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Asymmetric ring cleavage reaction with a combination of optically active cycloalkane-1,2-diol and Lewis acid: application to formal synthesis of (−)-alloyohimbane and approach to construction of adjacent chiral quaternary centers

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Abstract—Asymmetric ring cleavage reaction of *meso*-carbobicyclic ketones by a combination of benzaldehyde, chiral cycloalkane-1,2-diol, and Lewis acid gave optically active styrenyl esters of 26–69% ee in moderate yield. The ring cleavage reaction could be applied to the construction of adjacent chiral quaternary carbons, and also to the formal synthesis of natural alkaloid (−)-alloyohimbane.

1. Introduction

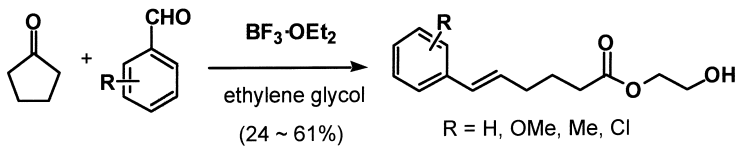
A combination of Lewis acid and 1,2-diol has been well known as reaction conditions for protection of the carbonyl function as an acetal.[1] We have already reported that these conditions could be used for ring transformation of diketo compounds,[2] and the ring transformation could be applied to synthesis of natural products, such as bulnesol,[2b] acorenone,[2d] and trichodiene.[2f] The reaction could also be developed into an asymmetric version which requires only non-metal elements, that is, $BF_3{\cdot}OEt_2$ and cycloalkane-1,2-diols but not transition metals.[3] The combination of Lewis acid and 1,2-diol or 1,3-diol could also be used for the ring cleavage reaction based on the intermolecular crossed aldol reaction of cycloalkanone and arylaldehydes.[4] Here we describe an asymmetric ring cleavage reaction of *meso*-carbobicyclic ketones **1**-**3** using the optically active cycloalkane-1,2-diols of C_2-symmetry,[5,6] and its application to the formal synthesis of a natural product, (−)-alloyohimbane, and to the construction of adjacent chiral quaternary carbons.

2. Results and discussion

2.1. Design of ring cleavage reaction based on the intermolecular crossed aldol reaction

We have already reported that the treatment of cyclopentanone and benzaldehydes under the acetalization conditions of $BF_3{\cdot}OEt_2$ and ethylene glycol, afforded styrenyl derivatives in 24–61% yields (Scheme 1).[4a]

We envisaged that the carbobicyclic ketones of σ-symmetry could be used as a substrate to develop asymmetric ring cleavage reaction by using chiral cycloalkane-1,2-diols. The asymmetric induction was thought to be possible because the asymmetric ring transformation of *meso*-diketo



Scheme 1. Ring cleavage reaction based on the intermolecular crossed aldol reaction.

Keywords: Asymmetric ring cleavage reaction; Cyclohexane-1,2-diol; Alloyohimbane; Quaternary carbon; Chiral 1,2-diol.
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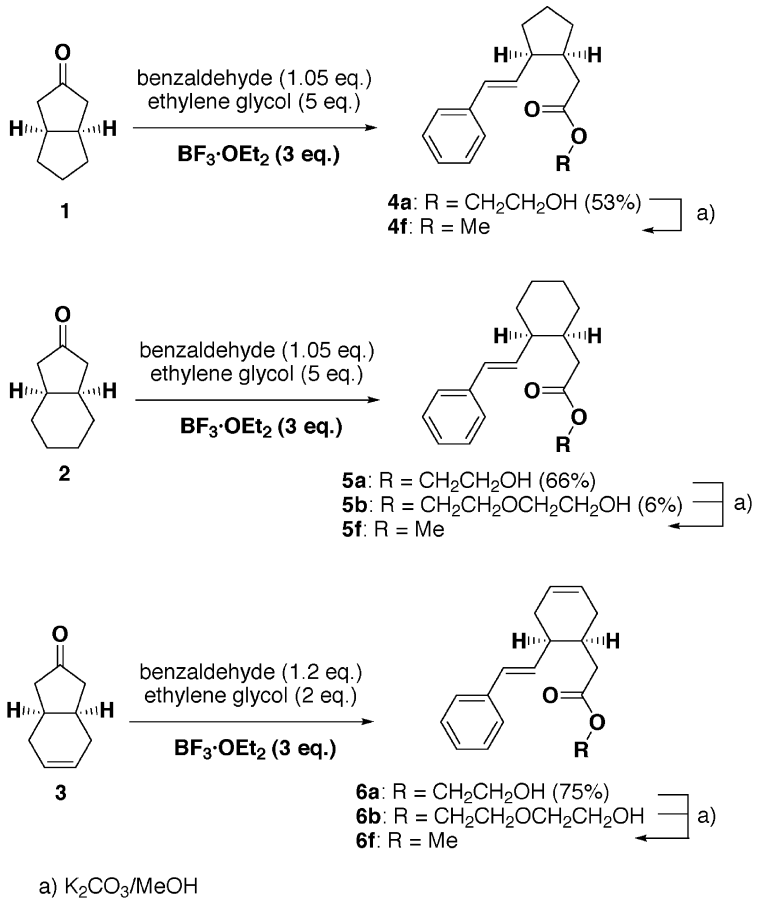


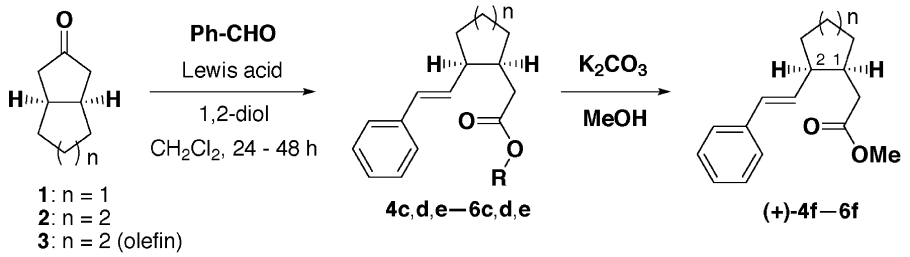
Scheme 2. Ring cleavage reaction of carbobicyclic ketones of symmetry.

compounds successfully occurred under the similar reaction conditions.[3] At first, the ring cleavage reaction of *meso*-carbobicyclic ketones **1**-**3** was examined by using achiral ethylene glycol. The results are depicted in Scheme 2. By treatment with benzaldehyde (1.05 equiv.), $BF_3{\cdot}OEt_2$ (3.0 equiv.), and ethylene glycol (5.0 equiv.) in CH_2Cl_2 at room temperature, the carbobicyclic ketones **1**-**3** were converted into the corresponding ring-cleaved styrenyl derivatives **4**-**6**. The ring cleavage reaction of bicyclo[4.3.0]nonanones **2** and **3** afforded the ethylene glycol half esters **5a** and **6a**, along with bis(ethylene glycol) esters **5b** and **6b**, respectively. The chemical yields of the ring-cleaved products were 53% (**4a**), 72% (**5a** and **5b**), and 29% (**6a** and **6b**), respectively. When the quantity of ethylene glycol was decreased to 2.0 equiv., the yield of **6a** was increased to 75% yield. The ethylene glycol esters in the products could be converted into the corresponding methyl esters **4f**-**6f** by treatment with K_2CO_3 in MeOH. The ^1H NMR spectra show the coupling constant of J=16 Hz between the olefinic protons, strongly suggesting the geometry of the double bond to be *trans*. The stereochemistry of carbobicyclic ketones **1**-**3** can be retained in the cleavage reaction, and, therefore, the relative stereochemistry of substituents at the cycloalkane is *cis* in the products **4**-**6**.

2.2. Asymmetric ring cleavage reaction based on the intermolecular crossed aldol reaction

We examined the asymmetric ring cleavage reaction by using the optically active 1,2-diols as a chiral source.[6] The results are summarized in Table 1. Several reaction conditions, such as the kind of 1,2-diol, the equivalence of the 1,2-diol, the ratio of the 1,2-diol to Lewis acid, and reaction temperature were studied. The obtained products were converted into the corresponding methyl esters **4f**-**6f** by treatment with K_2CO_3 in MeOH (85–95% yields), and their enantiomeric excesses (ee) were determined by measurement of the ^1H NMR spectra in the presence of a chiral shift reagent (+)-Eu(hfc)$_3$ or HPLC using a chiral column. In the case of substrate **1** having a bicyclo[3.3.0]-octane skeleton, the best chemical yield (81%) of the ring-cleaved product was attained when the reaction conditions of (*S*,*S*)-cycloheptane-1,2-diol **d** and $BF_3{\cdot}OEt_2$ at room temperature were adopted, albeit the enantiomeric excesses of product **4f** were not satisfactory (12–26% ee). In the case of substrate **2** having a bicyclo[4.3.0]nonane skeleton, the reaction using (*R*,*R*)-cyclohexane-1,2-diol **c** and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature afforded the ring-cleaved product **5c** of 49% de in 30% yield. When (*R*,*R*)-cycloheptane-1,2-diol **d** and $BF_3{\cdot}OEt_2$ were used, the chemical yield of **5d** was increased to 79% yield and the corresponding enantiomeric excess of **5f** was 60% ee (in entry 5). For improvement of the enantiomeric excess, the reaction was performed at 0 °C to give **5d** (64% de) but the isolated yield of **5d** was decreased to 34% yield and the starting material was recovered. The asymmetric induction by (*R*,*R*)-**d** afforded (−)-**5f**, and that of (*S*,*S*)-**d** gave the enantiomer (+)-**5f**. Almost the same result (63% yield, 59% de) was obtained when toluene was used as a solvent instead

Table 1. Asymmetric ring cleavage reaction based on the intermolecular crossed aldol reaction



Entry	Substrate	1,2-Diol (equiv.)	Lewis acid (equiv.)	Temperature	Product	
					Yield (%)	Enantiomeric excess (% ee)
1		(*R*,*R*)-**c** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**4c**: 34	(−)-**4c**: 26
2	**1**	(*S*,*S*)-**d** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**4d**: 81	(+)-**4f**: 14
3		(*R*,*R*)-**e** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**4e**: 72	(−)-**4f**: 12
4		(*R*,*R*)-**c** (2)	$BF_3{\cdot}OEt_2$ (4)	rt	**5c**: 30	(−)-**5f**: 49
5		(*R*,*R*)-**d** (3)	$BF_3{\cdot}OEt_2$ (3)	rt	**5d**: 79	(−)-**5f**: 60
6		(*S*,*S*)-**d** (3)	$BF_3{\cdot}OEt_2$ (3)	0 °C	**5d**: 34	(+)-**5f**: 64
7		(*R*,*R*)-**d** (2)	TMSOTf (2)	0 °C	**5d**: 54	(−)-**5f**: 69
8		(*R*,*R*)-**d** (2)	TMSOTf (2)	−50–30 °C	**5d**: 12	(−)-**5f**: 51
9	**2**	(*R*,*R*)-**d** (1.8)	TMSOTf (1.2)	0 °C	**5d**: 43	(−)-**5f**: 44
10		(*R*,*R*)-**e** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**5e**: 72	(−)-**5f**: 63
11		(*R*,*R*)-**e** (2)	TMSOTf (2)	0 °C	**5e**: 31	(−)-**5f**: 53
12		(*S*,*S*)-**c** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**6c**: 46	(+)-**6f**: 51
13		(*R*,*R*)-**d** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**6d**: 53	(−)-**6f**: 53[a]
14	**3**	(*R*,*R*)-**d** (2)	TMSOTf (3)	0 °C	**6d**: 7	(−)-**6f**: —

[a] Not determined.

of CH_2Cl_2, but the use of Et_2O was disadvantageous for both the reaction and the enantimeric excess of **5f**. The best enantiomeric excess of 69% ee in (−)-**5f** was accomplished when the reaction was carried out using (*R*,*R*)-cycloheptane-1,2-diol **d** (2 equiv.) and TMSOTf (2 equiv.) as Lewis acid at 0 °C, albeit in somewhat reduced isolated yield (54%) of **5d**. Further cooling of the reaction to −50 °C was detrimental for the ring cleavage. The use of (*R*,*R*)-butane-1,2-diol **e** as the 1,2-diol also afforded moderate enantiomeric excess of **5f** (in entries 10 and 11). By treatment with 1,2-diol and $BF_3{\cdot}OEt_2$, bicyclo[4.3.0]nonene **3** having an olefinic function was also converted into the ring-cleaved product **6** in 46–53% yield, albeit in moderate enantiomeric excess of **6f**. The reaction conditions of (*R*,*R*)-cycloheptane-1,2-diol **d** and TMSOTf at 0 °C were not practical for substrate **3**.

In the cases that the yield of the isolated ring cleavage products was low, the reaction afforded an acetal **7** composed of benzaldehyde and 1,2-diol, an acetal **8** of the bicyclic ketone and 1,2-diol, and a ring-cleaved carboxylic acid **9** as by-products, along with the recovered carbobicyclic ketone **2**. The absolute configuration of (+)-**5f** was determined to be 1*S*,2*R* by comparison of the specific rotation with that of the authentic sample, after conversion into diol (−)-**10** in Figure 1. That is to say, the ring cleavage reaction of **2** by (*R*,*R*)-1,2-diol afforded (1*R*,2*S*)-(−)-**5f**, while that by (*S*,*S*)-1,2-diol afforded (1*S*,2*R*)-(+)-**5f**.[7]

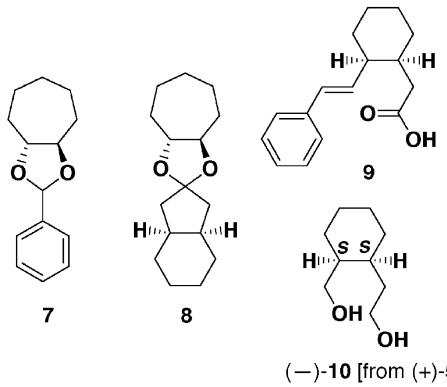


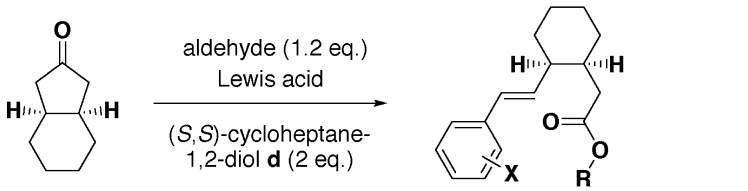
Figure 1. Structure of by-products.

Next, we examined the effect of benzaldehydes. Kabalka's group reported that the electronic nature of the substituent in aromatic aldehydes affected the $BF_3{\cdot}OEt_2$-catalyzed Aldol-Grob reaction sequence; especially, the electron-withdrawing group in aromatic aldehydes, such as *o*-chloro-, *p*-chloro and *p*-bromo functional groups, affected the reactivity to improve the isolated yields.[8,9] The results are summarized in Table 2. The *o*-chloro-, *p*-chloro- and *p*-bromobenzaldehye, which gave good results in Kabalka's reaction, did not give a better result than that of benzaldehyde in our 1,2-diol-assisted ring cleavage reaction neither in chemical yield nor enantiomeric excess. The reaction of *p*-tolualdehyde by using $BF_3{\cdot}OEt_2$ afforded the product **14d** of 63% de in 57% yield, but that by TMSOTf did not give better results. The reaction of *o*-salicyclaldehyde and *p*-anisaldehyde bearing an electron-donating group afforded a complex mixture, and no ring cleavage product was isolated at all.

2.3. Construction of adjacent chiral quaternary carbons

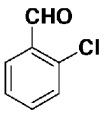
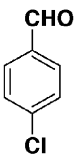
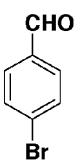
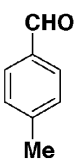
The ring cleavage reaction was applied to the construction of adjacent chiral quaternary carbons since the construction of a chiral quaternary carbon attracts many organic chemists.[10,11] Here we designed substrates **15** having a bicyclo[3.3.0]octane skeleton and **16** having bicyclo[4.3.0]-nonane skeleton. Both of the substrates **15** and **16** bear two adjacent quaternary carbons and σ-symmetry. We envisaged that if the asymmetric ring cleavage reaction occurs, the styrenyl ester bearing adjacent chiral quaternary carbons would be obtained. The preparation of chiral styrenyl esters **17** and **18** by a straightforward route might not be easily attained, and, furthermore, enantioselective synthesis might be more difficult without the ring cleavage

Table 2. Effect of the substituent in aromatic aldehydes on the asymmetric ring cleavage reaction



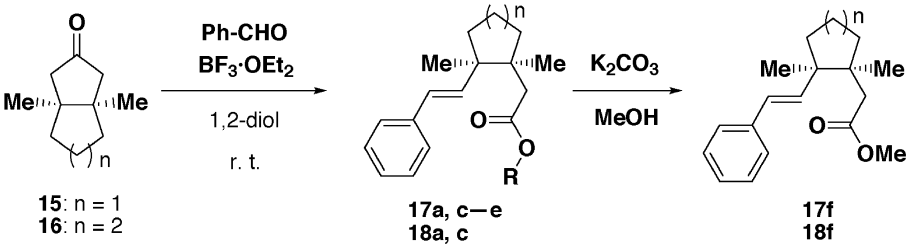
3

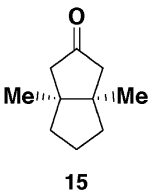
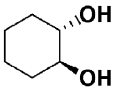
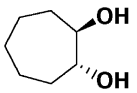
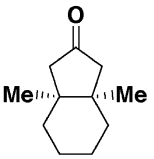
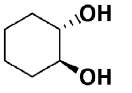
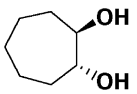
11-14d: R = cycloheptane-1,2-dioxy
11-14f: R = Me

Entry	Aldehyde[a]	Lewis acid (equiv.)	Temperature	Product	
				Yield (%)	ee (%)
1		$BF_3{\cdot}OEt_2$ (3)	rt	**11d**: 33	**11f**: 37
2		TMSOTf (2)	0 °C	**11d**: 9	**11f**: 20
3		$BF_3{\cdot}OEt_2$ (3)	rt	**12d**: 39	**12f**: 49
4		TMSOTf (2)	0 °C	**12d**: 30	**12f**: 42
5		$BF_3{\cdot}OEt_2$ (3)	rt	**13d**: 33	**13f**: 47
6		TMSOTf (2)	0 °C	**13d**: 13	**13f**: 42
7		$BF_3{\cdot}OEt_2$ (3)	rt	**14d**: 57	**14f**: 63
8		TMSOTf (2)	0 °C	**14d**: 38	**14f**: 49

[a] *o*-Salicylaldehyde and *p*-anisaldehyde were also tested, but the reaction afforded complex mixture.

Table 3. Construction of adjacent chiral quaternary carbons by the asymmetric ring cleavage reaction



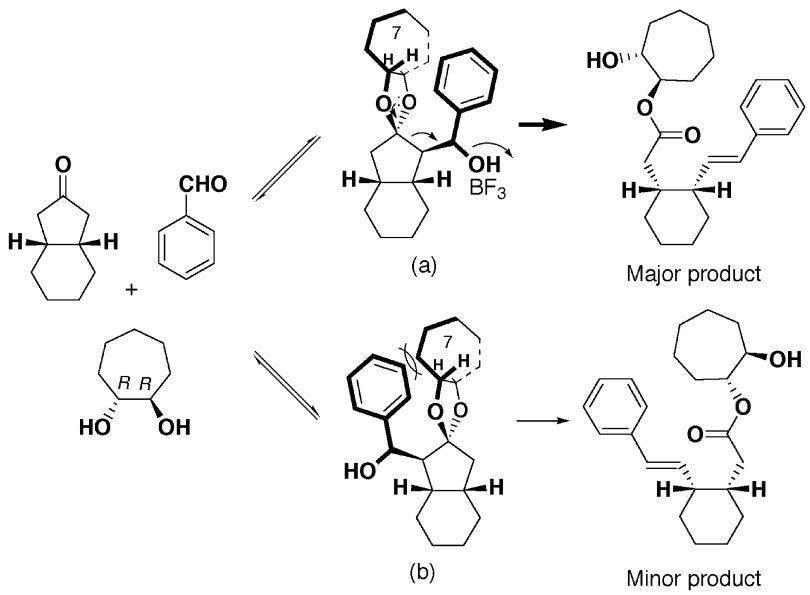
Entry	Substrate	1,2-Diol (equiv.)	$BF_3{\cdot}OEt_2$ (equiv.)	Product	
				Yield (%)	Enantiomeric excess (% ee)
1		Ethylene glycol (5)	6	**17a**: 40	-
2		 (*S*,*S*)-**c** (2)	3	**17c**: 9	**17f**: 6
3		 (*R*,*R*)-**d** (2)	3	**17d**: 20	**17f**: 32
4	**15**	 (*R*,*R*)-**e** (2)	3	**17e**: 15	**17f**: 28
5		Ethylene glycol (5)	6	**18a**: 12	—
6		 (*S*,*S*)-**c** (2)	4	**18c**: 15	**18f**: 34
7	**16**	 (*R*,*R*)-**d** (2)	3	**18d**: 0	—

reaction. The *meso*-carbobicyclic ketones **15** and **16** bearing two adjacent quaternary carbons could be easily prepared.[12,13] The results of ring cleavage reaction are shown in Table 3. By treatment with benzaldehyde, $BF_3{\cdot}OEt_2$, and ethylene glycol at room temperature, the carbobicyclic ketone **15** was converted into a chiral styrenyl ester **17a** in 40% yield, accompanied by the recovered material **15**. With the success of ring cleavage reaction of **15** by ethylene glycol, we next examined the asymmetric reaction using chiral 1,2-diols. In the cases that the chiral cyclic 1,2-diols **c** and **d**, and (*R*,*R*)-butane-1,2-diol **e** were used as a chiral source, the asymmetric ring cleavage occurred to give the corresponding styrenyl esters **17c**-**e**, albeit the yields of products (9–20%) were not satisfactory. Unfortunately, the enantiomeric excess of the corresponding **17f** was low (6–32% ee). The low enantiomeric excess may be attributed to the fact that the substrate **15** has a bicyclo[3.3.0]octane skeleton, as the reaction of **1** having the bicyclo[3.3.0]octane skeleton did not show good enantiomeric excess.

Next, we examined the substrate **16** having a bicyclo[4.3.0]-nonane skeleton. By treatment with benzaldehyde, $BF_3{\cdot}OEt_2$, and the 1,2-diols, the bicyclic ketone **16** was converted into styrenyl products **18** in low yields, except for the use of (*R*,*R*)-cycloheptane-1,2-diol. The ring cleavage by (*R*,*R*)-cycloheptane-1,2-diol often produced good enantiomeric excess, but the reaction of **16** did not proceed. The products **18** were converted into the corresponding methyl ester **18f**, and the enantiomeric excess was determined by HPLC using a chiral column. Unfortunately, the best enantiomeric excess was 34% ee in the case that (*S*,*S*)-cyclohexane-1,2-diol was used. In the reaction, the starting ketones **15** and **16** were recovered in 30–70% yields. These results might be attributed to the fact that the methyl substituents at the quaternary carbons hindered benzaldehyde from approaching the reactive site for aldol reaction.

2.4. Plausible reaction mechanisms

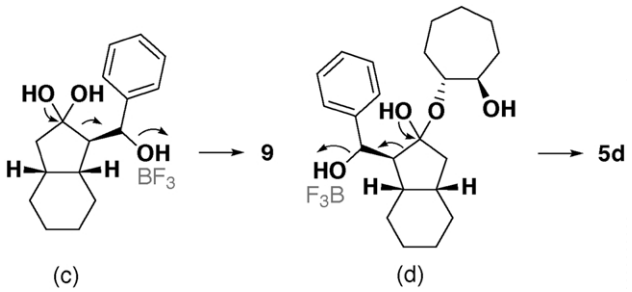
Plausible mechanisms for the diastereoselection of the ring cleavage reaction are proposed in Scheme 3. The crucial steps for the diastereoselection are C–C bond disconnection steps, that is, Grob fragmentations, which are irreversible.



Scheme 3. Plausible reaction mechanisms of the asymmetric ring cleavage reaction.

The diastereomeric intermediates (a) and (b) are interchangeable via aldol and retro-aldol reactions. The difference in stability between the diastereomeric intermediates (a) and (b) by the steric repulsions between the cycloheptane moiety and the phenyl group, or that of reactivity in Grob fragmentation between the intermediates (a) and (b) by the stereoelectronic effect might cause the asymmetric induction.[14]

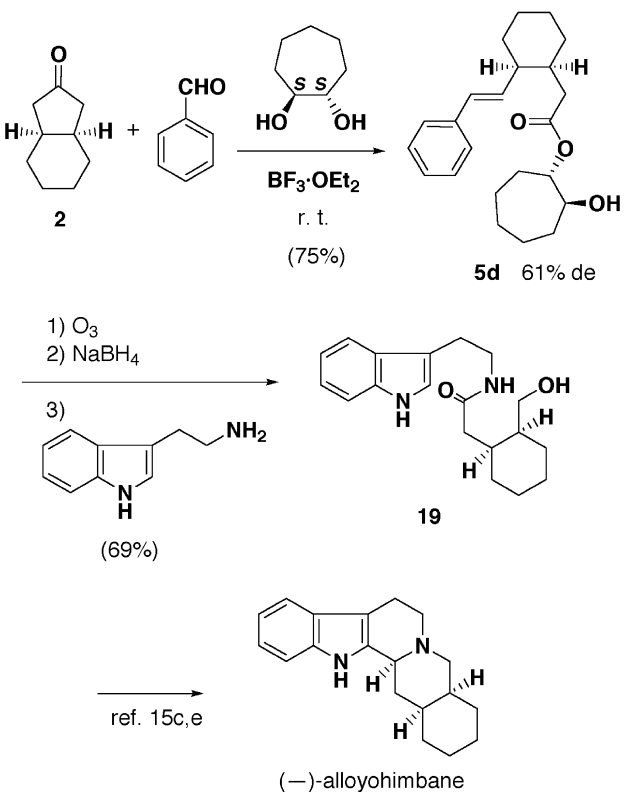
Even without 1,2-diol, the $BF_3{\cdot}OEt_2$-promoted Aldol–Grob reaction sequence proceeded via an intermediate (c) to give the acid **9** in 61% yield, albeit long reaction time was required at room temperature.[8] Thus, besides the intermediates (a) and (b), the Grob fragmentation might proceed via a hemiacetal intermediate (d), which may reduce the diastereoselectivity (Scheme 4).[9]



Scheme 4. Ring cleavage reaction via a hemiacetal intermediate.

2.5. Formal synthesis of (−)-alloyohimbane

The asymmetric ring cleavage reaction was applied to the synthesis of natural product (−)-alloyohimbane.[15] The ring cleavage reaction of **2** by treatment with benzaldehyde (1.2 equiv.), (*S*,*S*)-cycloheptane-1,2-diol (2 equiv.), and $BF_3{\cdot}OEt_2$ (3 equiv.) at room temperature afforded **5d** of 61% de in 75% yield. Compound **5d** was easily converted into an amide **19** by ozonolysis of the olefin in **5d**, $NaBH_4$ reduction, and subsequent coupling with tryptamine in 69% overall yield. The spectroscopic data of compound **19** was identical with the reported values. The specific rotation of **19** indicated $[\alpha]_D$ −7.5 and that of the reported value was $[\alpha]_D$ −11.8.[15c] The smaller specific rotation means that the enantiomeric excess of the prepared **19** is 61% ee. The synthesis of (−)-alloyohimbane has already been reported by way of the intermediate **19**.[15e] Thus, the formal synthesis of (−)-alloyohimbane has been completed by using the asymmetric ring cleavage reaction (Scheme 5).



Scheme 5. Formal synthesis of (−)-alloyohimbane.

3. Conclusion

We have succeeded in developing an asymmetric ring cleavage reaction of *meso*-carbobicyclic ketones **1**-**3** by a combination of benzaldehyde, the optically active cycloalkane-1,2-diols of C_2-symmetry, and Lewis acid. The reaction consists of aldol and Grob reaction sequences including acetalization of 1,2-diol. The asymmetric ring cleavage reaction requires only non-metal elements, that is, $BF_3{\cdot}OEt_2$ and cycloalkane-1,2-diols, and does not need binding a chiral auxiliary to the prochiral substrate. We could also apply the ring cleavage reaction to construct the adjacent chiral quaternary carbons, and to synthesize natural alkaloid (−)-alloyohimbane.

4. Experimental

4.1. General

^{1}H NMR spectra were determined at 270, 400, or 500 MHz. Infrared spectra were recorded on a JASCO A-100 or a NICOLET AVATAR-320 spectrometer. EIMS, FABMS, EI(+)HRMS and FAB(+)HRMS spectra were taken on a JEOL JMS 610H or JEOL SX102 spectrometer. The optically active cyclic 1,2-diols **c** and **d** were prepared by the enzymatic methods.[6,16] The substrates **1**, **2**, **3**, **15**, and **16** were known compounds, and prepared by the reported methods.[12,13]

4.2. General procedure for the ring cleavage reaction

$BF_3{\cdot}OEt_2$ solution (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of carbobicyclic ketone (1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and cyclic 1,2-diol (2.0 mmol) in CH_2Cl_2 (7 mL) at room temperature. After being stirred for 24 h, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to afford the ring cleaved-product.

4.2.1. Methyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4f). $BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of **1** (124 mg, 1.0 mmol), benzaldehyde (111 mg, 1.05 mmol), and ethylene glycol (0.28 mL, 5.0 mmol) in CH_2Cl_2 (7 mL) at room temperature. After being stirred overnight, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% EtOAc in hexane afforded the ring-cleaved product **4a** (129 mg, 53%) as a colorless oil. Compound **4a**: IR (neat) 3450 (br), 2950, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.50 (m, 5H), 6.36 (d, J=15.8 Hz, 1H), 6.11 (dd, J=15.8, 8.9 Hz, 1H), 4.12–4.16 (m, 2H), 3.72–3.80 (m, 2H), 2.85 (m, 1H), 2.40–2.58 (m, 2H), 2.28 (m, 1H), 1.35–2.00 (m, 7H); FAB(+)HRMS calcd for $C_{17}H_{23}O_3$ (M^++H): 275.1647. Found: 275.1639 (M^++H). Solvolysis of **4a** with K_2CO_3 in MeOH afforded **4f** (85%) as a colorless oil. Compound **4f**: IR (neat) 2950, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.32 (m, 5H), 6.34 (d, J=15.7 Hz, 1H), 6.08 (dd, J=9.0, 15.7 Hz, 1H), 3.58 (s, 3H), 2.79 (m, 1H), 2.34–2.48 (m, 2H), 2.16 (dd, J=8.6, 15.6 Hz, 1H), 1.70–1.93 (m, 3H), 1.42–1.70 (m, 2H), 1.36 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.6, 137.3, 130.8, 130.0, 128.1, 126.6, 125.7, 51.0, 45.7, 40.2, 35.7, 30.8, 30.6, 22.8; FAB(+)HRMS calcd for $C_{16}H_{20}O_2$ (M^+): 244.1463. Found: 244.1465 (M^+).

4.2.2. (1*R*,2*R*)-2-Hydroxycyclohexyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4c). $BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of **1** (124 mg, 1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and (*R*,*R*)-**c** (260 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred for 24 h, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **4c** (112 mg, 34%) as a colorless oil. Compound **4c**: IR (neat) 3444 (br), 2940, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.38 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.11 (dd, J=8.9, 15.8 Hz, 1H), 4.53 (m, 1H), 3.49 (m, 1H), 2.84 (m, 1H), 2.37–2.49 (m, 2H), 2.21 (m, 1H), 1.20–2.10 (m, 15H); EIMS m/z 328 (M^+, 6), 272 (9), 256 (15), 230 (11), 198 (26), 170 (76), 128 (100); EI(+)HRMS calcd for $C_{21}H_{28}O_3$ (M^+): 328.2038. Found: 328.2002 (M^+). Solvolysis of **4c** with K_2CO_3 in MeOH afforded (−)-**4f** as a colorless oil: $[\alpha]_D^{20}$ −12.4 (26% ee, $CHCl_3$, c=1.50). The enantiomeric excess of (−)-**4f** was determined to be 26% ee by HPLC (column; CHIRALPAK AS, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm: retention time (t_R), 11 and 13 min).

4.2.3. (1*S*,2*S*)-2-Hydroxycycloheptyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4d). Compound **4d** was prepared from **1** and (*S*,*S*)-**d** in a manner similar to that described for the preparation of **4c**. Compound **4d**: 81%; a colorless oil; IR (neat) 3468 (br), 2934, 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17–7.36 (m, 5H), 6.37 (d, J=15.6 Hz, 1H), 6.12 (dd, J=8.9, 15.6 Hz, 1H), 4.68 (m, 1H), 3.65 (m, 1H), 2.83 (m, 1H), 2.60 (br s, 1H), 2.38–2.55 (m, 2H), 2.22 (m, 1H), 1.35–2.00 (m, 16H); EIMS m/z 342 (M^+, 13), 230 (13), 213 (57), 185 (27), 171 (84), 91 (100); EI(+)HRMS calcd for $C_{22}H_{30}O_3$ (M^+): 342.2195. Found: 342.2137 (M^+). The HPLC analysis of (+)-**4f** prepared from **4d** indicated 14% ee.

4.2.4. (1*R*,2*R*)-2-Hydroxy-1-methylpropyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4e). Compound **4e** was prepared from **1** and (*R*,*R*)-**e** in a manner similar to that described for the preparation of **4c**. Compound **4e**: 72%; a colorless oil; IR (neat) 3432 (br), 2953, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19–7.40 (m, 5H), 6.36 (d, J=15.8 Hz, 1H), 6.11 (dd, J=8.9, 15.8 Hz, 1H), 4.75 (m, 1H), 3.69 (m, 1H), 2.83 (m, 1H), 2.37–2.55 (m, 2H), 2.24 (m, 1H), 1.35–1.98 (m, 7H), 1.10–1.20 (m, 6H); EIMS m/z 302 (M^+, 12), 213 (19), 170 (100), 141 (17); EI(+)HRMS calcd for $C_{19}H_{26}O_3$ (M^+): 302.1882. Found: 302.1898 (M^+). The HPLC analysis of (−)-**4f** prepared from **4e** indicated 12% ee.

4.2.5. Methyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5f). Compounds **5a**, **5b** and **5f** were prepared from

bicyclo[4.3.0]nonan-8-one **2** in a manner similar to that described for the preparation of **4a** and **4f**. Compound **5a**: 66%; a colorless oil; IR (neat) 3450 (br), 2920, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.40 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.35 (dd, J=15.8, 6.5 Hz, 1H) 4.16 (m, 2H), 3.78 (m, 2H), 2.55 (m, 1H), 2.15–2.40 (m, 3H), 1.79 (m, 1H), 1.47–1.67 (m, 8H); EIMS m/z 288 (M^+, 63), 227 (47), 184 (100), 141 (83); EI(+)HRMS calcd for $C_{18}H_{24}O_3$ (M^+): 288.1725. Found: 288.1753 (M^+). Compound **5b**: 6%; a colorless oil; IR (neat) 3445 (br), 2925, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.36 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.35 (dd, J=15.8, 6.5 Hz, 1H), 4.21 (m, 2H), 3.70 (m,2H), 3.65 (m, 2H), 3.56 (m, 2H), 2.55 (m, 1H), 2.33 (m, 1H), 2.36–2.26 (m, 2H), 1.40–1.75 (m, 9H); EIMS m/z 332 (M^+, 93), 271 (27), 227 (100), 198 (89), 169 (86), 156 (84); EI(+)HRMS calcd for $C_{20}H_{28}O_4$ (M^+): 332.1988. Found: 332.1985 (M^+). Compound **5f**: a colorless oil; IR (neat) 2925, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.38 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.35 (dd, J=15.8, 6.5 Hz, 1H), 3.63 (s, 3H), 2.53 (m, 1H), 2.16–2.32 (m, 3H), 1.40–1.75 (m, 8H); FAB(+)HRMS calcd for $C_{17}H_{23}O_2$ (M^++H): 259.1700. Found: 259.1698 (M^++H).

4.2.6. (1*R*,2*R*)-2-Hydroxycyclohexyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5c). Compound **5c** was prepared from **2** and (*R*,*R*)-**c** in a manner similar to that described for the preparation of **4c**. Compound **5c**: 30%; a colorless oil; IR (neat) 3468 (br), 2931, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.36 (m, 5H), 6.39 (d, J=15.8 Hz, 1H), 6.36 (dd, J=15.8, 6.4 Hz, 1H), 4.56 (m, 1H), 3.50 (m, 1H), 2.55 (m, 1H), 2.30 (m, 1H), 2.10–2.02 (m, 2H), 1.18–1.78 (m, 15H); EIMS m/z 342 (M^+, 39), 244 (44), 226 (28), 185 (72), 141 (61), 129 (100), 115 (80), 104 (99); EI(+)HRMS calcd for $C_{22}H_{30}O_3$ (M^+): 342.2195. Found: 342.2202 (M^+). Solvolysis of **5c** with K_2CO_3 in MeOH afforded (−)-**5f** as a colorless oil. The enantiomeric excess of (−)-**5f** was determined to be 49% ee by HPLC (column; CHIRALPAK AD, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm: retention time (t_R), 13 and 16 min).

4.2.7. (1*R*,2*R*)-2-Hydroxycycloheptyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5d). TMSOTf (0.36 mL, 2.0 mmol) was added dropwise to a stirred solution of **2** (138 mg, 1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and (*R*,*R*)-**d** (260 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred for 24 h at 0 °C, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **5d** (193 mg, 54%) as a colorless oil. Compound **5d**: IR (neat) 3500 (br), 2930, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–7.36 (m, 5H), 6.32–6.48 (m, 2H), 4.68 (m, 1H), 3.68 (m, 1H), 2.67 (m, 1H), 2.54 (m, 1H), 2.30 (m, 1H), 2.18–2.27 (m, 2H), 1.35–1.90 (m, 18H); EIMS m/z 356 (M^+, 60), 338 (14), 244 (95), 227 (66), 210 (36), 185 (100); EI(+)HRMS calcd for $C_{23}H_{32}O_3$ (M^+): 356.2351. Found: 356.2358 (M^+). Solvolysis of **5d** with K_2CO_3 in MeOH afforded (−)-**5f** as a colorless oil: $[\alpha]_D^{20}$ −53.3 (69% ee, $CHCl_3$, c=1.30). The enantiomeric excess of (−)-**5f** was determined to be 69% ee.

4.2.8. (1*R*,2*R*)-2-Hydroxy-1-methylpropyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5e). Compound **5e** was prepared from **2** and (*R*,*R*)-**e** in a manner similar to that described for the preparation of **4c**. Compound **5e**: 72%; a colorless oil; IR (neat) 3435 (br), 2977, 2926, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.36 (m, 5H), 6.36–6.40 (m, 2H), 4.74 (m, 1H), 3.70 (m, 1H), 2.54 (m, 1H), 2.30 (m, 1H), 2.18–2.23 (m, 2H), 1.80 (br s, 1H), 1.40–1.75 (m, 8H), 1.12–1.20 (m, 6H); EIMS m/z 316 (M^+, 100), 244 (60), 228 (92), 198 (78), 183 (72); EI(+)HRMS calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038. Found: 316.2069 (M^+). The methyl ester (−)-**5f** prepared from **5e** indicated 63% ee.

4.2.9. Methyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohex-4-enyl}-acetate (6f). Compounds **6a**, **6b** and **6f** were prepared from bicyclo[4.3.0]non-3-ene-8-one **3** in a manner similar to that described for the preparation of **4a** and **4f**. Compound **6a**: 75%; a colorless oil; IR (neat) 3440 (br), 2906, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–7.40 (m, 5H), 6.43 (d, J=15.9 Hz, 1H), 6.22 (dd, J=15.9, 8.2 Hz, 1H), 5.66–5.72 (m, 2H), 4.18–4.22 (m, 2H), 3.78–3.82 (m, 2H), 2.62 (m, 1H), 2.33–2.43 (m, 3H), 2.16–2.29 (m, 2H), 1.86–2.08 (m, 2H); EIMS m/z 286 (M^+, 9), 225 (21), 182 (63), 143 (30), 128 (45), 104 (100); EI(+)HRMS calcd for $C_{18}H_{22}O_3$ (M^+): 286.1569. Found: 286.1541 (M^+). Compound **6b**: a colorless oil; IR (neat) 3450 (br), 2925, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.43 (d, J=15.7 Hz, 1H), 6.22 (dd, J=15.7, 8.2 Hz, 1H), 5.65–5.73 (m, 2H), 4.21–4.25 (m, 2H), 3.67–3.75 (m, 4H), 3.57–3.60 (m, 2H), 2.63 (m, 1H), 2.34–2.43 (m, 3H), 2.17–2.29 (m, 2H), 1.87–2.07 (m, 3H); FAB(+)HRMS calcd for $C_{20}H_{27}O_4$ (M^++H): 331.1909. Found: 331.1918 (M^++H). Compound **6f**: a colorless oil; IR (neat) 2906, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.35 (m, 5H), 6.40 (d, J=15.9 Hz, 1H), 6.20 (dd, J=8.2, 15.9 Hz, 1H), 5.63–5.72 (m, 2H), 3.64 (s, 3H), 2.60 (m, 1H), 2.30–2.40 (m, 3H), 2.13–2.24 (m, 2H), 2.21 (m, 1H), 1.87 (m, 1H); EIMS m/z 256 (M^+, 51), 225 (44), 202 (51), 141 (77), 128 (100); EI(+)HRMS calcd for $C_{17}H_{20}O_2$ (M^+): 256.1463. Found: 256.1442 (M^+).

4.2.10. (1*S*,2*S*)-2-Hydroxycyclohexyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohex-4-enyl}acetate (6c). Compound **6c** was prepared from **3** and (*S*,*S*)-**c** in a manner similar to that described for the preparation of **4c**. Compound **6c**: 46%; a colorless oil; IR (neat) 3420 (br), 2938, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.40 (m, 5H), 6.42 (d, J=15.9 Hz, 1H), 6.21 (dd, J=15.9, 8.1 Hz, 1H), 5.60–5.65 (m, 2H), 4.60 (m, 1H), 3.55 (m, 1H), 2.61 (m, 1H), 2.30–2.42 (m, 3H), 1.20–2.30 (m, 13H); EIMS m/z 340 (M^+, 11), 286 (6), 182 (32), 156 (36), 128 (71), 104 (78), 91 (100); EI(+)HRMS calcd for $C_{22}H_{28}O_3$ (M^+): 340.2038. Found: 340.2086 (M^+). Solvolysis of **6c** with K_2CO_3 in MeOH afforded (+)-**6f** as a colorless oil: $[\alpha]_D^{25}$ +65.5 (51% ee, $CHCl_3$, c=1.01). The enantiomeric excess of (+)-**6f** was determined to be 51% ee by HPLC (column; CHIRALPAK AD, eluent; 0.3% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm: retention time (t_R), 33 and 36 min).

4.2.11. (1*R*,2*R*)-2-Hydroxycycloheptyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohex-4-enyl}acetate (6d). Compound **6d** was prepared from **3** and (*R*,*R*)-**d** in a manner similar to that described for the preparation of **4c**. Compound **6d**: 53%; a

colorless oil; IR (neat) 3435 (br), 2931, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.41 (m, 5H), 6.41 (d, J=15.7 Hz, 1H), 6.22 (dd, J=15.7, 8.4 Hz, 1H), 5.60–5.78 (m, 2H), 4.68 (m, 1H), 3.70 (m, 1H), 1.20–2.60 (m, 19H); EIMS m/z 354 (M^+, 6), 256 (7), 242 (15), 182 (87), 158 (100); EI(+)HRMS calcd for $C_{23}H_{30}O_3$ (M^+): 354.2195. Found: 354.2191 (M^+). The HPLC analysis of (−)-**6f** prepared from **6d** indicated 53% ee.

4.2.12. Acetal from benzaldehyde and (*S*,*S*)-cycloheptane-1,2-diol (7).[17] A colorless oil; IR (neat) 2928, 1454, 1093, 976, 766, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.49 (m, 2H), 7.30–7.39 (m, 3H), 5.99 (s, 1H), 3.80–3.93 (m, 2H), 2.16–2.32 (m, 2H), 1.45–1.70 (m, 8H); EIMS m/z 219 (M^++H, 67), 174 (44), 133 (80), 112 (100).

4.2.13. Acetal from bicyclo[4.3.0]nonane-8-one and cycloheptane-1,2-diol (8). A colorless oil; IR (neat) 2926, 2857, 1451, 1116, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.50–3.70 (m, 2H), 1.10–2.20 (m, 24H); EIMS m/z 250.4 (M^+, 100), 193.3 (66), 138.2 (22), 95.2 (77); EI(+)HRMS calcd for $C_{16}H_{26}O_2$ (M^+): 250.1933. Found: 250.1936 (M^+).

4.2.14. 2-{2-[(1*E*)-2-Phenylvinyl]cyclohexyl}acetic acid (9). A colorless oil; IR (neat) 2850–3500 (br), 2922, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.5 (br, 1H), 7.10–7.40 (m, 5H), 6.30–6.42 (m, 2H), 2.56 (m, 1H), 2.36 (m, 1H), 2.19–2.24 (m, 2H), 1.40–1.80 (m, 8H); ^{13}C NMR (100 MHz) δ 179.7, 137.6, 131.0, 130.6, 128.5, 127.0, 126.1, 42.3, 37.1, 36.8, 30.2, 28.6, 24.3, 22.5; EIMS m/z 244.2 (M^+, 29), 184.2 (86), 141.1 (55), 107.1 (61), 77.1 (100); EI(+)HRMS calcd for $C_{16}H_{20}O_2$ (M^+): 244.1463. Found: 244.1468 (M^+).

4.2.15. (−)-2-(2-Hydroxymethylcyclohexyl)ethanol (10). Ozone gas was bubbled into a solution of (+)-**5f** (400 mg, 1.55 mmol) in MeOH (20 mL) and CH_2Cl_2 (20 mL) at −78 °C, and the reaction was monitored by TLC. $NaBH_4$ (240 mg, 6.34 mmol) was added portionwise to the reaction mixture at −78 °C. After being stirred for 1 h, the reaction mixture was gradually warmed to 0 °C and neutralized with diluted aqueous HCl, and then the solution was evaporated. The residue and $LiAlH_4$ (135 mg, 3.56 mmol) in THF (20 mL) was stirred at room temperature overnight, and the reaction was quenched with EtOAc, H_2O, and then dried over $MgSO_4$. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel to afford **10** (53 mg, 21%) as a colorless oil; IR (neat) 3325 (br), 2925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45–3.85 (m, 4H), 2.25 (br, 2H), 1.20–2.00 (m, 12H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 63.7, 61.7, 42.1, 32.0, 30.5, 29.8, 25.3, 24.7, 22.5; FAB(+)HRMS calcd for $C_9H_{19}O_2$ (M^++H): 159.1385. Found: 159.1380 (M^++H). Compound (−)-**10** prepared from (+)-**5f** (64% ee) showed specific rotation $[\alpha]_D$ −21.9, and that of (1*S*,2*S*)-(−)-**10** prepared from known compound showed $[\alpha]_D$ −22.8 (64% ee).[7]

4.3. General procedure for the ring cleavage reaction of various arylaldehydes

$BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of **2** (138 mg, 1.0 mmol), arylaldehyde (1.2 mmol), and (*S*,*S*)-**c** (260 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred for 24 h, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **11**-**14d** as a colorless oil. Solvolysis with K_2CO_3 in MeOH afforded methyl esters **11**-**14f** as a colorless oil. The enantiomeric excesses of **11**-**14f** were determined by HPLC (column; CHIRALPAK AD, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm).

4.3.1. Compound 11d. A colorless oil; IR (neat) 3455 (br), 2928, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (d, J=7 Hz, 1H), 7.30 (d, J=7 Hz, 1H), 7.18 (t, J=7 Hz, 1H), 7.12 (t, J=7 Hz, 1H), 6.74 (d, J=15.8 Hz, 1H), 6.32 (dd, J=8.6, 15.8 Hz, 1H), 4.67 (m, 1H), 3.65 (m, 1H), 2.55–2.65 (m, 2H), 2.05–2.40 (m, 3H), 1.10–1.95 (m, 18H); EIMS m/z 390 (M^+, 6), 278 (17), 218 (100); EI(+)HRMS calcd for $C_{23}H_{31}O_3Cl$ (M^+): 390.1962. Found: 390.1956 (M^+).

4.3.2. Compound 11f. A colorless oil; 37% ee [HPLC retention time (t_R), 12 and 14 min]; IR (neat) 2930, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (dd, J=8, 2 Hz, 1H), 7.31 (dd, J=8, 2 Hz, 1H), 7.10–7.24 (m, 2H), 6.74 (d, J=15.8 Hz, 1H), 6.33 (dd, J=15.8, 8.6 Hz, 1H), 3.64 (s, 3H), 2.60 (m, 1H), 2.17–2.34 (m, 3H), 1.43–1.68 (m, 8H); EIMS m/z 292.2 (M^+, 6), 281.1 (13), 218.2 (16), 147.1 (35), 125.1 (39), 73.1 (78); EI(+)HRMS calcd for $C_{17}H_{21}O_2Cl$ (M^+): 292.1230. Found: 292.1221 (M^+).

4.3.3. Compound 12d. A colorless oil; IR (neat) 3468 (br), 2929, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.29 (m, 4H), 6.32–6.33 (m, 2H), 4.66 (m, 1H), 3.66 (m, 1H), 2.42–2.55 (m, 2H), 2.15–2.35 (m, 3H), 1.30–2.00 (m, 18H); EIMS m/z 390 (M^+, 2), 278 (8), 218 (30), 139 (100); EI(+)HRMS calcd for $C_{23}H_{31}O_3Cl$ (M^+): 390.1962. Found: 390.1922 (M^+).

4.3.4. Compound 12f. A colorless oil; 49% ee [HPLC retention time (t_R), 20 and 23 min]; IR (neat) 2929, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21–7.25 (m, 4H), 6.28–6.31 (m, 2H), 3.60 (s, 3H), 2.50 (m, 1H), 2.12–2.25 (m, 3H), 1.38–1.70 (m, 8H); EIMS m/z 292 (M^+, 15), 261 (18), 218 (39), 147 (36), 125 (49), 95 (47), 55 (100); EI(+)HRMS calcd for $C_{17}H_{21}O_2Cl$ (M^+): 292.1230. Found: 292.1281 (M^+).

4.3.5. Compound 13d. A colorless oil; IR (neat) 3479 (br), 2928, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.4 Hz, 2H), 6.27–6.33 (m, 2H), 4.65 (m, 1H), 3.62 (m, 1H), 2.45–2.60 (m, 2H), 2.05–2.30 (m, 3H), 1.30–1.98 (m, 18H); EIMS m/z 435 (M^+, 0.5), 185 (99), 171 (81), 112 (100); EI(+)HRMS calcd for $C_{23}H_{31}O_3Br$ (M^+): 434.1457. Found: 434.1505 (M^+).

4.3.6. Compound 13f. A colorless oil; 47% ee [HPLC retention time (t_R), 15 and 18 min]; IR (neat) 2926, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (d, J=8.5 Hz, 2H), 7.20 (d, J=8.5 Hz, 2H), 6.36 (d, J=15.9 Hz, 1H), 6.32 (dd, J=15.9, 8 Hz, 1H), 3.62 (s, 3H), 2.52 (m, 1H), 2.14–2.30 (m, 3H), 1.38–1.78 (m, 8H); EIMS m/z 336 (M^+, 14), 264

(39), 207 (16), 169 (46), 115 (49), 73 (100); EI(+)HRMS calcd for $C_{17}H_{21}O_2Br$ (M^+): 336.0725. Found: 336.0750 (M^+).

4.3.7. Compound 14d. A colorless oil; IR (neat) 3435 (br), 2930, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (d, J=7.5 Hz, 2H), 7.10 (d, J=7.5 Hz, 2H), 6.25–6.40 (m, 2H), 4.67 (m, 1H), 3.68 (m, 1H), 2.52–2.60 (m, 2H), 2.33 (s, 3H), 2.20–2.30 (m, 3H), 1.40–1.85 (m, 18H); EIMS m/z 370 (M^+, 13), 258 (37), 198 (100), 182 (28); EI(+)HRMS calcd for $C_{24}H_{34}O_3$ (M^+): 370.2508. Found: 370.2517 (M^+).

4.3.8. Compound 14f. A colorless oil; 63% ee [HPLC retention time (t_R), 13 and 15 min]; IR (neat) 2925, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (d, J=8.1 Hz, 2H), 7.10 (d, J=8.1 Hz, 2 h), 6.34 (d, J=15.9 Hz, 1H), 6.29 (dd, J=15.9, 7.3 Hz, 1H), 3.62 (s, 3H), 2.51 (m, 1H), 2.32 (s, 3H), 2.18–2.31 (m, 3H), 1.40–1.70 (m, 8H); EIMS m/z 272 (M^+, 41), 198 (100), 183 (24); EI(+)HRMS calcd for $C_{18}H_{24}O_2$ (M^+): 272.1776. Found: 272.1695 (M^+).

4.4. Methyl 2-{2-[(1*E*)-2-phenylvinyl]-1,2-dimethylcyclopentyl}acetate (17f)

$BF_3{\cdot}OEt_2$ (0.72 mL, 6.0 mmol) was added dropwise to a stirred solution of **15** (150 mg, 1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and ethylene glycol (0.28 mL, 5.0 mmol) in CH_2Cl_2 (7 mL) at room temperature. After being stirred overnight, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **17a** (121 mg, 40%) as a colorless oil. Compound **17a**: IR (neat) 3440 (br), 2961, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 4.13–4.16 (m, 2H), 3.76–3.79 (m, 2H), 2.26 (d, J=13.9 Hz, 1H), 2.25 (d, J=13.9 Hz, 1H), 1.67–1.96 (m, 7H), 1.10 (s, 3H), 1.06 (s, 3H); EIMS m/z 302 (M^+, 30), 241 (61), 199 (75), 129 (100); EI(+)HRMS calcd for $C_{19}H_{26}O_3$ (M^+): 302.1882. Found: 302.1840 (M^+). Solvolysis of **17a** with K_2CO_3 in MeOH afforded **17f** (85%) as a colorless oil. Compound **17f**: IR (neat) 2957, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 71.5–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 3.64 (s, 3H), 2.23 (d, J=13.6 Hz, 1H), 2.20 (d, J=13.6 Hz, 1H), 1.60–2.00 (m, 6H), 1.11 (s, 3H), 1.03 (s, 3H); EIMS m/z 272 (M^+, 32), 198 (34), 143 (69), 129 (100); EI(+)HRMS calcd for $C_{18}H_{24}O_2$ (M^+): 272.1776. Found: 272.1765 (M^+).

4.4.1. Compound 17c. IR (neat) 3447 (br), 2938, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 4.55 (m, 1H), 3.52 (m, 1H), 2.26 (d, J=13.9 Hz, 1H), 2.24 (d, J=13.9 Hz, 1H), 1.15–2.10 (m, 13H), 1.10 (s, 3H), 1.06 (s, 3H); EIMS m/z 356 (M^+, 21), 258 (33), 234 (73), 198 (99), 129 (100); EI(+)HRMS calcd for $C_{23}H_{32}O_3$ (M^+): 356.2351. Found: 356.2354 (M^+). The enantiomeric excess of **17f** prepared from **17c** was determined to be 6% ee by HPLC [column; CHIRALPAK AS, eluent; 0.03% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm, retention time (t_R); 33 and 38 min].

4.4.2. Compound 17d. IR (neat) 3435 (br), 2932, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 4.68 (m, 1H), 3.70 (m, 1H), 2.60 (br s, 1H), 2.25 (d, J=13.6 Hz, 1H), 2.22 (d, J=13.6 Hz, 1H), 1.30–2.00 (m, 16H), 1.10 (s, 3H), 1.07 (s, 3H); EIMS m/z 370 (M^+, 3), 279 (8), 241 (13), 199 (10), 149 (100); EI(+)HRMS calcd for $C_{24}H_{34}O_3$ (M^+): 370.2508. Found: 370.2610 (M^+). The enantiomeric excess of **17f** prepared from **17d** was determined to be 32% ee by HPLC.

4.4.3. Compound 17e. IR (neat) 3445 (br), 2971, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.39 (m, 5H), 6.31 (d, J=16.5 Hz, 1H), 6.29 (d, J=16.5 Hz, 1H), 4.73 (m, 1H), 3.72 (m, 1H), 2.21–2.28 (m, 2H), 1.60–2.05 (m, 7H), 1.15–1.22 (m, 6H), 1.10 (s, 3H), 1.06 (s, 3H); EIMS m/z 330 (M^+, 14), 272 (12), 241 (28), 198 (64), 181 (66), 129 (94), 91 (100); EI(+)HRMS calcd for $C_{21}H_{30}O_3$ (M^+): 330.2195. Found: 330.2159 (M^+). The enantiomeric excess of **17f** prepared from **17e** was determined to be 28% ee by HPLC.

4.4.4. Methyl 2-{2-[(1*E*)-2-phenylvinyl]-1,2-dimethylcyclohexyl}acetate (18f). Compounds **18a** and **18f** were prepared from **16** in a manner similar to that described for the preparation of **17f**. Compound **18a**: 12%; a colorless oil; IR (neat) 3446 (br), 2935, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–7.39 (m, 5H), 6.51 (d, J=16.3 Hz, 1H), 6.33 (d, J=16.3 Hz, 1H), 4.11–4.15 (m, 2H), 3.72–3.82 (m, 2H), 2.50 (d, J=13.2 Hz, 1H), 2.28 (d, J=13.2 Hz, 1H), 1.90 (m, 1H), 1.50–1.75 (m, 8H), 1.13 (s, 3H), 1.11 (s, 3H); EIMS m/z 316 (M^+, 16), 213 (14), 55 (100); EI(+)HRMS calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038. Found: 316.2027 (M^+). Compound **18f**: a colorless oil; IR (neat) 2933, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.37 (m, 5H), 6.50 (d, J=16.5 Hz, 1H), 6.29 (d, J=16.5 Hz, 1H), 3.57 (s, 3H), 2.44 (d, J=13.3 Hz, 1H), 2.23 (d, J=13.3 Hz, 1H), 1.43–1.70 (m, 8H), 1.10 (s, 3H), 1.07 (s, 3H); EIMS m/z 286 (M^+, 64), 255 (20), 213 (23), 154 (47), 149 (99), 91 (100); EI(+)HRMS calcd for $C_{19}H_{26}O_2$ (M^+): 286.1933. Found: 286.1951 (M^+).

4.4.5. Compound 18c. IR (neat) 3435 (br), 2935, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.40 (m, 5H), 6.51 (d, J=16.3 Hz, 1H), 6.32 (d, J=16.3 Hz, 1H), 4.54 (m, 1H), 3.52 (m, 1H), 2.51 (d, J=12.8 Hz, 1H), 2.24 (m, 1H), 1.95–2.10 (m, 3H), 1.20–1.70 (m, 14H), 1.11–1.13 (m, 6H); EIMS m/z 370 (M^+, 49), 316 (9), 272 (56), 254 (26), 212 (64), 184 (100); EI(+)HRMS calcd for $C_{24}H_{34}O_3$ (M^+): 370.2508. Found: 370.2489 (M^+). The enantiomeric excess of **18f** prepared from **18c** was determined to be 34% ee by HPLC (column; CHIRALPAK AD, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm, retention time (t_R); 20 and 23 min).

4.5. 2-[(1*S*,2*S*)-2-(Hydroxymethyl)cyclohexyl]-*N*-[2-(1*H*-indol-3-yl)ethyl]acetamide (19)

Ozone gas was bubbled into a solution of **5d** (220 mg, 0.62 mmol, 61% de) in MeOH (10 mL) and CH_2Cl_2 (10 mL) at −78 °C, and the reaction was monitored by TLC. $NaBH_4$ (70 mg, 1.84 mmol) was added portionwise to the solution at −78 °C. After being stirred at −78 °C for 2 h, the mixture was gradually warmed to 0 °C and diluted with

saturated aqueous NH_4Cl. After evaporation of MeOH and CH_2Cl_2, the solution was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue which was purified by column chromatography on silica gel to give alcohol (133 mg, 76%) as a colorless oil: $[\alpha]_D^{25}$ +12.0 ($CHCl_3$, c=1.00); IR (neat) 3377 (br), 2926, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.79 (m, 1H), 3.78 (m, 1H), 3.40–3.60 (m, 2H), 3.00–3.25 (br, 1H), 2.45 (m, 1H), 2.30 (br, 1H), 2.22 (m, 1H), 1.20–1.95 (m, 20H); FAB(+)HRMS calcd for $C_{16}H_{29}O_4$ (M^++H): 285.2066. Found: 285.2073 (M^++H). A mixture of the above alcohol (330 mg, 1.16 mmol) and tryptame (370 mg, 2.31 mmol) in xylene (5 mL) was heated at 100 °C for 3 h. After being cooled to room temperature, the solution was evaporated, and the residue was purified by column chromatography on silica gel to afford an amide **19** (252 mg, 69% from **5d**) as a colorless oil. $[\alpha]_D^{24}$ −7.5 ($CHCl_3$, c=1.24) {lit. $[\alpha]_D$ −11.8}[15c]; IR (neat) 3402 (br), 3292 (br), 2927, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (br s, 1H), 7.58 (d, J=7 Hz, 1H), 7.36 (d, J=7 Hz, 1H), 7.19 (t, J=7 Hz, 1H), 7.11 (t, J=7 Hz, 1H), 7.00 (s, 1H), 5.94 (br s, 1H), 3.84 (br s, 1H), 3.58 (m, 2H), 3.36 (m, 2H), 2.95 (t, J=6.7 Hz, 2H), 2.37 (m, 1H), 2.30 (dd, J=8.1, 14.6 Hz, 1H), 1.90 (dd, J=4.3, 14.6 Hz, 1H), 1.78 (m, 1H), 1.00–1.56 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 136.4, 127.3, 122.14, 122.07, 119.4, 118.6, 112.7, 111.3, 64.1, 41.7, 39.9, 36.4, 31.9, 31.3, 25.3, 25.2, 24.5, 22.7; FAB(+)HRMS calcd for $C_{19}H_{27}N_2O_2$ (M^++H): 315.2072. Found: 315.2109 (M^++H).

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