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Asymmetric total synthesis of enantiopure (−)-methyl jasmonate via catalytic asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfone

Hiroyuki Takeda, Hideaki Watanabe and Masahisa Nakada*

Department of Chemistry, Faculty of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

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Abstract—A new asymmetric total synthesis of enantiopure (–)-methyl jasmonate is described. This synthesis was accomplished starting from the new enantiopure building block prepared via the catalytic asymmetric intramolecular cyclopropanation (IMCP) of the α-diazo-β-keto 1-naphthyl sulfone, which was devised to give good selectivity both in the IMCP reaction and in the C-alkynylation of the intermediate required for the total synthesis of enantiopure (–)-methyl jasmonate.

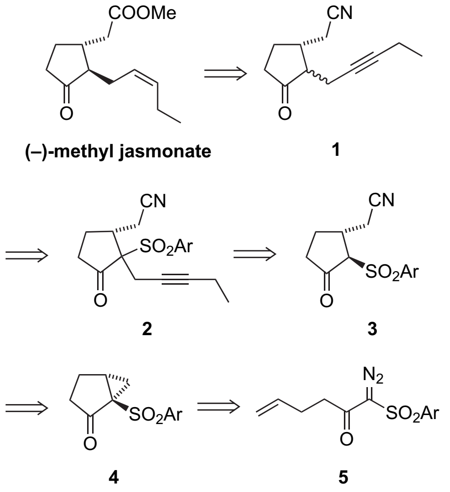
1. Introduction

(–)-Methyl jasmonate[1] is a key natural product occurring in *Jasminium grandiflorum* L. and in the blossoms of many flowers, and is used widely in the formulation of many perfumes. Although its structure is not complicated, key biological roles for (–)-methyl jasmonate have been noted[2] including roles in gene expression,[3] odor production,[4] and growth inhibition.[5] (–)-Methyl jasmonate possesses two stereogenic centers on a cyclopentanone ring substituted by a *cis*-2-pentenyl group and a methoxycarbonylmethyl group at its α- and β-positions of the carbonyl group, respectively. Its biological activities and structural features have motivated numerous attempts for total synthesis.[6] The asymmetric synthesis of enantiopure (–)-methyl jasmonate via enantioselective reaction has been limited[6] because an enantiopure cyclopentanone derivative suitable for the starting material is not commercially available, indicating one of the synthetic problems in the asymmetric total synthesis of this compound.

We report herein an asymmetric total synthesis of enantiopure (–)-methyl jasmonate starting from a new enantiopure chiral building block prepared via the originally developed catalytic asymmetric intramolecular cyclopropanation (IMCP) reaction of the α-diazo-β-keto sulfone.

2. Results and discussion

As outlined in Scheme 1, we expected that hydrogenation of the alkyne **1** with Lindlar's catalyst, following hydrolysis of the nitrile, and methylation of the resulting carboxylic acid would afford (–)-methyl jasmonate. The alkyne **1** could be produced as a mixture of diastereomers at the stereogenic center adjacent to the carbonyl group because it would be converged to the thermodynamically more stable *trans*-2,3-disubstituted isomer during the hydrolysis of the nitrile group under basic conditions. Alkyne **1** was difficult to obtain by direct alkynylation of the corresponding cyclopentanone derivative because the alkynylation would proceed at



Scheme 1. Retrosynthetic analysis of (−)-methyl jasmonate.

Keywords: Catalytic asymmetric synthesis; Chiral building blocks; Intramolecular cyclopropanation; Total synthesis.

* Corresponding author. Tel./fax: +813 5286 3240; e-mail: mnakada@waseda.jp

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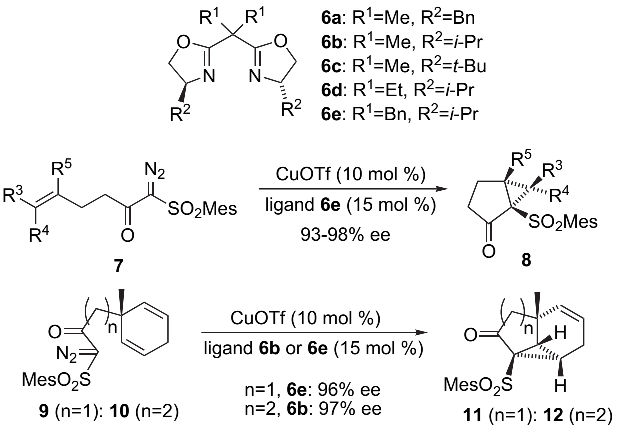
the less hindered α-position of the carbonyl group. Rather alkynylation of β-keto sulfone **3** was expected to produce **2** regioselectively because the aryl sulfonyl group stabilizes the anion generated at its α-position. Although O-alkynylation of **3** was also expected to occur as a side reaction, the *O*-alkynylated product would be hydrolyzed to regenerate **3** under acidic conditions. Since the bicyclo[3.1.0]hexan-2-one derivative **4** reacts with soft nucleophiles (such as sodium thiophenoxide)[7,8] to open the cyclopropane ring, and reaction of a cyanide ion with the cyclopropane derivative possessing an ester group in place of the sulfonyl group in **4** has been reported,[6bb] reaction of a cyanide ion with **4** was expected to afford β-keto sulfone **3**. Consequently, the bicyclo[3.1.0]hexan-2-one derivative **4** was envisioned to be a key intermediate for the asymmetric total synthesis of (−)-methyl jasmonate.

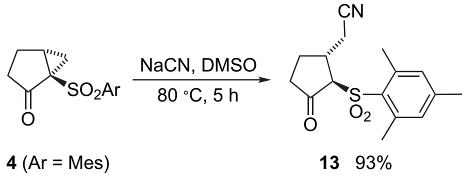
The asymmetric synthesis of natural products starting from the bicyclo[3.1.0]hexan-2-one derivatives prepared by the IMCP reaction of α-diazo-β-keto ester has been reported,[7,9] however, the reported preparation has been limited to the diastereoselective cyclopropanation reaction by use of a chiral auxiliary.[9]

We have studied the asymmetric catalysis of the IMCP reaction of α-diazo-β-keto ester, but found it to be difficult.[10a] Hence, we have developed the catalytic asymmetric IMCP reactions of α-diazo-β-keto sulfones **7**, **9**, and **10** (Scheme 2) by use of ligand **6** to afford the corresponding cyclopropanes **8**, **11**, and **12** with 93–98% ee, respectively.[10] Since cyclopropanes thus prepared from α-diazo-β-keto sulfones are highly crystalline and easily purified by recrystallization as enantiomerically pure compounds, this catalytic asymmetric IMCP reaction is useful for preparing new enantiopure chiral building blocks toward natural products' syntheses. Our recent reports regarding the asymmetric total synthesis of enantiopure (−)-malyngolide[8a] and the first asymmetric total synthesis of (−)-allocyathin B_2[8b] via the catalytic asymmetric IMCP reaction prove its wide applicability.



Scheme 2. Asymmetric catalysis of α-diazo-β-keto sulfones **7**, **9**, and **10**.

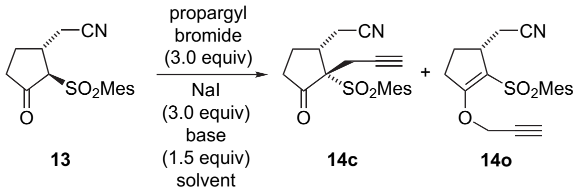
Initial synthetic studies on (−)-methyl jasmonate began with the previously reported enantiopure cyclopropane **4** (Ar=Mes) (Scheme 3).[10] Reaction of cyclopropane **4** (Ar=Mes) with sodium cyanide in DMSO at 80 °C smoothly produced β-keto sulfone **13**[11] in 93% yield. Since the alkylation reaction of β-keto phenyl sulfone was known to afford the *C*-alkylated product exclusively,[12] propargylation of **13** was studied as the model reaction for the conversion of **3** to **2** (Scheme 1) toward the total synthesis of (−)-methyl jasmonate.



Scheme 3. Reaction of **4** (Ar=Mes) with sodium cyanide.

The propargylation of **13** afforded the *O*-propargylated product, designated as **14o**, as the major product under various conditions (Table 1), while the best yield of the *C*-propargylated product, **14c**, was 27% (entry 2). We examined alkylation of **13** with less bulky methyl iodide (Table 2), too; however, all the reactions under several conditions afforded the *O*-methylated product **15o** as the major product.

Table 1. Propargylation of **13**



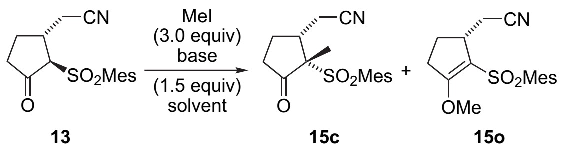
Entry	Base	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	
					14c[b]	**14o**
1	K_2CO_3	Acetone	Reflux	8	10	81
2	K_2CO_3	DMF	rt	2	27	63
3	K_2CO_3	DMSO	rt	2	23	68
4	K_2CO_3	CH_3CN	rt	4	16	82
5	NaH	THF	0→rt	36	7	92
6	TBAF	THF	Reflux	12	16	80
7	Cs_2CO_3	DMF	rt	2	22	70

The relative stereochemistry was determined by NOESY.

[a] Isolated yields.

[b] A single isomer.

Table 2. Methylation of **13**



Entry	Base	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	
					15c[b]	**15o**
1	K_2CO_3	Acetone	Reflux	5	5	92
2	K_2CO_3	CH_3CN	Reflux	12	27	71
3	K_2CO_3	DMF	rt	5	38	60
4	NaH	DMF	rt	3	15	78
5	TBAF	DMF	rt	3	12	81

The relative stereochemistry was determined by NOESY.

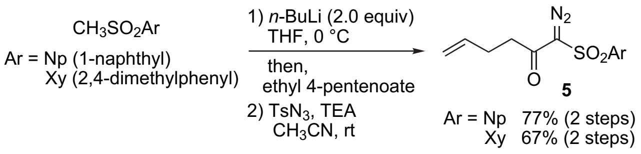
[a] Isolated yields.

[b] A single isomer.

The preferred formation of the *O*-alkylated products in the reaction of **13** could be attributed to the bulky mesityl group. The β-keto sulfone possessing a less bulky phenyl group in place of the mesityl group was expected to increase the ratio of *C*-alkylated product, however, the cyclopropane **4** (Ar=Ph) was generated with a relatively low ee (75% ee[10a]), not useful for the asymmetric synthesis of natural products. Consequently, we decided to find other α-diazo-β-keto sulfones, which afforded the products with high ee by the catalytic asymmetric IMCP reaction.

The enantioselectivity in the catalytic asymmetric IMCP reaction of **7** ($R^3{=}R^4{=}R^5{=}H$) was higher than that of the corresponding phenyl sulfone.[10a] This result suggested that the *ortho* methyl groups of 2,4,6-trimethylphenyl sulfone in **7** played a crucial role for the high enantioselectivity. Consequently, we examined the catalytic asymmetric IMCP reactions of α-diazo-β-keto sulfones **5** (Ar=Np, Xy) because a 1-naphthyl group and a 2,4-dimethylphenyl group are smaller than the mesityl group but retain sufficient bulkiness to give good selectivity both in the IMCP reaction and in the C-alkylation of the intermediates corresponding to **13**. In addition, commercial availability of the starting materials for the preparation of methyl 1-naphthyl sulfone[13] and 2,4-dimethylphenyl methyl sulfone[14] was also the point in employing these aryl groups.

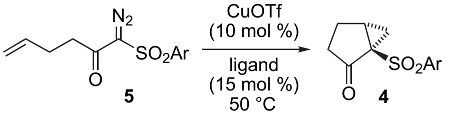
α-Diazo-β-keto sulfones **5** (Ar=Np, Xy) were successfully prepared according to the previously reported procedure for **7**[10a] (Scheme 4). Dianions of either methyl 1-naphthyl sulfone or 2,4-dimethylphenyl methyl sulfone were reacted with ethyl 4-pentenoate to produce the corresponding β-keto sulfones, which were converted to α-diazo-β-keto sulfones **5** (Ar=Np, Xy), respectively.[15]



Scheme 4. Preparation of **5**.

The relationships between the ligand and the enantioselectivity in the IMCP reaction of **5** (Ar=Np) differed from those of **7**, which were reported previously.[10a] As indicated in Table 3, ligand **6e**, which had endowed the highest ee in the IMCP reaction of **7** (Scheme 2), was not so effective in the IMCP reaction of **5** (Ar=Np), affording **4** with 79% ee (entry 5). The best result (83% ee) was obtained with ligand **6d** in the case of **5** (Ar=Np). On the other hand, the IMCP reaction of **5** (Ar=Xy) showed the same trend in the relationships between the ligand and the enantioselectivity as that of **7** because ligand **6e** gave the best result (81% ee).

Table 3. Enantioselective IMCP reaction of α-diazo-β-keto sulfone **5**



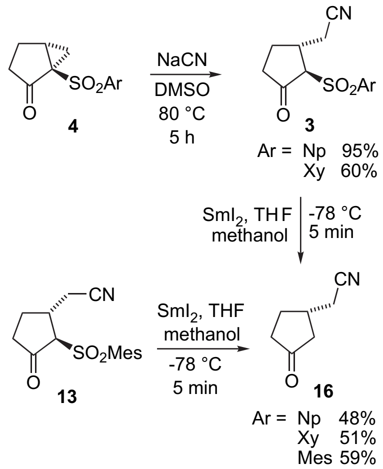
Entry	Ligand	Ar[a]	Time (h)	Yield (%)[b]	ee (%)[c]
1	**6a**	Np	4	91	71 (1*R*)
2	**6b**	Np	3	95	72 (1*R*)
3	**6c**	Np	14	59	45 (1*R*)
4	**6d**	Np	5	93	*83* (1*R*)
5	**6e**	Np	2	82	79 (1*R*)
6	**6a**	Xy	4	75	72 (1*R*)
7	**6b**	Xy	2	83	62 (1*R*)
8	**6c**	Xy	12	89	37 (1*R*)
9	**6d**	Xy	5	99	74 (1*R*)
10	**6e**	Xy	5	97	*81* (1*R*)

[a] Np=1-naphthyl; Xy=2,4-dimethylphenyl.

[b] Isolated yields.

[c] Enantiomeric excess (ee) determined by HPLC. For HPLC conditions, see Section 4.

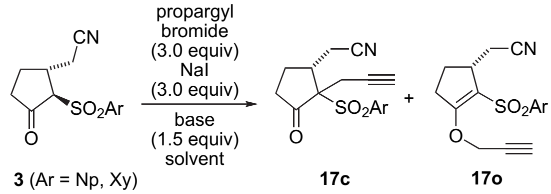
Since **4** (Ar=Np, Xy) and their crystalline derivatives were unsuitable for X-ray crystallographic analysis, we converted **4** (Ar=Np, Xy) to **16** to determine their absolute configuration by comparing their sign of the specific rotations with that of **16**, which was derived from the known **4** (Ar=Mes)[10a] via **13** (Scheme 5). As shown in Scheme 5, reactions of **4** (Ar=Np, Xy) with sodium cyanide in DMSO at 80 °C for 5 h opened the cyclopropane ring to generate **3** (Ar=Np, Xy)[11] in 95% and 60% yields, respectively. Desulfonylation of **3** (Ar=Np, Xy) and **13** with SmI_2 in the presence of methanol successfully afforded **16** in 48%, 51%, and 59% yields, respectively. Their specific rotations had a minus sign, elucidating that **4** possesses 1*R* configuration because the absolute configuration of **13**, which was derived from **4** (Ar=Mes),[10a] is known. These results indicate that enantioselectivity of the IMCP reaction of **5** (Ar=Np, Xy) with ligand **6e** is well explained by our previously reported model,[10a] which had been proposed to explain the enantioselectivity of the IMCP reaction of **7** ($R^3{=}R^4{=}R^5{=}H$).



Scheme 5. Conversion of **4** to **16** and **13** to **16**.

Since the catalytic asymmetric IMCP reactions of α-diazo-β-keto sulfone **5** (Ar=Np, Xy) afforded the products with high ee, which were isolated in enantiopure form by recrystallization, we next examined the propargylation of **3** (Ar=Np, Xy). Among various solvents examined, polar aprotic solvents were effective for the C-propargylation in both substrates **3** (Ar=Np, Xy) (Table 4). DMF and DMSO gave comparable yields in the reactions of both substrates **3** (Ar=Np, Xy) (entries 2 and 3, 9 and 10), but the ratio of **17c/17o** was slightly higher when the solvent was DMF. In DMF, the use of potassium carbonate as the base

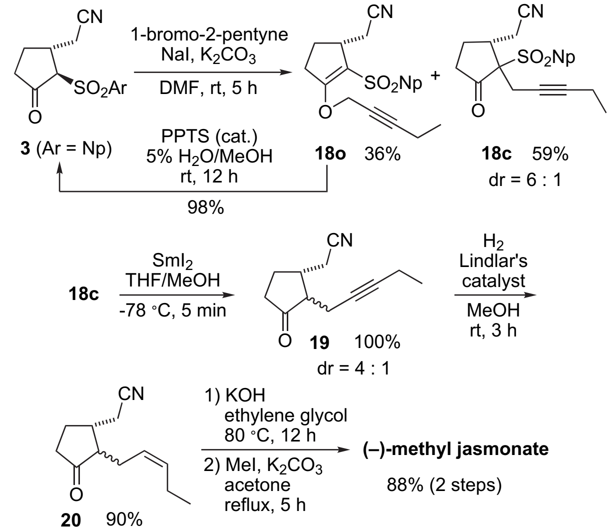
Table 4. Propargylation of **3** (Ar=Np, Xy)



Entry	Ar	Base	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	
						17c[b]	**17o**
1	Np	K_2CO_3	Acetone	Reflux	10	15	80
2	Np	K_2CO_3	DMF	rt	2	*75*	21
3	Np	K_2CO_3	DMSO	rt	2	72	26
4	Np	K_2CO_3	CH_3CN	rt	3	58	41
5	Np	NaH	THF	0→rt	12	11	81
6	Np	TBAF	THF	Reflux	10	55	40
7	Np	Cs_2CO_3	DMF	rt	2.5	72	24
8	Xy	K_2CO_3	Acetone	Reflux	5	21	72
9	Xy	K_2CO_3	DMF	rt	2	44	52
10	Xy	K_2CO_3	DMSO	rt	2	41	58
11	Xy	K_2CO_3	CH_3CN	rt	3	31	67
12	Xy	NaH	THF	0→rt	24	15	81
13	Xy	TBAF	THF	Reflux	6	27	64
14	Xy	Cs_2CO_3	DMF	rt	2	40	54

[a] Isolated yields.

[b] A mixture of diastereomers; dr=11/1 for entries 1–7; dr=7/1 for entries 8–14.[16]



Scheme 6. Total synthesis of (–)-methyl jasmonate.

gave a higher ratio of **17c/17o** than did cesium carbonate (entries 2 and 7, 9 and 14). A crucial factor in the ratio of **17c/17o** was attributed to the nature of the aryl sulfonyl group. Thus, Table 4 clearly shows that the ratio of **17c/17o** in the reaction is improved if the naphthyl substituent of **5** is used rather than the 2,4-dimethylphenyl substituent. Consequently, although both versions of **5** (Ar=Np, Xy) showed comparable enantioselectivities in the IMCP reaction, **3** (Ar=Np) was adopted for the synthesis of (–)-methyl jasmonate.

The reaction of **3** (Ar=Np) with 1-bromo-2-pentyne under the same conditions as those employed in entry 2 of Table 4 afforded *C*-alkylated product **18c** as a mixture of diastereomers (6/1)[16] in 59% yield and *O*-alkylated product **18o** in 36% yield (Scheme 6). The *C*- and *O*-alkylated products were separated by flash chromatography, and **18o** was successfully hydrolyzed under acidic conditions to regenerate **3** (Ar=Np) in 98% yield.

Desulfonylation of **18c** was successfully carried out by SmI_2 in 100% yield, but affording **19** as a mixture of diastereomers (dr=4/1).[16] This mixture was used for the next step without separation because the hydrolysis of nitrile **20** was anticipated to proceed with epimerization at its C-2 position. Hydrogenation of **19** with Lindlar's catalyst gave *cis*-alkene **20** in 90% yield, and successive treatment of **20** with KOH in ethylene glycol produced the corresponding carboxylic acid with concomitant epimerization at its C-2 position to afford the carboxylic acid expectedly as the single product. Finally, methylation of the obtained carboxylic acid with methyl iodide furnished methyl jasmonate (88%, two steps). Synthetic methyl jasmonate proved to be identical in all respects to the reported spectral data (^{1}H NMR, IR, MS, and ^{13}C NMR; >99% de[16])[1a] of methyl jasmonate. The specific rotation of the synthetic methyl jasmonate ($[\alpha]_D^{23}$) showed −90.2 (*c* 1.03, MeOH) (lit.[1a] $[\alpha]_D^{23}$ −90.3 (*c* 1.03, MeOH)), revealing that (–)-methyl jasmonate has been synthesized.

3. Conclusion

In summary, we found that catalytic asymmetric IMCP reactions of the 1-naphthyl sulfone **5** (Ar=Np) and 2,4-dimethylphenyl sulfone **5** (Ar=Xy) produced new cyclopropanes **4** (Ar=Np, Xy) in 83% and 81% ee, respectively, and **4** (Ar=Np) was successfully purified by recrystallization in optically pure form. Reaction of **4** (Ar=Np) with sodium cyanide gave **3** (Ar=Np), which was alkylated with 1-bromo-2-pentyne to produce *C*-alkylated product **18c** as the major product. *O*-Alkylated product **18o** was hydrolyzed under acidic conditions to regenerate **3** (Ar=Np), and *C*-alkylated product **18c** was successfully converted to enantiopure (–)-methyl jasmonate. Optically pure new chiral building blocks **4** (Ar=Np, Xy) developed in this study would be useful for the asymmetric total synthesis of enantiopure natural products, especially those containing a 2,3-disubstituted cyclopentanone ring in their molecules.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-400 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Melting points (mp) are uncorrected, recorded on a Yamato capillary melting point apparatus equipped with a digital thermometer. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP-1000. Chiral HPLC analysis was performed on JASCO PU-980 and UV-970. Mass spectrometric analyses and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). THF was distilled from sodium/benzophenone ketyl, and methylene chloride (CH_2Cl_2), benzene were distilled from calcium hydride. Toluene was distilled from sodium. Acetonitrile was distilled from CaH_2 under reduced pressure. $(CuOTf)_2C_6H_6$ and all other reagents were purchased from Aldrich, TCI, or Kanto Chemical Co. Ltd.

4.1.1. (1*R*,2*R*)-[3-Oxo-2-(2,4,6-trimethylphenylsulfonyl)-cyclopentyl]acetonitrile (13). To a solution of **4** (Ar=Mes)[10a] (1.00 g, 3.59 mmol) in DMSO (30 mL) was added sodium cyanide (194.0 mg, 3.95 mmol) and the reaction mixture was stirred at 80 °C for 5 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (30 mL×2). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **13** (1.02 g, 93%) as a white solid.

Mp=117–118 °C (CH_2Cl_2/hexane); $[\alpha]_D^{24}$ −78.2 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}: 2247, 1654, 1449, 1143, 932, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.01 (s, 2H), 3.73 (d, *J*=9.8 Hz, 1H), 3.34–3.24 (m, 1H), 3.08 (dd, *J*=5.9, 17.1 Hz, 1H), 2.84 (dd, *J*=3.9, 17.1 Hz, 1H), 2.60 (s, 6H), 2.56–2.36 (m, 3H), 2.33 (s, 3H), 1.82 (dddd, *J*=1.7, 7.8, 9.3, 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.4, 144.3, 140.5, 132.4, 131.7, 116.9, 71.3, 38.9, 33.8, 25.9, 22.9, 22.5, 21.2; HRMS (FAB): *m/z* calcd for $C_{16}H_{19}NO_3S$+H 306.1164, found 306.1169. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; S, 10.50. Found: C, 62.89; H, 6.24; N, 4.61; S, 10.53.

4.1.2. (1*R*,2*S*)-[3-Oxo-2-(2-propynyl)-2-(2,4,6-trimethylphenylsulfonyl)cyclopentyl]acetonitrile (14c) and (*R*)-[3-(2-propynyloxy)-2-(2,4,6-trimethylphenylsulfonyl)-2-cyclopentenyl]acetonitrile (14o). To a solution of **13** (41.5 mg, 0.137 mmol) in DMF (2 mL) were added potassium carbonate (28.4 mg, 0.205 mmol), sodium iodide (61.6 mg, 0.411 mmol), and propargyl bromide (0.031 mL, 0.411 mmol) successively, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **14c** (12.7 mg, 27%, a single isomer) and **14o** (29.6 mg, 63%) as white solids.

Compound **14c**: mp=112–113 °C (CH_2Cl_2/hexane); $[\alpha]_D^{25}$ +67.4 (*c* 1.25, $CHCl_3$); IR (KBr) ν_{max}: 2260, 2132, 1666, 854, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.02 (s, 2H), 3.75–3.58 (m, 1H), 3.06 (dd, *J*=4.3, 16.8 Hz, 1H), 2.97 (dd, *J*=11.5, 16.8 Hz, 1H), 2.87 (dd, *J*=2.7, 16.0 Hz, 1H), 2.80–2.25 (m, 13H, including δ=2.33, s, 3H), 2.06 (dd, *J*=2.7, 2.7 Hz, 1H), 2.01–1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.8, 144.9, 133.1, 127.2, 117.5, 76.7, 75.9, 73.4, 39.0, 36.7, 26.0, 23.9, 21.1, 19.2, 18.7; HRMS (FAB): *m/z* calcd for $C_{19}H_{21}NO_3S$+H 344.1320, found 344.1389.

Compound **14o**: mp=94–96 °C (CH_2Cl_2/hexane); $[\alpha]_D^{24}$ −42.8 (*c* 1.40, $CHCl_3$); IR (KBr) ν_{max}: 2252, 854, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.91 (s, 2H), 4.42 (dd, *J*=2.4, 16.3 Hz, 1H), 4.37 (dd, *J*=2.4, 16.3 Hz, 1H), 3.50–3.32 (m, 1H), 3.00–2.85 (m, 2H), 2.75–2.57 (m, 8H, including δ=2.62, s, 6H), 2.47 (dd, *J*=2.4, 2.4 Hz, 1H), 2.38–2.25 (m, 4H, including δ=2.30, s, 3H), 1.94 (dddd, *J*=3.2, 7.8, 9.0, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.9, 142.6, 140.1, 135.1, 131.7, 118.3, 117.5, 76.6, 57.9, 39.9, 28.9, 25.7, 23.4, 22.5, 20.9; HRMS (FAB): *m/z* calcd for $C_{19}H_{21}NO_3S$+H 344.1320, found 344.1307.

4.1.3. (1*R*,2*S*)-[2-Methyl-3-oxo-2-(2,4,6-trimethylphenylsulfonyl)cyclopentyl]acetonitrile (15c) and (*R*)-[3-methoxy-2-(2,4,6-trimethylphenylsulfonyl)-2-cyclopentenyl]-acetonitrile (15o). To a solution of **13** (1.00 g, 3.27 mmol) in DMF (30 mL) were added potassium carbonate (452.0 mg, 4.91 mmol) and methyl iodide (0.61 mL, 9.81 mmol) successively, and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with ether (30 mL×2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **15c** (397 mg, 38%, a single isomer) and **15o** (626 mg, 60%) as white solids.

Compound **15c**: mp=108–109 °C (CH_2Cl_2/hexane); $[\alpha]_D^{26}$ −60.6 (*c* 1.01, $CHCl_3$); IR (KBr) ν_{max}: 2240, 1657, 1452, 1126, 857, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.94 (s, 2H), 3.65–3.40 (m, 1H), 2.88 (dd, *J*=4.6, 16.8 Hz, 1H), 2.70–2.05 (m, 9H, including δ=2.53, s, 3H; δ=2.51, s, 3H), 2.26 (s, 3H), 1.75–1.45 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=208.3, 144.4, 132.9, 128.1, 117.7, 75.0, 38.5, 36.5, 24.7, 23.9, 21.0, 19.7, 13.5; HRMS (FAB): *m/z* calcd for $C_{17}H_{21}NO_3S$+H 320.1320, found 320.1343.

Compound **15o**: mp=139–140 °C (CH_2Cl_2/hexane); $[\alpha]_D^{26}$ −34.5 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}: 2241, 1445, 1136, 877, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.91 (s, 2H), 3.63 (s, 3H), 3.42–3.32 (m, 1H), 2.89 (dd, *J*=3.7, 16.8 Hz, 2H), 2.75–2.50 (m, 8H, including δ=2.60, s, 6H), 2.45–2.20 (m, 4H, including δ=2.30, s, 3H), 2.00–1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.6, 142.5, 140.0, 135.4, 131.7, 118.5, 114.7, 57.9, 40.2, 28.8, 25.6, 23.5, 22.4, 20.9; HRMS (FAB): *m/z* calcd for $C_{17}H_{21}NO_3S$+H 320.1320, found 320.1335.

4.1.4. 1-(1-Naphthalenesulfonyl)-5-hexen-2-one. To a solution of methyl 1-naphthyl sulfone (347.0 mg, 1.68 mmol) in THF (10 mL) was added *n*-butyllithium in hexane (2.12 mL, 3.36 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 15 min. Then to the reaction mixture was added ethyl 4-pentenoate (227 mg, 1.77 mmol) at 0 °C, and the stirring was continued for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford 1-(1-naphthalenesulfonyl)-5-hexen-2-one (461 mg, 95%) as a white solid.

Mp=37.5–37.6 °C (CH_2Cl_2/hexane); IR (KBr) ν_{max}: 1660, 1507, 1316, 1157, 1127, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.62 (d, *J*=8.7 Hz, 1H), 8.20 (d, *J*=7.3 Hz, 1H), 8.10 (d, *J*=8.3 Hz, 1H), 7.93 (d, *J*=8.3 Hz, 1H), 7.66 (dd, *J*=8.7, 8.3 Hz, 1H), 7.58 (dd, *J*=7.3, 8.3 Hz, 1H), 7.54 (dd, *J*=8.3, 8.3 Hz, 1H), 5.67 (ddt, *J*=10.4, 17.0, 6.6 Hz, 1H), 4.94 (dd, *J*=1.5, 17.0 Hz, 1H), 4.91 (dd, *J*=1.5, 10.4 Hz, 1H), 4.26 (s, 2H), 2.75 (t, *J*=7.1 Hz, 2H), 2.32 (dt, *J*=6.6, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.9, 136.0, 135.8, 134.1, 133.7, 131.0, 129.4, 129.0, 128.5, 127.1, 124.3, 123.5, 115.7, 66.4, 43.7, 27.2; HRMS (FAB): *m/z* calcd for $C_{16}H_{16}O_3S$+H 289.0898, found 289.0901. Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; S, 11.12. Found: C, 66.71; H, 5.65; S, 11.36.

4.1.5. 1-Diazo-1-(1-naphthalenesulfonyl)-5-hexen-2-one (5 (Ar=Np)). To a solution of 1-(1-naphthalenesulfonyl)-5-hexen-2-one (417.0 mg, 1.44 mmol) in CH_3CN (10 mL) was added triethylamine (0.482 mL, 3.47 mmol) at 0 °C, and then a solution of *p*-toluenesulfonyl azide (456.0 mg, 2.31 mmol) in CH_3CN (1.5 mL×2) via a canula. The reaction mixture was stirred at room temperature for 6 h. The light yellow reaction mixture was concentrated under reduced pressure and diluted with ether (100 mL). To the ether solution was added 1 M KOH aqueous solution (10 mL), and the separated aqueous solution was extracted with ether (10 mL×2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=15/1) to afford **5** (Ar=Np) (366.0 mg, 81%) as a yellow-green solid.

Mp=84–86 °C; IR (KBr) ν_{max}: 1666, 1334, 1127, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.36 (d, *J*=7.6 Hz, 1H), 8.35 (d, *J*=7.6 Hz, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=7.6, 8.1 Hz, 1H), 7.59 (dd, *J*=7.6, 8.1 Hz, 1H), 7.57 (dd, *J*=8.1, 8.3 Hz, 1H), 5.47 (ddt, *J*=11.2, 15.6, 6.6 Hz, 1H), 4.78 (dd, *J*=1.3, 11.2 Hz, 1H), 4.76 (dd, *J*=1.3, 15.6 Hz, 1H), 2.48 (t, *J*=7.3 Hz, 2H), 2.11 (dt, *J*=6.6, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=187.6, 136.2, 135.8, 135.7, 134.3, 131.3, 129.1, 127.6, 127.2, 124.1, 123.2, 115.6, 38.1, 27.4; HRMS (FAB): *m/z* calcd for $C_{16}H_{14}N_2O_3S$+H 315.0803, found 315.0808.

4.1.6. 1-(2,4-Dimethylphenylsulfonyl)-5-hexen-2-one. To a solution of 2,4-dimethylphenyl methyl sulfone (3.05 g, 16.6 mmol) in THF (160 mL) was added *n*-butyllithium (21.5 mL, 33.1 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. After cooling the reaction mixture to 0 °C again, ethyl 4-pentenoate (2.34 g, 18.2 mmol) was added to the reaction mixture at the same temperature. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (60 mL) and extracted with ether (10 mL×2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford 1-(2,4-dimethylphenylsulfonyl)-5-hexen-2-one (3.56 g, 80%) as a white solid.

Mp=33–34 °C (CH_2Cl_2/hexane); IR (KBr) ν_{max}: 1684, 1462, 884, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.79 (d, *J*=8.5 Hz, 1H), 7.15 (d, *J*=8.5 Hz, 1H), 7.14 (s, 1H), 5.74 (ddt, *J*=10.5, 17.1, 6.6 Hz, 1H), 5.02 (dd, *J*=1.5, 17.1 Hz, 1H), 4.97 (dd, *J*=1.5, 10.5 Hz, 1H), 4.16 (s, 2H), 2.80 (t, *J*=7.1 Hz, 2H), 2.63 (s, 3H), 2.37 (s, 3H), 2.28 (dt, *J*=6.6, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.2, 145.0, 137.7, 136.0, 133.8, 133.4, 130.1, 127.1, 115.5, 66.2, 43.3, 27.0, 21.3, 20.2; HRMS (FAB): *m/z* calcd for $C_{14}H_{18}O_3S$+H 267.1055, found 267.1057.

4.1.7. 1-Diazo-1-(2,4-dimethylphenylsulfonyl)-5-hexen-2-one (5 (Ar=Xy)). To a solution of 1-(2,4-dimethylphenylsulfonyl)-5-hexen-2-one (3.56 g, 13.4 mmol) in CH_3CN (150 mL) was added triethylamine (4.47 mL, 32.1 mmol) at 0 °C, and then a solution of *p*-toluenesulfonyl azide (3.16 g, 16.0 mmol) in CH_3CN (15 mL×2) was added via a canula. The reaction mixture was stirred at room temperature for 8 h. The light yellow reaction mixture was concentrated under reduced pressure and diluted with ether (300 mL). To the ether solution was added 1 M KOH aqueous solution (50 mL), and the separated aqueous layer was extracted with ether (20 mL×2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=15/1) to afford **5** (Ar=Xy) (3.27 g, 84%) as a yellow-green solid.

Mp=78–79 °C; IR (KBr) ν_{max}: 2139, 1653, 1330, 923, 831, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.00 (d, *J*=8.5 Hz, 1H), 7.21 (d, *J*=8.5 Hz, 1H), 7.18 (s, 1H), 5.67 (ddt, *J*=10.0, 17.2, 6.9 Hz, 1H), 4.94 (dd, *J*=1.5, 17.2 Hz, 1H), 4.89 (dd, *J*=1.5, 10.0 Hz, 1H), 2.56 (s, 3H), 2.55 (t, *J*=7.9 Hz, 2H), 2.41 (s, 3H), 2.24 (dt, *J*=6.9, 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.1, 145.3, 137.2, 136.6, 136.0, 133.7, 130.3, 127.3, 115.6, 38.0, 27.4, 21.3, 19.9; HRMS (FAB): *m/z* calcd for $C_{14}H_{16}N_2O_3S$+H 293.0960, found 293.0986.

4.1.8. (1*R*,5*R*)-1-(1-Naphthalenesulfonyl)bicyclo[3.1.0]-hexan-2-one (4 (Ar=Np)). A toluene azeotroped $(CuOTf)_2\cdot C_6H_6$ (50.0 mg, 0.110 mmol, 10 mol % as CuOTf (90% purity)) was placed in a dried flask (100 mL) under Ar atmosphere. To this flask was added a solution of toluene azeotroped ligand **6d** (98.0 mg, 0.331 mmol, 15 mol %) in toluene (5 mL×3) via a canula. The mixture was stirred at room temperature for 0.5 h and then to the light blue solution was added a solution of toluene azeotroped **5** (Ar=Np) (624.0 mg, 1.99 mmol) in toluene (5 mL×3) via a canula. The reaction mixture was stirred at 50 °C for 5 h, quenched with aqueous NH_4OH solution (10 mL), and the separated aqueous layer was extracted with ether (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (5 mL×2). The combined organic layer was washed with brine

(10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford **4** (Ar=Np) (528.0 mg, 93%, 83% ee) as a white solid.

Enantiomeric excess (ee) was determined by HPLC (254 nm); DAICEL CHIRALCEL OD-H (0.46 cm $\phi\times$ 25 cm; hexane/2-propanol=4/1; flow rate=5 mL min^{-1}); retention time: 42 min for **4** (Ar=Np), 38 min for ***ent*-4** (Ar=Np).

Mp=111–112 °C (CH_2Cl_2/hexane); $[\alpha]_D^{23}$ −60.3 (*c* 1.00, $CHCl_3$, >99% ee); IR (KBr) ν_{max}: 1737, 1302, 1124, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.75 (d, *J*=8.8 Hz, 1H), 8.51 (d, *J*=7.5 Hz, 1H), 8.12 (d, *J*=8.1 Hz, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.67–7.55 (m, 3H), 3.15–3.10 (m, 1H), 2.47 (dd, *J*=3.9, 17.1 Hz, 1H), 2.18–1.94 (m, 4H), 1.58 (dd, *J*=5.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.9, 135.2, 132.8, 129.6, 129.1, 128.1, 126.6, 126.4, 124.4, 124.3, 53.5, 33.5, 31.3, 20.2, 20.0; HRMS (FAB): *m/z* calcd for $C_{16}H_{14}O_3S$+H 287.0742, found 287.0773. Anal. Calcd for $C_{16}H_{14}NO_3S$: C, 67.11; H, 4.93; S, 11.20. Found: C, 66.13; H, 4.88; S, 11.87.

4.1.9. (1*R*,5*R*)-1-(2,4-Dimethylphenylsulfonyl)bicyclo[3.1.0]hexan-2-one (4 (Ar=Xy)).

A toluene azeotroped $(CuOTf)_2\cdot C_6H_6$ (6.0 mg, 0.0132 mmol, 10 mol % as CuOTf (90% purity)) was placed in a dried flask (20 mL) under Ar atmosphere and to this flask was added a solution of toluene azeotroped ligand **6e** (17.0 mg, 0.397 mmol, 15 mol %) in toluene (2 mL×2) via a canula. The mixture was stirred at 50 °C for 5 h and then to the blue-green solution was added a solution of toluene azeotroped **5** (Ar=Xy) (77.0 mg, 0.264 mmol) in toluene (2 mL×2) via a canula. The reaction mixture was stirred at 50 °C for 5 h, quenched with a mixture of saturated aqueous NH_4Cl solution (2 mL) and aqueous NH_4OH solution (10 mL), and the separated aqueous layer was extracted with ether (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (5 mL×2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=3/1) to afford (1*R*,5*R*)-1-(2,4-dimethylphenylsulfonyl)bicyclo[3.1.0]hexan-2-one **4** (Ar=Xy) (98.0 mg, 97%, 81% ee) as a white solid.

Enantiomeric excess (ee) was determined by HPLC (254 nm); DAICEL CHIRALPAK AS-H (0.46 cm $\phi\times$25 cm; hexane/2-propanol=4/1; flow rate=5 mL min^{-1}); retention time: 89 min for **4** (Ar=Xy), 86 min for ***ent*-4** (Ar=Xy).

Mp=98–99 °C (CH_2Cl_2/hexane); $[\alpha]_D^{27}$ −48.5 (*c* 1.00, $CHCl_3$, >99% ee); IR (KBr) ν_{max}: 1686, 1035, 967, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.88 (d, *J*=8.1 Hz, 1H), 7.09 (d, *J*=8.1 Hz, 1H), 7.03 (s, 1H), 2.96–2.90 (m, 1H), 2.58 (s, 3H), 2.34–2.23 (m, 4H, including δ=2.30, s, 3H), 2.21–2.09 (m, 3H), 2.02–1.90 (m, 1H), 1.52 (dd, *J*=5.5, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.4, 144.3, 138.1, 133.2, 131.5, 126.9, 53.5, 33.6, 30.7, 21.4, 20.8, 20.4, 20.2; HRMS (FAB): *m/z* calcd for $C_{14}H_{16}O_3S$+H 265.0898, found 265.0890.

4.1.10. (1*R*,2*R*)-[2-(1-Naphthalenesulfonyl)-3-oxocyclopentyl]acetonitrile (3 (Ar=Np)).

To a solution of **4** (Ar=Np) (1.36 g, 4.76 mmol) in DMSO (40 mL) was added sodium cyanide (257.0 mg, 5.24 mmol) and the reaction mixture was stirred at 80 °C for 5 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 mL), and extracted with ethyl acetate (40 mL×2). The combined organic layer was washed with brine (8 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **3** (Ar=Np) (1.41 g, 95%) as a white solid.

Mp=137–138 °C (CH_2Cl_2/hexane); $[\alpha]_D^{23}$ +20.0 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}: 1737, 1302, 1124, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.62 (d, *J*=8.6 Hz, 1H), 8.27 (d, *J*=7.3 Hz, 1H), 8.25 (d, *J*=7.3 Hz, 1H), 8.01 (d, *J*=8.3 Hz, 1H), 7.80–7.58 (m, 3H), 3.92 (d, *J*=9.8 Hz, 1H), 3.50–3.32 (m, 1H), 3.08 (dd, *J*=4.9, 17.1 Hz, 1H), 2.88 (dd, *J*=3.9, 17.1 Hz, 1H), 2.60–2.30 (m, 3H), 1.90–1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.4, 136.2, 134.2, 134.1, 132.4, 131.8, 129.3, 127.2, 124.3, 123.0, 116.7, 70.9, 38.6, 34.4, 25.7, 22.5, 21.9; HRMS (FAB): *m/z* calcd for $C_{17}H_{15}NO_3S$+H 314.0851, found 314.0857.

4.1.11. (1*R*,2*R*)-[2-(2,4-Dimethylphenylsulfonyl)-3-oxocyclopentyl]acetonitrile (3 (Ar=Xy)).

To a solution of **4** (Ar=Xy) (1.12 g, 4.24 mmol) in DMSO (40 mL) was added sodium cyanide (229.0 mg, 4.66 mmol) and the reaction mixture was stirred at 80 °C for 5 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with ethyl acetate (40 mL×2). The combined organic layer was washed with brine (6 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **3** (Ar=Xy) (740.0 mg, 60%) as a white solid.

Mp=89–90 °C (CH_2Cl_2/hexane); $[\alpha]_D^{23}$ −23.5 (*c* 1.14, $CHCl_3$); IR (KBr) ν_{max}: 1758, 1407, 827, 742, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.79 (d, *J*=8.1 Hz, 1H), 7.18 (d, *J*=8.1 Hz, 1H), 7.13 (s, 1H), 3.69 (d, *J*=9.8 Hz, 1H), 3.40–3.18 (m, 1H), 2.97 (dd, *J*=3.7, 17.1 Hz, 1H), 2.81 (dd, *J*=1.2, 17.1 Hz, 1H), 2.62 (s, 3H), 3.02–2.30 (m, 6H, including δ=2.41, s, 3H), 1.85–1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.9, 145.5, 138.2, 133.5, 132.7, 131.4, 127.2, 116.8, 70.8, 38.6, 34.1, 25.6, 22.2, 21.4, 20.3; HRMS (FAB): *m/z* calcd for $C_{15}H_{17}NO_3S$+H 292.1007, found 292.1009.

4.1.12. (*R*)-(3-Oxocyclopentyl)acetonitrile (16).

To a SmI_2 solution in THF, which was prepared from samarium (1.33 g, 8.87 mmol) and 1,2-diiodoethane (1.24 g, 4.43 mmol) in THF (10 mL), was added methanol (1 mL), and the solution was cooled to −78 °C. To this cooled solution was added a solution of **13** (536.0 mg, 1.77 mmol) in THF (3 mL) via a canula, and the reaction mixture was stirred at the same temperature for 5 min. The reaction was quenched by introducing air into the solution, and to the resultant solution was added saturated aqueous NH_4Cl solution (10 mL) and extracted with ether (4 mL×2). The combined organic layer was washed with brine (6 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **16** (135.0 mg, 59%) as a colorless oil.

$[\alpha]_D^{22}$ −70.1 (*c* 1.20, $CHCl_3$); IR (neat) ν_{max}: 1744, 1462, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.56–2.10 (m, 7H), 1.98–1.92 (m, 1H), 1.73–1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=215.9, 117.6, 43.4, 37.9, 33.1, 28.3, 22.2; HRMS (FAB): *m/z* calcd for C_7H_9NO+Na 146.0582, found 146.0582.

According to the above procedure, **16** was also obtained from **3** (Ar=Np, Xy) in 48% and 51% yields, respectively.

$[\alpha]_D^{22}$ −70.1 (*c* 1.20, $CHCl_3$) (from **3** (Ar=Np)).

$[\alpha]_D^{23}$ −70.0 (*c* 1.20, $CHCl_3$) (from **3** (Ar=Xy)).

4.1.13. (1*R*,2*RS*)-[2-(1-Naphthalenesulfonyl)-3-oxo-2-(2-propynyl)cyclopentyl]acetonitrile (17c (Ar=Np)) and (*R*)-[2-(1-naphthalenesulfonyl)-3-(2-propynyloxy)-2-cyclopentenyl]acetonitrile (17o (Ar=Np)). To a solution of **3** (Ar=Np) (200.0 mg, 0.638 mmol) in DMF (6 mL) were added potassium carbonate (132.0 mg, 0.957 mmol), sodium iodide (286.0 mg, 1.91 mmol), and propargyl bromide (0.170 mL, 1.91 mmol) successively, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (1 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **17c** (Ar=Np) (161.0 mg, 75%, a mixture of diastereomers, dr=11/1) as a white solid and **17o** (Ar=Np) as a yellow oil (45.0 mg, 21%).

Compound **17c** (Ar=Np): IR (KBr) ν_{max}: 2250, 1681, 809, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): major product: δ=8.78 (d, *J*=8.5 Hz, 1H), 8.22 (d, *J*=7.8 Hz, 1H), 8.14 (d, *J*=7.6 Hz, 1H), 7.96 (d, *J*=7.8 Hz, 1H), 7.69 (dd, *J*=7.6, 8.5 Hz, 1H), 7.62 (dd, *J*=7.8, 8.5 Hz, 1H), 7.59 (dd, *J*=7.8, 8.5 Hz, 1H), 3.70–3.58 (m, 1H), 3.10–2.90 (m, 2H), 2.83 (dd, *J*=1.5, 16.3 Hz, 1H), 2.69 (dd, *J*=1.5, 16.3 Hz, 1H), 2.60–2.40 (m, 3H), 2.10–1.90 (m, 2H); minor product: δ=8.78 (d, *J*=8.5 Hz, 1H), 8.22 (d, *J*=7.8 Hz, 1H), 8.14 (d, *J*=7.6 Hz, 1H), 8.00 (d, *J*=7.8 Hz, 1H), 7.69 (dd, *J*=7.6, 8.5 Hz, 1H), 7.62 (dd, *J*=7.8, 8.5 Hz, 1H), 7.59 (dd, *J*=7.8, 8.5 Hz, 1H), 3.70–3.58 (m, 1H), 3.10–2.90 (m, 2H), 2.83 (dd, *J*=1.5, 16.3 Hz, 1H), 2.69 (dd, *J*=1.5, 16.3 Hz, 1H), 2.60–2.40 (m, 3H), 2.10–1.90 (m, 2H); HRMS (FAB): *m/z* calcd for $C_{20}H_{17}NO_3S$+H 352.1007, found 352.0970.

Compound **17o** (Ar=Np): $[\alpha]_D^{27}$ +10.1 (*c* 1.30, $CHCl_3$); IR (neat) ν_{max}: 2248, 866, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.69 (d, *J*=8.5 Hz, 1H), 8.34 (d, *J*=7.3 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 1H), 7.67 (dd, *J*=8.0, 8.5 Hz, 1H), 7.62 (dd, *J*=7.3, 7.8 Hz, 1H), 7.59 (dd, *J*=7.8, 8.0 Hz, 1H), 4.52 (dd, *J*=2.2, 16.3 Hz, 1H), 4.46 (dd, *J*=2.2, 16.3 Hz, 1H), 3.32–3.22 (m, 1H), 2.93 (dd, *J*=3.7, 16.8 Hz, 2H), 2.75–2.62 (m, 2H), 2.43 (dd, *J*=2.2, 2.2 Hz, 1H), 2.29–2.18 (m, 1H), 1.94–1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.6, 136.3, 134.5, 134.0, 129.7, 128.9, 128.8, 128.1, 126.7, 124.3, 124.1, 118.2, 114.3, 76.8, 76.6, 58.1, 39.9, 29.0, 25.5, 23.4; HRMS (FAB): *m/z* calcd for $C_{20}H_{17}NO_3S$+H 352.1007, found 352.1008.

4.1.14. (1*R*,2*RS*)-[2-(2,4-Dimethylphenylsulfonyl)-3-oxo-2-(2-propynyl)cyclopentyl]acetonitrile (17c (Ar=Xy)) and (*R*)-[2-(2,4-dimethylphenylsulfonyl)-3-(2-propynyloxy)-2-cyclopentenyl]acetonitrile (17o (Ar=Xy)). To a solution of **3** (Ar=Xy) (200.0 mg, 0.686 mmol) in DMF (6 mL) were added potassium carbonate (142.0 mg, 1.02 mmol), sodium iodide (307.0 mg, 2.05 mmol), and propargyl bromide (0.182 mL, 2.05 mmol) successively, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (1 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **17c** (Ar=Xy) (95.0 mg, 44%, a mixture of diastereomers, dr=7/1) as a white solid and **17o** (Ar=Xy) (112.0 mg, 52%) as a yellow oil.

Compound **17c** (Ar=Xy): IR (KBr) ν_{max}: 2263, 1661, 822, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): major product: δ=7.63 (d, *J*=8.0 Hz, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 7.13 (s, 1H), 3.66–3.52 (m, 1H), 3.10–2.75 (m, 3H, including δ=2.83, dd, *J*=2.7, 16.5 Hz, 1H), 2.64–2.45 (m, 8H, including δ=2.50, s, 3H), 2.41 (s, 3H), 2.10–1.90 (m, 1H); minor product: δ=7.56 (d, *J*=8.3 Hz, 1H), 7.16 (d, *J*=8.3 Hz, 1H), 7.13 (s, 1H), 3.66–3.52 (m, 1H), 3.10–2.75 (m, 3H, including δ=2.76, dd, *J*=2.4, 16.5 Hz, 1H), 2.66–2.45 (m, 8H, including δ=2.53, s, 3H), 2.41 (s, 3H), 2.10–1.90 (m, 1H); HRMS (FAB): *m/z* calcd for $C_{18}H_{19}NO_3S$+H 330.1164, found 330.1177.

Compound **17o** (Ar=Xy): $[\alpha]_D^{23}$ −9.82 (*c* 1.15, $CHCl_3$); IR (neat) ν_{max}: 2240, 854, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.89 (d, *J*=8.0 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 7.08 (s, 1H), 4.53 (dd, *J*=2.4, 16.0 Hz, 1H), 4.48 (dd, *J*=2.4, 16.0 Hz, 1H), 3.30–3.20 (m, 1H), 3.02–2.85 (m, 1H), 2.80 (dd, *J*=3.7, 14.6 Hz, 2H), 2.72 (dddd, *J*=3.7, 3.7, 7.1, 10.0 Hz, 1H), 2.67–2.55 (m, 4H, including δ=2.58, s, 3H), 2.52 (dd, *J*=2.4, 2.4 Hz, 1H), 2.37 (s, 3H), 1.90 (dddd, *J*=3.7, 7.8, 9.0, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.8, 143.8, 137.9, 136.5, 133.0, 129.5, 126.6, 118.2, 114.4, 76.8 (6), 76.8 (2), 58.0, 39.8, 29.0, 25.6, 23.3, 21.2, 19.9; HRMS (FAB): *m/z* calcd for $C_{18}H_{19}NO_3S$+H 330.1164, found 330.1171.

4.1.15. (1*R*,2*RS*)-[2-(1-Naphthalenesulfonyl)-3-oxo-2-(2-pentynyl)cyclopentyl]acetonitrile (18c) and (*R*)-[2-(1-naphthalenesulfonyl)-3-(2-pentynyloxy)-2-cyclopentenyl]-acetonitrile (18o). To a solution of **3** (Ar=Np) (564.0 mg, 1.80 mmol) in DMF (20 mL) were added potassium carbonate (373.0 mg, 2.70 mmol), sodium iodide (809.0 mg, 5.40 mmol), and 1-bromo-2-pentyne (0.533 mL, 5.40 mmol) successively, and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with ether (30 mL×2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford **18c** (399.0 mg, 59%, a mixture of diastereomers, dr=6/1) as a white solid and **18o** (243.0 mg, 36%) as a yellow oil.

Compound **18c**: IR (KBr) ν_{max}: 2921, 1662, 1508, 1309, 1123, 808, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): major product: δ=8.79 (d, J=8.8 Hz, 1H), 8.20 (d, J=8.1 Hz, 1H), 8.13 (d, J=7.6 Hz, 1H), 7.95 (d, J=7.8 Hz, 1H), 7.66 (dd, J=7.6, 8.8 Hz, 1H), 7.62 (dd, J=7.6, 8.1 Hz, 1H), 7.60 (dd, J=7.6, 7.8 Hz, 1H), 3.67–3.56 (m, 1H), 3.08–2.85 (m, 2H), 2.81 (dd, J=2.4, 16.1 Hz, 1H), 2.65 (dd, J=2.2, 16.1 Hz, 1H), 2.58–2.40 (m, 3H), 2.10–1.70 (m, 3H), 1.01 (t, J=7.3 Hz, 3H); minor product: δ=8.79 (d, J=8.8 Hz, 1H), 8.20 (d, J=8.1 Hz, 1H), 8.13 (d, J=7.6 Hz, 1H), 8.00 (d, J=7.8 Hz, 1H), 7.66 (dd, J=7.6, 8.8 Hz, 1H), 7.62 (dd, J=7.6, 8.1 Hz, 1H), 7.60 (dd, J=7.6, 7.8 Hz, 1H), 3.67–3.56 (m, 1H), 3.08–2.85 (m, 2H), 2.81 (dd, J=2.4, 16.1 Hz, 1H), 2.65 (dd, J=2.2, 16.1 Hz, 1H), 2.58–2.40 (m, 3H), 2.10–1.70 (m, 3H), 1.00 (t, J=7.3 Hz, 3H); HRMS (FAB): m/z calcd for $C_{22}H_{21}NO_3S$+H 380.1320, found 380.1316.

Compound **18o**: $[\alpha]_D^{26}$ −17.6 (c 1.00, $CHCl_3$); IR (neat) ν_{max}: 2934, 1507, 1349, 1122, 1021, 928, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.73 (d, J=8.3 Hz, 1H), 8.33 (d, J=7.3 Hz, 1H), 8.07 (d, J=8.3 Hz, 1H), 7.91 (d, J=7.9 Hz, 1H), 7.65 (dd, J=7.3, 8.6 Hz, 1H), 7.57 (dd, J=8.3, 8.6 Hz, 1H), 7.55 (dd, J=7.9, 8.3 Hz, 1H), 4.48 (dt, J=15.6, 2.0 Hz, 1H), 4.43 (dt, J=15.6, 2.1 Hz, 1H), 3.70–3.20 (m, 1H), 2.95–2.80 (m, 2H, including δ=2.82, dd, J=3.7, 16.1 Hz, 1H), 2.75–2.60 (m, 2H), 2.30–2.20 (m, 3H), 1.95–1.80 (m, 1H), 1.02 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.5, 136.7, 134.5, 134.1, 129.8, 129.0, 128.9, 128.1, 126.7, 124.6, 124.2, 118.4, 113.6, 91.0, 72.7, 59.1, 40.0, 29.2, 25.7, 23.5, 13.3, 12.3; HRMS (FAB): m/z calcd for $C_{22}H_{21}NO_3S$+H 380.1320, found 380.1346.

4.1.16. (1*R*,2*R*)-[2-(1-Naphthalenesulfonyl)-3-oxocyclopentyl]acetonitrile (3 (Ar=Np)). To a solution of **18o** (100.0 mg, 0.264 mmol) in 5% H_2O/MeOH (methanol including 5% H_2O, 3.0 mL) was added PPTS (10.0 mg, 0.026 mmol) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **3** (Ar=Np) (81.0 mg, 98%) as a white solid.

4.1.17. (1*R*,2*RS*)-[3-Oxo-2-(2-pentynyl)cyclopentyl]acetonitrile (19). To a suspension of samarium chip (402.0 mg, 2.68 mmol) in THF (3.0 mL) was added a solution of 1,2-diiodoethane (377 mg, 1.34 mmol) in THF (2 mL) via a canula at room temperature, and the reaction mixture was stirred at this temperature for 2 h. To the resultant SmI_2 solution in THF was added methanol (0.4 mL) at −78 °C, and then a solution of **18c** (203.0 mg, 0.535 mmol) in THF (2 mL). The reaction mixture was stirred at this temperature for 5 min. After air was bubbled into the solution, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **19** (101.0 mg, 100%, a mixture of diastereomers, dr=4/1) as a colorless oil.

IR (neat) ν_{max}: 1748, 1560, 1462, 1324, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): major product: δ=2.83 (dd, J=4.4, 17.1 Hz, 1H), 2.70 (dd, J=6.8, 17.1 Hz, 1H), 2.61 (ddt, J=4.4, 17.1, 2.4 Hz, 1H), 2.57–1.99 (m, 8H), 1.78–1.68 (m, 1H), 1.09 (t, J=7.6 Hz, 3H); minor product: δ=2.83 (dd, J=4.4, 17.1 Hz, 1H), 2.66 (dd, J=7.1, 17.1 Hz, 1H), 2.61 (ddt, J=4.4, 17.1, 2.4 Hz, 1H), 2.57–1.99 (m, 8H), 1.78–1.68 (m, 1H), 1.10 (t, J=7.6 Hz, 3H); HRMS (FAB): m/z calcd for $C_{12}H_{15}NO$+H 190.1232, found 190.1236.

4.1.18. (1*R*,2*RS*,*Z*)-[3-Oxo-2-(2-pentenyl)cyclopentyl]acetonitrile (20). A mixture of **19** (57.0 mg, 0.301 mmol, a mixture of diastereomers) and a catalytic amount of Lindlar's catalyst in MeOH (3 mL) was stirred under an atmosphere of hydrogen. After 3 h, the mixture was filtered through Celite, and the residue was washed with ether. The combined filtrate was concentrated under reduced pressure, and the resulting oil was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **20** (52.0 mg, 90%, a mixture of diastereomers at the C-2 position) as a colorless oil.

IR (neat) ν_{max}: 1742, 1652, 1464, 1288, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): major product: δ=5.60–5.47 (m, 1H), 5.31–5.21 (m, 1H), 2.70 (dd, J=4.4, 17.1 Hz, 1H), 2.51–1.97 (m, 10H), 1.75–1.61 (m, 1H), 0.96 (t, J=7.6 Hz, 3H); minor product: δ=5.60–5.47 (m, 1H), 5.31–5.21 (m, 1H), 2.66 (dd, J=4.4, 17.1 Hz, 1H), 2.51–1.97 (m, 10H), 1.75–1.61 (m, 1H), 0.97 (t, J=7.5 Hz, 3H); HRMS (FAB): m/z calcd for $C_{12}H_{17}NO$+H 192.1388, found 192.1397.

4.1.19. (−)-Methyl jasmonate. To a solution of **20** (30.0 mg, 0.157 mmol, a mixture of diastereomers at C-2 position) in ethylene glycol (2 mL) was added KOH (35.0 mg, 0.627 mmol), and the mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (2 mL×3). The aqueous layer was acidified with 2 M HCl (1 mL) and was extracted with CH_2Cl_2 (2 mL×3). The combined organic layer was washed with brine (1 mL), dried over Na_2SO_4, and evaporated. The residue was dissolved in acetone (3 mL), and to this solution were added potassium carbonate (32.0 mg, 0.235 mmol) and methyl iodide (0.029 mL, 0.471 mmol). The reaction mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (2 mL) and extracted with ether (3 mL×2). The combined organic layer was washed with brine (1 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford (–)-methyl jasmonate (35.0 mg, 88%, two steps) as a colorless oil.

$[\alpha]_D^{23}$ −90.2 (c 1.03, MeOH); IR (neat) ν_{max}: 1738, 1438, 1198, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.48–5.41 (m, 1H), 5.29–5.22 (m, 1H), 3.69 (s, 3H), 2.74–2.67 (m, 1H), 2.42–2.01 (m, 9H), 1.89–1.87 (m, 1H), 1.51–1.43 (m, 1H), 0.95 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ=219.0, 172.6, 134.1, 124.9, 54.1, 51.6, 38.8, 38.1, 37.8, 27.2, 25.6, 20.6, 14.1; HRMS (FAB): *m/z* calcd for $C_{13}H_{20}O_3$+H 225.1491, found 225.1465.

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