HCl aq (5 ml) was added at $0\text{ }^\circ\text{C}$ carefully. The aqueous solution was extracted with CHCl_3 . The obtained organic solution was dried over Na_2SO_4 . After passed through a very short silica gel column (ca 2 cm) to remove magnesium salt, the organic layer was concentrated in *vacuo*. ^1H NMR analysis of crude product using CHBr_3 as an internal standard show the formation of **7** and **7'** in 70% and 16 % yields respectively with a recovery of **6** in 12%. Purification by preparative thin-layer chromatography (Hexane/ AcOEt = 1/2) gave **7** in 64% yield (R_f 0.75, 262 mg) as a white solid. The minor product **7'** was isolated in 10% yield as a colorless oil (R_f 0.2, 41 mg).

7: ^1H NMR (CDCl_3 , 500 MHz): δ 4.26-4.23 (m, 1H), 4.11-4.06 (m, 1H), 4.03-3.95 (m, 1H), 3.84-3.76 (m, 2H), 3.62 (dt, 1H, $J = 10.0, 5.0\text{ Hz}$), 3.57 (dt, 1H, $J = 10.0, 5.0\text{ Hz}$), 3.15 (dq, 1H, $J = 6.5, 3.0\text{ Hz}$), 2.94 (dq, 1H, $J = 9.0, 7.0\text{ Hz}$), 2.16-2.04 (m, 1H), 1.94-1.61 (m, 11H), 1.60-1.40 (m, 5H), 1.32 (d, 3H, $J = 6.5\text{ Hz}$), 1.24 (d, 3H, $J = 7.0\text{ Hz}$), 1.26-1.00 (m, 8H), 0.86 (s, 9H), 0.82-0.69 (m, 2H), 0.013 (s, 3H), 0.011 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 173.5, 172.7, 63.9, 62.8, 61.9, 58.6, 57.7, 55.5, 49.5, 47.30, 47.26, 46.7, 43.8, 41.1, 41.0, 32.2, 32.0, 30.5, 28.6, 28.1, 26.8, 26.6, 26.5, 26.4, 26.3, 26.2, 26.0, 18.4, 17.6, 15.0, -5.32, -5.40 ppm; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{35}\text{H}_{58}\text{NO}_4\text{Si}$ 562.4135; Observed 584.4129; IR (Film): 1617, 1103 cm^{-1} .

7': ^1H NMR (CDCl_3 , 500 MHz): δ 4.26-4.21 (m, 1H), 4.14-4.08 (m, 1H), 4.05-4.01 (m, 1H), 3.87-

3.82 (m, 1H), 3.82-3.78 (m, 1H), 3.62 (dt, 1H, $J = 13.0, 6.5$ Hz), 3.60 (dt, 1H, $J = 13.0, 6.5$ Hz), 3.16 (dq, 1H, $J = 7.0, 2.0$ Hz), 2.97 (dq, 1H, $J = 9.0, 6.5$ Hz), 2.18-2.06 (m, 1H), 1.96-1.45 (m, 14H), 1.32 (d, 3H, $J = 7.0$ Hz), 1.35-1.00 (m, 10H), 1.17 (d, 3H, $J = 6.5$ Hz), 0.89 (s, 9H), 0.82-0.69 (m, 2H), 0.046 (s, 6H) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 173.4, 172.2, 63.1, 61.3, 59.2, 58.7, 55.6, 49.7, 47.2, 47.0, 46.6, 42.2, 41.5, 41.3, 33.9, 32.2, 31.9, 31.1, 29.7, 29.3, 27.1, 26.6, 26.53, 26.46, 26.39, 26.36, 26.04, 26.01, 18.5, 17.6, 15.7, -5.26, -5.27 ppm; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{35}\text{H}_{57}\text{NO}_4\text{SiNa}$ 606.3955; Observed 606.3946; IR (Film): 1694, 1080 cm^{-1} .

1. 4. 2 X-ray Diffraction Analysis

Datablock: shelxl

Bond precision:	C-C = 0.0034 Å	Wavelength=0.71075	
Cell:	a=10.654 (3)	b=14.873 (5)	c=16.306 (5)
	alpha=90	beta=90	gamma=90
Temperature:	143 K		
	Calculated	Reported	
Volume	2583.8 (14)	2583.8 (14)	
Space group	P 21 21 21	P 21 21 21	
Hall group	P 2ac 2ab	P 2ac 2ab	
Moiety formula	C29 H41 N O3	C29 H41 N O3	
Sum formula	C29 H41 N O3	C29 H41 N O3	
Mr	451.63	451.63	
Dx, g cm-3	1.161	1.161	
Z	4	4	
Mu (mm-1)	0.074	0.074	
F000	984.0	984.0	
F000'	984.40		
h, k, lmax	13, 19, 21	13, 19, 20	
Nref	5923 [3328]	5846	
Tmin, Tmax	0.987, 0.990	0.852, 0.990	
Tmin'	0.987		
Correction method= # Reported T Limits: Tmin=0.852 Tmax=0.990			
AbsCorr = MULTI-SCAN			
Data completeness=	1.76/0.99	Theta (max)= 27.481	
R(reflections)=	0.0450 (4791)	wR2 (reflections)=	
		0.1010 (5846)	
S = 1.000	Npar= 298		

A crystal of **4** was mounted on the CryoLoop (Hampton Research Corp.) with a layer of light mineral oil and placed in a nitrogen stream at 143 K. The X-ray structural determinations of **4** was performed on a Rigaku/Saturn724+ CCD diffractometers using graphite-monochromated Mo K α radiation ($\lambda = 0.71075$ Å) at 153 K, and processed using CrystalClear (Rigaku, Tokyo, Japan).²² The structure of **4** was solved by SHELX version 2013/1 (Sheldrick, 2008)²³ and refined by SHELX version 2018/3 (Sheldrick, 2008)²⁴ Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. CCDC 2214635 contains the supplementary crystallographic data. The data is available from The Cambridge Crystallographic Data Centre.

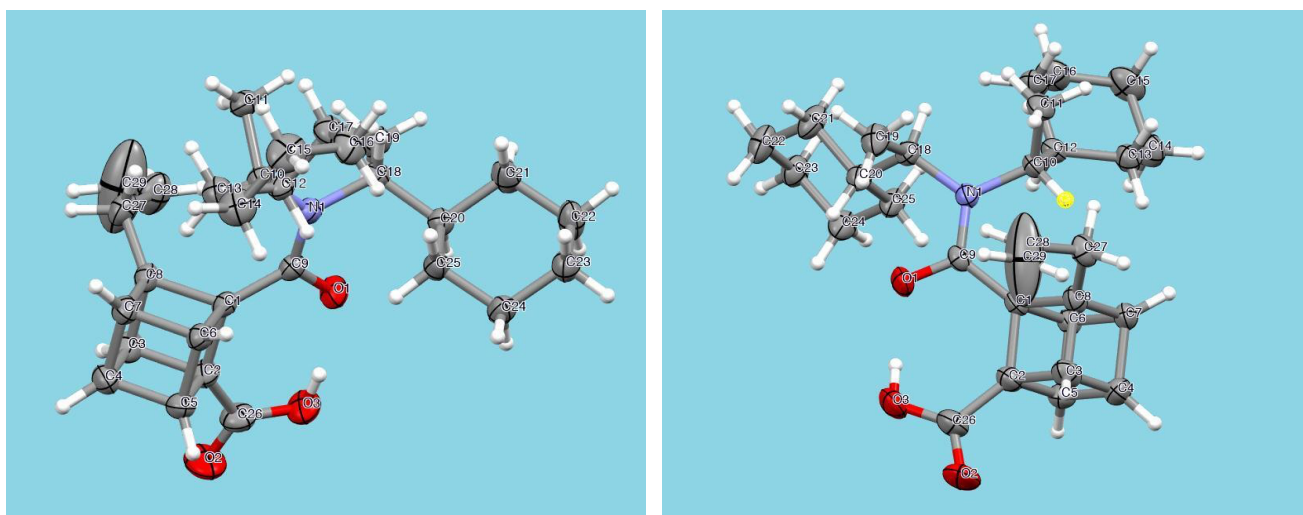
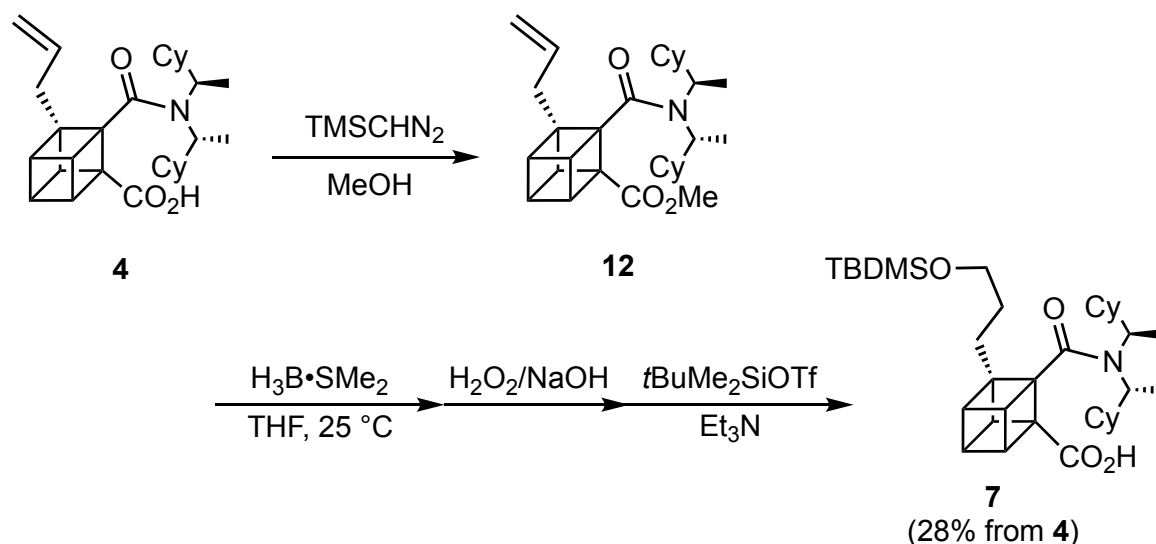


Figure 1-3. Molecular structure of **4** with thermal ellipsoids at 50% probability.

1. 4. 3 Determination of Absolute Configuration of **7**.

The absolute configuration defined **4** was converted into **7** stereospecifically as shown in the following Scheme 1-3, those ¹H and ¹³C NMR spectra were identified with the compound **7** obtained in Scheme 1-1.

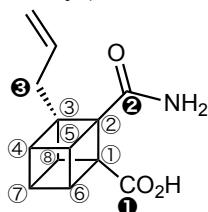


Scheme 1-3. Conversion of **4** into **7**.

To a solution of **4** (0.225 g, 0.5 mmol) in MeOH (1 mL) and benzene (5 mL), TMSCHN₂ (0.6 M in hexane, 2 mL) was added at 25 °C. After stirred for 0.5 h, acetic acid (0.5 mL) was added dropwise. After the mixture was passed through a short silica gel column (washed with H/AcOEt=2/1), the solution was concentrated in vacuo. The residue was dissolved with THF 5 mL, H₃B·SMe₂ (0.22 g, 3.0 mmol) was added at 0 °C. After stirred for 1 h at 25 °C, a mixture of 30% hydrogen peroxide (1.0 mL) and 10 wt% NaOH aqueous solution (1.0 mL) was added carefully at 0 °C. The hydrolysis of methyl ester proceeded at this stage. The resulting mixture was stirred for 60 min at 25 °C. The mixture was diluted with dichloromethane (40 mL) and washed with 10% Na₂S₂O₃ aqueous solution. The aqueous layer was extracted with chloroform. The combined organic layers were passed through a very short silica gel column (ca 1 cm) to remove boronic acid and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. To the residue, dichloromethane (8 mL), triethylamine (2 mL), 4-*N,N*-dimethylaminopyridine (ca 10 mg), and *t*BuMe₂SiOTf (0.39 g, 1.5 mmol) were added subsequently at 25 °C. The resulting mixture was stirred for 12 h at 25 °C. The solution was diluted with chloroform (20 mL) and washed with 3 wt% HCl aqueous solution. The resulting organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. Purification by preparative thin-layer chromatography (Hexane/AcOEt = 2/1) gave a mixture of **7** in 28% yield (R_f 0.7, 82mg) as a white solid.

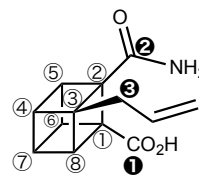
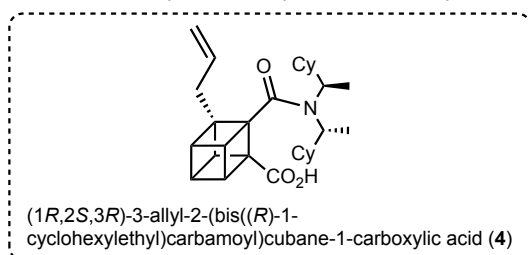
1.4.4 Assignment of Absolute Configuration of Chiral Cubanes **4**, **4'**, **5**, **5'**, **7** and **7'** by CIP rule.

The assignment of absolute configuration for **4**, **4'**, **5**, **5'**, **7** and **7'** by CIP rules is shown as follows. For example, compound **4** is named as (1*R*,2*S*,3*R*)-3-allyl-2-(bis(*R*)-1-cyclohexylethyl)carbamoylcubane-1-carboxylic acid. In these trisubstituted cubanes, the remaining two positions can be determined automatically by only indicating the absolute configuration of one position (see left). For compound **4**, it is sufficient to name **4** as (2*S*)-3-allyl-2-(bis(*R*)-1-cyclohexylethyl)carbamoylcubane-1-carboxylic acid. Other compounds are similarly named.



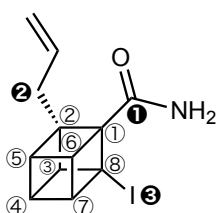
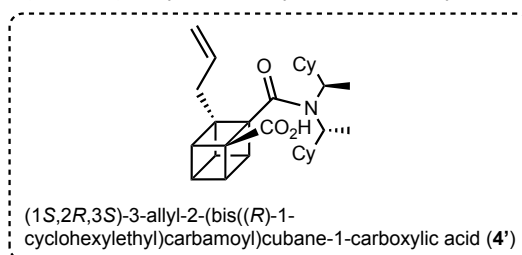
CIP for ① : ①>②>⑧>⑥ 1*R*
 ⑥ : (C5,C7,H) ⑧ : (C3,C7,H) C3>C5
 CIP for ② : ②>①>③>⑤ 2*S*

CIP for ③ : ②>⑧>④>⑤ 3*R*
 ④ : (C5,C7,H) ⑧ : (C1,C7,H) C1>C5
 (1*R*,2*S*,3*R*)-3-allyl-2-carbamoylcubane-1-carboxylic acid



CIP for ① : ①>②>⑧>⑥ 1*S*
 ⑥ : (C5,C7,H) ⑧ : (C3,C7,H) C3>C5
 CIP for ② : ②>①>③>⑤ 2*R*

CIP for ③ : ②>⑧>④>⑤ 3*S*
 ④ : (C5,C7,H) ⑧ : (C1,C7,H) C1>C5
 (1*S*,2*R*,3*S*)-3-allyl-2-carbamoylcubane-1-carboxylic acid

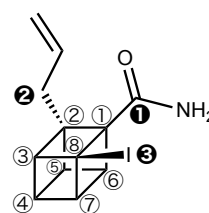
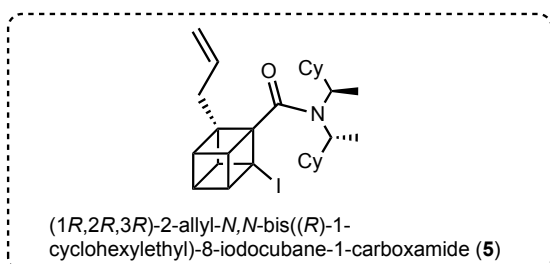


CIP for ① : ⑧>①>②>⑥ 1*R*

CIP for ② : ①>③>⑤>② 2*R*

CIP for ⑧ : ③>①>③>⑦ 3*R*

(1*R*,2*R*,3*R*)-2-allyl-8-iodocubane-1-carboxamide

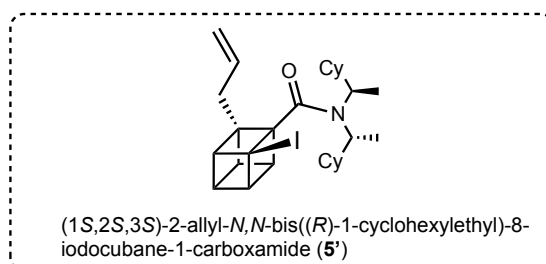


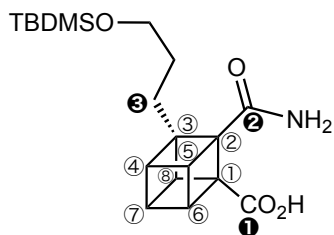
CIP for ① : ⑧>①>②>⑥ 1*S*

CIP for ② : ①>③>⑤>② 2*S*

CIP for ⑧ : ③>①>③>⑦ 3*S*

(1*S*,2*S*,3*S*)-2-allyl-8-iodocubane-1-carboxamide



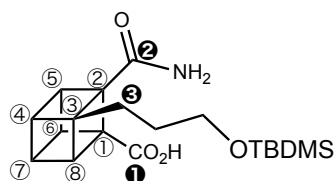


CIP for ① : ①>②>⑧>⑥ 1R
⑥ : (C5,C7,H) ⑧ : (C3,C7,H) C3>C5

CIP for ② : ②>①>③>⑤ 2S

CIP for ③ : ②>⑧>④>③ 3R
④ : (C5,C7,H) ⑧ : (C1,C7,H) C1>C5

(1R,2S,3R)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-2-carbamoylcubane-1-carboxylic acid

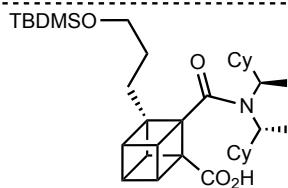


CIP for ① : ①>②>⑧>⑥ 1S
⑥ : (C5,C7,H) ⑧ : (C3,C7,H) C3>C5

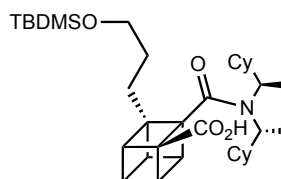
CIP for ② : ②>①>③>⑤ 2R

CIP for ③ : ②>⑧>④>③ 3S
④ : (C5,C7,H) ⑧ : (C1,C7,H) C1>C5

(1S,2R,3S)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-2-carbamoylcubane-1-carboxylic acid



(1R,2S,3R)-2-bis((R)-1-cyclohexylethyl)carbamoyl-3-(3-((tert-butyldimethylsilyl)oxy)propyl)cubane-1-carboxylic acid (7)



(1S,2R,3S)-2-bis((R)-1-cyclohexylethyl)carbamoyl-3-(3-((tert-butyldimethylsilyl)oxy)propyl)cubane-1-carboxylic acid (7')

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Chapter 2

Directed Metalation of 1-Cuneanecarboxamide: Simple Route to 1,2-Disubstituted Cuneanes

Cuneane is a structural isomer of cubane, and a stable C_{2v} symmetric hexahedron. The introduction of substituents into a cuneane has not been investigated, and the author found that site-selective deprotonation of 1-cuneanecarboxamide proceeds by treatment with $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$. The metalated cuneane reacted with various electrophiles to give 2-substituted 1-cuneanecarboxamide, including 2-iodo-1-cuneanecarboxamide. The obtained iodide was converted into 2-metalated 1-cuneanecarboxamide by $i\text{PrMgCl}$, which also reacted with various electrophiles.

2.1 Introduction

Since cubane was synthesized by Eaton,¹ a number of studies have been conducted on the synthesis of highly substituted derivatives.² In Chapter 1, it was demonstrated that the asymmetric synthesis of chiral substituted cubane is feasible by introducing three substituents in a site-selective manner with the use of a chiral auxiliary.³ This approach allows for the asymmetric synthesis of chiral substituted cubane by site-selective introduction of substituents with the use of chiral auxiliaries. As previously stated in the General Introduction of this thesis, incorporating at least three substituents is necessary to express chirality for cubane with O_h symmetry. However, this approach is not a viable synthetic method for use as a chiral scaffold. Identifying a solution to this problem became the most crucial objective of my thesis.

It is noteworthy that Eaton documented a rearrangement of cubane to cuneane in 1970.⁴ Cubane is known to transform into cyclooctatetraene by heating above 230 °C while changing its shape and releasing distortion.⁵ In this case, the first product is the C_{2v} symmetric cuneane, which can be a chiral molecule with a single substituent on the 2-position,^{6,7} but the reaction introducing substituents to this convex hexahedral molecule has not been investigated. In the case of cubane, the introduction of substituents can be classified into two types. One is the reaction via cubyl radical such as halogenation or chlorocarbonylation,⁸ and the other is anion formation via deprotonation using the amide group as a directing group.⁹ Recently, Pd-catalyzed C–H functionalization using oxime as a directing group was also shown.¹⁰ On the other hand, in the case of cuneane, unlike cubane, the radical formed at the vertex is not stable, and the action of the metal catalyst is more likely to induce further skeletal rearrangement. Here, the author examines the feasibility of *ortho*-metalation of 1-cuneanecarboxamide by treating it with a base.

2.2 Results and Discussion

Cuneanes are easily prepared by a constitutional isomerization of cubane, catalyzed by Ag^+ salt.⁴ As shown in Figure 2-1, treatment of *N,N*-diisopropylcubane-1-carboxamide (**1a**) with a catalytic amount of AgOTf gave *N,N*-diisopropylcuneane-1-carboxamide (**2a**) in 94% yield accompanied by *N,N*-diisopropylcuneane-2-carboxamide (**3a**, 4.6% yield).¹¹ As the isomerization proceeds by Lewis acidic Ag^+ catalyst, the regioselectivity can be rationalized from the view point of steric hindrance and electron-withdrawing effect of diisopropylamide. The silver(I) salt-catalyzed reaction, as reported by Eaton,⁴ was previously thought to proceed via cationic species. In order for a cubane to isomerize into a cuneane, it is necessary for a pair of skew bonds to be cleaved and then recombined. Given that a Lewis acid (Ag^+) should interact with a reactive C–C σ -bond electrophilically to initiate the isomerization, it can be postulated that the reaction may proceed preferentially between electron-rich bonds. Furthermore, the bulky amide impedes the approach of the catalyst. Consequently, as illustrated in Figure 2-2, the reaction may commence at the red bonds (Step 1) due to steric hindrance, and select the reaction partner bond from the gray bonds. When the reaction proceeds along this presumed reaction path, the product will be *N,N*-diisopropylcuneane-1-carboxamide **2a**. Using GCNN (Graph Convolutional Neural Networks)-driven estimation, which was developed by Grzybowski as “pKa predictor”,¹² there are clearly three acidic protons (**2**, **5**, **8**). If there is a selectivity between **5** and **2** (= **8**), successful site-selective deprotonation can be expected. As shown in Table 2-1, a deprotonation of **2a** by various lithium and magnesium amides was examined and quenched with D_2O .

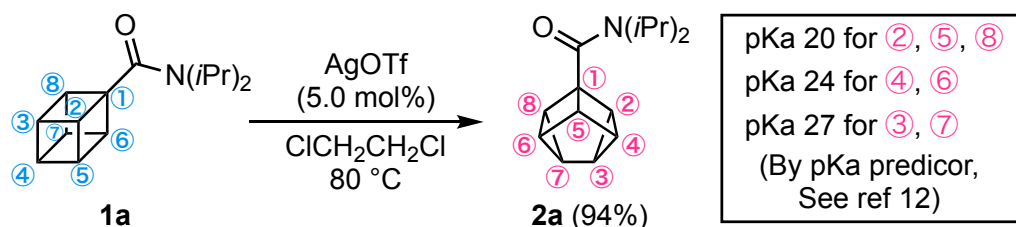


Figure 2-1. Preparation of *N,N*-diisopropylcuneane-1-carboxamide (**2a**) from *N,N*-diisopropylcubane-1-carboxamide (**1a**) by Ag^+ catalyst.

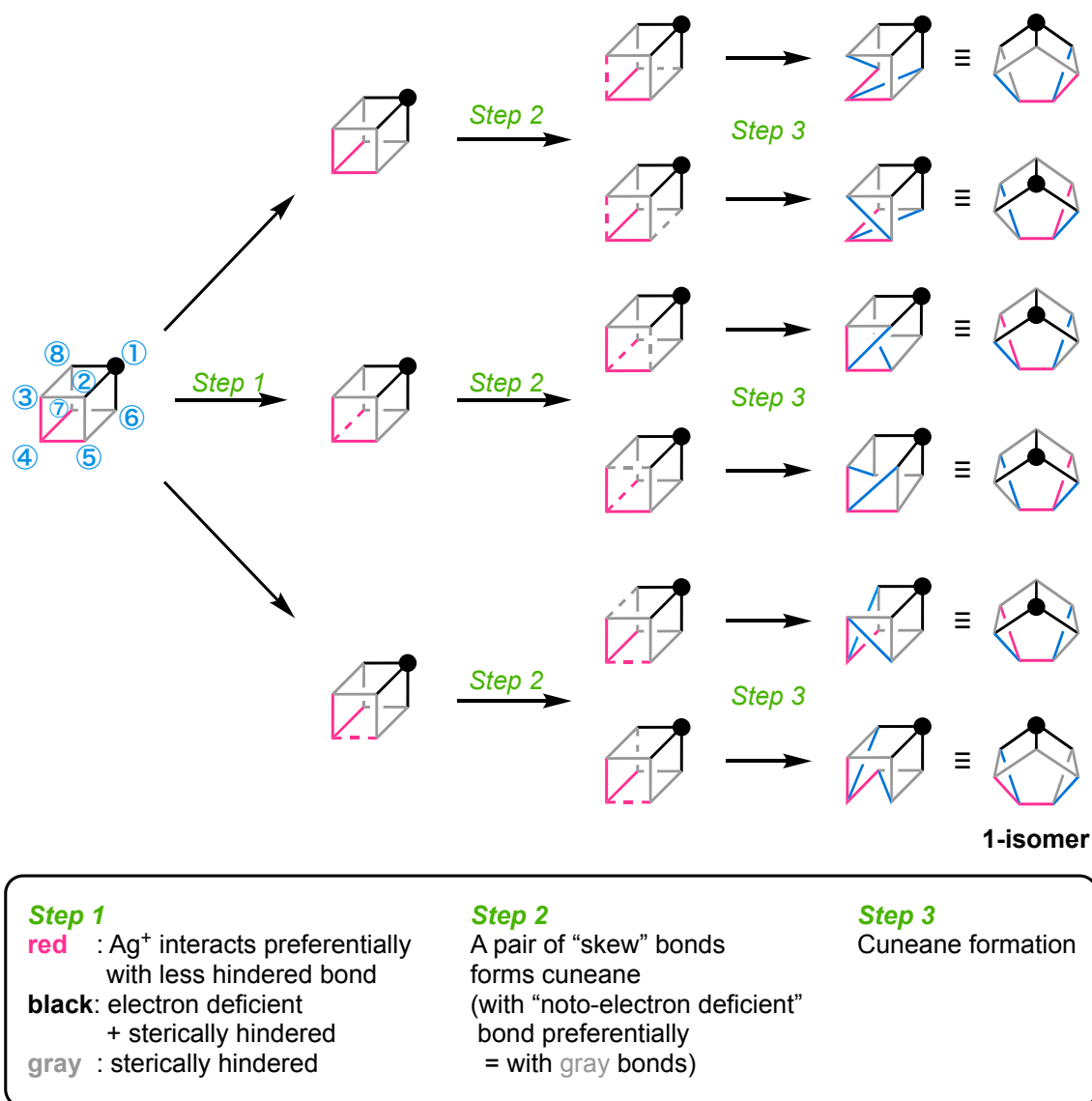
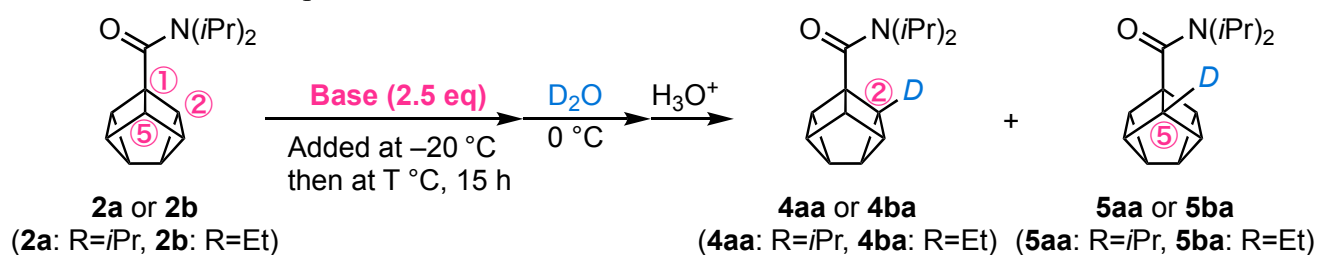


Figure 2-2. Rationalization for selective formation of *N,N*-diisopropylcuneane-1-carboxamide.

Table 2-1. Directed deprotonation of 1-cuneanecarboxamide. ^a

entry	base	T (°C)	R	yield of 4 (%)	yield of 5 (%)	recov. of 2 (%)
1	LDA	-20	<i>i</i> Pr	<1	<1	>90
2	TMPLi	0	<i>i</i> Pr	44	8	48
3	TMPMgCl•LiCl	0	<i>i</i> Pr	34	6	60
4	TMPMgCl•LiCl ^b	0	<i>i</i> Pr	26	9	63
5	TMP ₂ Mg•2LiCl	-10	<i>i</i> Pr	68	<1	32
6	TMP ₂ Mg•2LiCl	0	<i>i</i> Pr	>99	<1	<1
7	TMP ₂ Mg•2LiCl (1.5) ^c	0	<i>i</i> Pr	10	<1	90
8	TMP ₂ Mg•2LiCl	0	Et	95	<1	5

^a All reactions were performed using 0.3 mmol of **2**, 0.9 mmol base, and quenched with 1 M DCl/D₂O. The ratio of products was obtained by ¹H NMR. ²H NMR was also measured to detect **4** and **5**.

^b The reaction was performed at 0 °C for 5 d. ^c Amount of base was decreased to 1.5 eq.

As shown in entries 1 and 2, LDA did not yield any deuterated products, and TMPLi¹³ had a ratio of 52/48 between deuterated products (**4aa** + **5aa**) and non-deuterated **2a**. The deuterated sites were the 2- and 5-positions adjacent to the carbons substituted by the amide, with a ratio of approximately 5/1 (52% yield). This tendency was the same when TMPMgCl•LiCl¹⁴ was used (entry 3). A longer reaction period did not change the results (entry 4). The efficiency and site-selectivity of deprotonation were dramatically improved by using TMP₂Mg•2LiCl^{15,16} at 0 °C, and the 2-deuterated product was obtained quantitatively and selectively (entry 6). When the amount of base, TMP₂Mg•2LiCl, was decreased to 1.5 equivalent, the deprotonation did not proceed efficiently (entry 7). In addition to **2a**, *N,N*-diethylcuneane-1-carboxamide (**2b**) was treated with TMP₂Mg•2LiCl to examine the ability of a directing group. Treatment of **2b** with TMP₂Mg•2LiCl (3.0 eq) gave 95% of the 2-deuterated product **4ba**.¹⁷

As shown in Table 2-2, metalated **2a** was treated with CO₂, allyl bromide, iodine, and I–Cl (entries 1-4). Unfortunately, the reaction conditions with excess TMP–Mg limited the electrophile scope. The iodine-metal exchange reaction of the obtained iodide **4d** was investigated to enable reactions with various electrophiles.

Table 2-2. Reaction of 2-metalated-1-cuneanecarboxamide via deprotonation with various electrophiles. ^{a,b}

entry	E^+	R	yield of 4 (%)		recov. of 2a (%)
1	CO ₂ (then treatment with diazomethane)	CO ₂ Me	80	4b	<3
2	Allyl bromide / CuI	Allyl	90	4c	<3
3	I ₂	I	76	4d	<3
4	ICl	I	88	4d	<3

^a All reactions were performed using 0.5 mmol of **2a**, 1.5 mmol of base, and 4.0 mmol of electrophile.

^b As an electrophile, ClCO₂Et, ClCH₂OEt, Me₃SiCN, and *i*PrOBpin (4.0 mmol) were examined. Any adduct corresponding to **4** was not observed.

As shown in Table 2-3, the iodide **4d** was examined with the reported iodine-metal exchange reagents. Both *i*PrMgCl¹⁸ and its turbo form (*i*PrMgCl·LiCl)¹⁹ efficiently gave the corresponding metalated cuneane from iodide **4d** and gave deuterated product **4aa** quantitatively by quenching with D₃O⁺ (entries 1 and 2). Although *n*BuLi²⁰ also performed complete iodine-metal exchange, but a small amount of **5** was observed due to the formation of a 5-lithio form generated by proton transfer (entry 3). Dianionic zincate, which was used iodine-metal exchange for 4-iodo-*N,N*-diisopropylcuneane-2-carboxamide previously also gave **4aa** in good yield (entry 4).^{20b} Treatment of **4d** with diiodosamarium resulted in complete recovery (entry 5). For these reasons, using Grignard-based reagents, iodine-metal exchange was carried out, and followed by treatment with various electrophiles.

Table 2-3. Iodine-metal exchange reaction of **4d** and quenching with DCl–D₂O. ^a

$\text{4d} \xrightarrow[\text{T } ^\circ\text{C, 1.0 h}]{\text{R-M}} \xrightarrow{\text{D}_3\text{O}^+} \text{4aa}$				
entry	T (°C)	R–M	yield of 4aa (%)	yield of 4d (%)
1	–25	<i>i</i> PrMgCl	>90	<5
2	–25	<i>i</i> PrMgCl•LiCl	>90	<5
3	–40	<i>n</i> BuLi	80 ^b	<5
4	0	<i>n</i> Bu ₄ ZnLi ₂	82	<5
5	25 ^c	SmI ₂	<5	>95

^a All reactions were performed using 0.5 mmol of **4d**, and 1.0 mmol *R–M*. The ratio of products was obtained by ¹H NMR and also checked by ²H NMR. ^b The product via proton migration (2→5) was also obtained (**4aa**/**5aa** = 100/7 by ²H NMR analysis). ^c The reaction period was 9 h.

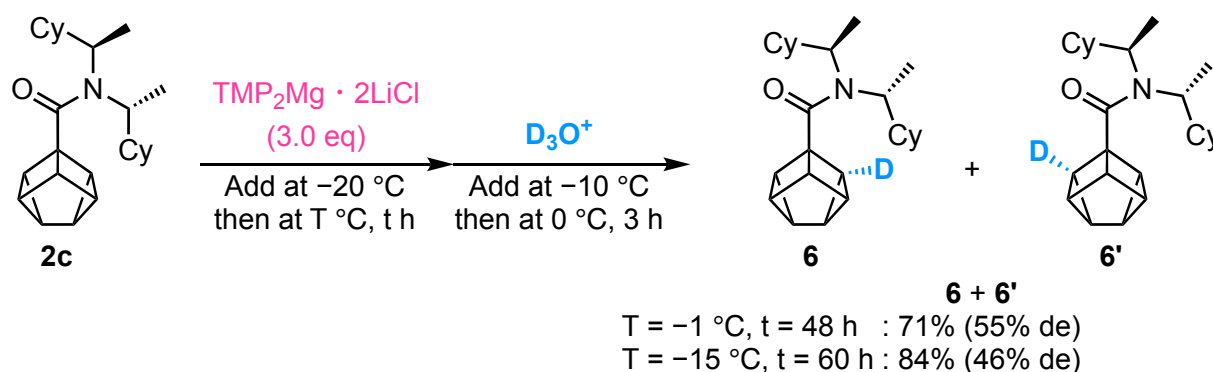
As shown in Table 2-4, the reagent prepared from **4d** and *i*PrMgCl was treated with various electrophiles. The ester **4b**, ether **4e**, organosilane **4f**, and organoboronic ester **4g** were obtained in reasonable yields.

Table 2-4. Reaction of 2-metalated-1-cuneanecarboxamide with various electrophiles via iodine-metal exchange. ^a

$\text{4d} \xrightarrow[\text{–25 } ^\circ\text{C, 0.5 h}]{\text{iPrMgCl}} \xrightarrow[\text{0 } ^\circ\text{C}]{\text{E}^+} \text{4b, e-g}$				
entry	E ⁺	R	yield of 4 (%)	
1	ClCO ₂ Me	CO ₂ Me	52	4b
2	ClCH ₂ OEt	CH ₂ OEt	80	4e
3	Me ₃ SiCN	Me ₃ Si	72	4f
4	<i>i</i> PrOBpin	Bpin	70	4g

^a All reactions were performed using 0.5 mmol of **4d**, 1.0 mmol of *i*PrMgCl, and 1.0 mmol electrophile.

It is notable that all of the products in this method—1,2-disubstituted cuneanes—are chiral molecules.²¹ In chapter 1, the asymmetric synthesis of trisubstituted cubanes using a chiral amide as a chiral auxiliary was examined.^{3a} In the same way, bis((*R*)-1-cyclohexylethyl)amine, which had been developed as a chiral auxiliary for bicyclo[1.1.1]pentane transformation by Anderson,²² had been introduced in 1-cuneanecarboxamide **2c**, which was prepared by Ag⁺ catalyzed isomerization of the corresponding cubane **1c**. As reasonable diastereoselectivities were observed in the deprotonation of **2c** (Scheme 2-1), the possibility for asymmetric induction using a chiral auxiliary was also implied.



Scheme 2-1. Directed deprotonation of 1-cuneanecarboxamide **2c** with chiral auxiliary.

2.3 Conclusion

In conclusion, the author has demonstrated a regioselective synthesis of 1,2-disubstituted cuneane using *ortho*-metalation of a substrate. The usefulness of iodine-metal exchange reaction was also demonstrated. Although the method is of a classical nature, this is the first example of an introduction of substituent via a cuneane anionic species.

2. 4 Experimental Section

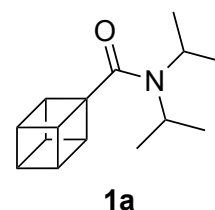
2. 4. 1 Synthetic Procedure

Preparation of Cubanecarboxamides (**1a**, **b**)

Cubane-1-carbonyl chloride (5.0 mmol), prepared following the reported procedure,²³ was treated with the corresponding amine (6.0 mmol, 1.2 equiv) in the presence of triethylamine (6.0 mmol, 1.2 equiv) and a catalytic amount of DMAP in dichloromethane (30 mL) at 25 °C. After 3 h stirring, the mixture was diluted with chloroform (20 mL) and washed with 1 M HCl aq. The obtained organic solution was dried over Na₂SO₄ and concentrated in *vacuo*. Purification by Silica gel column chromatography (Hexane/AcOEt = 10/1) gave the corresponding amides **1a** (96% yield) and **1b** (95% yield).

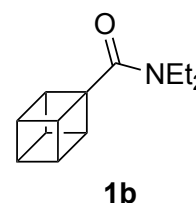
N,N-Diisopropylcubane-1-carboxamide (**1a**)

Isolated as a white solid (1.1 g, 96% yield). ¹H NMR (CDCl₃, 500 MHz): δ 4.19 (m, 3H), 3.97 (m, 4H), 3.53 (sept, 1H, *J* = 6.5 Hz), 3.30 (sept, 1H, *J* = 6.5 Hz), 1.42 (d, 6H, *J* = 6.5 Hz), 1.19 (d, 6H, *J* = 6.5 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 171.2, 59.2, 49.4, 48.1, 46.7, 45.8, 44.2, 21.0, 20.6 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₅H₂₁NONa 254.1526; Found 254.1513; IR (film): 1616, 1447, 1344 cm⁻¹.



N,N-Diethylcubane-1-carboxamide (**1b**)

Isolated as a colorless oil (1.1 g, 96% yield). ¹H NMR (CDCl₃, 500 MHz): δ 4.29–4.20 (m, 3H), 4.02–3.90 (m, 4H), 3.36 (q, 2H, *J* = 7.0 Hz), 3.14 (q, 2H, *J* = 7.5 Hz), 1.19 (q, 3H, *J* = 7.0 Hz), 1.12 (q, 3H, *J* = 7.5 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 171.2, 58.3, 49.6, 46.8, 44.4, 40.6, 39.1 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₃H₁₇NONa 226.1208; Found 226.1201; IR (film): 1609, 1427, 1246 cm⁻¹.



***N,N*-Bis((*R*)-1-cyclohexylethyl)cubane-1-carboxamide (**1c**)**

Isolated as a white solid (1.65 g, 95% yield). ¹H NMR (CDCl₃, 500 MHz): δ 4.29–

4.23 (m, 3H), 3.99–3.90 (m, 4H), 3.04 (dq, 1H, *J* = 8.0, 6.5 Hz), 2.75 (dq, 1H, *J* =

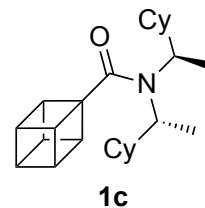
8.0, 6.5 Hz), 2.14–2.06 (m, 1H), 1.93 (t, 2H, *J* = 10 Hz), 1.81–1.60 (m, 9H), 1.45–1.38 (m, 1H), 1.32

(d, 3H, *J* = 6.5 Hz), 1.30–1.00 (m, 5H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.00–0.70 (m, 4H) ppm; ¹³C NMR

(CDCl₃, 125.7 MHz): δ 172.1, 59.4, 58.1, 56.9, 49.9, 46.6, 44.1, 42.3, 41.3, 33.2, 31.9, 31.4, 29.9, 26.8,

26.6, 26.5, 26.4, 26.3, 17.6, 17.4 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₂₅H₃₇NONa 390.2766;

Found 390.2778; IR (film): 1622, 1446 cm⁻¹; [α]_D²⁰ = −19.4 (*c* 0.51, CH₂Cl₂).

**Preparation of Cuneanecarboxamides (**2a**, **b**, **c**, **3a**)**

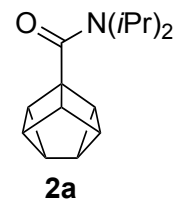
To a solution of cubanecarboxamide (**1a**, 5.0 mmol) in 1,2-dichloroethane (20 mL), AgOTf (5 mol%, 64 mg, 0.25 mmol) was added. The resulting solution was stirred at 75 °C under Ar atmosphere.

Aluminum foil was wrapped around the flask to prevent light. After stirred for 15 h, the resulting mixture was passed through a short silica gel and Celite column, concentrated under vacuum and purified by silica gel column chromatography using hexane/ethyl acetate/dichloromethane (8/1/4) as eluent. The corresponding *N,N*-diisopropylcuneane-1-carboxamide (**2a**) was obtained in 95% yield accompanying *N,N*-diisopropylcuneane-2-carboxamide (**3a**) in 4.6% yield. The ratio of regioisomers **2a/3a** was sensitive to the amount of AgOTf. Increased amount of catalyst caused the low selectivity.

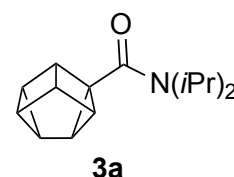
When the reaction was performed using 20 mol% amount of AgOTf, the ratio of regioisomers **2a/3a** was 3/1. The same procedure using **1b** gave *N,N*-diethylcuneane-1-carboxamide (**2b**) predominantly (75% yield). The same procedure using **1c** gave *N,N*-bis((*R*)-1-cyclohexylethyl)cuneane-1-carboxamide (**2c**) predominantly (80% yield).

***N,N*-Diisopropylcuneane-1-carboxamide (2a)**

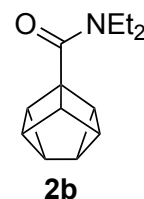
Isolated as a white solid (1.09 g, 95% yield). mp. 118.0 °C; ¹H NMR (CDCl₃, 500 MHz): δ 3.56 (sept, 1H, *J* = 7.0 Hz), 3.30 (sept, 1H, *J* = 7.0 Hz), 3.19 (bs, 1H), 2.49–2.45 (m, 2H), 2.28–2.20 (m, 4H), 1.45 (d, 6H, *J* = 7.0 Hz), 1.18 (d, 6H, *J* = 7.0 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 169.6, 56.0, 48.2, 45.8, 43.4, 35.2, 32.0, 31.9, 21.0, 20.6 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₅H₂₁NONa 254.1520; Found 254.1510; IR (film): 1622, 1373 cm⁻¹.



***N,N*-Diisopropylcuneane-2-carboxamide (3a)** Isolated as a white solid (0.52 g, 4.6% yield). mp. 54.0 °C; ¹H NMR (CDCl₃, 500 MHz): δ 3.61–3.52 (m, 1H), 3.30–3.20 (m, 1H), 3.30–3.20 (m, 1H), 2.88–2.82 (m, 1H), 2.78–2.75 (m, 1H), 2.75–2.71 (m, 1H), 2.66–2.62 (m, 1H), 2.42–2.38 (m, 1H), 2.26–2.22 (m, 1H), 2.20–2.18 (m, 1H), 1.37 (d, 3H, *J* = 6.5 Hz), 1.35 (d, 3H, *J* = 6.5 Hz), 1.18 (d, 3H, *J* = 6.5 Hz), 1.11 (d, 3H, *J* = 6.5 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 169.1, 48.1, 47.4, 45.5, 43.8, 38.9, 38.1, 37.7, 32.7, 31.5, 30.2, 21.0, 20.9, 20.7, 20.2 ppm; HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₂NO 232.1701; Found 232.1695; IR (film): 1622, 1368 cm⁻¹.

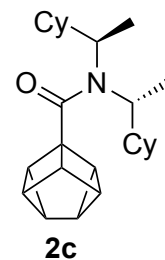
***N,N*-Diisopropylcuneane-1-carboxamide (2b)**

Isolated as a colorless oil (0.76 g, 75% yield). ¹H NMR (CDCl₃, 500 MHz): δ 3.39 (q, 2H, *J* = 7.0 Hz), 3.21 (bs, 1H), 3.18 (q, 2H, *J* = 7.5 Hz), 2.50–2.45 (m, 2H), 2.32–2.27 (m, 2H), 2.24–2.20 (m, 2H), 1.18 (t, 3H, *J* = 7.0 Hz), 1.14 (t, 3H, *J* = 7.0 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 170.0, 55.2, 44.0, 40.7, 38.8, 35.2, 31.9, 31.8, 14.5, 12.8 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₃H₁₇NONa 226.1208; Found 226.1264; IR (film): 1685, 1458, 1276 cm⁻¹.

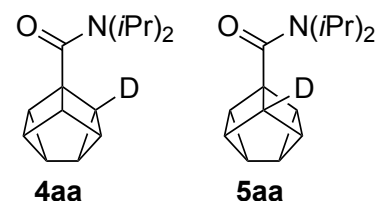


***N,N*-Bis((*R*)-1-cyclohexylethyl)cuneane-1-carboxamide (**2c**)**

Isolated as a colorless oil (1.47 g, 80% yield). ¹H NMR (CDCl₃, 500 MHz): δ 3.22–3.18 (m, 1H), 3.01 (dq, 1H, *J* = 6.5, 6.5 Hz), 2.76 (dq, 1H, *J* = 8.5, 7.0 Hz), 2.48–2.43 (m, 1H), 2.36 (dd, 1H, *J* = 5.0, 5.0 Hz), 2.25 (dd, 1H, *J* = 5.0, 5.0 Hz), 2.22–2.18 (m, 2H), 2.18–2.10 (m, 1H), 2.00–1.88 (m, 2H), 1.82–1.60 (m, 8H), 1.45–1.38 (m, 1H), 1.35 (d, 3H, *J* = 7.0 Hz), 1.32–1.05 (m, 7H), 1.16 (d, 3H, *J* = 6.5 Hz), 1.00–0.70 (m, 4H) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 170.6, 58.0, 57.1, 56.2, 44.1, 42.2, 41.4, 35.7, 35.2, 33.4, 32.1, 32.0, 31.8, 31.3, 29.6, 26.8, 26.6, 26.6, 26.5, 26.4, 26.2, 17.8, 17.3 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₂₅H₃₈NONa 390.2766; Found 390.2767; IR (film): 1616, 1336, 1279 cm⁻¹; [α]_D²⁰ = –28.4 (*c* 5.6, CH₂Cl₂).

**Deuteration via Directed-deprotonation of **2a** (**4aa** and **5aa** in Table 2-1)**

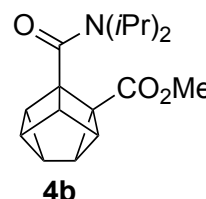
The base was prepared following the reported procedure. LDA and LiTMP were prepared from *n*BuLi and the corresponding amine in THF.²⁴ TMPMgCl•LiCl and TMP₂Mg•2LiCl were prepared by



Knochel's procedure.^{14,15b} The representative example (entry 6 in Table 2-1) was as follows. To a solution of TMP₂Mg•2LiCl (0.90 mmol in THF 3 mL, 3.0 equiv), a solution of **2a** (70 mg, 0.3 mmol) in THF (1.0 mL) was added at –20 °C. The reaction temperature was raised to 0 °C and stirred for 15 h at 0 °C. To a resulting mixture, 1M DCl in D₂O (3 mL) was added at 0 °C. After stirring for 15 min, the mixture was extracted with CHCl₃. The obtained organic solution was dried over Na₂SO₄ and concentrated in *vacuo*. ¹H NMR analysis gave the ratio of **4aa** and **5aa**. The ratio of deuteration at 2 (or 7)- position was calculated from the integration at 3.56 ppm (1H) and that at 2.28–2.20 ppm. And, the integration of the signal at 3.19 ppm shows the ratio of deuteration at 5-position. Furthermore, the existence of D-atm was also supported using ²H NMR (p 20). Deuteration of **2b** was also examined using 3.0 equivalent of TMP₂Mg•2LiCl (Table 2-1, entry 8, Reference 17), and gave **4ba** quantitatively.

Carboxylation via Directed-deprotonation of **2a**; Preparation of methyl 1-(diisopropylcarbamoyl)cuneane-2-carboxylate (**4b** in Table 2-2)

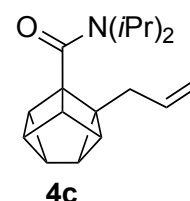
TMP₂Mg•2LiCl was prepared by Knochel's procedure. To a solution of TMP₂Mg•2LiCl (1.5 mmol in THF 5 mL, 3.0 equiv), a solution of **2a** (116 mg, 0.5 mmol) in THF (1.5 mL) was added at −20 °C. The reaction temperature was raised to 0 °C and stirred for 15 h at 0 °C. To a resulting mixture at −10 °C, CO₂ (ca 1 L) gas was bubbled for 2 min and the whole was stirred for 3 h under CO₂ atmosphere at 0 °C. The solvent was removed under reduced pressure. The residue was washed by ether. The washed residue dissolved in 10% HCl_{aq} (15 ml). The aqueous solution was extracted with CHCl₃. The obtained organic solution was dried over Na₂SO₄ and concentrated in *vacuo*. To the obtained residue, ether (5 mL) and methanol (2 mL) was added. To a mixture, 2.5 mL of a hexane solution of trimethylsilyldiazomethane (TCI, 0.6 mol/L) was added dropwise at 0 °C. The mixture was stirred for 1 h at 25 °C. Acetic acid (3~4 drops) was added carefully until the methane gas evaluation stopped. The mixture was concentrated in *vacuo*. Purification by a short silica gel chromatography (Hexane/AcOEt = 1/2 as an eluent) gave **4b** in 80% yield (116 mg) as a colorless oil.



¹H NMR (CDCl₃, 500 MHz): δ 3.72 (sept, 1H, *J* = 6.5 Hz), 3.57 (s, 3H), 3.34 (sept, 1H, *J* = 6.5 Hz), 3.21 (bs, 1H), 3.16 (dd, 1H, *J* = 4.5, 2.5 Hz), 2.98 (dd, 1H, *J* = 4.5, 2.5 Hz), 2.53 (dd, 1H, *J* = 5.0, 5.0 Hz), 2.51–2.47 (m, 1H), 2.23–2.18 (m, 1H), 1.47 (d, 3H, *J* = 6.5 Hz), 1.47 (d, 3H, *J* = 6.5 Hz), 1.22 (d, 3H, *J* = 6.5 Hz), 1.17 (d, 3H, *J* = 6.5 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 168.9, 167.6, 55.7, 51.3, 48.8, 46.1, 45.3, 43.8, 43.7, 42.0, 34.9, 31.5, 31.0, 21.4, 20.5, 20.3, 20.1 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₇H₂₃NO₃Na 312.1575; Found 312.1570; IR (film): 1723, 1623, 1368 cm^{−1}.

Allylation via Directed-deprotonation of **2a**; Preparation of 2-allyl-*N,N*-diisopropylcuneane-1-carboxamide (**4c**)

To a solution of TMP₂Mg•2LiCl (1.5 mmol in THF 5 mL, 3.0 equiv), a solution of **2a** (116 mg, 0.5 mmol) in THF (1.5 mL) was added at −20 °C. The reaction

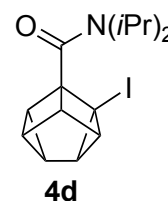


temperature was raised to 0 °C and stirred for 15 h at 0 °C. To a resulting solution, a mixture of allyl bromide (0.48 g, 4.0 mmol) and CuI (9 mg, 0.05 mmol, 10 mol%) in THF (2.0 mL) was added dropwise at –15 °C. The resulting mixture was stirred for 4 h at 0 °C. To a solution, 10wt% HCl_{aq} (15 ml) was added. The aqueous solution was extracted with CHCl₃. The obtained organic solution was dried over Na₂SO₄ and concentrated in *vacuo*. Purification by a short silica gel chromatography (Hexane/AcOEt = 5/1 as an eluent) gave **4c** in 90% yield (115 mg) as a colorless oil.

¹H NMR (CDCl₃, 500 MHz): δ 5.47 (ddt, 1H, *J* = 17.0, 10.0, 6.0 Hz), 4.98 (dd, 1H, *J* = 17.0, 1.5 Hz), 4.93 (dd, 1H, *J* = 10.0, 1.5 Hz), 3.67 (sept, 1H, *J* = 6.5 Hz), 3.34 (sept, 1H, *J* = 6.5 Hz), 3.15 (bs, 1H), 2.45 (dd, 1H, *J* = 17.5, 6.5 Hz), 2.38 (ddd, 1H, *J* = 5.5, 5.5, 2.5 Hz), 2.31–2.28 (m, 1H), 2.30 (dd, 1H, *J* = 17.5, 6.5 Hz), 2.26 (dd, 1H, *J* = 5.5, 2.5 Hz), 2.23 (dd, 1H, *J* = 5.5, 2.5 Hz), 2.18 (ddd, 1H, *J* = 5.5, 5.5, 2.5 Hz), 1.46 (d, 3H, *J* = 7.0 Hz), 1.43 (d, 3H, *J* = 7.0 Hz), 1.22 (d, 3H, *J* = 6.5 Hz), 1.21 (d, 3H, *J* = 6.5 Hz) ppm; ¹³C NMR (CDCl₃, 125.7 MHz): δ 169.2, 134.5, 116.6, 57.7, 48.2, 46.9, 45.9, 42.7, 34.6, 34.2, 33.8, 32.0, 31.7, 31.2, 21.7, 21.1, 20.7, 20.7 ppm; HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₈H₂₅NONa 294.1833; Found 294.1829; IR (film): 1626, 1341 cm^{–1}.

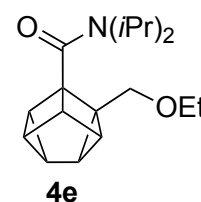
Iodination via Directed-deprotonation of **2a**; Preparation of 2-iodo-*N,N*-diisopropylcuneane-1-carboxamide (**4d**)

To a solution of TMP₂Mg•2LiCl (1.5 mmol in THF 5 mL, 3.0 equiv), a solution of **2a** (116 mg, 0.5 mmol) in THF (1.5 mL) was added at –20 °C. The reaction temperature was raised to 0 °C and stirred for 15 h at 0 °C. To a resulting solution, a solution of ICl (0.65 g, 4.0 mmol) in THF (2.0 mL) was added dropwise at –15 °C. The resulting mixture was stirred for 2 h at 0 °C. To a solution, 10wt% HCl_{aq} (15 ml) was added. The aqueous solution was extracted with CHCl₃. The obtained organic solution was washed with saturated NaHSO₃aq (20 mL). The resulting solution was dried over Na₂SO₄ and concentrated in *vacuo*. Purification by a short silica gel chromatography (Hexane/AcOEt/CH₂Cl₂ = 7/1/4 as an eluent) gave **4d** in 88% yield (126 mg) as a white solid. mp. 108.0 °C; ¹H NMR (CDCl₃, 500 MHz): δ 3.54 (sept, 1H, *J* = 6.5 Hz), 3.40 (bs, 1H), 3.30 (sept,



1H, $J = 6.5$ Hz), 2.72–2.70 (m, 1H), 2.72–2.70 (m, 1H), 2.65–2.56 (m, 2H), 2.50–2.42 (m, 1H), 2.41–2.36 (m, 1H), 1.46 (d, 3H, $J = 6.5$ Hz), 1.45 (d, 3H, $J = 6.5$ Hz), 1.38 (d, 3H, $J = 6.5$ Hz), 1.21 (d, 3H, $J = 6.5$ Hz) ppm ; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 169.6, 56.0, 48.2, 45.8, 43.4, 35.2, 32.0, 31.9, 21.0, 20.6 ppm; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{15}\text{H}_{20}\text{INa}$ 380.0487; Found 380.0485; IR (film): 1630, 1442 cm^{-1} .

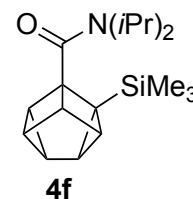
Iodine-Magnesium Exchange Reaction: Preparation of 2-(ethoxymethyl)-*N,N*-diisopropylcuneane-1-carboxamide (4e)



To a solution of iodide **4d** (0.13 g, 0.5 mmol) in THF (2 mL), a solution of $i\text{PrMgCl}$ (Sigma-Aldrich, 0.5 mL, 1.0 mmol, 2.0 M in THF) was added dropwise at -25 °C.

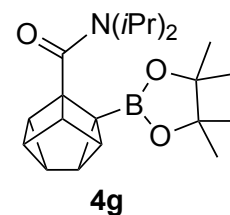
After the mixture was stirred for 0.5 h at -25 °C, a solution of chloromethyl ethyl ether (94 mg, 1.0 mmol) in THF (1.5 mL) was added at -25 °C. The reaction temperature was raised to 0 °C and stirred for 2 h at 0 °C. To a resulting solution, 10wt% HCl_{aq} (15 ml) was added. The aqueous solution was extracted with CHCl_3 . The obtained organic solution was washed with saturated NaHCO_3aq (5 mL). The resulting solution was dried over Na_2SO_4 and concentrated in *vacuo*. Purification by preparative thin-layer chromatography (Hexane/ $\text{AcOEt} = 4/1$) gave **4e** in 80% yield (R_f 0.45, 116 mg) as a colorless oil.

^1H NMR (C_6D_6 , 500 MHz): δ 3.67 (dd 1H, $J = 7.0, 7.0$ Hz), 3.49 (dd 1H, $J = 9.5, 7.0$ Hz), 3.47 (dd 1H, $J = 20.0, 11.5$ Hz), 3.47 (dd 1H, $J = 20.0, 11.5$ Hz), 3.34 (dd 1H, $J = 20.0, 11.5$ Hz), 3.32 (dq 1H, $J = 14.0, 7.0$ Hz), 3.30 (dq 1H, $J = 14.0, 7.0$ Hz), 3.20–3.17 (m, 1H), 2.44–2.40 (m, 1H), 2.39–2.35 (m, 1H), 2.30 (dd, 1H, $J = 5.0, 4.0$ Hz), 2.19 (ddd, 1H, $J = 5.5, 4.5, 3.0$ Hz), 2H), 1.45 (d, 3H, $J = 7.0$ Hz), 1.44 (d, 3H, $J = 7.0$ Hz), 1.19 (d, 3H, $J = 6.5$ Hz), 1.17 (d, 3H, $J = 6.5$ Hz), 1.12 (t, 3H, $J = 6.5$ Hz) ppm ; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 168.7, 68.7, 65.6, 57.1, 48.5, 47.2, 45.8, 42.7, 37.3, 34.9, 34.3, 31.9, 31.4, 21.6, 20.8, 20.7, 20.5, 15.1 ppm; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_2\text{Na}$; 312.1939; Found 312.1943; IR (Film): 1622, 1343 cm^{-1} .

***N,N*-Diisopropyl-2-(trimethylsilyl)cuneane-1-carboxamide (4f):**

A solution of TMSCN (0.10 g, 1.0 mmol) in THF (1.5 mL) was added at $-25\text{ }^{\circ}\text{C}$ to a solution of the reagent prepared from **4d** (0.5 mmol) and *i*PrMgCl (1.0 mmol) as shown in the preparation of **4e**. The reaction temperature was raised to $0\text{ }^{\circ}\text{C}$ and stirred for 2 h at $0\text{ }^{\circ}\text{C}$. To a resulting solution, 10wt% HCl_{aq} (15 ml) was added. The aqueous solution was extracted with CHCl₃. The obtained organic solution was washed with saturated NaHCO₃_{aq} (5 mL). The resulting solution was dried over Na₂SO₄ and concentrated in *vacuo*. Purification by preparative thin-layer chromatography (Hexane/AcOEt = 5/1) gave **4d** in 72% yield (R_f 0.6, 109 mg) as a colorless oil.

¹H NMR (CDCl₃, 500 MHz): δ 3.71 (sept, 1H, J = 6.5 Hz), 3.34 (sept, 1H, J = 6.5 Hz), 3.10 (bs, 1H), 2.43 (dddd, 1H, J = 5.0, 5.0, 2.5, 0.5 Hz), 2.36–2.30 (m, 2H), 2.25 (ddd, 1H, J = 5.0, 4.5, 3.0 Hz), 2.19 (ddd, 1H, J = 5.0, 2.5, 1.0 Hz), 1.46 (d, 3H, J = 6.5 Hz), 1.44 (d, 3H, J = 6.5 Hz), 1.46 (d, 3H, J = 6.5 Hz), 1.44 (d, 3H, J = 6.5 Hz), 1.24 (d, 3H, J = 6.5 Hz), 1.22 (d, 3H, J = 6.5 Hz), -0.06 (s, 9H) ppm ; ¹³C NMR (CDCl₃, 125.7 MHz): δ 170.2, 57.0, 48.0, 46.1, 44.4, 36.6, 36.1, 35.9, 35.4, 33.0, 32.6, 21.9, 21.6, 20.8, 20.4, -1.5 ppm; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₈H₂₉NOSiNa 329.1916; Found 326.1911; IR (film): 1627, 1333 cm⁻¹.

***N,N*-Diisopropyl-2-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)cuneane-1-carboxamide (4g):**

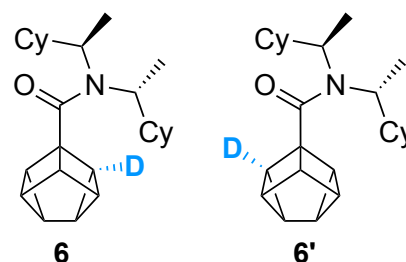
A solution of pinBO*i*Pr (0.19 g, 1.0 mmol) in THF (2.0 mL) was added at $-25\text{ }^{\circ}\text{C}$ to a solution of the reagent prepared from **4d** (0.5 mmol) and *i*PrMgCl (1.0 mmol) as shown in the preparation of **4e**. The reaction temperature was raised to $0\text{ }^{\circ}\text{C}$ and stirred for 4 h at $0\text{ }^{\circ}\text{C}$. To a resulting solution, 3wt% HCl_{aq} (15 ml) was added. The aqueous solution was extracted with CHCl₃. The resulting solution was dried over Na₂SO₄ and concentrated in *vacuo*. Purification by preparative thin-layer chromatography (Hexane/AcOEt = 2/1) gave **4d** in 72% yield (R_f 0.5, 109 mg) as a colorless oil.

¹H NMR (CDCl₃, 500 MHz): δ 3.59 (sept, 1H, J = 7.0 Hz), 3.30 (sept, 1H, J = 7.0 Hz), 3.13 (bs, 1H), 2.73 (ddd, 1H, J = 5.0, 2.5, 0.5 Hz), 2.48–2.42 (m, 2H), 2.39 (ddd, 1H, J = 4.5, 4.5, 1.0 Hz), 2.20 (ddd,

1H, $J = 5.0, 3.0, 0.5$ Hz), 1.46 (d, 6H, $J = 7.0$ Hz), 1.30 (d, 3H, $J = 6.5$ Hz), 1.17 (d, 3H, $J = 6.5$ Hz), 1.15 (s, 12H) ppm ; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 169.4, 82.9, 55.2, 48.3, 45.9, 43.7, 39.0, 38.4, 36.1, 32.6, 32.2, 25.1, 24.4, 22.0, 20.9, 20.1, 20.0 ppm; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{29}\text{NOSiNa}$ 329.1916; Found 326.1911; IR (film): 1627, 1333 cm^{-1} .

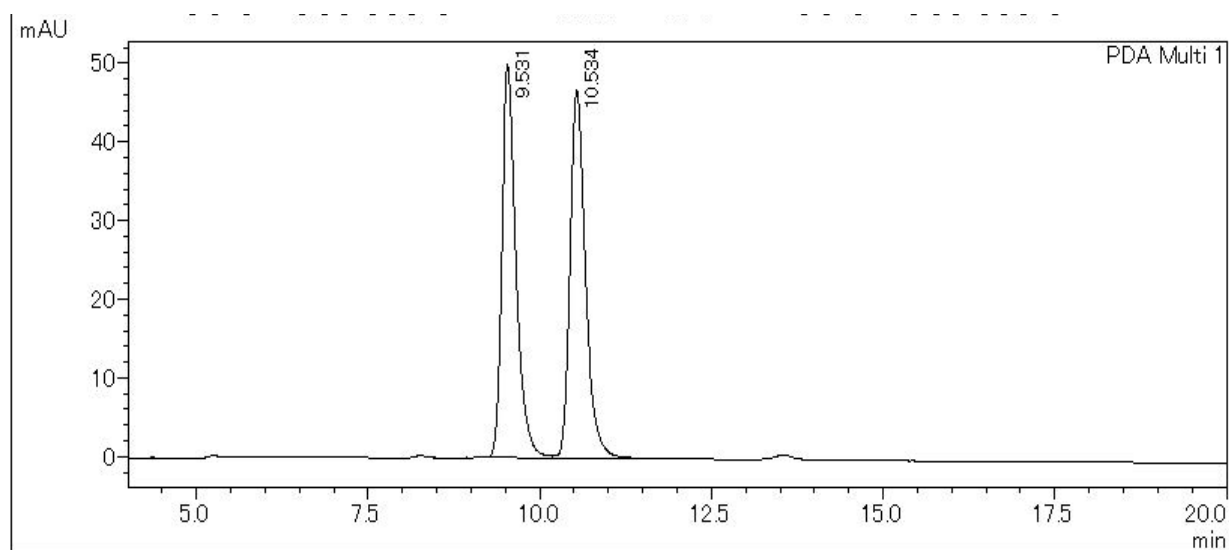
Deuteration via Directed-deprotonation of **2b** (Scheme 2-2)

To a solution of $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (0.90 mmol in THF 3 mL, 3.0 equiv), a solution of **2b** (0.11 g, 0.3 mmol) in THF (1.0 mL) was added at -20°C . The reaction temperature was raised to the indicated temperature and stirred for the indicated period at the same temperature. To a resulting mixture, 1M DCl in D_2O (3 mL) was added at the same temperature. After stirring for 15 min at 0°C , the mixture was extracted with CHCl_3 . The obtained organic solution was dried over Na_2SO_4 and concentrated in *vacuo*. ^1H NMR analysis gave the ratio of **6** and **6'**. The integration of the signal at 2.36 and 2.25 ppm show the ratio of **6** and **6'**. Although the ratio of diastereomers was determined, the structure of the major diastereomer was not determined. Furthermore, the ratio of diastereomers was also shown using ^2H NMR.



2. 4. 2 Chiral HPLC Analysis of Racemic 4d

HPLC DAICEL CHIRALPAK IA, *i*PrOH/Hexane: 1/99, 1 mL/min (220 nm)



Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	9.531	718522	49925	49.876	51.593
2	10.534	722106	46841	50.124	48.407
Sum		1440627	96766	100.000	100.000

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Chapter 3

Studies for Absolute Configuration of Chiral Cuneane-2,6-dicarboxylic Acid Esters

The unique polyfused cyclic hydrocarbon, cuneane, was obtained by structural isomerization of cubane. Eaton has reported that cubane-1,4-dicarboxylic acid ester is selectively isomerized to cubane-2,6-dicarboxylic acid ester catalyzed by silver (I). The cuneane has C_2 symmetry. Chiral resolution of bis(2-phenylethyl) cuneane-2,6-dicarboxylate by chiral HPLC was performed; determination of the absolute configuration of each enantiomer was performed based on ECD spectra and DFT calculation.

3.1 Introduction

Cubane is a highly symmetric molecule that Eaton first reported for practical synthesis in 1964.¹ As the author describes in Chapter 1, the introduction of three substituents onto it results in the formation of a chiral molecule.² In Chapter 1, the author has synthesized trisubstituted chiral cubanes as optically active molecules and also reported their optical properties.³ While the cubane skeleton has potential as a chiral scaffold, the difficulty of introducing at least three substituents site-selectively onto cubane skeleton does not easily allow even its racemic synthesis. Therefore, the author described in Chapter 2 that it is better to use other less symmetrical scaffolds like cuneane, and the author has demonstrated a regioselective synthesis of 1,2-disubstituted cuneane using *ortho*-metalation of the corresponding cuneane-1-carboxamide.

Cubane has a high symmetry O_h , but it is known that through pyrolysis at over 230 °C, cyclooctatetraene is finally produced via cuneane having C_{2v} symmetry.⁴ This cuneane is relatively stable even at 180 °C,⁴ so can be isolated as a stable cage-like hexahedral hydrocarbon. Eaton first reported structural isomerization of cubanes into cuneanes catalyzed by silver (I) or palladium (II) salt.^{5a} According to this report, dimethyl cubane-1,4-dicarboxylate was selectively isomerized to dimethyl cuneane-2,6-dicarboxylate. The selective isomerization can be explained the electron-withdrawing groups on the cubane having a decisive influence on the cationic process assumed by Eaton.^{5b} Although this cuneane-2,6-dicarboxylic acid ester has chirality, there have been no attempts to perform optical resolution and measurement of optical properties.

3.2 Results and Discussion

As shown in Figure 3-1, treatment of bis(2-phenylethyl) cubane-1,4-dicarboxylate (**1**) with a catalytic amount of silver triflate (5 mol%) gave the corresponding bis(2-phenylethyl) cuneane-1,4-dicarboxylate (**2**) in 95% yield as a racemic mixture. For assignment of the complicated absolute configuration of the 2,6-disubstituted cuneanes, we followed the rule for atropisomeric molecules. Viewed from an angle with respect to the main axis ((3)–(7)) where atropisomers can be set, when the near and far substituents are placed clockwise, the isomer is *P*. If it is counterclockwise, it is *M*. In detail, see experimental section 3.4.1. A chiral resolution of **2** into (+)-**2** and (–)-**2** using chiral HPLC showed both enantiomers separable. As shown in Figure 3-2, the isolated enantiomers showed the reversal of optical rotations. The ECD of these enantiomers also supported the successful resolution.

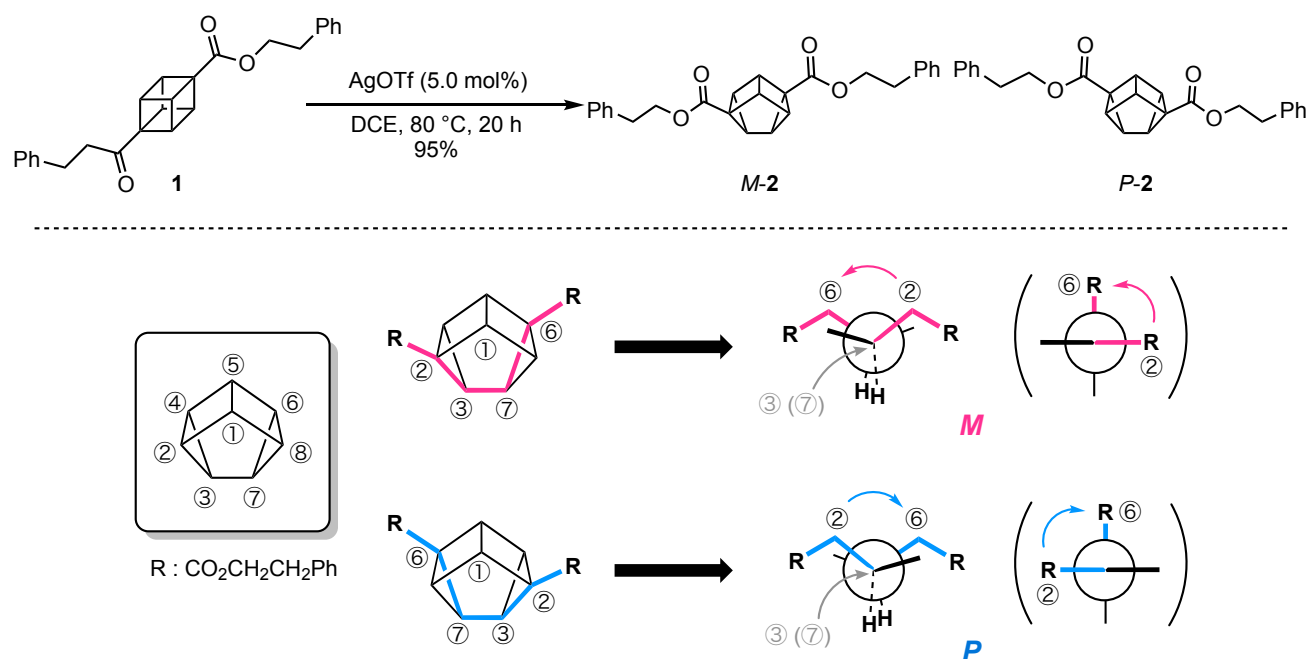


Figure 3-1. Preparation of bis(2-phenylethyl) cuneane-2,6-dicarboxylate as racemate.

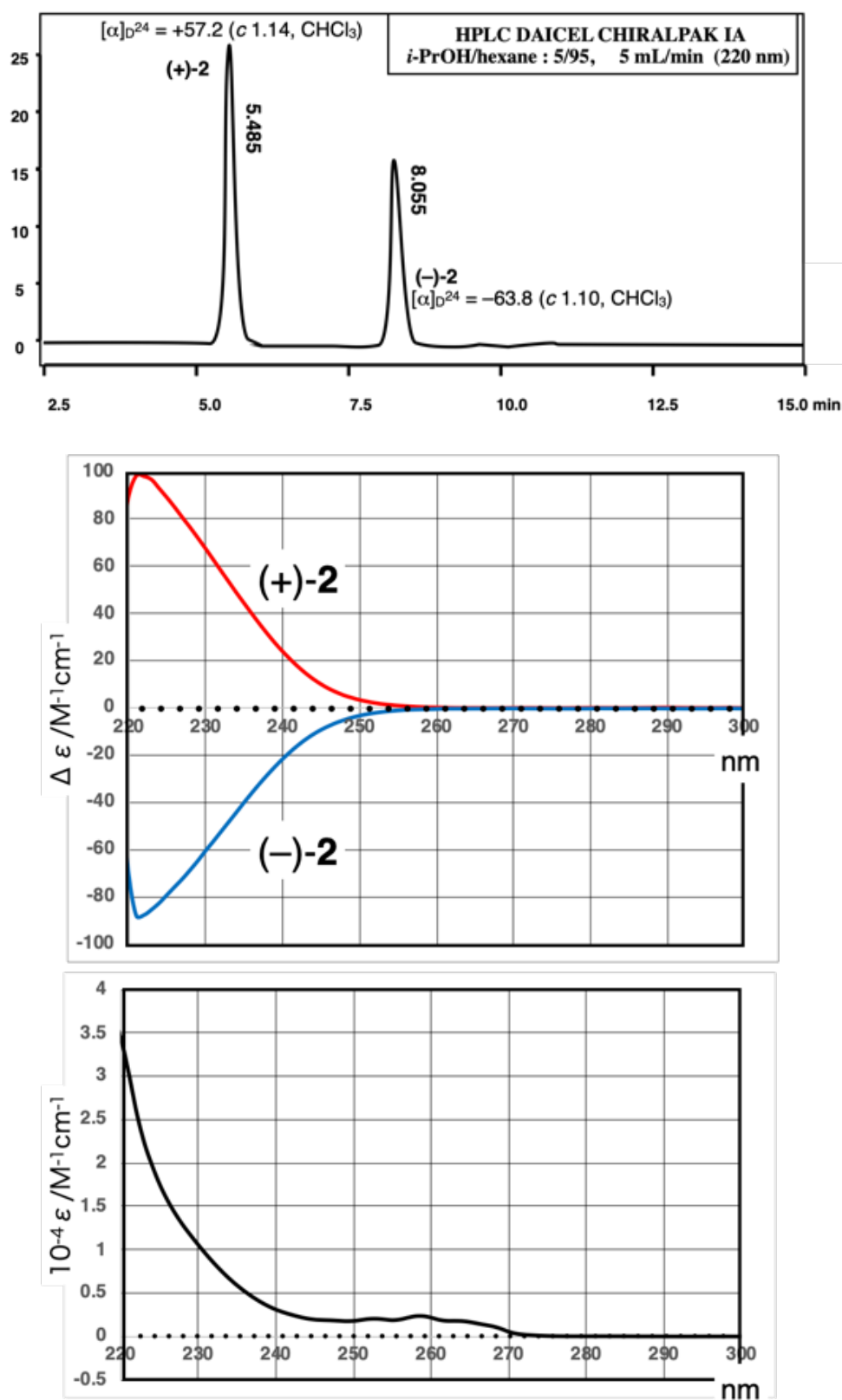


Figure 3-2. chPLC separation of enantiomers of chiral cuneane (+)-2/(-)-2 (top). ECD of (+)-2 (red) and (-)-2 (blue); UV (black) in ethanol (bottom).

A positive or negative ECD signal was observed for (+)-**2** and (–)-**2**, respectively, in the 220–250 nm region. ECD was almost silent in the 250–270 nm region despite the fact that several weak absorption bands were seen in the UV spectrum of (+)/(–)-**2**. These absorption bands are attributable to the π - π^* transition of the phenylethyl moiety.⁶

To determine the absolute configuration of (+)/(–)-**2**, we performed DFT calculations. As the rigid structure and NMR data suggest that **2** adopts a C_2 -symmetric structure in solution, low-energy conformers with C_2 symmetry were only taken into consideration for the conformational analysis. Geometry optimizations of the *P* isomer (**P-2**) gave six low-energy conformers (**A–F**) whose energy differences were less than 0.5 kcal/mol (Figure 3-3 and Table 3-1). The orientation of the carboxylate moieties relative to the cuneane skeleton in the three lowest-energy conformers (**A–C**) is the same as that of the X-ray structure of cuneane-2,6-dicarboxylic acid,⁷ whereas the carboxylate groups are rotated by 180° for the other three conformers (**D–F**).

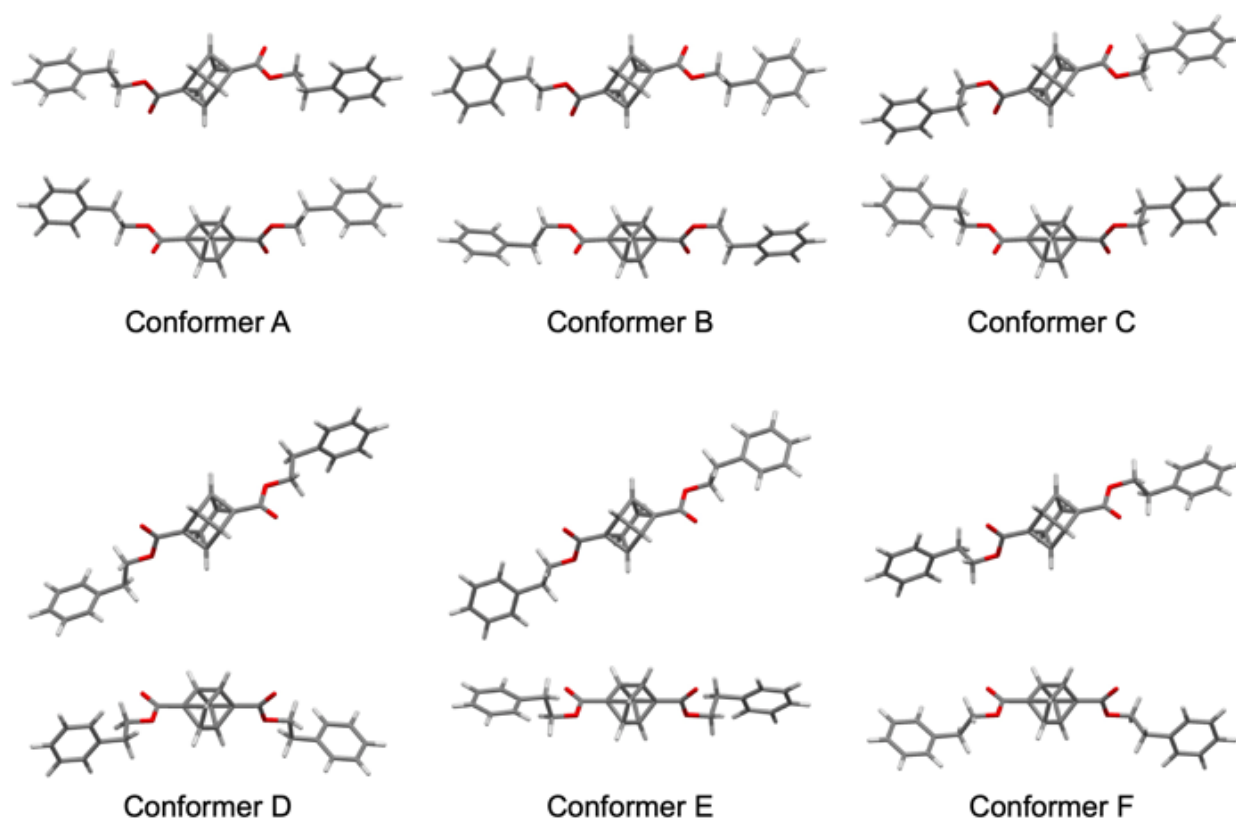


Figure 3-3. Top view (top) and side view (bottom) of the optimized structures of six possible C_2 conformers for **P-2**. All calculations were performed at the B3LYP/6-311+G(d,p) level.

Table 3-1. Energy difference (ΔE), Boltzmann distributions, and specific rotation at the sodium D line ($[\alpha]_D$) of **P-2** conformers at 298 K. ΔE was based on total energies corrected with the zero-point vibrational energies.

conformer	ΔE (kcal/mol)	%	$[\alpha]_D$ (deg)
A	0.00	22.6	−47.33
B	0.13	18.0	−29.44
C	0.17	17.0	−99.94
D	0.23	15.4	−78.45
E	0.29	13.8	−44.29
F	0.32	13.2	−114.97

UV and ECD spectra were then calculated for the six low-energy conformers (Figure 3-4). Each conformer has an absorption band peak at ~210 nm and there is no distinct difference among the conformers. A negative-to-positive ECD sign sequence in ascending energy was predicted for conformers **A–C**, whereas conformers **D–F** were calculated to have a negative ECD band. These computational results indicate that the phenylethyl moieties do not play any essential role in the ECD spectrum, which is in accord with the experimental observation. Figure 3-5 shows the averaged UV and ECD spectra generated based on the Boltzmann distribution at 298 K. As the calculated spectral patterns agree well with the observed patterns for the second fraction, the author can assign (+)-**2** and (−)-**2** as the *M* and *P* isomers, respectively. Optical rotation calculations⁸ support this assignment. All six conformers of the *P* isomer were predicted to have a negative value and the calculated Boltzmann-averaged optical rotation value was −66.39. It was in good agreement with the observed value −63.8 (CHCl₃, *c* 1.10, Figure 3-2).

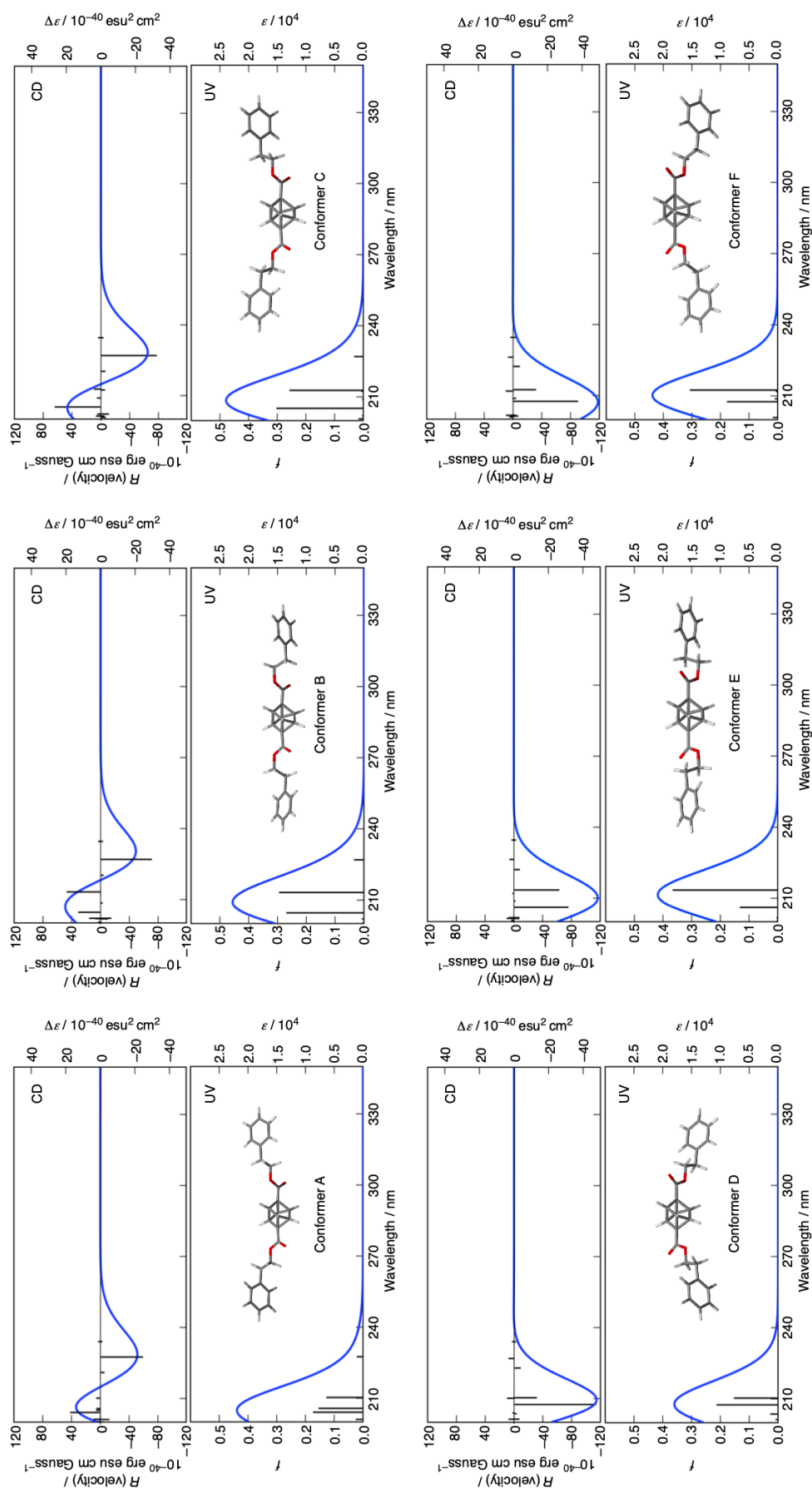


Figure 3-4. Calculated ECD (top) and UV (bottom) spectra for each C_2 conformer of **P-2**.

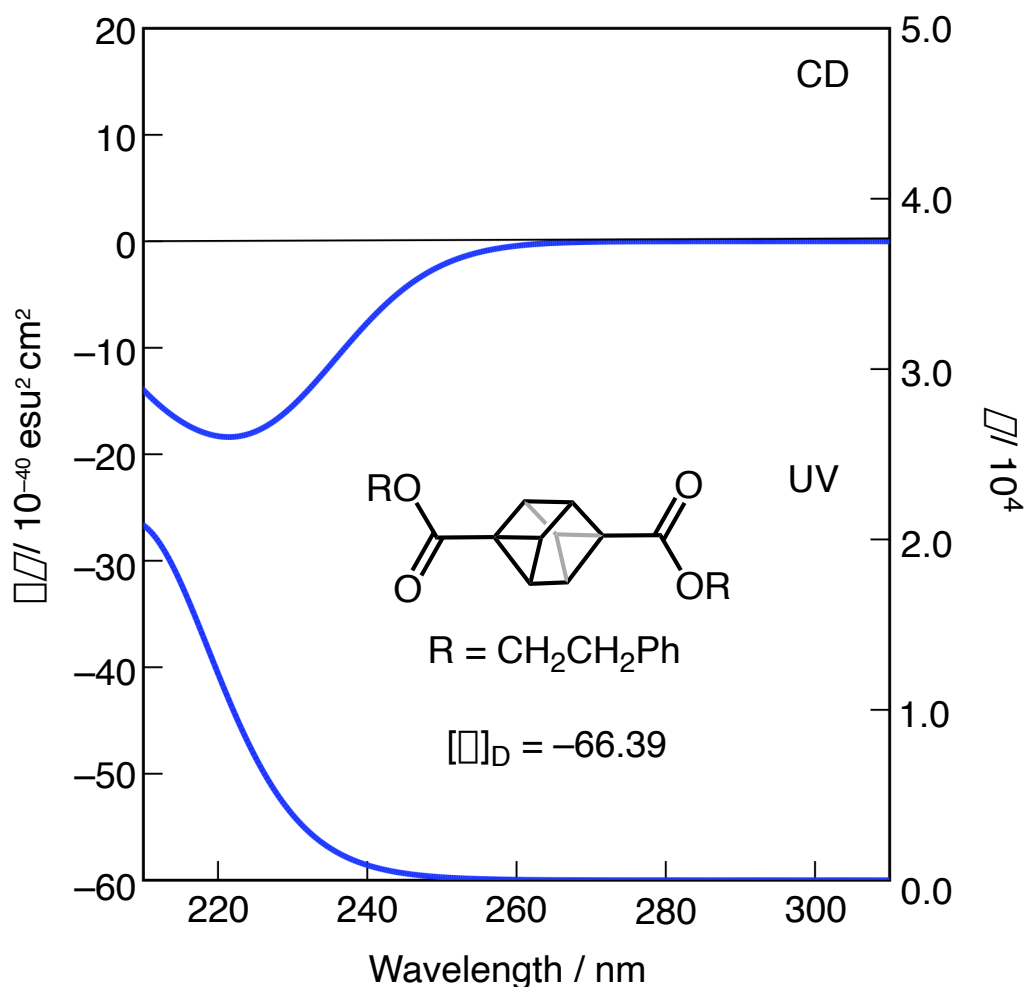


Figure 3-5. Calculated Boltzmann-averaged ECD (top) and UV (bottom) spectra of **P-2** in the 210–310 nm region. Calculated Boltzmann-averaged optical rotation value is also shown. All calculations were performed at the B3LYP/6-311+G(d,p) level.

3.3 Conclusion

Among the issues of chirality of cubane-related molecules submitted by Eaton since 1964, the determination of the absolute structure of cuneane, which is a primary isomer of cubane, was completed here. With this research as a starting point, the author would like to consider the use of cuneane, which is a chiral cage-like hexahedron, as an optically active substance.

3. 4 Experimental Section

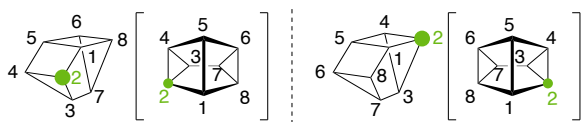
3. 4. 1 A Suggestion for Configuration Notation for Cuneane's Atropisomerism⁹

Since unsubstituted cuneane has C_{2v} symmetry, introducing substituents can potentially induce chirality. The arrangement of atoms around the single bond connecting the two cyclopropane rings gives rise to optical isomers. Since this occurs around an axis, it would be appropriate to use the designations *M* and *P* for naming in the context of atropisomerism. Since cuneane has rarely been studied as an optically active molecule, the notation of absolute configuration has not been sufficiently discussed. Here, we aim to understand the chirality of substituted cuneane molecules by suggesting a notation for the absolute configuration. Figure 3-6-(1) shows the numbering from 1 to 8 according to IUPAC nomenclature. Even if this numbering is strictly applied to this cuneane, distinguishing enantiomers is impossible (*i.e.* Compound **3** and **4**). To further the discussion, let's consider the numbering conducted in a clockwise manner (*i.e.* **A**, ①–⑧: **Note** that these numbers are different from those used in IUPAC nomenclature.). Assuming the bond between carbon atoms ③ and ⑦ as the axis of axial chirality, it is possible to set two types of fixed twisted conformers with four carbons (②, ④, ⑥, ⑧) fixed. Therefore, if even one of these four becomes non-equivalent, the expression of axial chirality becomes possible. The fixed eclipsed conformation by ②–③–⑦–⑥ (**blue**) can be described as counter-clockwise (**M**), and that by ④–③–⑦–⑧ (**red**) can be described as clockwise (**P**) (see Figure 3-6-(2)). The absolute configuration of cuneane can be expressed based on which of these two fixed conformers gains higher priority due to its substituents. The priorities caused by substituents on the carbons ②, ④, ⑥, ⑧ (according to CIP rules) can determine the priority of **blue** or **red**. Follow the sequence diagram in Figure 3-6-(3). It is important to note that chirality is expressed even if the substituents at both ends of each conformer (e.g., ② and ⑥) are identical, due to C_2 symmetry. The two orthogonal twisted bonds ①–⑤ and ③–⑦ can assign priority when the substituents on their carbons ②, ④, ⑥, ⑧ are identical (in the initial classification, when the answer is “YES”). The substituent on ① gives priority to ② and ⑧, while the substituent on ③ gives priority to ② and ④. Therefore, when ①>⑤ and ③>⑦, ② is defined as having the highest priority (See

the box in the upper right of Figure 3-6-(3). For example, compound **5** can be named *P*-3-ethyl-7-propylcuneane-1-carboxylic acid, because ⑧ is defined as having the highest priority, making ④–③–⑦–⑧ the higher priority conformer. Thus, cuneane is a hexahedral hydrocarbon with eight distinct vertices and unique symmetry. As shown in Figure 3-6-(4), monosubstituted and disubstituted cuneanes can exhibit chirality. Please be aware that the numbers (①–⑧) do not necessarily correspond to IUPAC numbering 1-8.

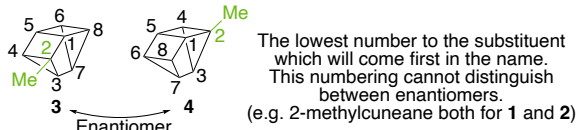
Suggestion: Absolute Configuration Notation for Cuneane's Atropisomerism

- 1) Numbering the vertexes according to IUPAC rule.



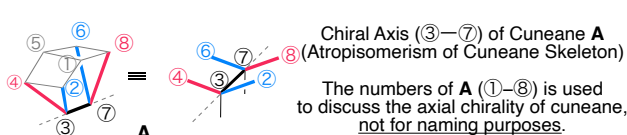
A 2-Substituted Cuneane Enantiomers

In the numbering of vertices (1–8) in a cuneane structure, the numbering begins from the vertex at the junction of the connected squares, ensuring that vertices with substituents are assigned smaller numbers, as shown above.

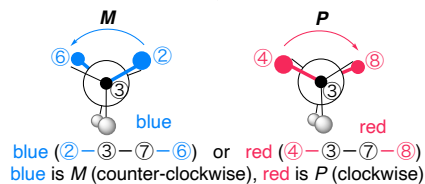


The lowest number to the substituent which will come first in the name.
This numbering cannot distinguish between enantiomers.
(e.g. 2-methylcuneane both for **1** and **2**)

- 2) Determine the High-Priority Substructure (blue or red?).

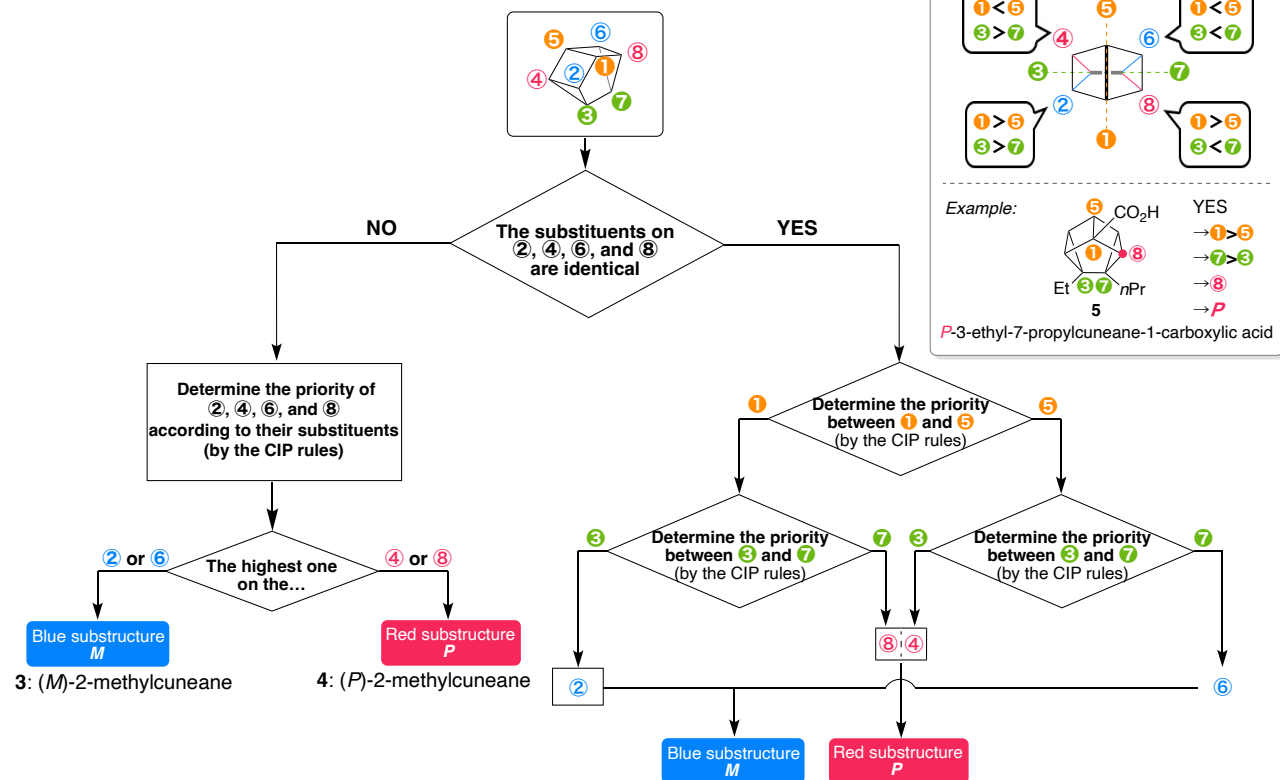


The numbers of **A** (①–⑧) is used to discuss the axial chirality of cuneane, not for naming purposes.



blue (②-③-⑦-⑥) or red (④-③-⑦-⑧)
blue is M (counter-clockwise), red is P (clockwise)

- 3) Sequence Diagram **Only for Determining P/M** (CAUTION: The number is **Not** for IUPAC name)



- 4) The compound name of monosubstituted and disubstituted cuneanes can exhibit chirality

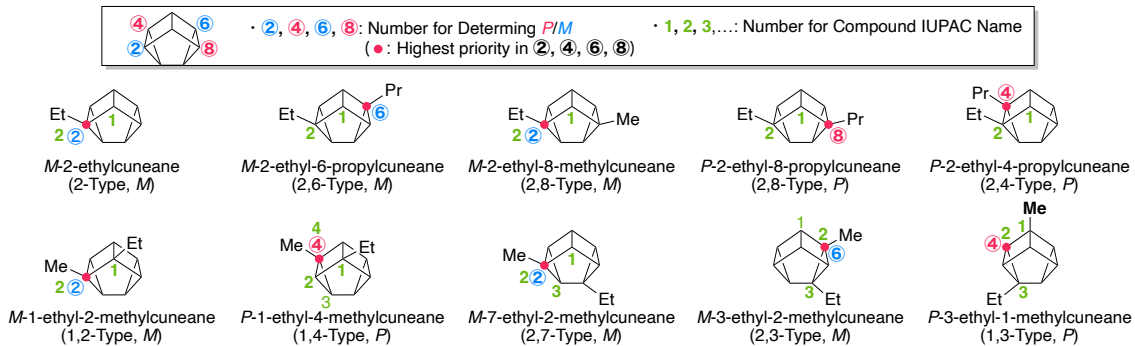
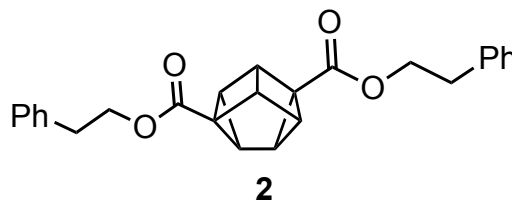


Figure 3-6. My suggestion for absolute configuration notation for chiral cuneanes. (1) The numbering for vertices of cuneane according to IUPAC rule. (2) Determining the high-priority substructure around the chiral axis. (3) Sequence diagram for determining P/M. (4) Examples of mono- and di-substituted cuneanes.

3. 4. 2 Synthetic Procedure

Bis(2-phenylethyl) cuneane-2,6-dicarboxylate (**2**)

A mixture of bis(2-phenylethyl) cubane-1,4-dicarboxylate (0.5 mmol, 200 mg) and AgOTf (0.025mmol, 6.4 mg) in 1,2-dichloroethane (7 ml) was stirred for 20 h at 80 °C. The



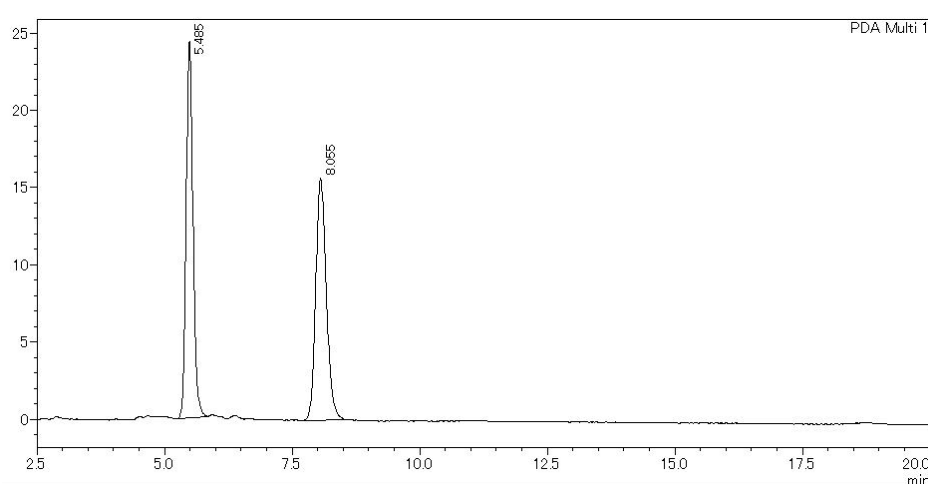
mixture was passed through a short silica-gel column, concentrated under vacuum and chromatographed on silica-gel using ethyl acetate/hexane (1/4) as eluent. The title compound was isolated in 74 % yield (148 mg).

^1H NMR (500 MHz, CDCl_3): δ 7.32-7.29 (m, 4H), 7.28-7.19 (m, 2H), 7.19-7.08 (m, 4H), 4.26-4.18 (m, 4H), 3.06-3.05 (m, 4H), 3.01- 2.99 (m, 2H), 2.89 (t, $J = 7.0$ Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.1, 137.8, 128.9, 128.5, 126.6, 64.8, 43.7, 43.6, 40.5, 38.4, 35.1. HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{24}\text{O}_4$ 401.1747; Found 401.1742; IR (KBr): 1714, 1194 cm^{-1} .

3. 4. 3 Chiral HPLC Analysis

Chiral HPLC analysis of racemic **2**.

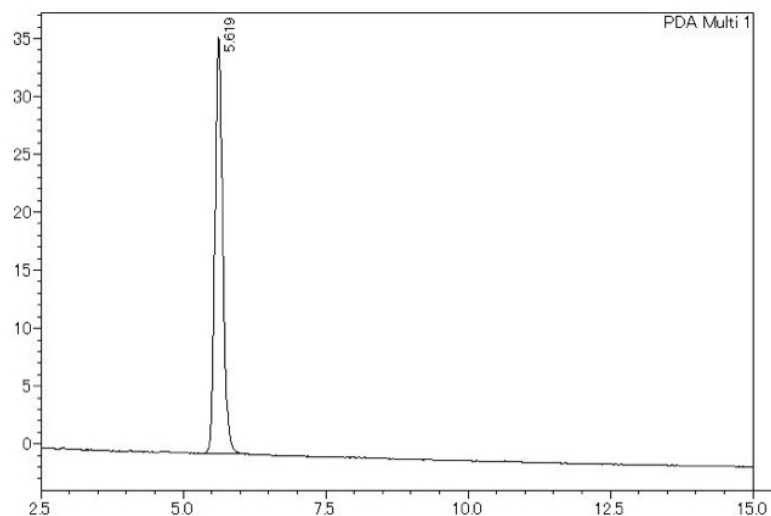
DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min



Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	5.485	227841	24337	50.144	60.892
2	8.055	226532	15631	49.856	39.108
Sum		454372	39968	100.000	100.000

Chiral HPLC analysis of *P/M*-2 after separation and specific rotation *M*-2 and *P*-2.

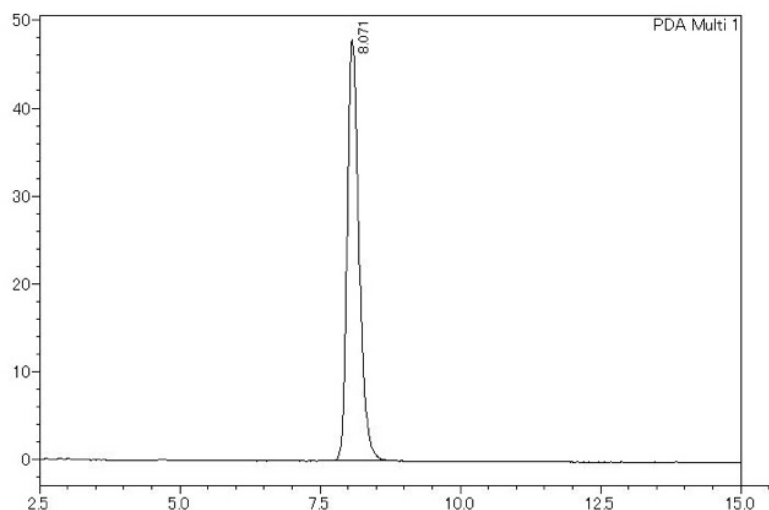
***M*-2** DAICEL CHIRA PAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min



Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	5.619	343315	35948	100.000	100.000
Sum		343315	35948	100.000	100.000

589 nm, Cell 10 cm, 11.4 mg/ml, 24.4 °C, $[\alpha]_D^{24} = +56.7$ (*c* 1.14, CHCl₃)

***P*-2** DAICEL CHIRA PAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min



Peak No.	Reaction Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	8.071	70618	48007	100.000	100.000
Sum		70618	48007	100.000	100.000

589 nm, Cell 10 cm, 11.0 mg/ml, 24.5 °C, $[\alpha]_D^{24} = -63.8$ (*c* 1.10, CHCl₃)

3. 4. 4 Computational Details

All calculations were performed with Gaussian 16 package.¹⁰ Geometry optimizations of the *P* isomer of diphenylethyl-2,6-cuneanedicarboxylate (***P*-2**) were carried out at the B3LYP/6-311+G(d,p) level under a C_2 symmetry constraint. To gain an insight into the effects of side group geometries on chiroptical properties, various conformations were calculated by considering the reported X-ray geometries of related compounds containing a cuneane skeleton¹¹ or a phenylethylcarboxylate moiety¹². Six low-energy conformers whose energy differences were less than 0.5 kcal/mol were obtained. Vibrational frequency computations of these structures verified the nature of the stationary points. Excitation wavelengths, oscillator strengths, rotatory strengths, and specific rotation at the sodium D line ($[\alpha]_D$) were calculated by the TD-DFT approach at the same level as above. Gaussian bands with a half width at half maximum of 2500 cm^{-1} were used to produce the calculated UV and ECD spectra of each conformer, and overall theoretical spectra were generated based on the Boltzmann factors (298 K).

3. 4. 5 Cartesian Coordinates (in Å) and Energies

***P*-2** conformer A

E(RB3LYP) = -1306.36329443 A.U.

O	-1.80029700	3.25257700	-1.61192700	C	1.46769100	-0.16236500	-0.88935700
O	-0.11408800	3.55919200	-0.13722800	C	-0.48362000	-0.61970400	0.01720300
C	-0.52879800	1.37956300	-0.87147600	C	0.90141000	-2.80302900	-0.93633000
C	-0.61274800	0.45186000	-2.08493900	H	1.05661300	-0.83148100	-2.99457300
C	-1.46769100	0.16236500	-0.88935700	H	2.55011300	-0.16369900	-0.89166700
C	0.48362000	0.61970400	0.01720300	H	-0.82937300	-1.06614200	0.94360500
C	-0.90141000	2.80302900	-0.93633000	C	-0.38797600	4.98079300	-0.12473300
H	-1.05661300	0.83148100	-2.99457300	H	-1.41848000	5.14280500	0.19919400
H	-2.55011300	0.16369900	-0.89166700	H	-0.29097200	5.37191200	-1.13995500
H	0.82937300	1.06614200	0.94360500	C	0.38797600	-4.98079300	-0.12473300
O	1.80029700	-3.25257700	-1.61192700	H	1.41848000	-5.14280500	0.19919400
O	0.11408800	-3.55919200	-0.13722800	H	0.29097200	-5.37191200	-1.13995500
C	0.52879800	-1.37956300	-0.87147600	C	-0.61274800	-5.62819800	0.82812900
C	0.61274800	-0.45186000	-2.08493900	H	-0.50132300	-5.17577400	1.81769400

H	-1.62553000	-5.40179100	0.48281900	H	1.35126700	-9.46579900	2.65432200
C	0.61274800	5.62819800	0.82812900	H	0.16990900	-10.97468900	1.07543900
H	0.50132300	5.17577400	1.81769400	C	0.41157000	7.12600000	0.91272000
H	1.62553000	5.40179100	0.48281900	C	1.07221700	7.98838200	0.03086000
C	-0.41157000	-7.12600000	0.91272000	C	-0.46255700	7.67939400	1.85476100
C	-1.07221700	-7.98838200	0.03086000	C	0.86506700	9.36540100	0.08650500
C	0.46255700	-7.67939400	1.85476100	H	1.76037400	7.57859600	-0.70207400
C	-0.86506700	-9.36540100	0.08650500	C	-0.67292600	9.05577500	1.91431000
H	-1.76037400	-7.57859600	-0.70207400	H	-0.97852000	7.02716400	2.55267700
C	0.67292600	-9.05577500	1.91431000	C	-0.00968200	9.90350900	1.02880800
H	0.97852000	-7.02716400	2.55267700	H	1.38959800	10.01757400	-0.60299200
C	0.00968200	-9.90350900	1.02880800	H	-1.35126700	9.46579900	2.65432200
H	-1.38959800	-10.01757400	-0.60299200	H	-0.16990900	10.97468900	1.07543900

P-2 conformer B

E(RB3LYP) = -1306.36371176 A.U.

O	0.76330900	3.63807100	0.65586000	H	-0.14714700	5.34561600	-0.78508600
O	-0.95216700	3.42890300	-0.80890700	C	1.12531200	-4.86668200	-0.83780100
C	0.09521500	1.47426200	-0.07685500	H	1.57862700	-5.06986200	-1.80830500
C	0.45112400	0.61324800	1.13707800	H	0.14714700	-5.34561600	-0.78508600
C	1.35315500	0.59079100	-0.05847000	C	2.03101200	-5.34294200	0.30232100
C	-0.64593000	0.44811200	-0.96529500	H	2.98175000	-4.80540700	0.24373700
C	0.02974400	2.94363200	-0.01346800	H	1.56083700	-5.08294600	1.25378400
H	0.76256600	1.10718400	2.04680800	C	-2.03101200	5.34294200	0.30232100
H	2.38610500	0.91418300	-0.05647500	H	-2.98175000	4.80540700	0.24373700
H	-1.10868500	0.77188700	-1.89154900	H	-1.56083700	5.08294600	1.25378400
O	-0.76330900	-3.63807100	0.65586000	C	2.26790800	-6.83536200	0.22842900
O	0.95216700	-3.42890300	-0.80890700	C	3.38472700	-7.35469200	-0.43527400
C	-0.09521500	-1.47426200	-0.07685500	C	1.35315500	-7.73085000	0.79520500
C	-0.45112400	-0.61324800	1.13707800	C	3.58491500	-8.73096300	-0.53085600
C	-1.35315500	-0.59079100	-0.05847000	H	4.10915500	-6.67526600	-0.87393800
C	0.64593000	-0.44811200	-0.96529500	C	1.54946800	-9.10713500	0.70159100
C	-0.02974400	-2.94363200	-0.01346800	H	0.48425600	-7.34498300	1.31904500
H	-0.76256600	-1.10718400	2.04680800	C	2.66647500	-9.61183800	0.03715700
H	-2.38610500	-0.91418300	-0.05647500	H	4.45982000	-9.11413300	-1.04441400
H	1.10868500	-0.77188700	-1.89154900	H	0.83250500	-9.78512300	1.15131500
C	-1.12531200	4.86668200	-0.83780100	H	2.82199300	-10.68247800	-0.03311400
H	-1.57862700	5.06986200	-1.80830500	C	-2.26790800	6.83536200	0.22842900

C	-3.38472700	7.35469200	-0.43527400	H	-0.48425600	7.34498300	1.31904500
C	-1.35315500	7.73085000	0.79520500	C	-2.66647500	9.61183800	0.03715700
C	-3.58491500	8.73096300	-0.53085600	H	-4.45982000	9.11413300	-1.04441400
H	-4.10915500	6.67526600	-0.87393800	H	-0.83250500	9.78512300	1.15131500
C	-1.54946800	9.10713500	0.70159100	H	-2.82199300	10.68247800	-0.03311400

P-2 conformer C

E(RB3LYP) = -1306.36366229 A.U.

O	-1.02095400	3.56941400	-1.65287000	H	1.26161900	-5.23968900	0.57648500
O	0.67810500	3.49152000	-0.15659000	H	0.05867200	-5.08002400	1.85885000
C	-0.20711900	1.46267300	-0.90091700	C	-0.25047400	5.52387700	0.87770500
C	-0.49663000	0.57705900	-2.11422100	H	-1.26161900	5.23968900	0.57648500
C	-1.39442200	0.48533400	-0.91887100	H	-0.05867200	5.08002400	1.85885000
C	0.60968600	0.49624300	-0.01199400	C	0.13288400	-7.03034300	0.95306900
C	-0.25190800	2.93275800	-0.96617300	C	-0.69164900	-7.64113100	1.90416100
H	-0.84427600	1.04635700	-3.02382900	C	0.82263200	-7.84491200	0.04720300
H	-2.44931900	0.72789400	-0.92106900	C	-0.82454900	-9.02800200	1.95158300
H	1.04657600	0.85459100	0.91411900	H	-1.22826600	-7.02587500	2.61996500
O	1.02095400	-3.56941400	-1.65287000	C	0.69224600	-9.23147700	0.09110600
O	-0.67810500	-3.49152000	-0.15659000	H	1.47117000	-7.38791000	-0.69362200
C	0.20711900	-1.46267300	-0.90091700	C	-0.13288400	-9.82773000	1.04375500
C	0.49663000	-0.57705900	-2.11422100	H	-1.46416000	-9.48305500	2.69981200
C	1.39442200	-0.48533400	-0.91887100	H	1.23834000	-9.84628100	-0.61582300
C	-0.60968600	-0.49624300	-0.01199400	H	-0.23227300	-10.90667600	1.08095200
C	0.25190800	-2.93275800	-0.96617300	C	-0.13288400	7.03034300	0.95306900
H	0.84427600	-1.04635700	-3.02382900	C	0.69164900	7.64113100	1.90416100
H	2.44931900	-0.72789400	-0.92106900	C	-0.82263200	7.84491200	0.04720300
H	-1.04657600	-0.85459100	0.91411900	C	0.82454900	9.02800200	1.95158300
C	0.74338600	4.93827700	-0.13049600	H	1.22826600	7.02587500	2.61996500
H	0.55392400	5.32303500	-1.13299300	C	-0.69224600	9.23147700	0.09110600
H	1.77080600	5.16215100	0.15737400	H	-1.47117000	7.38791000	-0.69362200
C	-0.74338600	-4.93827700	-0.13049600	C	0.13288400	9.82773000	1.04375500
H	-0.55392400	-5.32303500	-1.13299300	H	1.46416000	9.48305500	2.69981200
H	-1.77080600	-5.16215100	0.15737400	H	-1.23834000	9.84628100	-0.61582300
C	0.25047400	-5.52387700	0.87770500	H	0.23227300	10.90667600	1.08095200

P-2 conformer D

E(RB3LYP) = -1306.36285323 A.U.

O	1.99494200	-3.05142300	-1.67431900	H	-0.00126400	5.28776100	1.76278100
O	0.36210800	-3.62714900	-0.21950500	H	1.02869400	5.74325800	0.41043200
C	0.39247000	-1.42345800	-1.01793500	C	-0.00064600	-5.77326700	0.78263100
C	-0.22538800	-0.72761900	0.19657100	H	0.00126400	-5.28776100	1.76278100
C	-1.08655300	-1.00024100	-1.00047300	H	-1.02869400	-5.74325800	0.41043200
C	0.75677600	-0.21341600	-1.90502100	C	-0.46790900	7.20697700	0.90921500
C	1.01732600	-2.75631000	-1.02504400	C	-0.00064600	8.19316100	0.03346200
H	-0.36306500	-1.28939100	1.10944400	C	-1.40162700	7.57206800	1.88524500
H	-1.96287200	-1.63538000	-0.99704900	C	-0.45416400	9.50752700	0.12791500
H	1.30183500	-0.37578200	-2.82900700	H	0.72992500	7.93104600	-0.72564700
O	-1.99494200	3.05142300	-1.67431900	C	-1.85808200	8.88515800	1.98366700
O	-0.36210800	3.62714900	-0.21950500	H	-1.77022100	6.82265200	2.57895300
C	-0.39247000	1.42345800	-1.01793500	C	-1.38582700	9.85744100	1.10375000
C	0.22538800	0.72761900	0.19657100	H	-0.07705100	10.25830600	-0.55763800
C	1.08655300	1.00024100	-1.00047300	H	-2.57898400	9.14917700	2.74948400
C	-0.75677600	0.21341600	-1.90502100	H	-1.73767600	10.87998000	1.18049300
C	-1.01732600	2.75631000	-1.02504400	C	0.46790900	-7.20697700	0.90921500
H	0.36306500	1.28939100	1.10944400	C	0.00064600	-8.19316100	0.03346200
H	1.96287200	1.63538000	-0.99704900	C	1.40162700	-7.57206800	1.88524500
H	-1.30183500	0.37578200	-2.82900700	C	0.45416400	-9.50752700	0.12791500
C	0.88926700	-4.97393500	-0.16489000	H	-0.72992500	-7.93104600	-0.72564700
H	1.92341100	-4.93944200	0.18520300	C	1.85808200	-8.88515800	1.98366700
H	0.89076000	-5.39822100	-1.17142100	H	1.77022100	-6.82265200	2.57895300
C	-0.88926700	4.97393500	-0.16489000	C	1.38582700	-9.85744100	1.10375000
H	-1.92341100	4.93944200	0.18520300	H	0.07705100	-10.25830600	-0.55763800
H	-0.89076000	5.39822100	-1.17142100	H	2.57898400	-9.14917700	2.74948400
C	0.00064600	5.77326700	0.78263100	H	1.73767600	-10.87998000	1.18049300

P-2 conformer E

E(RB3LYP) = -1306.36335132 A.U.

O	-1.50912600	3.31887600	-0.73518500	C	-0.58175500	2.87927800	-0.09274700
O	0.20595000	3.63536500	0.71150300	H	0.55580500	1.21894100	2.03856500
C	-0.16961700	1.46675900	-0.08903500	H	2.19017900	1.31538700	-0.06755100
C	0.33448200	0.68428100	1.12590400	H	-1.22924000	0.56994400	-1.89983300
C	1.22706500	0.82173300	-0.07078200	O	1.50912600	-3.31887600	-0.73518500
C	-0.71521500	0.32686600	-0.97574700	O	-0.20595000	-3.63536500	0.71150300

C	0.16961700	-1.46675900	-0.08903500	C	0.84059900	-7.87790900	-0.75278200
C	-0.33448200	-0.68428100	1.12590400	C	-1.21689400	-8.15040800	0.46187500
C	-1.22706500	-0.82173300	-0.07078200	C	1.10424100	-9.23910600	-0.61455200
C	0.71521500	-0.32686600	-0.97574700	H	1.54169000	-7.24487400	-1.28757700
C	0.58175500	-2.87927800	-0.09274700	C	-0.95688800	-9.51278100	0.60215900
H	-0.55580500	-1.21894100	2.03856500	H	-2.12897200	-7.73261400	0.87711700
H	-2.19017900	-1.31538700	-0.06755100	C	0.20595000	-10.06124500	0.06446300
H	1.22924000	-0.56994400	-1.89983300	H	2.00891700	-9.65833100	-1.04089000
C	-0.09580700	5.04937500	0.78891300	H	-1.66435200	-10.14545800	1.12679000
H	0.28250900	5.35944100	1.76336100	H	0.40845000	-11.12113600	0.16944100
H	-1.17711000	5.18659000	0.75835400	C	0.32359500	7.31450600	-0.21693800
C	0.09580700	-5.04937500	0.78891300	C	-0.84059900	7.87790900	-0.75278200
H	-0.28250900	-5.35944100	1.76336100	C	1.21689400	8.15040800	0.46187500
H	1.17711000	-5.18659000	0.75835400	C	-1.10424100	9.23910600	-0.61455200
C	-0.58688700	-5.82969800	-0.33893900	H	-1.54169000	7.24487400	-1.28757700
H	-1.66204100	-5.63186400	-0.30273200	C	0.95688800	9.51278100	0.60215900
H	-0.21324100	-5.45852000	-1.29634700	H	2.12897200	7.73261400	0.87711700
C	0.58688700	5.82969800	-0.33893900	C	-0.20595000	10.06124500	0.06446300
H	1.66204100	5.63186400	-0.30273200	H	-2.00891700	9.65833100	-1.04089000
H	0.21324100	5.45852000	-1.29634700	H	1.66435200	10.14545800	1.12679000
C	-0.32359500	-7.31450600	-0.21693800	H	-0.40845000	11.12113600	0.16944100

P-2 conformer F

E(RB3LYP) = -1306.36331326 A.U.

O	-0.85813700	3.54104900	-1.72196100	C	-1.35713400	-0.58234900	-1.03919200
O	0.86555900	3.53550100	-0.25137200	C	0.64298600	-0.45263700	-1.94410200
C	0.10247900	1.47290000	-1.05697900	C	0.04049600	-2.93732900	-1.06394800
C	0.45453600	0.61125500	0.15763300	H	-0.77100400	-1.09560800	1.07034100
C	1.35713400	0.58234900	-1.03919200	H	-2.39418100	-0.89183900	-1.03647400
C	-0.64298600	0.45263700	-1.94410200	H	1.10307800	-0.78635800	-2.86827800
C	-0.04049600	2.93732900	-1.06394800	C	0.83807700	4.98160000	-0.18610600
H	0.77100400	1.09560800	1.07034100	H	0.60818200	5.37975900	-1.17489400
H	2.39418100	0.89183900	-1.03647400	H	1.85354400	5.26455000	0.09237200
H	-1.10307800	0.78635800	-2.86827800	C	-0.83807700	-4.98160000	-0.18610600
O	0.85813700	-3.54104900	-1.72196100	H	-0.60818200	-5.37975900	-1.17489400
O	-0.86555900	-3.53550100	-0.25137200	H	-1.85354400	-5.26455000	0.09237200
C	-0.10247900	-1.47290000	-1.05697900	C	0.17435600	-5.47655700	0.85176400
C	-0.45453600	-0.61125500	0.15763300	H	1.17016600	-5.13536900	0.55866500

H	-0.06176200	-5.02166100	1.81812600	H	1.46163800	-9.76267000	-0.51264100
C	-0.17435600	5.47655700	0.85176400	H	0.03374900	-10.87241300	1.18905600
H	-1.17016600	5.13536900	0.55866500	C	-0.15221100	6.98506400	0.96493100
H	0.06176200	5.02166100	1.81812600	C	0.64738100	7.62351600	1.91917000
C	0.15221100	-6.98506400	0.96493100	C	-0.90766100	7.77614100	0.09121700
C	-0.64738100	-7.62351600	1.91917000	C	0.69203100	9.01442100	2.00103000
C	0.90766100	-7.77614100	0.09121700	H	1.23412300	7.02627200	2.61050000
C	-0.69203100	-9.01442100	2.00103000	C	-0.86555900	9.16667200	0.16957800
H	-1.23412300	-7.02627200	2.61050000	H	-1.53799500	7.29718700	-0.65144700
C	0.86555900	-9.16667200	0.16957800	C	-0.06446400	9.79058900	1.12502000
H	1.53799500	-7.29718700	-0.65144700	H	1.31361300	9.49069000	2.75124800
C	0.06446400	-9.79058900	1.12502000	H	-1.46163800	9.76267000	-0.51264100
H	-1.31361300	-9.49069000	2.75124800	H	-0.03374900	10.87241300	1.18905600

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Chapter 4

Catalytic Asymmetric Synthesis of 2,6-Disubstituted Cuneanes through Enantioselective Constitutional Isomerization of 1,4-Disubstituted Cubanes

2,6-Disubstituted cuneane has potential as a *p*-substituted benzene bioisostere and a novel chiral scaffold. It is a constitutional isomer of a 1,4-disubstituted cubane obtained via a metal-catalyzed skeletal rearrangement. Unlike the highly symmetrical 1,4-disubstituted cubane, the isomerized 2,6-disubstituted cuneane is a chiral molecule possessing C_2 symmetry. Examining various chiral catalysts revealed that the Pd-pincer catalyst provides a good asymmetric induction.

4.1 Introduction

As I have demonstrated in the previous chapters, I have focused my research on the potential of cubane and its structural isomer, cuneane, as chiral scaffolds. After Eaton published the synthesis of cubane,^{1,2} its interest as a benzene bioisostere had already been mentioned. In particular, dimethyl cubane-1,4-dicarboxylate obtained from the initial synthesis was superimposed with *p*-substituted benzene.^{3,4} In actual pharmaceuticals, not only *p*-substituted benzene skeletons are used, but also *o*- and *m*-substituted ones. From this perspective, it is considered effective to utilize not only cubane as a benzene bioisostere, but also cuneane, which allows substituents to be arranged at different angles due to the distortion of the cage, rather than symmetrically placing eight substituents at equal angles from a central point as in the case of cubane. However, as described in Chapter 2 and 3, the most prominent feature of the cuneane skeleton is its C_{2v} symmetry. Using this framework, a chiral molecule can be obtained with even a single substituent. This makes the expression of chirality much easier with cuneane compared to introducing three substituents into cubane.^{5,6,7} In other words, the major advantage of using cuneane as a chiral scaffold lies in this aspect. Thermally stable regular hexahedral cubane begins to decompose when the temperature exceeds 230 °C and undergoes skeletal isomerization and finally becomes cyclooctatetraene.⁸ During this decomposition process, cubane is sequentially isomerized into various fused cyclic polyhedral hydrocarbons. The first constitutional isomerized product, cuneane, is a stable and isolable cage-like hexahedral hydrocarbon with 3-membered (×2), 4-membered (×2), and 5-membered rings (×2).⁹ Eaton also reported that cuneanes are obtained by isomerization of cubanes with Ag(I) or Pd(II) salt.¹⁰ Despite this very interesting structure, cuneanes have not been given much consideration.¹¹

The starting material, 1,4-disubstituted cubane, is achiral, but a C_2 symmetrical 2,6-disubstituted cuneane derivative can be a chiral molecule. According to Eaton's first report,¹⁰ cubanes, which have electron-withdrawing substituents such as an ester group at the 1,4-position, can predominantly give the corresponding chiral 2,6-disubstituted cuneane with a small amount of the 1,3-disubstituted isomer is produced (Figure 4-1).

4.2 Results and Discussion

The author reexamined the isomerization of dimethyl cubane-1,4-dicarboxylate (**1a**) using Ag, Pd, and Au catalysts as shown in Table 4-1. In these cases, dimethyl cuneane-2,6-dicarboxylate (**2a**) tends to be the major product. Especially, treatment of **1a** with 5.0 mol% of AgOTf in 1,2-dichloroethane gave **2a** selectively (entry 2). As reported previously,¹⁰ Ag(I) or Pd(II) salt showed catalytic activity, but the catalytic ability of palladium(II) salt was not as high at 80 °C as expected. Au(I) complex has been expected to promote the reaction considering its high activity for σ - π isomerization reaction,¹² and showed a certain level of catalytic activity. Among them, AgOTf, which had the highest activity and selectivity was examined to the isomerization of other 1,4-cubane derivatives (Scheme 4-1). The reactions shown in Scheme 4-1 gave the corresponding 2,6-disubstituted racemic cuneanes including iodo-substituted ones.

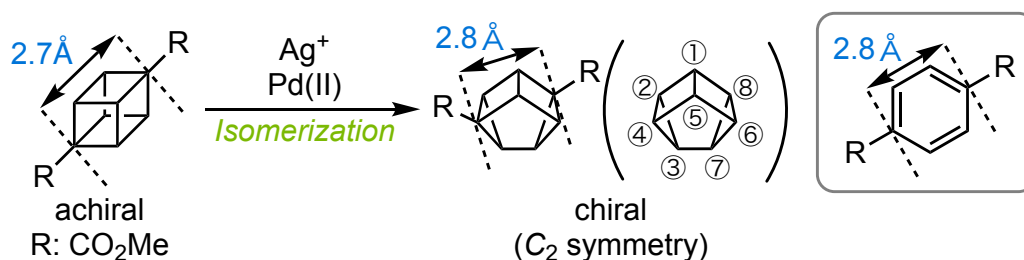
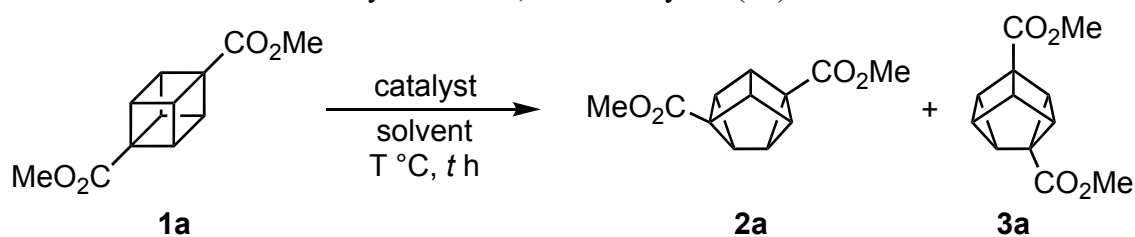


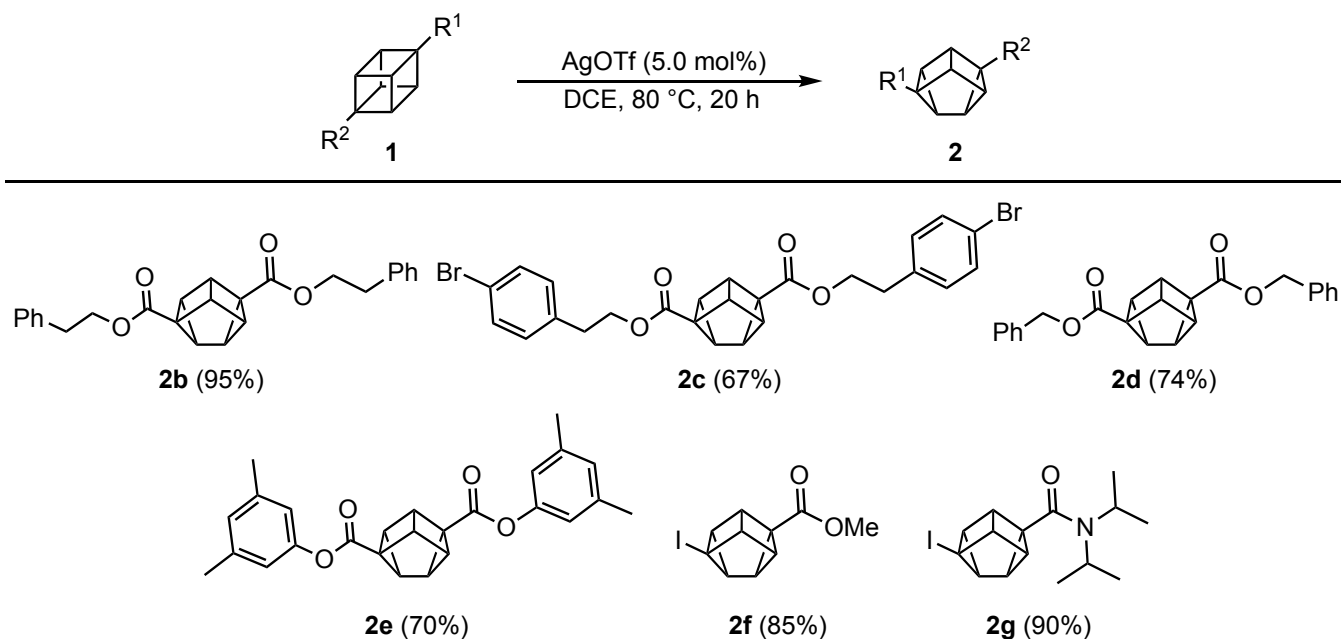
Figure 4-1. Constitutional isomerization of achiral 1,4-cubanes to chiral 2,6-cuneanes.

The chiral resolution of diester **2b** using chiral HPLC was examined. Both enantiomers are separable. The isolated enantiomers show the reversal of optical rotations (Figure 4-2). Based on the DFT-calculated ECD spectra for the preferable conformers, the *P*-isomer of **2b** should have a negative $[\alpha]$ value.¹³ For the assignment of the absolute configuration of the 2,6-disubstituted cuneanes **2b**, the author followed the rule for axially chiral molecules as discussed in Chapter 3. Accordingly, it was viewed from an angle with respect to the main axis (③–⑦), where the chirality can be set. The *P* isomer denotes the clockwise placement of the near and far substituents, while *M* indicates a counterclockwise placement.

Table 4-1. Isomerization of dimethyl cubane-1,4-dicarboxylate (**1a**). ^a

entry	cat / mol%	solvent	T (°C)	t (h)	yield of 2a (%)	yield of 3a (%)	recov. of 1a (%)
1	AgOTf / 50	PhCH ₃	100	20	99	<1	<1
2	AgOTf / 5.0	DCE	80	20	96	<1	<1
3	AgOTf / 5.0	DCM	80	20	69	<1	30
4	AgPF ₆ / 5.0	DCE	60	20	48	6	14
5	AgSbF ₆ / 5.0	DCE	80	20	46	8	31
6	Pd(OAc) ₂ / 5.0	DCE	80	20	3	<1	22
7	Pd(TFA) ₂ / 5.0	DCE	80	20	3	4	8
8	PdCl ₂ (MeCN) / 5.0	DCE	80	20	25	4	25
9	(AuPPh ₃)OTf / 5.0	DCM	20	4	9	<1	33
10	(AuPPh ₃)OTf / 5.0	DCM	60	20	48	6	10
11	(AuPPh ₃)OTf / 5.0	DCE	80	20	21	4	76

^a **1** (0.3 mmol), solvent (3 ml), under Ar.

**Scheme 4-1.** Ag⁺-catalyzed constitutional isomerization of 1,4-cubanes to 2,6-cuneanes.

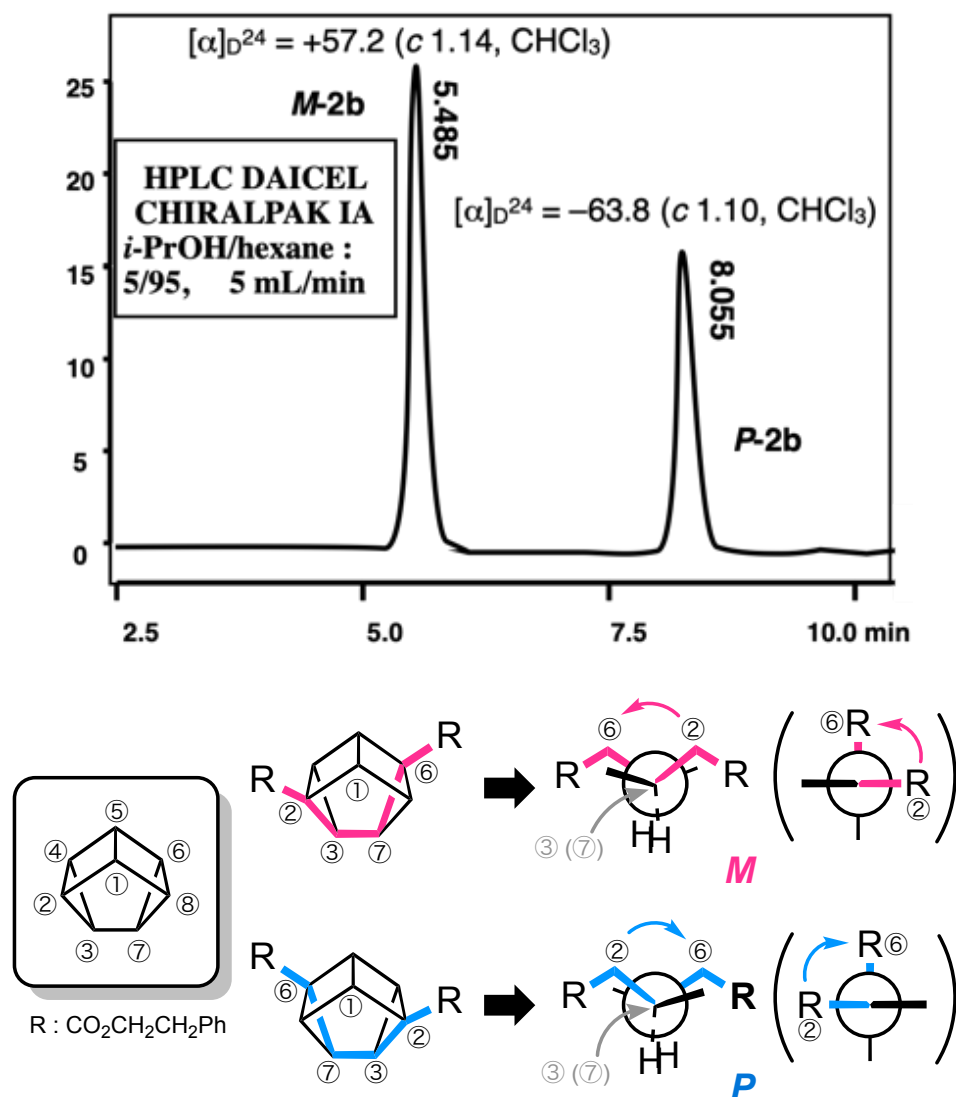


Figure 4-2. cHPLC separation of enantiomers of chiral cuneane (+)-**2b**/(-)-**2b**; assignment of the stereochemical description (Absolute configuration of each enantiomer was determined as shown in Chapter 3).

Eaton reported that the mechanism of the isomerization involves a cationic intermediate, which is formed by the interaction of Ag^+ with strained σ -bond of cubane.^{10,14} The detailed mechanism was not shown, but the use of Ag(I) or Pd(II) with a chiral ligand may result in asymmetric induction. Figure 4-3 shows the schematic analysis of the isomerization from 1,4-cubane into 2,6-cuneane. In the 1,4-disubstituted cubane, whose substituents on ① and ④ are electron-withdrawing such as ester, Lewis acidic catalyst will not interact with the electron-deficient bonds (black), but does preferentially with bonds a-f (red and blue). For isomerization into cuneanes, two C–C bonds in cubanes should be cleaved and recombined. In addition, these two bonds should be skew. When the two skew blue bonds participate in the reaction in Figure 4-3 (ie, a–c, a–e, or c–e), the product will be the *P*-isomer, whereas the reaction of the two skew red bonds (ie, b–d, b–f, or d–f), will give the *M*-isomer. For asymmetric induction, the catalyst must perform the very difficult task of choosing three of the six alternating arrangements around the 1,4-axis of cubane as it approaches.

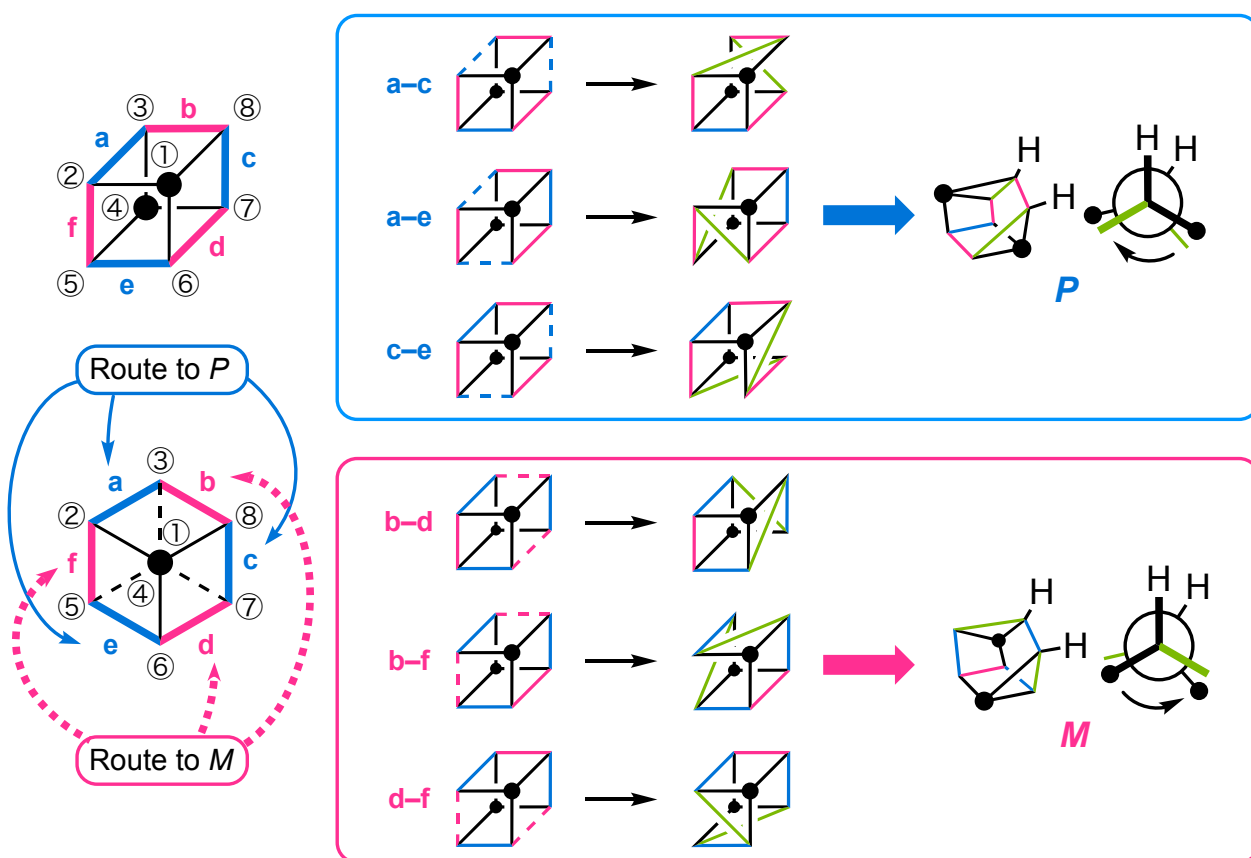


Figure 4-3. Schematic explanation for the asymmetric isomerization.

If the reaction proceeds via a cationic intermediate as formerly suggested, the use of Ag^+ accompanying an optically active anion such as BINAPHOS may show some asymmetric induction. Various catalysts of Ag^+ -chiral phosphate were examined,¹⁵ but a positive result was not obtained (Table 4-2, entries 1–5). Employing specific Pd catalysts may change the reaction mechanism. If a Pd-coordinated intermediate is formed, cubane would be diastereomers **A** and **B**. If one matched diastereomer (**A**) isomerizes to the cuneane faster than the other **B**, the product will display optical activity (Figure 4-4). The mismatched **B** would be converted into the matched one (**A**) via starting material under equilibrium. The back-donation character of Pd metal may provide enough stabilization for the equilibrium between diastereomers.

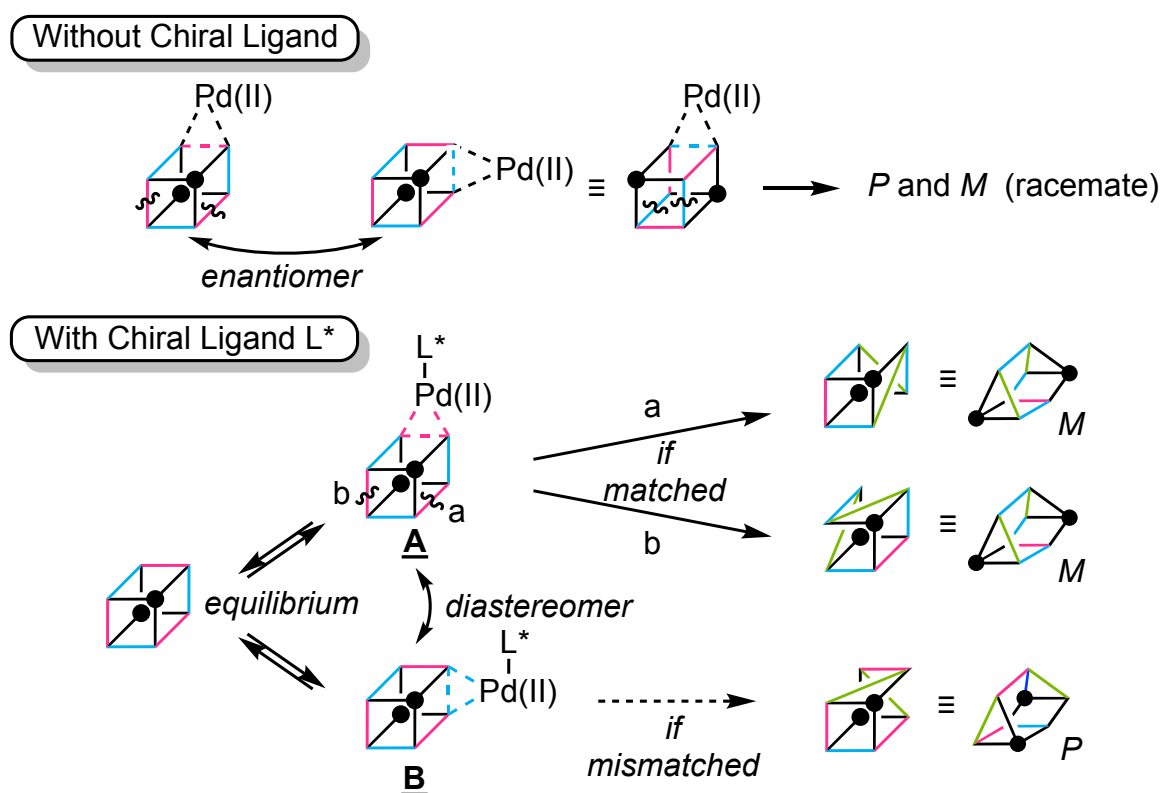
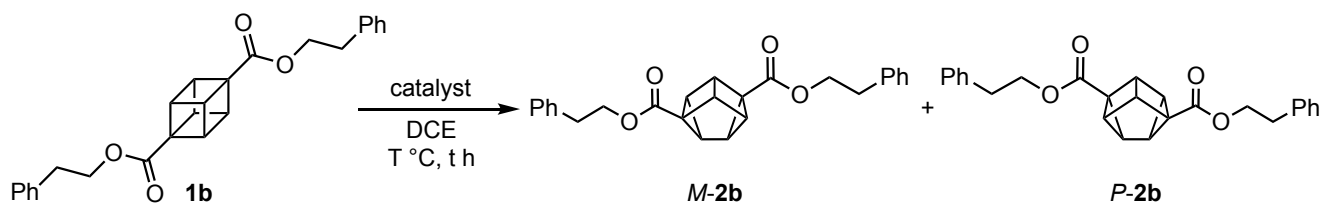
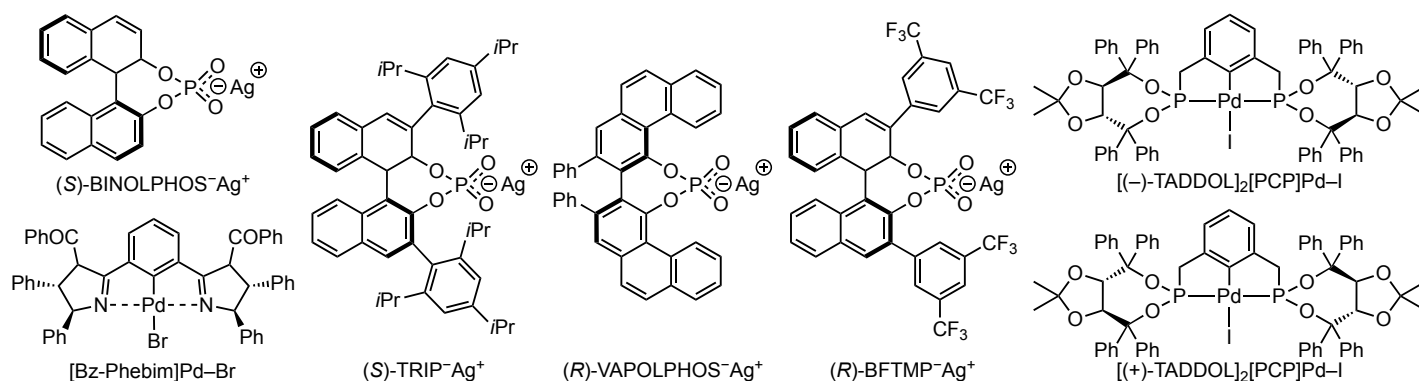


Figure 4-4. Working-hypothesis for asymmetric induction via palladacycle.

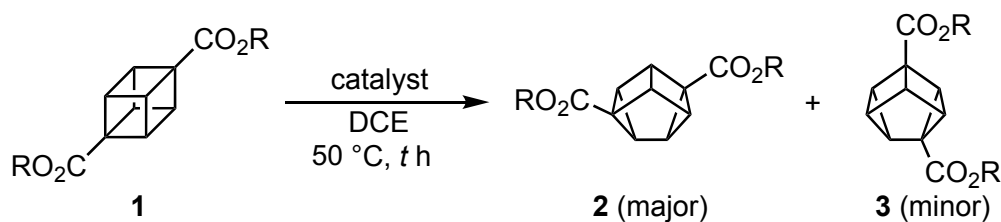
The author then examined a series of Pd catalysts. Pd(II) salts are not active enough for the rearrangement (Table 4-1), so, a cationic Pd(II) species formed by treatment of Pd–X with AgOTf was also examined. The catalyst prepared from BINAP-PdCl₂/AgOTf via an asymmetric C–C bond-forming reaction as reported by Mikami and Sodeoka¹⁶ did not work well (entry 6) in this case. A cationic Pd(II) with a chiral pincer ligand was investigated (entries 8, 10–11). The N–C–N pincer ligand was not active for isomerization (entry 8). However, the P–C–P ligand gave **2** with a reasonable asymmetric induction (entry 10). Using the enantiomer of the ligand showed the opposite asymmetric induction (entry 11).¹⁷ Entries 12–15 show the results of tuning the ester group in **1**. The substrate scope of this asymmetric reaction was shown in Table 4-3. In the case of Pd-pincer catalyzed reaction, 1,3-isomers were formed in a significant amount. This is a sharp contrast from the usual isomerization reaction using Pd(II) catalyst in Table 4-1.

Table 4-2. Asymmetric isomerization of bis(2-phenylethyl) cubane-1,4-dicarboxylic acid ester (**1b**) into bis(2-phenylethyl) cuneane-2,6-dicarboxylic acid ester (**2b**).^a

entry	catalyst	T (°C)	t (h)	yield of 2b (%)	% ee	[α] _D ²⁰	recov. of 1b (%)
1	(<i>S</i>)-BINAP / AgOTf	80	20	<1	NA	NA	89
2	(<i>S</i>)-BINOLPHOS [−] Ag ⁺	80	24	20	2	NA	38
3	(<i>S</i>)-TRIP [−] Ag ⁺	80	84	15	10	NA	81
4	(<i>R</i>)-VAPOLPHOS [−] Ag ⁺	60	72	30	2	NA	65
5	(<i>R</i>)-BFTMP [−] Ag ⁺	80	72	<1	NA	NA	<1
6	[(+)-BINAP] ₂ PdCl ₂ / AgOTf	80	20	<1	–	NA	>90
7	[Bz-Phebim]Pd–Br	80	20	<1	–	NA	>90
8	[Bz-Phebim]Pd–Br / AgOTf	80	20	<1	–	NA	>90
9	[(-)-TADDOL] ₂ [PCP]Pd–I	80	20	<1	NA	NA	>90
10	[(-)-TADDOL] ₂ [PCP]Pd–I / AgOTf	50	72	31	67	+42.7 (<i>c</i> 1.03) ^b	39 ^c
11	[(+)-TADDOL] ₂ [PCP]Pd–I / AgOTf	50	72	52	–55	–39.0 (<i>c</i> 1.05) ^b	15 ^c



^a **1** (0.3 mmol), solvent (3 ml), under Ar. ^b The positive optical rotation corresponds to the *M*-isomer; the negative one corresponds to *P*-isomer. ^c 1,3-Isomers were also observed; see Table 4-3.

Table 4-3. Substrate scope of asymmetric isomerization of cubane-1,4-dicarboxylic acid ester (**1**) into cuneane-2,6-dicarboxylic acid ester (**2**).

entry	catalyst	R in 1	yield of 2 (%)	% ee	$[\alpha]_D^{20}$	recov. of 1 (%)	yield of 3 (%)
1	[(-)-TADDOL] ₂ [PCP]Pd-I / AgOTf	CH ₂ CH ₂ Ph ^a (1b)	31 (2b)	67	+42.7 (<i>c</i> 1.03) ^b	39	28
2	[(+)-TADDOL] ₂ [PCP]Pd-I / AgOTf	CH ₂ CH ₂ Ph ^a (1b)	52 (2b)	-55	-39.0 (<i>c</i> 1.05) ^c	15	24
3	[(-)-TADDOL] ₂ [PCP]Pd-I / AgOTf	CH ₂ CH ₂ <i>p</i> C ₆ H ₄ Br (1c)	23 (2c)	78	+41.7 (<i>c</i> 0.79) ^c	40	14
4	[(+)-TADDOL] ₂ [PCP]Pd-I / AgOTf	1c	41 (2c)	-52	-20.2 (<i>c</i> 0.79) ^c	30	15
5	[(-)-TADDOL] ₂ [PCP]Pd-I / AgOTf	CH ₂ CH ₂ <i>p</i> C ₆ H ₄ F (1h)	28 (2h)	62	+17.1 (<i>c</i> 0.85) ^c	32	18
6	[(-)-TADDOL] ₂ [PCP]Pd-I / AgOTf	CH ₂ CH ₂ <i>p</i> C ₆ H ₄ Cl (1i)	40 (2i)	63	+2.4 (<i>c</i> 0.82) ^c	21	20

^a The major enantiomer of entry 1 was *M*-isomer; that of entry 2 was *P*-isomer. See chapter 3. ^b In DCM. ^c In CH₃CN. $[\alpha]_D^{20}$ values are reported in [deg · dL · g⁻¹ · dm⁻¹].

4.3 Conclusion

The highly symmetric regular hexahedral hydrocarbon first reported in 1964 can be converted into an optically active cage-like hexahedral hydrocarbon cuneane in one step, although the yield and ee in this study were not always sufficient. The racemic isomer formation was demonstrated in 1970, and this study is the first to report the development of the asymmetric version. It is interesting that the isomerization of cubic molecules with a very high symmetry induces asymmetry at the rigid reaction site of the chiral Pd-pincer catalyst. This approach should be applicable to similar isomerization reactions. This study focuses on the asymmetric synthesis of the major product, 2,6-disubstituted

cuneanes; however, 1,3-disubstituted cuneanes, which are produced as a by-product, are also chiral molecules. In the future, the author plans to expand the range of disubstituted cuneanes that can be asymmetrically synthesized as well as 1,3-disubstituted ones from achiral cubanes. The asymmetric synthesis of these chiral cage-shaped polyhedral hydrocarbons indicates the emergence of new chiral scaffolds.

4.4 Experimental Section

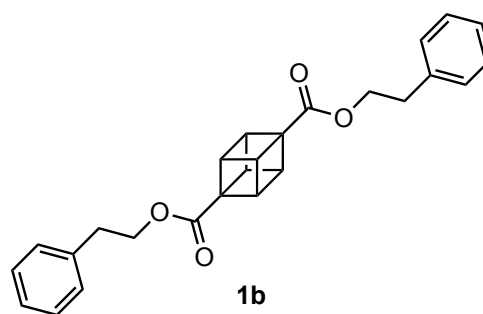
4.4.1 Synthetic Procedure

Preparation of Cubane-1,4-dicarboxylic acid ester as starting material (1a-1e, 1h, 1i)

A mixture of cubane-1,4-dicarboxylic acid (2.0 mmol) and thionyl chloride (4.0 mL) was heated and stirred under reflux for 3 h in Ar. The excess thionyl chloride were removed by short-path distillation and volatiles were completely removed under vacuum at rt for 30 min. To the residue, dichloromethane (DCM, 5.0 mL) was added. The resulting solution was cooled to 0 °C under Ar. To the cooled solution, a solution of alcohol (4.4 mmol) and Et₃N (6.0 mmol) in DCM (4.0 mL) was added dropwise at 0 °C under Ar, followed by an addition of a catalytic amount of DMAP. The mixture was stirred for 15 min at 0 °C, and then warmed to rt over 12 h. About 20mL of DCM was added to the mixture, and the organic layer was washed with HCl (1.0 M). After extracting the aqueous solution with DCM, the organic layer is washed lightly with brine (10 mL). The combined organic layers were concentrated under vacuum. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/4) as eluent. The title compound was isolated.

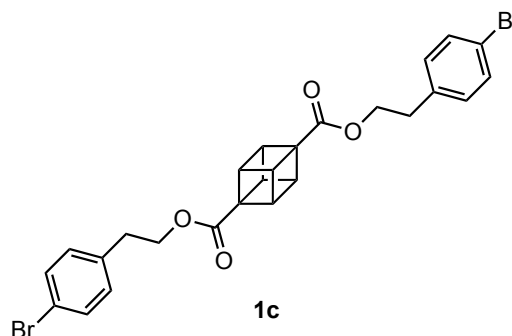
Diphenethyl cubane-1,4-dicarboxylate (1b)

¹H NMR (500 MHz, CDCl₃): δ 7.32 - 7.22 (m, 10H), 4.33 (t, J = 7.00 Hz, 4H), 4.19 (s, 6H), 2.97 (t, J = 7.0 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 171.5, 137.8, 129.0, 128.5, 126.6, 64.8, 47.0, 35.2; HRMS (APCI) m/z : [M+H]⁺ Calcd for C₂₆H₂₄O₄H 401.1747; Found 401.1742; IR (KBr): 1714, 1194 cm⁻¹.



Bis(4-bromophenethyl) cubane-1,4-dicarboxylate (1c)

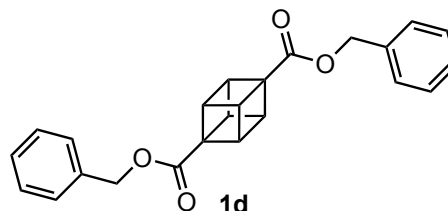
¹H NMR (500 MHz, CDCl₃): δ 7.42 (d, J = 8.50 Hz, 4H), 7.09 (d, J = 8.50 Hz, 4H), 4.28 (t, J = 6.75 Hz, 4H), 4.17 (s, 6H), 2.91 (t, J = 6.75 Hz, 4H); ¹³C NMR (125 MHz,



CDCl_3): δ 171.3, 136.7, 131.5, 130.7, 120.5, 64.4, 55.8, 47.0, 34.5; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{22}\text{Br}_2\text{O}_4\text{H}$ 556.9958; Found 556.9952; IR (KBr): 1718, 1192 cm^{-1} .

Dibenzyl cubane-1,4-dicarboxylate (1d)

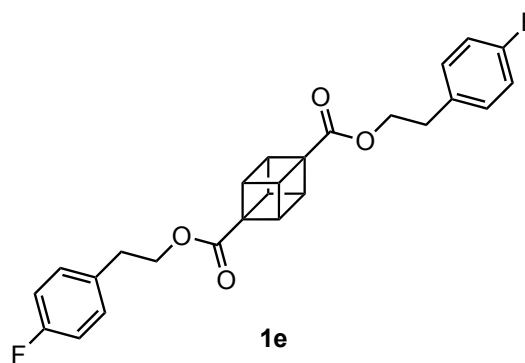
^1H NMR (500 MHz, CDCl_3): δ 7.27 - 7.24 (m, 10H), 5.05 (s, 4H), 4.14 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.4, 136.0, 128.6, 128.3, 128.2, 66.1, 55.8, 47.1; HRMS (APCI) m/z :



$[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}\text{O}_4\text{H}$ 373.1434; Found 373.1429; IR (KBr): 1716, 1194 cm^{-1} .

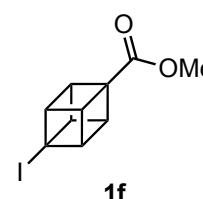
Bis(3,5-dimethylphenyl) cubane-1,4-dicarboxylate (1e)

^1H NMR (500 MHz, CDCl_3): δ 6.88 (s, 2H), 6.74 (s, 4H), 4.45 (s, 6H), 2.33 (s, 12H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.0, 150.4, 139.3, 127.6, 119.1, 55.9, 47.3, 21.2; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{24}\text{O}_4\text{H}$ 401.1747; Found 401.1742; IR(KBr): 1730, 1177 cm^{-1} .



Methyl 4-iodocubane-1-carboxylate (1f)

This compound was prepared from 4-(methoxycarbonyl)cubane-1-carboxylic acid following the iododecarbonylation procedure by Gandelman.¹⁸ In a pyrex flask, a mixture of 4-(methoxycarbonyl)cubane-1-carboxylic acid (900 mg, 4.37 mmol) and 1,3-diiodo-5,5-dimethylhydantoin (1.99 g, 5.24 mmol) in 1,2-dichloroethane was added. The reaction vial was purged with argon, and heated under reflux, followed by irradiated with visible light for 5 h. Aldrich® Micro Photochemical Reactor blue LED (ALDKIT001) was used as a light source. The pyrex flask was placed in the middle of a circle device (ALDKIT001) with a diameter of 11 cm. After cooled to rt, the mixture was diluted with chloroform (20 mL) and washed with saturated Na_2SO_3 aq to reduce existing iodine. The aqueous layer was extracted with chloroform. The combined organic layers were washed

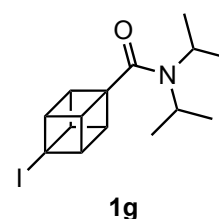


with saturated NaHCO_3aq and brine. After dried by Na_2SO_4 , the resulting solution was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/5) as eluent. The title compound was isolated in 91% yield (1.14 g).

^1H NMR (500 MHz, CDCl_3): δ 4.39-4.38 (m, 3H), 4.29- 4.27 (m, 3H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.8, 56.1, 54.9, 51.7, 50.2, 36.1; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_9\text{IO}_2\text{H}$ 288.9720; Found 288.9714; IR(KBr): 1716, 1221 cm^{-1} .

4-Iodo-*N,N*-diisopropylcubane-1-carboxamide (**1g**)

To a solution of methyl 4-iodocubane-1-carboxylate (**1f**) (4.96 mmol, 1.43 g) and THF (45 ml), a solution of NaOH in MeOH (2 M, 2.91 mL, 5.82 mmol) was added at rt. The resulting mixture was stirred vigorously for 15 h. The mixture was



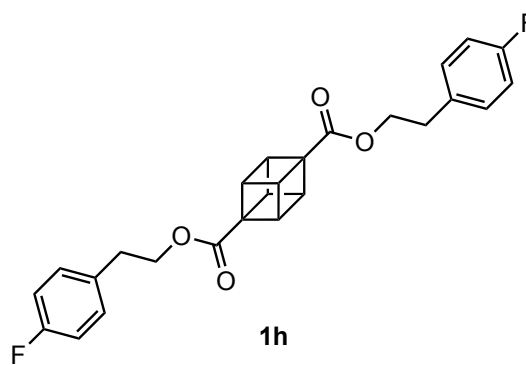
concentrated in vacuo to obtain a white residue. To the obtained residue, distilled water (ca 30 mL) was added to get a clear solution. The obtained solution was acidified completely with conc HCl_{aq} (10 M). The precipitated white solid was collected and washed with distilled water followed by methanol. After dried in vacuo, the crude 4-iodocubane-1-carboxylic acid was obtained (1.2 g, 86%). To a mixture of the obtained carboxylic acid and DMF (1 drop) in dichloromethane (40 mL), oxalyl chloride (0.66 mL, 7.8 mmol) was added dropwise. The whole was stirred for 1 h, a clear solution was formed. The resulting solution was concentrated completely in vacuo to remove excess oxalyl chloride. To the obtained residue, dichloromethane (40 ml) was added. To the obtained solution, *N,N*-diisopropylamine (1.2 mL, 9.5 mmol) was added dropwise at 0 °C. The mixture was stirred for 1 h, and then diluted with chloroform (40 mL). The obtained solution was washed with 2 M HCl_{aq}, saturated NaHCO_3aq , and brine sequentially. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/5) as eluent. The title compound was isolated in 98% yield (1.14 g)

^1H NMR (500 MHz, CDCl_3): δ 4.35-4.33 (m, 3H), 4.27-4.25 (m, 3H), 3.37 (sept, J = 7.0 Hz, 1H), 3.30 (sept, J = 7.0 Hz, 1H), 1.41 (d, J = 7.0 Hz, 6H), 1.19(d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3):

δ 160.8, 59.7, 54.2, 50.1, 48.4, 45.9, 36.0, 20.9, 20.4; HRMS (APCI) m/z : $[M+H]^+$ Calcd for $C_{10}H_9IO_2H$ 288.9720; Found 288.9714; IR(KBr): 1716, 1221 cm^{-1} .

Bis(4-fluorophenyl) cubane-1,4-dicarboxylate (1h)

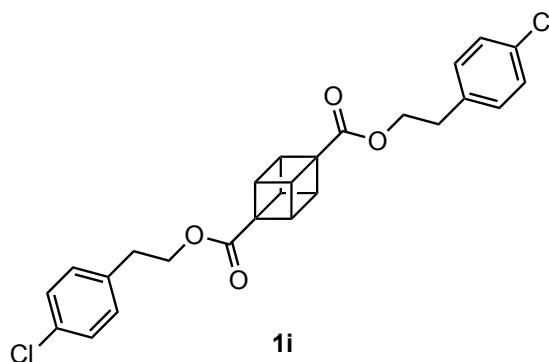
1H NMR (500 MHz, $CDCl_3$): δ 7.19-7.16 (m, 4H), 7.01-6.97 (m, 4H), 4.29 (t, $J = 7.0$ Hz, 4H), 4.17 (s, 6H), 2.93 (t, $J = 7.0$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 161.7 (d, 162.7, 160.7), 133.39 (d, 133.41, 133.38), 130.39 (d, 130.43, 130.36), 115.27 (d, 115.36, 115.19), 64.7, 55.8,



47.0, 34.3; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_{26}H_{22}F_2O_4Na$ 459.1378; Found 459.1374; IR(KBr): 1720, 1218 cm^{-1} .

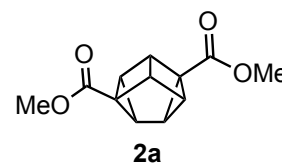
Bis(4-chlorophenethyl) cubane-1,4-dicarboxylate (1i)

1H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, $J = 8.0$ Hz, 4H), 7.15 (d, $J = 8.0$ Hz, 4H), 4.29 (t, $J = 7.0$ Hz, 4H), 4.17 (s, 6H), 2.93 (t, $J = 7.0$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 136.2, 132.5, 130.3, 128.6, 64.4, 55.7, 47.0, 34.5; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_{26}H_{22}Cl_2O_4Na$ 491.0787; Found 491.0788; IR(KBr): 1719, 1221 cm^{-1} .



Dimethyl cuneane-2,6-dicarboxylate (2a)

A mixture of dimethyl cubane-1,4-dicarboxylate (0.5 mmol, 110 mg) and catalyst (0.025 mmol entries 2–11; 0.25 mmol in entry 1) in solvent (7 ml) was



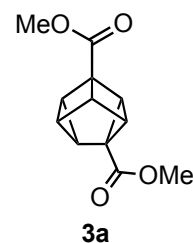
stirred at the indicated temperature in Table 4-1 under Ar atmosphere. Aluminum foil was wrapped around the flask to prevent light. After stirred for the period shown in Table 1, the resulting mixture

was passed through a short silica-gel column, concentrated under vacuum and purified by silica gel column chromatography using ethyl acetate/hexane (1/4) as eluent. The title compound was isolated in 96 % yield (entry 2, 106 mg), a white solid.

^1H NMR (500 MHz, CDCl_3): δ 3.62 (s, 6H), 3.12-3.06 (m, 4H), 3.05-3.04 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.6, 51.5, 43.6, 43.5, 40.5, 38.5. HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4\text{H}$ 221.0808; Found 221.0802 IR (KBr): 1717, 1122 cm^{-1} . Dimethyl cuneane-1,3-dicarboxylate (**3a**) was isolated containing a small amount of **2a** in entries 4 and 5.

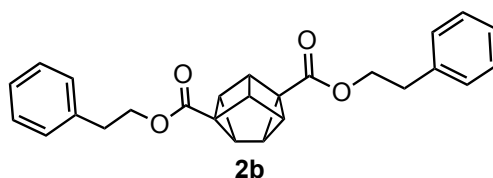
Dimethyl cuneane-1,3-dicarboxylate (**3a**)

^1H NMR (500 MHz, CDCl_3): δ 3.77 (s, 3H), 3.74 (s, 3H), 3.15 (bs, 1H), 3.04 (m, 1H), 2.89 (m, 2H), 2.51 (m, 1H), 2.38 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.83, 171.78, 52.0, 51.9, 47.3, 43.8, 43.0, 31.9, 30.6, 29.8; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4\text{H}$ 221.0813; Found 221.0807; IR (film): 1719, 1225, 1190 cm^{-1} .



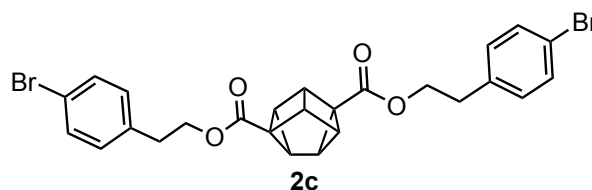
Bis(2-phenylethyl) cuneane-2,6-dicarboxylate (**2b**)

95 % yield (190 mg), white solid; ^1H NMR (500 MHz, CDCl_3): δ 7.32-7.29 (m, 4H), 7.28-7.19 (m, 2H), 7.19-7.08 (m, 4H), 4.26-4.18 (m, 4H), 3.06-3.05 (m, 4H), 3.01- 2.99 (m, 2H), 2.89 (t, J = 7.0 Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.1, 137.8, 128.9, 128.5, 126.6, 64.8, 43.7, 43.6, 40.5, 38.4, 35.1; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{24}\text{O}_4\text{H}$ 401.1747; Found 401.1742; IR (KBr): 1714, 1194 cm^{-1} .



Bis[2-(4-bromophenyl)ethyl] cuneane-2,6-dicarboxylate (**2c**)

67 % yield (112 mg), white solid; ^1H NMR (500 MHz, CDCl_3): δ 7.42 (d, J = 8.00 Hz, 4H), 7.05 (d, J = 8.00 Hz, 4H), 4.21-4.18 (m, 4H), 3.05 - 3.04 (m, 4H), 3.00-



2.99 (m, 2H), 2.84 (t, $J = 7.00$ Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.0, 136.8, 131.6, 130.7, 120.5, 64.4, 43.7, 43.6, 40.6, 38.4, 34.5; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{22}\text{Br}_2\text{O}_4\text{H}$ 556.9958; Found 556.9952; IR (KBr): 1718, 1192 cm^{-1} .

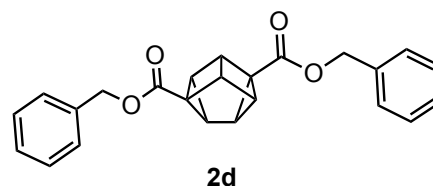
Dibenzyl cuneane-2,6-dicarboxylate (2d)

74 % yield (82 mg), white solid; ^1H NMR (500 MHz, CDCl_3): δ

7.36 - 7.31 (m, 10H), 5.09 (d, $J = 12.50$ Hz, 2H), 5.05 (d, $J = 12.50$

Hz, 2H), 3.16-3.07 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ

170.0, 135.9, 128.5, 128.2, 128.1, 66.0, 43.8, 43.7, 40.6, 38.5; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}\text{O}_4\text{H}$ 373.1434; Found 373.1429; IR (KBr): 1716, 1194 cm^{-1} .



Bis(3,5-diphenyl) cuneane-2,6-dicarboxylate (2e)

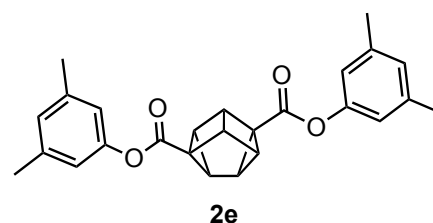
70 % yield (84 mg), white solid; ^1H NMR (500 MHz, CDCl_3): δ

6.85 (s, 2H), 6.67 (s, 4H), 3.38-3.36 (m, 4H), 3.29-3.28 (m, 2H),

2.30 (s, 12H); ^{13}C NMR (125 MHz, CDCl_3): δ 168.8, 150.3,

139.3, 127.5, 119.1, 44.6, 43.9, 41.3, 38.7, 21.2; HRMS (APCI)

m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{24}\text{O}_4\text{H}$ 401.1747; Found 401.1742; IR(KBr): 1730, 1177 cm^{-1} .



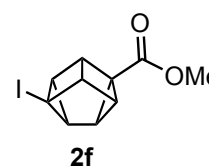
Methyl 4-iodo-cuneanecarboxylate (2f)

85 % yield (73 mg), a white solid; ^1H NMR (500 MHz, CDCl_3): δ 3.61 (s, 3H), 3.22-

3.22 (m, 1H), 3.15 - 3.14 (m, 1H), 3.06-3.02 (m, 2H), 2.69-2.68 (m, 2H); ^{13}C NMR

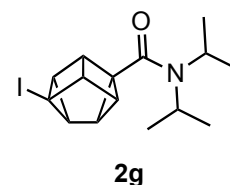
(125 MHz, CDCl_3): δ 170.6, 51.6, 48.9, 43.2, 42.8, 41.9, 41.6, 41.0, 39.6, 6.8;

HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_9\text{IO}_2\text{H}$ 288.9720; Found 288.9714; IR(KBr): 1716, 1221 cm^{-1} .



4-Iodo-*N,N*-diisopropylcubane-1-carboxamide (2g)

90 % yield (108 mg), a white solid; ^1H NMR (500 MHz, CDCl_3): δ 3.40 (m, 1H), 3.27 (m, 1H), 3.06 (m, 1H), 3.00 (m, 1H), 2.96 (m, 1H), 2.76 (m, 1H), 2.69 (m, 1H), 2.65 (m, 1H), 1.35 (s, 6H), 1.15 (d, $J = 5.5$ Hz, 3H), 1.10 (d, $J = 5.5$ Hz, 3H);



^{13}C NMR (125 MHz, CDCl_3): δ 168.1, 48.3, 48.2, 46.6, 45.7, 44.7, 40.8, 39.9, 38.6, 37.3, 20.9, 20.7, 20.2, 7.15; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{15}\text{H}_{20}\text{IONa}$ 300.0482; Found 300.0487; IR(KBr): 1635 cm^{-1} .

Reaction of cubane-1,4-dicarboxylic acid ester with silver-chiral phosphoric acid (Table 4-2, entries 2–5)

The silver-chiral phosphoric acid catalyst was prepared from Ag_2CO_3 and the corresponding phosphoric acid following the procedure by Echavarren.¹⁹ A mixture of dimethyl 1,4-cubanedicarboxylic acid ester (0.3 mmol) and catalyst (0.030 mmol entry 2; 0.038 mmol in entries 3–5) in solvent (5 ml) was stirred at the indicated temperature in Table 2 under Ar atmosphere. Aluminum foil was wrapped around the flask to prevent light. After stirred for the period shown in Table 2, the resulting mixture was passed through a short silica-gel column, concentrated under vacuum and purified by silica gel column chromatography using ethyl acetate/hexane (1/4) as eluent. After purification, the ee of the product was measured by chPLC (DAICEL CHIRALPAK IA *i*-PrOH/Hexane: 5/95).

Reaction of cubane-1,4-dicarboxylic acid ester with [(+)-BINAP] PdCl_2 / AgOTf (Table 4-2, entry 6)

The catalyst was prepared $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ and (*R*)-(+)-BINAP following the procedure by Mikami and Sodeoka.^{16a} To a solution of (*R*)-(+)-BINAP- PdCl_2 (0.01 mmol, 8.0 mg) in dichloromethane (2.0 mL) was added AgOTf (0.02 mmol, 5.1 mg) at room temperature under Ar atmosphere. After stirring for 30 min, bis(2-phenylethyl) 1,4-cubanedicarboxylate (0.20 mmol) was added to the mixture. The mixture was stirred at 80 °C. After stirred for 20 h, the resulting mixture was passed through a short

silica gel column, concentrated under vacuum and purified by silica gel column chromatography using ethyl acetate/hexane (1/4) as eluent. After purification, the *ee* of the product was measured by chPLC (DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95).

Reaction of cubane-1,4-dicarboxylic acid ester with [(–)-TADDOL]₂[PCP]Pd–I / AgOTf (Table 4-2 entries 8, 10, 11, Table 4-3)

[(–)-TADDOL]₂[PCP]Pd–I was prepared followed by the procedure of Szabó.¹⁷ AgOTf (0.015 mmol, 3.8 mg) and [(–)-TADDOL]₂[PCP]Pd–I (0.02 mmol, 26 mg) were dissolved to dichloroethane (3.0 mL) under Ar atmosphere and stirred for 10 min at room temperature. Then, 1,4-cubanedicarboxylate (0.30 mmol) in dichloroethane (3.0 mL) was added to this mixture and stirred at the indicated temperature in Table 2. After stirred for the period shown in Table 2, the resulting mixture was passed through a short silica-gel column, concentrated under vacuum and purified on silica-gel using ethyl acetate/hexane (1/4) as eluent. After purification, the *ee* of the product was measured by chPLC (DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95).

Bis[2-(4-fluorophenyl)ethyl] cuneane-2,6-dicarboxylate (2h)

A white solid; ¹H NMR (500 MHz, CDCl₃): δ 7.15-

7.12 (m, 4H), 7.01-6.96 (m, 4H), 4.23-4.15 (m, 4H),

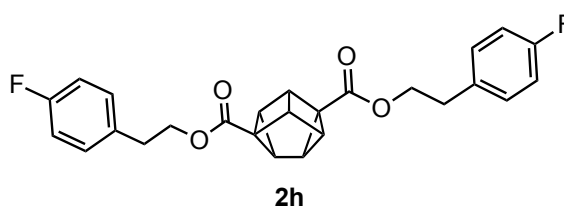
3.05-3.04 (m, 4H), 3.01-2.99 (m, 2H), 2.86 (t, *J* = 7.00

Hz, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 170.0, 161.7

(d, 162.7, 160.7), 133.4 (d, 133.41, 133.38), 130.3, (d, 13.34, 130.28), 115.2 (d, 115.33, 115.16), 64.7,

46.9, 43.6, 40.5, 38.4, 34.3; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₂₆H₂₂F₂O₄Na 459.1378; Found

459.1379; IR(KBr): 1720, 1218 cm^{–1}.



Bis[2-(4-chlorophenyl)ethyl]cuneane-2,6-dicarboxylate (2i)

A white solid; ^1H NMR (500 MHz, CDCl_3): δ 7.28 -

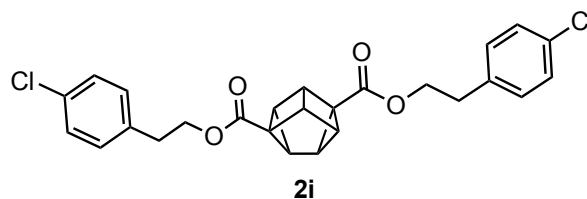
7.25 (m, 4H), 7.12-7.09 (m, 4H), 4.23-4.15 (m, 4H),

3.05-3.04 (m, 4H), 3.00-2.98 (m, 2H), 2.86 (t, $J = 7.00$

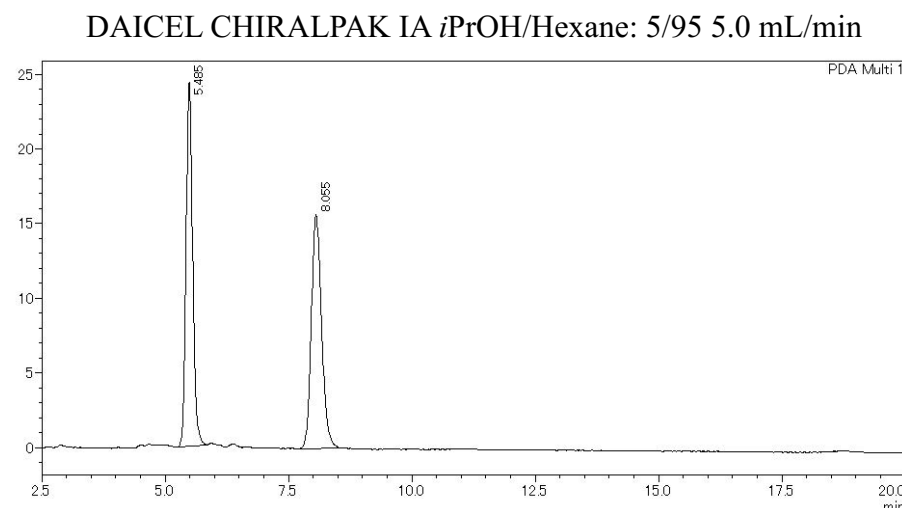
Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.9,

136.2, 132.4, 130.2, 128.5, 64.4, 43.6, 43.5, 40.5, 38.4, 34.4; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for

$\text{C}_{26}\text{H}_{22}\text{Cl}_2\text{O}_4\text{Na}$ 491.0787; Found 491.0788; IR(KBr): 1719, 1221 cm^{-1} .

**4.4.2 Chiral HPLC Data****Chiral HPLC analysis of racemic and optically pure 2b**

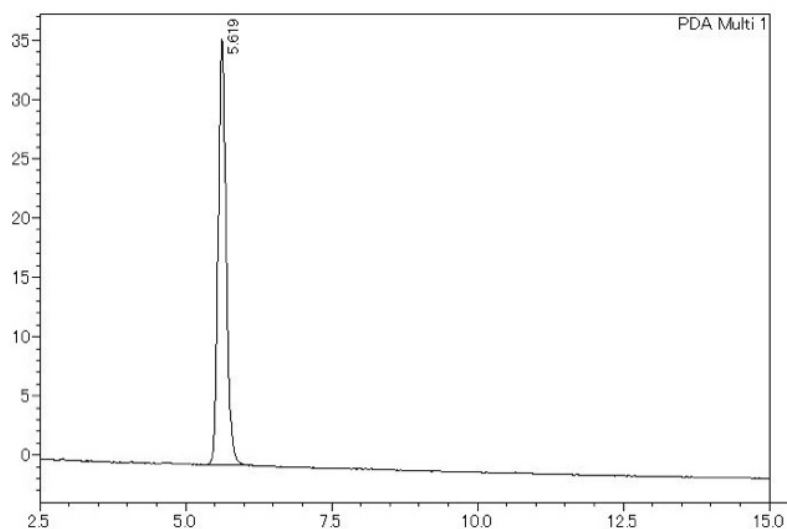
Optically pure cuneanes, **M-2b** and **P-2b**, were obtained by optical resolution using chiral HPLC of racemic **2b** obtained by the reaction of the corresponding cubane with catalytic amount of AgOTf (entry 2 in Table 4-1).

Chiral HPLC analysis of racemic 2b.

Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	5.485	227841	24337	50.144	60.892
2	8.055	226532	15631	49.856	39.108
Sum		454372	39968	100.000	100.000

Chiral HPLC analysis of *P*-2b and *M*-2b after separation and specific rotations

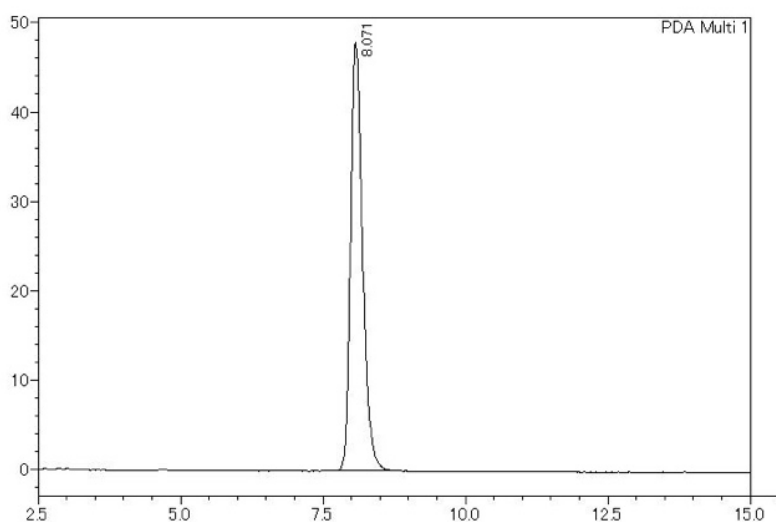
***M*-2b** DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min



Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	5.619	343315	35948	100.000	100.000
Sum		343315	35948	100.000	100.000

589 nm, Cell 10 cm, 11.4 mg/ml, 24.4 °C, $[\alpha]^{24}_{\text{D}} = +56.7$ (*c* 1.14, CHCl₃)

***P*-2b** DAICEL CHIRA PAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min



Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	8.071	701618	48007	100.000	100.000
Sum		701618	48007	100.000	100.000

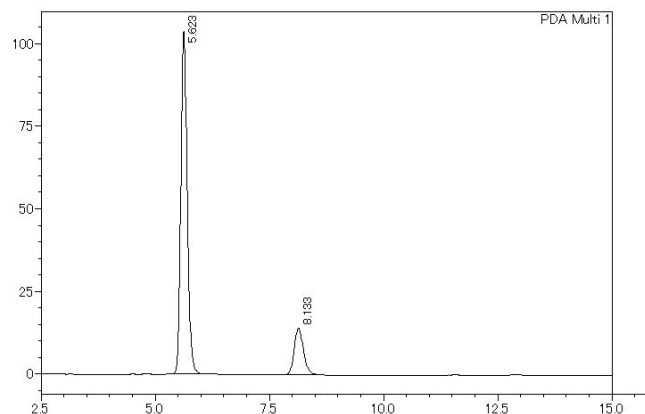
589 nm, Cell 10 cm, 11.0 mg/ml, 24.5 °C, $[\alpha]^{24}_{\text{D}} = -63.8$ (*c* 1.10, CHCl₃)

Chiral HPLC analysis of the 1,4-cuneanedicarboxylic acid esters (2b,c,h,i) obtained by the reaction using [(-)/(+)-TADDOL]₂[PCP]Pd-I/AgOTf (5 mol%) (entries 10, 11 in Table 4-2, Table 4-3)

Bis(2-phenylethyl) cuneane-2,6-dicarboxylate (2b) (entry 10 in Table 4-2)

2b (67 % ee, using (-)-TADDOL]₂[PCP]Pd-I/AgOTf as a catalyst).

DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min.

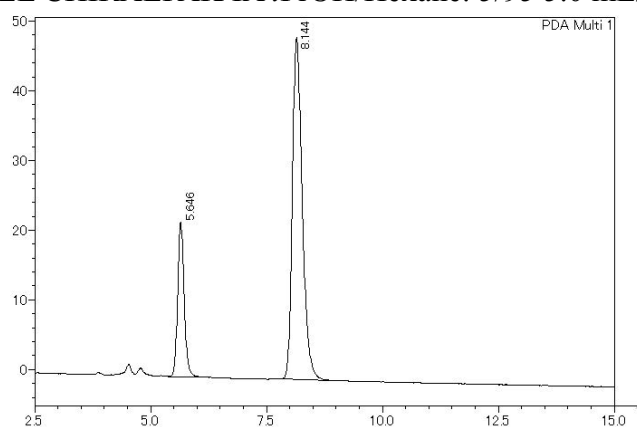


Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	5.623	1005829	103718	83.289	87.990
2	8.133	201803	14156	16.711	12.010
Sum		1207632	117875	100.000	100.000

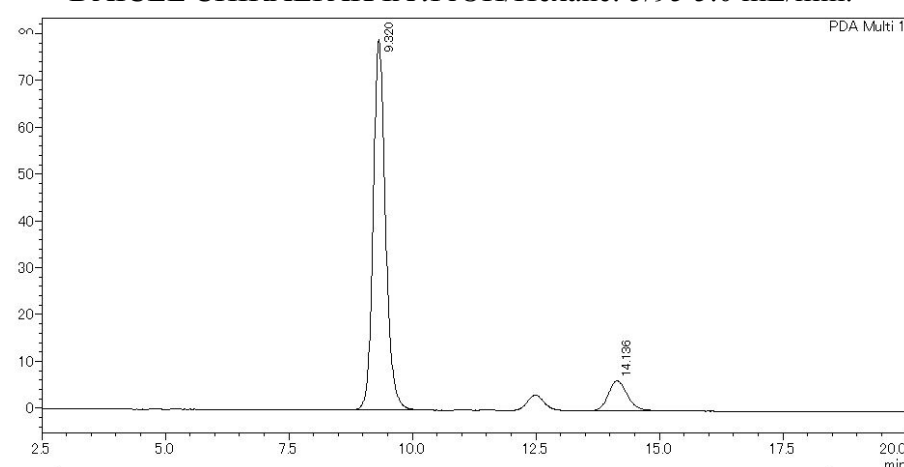
Bis(2-phenylethyl) cuneane-2,6-dicarboxylate (2b) (entry 11 in Table 4-2)

2b (-55 % ee, using (+)-TADDOL]₂[PCP]Pd-I/AgOTf as a catalyst).

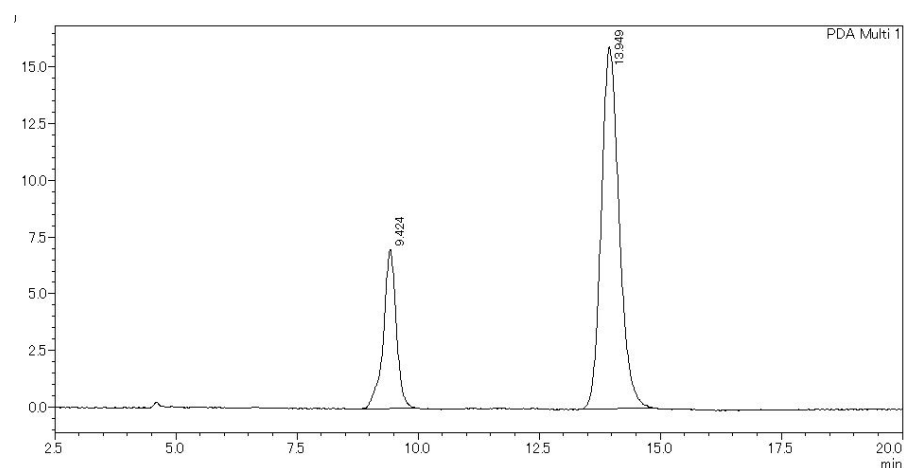
DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min.



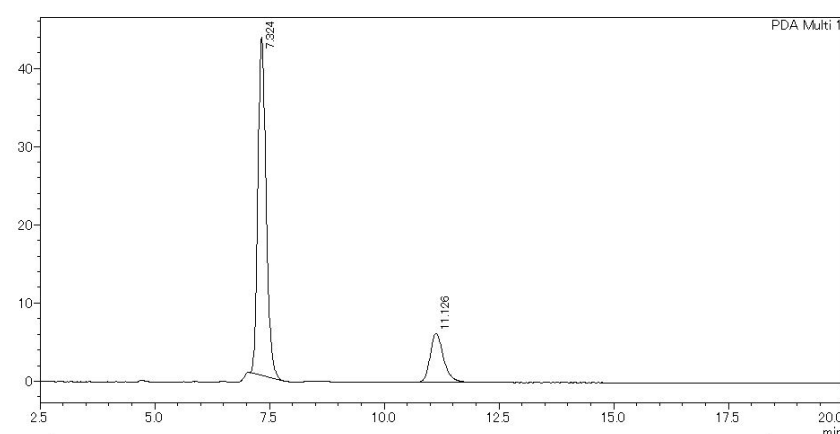
Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	5.646	214745	22167	22.743	31.100
2	8.144	729492	49109	77.257	68.900
Sum		944237	71275	100.000	100.000

Bis[2-(4-bromophenyl)ethyl] cuneane-2,6-dicarboxylate (2c) (entry 3 in Table 4-3)**2c** (78% ee, using (–)-TADDOL]₂[PCP]Pd–I/AgOTf as a catalyst).DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min.

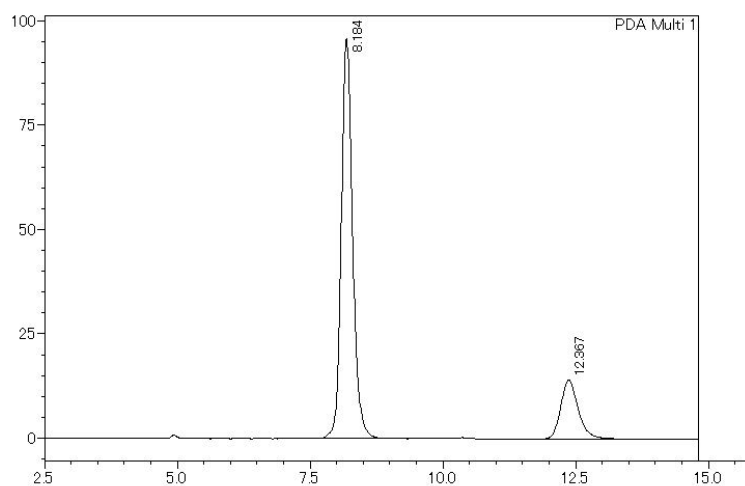
Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	9.320	1374497	79182	88.959	92.506
2	14.136	170600	6415	11.041	7.494
Sum		1545097	85597	100.000	100.000

Bis[2-(4-bromophenyl)ethyl] cuneane-2,6-dicarboxylate (2c) (entry 4 in Table 4-3)**2c** (–62 % ee, using (+)-TADDOL]₂[PCP]Pd–I/AgOTf as a catalyst).DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min.

Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	9.424	129671	7022	24.039	30.540
2	13.949	409756	15971	75.961	69.460
Sum		539427	22993	100.000	100.000

Bis[2-(4-fluorophenyl)ethyl] cuneane-2,6-dicarboxylate (2h) (entry 5 in Table 4-3)**2h** (62 % ee, using (–)-TADDOL]₂[PCP]Pd–I/AgOTf as a catalyst).DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min

Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	7.324	539433	43230	80.986	87.349
2	11.126	126648	6261	19.014	12.651
Sum		666081	49490	100.000	100.000

Bis[2-(4-chlorophenyl)ethyl] cuneane-2,6-dicarboxylate (2i) (entry 6 in Table 4-3)**2i** (63 % ee, using (–)-TADDOL]₂[PCP]Pd–I/AgOTf as a catalyst).DAICEL CHIRALPAK IA *i*PrOH/Hexane: 5/95 5.0 mL/min

Peak No.	Retention Time (min)	Area Integration	Hight	Area (%)	Hight (%)
1	8.184	1422126	95823	81.501	87.218
2	12.367	322789	14044	18.499	12.782
Sum		1744914	109867	100.000	100.000

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Chapter 5

Constitutional Isomerization of Cubane to Semibullvalene via Cuneane in Hot Water

The construction of cage-type hydrocarbon scaffolds, potential bioisosteres for benzene, often involves multiple steps, making their selective syntheses challenging. However, by employing a scaffold editing technique that leverages the isomerization of the highly symmetrical cubane as a precursor, these can be synthesized more efficiently with fewer steps. In this study, the author presents a method for the selective synthesis of semibullvalene-1,3-dicarboxylic acid with a good yield, starting from dimethyl cubane-1,4-dicarboxylate, using a reaction in hot water.

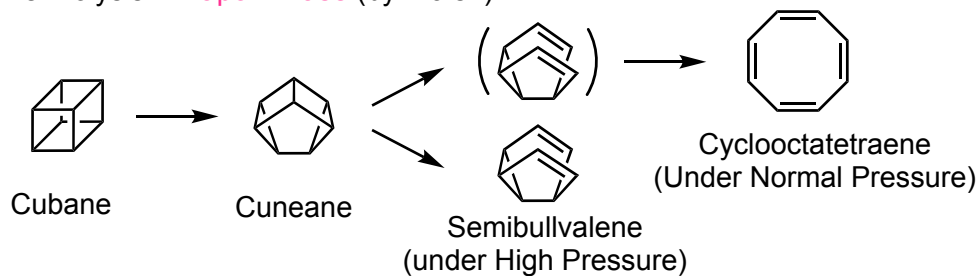
5.1 Introduction

Cubane, a cubic hydrocarbon, is being explored as a benzene bioisostere and has been introduced in various bioactive compounds.¹ As I have demonstrated so far, my research has aimed to utilize cage-shaped molecules like cubane as chiral scaffolds. This hydrocarbon undergoes thermal isomerization at temperatures above 230 °C. During this process, it transitions through cuneane and semibullvalene, ultimately converting to cyclooctatetraene.² The asymmetric build-up synthesis of these cage-shaped molecules that appear as intermediates is extremely difficult.³ Notably, these isomerized molecules, in contrast to cubane, exhibit chirality even when monosubstituted. Therefore, if it is possible to introduce chirality during the isomerization of cubane to cuneane, cubane could serve as a highly effective starting material for synthesizing optically active cage-shaped molecules. In fact, as demonstrated in Chapter 4 of this thesis, I successfully performed asymmetric induction during the isomerization from 1,4-disubstituted cubane to 2,6-cuneane. Building upon this reaction, further skeletal transformation reactions from the chiral cuneane could lead to the possibility of utilizing optically active semibullvalene as a new chiral scaffold.⁵ At this point, let us revisit Eaton's cubane isomerization reaction.

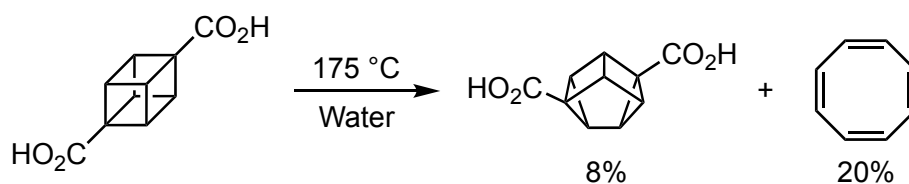
Eaton has already shown the feasibility of isomerizing cubane to cuneane in the presence of catalysts such as Ag(I) or Pd(II).⁴ In this reaction, when cubane-1,4-dicarboxylic acid ester is employed, a chiral cuneane-2,6-dicarboxylic acid ester is produced. Until our research, asymmetric synthesis had not been attempted at all. These have been described in chapter 2, 3 and 4.⁵ Furthermore, Eaton indicated that when substituents like hydroxymethyl groups or other electron-donating groups are attached at the 1,4-positions on cubane, 1,3-disubstituted cuneane is generated.⁴ Further research on this 1,3-disubstituted cuneane synthesis has been recently documented.⁶ The isomerization from cuneane to semibullvalene has been also mentioned to proceed with Rh, though no synthetic methodology had been previously studied.⁴ Semibullvalene was initially synthesized by Zimmerman via photoisomerization of barrelene.⁷ Subsequent to this, discussions concerning its molecular stability were conducted from the perspective of skeletal Cope rearrangement.⁸ Several semibullvalenes with

substituents have been prepared through the ring-closing of tetrahydropentalenes, and their isolation proved challenging due to their thermal instability.^{9,10} The isomerization from cuneane to semibullvalene, which extends to cyclooctatetraene, has been thought to be difficult to control, however, Walsh provided intriguing insights during vapor-phase pyrolysis (Scheme 5-1a).¹¹ Under normal pressure, cuneane transitions to cyclooctatetraene through semibullvalene, yet under increased pressure, semibullvalene becomes predominant. Hydrothermal conditions offer a feasible approach to achieve these high-pressure reaction environments.¹² Therefore, the author hypothesized that a similar advantageous effect could be expected during the formation of semibullvalene in water. Durkó reported that the non-catalytic isomerization of cubane-1,4-dicarboxylic acid in hot water (175 °C) predominantly produced cyclooctatetraene, but there was no detection of semibullvalene in his study (Scheme 5-1b).¹³ To suppress the formation of cyclooctatetraene, it is effective to lower the reaction temperature by using a catalyst. Consequently, the author decided to use a Pd(II) catalyst that can be formed and utilized in water. In the author's laboratory, it was previously reported that the efficient H/D exchange reaction of hydrocarbons catalyzed by Pd/C in hot water. The hot water should partially oxidize the Pd metal surface to generate the reactive $[\text{Pd-H}]^+\text{OH}^-$ species.¹⁴ Using this cationic Pd(II) species, the author studied the structural isomerization of alkali metal cubane-1,4-dicarboxylate in water (Scheme 5-1c).

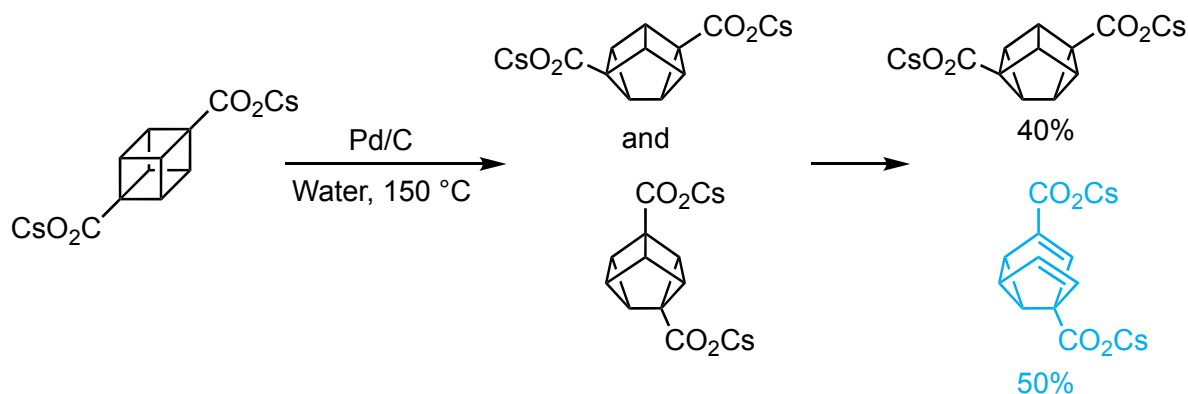
a) Thermolysis in **Vapor Phase** (by Walsh)



b) Non-catalytic Isomerization in **Hot Water** (by Durkó)



c) Reaction by **Pd/C-Hot Water** (**This Work**)



Scheme 5-1. Isomerization of cubanes to semibullvalenes.

5.2 Results and Discussion

Cubane-1,4-dicarboxylic acid was used as various alkali metal base solutions in D₂O.¹⁵ To thus prepared carboxylate **1** in D₂O, 10 mol% Pd/C (10 wt% on charcoal) was added as the catalyst, and the mixture was heated in a sealed tube for 15 h (Table 5-1). When using lithium, sodium, and potassium salts, both semibullvalene-1,3-dicarboxylate (**2**) and cuneane-2,6-dicarboxylate (**4**) were produced, with a 20-40% recovery of the starting material **1** (entries 1-3). In contrast, using cesium salt resulted in a complete 100% conversion, predominantly yielding semibullvalene **2** (entries 4 and 5). Given the structure of semibullvalene **2**, it's plausible that cuneane-1,3-dicarboxylate (**3**), undetected in the reactions at 150 °C (entries 1–5), might have isomerized to form **2**. Supporting this, when the reaction was carried out with cesium salt at 100 °C, the presence of **3** was indeed verified (entry 6). Without any catalyst, the starting cubane **1** was fully recovered (entry 7).

Table 5-1. Reaction of metal cubane-1,4-dicarboxylate Pd/C in hot D₂O.^{a,b,c}

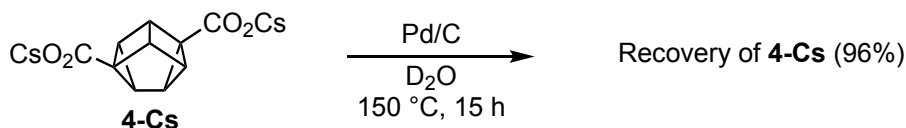
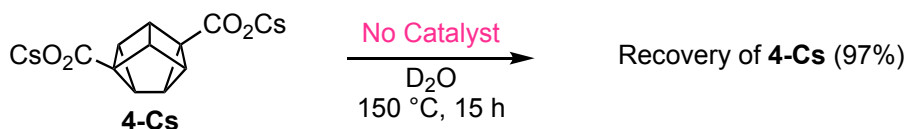
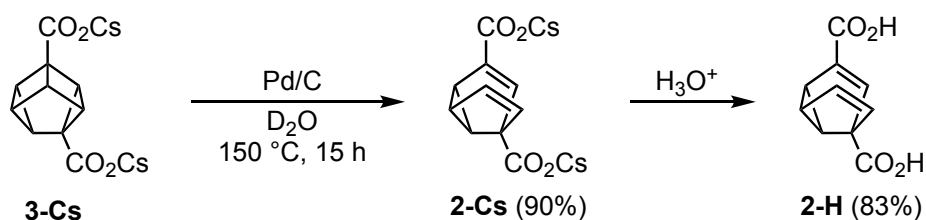
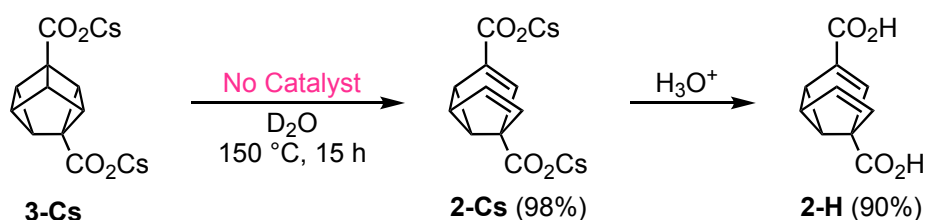
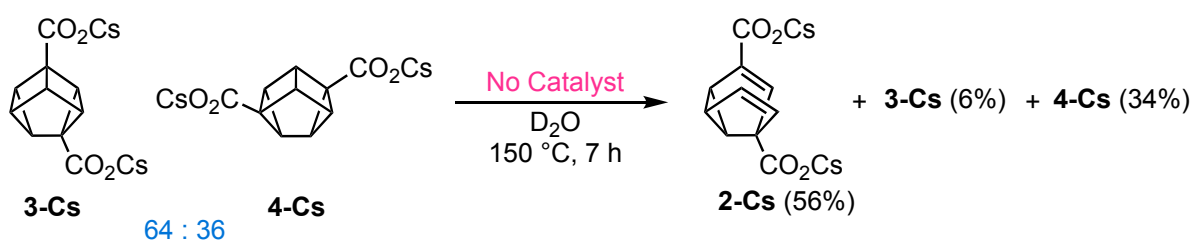
Reaction scheme: Cubane-1,4-dicarboxylate **1** (with CO₂Mtl groups) reacts with Pd/C in D₂O at T °C for 15 h to produce semibullvalene-1,3-dicarboxylate **2**, cuneane-1,3-dicarboxylate **3**, and cuneane-2,6-dicarboxylate **4**.

entry	Mtl	T (°C)	yield of 2 (%)	yield of 3 (%)	yield of 4 (%)	recov. of 1 (%)
1	Li	150	20	0	54	20
2	Na	150	26	0	20	38
3	K	150	28	0	28	37
4	Cs	150	45	0	40	0
5	Cs	150	50	0	40	0
6	Cs	100	3	32	31	21
7 ^d	Cs	150	0	0	0	96

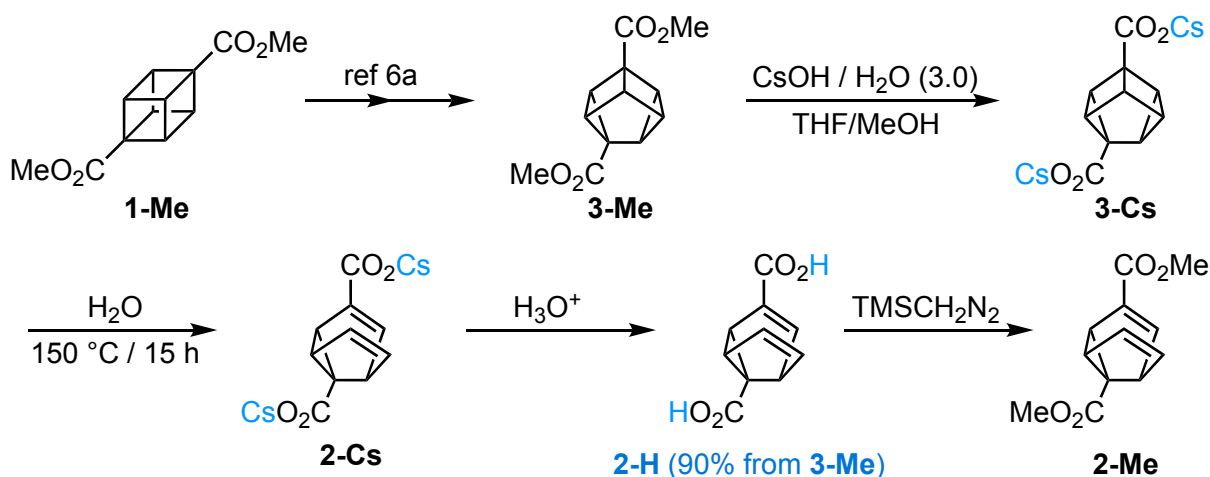
^a Cubane-1,4-dicarboxylic acid (0.2 mmol), base (0.5 mmol of LiOH, NaOH, KOH, and CsOH; 0.25 mmol of Cs₂CO₃ for entries 5 to 7), and 10 wt% Pd/C (5 mol% Pd) in D₂O (2.5 mL), using cap-sealed 5 mL glass tube (for Biotage microwave reactor). ^b Yields were calculated by ¹H NMR using *t*BuOH as an internal standard. ^c In the product, no H/D exchange was observed on the skeleton. ^d Without Pd/C catalyst.

Entries 4 and 5 in Table 5-1 suggest that semibullvalene **2** originates from cuneane-1,3-dicarboxylate **3**. To further explore this, the author examined the reaction in hot water using dicesium cuneane-2,6-dicarboxylate (**4-Cs**) and dicesium cuneane-1,3-dicarboxylate (**3-Cs**) as the starting compounds. When **4-Cs** was subjected to hot water at 150 °C for 15 h, the starting material was fully recovered, with or without the presence of Pd/C (Scheme 5-2a and b). Conversely, **3-Cs** yielded semibullvalene **2** in the presence of the Pd/C catalyst and was isolated post-protonolysis with an 83% yield (Scheme 5-2c). Notably, semibullvalene **2** was also quantitatively detected via ¹H NMR analysis, even without the Pd/C catalyst (Scheme 5-2d). Heating a mixture of **3-Cs** and **4-Cs** (64/36) in D₂O at 150 °C for 7 h led to the selective isomerization of **3-Cs** to **2-Cs**, while **4-Cs** remained unaffected (Scheme 5-2e).

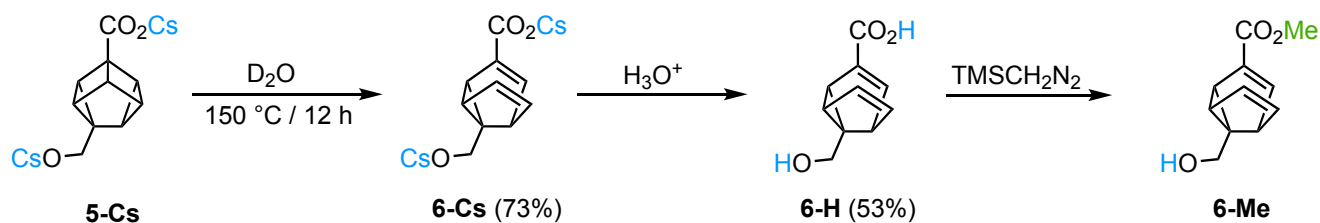
The selective preparation of semibullvalene **2-H** was demonstrated as shown in Scheme 5-3. The selective preparation of 1-methoxycarbonyl-3-cuneanecarboxylic acid from dimethyl cubane-1,4-dicarboxylate (**1-Me**) is detailed in ref 6a.¹⁶ This acid was converted to dimethyl cuneane-1,3-dicarboxylate (**3-Me**) by treatment of trimethylsilyldiazomethane, and **3-Me** was purified by a silica gel column. The THF solution of **3-Me** was treated with a three-fold molar amount of cesium hydroxide in H₂O/MeOH to obtain dicesium cuneane-1,3-dicarboxylate (**3-Cs**). Subsequently, all volatiles were removed under reduced pressure. Distilled water was then added to make the concentration approximately 0.15 M, and the mixture was heated in a sealed tube at 150 °C for 12 h. After acidified with conc HCl(aq), the mixture was extracted with chloroform and ethyl acetate. Semibullvalene-1,3-dicarboxylate (**2-H**) was isolated in 90% yield.

a) Reaction of **4-Cs** with Pd/Cb) Reaction of **4-Cs** without Pd/Cc) Reaction of **3-Cs** with Pd/Cd) Reaction of **3-Cs** without Pd/Ce) Heating a mixture of **3-Cs** and **4-Cs** (64/36) in D₂O

Scheme 5-2. Reaction in hot water using dicesium cuneanedicarboxylate.

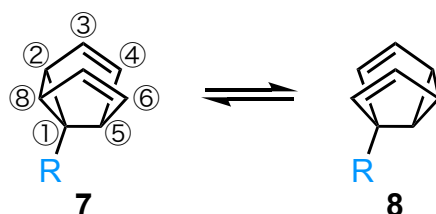
Scheme 5-3. The selective preparation of semibullvalene **2-H**.

In Scheme 5-4, when the cesium salt of 1-hydroxymethyl-3-cuneanecarboxylic acid (**5-Cs**) was heated in D₂O at 150 °C for 12 h, it isomerized to semibullvalene **6-Cs** with a 73% yield. Following protonation, the product **6-H** was isolated with a 53% yield.



Scheme 5-4. The selective preparation of semibullvalene **6-H**.

As illustrated in Scheme 5-3 and Scheme 5-4, irrespective of the 3-position substituent on 1-cuneanecarboxylic acid being either the π -electron-withdrawing $-\text{CO}_2^-$ or the σ -electron-withdrawing $-\text{CH}_2\text{O}^-$, the resultant semibullvalenes were consistently 1,3-disubstituted isomers. Hoffmann posited that the equilibrium of semibullvalene isomers **7** and **8**, mediated via Cope-rearrangement, tends to favor **7** when R is a π -acceptor, as shown in Scheme 5-5.^{8d} This preference was rationalized in his work by the R group's fortification of the C(2)–C(8) bond. The selective formation of **2-Cs** and **6-Cs** can likely be explained by this thermodynamic preference.



Scheme 5-5. Cope-rearrangement of semibullvalene.^{8d}

5.3 Conclusion

The conversion of cesium cubane-1,4-dicarboxylate (**1-Cs**) to cesium semibullvalene-1,3-dicarboxylate (**2-Cs**) using a Pd/C catalyst in hot water has been elucidated as a two-step process, proceeding via cesium cuneane-1,3-dicarboxylate (**3-Cs**). The initial formation of cuneane necessitates a Pd(II) catalyst, derived from the interaction of Pd/C with hot water.^{14,17} This is followed by a non-catalytic thermal rearrangement. Notably, the resulting semibullvalene-1,3-dicarboxylic acid is chiral. This chirality is believed to retain the inherent chirality of the precursor, cesium cuneane-1,3-dicarboxylate (**3-Cs**).¹⁸ The author has previously explored asymmetric induction during cuneane formation from cubane-1,4-dicarboxylic acid ester and are currently advancing towards the synthesis of optically active semibullvalene.⁵

5.4 Experimental Section

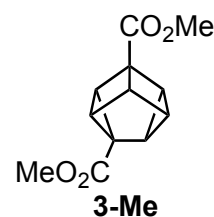
Synthetic Procedures

Reaction of alkali metal cubane-1,4-dicarboxylate (Table 5-1)

To a solution of alkali metal hydroxide (0.5 mmol) in deuterium oxide (2 mL) in a glass vial (Biotage Microwave Vial 2–5 mL), cubane-1,4-dicarboxylic acid (0.38 g, 0.2 mmol) was added. The acid was dissolved to obtain a clear solution. To this vial, Pd/C 10 wt% (0.01 mmol Pd, 10.6 mg) was added. The vessel was sealed with cap, and heated in oil-bath at 150 °C (or 100 °C). After 15 h, the vial was cooled to room temperature. To the mixture, 0.01 mmol of *t*BuOH as ¹H internal NMR standard (0.1 mL of 0.1 M solution of *t*BuOH in D₂O). After the reaction mixture was centrifuged to remove the solids, the products were analyzed by ¹H NMR.

Preparation of dimethyl cuneane-1,3-dicarboxylate (3-Me)

AgOTf (0.14 g, 0.05 mmol) was dissolved to 0.2 mL of acetonitrile and 0.8 mL of 1,2-dichloroethane. Thus, prepared catalyst solution was added to a solution methyl 4-hydroxymethylcubane-1-dicarboxylate (0.96 g, 5.0 mmol) in 15 mL of 1,2-dichloroethane. The mixture was stirred for 60 h at 60 °C. After an addition of a few drops of 30% aqNH₃, the mixture was filtered through a silica gel and Celite 545. Thus, obtained crude methyl 3-hydroxymethylcuneane-1-carboxylate (0.97 g, ca 100% yield) was used for the further transformation without purification. Followed by the reported procedure,¹⁹ methyl 3-hydroxymethylcuneane-1-carboxylate (0.19 g, 1.0 mmol) was dissolved to a mixture of acetonitrile (2.5 mL) and dichloromethane (2.5 mL). To the solution, a solution of NaIO₄ (0.85 g, 4 mmol) and RuCl₃ hydrate (10 mg, ca 0.05 mmol) in distilled water (2.0 mL) was added. The mixture was stirred for 2 h at 25 °C. The suspension was filtered through a pad of Celite and rinsed with EtOAc. The filtrates were dried over Na₂SO₄ and concentrated in vacuo. The residue was dissolved with THF (5 mL) and methanol (3 mL). A hexane solution of trimethylsilyldiazomethane (ca 0.6 M, 4 mL) was added to the solution. The mixture was stirred for 1 h at 25 °C. To the mixture, 0.5 mL of acetic acid to quench. The resulting

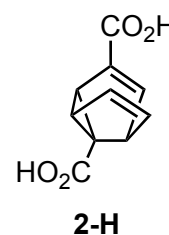


mixture was concentrated in vacuo and purified with silica gel chromatography (H/AcOEt = 8/1). The title compound was obtained in 36% yield (72 mg).

^1H NMR (CDCl_3 , 500 MHz): δ 3.76 (s, 3H), 3.74 (s, 3H), 3.15 (d, 1H, $J = 1.0$ Hz), 3.06-3.02 (m, 1H), 2.91-2.86 (m, 2H), 2.51 (dd, 1H, $J = 5.0, 5.0$ Hz), 2.40-2.36 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 171.8, 171.7, 54.4, 52.0, 51.9, 47.3, 47.2, 43.8, 43.0, 31.9, 30.7, 29.8 ppm; HRMS (APCII) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4\text{H}$ 221.0813; Found 221.0807; IR (film): 1719, 1225, 1190 cm^{-1} .

Preparation of semibullvalene-1,3-dicarboxylic acid (**2-H**, Scheme 5-3)

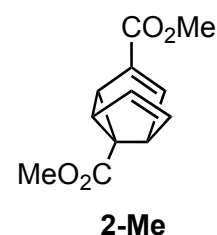
To a solution of a solution of dimethyl cuneane-1,3-dicarboxylate (**3-Me**, 96 mg, 0.50 mmol) in THF (3 mL) and MeOH (1 mL), a solution of CsOH (180 mg, 1.2 mmol) in distilled water (1.5 mL) was added. The mixture was stirred for 1 h at 25 °C. Volatiles were removed by evaporator and vacuum pump. To the residue, distilled water (2.0 mL) was added. The obtained solution (pale orange) was heated in a sealed vial for 12 h. After being cooled to room temperature, the mixture was acidified with conc HCl(aq). The mixture was extracted with chloroform and ethyl acetate. The organic layers was dried over Na_2SO_4 , and concentrated in vacuo. The title compound was obtained in 90% yield (84 mg).



^1H NMR (as cesium salt in D_2O , 500 MHz): δ 6.13 (dd, $J = 1.0, 1.0$ Hz, 1H), 5.63 (dd, $J = 5.5, 1.0$ Hz, 1H), 5.23 (dd, $J = 5.0, 2.5$ Hz, 1H), 3.46 (dd, $J = 5.5, 5.5$ Hz, 1H), 3.41 (ddd, $J = 7.0, 1.0, 1.0$ Hz, 1H), 3.30 (dddd, $J = 7.0, 2.5, 1.0, 1.0$ Hz, 1H) ppm; ^{13}C NMR (as cesium salt in D_2O /acetone- d_6 , 125.7 MHz): δ 181.7, 175.3, 136.3, 132.1, 131.0, 123.0, 64.2, 55.0, 50.6, 50.2 ppm; HRMS (ESI) m/z : $[\text{M}-\text{H}]^-$ Calcd for $\text{C}_{10}\text{H}_7\text{O}_4$ 191.0344; Found 191.0355; IR (film): 2924 (br), 1682, 1269, 725 cm^{-1} .

Dimethyl semibullvalene-1,3-dicarboxylate (**2-Me**)

To a solution of dicarboxylic acid **2-H** (20 mg, 0.11 mmol) in THF (2 mL) and MeOH (1 mL), trimethylsilyldiazomethane (ca 0.6 M solution in hexane, 1.5 mL) was added at 25 °C. After 1 h, 0.3 mL of acetic acid was added to quench the



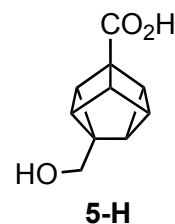
reaction. After the mixture was passed through a short silica-gel column, the mixture was concentrated *in vacuo*. Purification by PLC (hexane/EtOAc = 8/1) gave the title compound in 70% yield (15 mg).

^1H NMR (CDCl_3 , 500 MHz): δ 6.61 (d, J = 2.5 Hz, 1H), 5.75 (dd, J = 5.5, 2.5 Hz, 1H), 5.36 (dd, J = 5.5, 2.5 Hz, 1H), 3.84 (d, J = 7.0 Hz, 1H), 3.83 (dd, J = 2.5, 2.5 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.58 (dd, J = 7.0, 2.5 Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , MeOH as internal standard, 125.7 MHz): δ 169.0, 162.1, 137.4, 127.7, 122.3, 120.1, 57.4, 50.6, 49.3, 49.1, 46.2, 44.9 ppm; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4\text{H}$ 221.0813; Found 221.0808; IR (film): 1718, 1250, 748 cm^{-1} .

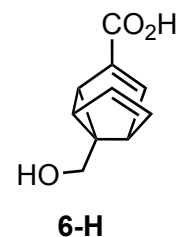
Preparation of 1-hydroxymethylsemibullvalene-3-carboxylic acid (**6-H**)

Silver triflate (56 mg, 0.02 mmol) was dissolved to 0.1 mL of acetonitrile and 0.9 mL of 1,2-dichloroethane. Thus, prepared catalyst solution was added to a solution methyl 4-hydroxymethylcubane-1-dicarboxylate (0.38 g, 2.0 mmol) in 5 mL of 1,2-dichloroethane. The mixture was stirred for 60 h at 60 °C. After an addition of a few drops of 30% aqNH₃, the mixture was filtered through a silica gel and Celite 545. Purification by a silica gel column chromatography (Hexane/AcOEt = 1/1) gave methyl 3-hydroxymethyl-1-cuneanecarboxylate in 80% yield (**5-H**, 307 mg). To a solution of a solution of methyl 3-hydroxymethylcuneane-1-carboxylate (**5-H**, 58 mg, 0.3 mmol) in THF (2 mL) and MeOH (0.5 mL), a solution of CsOH (105 mg, 0.7 mmol) in D₂O (1.5 mL) was added. The mixture was stirred for 1 h at 25 °C. Volatiles were removed by evaporator and vacuum pump. To the residue, D₂O (2.0 mL) was added. The obtained solution (pale orange) was heated in a sealed vial for 12 h. After being cooled to room temperature, the yield of semibullvalene (**6-Cs**, 73%) was determined by ^1H NMR using *t*BuOH as an internal standard. The mixture was acidified with conc HCl_{aq}. The mixture was extracted with chloroform and ethyl acetate. The organic layer was dried over Na₂SO₄, and concentrated *in vacuo*. The title compound (**6-H**) was obtained in 90% yield (48 mg).

5-H: ^1H NMR (CDCl_3 , 500 MHz): δ 4.01 (d, $J = 1.5$ Hz, 1H), 3.98 (d, $J = 1.5$ Hz, 1H), 3.73 (s, 3H), 3.02-3.00 (m, 1H), 2.45 (d, $J = 6.5$ Hz, 3H), 2.32-2.26 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 125.7 MHz): δ 170.4, 59.0, 51.3, 49.3, 44.5, 44.4, 33.9, 32.7, 29.5, 28.4, 28.1 ppm; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{H}$ 193.0864; Found 193.0860; IR (film): 3400, 1724, 1339, 1225 cm^{-1} .

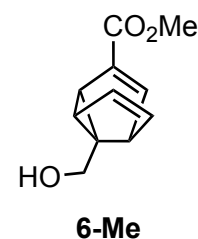


6-H: ^1H NMR (CD_3CN , 500 MHz): δ 5.77 (dd, $J = 2.0, 2.0$ Hz, 1H), 5.37 (dd, $J = 5.0, 3.0$ Hz, 1H), 5.10-5.09 (m, 1H), 3.88 (d, $J = 5.5$ Hz, 1H), 3.56 (dd, $J = 4.5, 3.5$ Hz, 1H), 3.49 (s, 3H), 3.17 (dd, $J = 3.5, 3.5$ Hz, 1H) ppm; ^{13}C NMR (CD_3CN , 125.7 MHz): δ 168.0, 128.1, 126.5, 119.4, 111.8, 68.2, 66.9, 66.1, 65.2, 56.5 ppm; HRMS (ESI) m/z : $[\text{M}-\text{H}]^-$ Calcd for $\text{C}_{10}\text{H}_{10}\text{O}_3\text{H}$ 177.0551; Found 177.0557; IR (film): 3055, 1681, 1014, 756 cm^{-1} .



Methyl 1-hydroxymethylsemibullvalene-3-carboxylate (6-Me)

To a solution of dicarboxylic acid **6-H** (35 mg, 0.2 mmol) in THF (2 mL) and MeOH (1 mL), trimethylsilyldiazomethane (ca 0.6 M solution in hexane, 1.5 mL) was added at 25 °C. After 1 h, 0.3 mL of acetic acid was added to quench the reaction. After the mixture was passed through a short silica-gel column, the mixture was concentrated *in vacuo*. Purification by PLC (hexane/EtOAc = 1/1) gave the title compound in 60% yield (23 mg).



^1H NMR (CDCl_3 , 500 MHz): δ 5.89 (bs, 1H), 5.41 (dd, $J = 5.5, 2.5$ Hz, 1H), 5.36 (dd, $J = 5.0, 3.0$ Hz, 1H), 5.15 (bs, 1H), 3.92 (d, $J = 5.0$ Hz, 1H), 3.69 (s, 3H), 3.66 (s, 2H), 3.53 (dd, $J = 2.0, 2.0$ Hz, 1H), 3.27 (dd, $J = 3.0, 3.0$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , MeOH as internal standard, 125.7 MHz): δ 165.1, 125.8, 124.4, 118.2, 110.9, 64.1, 63.3, 63.1, 62.5, 54.0, 51.6, 29.7 ppm; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{H}$ 193.0864; Found 193.0858; IR (film): 3400, 1712, 1223, 748 cm^{-1} .

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- (15) For direct measurement of ^1H NMR of the reaction mixtures, D_2O was used instead of H_2O . Durkó reported in ref 13 that alkali metal 1,4-cubanedicarboxylate did not isomerize into cuneane in hot water, while carboxylic acid in hot water gave cuneane-2,6-dicarboxylic acid (see Scheme 5-1b).
- (16) Following the procedure in ref 6a, methyl 1-methoxycarbonyl-3-cuneanecarboxylic acid, which is a precursor of **3-Me**, was able to be prepared with reasonable yield from **1-Me**.
- (17) Pd/C catalyzed reaction of dicesium 1,4-cubane dicarboxylate (entry 4 in Table 5-1) was also examined in toluene without water, and resulted in the recovery of starting material in 85 % because of the lack of formation of Pd(II). Reaction of dicesium 1,3-cuneane dicarboxylate in benzene (dispersion) at 150 °C for 9 h also gave the complete recovery.
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Chapter 6

Scaffold Editing of Cubanes into Homocubanes, Homocuneanes via Cuneanes

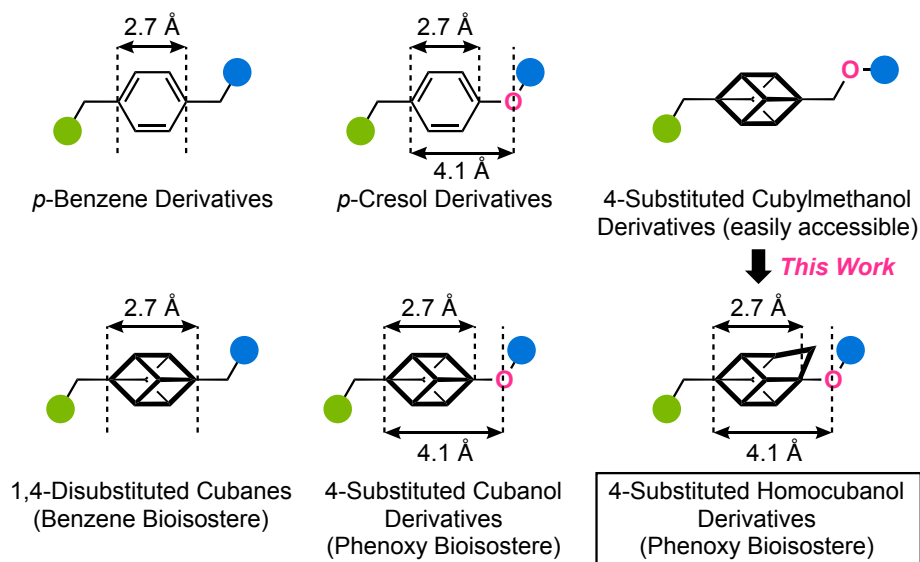
The selective synthesis of asymmetric cage-type hydrocarbons through the editing of the highly symmetric molecule cubane can be anticipated as one of the efficient approaches. In this chapter, the author identifies a catalyst that facilitates the efficient scaffold isomerization of cubanes into homocubanes. This approach, which involves the direct synthesis of homocubanol esters, is promising as a novel method for the synthesis of phenoxy bioisosteres. Additionally, the author observed that the isomerization of 1,4-bis(acyloxymethyl)cubane results in the generation of both D_2 - and C_2 -symmetrical bishomocubanes. The same catalyst was also applied to the isomerization of acyloxymethylcuneanes, producing homocuneanol esters.

6.1 Introduction

Professor Eaton's pioneering research has not only sparked interest in the synthetic chemistry of cubane, a unique hexahedral hydrocarbon, but also initiated discussions on the potential of molecules containing cubane.¹ This ignited significant interest in its pharmaceutical applications, particularly as a benzene bioisostere.² The strategy of substituting a benzene ring with cubane to potentially enhance the activity of bioactive compounds has been explored extensively. Of the three isomers of disubstituted benzene (*ortho*, *meta*, and *para*), cubane research has largely centered on the *para*-position, aligning with 1,4-disubstituted cubanes. This focus is due to the prevalent use of *p*-disubstituted benzene derivatives in pharmaceuticals³ and the synthetic feasibility of 1,4-disubstituted cubanes.⁴ While cubane provides improved metabolic stability over benzene,^{2a} its potential as a phenoxy bioisostere is especially compelling (Figure 6-1a). However, the precursor molecule, cubanol, tends to undergo ring-opening reactions more readily than cubane itself via oxygen-based anionic or cationic pathways.⁵ This complicates the integration of cubanol into bioactive molecules. As an alternative to using cubanol, a proposed method involves employing a Wagner–Meerwein-type rearrangement to convert readily synthesized cubylmethanol esters into acyloxyhomocubanes.⁶ Beyond the chemistry of the Platonic solid “cubane”, Professor Eaton revealed the potential for isomerizing cubanes into various polyhedral structures. In 1970, he introduced a silver(I) or palladium(II)-catalyzed transformation of cubanes into cuneanes, which are stable three-dimensional frameworks that also have potential as benzene bioisosteres.⁷ More recently, the author published findings on a catalytic asymmetric synthesis of 2,6-disubstituted cuneanes, derived from the structural isomerization of 1,4-disubstituted cubanes (chapter 4).⁸ This underscored the versatility of cubane skeletal isomerization in devising new chiral scaffolds and bioisosteres. During our research for scaffold editing of cubanes using Ag-based catalyst, the author found a novel catalyst that efficiently isomerizes acyloxymethylcubanes into 1-acyloxyhomocubanes efficiently. In this isomerization, the sequential isomerization of 1,4-bis(acyloxymethyl)cubanes gave the corresponding bishomocubanes stereoisomeric mixtures. This mixture consists of both D_2 -symmetric and C_2 -

symmetric entities, and it should be noted that the latter is a chiral compound. Moreover, the same catalyst converted acyloxymethylcuneane to its ring-enlarged counterpart, homocuneanol ester (Figure 6-1b).

a) Benzene vs Phenoxy Bioisosteres



b) Scaffold Editing of 1,4-Disubstituted Cubanes

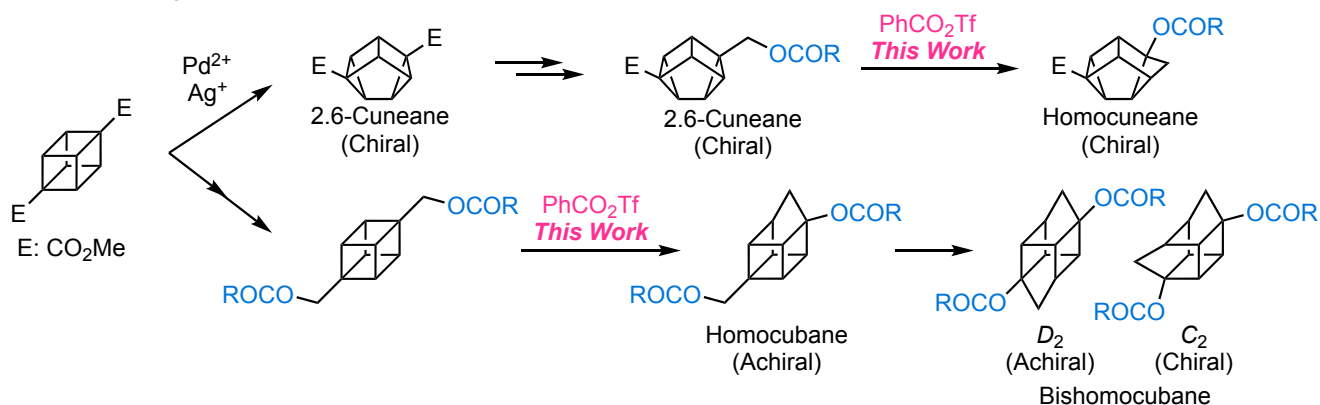
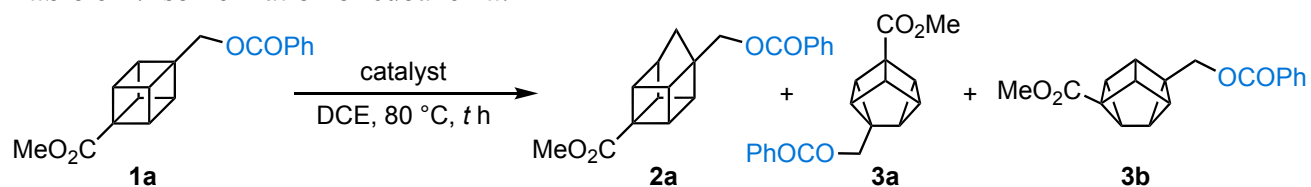


Figure 6-1. (a) A use of homocubanes as phenoxy bioisostere. (b) Scaffold editing strategy of 1,4-disubstituted cubanes into other hexahedrons by PhCO_2Tf catalyst.

6.2 Results and Discussion

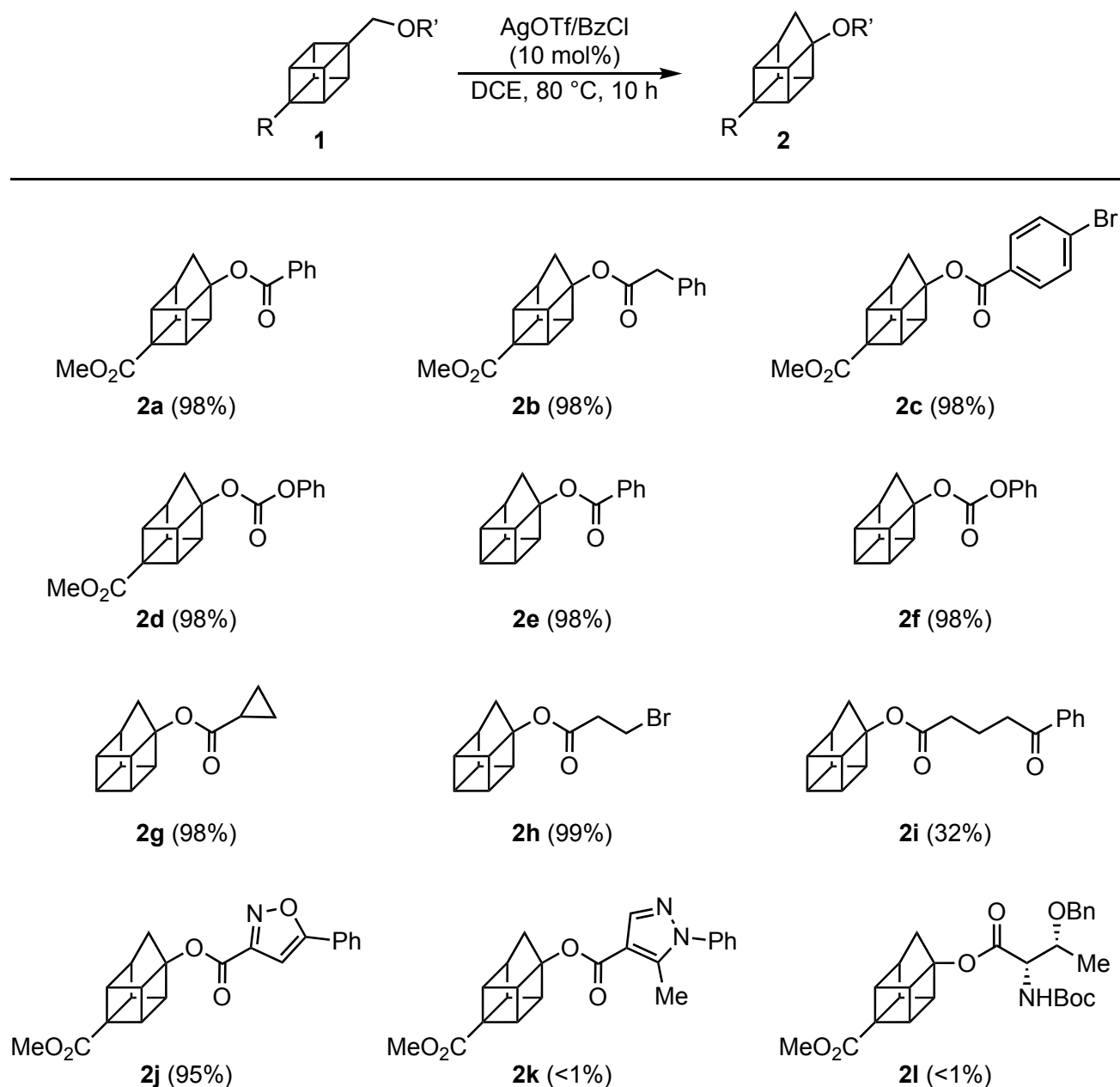
The isomerization of cubane to cuneane upon reaction with Ag(I) salts was reported by Eaton in 1970, and has been the subject of more detailed investigations in recent years.⁹ Indeed, when a catalytic amount of AgOTf is applied to methyl 4-benzoyloxymethyl-1-cubanecarboxylate **1a**, a 1,3-substituted cuneane **3a** was primarily produced (Table 6-1, entry 1). However, when a combination of an equimolar amount of benzoyl chloride and AgOTf was added to this reaction, there is no isomerization to cuneane at all, and it was found that homocubane **2a** can be quantitatively obtained (entry 2). Benzoic anhydride had no effect, and silver chloride itself had no catalytic activity (entries 3, 4). It was already known that a mixture of benzoyl chloride and AgOTf afforded benzoyl triflate,¹⁰ so **1a** was treated with 10 mol% of benzoyl triflate to afford **2a** in 93 % yield (entry 5). The longer reaction period was necessary in the case of 5 mol% catalyst (entries 6, 7). It was also possible to obtain an active catalyst in combination with acetyl chloride (entry 8) instead of benzoyl chloride. To adjust the catalyst for the reactions to be shown later, a mixture of PhCOCl and Ag(I), which forms PhCO₂Tf *in situ*, was used in the following examples in Scheme 6-1, instead of benzoyl triflate itself.

Table 6-1. Isomerization of cubane **1a**.^a



entry	catalyst (mol %)	<i>t</i> (h)	yield of 2a (%)	yield of 3a (%)	yield of 3b (%)	recov. of 1a (%)
1	AgOTf (10)	12	0	87	5	0
2	AgOTf (10) + PhCOCl (10)	12	98	0	0	0
3	AgOTf (10) + (PhCO) ₂ O (10)	12	0	75	8	0
4	AgCl (30)	12	0	0	0	98
5	PhCO ₂ Tf (10)	12	93	0	0	0
6	AgOTf (5) + PhCOCl (5)	12	65	0	0	30
7	AgOTf (5) + PhCOCl (5)	20	98	0	0	0
8	AgOTf (5) + AcCl (5)	20	90	0	0	0

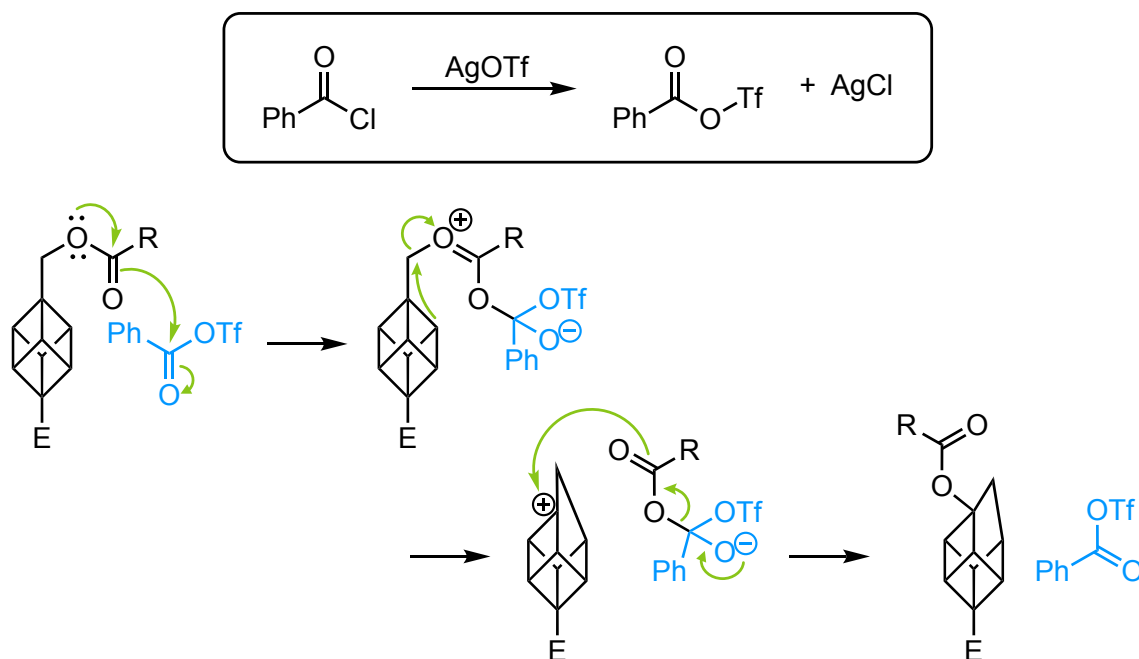
^a **1a** (0.2 mmol), AgOTf (0.1 M solution of CH₃CN/DCE (5/95)), and additive (0.1 M solution of DCE) were used.



Scheme 6-1. Isomerization of acyloxymethylcubanes **1** into acyloxycubanes **2**.

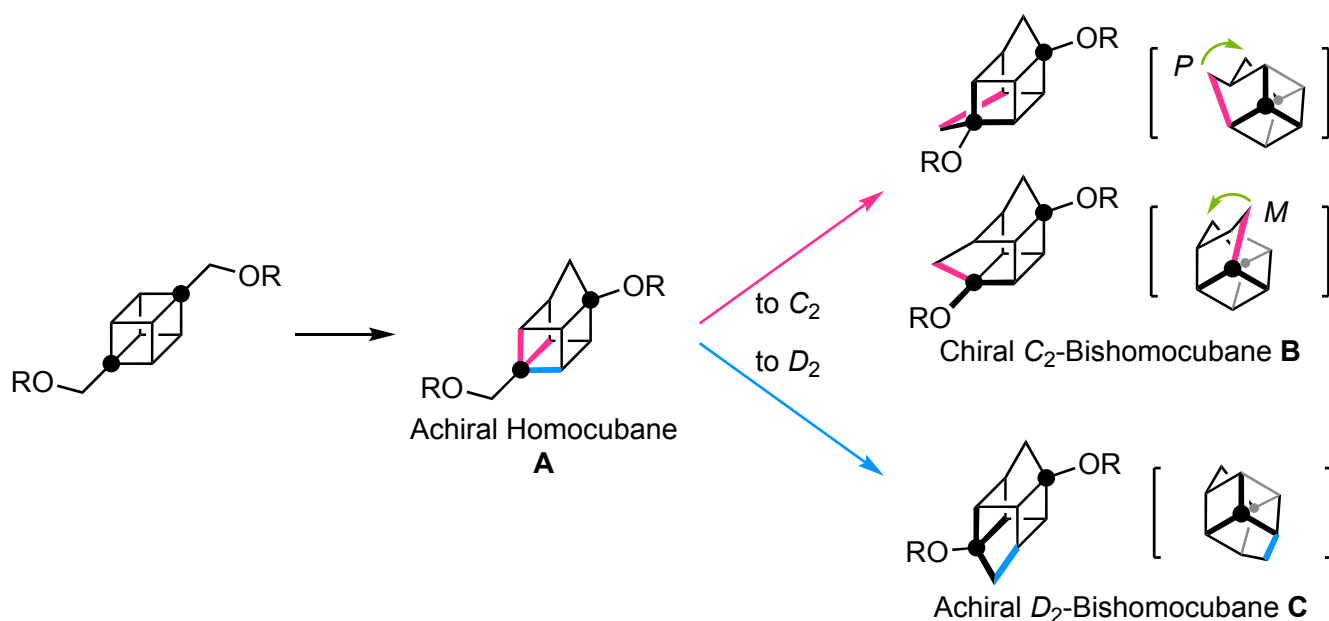
While the syntheses of homo- and bishomocubanes have been well studied from the viewpoint of the “build-up” method via cycloaddition and cyclization,^{6a} there are limited reported cases of the Wagner-Meerwein type rearrangement from cubane to homocubane. For instance, there are acid-catalyzed reactions of cubane derivatives bearing a tertiary alcohol group on the cubane,^{6b,6c} and the rearrangement of bromomethylcubane to bromohomocubane in the presence of SiO₂¹¹ or AgNTf₂.^{9b} To date, no efficient catalysts have been reported for the rearrangement of esters of cubylmethanol, a

primary alcohol, except in the present case. As depicted in Scheme 6-1, various cubanes **1** were treated with the *in situ* prepared PhCO_2Tf from 10 mol% of AgOTf and PhCOCl at 80 °C for 10 h. In most cases, homocubanes **2** were obtained quantitatively. Not only esters but also carbonates yielded the corresponding homocubanes **2d** and **2f** quantitatively. To understand the scope of this method, the functional group tolerability was also examined (**2h–l**). As reported, benzoyl triflate acts as an efficient benzoylation reagent for alcohols;¹² hence, cubane precursors with a nucleophilic site might affect the catalytic activity. While the isomerization of substrates with β -bromo ester (**2h**), γ -ketoester (**2i**), and oxazole (**2j**) proceeded in reasonable yields, those with strong basic pyrazole (**2k**) and *N*-Boc protected amino acid ester (**2l**) resulted in the recovery of starting materials. As mentioned, the transformation from cubane to homocubane allows the direct substitution of the acyloxy group with a cage hydrocarbon. Considering that cubane serves as a benzene bioisostere, it suggests that homocubane, a molecule of a similar size, could be utilized as an equivalent to phenoxy bioisostere via this molecular editing protocol. Benzoyl triflate had been used as a stoichiometric reagent for a ring expansion of adamantyl aldehyde via activation of aldehyde group.¹³ In the current homocubane formation reaction, it serves as a catalyst for the rearrangement via the activation of the acyloxy group (Scheme 6-2).

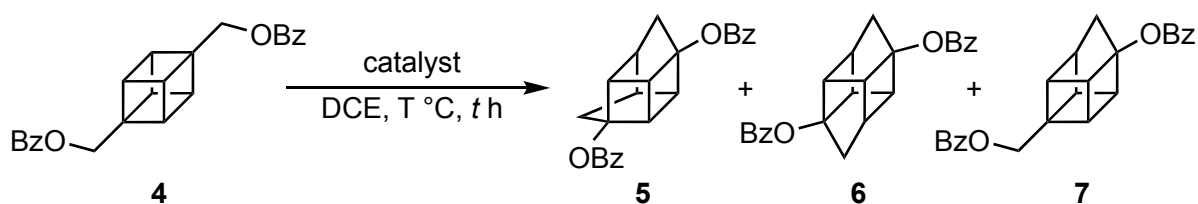


Scheme 6-2. Plausible explanation of isomerization to homocubane.

Although homocubane itself doesn't exhibit chirality, the sequential isomerization of 1,4-bis(acyloxymethyl)cubanes might afford chiral bishomocubane. In the achiral homocubane **A**, three C–C bonds potentially undergo rearrangement (two red and one blue bonds in Scheme 6-3). If the blue-colored bond cleaves, achiral D_2 -bishomocubane **C** forms. When either of the two red bonds breaks, it results in the chiral C_2 -bishomocubane **B**, generating a pair of enantiomers. Various isomerization catalysts, *in situ* prepared by different combinations of various silver salts and acyl chlorides, were examined that the product ratio between C_2 - and D_2 -forms would change. As shown in Table 6-2, the ratio remained almost unchanged in all cases. Neither 1,3- (**8a**) nor 2,6-cuneane (**8b**) formation was observed.

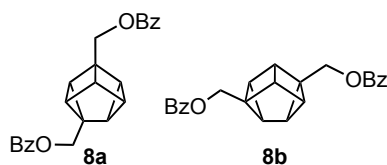


Scheme 6-3. Formation of C_2 -(**B**) and D_2 -homocubanes **C** via sequential rearrangements from 1,4-bis(acyloxymethyl)cubane using *in situ* prepared catalyst.

Table 6-2. Isomerization of cubane **4**.^{a,b}

entry	catalyst (mol %)	T (°C)	<i>t</i> (h)	yield of 5 (%)	yield of 6 (%)	yield of 7 (%)	recov. of 4 (%)
1	AgOTf / PhCOCl (10)	80	10	42	17	35	<5
2	AgOTf / PhCOCl (10)	50	10	48	18	29	<5
3	AgOTf / PhCOCl (15)	80	10	68	27	<5	<5
4	PhCO ₂ Tf (15)	80	10	69	26	<5	<5
5	AgOTf / MesCOCl (15)	80	12	69	27	<5	<5
6	AgOMs / PhCOCl (15)	80	10	0	0	0	>95
7	AgBF ₄ / PhCOCl (15)	80	24	40	15	40	<5

^a **4** (0.2 mmol) was used. ^b Cuneane **8a** nor **8b** was observed.



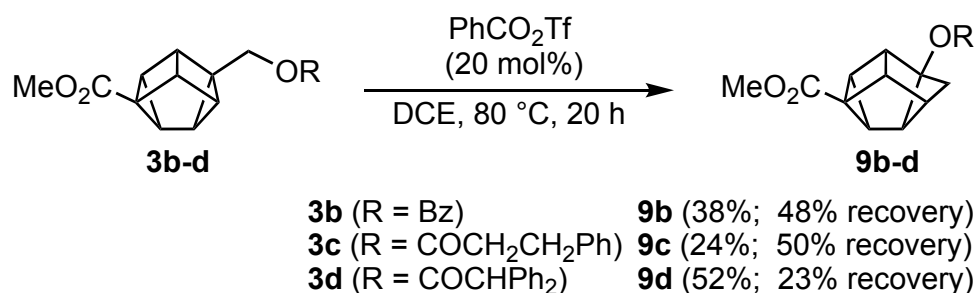
In the absence of a sufficient amount of catalyst or at low reaction temperatures (50 °C), the formation of homocubane **7** was observed (entries 1, 2). By increasing the catalyst amount to 15 mol% at 80 °C, the two types of bishomocubanes (**5** and **6**) were produced in approximately a 2 : 1 ratio. Whether using PhCO₂Tf directly or the bulky carboxylic acid chloride MesCOCl as a catalyst precursor, the product ratio between C₂ (**5**) and D₂ (**6**) remained approximately 2: 1. This aligns with the ratio of C–C bonds involved in the rearrangement (two red and one blue bonds in Scheme 6-3). When the counter-anion of the silver salt was changed to OMs or BF₄, the former showed no catalytic activity, while the latter experienced decreased activity (entries 6, 7). As shown in Table 6-3, hoping for reaction control imparted by chiral catalysts, Mosher's reagent, chiral phosphoric acid silver salts,¹⁴ and (+)-CSA (camphor sulfonic acid) silver salt¹⁵ were examined. However, none of these catalysts effectively promoted the rearrangement to homocubane. Additionally, a variety of other Lewis acids were investigated for their product ratios, but no positive outcomes were observed for the rearrangement.

Table 6-3. Isomerization of cubane **4** using various Lewis acids.^a

entry	catalyst (mol %)	yield of 5 (%)	yield of 6 (%)	yield of 7 (%)	recov. of 4a (%)	Comment
1	Yb(OTf) ₃ (20)	<5	<5	<5	>95	No reaction
2	Zn(OTf) ₂ (20)	<5	<5	<5	>95	No reaction
3	MgBr ₂ •OEt ₂	<5	<5	<5	>95	No reaction
4	FeBr ₃ (20)	<5	<5	<5	<5	Complex mixture
5	BF ₃ •OEt ₂ (20)	<5	<5	<5	<5	Complex mixture
6	AgOTf / (+)-Mosher-Cl (15)	<5	<5	<5	>95	Formation of cuneanes (8a , 8b)
7	(<i>S</i>)-BINOL-P(O)O-Ag / PhCOBr (15)	<5	<5	<5	>95	
8	(<i>R</i>)-TRIP-Ag / PhCOBr (15)	<5	<5	<5	<5 ^b	
9	(<i>R</i>)-VAPOL-Ag / PhCOBr (15)	<5	<5	<5	>95	
10	(+)-CSA-Ag / PhCOBr (15)	<5	<5	<5	>95	

^a **1a** (0.2 mmol) was used. ^b Cuneanes **8a** (major product, 1,3-disubstituted) and **8b** (2,6-disubstituted) were formed in 86% yield (90/10).

In scaffold editing from homocubane to bishomocubane, achieving asymmetric induction is crucial, especially in reactions accelerated by strain release. However, this process has proven to be exceptionally challenging. If one were to start with cuneane and undergo a rearrangement to produce “acyloxyhomocuneane”, it would lead to the stereospecific conversion of chiral cuneanes. In simpler terms, after inducing asymmetry during cuneane synthesis, one would merely need to perform the rearrangement. Hence, the author tested the catalytic effect of PhCO₂Tf on the 2,6-disubstituted cuneane **3b** (Scheme 6-4). In fact, new cage compound **9b** was obtained in 38 % yield. Other substrates, **3c** and **3d**, also yielded the corresponding **9c** and **9d**.¹⁶ The yield cannot always be considered as favorable. The pentacyclo[4.3.0.0^{2,4}.0^{3,9}.0^{5,8}]nonane skeleton in compound **9** had been found during the photoisomerization of nortriquinacene by Paquette in the quest for his dodecahedron chemistry.¹⁷



Scheme 6-4. Rearrangements of cuneanes **3b–d** into homocuneanes **9b–d**

6.3 Conclusion

As highlighted above, benzoyl triflate, primarily employed as a benzylation reagent, has been definitively demonstrated to be exceptionally effective as a catalyst for the homologative ring expansion reactions of acyloxymethylcubanes. Although the catalyst proved effective for the ring expansion of acyloxymethylcuneanes into homocuneane, there's still a compelling need to develop a novel catalyst for this selective transformation. Conveniently, this catalyst can be synthesized *in situ* from AgOTf and benzoyl chloride. These acyloxy small cages, with an oxygen atom directly substituted onto them, show promise as phenoxy bioisosteres in a range of molecules. The author has illustrated scaffold editing as a unique approach, distinct from complex cage hydrocarbon synthesis executed through various buildup methods.¹⁷⁻¹⁹ The cornerstone of synthesizing optically active compounds lies in the asymmetric induction from cubane to cuneane, a technique the author has already mastered. Therefore, scaffold editing starting from cubane holds considerable promise for the creation of new small molecular cages.

6.4 Experimental Section

6.4.1 Synthetic Procedure

Preparation of methyl 4-acyloxymethylcubanecarboxylate (**1a-d**)

Substrates **1a-d** were prepared from methyl 4-hydroxymethylcarboxylate²⁰ and the corresponding acyl chloride. To a solution of methyl 4-hydroxymethylcarboxylate (2.0 mmol) in DCM (10 mL), acyl chloride (3.0 mmol) in DCM (1 mL), triethylamine (3.0 mmol) in DCM (1 mL), and DMAP (ca 20 mg) were added subsequently at 0 °C. The mixture was stirred for 2 h at 25 °C. About 20 mL of DCM was added to the mixture, and the combined organic layer was washed with HCl(aq) (1.0 M). After extracting the aqueous solution with chloroform, the combined organic layers were washed lightly with brine (10 mL). The resulting solution was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/8) as an eluent.

Preparation of acyloxymethylcubane (**1e-h**)

Substrates **1e-h** were prepared from cubylmethanol^{14b} and the corresponding acyl chloride. To a solution of cubylmethanol (2.0 mmol, 0.26 g) in DCM (10 mL), acyl chloride (3.0 mmol) in DCM (1 mL), triethylamine (3.0 mmol) in DCM (1 mL), and DMAP (ca 20 mg) were added subsequently at 0 °C. The mixture was stirred for 2 h at 25 °. About 20 mL of DCM was added to the mixture, and the organic layer was washed with HCl(aq) (1.0 M). After extracting the aqueous solution with chloroform, the organic layers were washed lightly with brine (10 mL). The resulting solution was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/8) as an eluent.

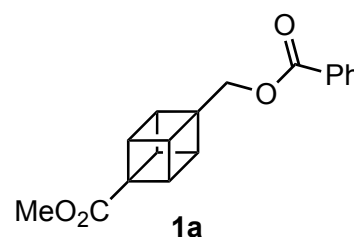
Preparation of methyl 4-acyloxymethylcubanecarboxylate with functional groups (**1i-l**)

Substrates **1i-l** were prepared from methyl 4-hydroxymethyl-1-cubanecarboxylate and the corresponding carboxylic acid. To a mixture of methyl 4-hydroxymethyl-1-cubanecarboxylate (2.0 mmol, 0.38 g), carboxylic acid (2.5 mmol), and DMAP (ca 20 mg) in DCM (20 mL), 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (4.0 mmol, 0.77 g) was added. The mixture was stirred for 12 h at 25 °C. About 20 mL of DCM was added to the mixture, and the organic layer was washed with saturated NaHCO₃ aq. After extracting the aqueous solution with chloroform, the combined organic layers were washed lightly with brine (10 mL). The resulting solution was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/5) as an eluent.

Methyl 4-((benzoyloxy)methyl)cubane-1-carboxylate (1a)

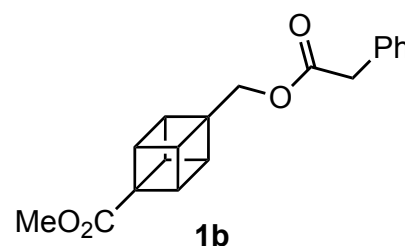
536 mg (90% yield); ¹H NMR (500 MHz, CDCl₃): δ 8.05-8.01 (m, 2H), 7.60-8.53 (m, 1H), 7.48-7.42 (m, 2H), 4.49 (s, 2H), 4.22-4.17 (m, 3H), 3.99-3.94 (m, 3H), 3.71 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 172.8,



167.1, 133.3, 130.6, 130.0, 128.7, 65.2, 56.8, 56.7, 51.9, 46.9, 45.5; HRMS (APCI) m/z: [M+H]⁺ Calcd for C₁₈H₁₆O₄H 297.1127; Found 297.1124; IR (film): 1720, 1269 cm⁻¹.

Methyl 4-((2-phenylacetoxy)methyl)cubane-1-carboxylate (1b)

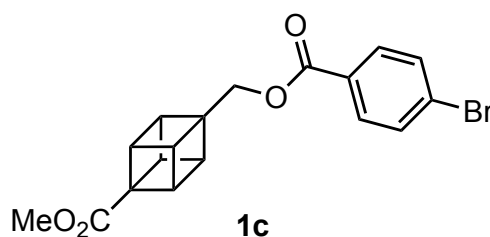
553 mg (93% yield); ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.27 (m, 5H), 4.29 (s, 2H), 4.13-4.09 (m, 3H), 3.85-3.80 (m, 3H), 3.73 (s, 3H), 3.66 (s, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 172.5, 171.8, 134.2



129.2, 128.6, 127.1, 64.6, 56.3, 56.2, 51.5, 46.4, 45.0, 41.5; HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₁₉H₁₈O₄Na 333.1102; Found 333.1094; IR (film): 1725, 1209, 1086 cm⁻¹.

Methyl 4-(((4-bromobenzoyl)oxy)methyl)cubane-1-carboxylate (1c)

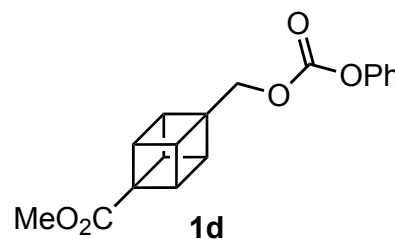
585 mg (78%); ¹H NMR (500 MHz, CDCl₃): δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 4.52 (s, 2H), 4.22 – 4.19 (m, 3H), 3.99-3.96 (m, 3H), 3.74 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 172.5, 166.0, 131.8, 131.2, 129.1, 128.1,



65.1, 56.4, 56.2, 51.6, 46.6, 45.1; HRMS (APCI) m/z : $[M+H]^+$ Calcd for $C_{18}H_{15}BrO_4H$ 375.0231; Found 375.0229; IR (film): 1725, 1209, 1086 cm^{-1} .

Methyl 4-(((phenoxycarbonyl)oxy)methyl)cubane-1-carboxylate (1d)

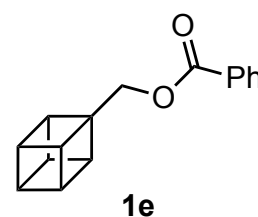
500 mg (80%); 1H NMR (500 MHz, $CDCl_3$): δ 7.39 (dd, $J = 7.5, 7.5$ Hz, 2H), 7.25 (dd, $J = 7.5$ Hz, 1H), 7.17 (d, $J = 7.5$ Hz, 2H), 4.45 (s, 2H), 4.22-4.19 (m, 3H), 4.01-3.98 (m, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 154.0, 151.1, 129.5, 126.1, 121.0, 68.6,



56.3, 55.8, 51.6, 46.6, 45.0; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_{18}H_{16}O_5Na$ 335.0895; Found 335.0887; IR (film): 1759, 1729, 1238, 1203 cm^{-1} .

(Cubane-1-yl)methyl benzoate (1e)

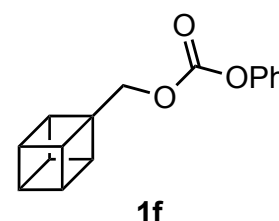
428 mg (90%); 1H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, $J = 7.5$ Hz, 2H), 7.54 (dd, $J = 7.5$ Hz, 1H), 7.44 (dd, $J = 7.5, 7.5$ Hz, 2H), 4.48 (s, 2H), 4.08-4.01 (m, 1H), 3.97 (bs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 152.8, 130.5, 129.6



126.3, 65.5, 55.9, 48.6, 47.4, 44.6; HRMS (API) m/z : $[M+H]^+$ Calcd for $C_{16}H_{14}O_2H$ 239.1072; Found 239.1066; IR (film): 1716, 1252, 708 cm^{-1} .

(Cubane-1-yl)methyl phenyl carbonate (1f)

428 mg (73%); 1H NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, $J = 6.5, 6.5$ Hz, 2H), 7.25 (dd, $J = 6.5, 6.5$ Hz, 1H), 7.21 (d, $J = 6.5$ Hz, 1H), 4.44 (s, 2H), 4.08-4.05 (m, 1H), 4.00 (bs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.2, 129.5,



126.0, 121.1, 69.3, 55.4, 48.5, 47.3, 44.6; HRMS (APCI) m/z : $[M+H]^+$ Calcd for $C_{16}H_{14}O_3H$ 255.1021; Found 255.1014; IR (film): 1755, 1232, 1203 cm^{-1} .

(Cubane-1-yl)methyl cyclopropanecarboxylate (1g)

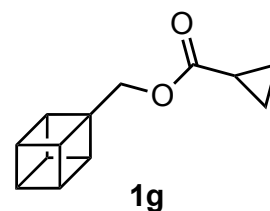
300 mg (74%); ^1H NMR (500 MHz, CDCl_3): δ 4.22 (s, 2H), 4.05-3.99 (m, 1H),

3.95-3.85 (m, 6H), 1.66-1.59 (m, 1H), 0.98 (ddd, $J = 7.5, 4.0, 4.0$ Hz, 2H), 0.85

(ddd, $J = 11.0, 4.0, 4.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 175.3, 65.0,

55.7, 48.5, 47.3, 44.5, 12.9, 8.5; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{H}$ 203.1072; Found

203.1065; IR (film): 2726, 1729, 1170 cm^{-1} .

**(2-Cubane-1-yl)methyl 3-bromopropanoate (1h)**

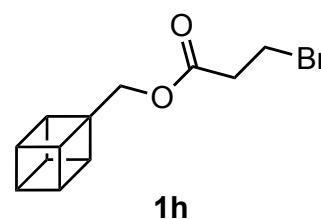
344 mg (64%); ^1H NMR (500 MHz, CDCl_3): δ 4.29 (s, 2H), 4.05-3.99 (m,

1H), 3.95-3.85 (m, 6H), 3.58 (t, $J = 7.0$ Hz, 2H), 2.94 (t, $J = 7.0$ Hz, 2H);

^{13}C NMR (125 MHz, CDCl_3): δ 170.8, 65.5, 55.7, 48.5, 47.3, 44.5, 37.9,

26.1; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{13}\text{BrO}_2\text{H}$ 269.0177; Found 269.0173; IR (film): 1740,

1215, 1190 cm^{-1} .

**Methyl 4-(((5-oxo-5-phenylpentanoyl)oxy)methyl)cubane-1-carboxylate (1i)**

192 mg (56%); ^1H NMR (500 MHz, CDCl_3): δ 7.95 (d, J

= 8.5 Hz, 2H), 7.56 (dd, $J = 8.5, 8.5$ Hz, 1H), 7.46 (dd, $J =$

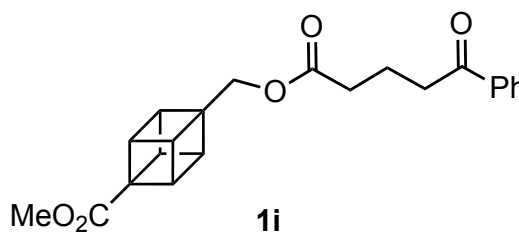
8.5, 8.5 Hz, 2H), 4.28-4.25 (m, 2H), 4.17-4.09 (m, 3H),

3.89-3.81 (m, 3H), 3.72 (s, 3H), 3.07 (t, $J = 7.0$ Hz, 2H),

2.50 (t, $J = 7.0$ Hz, 2H) 2.08 (tt, $J = 7.0, 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 199.3, 173.5,

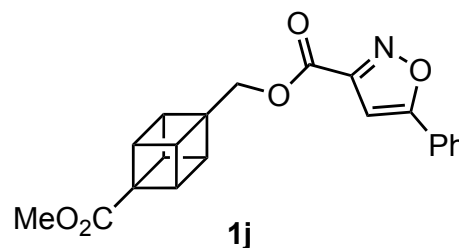
172.5, 136.7 133.1, 128.6, 128.0, 64.4, 56.2, 51.5, 47.1, 46.5, 45.0, 37.4, 33.3, 19.5; HRMS (ESI) m/z :

$[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{22}\text{H}_{22}\text{O}_5\text{Na}$ 389.1364; Found 389.1361; IR (film): 1703, 1234, 1086 cm^{-1} .

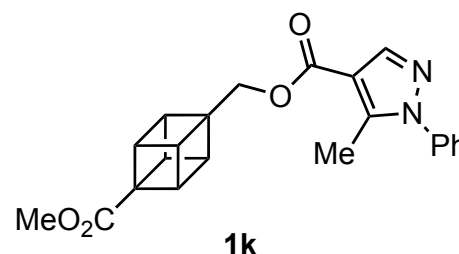


(4-(Methoxycarbonyl)cubane-1-yl)methyl 5-phenylisoxazole-3-carboxylate (1j)

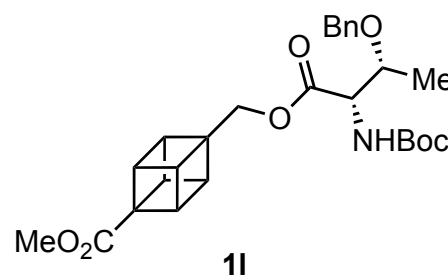
508 mg (72%); ^1H NMR (500 MHz, CDCl_3): δ 7.85-7.79 (m, 2H), 7.54-7.46 (m, 3H), 6.91 (s, 1H), 4.59 (s, 2H), 4.20 (dd, $J = 4.5, 4.5$ Hz, 3H), 3.99 (dd, $J = 4.5, 4.5$ Hz, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 172.4, 171.8, 160.3, 156.7, 130.9, 129.2, 126.6, 126.0, 100.0, 66.0, 56.4, 56.0, 51.6, 46.6, 45.2; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{17}\text{NO}_5\text{Na}$ 386.1001; Found 386.1004; IR (film): 1725, 1246, 1213 cm^{-1} .

**(4-(Methoxycarbonyl)cubane-1-yl)methyl 5-methyl-1-phenyl-1H-pyrazole-4-carboxylate (1k)**

631 mg (84%); ^1H NMR (500 MHz, CDCl_3): δ 8.02 (s, 1H), 7.54-7.37 (m, 5H), 4.43 (s, 3H), 4.19 (dd, $J = 5.0, 5.0$ Hz, 3H), 3.94 (dd, $J = 5.0, 5.0$ Hz, 3H), 3.71 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 172.5, 163.9, 143.5, 142.0, 138.8, 129.3, 128.7, 125.6, 112.9, 63.9, 56.4, 56.3, 51.6, 46.5, 45.1, 12.0; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ 399.1320; Found 399.1317; IR (film): 1703, 1234, 1986 cm^{-1} .

**4-(((O-Benzyl-N-(tert-butoxycarbonyl)-L-threonyl)oxy)methyl)cubane-1-carboxylate (1l)**

608 mg (65%); ^1H NMR (500 MHz, CDCl_3): δ 7.40-7.22 (m, 5H), 5.32 (d, $J = 10.0$ Hz, 1H), 4.58 (d, $J = 11.5$ Hz, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.35-4.31 (m, 1H), 4.28 (d, $J = 15.5$ Hz, 1H), 4.21 (d, $J = 15.5$ Hz, 1H), 4.19-4.09 (m, 4H), 3.82 (dd, $J = 5.0, 5.0$ Hz, 3H), 3.72 (s, 3H), 1.72 (s, 9H), 1.29 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 172.5, 171.4, 156.2, 137.9, 128.4, 127.8, 127.6, 79.9, 74.7, 70.8, 65.3, 58.3, 56.3, 55.9, 51.5, 47.1, 46.5, 44.9, 28.3, 16.3; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_7\text{Na}$ 506.2154; Found 506.2145; IR (film): 3350 (weak), 1719, 1163, 1085, 1070 cm^{-1} .



Catalyst tuning experiments in Table 6-1

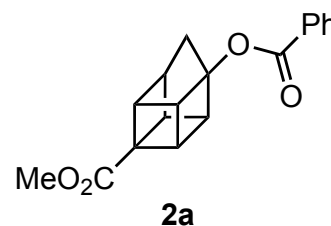
Compound **1a** (0.2 mmol) was treated with the catalyst shown in Table 6-1. To a solution of catalyst in DCE (1 mL), a solution of **1a** (0.2 mmol) in DCE (2 mL) was added at 25 °C. The resulting mixture was stirred for the indicated reaction period. After one drop of 30% NH₃aq was added, the mixture was passed through a short column (lower phase: silica gel (1 cm), upper phase: celite 545 (0.5 cm)). The resulting solution was concentrated in vacuo. The yield of the product was calculated by ¹H NMR using CHBr₃ as an internal standard. The catalyst was prepared using the following solutions: AgOTf (0.1 M in 5 vol% CH₃CN in DCE); PhCOCl (0.1 M in DCE); PhCO₂COPh (0.1 M in DCE); AcCl (0.1 M in DCE). The catalyst was prepared by a subsequent addition of AgOTf solution and the additive solution to DCE (0.5 mL) at 25 °C followed by stirring for 1 min under Ar. In the use of AgCl as a catalyst, a dispersion of AgCl in DCE was used. PhCO₂OTf (0.1 M in DCE) was also used as a catalyst.

Preparation of homocubanes (2a-2l)

A solution of compound **1a-l** (0.5 mmol) in DCE (2 mL) was added to a solution of the catalyst (0.05 mmol) prepared from AgOTf (0.1 M in 5 vol% CH₃CN in DCE) and PhCOCl (0.1 M in DCE) in DCE (1 mL). The mixture was stirred for 10 h at 80 °C. After one drop of 30% NH₃aq was added, the mixture was passed through a short column (lower phase: silica gel (1 cm), upper phase: celite 545 (0.5 cm)). The resulting solution was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/7) as eluent.

Methyl 1-(benzoyloxy)pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylate (**2a**)

145 mg (98%); ¹H NMR (500 MHz, CDCl₃): δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.57 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.74-3.66 (m, 3H), 3.69 (s, 3H), 3.59-3.53 (m, 2H), 3.36-3.30 (m, 1H), 2.25 (*J* = 2.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 172.8, 165.8, 133.0, 130.4, 129.7



128.4, 92.9, 51.5, 49.2, 46.6, 44.9, 44.1, 43.8, 38.5; HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₈H₁₆O₄Na 319.0946; Found 319.0942; IR (film): 1725, 1278, 1229 cm⁻¹.

Methyl 1-(2-phenylacetoxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylate (2b)

152 mg (98%); ¹H NMR (500 MHz, CDCl₃): δ 7.41-7.23 (m, 5H), 3.68

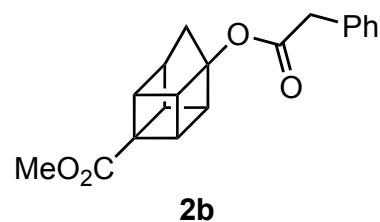
(s, 2H), 3.67 (s, 3H), 3.65-3.58 (m, 3H), 3.43-3.37 (m, 2H), 3.28-3.22

(m, 1H), 2.11 (*J* = 1.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 172.7,

170.9, 134.0, 129.2, 128.6 127.1, 92.8, 51.5, 49.1, 46.4, 44.8, 44.0,

43.7, 41.5, 38.4; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₁₉H₁₈O₄H 311.1277; Found 311.1283; IR

(film): 1722, 1224, 1076 cm⁻¹.

**Methyl 1-((4-bromobenzoyl)oxy)pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylate (2c)**

184 mg (98%); ¹H NMR (500 MHz, CDCl₃): δ 7.92 (d, *J* = 7.0 Hz,

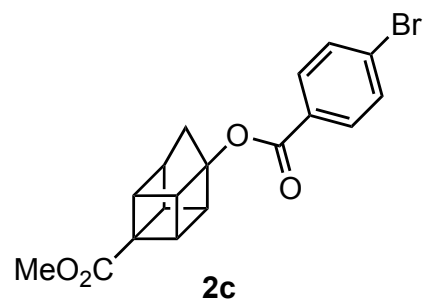
2H), 7.59 (d, *J* = 7.0 Hz, 2H), 3.74-3.66 (m, 3H), 3.69 (s, 3H), 3.57-

3.52 (m, 2H), 3.37-3.30 (m, 1H), 2.23 (*J* = 2.0 Hz, 2H); ¹³C NMR

(125 MHz, CDCl₃): δ 172.7, 165.1, 131.7, 131.3, 129.3 128.2, 93.2,

51.5, 49.1, 46.5, 44.8, 44.1, 43.8, 38.5; HRMS (APCI) *m/z*: [M+H]⁺

Calcd for C₁₈H₁₅BrO₄H 375.0231; Found 375.0277; IR (film): 1720, 1274, 1188 cm⁻¹.

**Methyl 1-((phenoxycarbonyl)oxy)pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylate (2d)**

153 mg (98%); ¹H NMR (500 MHz, CDCl₃): δ 7.39 (dd, *J* = 6.5, 6.5 Hz,

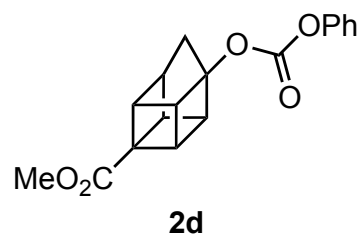
2H), 7.29-7.18 (m, 3H), 3.72-3.64 (m, 3H), 3.68 (s, 3H), 3.57-3.51 (m,

2H), 3.34-3.28 (m, 1H), 2.24 (*J* = 1.5 Hz, 2H); ¹³C NMR (125 MHz,

CDCl₃): δ 172.4, 152.2, 151.0, 129.5, 126.1, 121.0, 94.6, 51.5, 49.2,

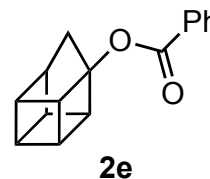
46.6, 44.3, 43.8, 38.4; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₁₈H₁₆O₅H 313.1076; Found 313.1069;

IR (film): 1759, 1720, 1238, 1203 cm⁻¹.

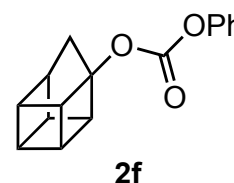


Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-1-yl benzoate (2e)

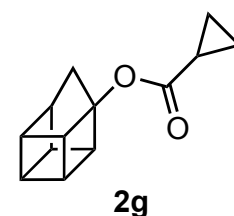
116 mg (98%); ¹H NMR (500 MHz, CDCl₃): δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.58-3.52 (m, 2H), 3.52-3.45 (m, 3H), 3.21-3.15 (m, 2H), 2.22 (*J* = 1.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 165.9, 132.8, 130.8, 129.7, 128.3, 93.7, 46.4, 45.6, 44.0, 42.4, 40.5, 40.1; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₁₆H₁₄O₂H 239.1072; Found 239.1067; IR (film): 1720, 1218 cm⁻¹.

**Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-1-yl phenyl carbonate (2f)**

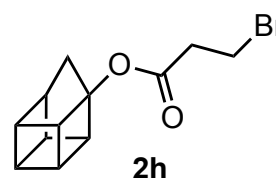
124 mg (98%); ¹H NMR (500 MHz, CDCl₃): δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.37 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.26 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.60-3.50 (m, 2H), 3.50-3.40 (m, 3H), 3.20-3.15 (m, 2H), 2.19 (*J* = 1.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 152.3, 151.1, 129.5, 126.0, 121.1, 95.5, 46.0, 45.0, 44.1, 42.3, 40.5, 39.9; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₁₆H₁₄O₃H 255.1021; Found 255.1015; IR (film): 1759, 1492, 1254, 1175 cm⁻¹.

**Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-1-yl cyclopropanecarboxylate (2g)**

99 mg (98%); ¹H NMR (500 MHz, CDCl₃): δ 3.43-3.34 (m, 5H), 3.14-3.07 (m, 2H), 2.07 (d, *J* = 2.0 Hz, 2H), 1.65 (ddd, *J* = 8.0, 4.5, 4.5 Hz, 1H), 0.99 (ddd, *J* = 7.5, 4.5, 4.5 Hz, 2H), 0.85 (ddd, *J* = 10.1, 4.5, 4.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 174.2, 93.3, 46.3, 45.5, 43.9, 42.3, 40.4, 40.0, 13.2, 8.5; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₁₃H₁₄OH 203.1072; Found 203.1064; IR (film): 2938, 1732, 1388, 1175 cm⁻¹.

**Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-1-yl 3-bromopropanoate (2h)**

133 mg (99%); ¹H NMR (500 MHz, CDCl₃): δ 3.59 (t, *J* = 7.5 Hz, 2H), 3.45-3.35 (m, 5H), 3.18-3.08 (m, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.08 (d, *J* = 1.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 170.0, 93.8, 46.2, 45.4, 43.9, 42.3, 40.4, 39.9, 38.0, 26.1; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₁₂H₁₃BrO₂H 269.0177; Found 269.0170; IR (film): 2977, 1730, 1175 cm⁻¹.



Methyl 1-((5-oxo-5-phenylpentanoyl)oxy)pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylate (2i)

59 mg (32%); ¹H NMR (500 MHz, CDCl₃): δ 7.99 (d, *J* = 8.5

Hz, 2H), 7.59 (dd, *J* = 8.5, 8.5 Hz, 1H), 7.49 (dd, *J* = 8.5 Hz,

2H), 3.71 (s, 3H), 3.69-3.62 (m, 3H), 3.48-3.39 (m, 2H), 3.34-

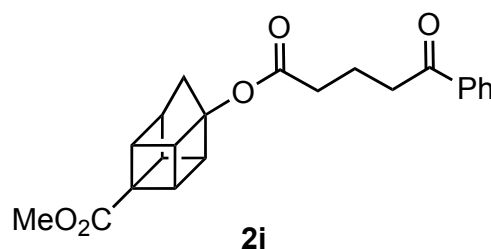
3.23 (m, 1H), 3.10 (t, *J* = 6.5 Hz, 2H), 2.53 (t, *J* = 6.5 Hz, 2H),

2.20 (s, 2H), 2.13 (tt, *J* = 6.5, 6.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 199.4, 172.7, 172.6, 136.8,

133.1, 128.6, 128.0, 92.4, 51.5, 49.1, 47.1, 46.4, 44.7, 44.0, 43.6, 38.4, 37.4, 33.6, 19.4; HRMS (ESI)

m/z: [M+Na]⁺ Calcd for C₂₂H₂₂O₅Na 389.1364; Found 389.1359; IR (film): 1725, 1683, 1224, 1201,

1186 cm⁻¹.

**2i****4-(Methoxycarbonyl)pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-1-yl 5-phenylisoxazole-3-carboxylate (2j)**

222mg (95%); ¹H NMR (500 MHz, CDCl₃): δ 7.86-7.74 (m, 2H),

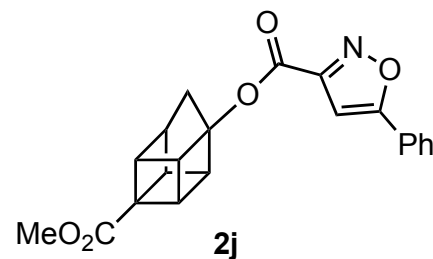
7.54-7.44 (m, 3H), 6.96-6.91 (m, 1H), 3.77-3.70 (m, 3H), 3.69 (s,

3H), 3.64-3.57 (m, 2H), 3.39-3.31 (m, 1H), 2.32 (d, *J* = 1.5 Hz,

2H); ¹³C NMR (125 MHz, CDCl₃): δ 172.5, 171.9, 159.2, 157.0,

130.9, 129.2, 126.6, 126.0, 100.0, 94.1, 51.6, 49.1, 46.6, 44.7, 44.0, 43.8, 38.4; HRMS (ESI) *m/z*:

[M+Na]⁺ Calcd for C₂₆H₂₂Cl₂O₄Na 491.0787; Found 491.0788; IR (film): 1719, 1221 cm⁻¹.

**2j****Methyl 3-benzyloxymethylcuneane-1-carboxylate (3a)**

¹H NMR (500 MHz, CDCl₃): δ 8.10 (d, *J* = 7.5 Hz, 2H), 7.56 (dd, *J* = 7.5, 7.5 Hz, 1H),

7.45 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 3.75

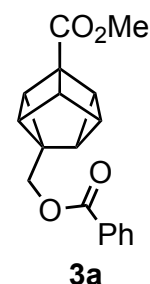
(s, 3H), 3.08-3.04 (m, 1H), 2.60 (d, *J* = 4.5 Hz, 1H), 2.52 (ddd, *J* = 5.5, 5.5, 1.0 Hz, 1H),

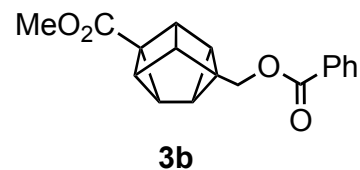
2.49 (dd, *J* = 5.5, 5.5 Hz, 1H), 2.42 (ddd, 4.0, 3.0 Hz, 1H), 2.35 (dd, *J* = 7.5, 4.5 Hz, 1H); ¹³C NMR

(125 MHz, CDCl₃): δ 172.8, 166.7, 133.0, 130.3, 129.7, 128.4, 63.7, 53.9, 51.9, 47.0, 43.8, 37.2, 36.1,

32.1, 31.3, 30.8; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₁₈H₁₆O₄H 297.1127; Found 297.1123; IR

(film): 1717, 1269, 1223 cm⁻¹.

**3a**

Methyl 6-benzoyloxymethylcuneane-2-carboxylate (3b)

^1H NMR (500 MHz, CDCl_3): δ 8.03 (d, $J = 8.5$ Hz, 2H), 7.57 (dd, $J = 8.5$, 8.5 Hz, 1H), 7.43 (dd, $J = 8.5$, 8.5 Hz, 2H), 4.38 (d, $J = 12.5$ Hz, 1H), 4.33 (d, $J = 12.5$ Hz, 1H), 3.61 (s, 3H), 3.08-3.04 (m, 2H), 2.99-2.96 (m, 1H), 2.85 (ddd, $J = 8.0$, 2.0, 1.0 Hz, 1H), 2.58 (ddd, $J = 5.5$, 3.0, 1.5 Hz, 1H), 2.49 (dd, $J = 5.5$, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.2, 166.6, 133.0, 130.3, 129.6, 128.4, 64.3, 51.4, 44.3, 44.3, 43.4, 40.1, 40.0, 38.9, 37.0, 34.8; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_4$ 297.1127; Found 297.1118; IR (film): 1725, 1271, 1101 cm^{-1} .

Catalyst tuning experiments in Table 6-2

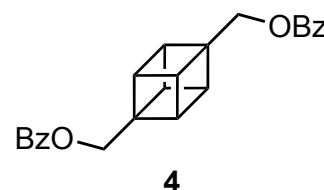
The catalyst was prepared as described in the procedure for Table 6-1. In addition of Table 6-1, AgOMs (0.1 M in CH_3CN), AgBF_4 (0.1 M in DCE), PhCOBr (0.1 M in DCE), and (+)-Mosher's reagent (1.0 M in dichloromethane from TCI) were also used. Silver-Chiral phosphoric acid complexes were prepared from the corresponding chiral phosphoric acid and Ag_2CO_3 according to the procedure in ref 14. Silver-CSA complex was prepared from Ag_2O and (+)-CSA according to the procedure in ref 15. Compound **4** (0.2 mmol) was treated with the catalyst shown in Table 6-2. The resulting mixture was stirred for the indicated reaction period. After one drop of 30% NH_3aq was added, the mixture was passed through a short column (lower phase: silica gel (1 cm), upper phase: celite 545 (0.5 cm)). The resulting solution was concentrated in vacuo. The yield and the ratio of the products were calculated by ^1H NMR using CHBr_3 as an internal standard. In addition to Table 6-2, examples using various Lewis acids were shown in Table 6-3.

Isolation of C_2 -bishomocubane **5**, D_2 -bishomocubane **6**, homocubane **7**, 1,3-bis(benzyloxymethyl)cuneane **8a**, and 2,6-bis(benzyloxymethyl)cuneane **8b** were performed as follows. Separation by silica gel column chromatography ($\text{H}/\text{AcOEt} = 1/7$) gave **7**, **8a**, and **8b** in a pure form. Bishomocubanes (**5** and **6**) were obtained as a mixture. The mixture (120 mg) was dissolved with the minimum amount of dicholomethane (0.8 mL). Hexane (5 mL) was added to the solution. The

solution was cooled to -20 °C. After 5 h, the obtained white solid was **6** (28 mg). Repeating the same procedure twice, the remaining solution was concentrated in vacuo. The recrystallization of the obtained mixture from dichloromethane and hexane at 25 °C gave **5**. Single crystal X-ray analysis of **5** was performed.

1,4-Bis(benzyloxymethyl)cubane (**4**)

To 1,4-bis(hydroxymethyl)cubane (3.0 mmol, 0.49 g)²¹ in DCM (20 mL), benzoyl chloride (7.0 mmol, 0.98 g) in DCM (1 mL), triethylamine (7.0

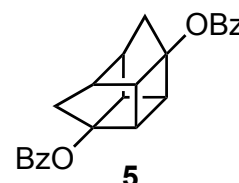


mmol, 0.70 g) in DCM (1 mL), and catalytic amount of DMAP were added at 0 °C. The mixture was stirred for 2 h at 25 °C. About 20 mL of DCM was added to the mixture, and the combined organic layer was washed with HCl_{aq} (1.0 M). The aqueous layer was extracted with chloroform. The combined organic layers were washed with sat NaHCO₃, and dried over Na₂SO₄. After purification by silica gel column chromatography (H/AcOEt = 8/1), the obtained solid was purified further by recrystallization from dichloromethane and hexane. The title compound **4** was obtained in 78% yield (0.87 g).

¹H NMR (500 MHz, CDCl₃): δ 8.07 (d, *J* = 8.0 Hz, m, 2H), 7.57 (dd, *J* = 8.0, 8.0 Hz, m, 1H), 7.47 (dd, *J* = 8.0, 8.0 Hz, m, 2H), 4.53 (s, 4H), 3.95 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 166.8, 132.9, 130.4, 129.6, 128.4, 65.3, 56.9, 44.5; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₂₄H₂₀O₄H 373.1439; Found 373.1432; IR (film): 2960, 1712, 1252 cm⁻¹.

5,9-Bis(benzyloxy)pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**5**)

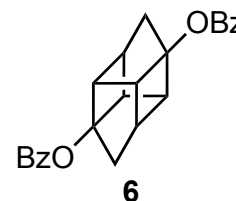
¹H NMR (500 MHz, CDCl₃): δ 8.10-8.05 (m, 4H), 7.60-7.50 (m, 2H), 7.50-7.42 (m, 4H), 3.28 (dd, *J* = 6.0, 3.0 Hz, 2H), 3.20 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.76 (dd, *J*



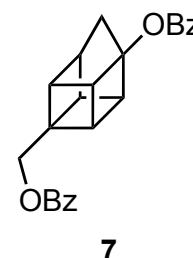
= 4.5, 3.5 Hz, 2H), 2.22 (d, *J* = 10.0 Hz, 2H), 2.00 (d, *J* = 10.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 166.0, 132.9, 130.6, 129.7, 128.4, 90.6, 47.7, 44.0, 42.1, 40.9; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₂₄H₂₀O₄H 373.1439; Found 373.1434; IR (film): 2984, 1712, 1252 cm⁻¹.

1,4-Bis(benzyloxy)pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (6)

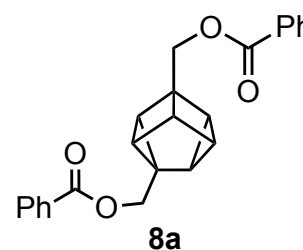
¹H NMR (500 MHz, CDCl₃): δ 8.12-8.08 (m, 4H), 7.61-7.56 (m, 2H), 7.50-7.42 (m, 4H), 3.13 (s, 6H), 2.12 (s, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 166.2, 133.0, 130.7, 129.7, 128.4, 90.8, 45.9, 40.6, 39.9; HRMS (APCI) m/z: [M+H]⁺ Calcd for C₂₄H₂₀O₄H 373.1439; Found 373.1435; IR (film): 2984, 1712, 1278, 1252 cm⁻¹.

**(4-((Benzoyloxy)methyl)pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-1-yl benzoate) (7)**

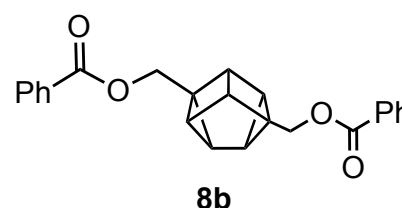
¹H NMR (500 MHz, CDCl₃): δ 8.15-8.08 (m, 4H), 7.62-7.58 (m, 2H), 7.52-7.42 (m, 4H), 4.45 (s, 2H), 3.58-3.45 (m, 5H), 3.22 (dd, *J* = 2.0, 2.0 Hz, 1H), 2.27 (d, *J* = 2.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 166.8, 165.9, 132.9, 130.6, 130.4, 129.7, 129.6, 128.4, 128.3, 93.6, 64.5, 49.2, 45.1, 44.5, 43.8, 42.4, 37.8; HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₂₄H₂₀O₄Na 395.1259; Found 395.1256; IR (film): 1712, 1277, 709 cm⁻¹.

**1,3-Bis(benzoyloxymethyl)cuneane (8a)**

¹H NMR (500 MHz, CDCl₃): δ 8.15-8.08 (m, 4H), 7.61-7.54 (m, 2H), 7.50-7.42 (m, 4H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.58 (s, 2H), 2.71 (bs, 1H), 2.48 (dd, *J* = 5.0, 5.0 Hz, 1H), 2.37 (ddd, *J* = 7.0, 4.5, 4.5 Hz, 2H), 2.28 (ddd, *J* = 7.0, 2.5, 2.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 166.9, 166.8, 133.0, 132.9, 130.5, 130.3, 129.7, 129.6, 128.4, 128.3, 64.3, 63.9, 52.4, 44.2, 43.2, 38.4, 35.8, 32.9, 31.9, 30.4; HRMS (APCI) m/z: [M+H]⁺ Calcd for C₂₄H₂₀O₄H 373.1439; Found 373.1431; IR (film): 1716, 1269, 1095, 1069 cm⁻¹.

**2,6-Bis(benzoyloxymethyl)cuneane (8b)**

¹H NMR (500 MHz, CDCl₃): δ 8.15-8.08 (m, 4H), 7.62-7.58 (m, 2H), 7.52-7.42 (m, 4H), 4.44 (d, *J* = 12.5 Hz, 2H), 4.35 (d, *J* = 12.5 Hz, 2H), 2.86 (bs, 2H), 2.51-2.49 (m, 2H), 2.46-2.41 (m, 2H); ¹³C



NMR (125 MHz, CDCl₃): δ 166.7, 132.8, 130.5, 129.7, 128.4, 128.3, 64.8, 44.7, 40.3, 36.2, 34.8; HRMS (APCI) *m/z*: [M+H]⁺ Calcd for C₂₄H₂₀O₄H 373.1439; Found 373.1434; IR (film): 1716, 1200, 1101 cm⁻¹.

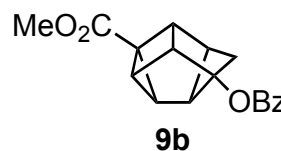
Isomerization of cuneane (Scheme 6-4): Methyl 6-benzoyloxymethylcuneane-2-carboxylate (**3b**)

The title compound **3b** was a minor product of AgOTf catalyzed isomerization of methyl 4-benzoyloxymethylcubane-1-carboxylate (**1a**) in Table 6-1 (entry 1). As a starting material of the isomerization reaction in Scheme 6-4, **3b** was prepared by benzylation of methyl 4-hydroxymethyl-1-cuneanecarboxylate. To a solution of dimethyl 2,6-cunanedicarboxylate (5.0 mmol, 1.1 g) in THF (30 mL), anhydrous NaOMe in MeOH (5 M solution; 6 mmol, 1.2 mL) was added. To this mixture, distilled water (5.2 mmol, 94 mg) in MeOH (1 mL) was added at 25 °C. The mixture was stirred vigorously for 6 h. The volatile solvents were removed in vacuo. The remaining white solid was dissolved into distilled water (15 mL). After acidified with conc HCl_{aq}, the mixture was extracted with chloroform. The obtained organic layers were dried over Na₂SO₄ and concentrated in vacuo. The obtained white solid (0.93 g, 95% yield) was dissolved into anhydrous THF (30 mL). To the solution, H₃B•SMe₂ (7.0 mmol, 0.7 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 2 h at 25 °C. The whole was cooled to 0 °C, 1.0 mL of water was added dropwise carefully. To the solution, 10 mL of water was added, and the resulting mixture was stirred for 0.5 h at 25 °C. To the mixture, 5 mL of sat NaHCO₃aq was added. The mixture was extracted with chloroform and ethyl acetate. The organic layers were dried over Na₂SO₄ and concentrated in vacuo. Without purification, the obtained viscous oil was dissolved into dichloromethane (20 mL). Benzoic acid (7 mmol, 0.85 g), catalytic amount of DMAP, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (10.0 mmol, 1.9 g) was added. The mixture was stirred for 12 h at 25 °C. About 20 mL of chloroform was added to the mixture, and the organic layer was washed with saturated NaHCO₃aq. After extracting the aqueous solution with chloroform, the combined organic layers were washed lightly with brine (10 mL). The combined organic layers were concentrated in vacuo. The obtained residue was purified by silica gel

column chromatography using ethyl acetate/hexane (1/8) as an eluent. The title compounds were isolated in 65% yield (0.96 g, via three steps from dimethyl 2,6-cuneanedicarboxylate).

Methyl 8-(benzoyloxy)pentacyclo[4.3.0.0^{2,4}.0^{3,6}.0^{5,8}]nonane-2-carboxylate (**9b**)

To a solution of **3b** (0.2 mmol, 59 mg) in DCE (2 mL), a solution of PhOTf in DCE (0.04 mmol, 0.4 mL of 0.1M in DCE) was added. The whole was stirred for 18 h at 80 °C. To the mixture, one drop of 30% NH₃aq was added. The

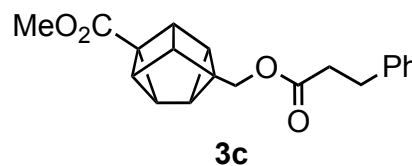


resulting mixture was passed through a short column (lower phase: silica gel (1 cm), upper phase: celite 545 (0.5 cm)). the resulting solution was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/6) as eluent to separate unreacted **3b** and products. The title compound was isolated from the product mixture using PLC (DCM/hexane = 6/1). The starting material **3b** was recovered in 37% yield (21 mg) and the title compound was obtained in 38% yield (22 mg).

¹H NMR (500 MHz, CDCl₃): δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 2H), 3.66 (s, 3H), 3.36 (bs, 1H), 3.13 (ddd, *J* = 5.0, 2.5, 0.5 Hz, 1H), 3.04 (d, *J* = 6.5 Hz, 1H), 2.93 (dd, *J* = 5.5, 3.5 Hz, 1H), 2.87 (d, *J* = 6.5 Hz, 1H), 2.51 (dd, *J* = 5.0, 3.5 Hz, 1H), 2.17 (dd, *J* = 8.0, 3.5 Hz, 1H), 1.87 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 171.8, 165.7, 133.0, 130.3, 129.7, 128.4, 94.6, 57.5, 51.5, 46.1, 45.0, 42.4, 41.9, 39.3, 38.6, 33.4; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₈H₁₆O₄Na 319.0946; Found 319.0936; IR (film): 1716, 1265, 1096, 709 cm⁻¹.

Methyl 6-(3-phenylpropionyloxymethyl)cuneane-2-carboxylate (**3c**)

¹H NMR (500 MHz, CDCl₃): δ 7.32-7.25 (m, 2H), 7.25-7.18 (m, 3H), 4.11 (d, *J* = 12.5 Hz, 1H), 4.07 (d, *J* = 12.5 Hz, 1H), 3.62 (s, 3H), 3.02-2.98 (m, 3H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.92 (ddd, *J* = 4.8,

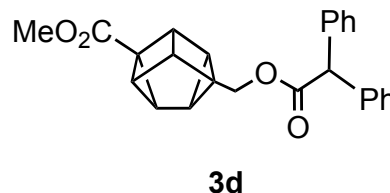


2.5, 1.0 Hz, 1H), 2.71 (ddd, *J* = 7.5, 2.5, 1.0 Hz, 1H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.46 (ddd, *J* = 6.0, 2.5, 1.0 Hz, 1H), 2.37 (ddd, *J* = 6.5, 3.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 173.0, 171.2, 140.5, 128.5,

128.3, 126.3, 63.9, 51.5, 44.3, 44.1, 43.3, 40.9, 39.9, 38.8, 36.9, 35.8, 34.7, 31.0; HRMS (APCI) m/z : $[M+H]^+$ Calcd for $C_{20}H_{20}O_4H$ 325.1439; Found 325.1432; IR (film): 1717, 1200, 1101, 698 cm^{-1} .

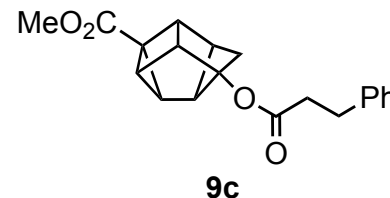
Methyl 6-(diphenylacetyloxymethyl)cuneane-2-carboxylate (3d)

1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.22 (m, 10H), 5.03 (s, 1H), 4.24 (d, $J = 12.5$ Hz, 1H), 4.15 (d, $J = 12.5$ Hz, 1H), 3.61 (s, 3H), 2.97-2.83 (m, 2H), 2.89-2.85 (m, 1H), 2.66 (dd, $J = 6.5, 1.0$ Hz, 1H), 2.47 (ddd, $J = 6.0, 2.5, 1.5$ Hz, 1H), 2.38 (dd, $J = 6.0, 2.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 171.1, 138.7, 138.6, 128.7, 128.6, 127.3, 64.4, 57.2, 51.5, 44.3, 44.2, 43.3, 40.9, 40.0, 38.8, 37.1, 34.8; HRMS (APCI) m/z : $[M+H]^+$ Calcd for $C_{25}H_{22}O_4H$ 387.1596; Found 387.1591; IR (film): 1719, 1200, 1142, 1105 cm^{-1} .



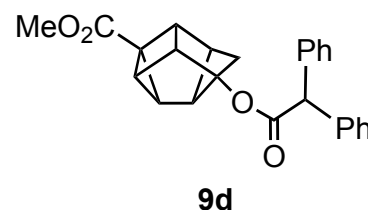
Methyl 8-((3-phenylpropionyloxymethyl)pentacyclo[4.3.0.0^{2,4}.0^{3,9}.0^{5,8}]nonane-2-carboxylate (9c)

1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.25 (m, 2H), 7.24-7.18 (m, 3H), 3.64 (s, 3H), 3.18 (bs, 1H), 3.06-3.03 (m, 1H), 2.98-2.95 (m, 1H), 2.91 (t, $J = 8.0$ Hz, 2H), 2.88-2.84 (m, 1H), 2.70-2.66 (m, 1H), 2.67 (t, $J = 8.0$ Hz, 2H), 2.44-2.41 (m, 1H), 2.00 (dd, 8.0, 3.5 Hz, 1H), 1.72 (d, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 171.8, 140.3, 128.5, 128.3, 126.3, 94.2, 57.3, 51.5, 46.0, 44.8, 42.3, 41.8, 39.1, 36.1, 33.2, 30.9, 29.7; HRMS (APCI) m/z : $[M+H]^+$ Calcd for $C_{20}H_{20}O_4H$ 325.1439; Found 325.1438; IR (film): 1720, 1198, 1148 cm^{-1} .



Methyl 8-((diphenylacetyloxymethyl)pentacyclo[4.3.0.0^{2,4}.0^{3,9}.0^{5,8}]nonane-2-carboxylate (9d)

1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.20 (m, 10H), 5.00 (s, 1H), 3.66 (s, 1H), 3.27-3.23 (m, 1H), 3.24-3.21 (m, 1H), 3.05 (ddd, $J = 5.5, 2.5, 1.0$ Hz, 1H), 2.89 (dd, $J = 6.0, 2.5$ Hz, 1H), 2.99 (d, $J = 6.5$ Hz, 1H), 2.89 (dd, $J = 6.0, 2.5$ Hz, 1H), 2.76 (d, $J = 7.0$ Hz, 1H), 2.42 (dd, $J = 5.0, 3.0$ Hz, 1H), 2.05 (dd, 7.5,



3.5 Hz, 1H), 1.76 (d, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.7, 171.6, 138.7, 138.6, 128.7, 128.6, 128.6, 128.5, 127.2, 94.7, 57.4, 57.1, 51.5, 46.0, 44.8, 42.4, 41.7, 39.0, 38.5, 33.2; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{25}\text{H}_{22}\text{O}_4\text{H}$ 387.1596; Found 387.1591; IR (film): 1718, 1200, 1142, 1105 cm^{-1} .

6. 4. 2 X-ray diffraction analysis

A crystal of **5** was mounted on the CryoLoop (Hampton Research Corp.) with a layer of light mineral oil and placed in a nitrogen stream at 143 K. The X-ray structural determinations of **5** was performed on a Rigaku/Saturn724+ CCD diffractometers using graphite-monochromated Mo Ka radiation ($\lambda = 0.71075 \text{ \AA}$) at 153 K, and processed using CrystalClear (Rigaku, Tokyo, Japan).^{22a} The structure of **5** was solved by SHELEX version 2013/1 (Sheldrick, 2008)^{22b} and refined by SHELEX version 2018/3 (Sheldrick, 2008).^{22c} Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. CCDC 2295366 contains the supplementary crystallographic data. The data is available from The Cambridge Crystallographic Data Centre.

Datablock: matsubara220715a

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Bond precision:   C-C = 0.0038 A           Wavelength=0.71075

Cell:             a=10.237 (9)             b=13.814 (14)             c=6.602 (7)
                  alpha=90                 beta=90                 gamma=90
Temperature:      293 K

Volume            Calculated                Reported
Volume            933.6 (16)                933.6 (16)
Space group       P 21 21 2                 P 21 21 2
Hall group        P 2 2ab                    P 2 2ab
Moiety formula    C24 H20 O4                 C24 H18 O4
Sum formula       C24 H20 O4                 C24 H18 O4
Mr                372.40                     370.40
Dx, g cm-3        1.325                      1.318
Z                 2                          2
Mu (mm-1)         0.090                      0.089
F000              392.0                      388.0
F000'            392.20
h, k, lmax        13, 17, 8                  13, 17, 8
Nref              2116 [ 1247 ]               2110
Tmin, Tmax        0.989, 0.991                0.719, 0.991
Tmin'            0.982

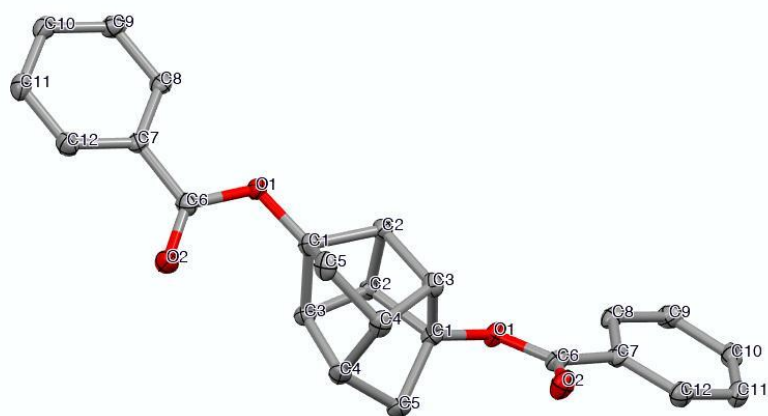
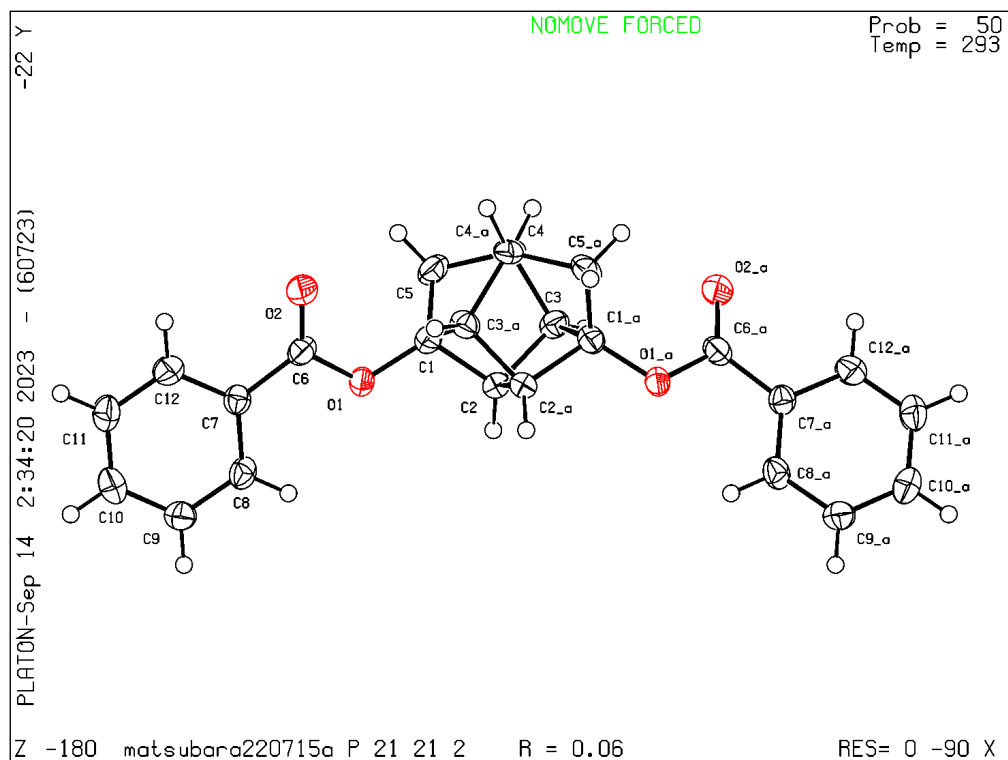
Correction method= # Reported T Limits: Tmin=0.719 Tmax=0.991
AbsCorr = MULTI-SCAN

Data completeness= 1.69/1.00           Theta (max)= 27.350

R(reflections)= 0.0596 ( 1630)          wR2(reflections)=
S = 1.023                               0.1139 ( 2110)
Npar= 127

```

Datablock matsubara220715a - ellipsoid plot



References

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List of Publications

All the present Thesis have been published in the following journals. The following parts of the accepted materials were modified:

- A) A word 'we' is replaced to 'the author'.
- B) Words 'see supporting information' and similar expressions are deleted and corresponding materials (text, figures, and/or schemes) are moved from supporting information of accepted works to the main text of the Thesis or the Experimental section.
- C) Subtitles are inserted to the section heads.
- D) Parts of the introduction, results and discussion, and conclusion are modified according to the context of the Thesis.
- E) Words listed in Abbreviations are replaced to the corresponding abbreviations.

General Introduction

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- (2) H. Takebe and S. Matsubara, How to Set the "Chirality" of Polyhedral Small Molecule Hydrocarbons: Decoration and Skeleton Editing of Cubane, *European Journal of Organic Chemistry*, **2023**, e202300891.
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Chapter 2

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Chapter 4

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Chapter 6

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