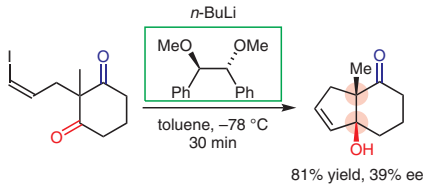
Synthesis T. Yoshimura et al. Paper

Asymmetric Synthesis of a Bicyclo[4.3.0]nonene Derivative Bearing a Quaternary Carbon Stereocenter: Desymmetrization of σ-Symmetrical Diketones through Intramolecular Addition of an Alkenyl Anion

Tomoyuki Yoshimura*
Yuki Enami
Jun-ichi Matsuo

Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan
yosimura@p.kanazawa-u.ac.jp



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Abstract The enantioselective synthesis of a bicyclo[4.3.0]nonene derivative bearing a quaternary carbon stereocenter is achieved by employing a desymmetrization strategy involving an intramolecular addition. The intramolecular nucleophilic addition of a highly reactive carbanion generated from an alkenyl iodide in the presence of a chiral ligand occurs with discrimination of two keto carbonyl groups to give the corresponding bicyclic compound in 81% yield and 39% ee. Asymmetric synthesis via an intramolecular desymmetrization strategy using a chiral ligand–carbanion complex represents a complementary approach to using chiral organocatalysts or chiral ligand–transition-metal complexes.

Key words desymmetrization, asymmetric synthesis, alkenyl lithium, quaternary carbon stereocenter, bicyclo[4.3.0]nonene

The stereoselective construction of a quaternary carbon stereocenter, as commonly found in useful organic molecules, is a key step in the synthesis of such molecules due to challenges associated with steric hindrance. These challenges also affect the transformation of functional groups and the construction of other stereocenters close to the quaternary carbon stereocenter. Therefore, developing a new method for the effective construction of a quaternary carbon stereocenter including the surrounding scaffold is an important challenge in synthetic organic chemistry.[1] Desymmetrization of prochiral compounds is expected to be a valuable method for the enantioselective construction of quaternary carbon stereocenters because asymmetric induction occurs by discrimination of identical residues remote from the preexisting quaternary carbon stereocenter.[2] With this approach, steric repulsion caused by a quaternary carbon has minimal influence on asymmetric induction. This method is applied in the proline-catalyzed preparation of Wieland–Miescher (**1**)[3] and Hajos–Parrish (**2**)[4] ketones, which are useful compounds for the synthesis of cyclic molecules having a quaternary carbon stereocenter (Figure 1).[5,6]

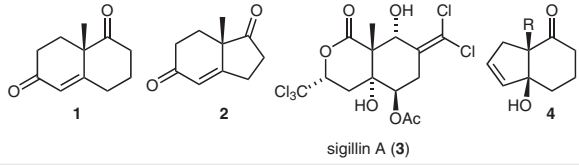

Figure 1 Structures of bicyclic compounds and sigillin A (**3**)

The asymmetric synthesis of bicyclic compounds similar to **1** and **2** via desymmetrization strategies involving intramolecular reactions has also been reported;[7–9] such compounds show valuable potential as synthons for the synthesis of certain functional molecules. Our plan for the total synthesis of sigillin A (**3**), isolated from *Ceratophysella sigillata*,[10] included the use of chiral bicyclo[4.3.0]nonene derivative **4** (R = Me) as the starting material (Figure 1). The synthesis of **4** (R = Me) in racemic form has been reported,[9] while the synthesis of the chiral form is unknown. Herein, we report a novel enantioselective synthesis of **4** by desymmetrization of 2,2-disubstituted cyclohexane-1,3-dione **5** through intramolecular nucleophilic addition of an alkenyl anion to a carbonyl group (Scheme 1).

The synthetic plan involved treatment of 2-alkyl-2-(3′-halo-2′-propenyl)-1,3-diketone **5** with an alkylmetal in the presence of a chiral ligand to give intermediate **A**, which would undergo intramolecular nucleophilic addition with discrimination between the two carbonyl groups to afford chiral bicyclic compound **4**. Asymmetric syntheses using a

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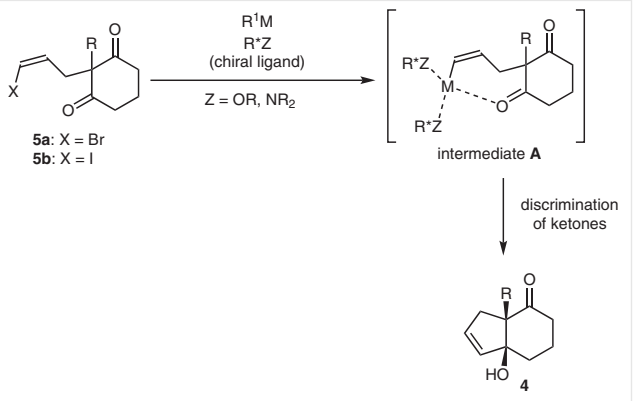
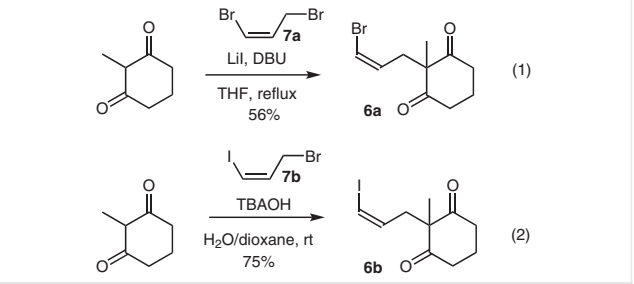


Scheme 1 Strategy for the asymmetric synthesis of **4**

desymmetrization strategy with an intramolecular reaction have been developed using functional-group-tolerant reagents such as organocatalysts or catalysts of chiral ligand–transition-metal complexes. However, the use of highly reactive carbanion intermediates in reactions involving desymmetrization with an intramolecular reaction have been reported infrequently,[11] likely due to the poor compatibility of reactive carbanions with various functional groups. The success of this strategy requires (1) the faster generation of chiral intermediate **A** than deprotonation or nucleophilic addition of an alkylmetal, and (2) effective discrimination between carbonyl groups by a chiral ligand. While lithium–halogen exchange is known to selectively occur in the presence of carbonyl groups, the selective addition of alkyllithium nucleophiles to one of the carbonyl groups represents a challenge.[12]

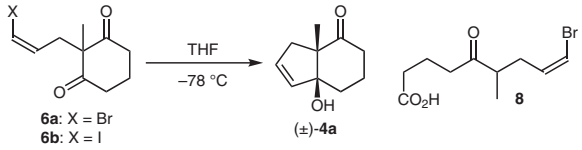
The reaction conditions were optimized using diketones **6a** and **6b**,[9] which were prepared using reported procedures (Scheme 2, eqs 1 and 2).[13,14] Alkylation of 2-methylcyclohexane-1,3-dione with the corresponding *cis*-1-halo-3-bromopropene **7a** or **7b** gave products **6a** and **6b** in 56% and 75% yields, respectively.



Scheme 2 Preparation of precursors **6a** and **6b**

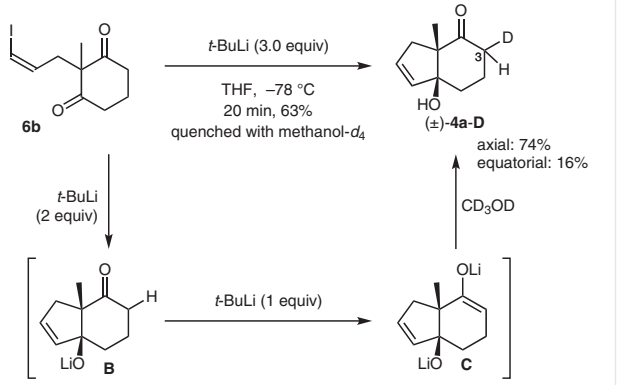
Cyclization of **6a** was first attempted without a chiral ligand to confirm whether bicyclic ketone **4a** would be obtained (Table 1). Treatment of **6a** with *n*-BuLi or *t*-BuLi in THF afforded linear ketone **8** (77%) or recovered starting material **6a** (75%), respectively, instead of the desired product (±)-**4a** (entries 1 and 2). It was assumed that carboxylic acid **8** was produced through a retro-Claisen reaction after aqueous work-up. These results suggested that effective lithium–bromine exchange did not occur. Therefore, the reaction with ketone **6b** having an alkenyl iodide was attempted because lithium–iodine exchange proceeds more effectively than lithium–bromine exchange. Treatment of **6b** with 1.5 equivalents of *n*-BuLi afforded (±)-**4a** in 37% yield, while the reaction with 1.2 equivalents of *t*-BuLi afforded (±)-**4a** in 34% yield (entries 3 and 4). The reaction with *n*-BuLi resulted in a more complex reaction mixture than that with *t*-BuLi, although a similar yield was observed for both cases in the production of (±)-**4a**. Therefore, optimization of the reaction conditions using *t*-BuLi was investigated. Increasing the number of equivalents of *t*-BuLi resulted in an improved yield of (±)-**4a** from 34% to 78% (entries 4–6). No effect on the yield of (±)-**4a** was observed when more than 3.0 equivalents of *t*-BuLi were used (entries 6 vs 7). Because 3 equivalents of *t*-BuLi was required to complete the reaction, it was assumed that an excess amount of *t*-BuLi would work as a base. To investigate this possibility, compound **6b** was treated under conditions identical to those indicated in Table 1 entry 6, except for the reaction time, which was reduced from 5 hours to 20 minutes, and then quenched by the addition of methanol-d_4 (Scheme 3). Deuterium incorporation of 90% was observed at C(3) of (±)-**4a-D**. This indicates that 2 equivalents of *t*-BuLi were consumed for lithium–iodine exchange to give the intermediate **B** and that 1 equivalent of *t*-BuLi deprotonates at C(3) of intermediate **B** to generate the dianion **C**.

Table 1 Investigation of the Reaction Conditions in Racemic Form[a]



Entry	Precursor	Reagent (equiv)	Time (h)	Product (% yield)[b]
1[c]	**6a**	*n*-BuLi (1.3)	22	**8** (77)
2	**6a**	*t*-BuLi (3.0)	6.5	**6a** (75)
3	**6b**	*n*-BuLi (1.5)	3	**4a** (37)
4	**6b**	*t*-BuLi (1.2)	7	**4a** (34)[d]
5	**6b**	*t*-BuLi (2.2)	5.5	**4a** (54)[d]
6	**6b**	*t*-BuLi (3.0)	5	**4a** (78)
7	**6b**	*t*-BuLi (6.0)	1	**4a** (73)

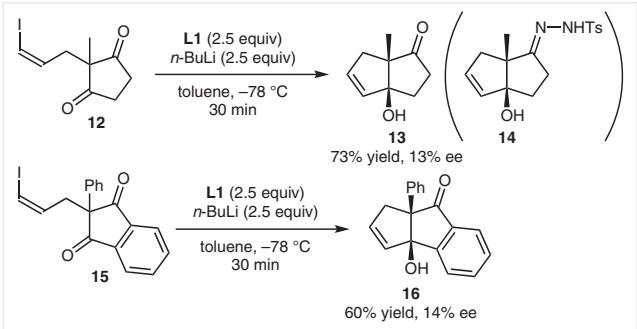
[a] A stirring solution of **6** was treated with RLi.
[b] A small amount of an inseparable impurity was present.
[c] The reaction temperature was allowed to increase gradually from –78 °C to rt over 12 h.
[d] Starting material **6b** was recovered (entry 4: 47%, entry 5: 26%).



Scheme 3 Deuteration experiment

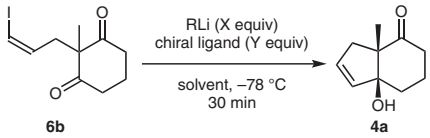
Next, the enantioselective synthesis of **4a** was investigated using the optimized conditions identified for the racemic synthesis (Table 2). Treatment of **6b** with 3.3 equivalents of *t*-BuLi in the presence of 6.0 equivalents of chiral ligand **L1**[11a,b,15] in THF at –78 °C afforded the desired product **4a** in 66% yield as an almost racemic product (–1% ee) (entry 1). The highly coordinating property of THF was thought to be the cause of the failed asymmetric induction, presumably due to THF preventing coordination of the chiral ligand **L1** to the lithium cation. When the reaction was carried out in toluene as the solvent, which has a lower coordinating ability than THF, the cyclization of **6b** afforded **4a** in 61% yield and 5% ee (entry 2). Because the ee value was not improved with a different solvent, the effect of the alkyllithium was revisited. Reinvestigation of alkyllithium reagents in the presence of **L1** showed that *n*-BuLi was more appropriate for the enantioselective cyclization of **6b**. Treatment of **6b** with 3.3 equivalents of *n*-BuLi in the presence of 6.6 equivalents of **L1** in toluene gave **4a** in 56% yield and 37% ee (entry 3). When the equivalent ratio of *n*-BuLi to **L1** was kept at 1:2 and the number of equivalents of *n*-BuLi was reduced from 3.3 to 2.5, both the yield and ee were improved (entries 3 vs 4), while reduction from 3.3 to 1.5 equivalents of *n*-BuLi resulted in a low yield and ee (entries 3 vs 5). It is well known that the aggregation state of intermediate **A** influences its reactivity and enantioselectivity.[16] Therefore, it was expected that the enantioselectivity would be improved by modifying the aggregation state of intermediate **A**. As the aggregation state of intermediate **A** can be modulated by changing the amount of chiral ligand relative to the concentration of the lithium cation,[16] the effect of the number of equivalents of **L1** versus the equivalents of *n*-BuLi was investigated. Treatment of **6b** with 2.5 equivalents each of *n*-BuLi and **L1** gave **4a** in 70% yield and 39% ee (entry 6). Reducing the number of equivalents of **L1** from 2.5 to 0.5 lowered both the yield and ee of **4a** (entries 6 vs 7 and 8). The effects of other alkylmetals on the yield and ee of **4a** were then investigated. Treatment with *sec*-BuLi improved the yield while that with PhLi reduced both the yield and ee (entries 9 and 10). The reaction with *i*-PrMgCl·LiCl resulted in recovery of **4a** (57%), probably due to the low efficiency of iodine–magnesium exchange (entry 11). Treatment of **6b** with *n*-BuLi in the presence of $ZnCl_2$ led to a slightly lowered yield and ee (entry 12). Although various chiral ligands (**L2**–**L6**) were evaluated using similar conditions to those of entry 6 (Table 2) in an attempt to improve the yield and ee of **4a**, these efforts were unsuccessful (entries 13–17). The following observations on the chiral ligands are noteworthy: (1) chiral ligands containing oxygen atoms tended to give better enantioselectivities than those possessing nitrogen atoms (entries 6 and 14 vs 16 and 17), (2) a methyl group was a suitable substituent on the oxygen atom of the chiral ligand (entries 6 and 14 vs 13), and (3) a phenolic oxygen on the chiral ligand decreased both the yield and ee of **4a** (entries 6 and 14 vs 15). An improvement in the yield was achieved by prolonging the time allowed for formation of the chiral ligand–lithium complex to give **4a** in 81% yield and 39% ee and by-product **11** in 15% yield (entry 18). The yield of recovered **L1** was not determined, however, the degradants from **L1** were thought to have little effect on the enantioselectivity of **4a** due to the same ee being obtained irrespective of the time for formation of the chiral ligand–lithium complex (entries 6 and 18). The addition of 1.0 equivalent of LiI, which it was hoped would influence the aggregation state of **A**, proved fruitless (entry 19).[16] It was assumed that the lower ee with *t*-BuLi rather than with *n*-BuLi should be attributed to the higher concentration of LiI (entries 2 vs 19 and 3). The addition of triethylamine, which modifies the aggregation state[16] of intermediate **A**, resulted in a low yield of **4a** (entry 20).

The optimized method described above was applied to the synthesis of bicyclo[3.3.0]octene derivatives bearing a quaternary carbon stereocenter (Scheme 4). Treatment of diketone **12** with 2.5 equivalents of *n*-BuLi in the presence of 2.5 equivalents of **L1** afforded bicyclic ketone **13** in 73% yield and 13% ee. The ee of **13** was determined after its conversion into **14**. The reaction of **15** was also carried out similarly to give **16** in 60% yield and 14% ee. The enantioselectivity for the formation of bicyclo[3.3.0]octene derivatives

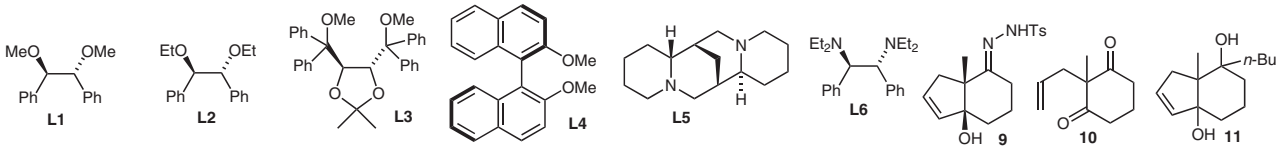


Scheme 4 Syntheses of bicyclo[3.3.0]octene derivatives. The relative and absolute configurations of **13** and **16** were tentatively assigned.

Table 2 Investigation of the Enantioselective Cyclization of **6b**[a]



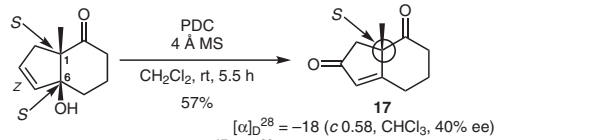
Entry	RM	X	Chiral ligand	Y	Solvent	Yield (%)[b] of **4a**	ee (%)[c] of **4a**
1	*t*-BuLi	3.3	**L1**	6.0	THF	66[d]	–1
2	*t*-BuLi	3.3	**L1**	6.0	toluene	61[d]	5
3	*n*-BuLi	3.3	**L1**	6.6	toluene	56[d,e,f]	37
4	*n*-BuLi	2.5	**L1**	5.0	toluene	64[d,e]	42
5	*n*-BuLi	1.5	**L1**	3.0	toluene	47[d,e,f]	35
6	*n*-BuLi	2.5	**L1**	2.5	toluene	70[d,e,f]	39
7	*n*-BuLi	2.5	**L1**	1.0	toluene	60[d,e,f]	29
8	*n*-BuLi	2.5	**L1**	0.5	toluene	66[d,e,f]	25
9	*s*-BuLi	2.5	**L1**	2.5	toluene	80[d]	23
10	PhLi	2.5	**L1**	2.5	toluene	18	19
11	*i*-PrMgCl·LiCl	2.5	**L1**	2.5	toluene	0[f]	–
12	*n*-BuLi[g]	2.5	**L1**	2.5	toluene	67[e]	31
13	*n*-BuLi	2.5	**L2**	2.5	toluene	76[e,f]	3
14	*n*-BuLi	2.5	**L3**	2.5	toluene	68[e,f]	22
15	*n*-BuLi	2.5	**L4**	2.5	toluene	5[d,f]	0
16	*n*-BuLi	2.5	**L5**	2.5	toluene	40[d,e,f]	7
17	*n*-BuLi	2.5	**L6**	2.5	toluene	31[d,e,f]	4
18[h]	*n*-BuLi	2.5	**L1**	2.5	toluene	81[e]	39
19[h]	*n*-BuLi[i]	2.5	**L1**	2.5	toluene	64	15
20[h]	*n*-BuLi[j]	2.5	**L1**	2.5	toluene	7[k]	–[l]



[a] A solution of **L1** and *n*-BuLi was stirred at –78 °C for 10 min before addition of **6b**.
[b] The absolute configuration was determined after conversion of **4a** into the known compound **17** (see Scheme 5) and its specific rotation was compared with that reported (*vide infra*).
[c] The ee of **4a** was determined by chiral stationary HPLC after conversion of **4a** into tosyl hydrazone **9**.
[d] Compound **10** was concomitantly produced (2–12%).
[e] Compound **11** was concomitantly produced (4–15%) as a single isomer.
[f] Diketone **6b** was recovered (2–57%).
[g] $ZnCl_2$ (2.5 equiv) was added.
[h] A solution of **L1** and *n*-BuLi was stirred at –78 °C for 1 h before addition of **6b**.
[i] LiI (1.0 equiv) was added.
[j] Et_3N (2.5 equiv) was added.
[k] Diketone **6b** was recovered in 79% yield.
[l] The ee was not determined because of the low yield of **4a**.

was found to be much lower than that of the bicyclo[4.3.0]nonene derivative.

The absolute configuration of **4a** was determined after its conversion into the known compound **17** (Scheme 5). Oxidation of **4a** (40% ee) with PDC in CH_2Cl_2 gave diketone **17** in 57% yield, which was identified by comparison with the reported proton NMR spectrum.[17] The reported specific rotation of (*R*)-**17** is +47.3 while the specific rotation of synthetic **17** was found to be –18.0 (40% ee). Therefore, the absolute configuration of the quaternary carbon in **17** was determined to be *S*. From these results, the absolute configurations of the newly formed contiguous tetrasubstituted carbons in **4a** were determined to be 1*S*,6*S* due to the known *cis*-fused structure. Mechanistic investigations of the stereochemical course of the reaction are in progress.



Scheme 5 Determination of the absolute configuration of **4a**

In conclusion, we have developed an asymmetric synthesis of bicyclo[4.3.0]nonene derivative **4a** through an intramolecular nucleophilic addition of an alkenyl anion with discrimination of two carbonyl groups. Highly reactive carbanion intermediates were compatible with this desymmetrization strategy undergoing intramolecular reactions under optimized conditions. Although further improvement of the enantioselectivity is needed for this reaction, the potency of carbanions in asymmetric synthesis through a desymmetrization strategy involving an intramolecular reaction has been demonstrated. These results are expected to provide opportunities for developing new methods in asymmetric synthesis using highly reactive carbanions.

Solutions of *n*-BuLi in hexane and *t*-BuLi in pentane were purchased from Kanto Chemical Co., Inc. and were titrated with diphenylacetic acid, which is a standard material and an indicator, when they were newly opened. Chiral ligands **L1**–**L4**[11b] and **L6**[18] were prepared according to reported procedures. Flash column chromatography was performed with SilicaFlash® F60 silica gel (40–50 micrometer). Thin-layer chromatography was performed on precoated plates (0.25 mm, silica gel, Merck Kieselgel $60F_{245}$), and compounds were visualized with UV light and *p*-anisaldehyde stain or phosphomolybdic acid stain. IR spectra were recorded on a Horiba IR-710 spectrophotometer. ^{1}H NMR spectra were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using JEOL JNM ECA-600 (600 MHz) or JEOL JNM ECA-400 (400 MHz) spectrophotometers, unless otherwise noted. ^{13}C NMR spectra were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) using JEOL JNM ECA-600 (150 MHz) or JEOL JNM ECX-400 (100 MHz) spectrophotometers, unless otherwise noted. Chemical shifts are reported in ppm. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on a JEOL JMS-T100TD mass spectrometer.

2-(2′*Z*,3′-Bromopropenyl)-2-methylcyclohexane-1,3-dione (6a)

To a mixture of 2-methylcyclohexane-1,3-dione (1.19 g, 9.45 mmol) and LiI (1.65 g, 12.3 mmol) in THF (75 mL) was added dropwise DBU (1.84 mL, 12.3 mmol) at rt. After being stirred for 30 min, a solution of 1,3-dibromopropene (**7a**)[19] (3.78 g, 18.9 mmol) in THF (30 mL) was added to the mixture at rt. The resulting mixture was stirred for 20 h under reflux. The reaction mixture was poured into ice water at 0 °C and the resulting mixture extracted with EtOAc. The organic layers were washed with sat. aq $Na_2S_2O_3$ solution, water, and brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to afford **6a** (1.30 g, 56%) as a yellow oil.

IR (neat): 1726, 1695, 1624 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (dt, *J* = 7.1, 1.6 Hz, 1 H), 5.94 (q, *J* = 7.1 Hz, 1 H), 2.79–2.64 (m, 6 H), 2.06–1.87 (m, 2 H), 1.31 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.0, 129.0, 110.9, 64.6, 37.6, 36.0, 19.1, 17.6.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}BrO_2$: 245.01772; found: 245.01871.

2-(2′*Z*,3′-Iodopropenyl)-2-methylcyclohexane-1,3-dione (6b)[9]

To a solution of 2-methylcyclohexane-1,3-dione (210.7 mg, 1.67 mmol) in 1,4-dioxane (5 mL) were added tetrabutylammonium hydroxide (TBAOH) (1.1 mL, 2.51 mmol, 40% in water) and a solution of 3-bromo-1-iodopropene (**7b**)[19] (800 mg, 2.51 mmol) in 1,4-dioxane (5 mL) at rt. After being stirred for 23 h at the same temperature, the reaction was quenched with 1 N HCl at rt. The resulting mixture was extracted with EtOAc. The extracts were washed with water and brine, and dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1) to give a colorless oil that was further purified by silica gel column chromatography (toluene/EtOAc, 9:1) to afford **6b** (365.7 mg, 75%) as a colorless oil.

IR (neat): 1726, 1691, 1608 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 7.6 Hz, 1 H), 6.00 (q, *J* = 7.6 Hz, 1 H), 2.79–2.63 (m, 6 H), 2.07–1.87 (m, 2 H), 1.32 (s, 3 H).

MS (DART): *m*/*z* = 293 [M + H]$^+$.

Cyclization Reactions in Table 1; General Procedure 1

To a solution of **6a** or **6b** (1 equiv) in THF (the volume was determined by the concentration of substrate being adjusted to 0.06 M) was added dropwise *n*-BuLi or *t*-BuLi (the equivalents are given in Table 1) at –78 °C. After being stirred for the time indicated in Table 1, the reaction was quenched by the addition of sat. aq NH_4Cl solution and the resulting mixture was extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residual oil was purified by silica gel column chromatography (hexane/EtOAc, 2:1 to 1:1) to give the products indicated in Table 1.

Cyclization Reactions in Table 2; General Procedure 2

To a solution of the chiral ligand (see Table 2) in THF or toluene was added the base (the indicated equivalents in Table 2) at –78 °C. The mixture was stirred for 10 min (entries 1–17) or 1 h (entries 18–20) at –78 °C. Next, a solution of **6b** (1 equiv) in THF or toluene (the total volume of THF or toluene was determined by the concentration of **6b**

being adjusted to 0.06 M) was added dropwise to the mixture at –78 °C. After being stirred at –78 °C for 30 min, the resulting mixture was quenched by the addition of a solution of AcOH (10 equiv) in toluene (1 mL) and then poured into sat. aq $NaHCO_3$ solution at 0 °C. The resulting mixture was extracted with EtOAc and the extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1 to 4:1) to afford the products indicated in Table 2. The ee of **4a** was determined by chiral stationary after its conversion into the corresponding tosyl hydrazone.

Deuteration Experiment

To a solution of **6b** (60 mg, 0.21 mmol) in THF (3 mL) was added dropwise *t*-BuLi (0.41 mL, 1.53 M in pentane, 0.63 mmol) at –78 °C. After being stirred for 20 min at –78 °C, the reaction was quenched by the addition of methanol-d_4 (1 mL) at –78 °C and the resulting mixture was poured into sat. aq NH_4Cl solution. The mixture was extracted with EtOAc and the extracts were washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified by silica gel column chromatography (hexane/EtOAc = 1:10) to give (±)-**4a-D** (22.1 mg, 63%) as a colorless oil.

(6*RS*,8*Z*)-9-Bromo-6-methyl-5-oxo-8-nonenoic Acid (8)

Yellow oil.

IR (neat): 3751, 1709, 1624 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.24 (d, *J* = 6.8 Hz, 1 H), 6.06 (dt, *J* = 6.8, 7.2 Hz, 1 H), 2.71–2.45 (m, 4 H), 2.42–2.29 (m, 3 H), 1.91 (quin, *J* = 7.2 Hz, 2 H), 1.14 (d, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.4, 179.3, 131.8, 109.8, 45.2, 39.5, 32.9, 32.6, 19.4, 16.1.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}BrO_3$: 263.02828; found: 263.02607.

(1*S*,6*S*)-6-Hydroxy-1-methylbicyclo[4.3.0]non-7-en-2-one (4a)[9]

Colorless oil; $[\alpha]_D^{28}$ = +9.3 (*c* 0.65, $CHCl_3$, 40% ee).

IR (neat): 3453, 1704, 1639 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.02 (dt, *J* = 6.0, 2.7 Hz, 1 H), 5.69 (dt, *J* = 6.0, 2.2 Hz, 1 H), 3.14 (ddd, *J* = 16.8, 3.0, 1.4 Hz, 1 H), 2.43 (ddd, *J* = 15.2, 12.4, 6.0 Hz, 1 H), 2.35–2.28 (m, 1 H), 2.17 (dt, *J* = 16.8, 2.3 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.96–1.85 (m, 2 H), 1.50–1.43 (m, 2 H), 1.25 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 214.6, 136.6, 136.0, 85.7, 59.7, 40.3, 37.3, 32.7, 19.2, 17.8.

MS (DART): *m*/*z* = 166 [M]$^+$.

The proton NMR spectrum of chiral **4a** is compared with that of the reported racemic example.

2-Methyl-2-(2′-propenyl)cyclohexane-1,3-dione (10)[71]

Colorless oil.

IR (neat): 1726, 1695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.63–5.53 (m, 1 H), 5.06–5.05 (m, 2 H), 2.71–2.61 (m, 4 H), 2.53 (d, *J* = 7.2 Hz, 2 H), 2.05–1.85 (m, 2 H), 1.25 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.9, 132.2, 119.2, 65.2, 41.3, 38.2, 19.5, 17.5.

MS (DART): *m*/*z* = 167 [M + H]$^+$.

2-Butyl-2,6-dihydroxy-1-methylbicyclo[4.3.0]non-7-ene (11)

Single isomer (the relative configuration was not determined); colorless oil.

IR (neat): 3423, 1637 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.72 (dd, *J* = 6.0, 3.0 Hz, 1 H), 5.65–5.64 (m, 1 H), 2.28 (s, 1 H), 2.24 (d, *J* = 15.0 Hz, 1 H), 1.98 (dd, *J* = 15.6, 3.6 Hz, 1 H), 1.96–1.93 (m, 1 H), 1.85–1.82 (m, 1 H), 1.72–1.66 (m, 1 H), 1.50–1.45 (m, 1 H), 1.42–1.26 (m, 8 H), 1.15 (s, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.7, 128.0, 85.1, 75.3, 52.5, 41.5, 37.4, 32.0, 24.8, 23.5, 16.6, 15.6, 14.2.

HRMS-DART: *m*/*z* [M – H_2O + H]$^+$ calcd for $C_{14}H_{23}O$: 207.17489; found: 207.17494.

N′-[(3a*R*,7a*S*)-7a-Hydroxy-3a-methyl-3,3a,5,6,7,7a-hexahydro-4*H*-inden-4-ylidene]-4-methylbenzenesulfonohydrazide (9)

To a solution of (1*S*,6*S*)-**4a** (20.5 mg, 0.12 mmol) in THF (2 mL) were added *p*-$TsNHNH_2$ (24.2 mg, 0.13 mmol) and PPTS (1.3 mg, 0.04 mmol) at rt. After being stirred at rt for 5 h, the resulting mixture was concentrated. The residual oil was dissolved in CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified through silica gel column chromatography (CH_2Cl_2/EtOAc, 9:1) to give product **9** (32.3 mg, 80%) as a colorless oil. HPLC conditions: DAICEL Chiralpak AD-H, hexane/2-propanol = 9:1, flow = 1 mL/min, λ_{max} = 254 nm, t_1 = 27.4 min for (1*S*,6*S*)-**4a**, t_2 = 33.1 min for (1*R*,6*R*)-**4a**.

$[\alpha]_D^{26}$ = +8.0 (*c* 1.04, $CHCl_3$, 41% ee).

IR (neat): 3508, 1626, 1599, 1335, 1169 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.8 Hz, 2 H), 7.68 (br s, 1 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 5.82–5.81 (m, 1 H), 5.50 (d, *J* = 5.4 Hz, 1 H), 2.78 (d, *J* = 16.8 Hz, 1 H), 2.43 (s, 3 H), 2.33 (d, *J* = 16.8 Hz, 1 H), 2.17–2.11 (m, 2 H), 1.79–1.70 (m, 3 H), 1.54–1.51 (m, 1 H), 1.43–1.26 (m, 1 H), 1.14 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.8, 143.8, 136.2, 135.2, 133.0, 129.3, 128.1, 86.0, 52.6, 44.6, 34.4, 24.3, 21.6, 20.3, 17.8.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_3S$: 335.14294; found: 335.13969.

2-(3′-Iodoallyl)-2-methylcyclopentane-1,3-dione (12)[9]

Compound **12** was synthesized from 2-methylcyclopentane-1,3-dione (250 mg, 2.22 mmol) by following a similar method to that used for the synthesis of **6b**. Compound **12** (268.8 mg, 44%) was obtained as a pale yellow oil.

IR (neat): 1724, 1610 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.44 (dt, *J* = 7.6, 1.2 Hz, 1 H), 6.11 (q, *J* = 7.2 Hz, 1 H), 2.86–2.76 (m, 4 H), 2.46 (dd, *J* = 6.8, 1.2 Hz, 2 H), 1.18 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 215.0, 134.3, 86.9, 55.5 39.5, 35.0, 17.9.

MS (DART): *m*/*z* = 278 [M + H]$^+$.

(3a*S*,6a*S*)-3a-Hydroxy-6a-methyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (13)

Following general procedure 2, compound **12** (60 mg, 0.22 mmol) was converted into **13**[9a] (24.6 mg, 73%, 13% ee) as a colorless oil.

$[\alpha]_D^{26}$ = +41.2 (*c* 0.96, $CHCl_3$, 13% ee).

IR (neat): 3439, 1738, 1612 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.96–5.95 (m, 1 H), 5.73–5.72 (m, 1 H), 2.66 (d, *J* = 17.4 Hz, 1 H), 2.35–2.30 (m, 2 H), 2.18–2.01 (m, 2 H), 1.64 (br s, 1 H), 1.11 (s, 3 H).

MS (DART): *m*/*z* = 153 $[M + H]^+$.

The ee of **13** was determined after its conversion into the corresponding tosyl hydrazone **14**.

N'-[(3a*S*,6a*R*)-3a-Hydroxy-6a-methyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-ylidene]-4-methylbenzenesulfonohydrazide (14)

Treatment of **13** (24.6 mg, 0.16 mmol) with $TsNHNH_2$ (33.5 mg, 0.18 mmol) and PPTS (1.5 mg, 0.006 mmol) in THF (3 mL) gave tosyl hydrazone **14** (27.3 mg, 53%) as a colorless oil. HPLC conditions: DAICEL Chiralpak AD-H, hexane/2-propanol = 9:1, flow = 1 mL/min, λ_{max} = 254 nm, t_1 = 34.0 min, t_2 = 40.9 min.

$[\alpha]_D^{24}$ = +13.9 (*c* 1.17, $CHCl_3$, 13% ee).

IR (neat): 3473, 1653, 1598 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.8 Hz, 2 H), 7.44 (br s, 1 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 5.81 (dt, *J* = 5.4, 2.6 Hz, 1 H), 5.58 (dt, *J* = 6.0, 2.0 Hz, 1 H), 2.61 (dt, *J* = 16.8, 2.1 Hz, 1 H), 2.43 (s, 3 H), 2.41–2.33 (m, 2 H), 2.16–2.12 (m, 1 H), 1.96–1.86 (m, 2 H), 1.65 (br s, 1 H), 1.07 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.8, 143.9, 136.2, 135.3, 134.4, 129.4, 127.9, 90.9, 53.6, 45.6, 32.2, 25.6, 21.6, 18.6.

HRMS-DART: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3S$: 321.12729; found: 321.12807.

2-(3-Iodoallyl)-2-phenyl-1*H*-indene-1,3(2*H*)-dione (15)

Compound **15** was synthesized from 2-phenylindane-1,3-dione (400 mg, 1.80 mmol) by following a similar method to that used for the synthesis of **6b**. Compound **15** (490.9 mg, 80%) was obtained as an orange oil.

IR (neat): 1706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.02 (m, 2 H), 7.90–7.85 (m, 2 H), 7.44–7.41 (m, 2 H), 7.35–7.26 (m, 3 H), 6.29 (dt, *J* = 7.2, 1.6 Hz, 1 H), 6.10 (q, *J* = 7.1 Hz, 1 H), 3.08 (dd, *J* = 6.9, 1.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.4, 141.5, 136.1, 135.7, 135.1, 128.9, 127.9, 127.1, 123.8, 86.4, 60.7, 40.4.

HRMS-DART: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}IO_2$: 389.00385; found: 389.00434.

(3a*R*,8a*R*)-3a-Hydroxy-8a-phenyl-3a,8a-dihydrocyclopenta[*a*]inden-8(1*H*)-one (16)

Following general procedure 2, compound **15** (81.5 mg, 0.21 mmol) was converted into **16** (38.4 mg, 60%, 14% ee) as a colorless oil. HPLC conditions: DAICEL Chiralpak AD-H, hexane/2-propanol = 9:1, flow = 1 mL/min, λ_{max} = 254 nm, t_1 = 8.1 min, t_2 = 12.0 min.

$[\alpha]_D^{25}$ = –9.2 (*c* 1.71, $CHCl_3$, 14% ee).

IR (neat): 3423, 1709, 1603 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.8 Hz, 1 H), 7.78 (d, *J* = 7.2 Hz, 1 H), 7.72 (t, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.25–7.22 (m, 3 H), 5.97–5.93 (m, 2 H), 3.28–3.21 (m, 2 H), 1.85 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 205.8, 156.1, 137.9, 135.8, 135.4, 135.2, 132.6, 129.2, 128.6, 128.1, 127.3, 124.3, 124.2, 91.2, 68.5, 41.8.

HRMS-DART: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{15}O_2$: 263.10720; found: 263.10561.

(*S*)-3a-Methyl-3,3a,6,7-tetrahydro-2*H*-indene-2,4(5*H*)-dione (17)

To a solution of chiral **4a** (20 mg, 0.12 mmol) and 4 Å MS (105 mg) in CH_2Cl_2 (1.0 mL) was added PDC (135.4 mg, 0.36 mmol) at 0 °C. After being stirred at rt for 5.5 h, the mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated to give a residue that was purified by preparative TLC (hexane/EtOAc = 1:1) to afford **17** (11.3 mg, 57%) as a colorless oil.

$[\alpha]_D^{28}$ = –18 (*c* 0.58, $CHCl_3$, 40% ee) {(*R*)-**17**[17]: Lit. $[\alpha]_D^{20}$ = +47.3 (*c* 0.42, $CHCl_3$)}.

IR (neat): 1712, 1622 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (d, *J* = 1.6 Hz, 1 H), 2.21 (d, *J* = 19.0 Hz, 1 H), 2.90–2.69 (m, 3 H), 2.49–2.43 (m, 1 H), 2.32–2.24 (m, 1 H), 2.14 (d, *J* = 19.0 Hz, 1 H), 1.80–1.67 (m, 1 H), 1.54 (s, 3 H).

MS (DART): *m*/*z* = 165 $[M + H]^+$.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706421.

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