Synthetic Studies towards Optically Active 13-Oxyingenol via Asymmetric Cyclopropanation

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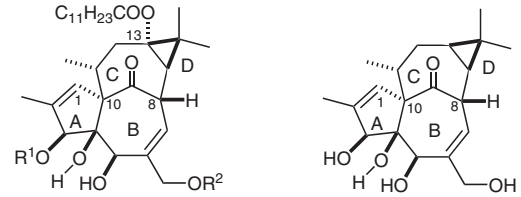
Abstract: The enantioselective synthesis of a seven-membered enone compound, the key intermediate of our previous synthesis of the *inside–outside* framework of 13-oxyingenol in racemic form, was achieved by using asymmetric cyclopropanation and reductive deoxygenation as key steps.

Key words: 13-oxyingenol, asymmetric cyclopropanation, chiral aza-semicorrin ligand, reductive deoxygenation, intramolecular aldol reaction

13-Oxyingenol (**1**) is a diterpenoid isolated from *Euphorbia kansui*,[2] whose derivatives have strong protein kinase C activation and anti-HIV activities (Figure 1).[3] Particularly, 13-oxyingenol derivatives such as **2** have strong anti-HIV activity. The structural features of ingenol (**3**) and 13-oxyingenol (**1**) are a high degree of oxygenation and a highly strained *inside–outside* bicyclic ring system. Because of their unique structures and strong bioactivities, ingenols have attracted the interest of synthetic organic chemists, and several groups have achieved the total synthesis of ingenol (**3**).[4] In 2004, we reported the formal total synthesis of optically active ingenol (**3**) by using ring-closing olefin metathesis as a key step.[5]

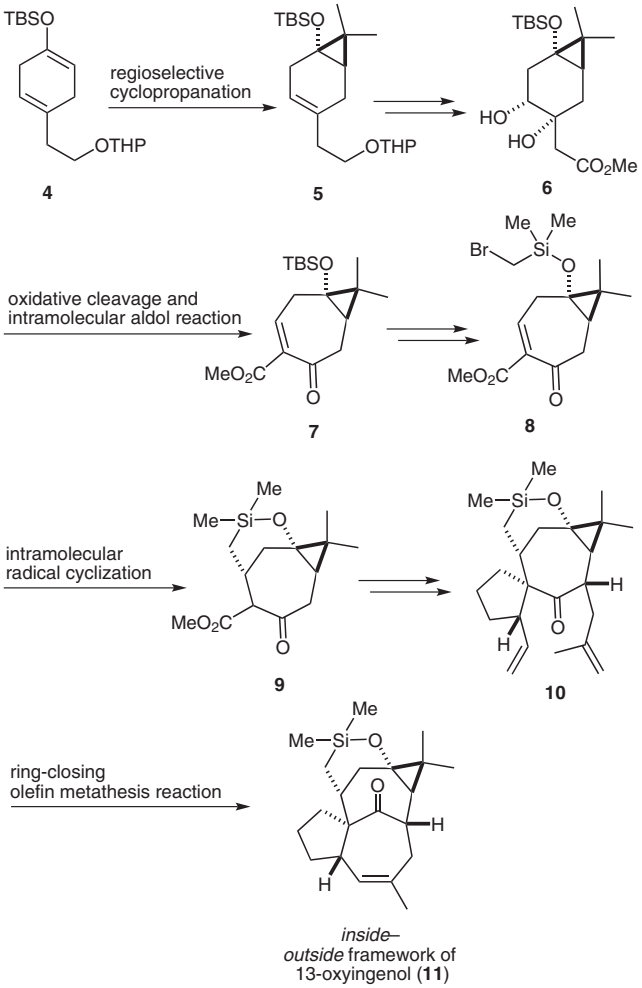


13-oxyingenol (**1**)
R^1 = H, R^2 = COC_5H_{11}
13-oxyingenol derivative RD4-2138 (**2**)
R^1 = CO-*t*-Bu, R^2 = H

ingenol (**3**)

Figure 1 Structures of ingenol, 13-oxyingenol, and its derivative RD4-2138

In 2007, we reported the construction of an *inside–outside* framework of 13-oxyingenol **11** in racemic form by using intramolecular radical cyclization and ring-closing olefin metathesis as key steps (Scheme 1).[6] In that synthesis, the cyclopropane ring in intermediate (±)-**5** was constructed by using regioselective cyclopropanation of *tert*-butyldimethylsilyl enol ether **4**. Pfaltz and co-workers had reported the asymmetric cyclopropanation of cyclic silyl enol ethers.[7] Therefore, it was planned to construct the optically active intermediate **5** of our previous synthesis of the *inside–outside* framework of 13-oxyingenol **11** in racemic form by using asymmetric cyclopropanation. In this paper, we report our synthetic approach to optically active 13-oxyingenol (**1**).



Scheme 1 Synthetic study of 13-oxyingenol (**1**): construction of the full carbon framework by our group.

The *tert*-butyldimethylsilyl enol ether **4**, a precursor of asymmetric cyclopropanation was synthesized from 2-(4-hydroxyphenyl)ethanol (**12**) (Scheme 2).[6] The selective protection of the primary hydroxy group of 2-(4-hydroxy-

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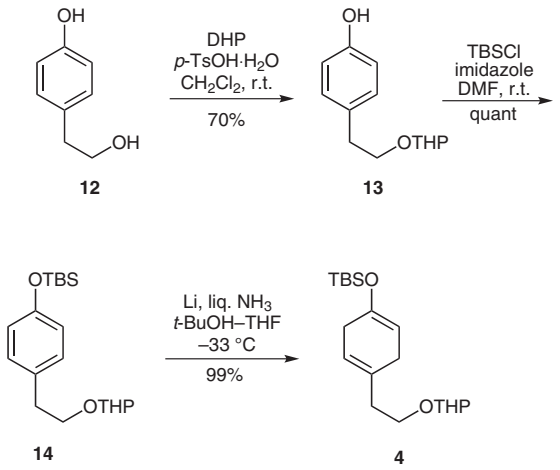
phenyl)ethanol (**12**) gave the THP ether **13**, which was converted into the TBS ether **14**. The Birch reduction of **14** afforded the *tert*-butyldimethylsilyl enol ether **4**.



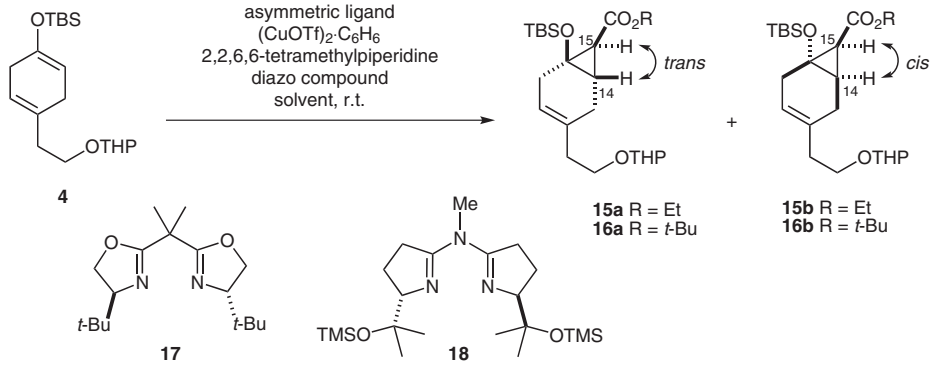
Scheme 2 Synthesis of *tert*-butyldimethylsilyl enol ether **4**

Our attempts at asymmetric cyclopropanation of *tert*-butyldimethylsilyl enol ether **4** are summarized in Table 1. Pfaltz and co-workers reported that the use of CuOTf with chiral heterocyclic nitrogen ligands such as bisoxazoline **17** or aza-semicorrin **18** was the most efficient method.[7] We followed their procedure and found that an asymmetric cyclopropanation between *tert*-butyldimethylsilyl enol ether **4** and ethyl diazoacetate with bisoxazoline ligand **17** gave the desired cyclopropanes **15a** and **15b**, but the yield was low (entry 1). The reaction with aza-semicorrin ligand **18** gave the desired cyclopropanes **15a** (46%, 91% ee) and **15b** (29%, 52% ee) (entry 2). Next, an asymmetric cyclopropanation was attempted by using *tert*-butyl diazoacetate with aza-semicorrin ligand **18**. However, the diastereoselectivity was not improved (*trans*/*cis* = 1.1:1) (entry 3). Other asymmetric cyclopropanations of **4** by using asymmetric Rh-catalyst[8] [Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTTL)$_4$] were not effective in this case. The determination of the stereostructures of **15a** and **15b** with the absolute configuration is discussed later (Scheme 7).

Thus, the optimization of a precursor for this asymmetric cyclopropanation was investigated next (Table 2). First, the asymmetric cyclopropanation of the sterically bulky silyl enol ethers, such as TIPS enol ether **19** or TES enol ether **20** was attempted. However, the diastereoselectivity was not affected (entries 1 and 2). The less-hindered methyl enol ether **21** undergoes cyclopropanation with high diastereoselectivity (*trans*/*cis* = 7.2:1), but the enantioselectivity was low (**26a** = 31% ee, entry 3). Also, the cyclopropanation of MEM enol ether **22** and SEM enol ether **23** gave results similar to that of **21** (entries 4 and 5).

From these results, the asymmetric cyclopropanation was most efficiently effected by using *tert*-butyldimethylsilyl enol ether **4** and ethyl diazoacetate with aza-semicorrin ligand **18** (Table 1, entry 2). Next, the transformation of compound **15a** into the optically active intermediate **5** reported in our previous synthetic study was tried (Scheme 3). Thus, the methylation of ester **15a** and the reduction of the ethyl ester group in compound **29** afforded the alcohol **30**. The stereochemistry of the methyl group at C-15 in **30** was determined by the NOESY correlation between C-14 proton and C-16 methyl protons.

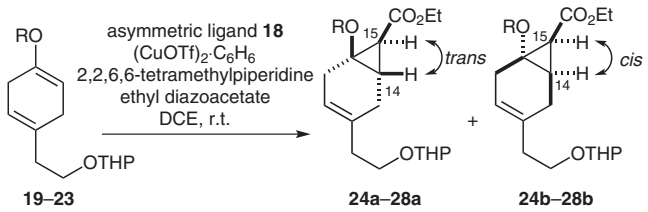
Table 1 Optimization of Reaction Conditions for Asymmetric Cyclopropanation



Entry	Asymmetric ligand	Diazo compound	Solvent	Yield (%) (ee, %)[a,b]	dr[a,c] *trans*/*cis*
1	**17**	ethyl diazoacetate	$CHCl_3$	**15a** = 9.5 (73) **15b** = 9.8 (78)	1.0:1
2	**18**	ethyl diazoacetate	DCE	**15a** = 46 (91) **15b** = 29 (52)	1.6:1
3	**18**	*tert*-butyl diazoacetate	DCE	**16a** = 44 (82) **16b** = 40 (76)	1.1:1

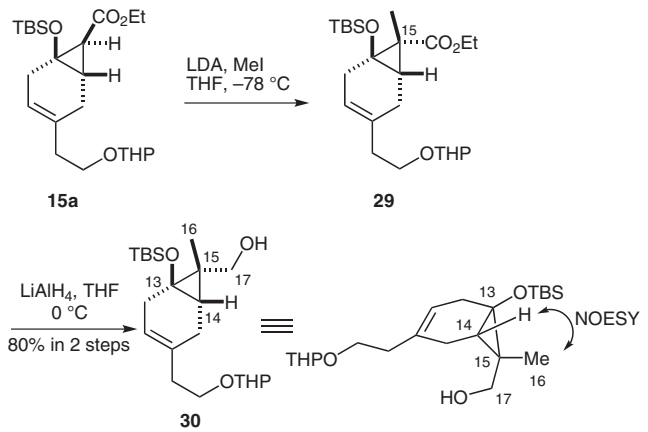
[a] The relative stereochemistry and the enantiomeric excess were determined after the removal of the THP group to the corresponding alcohol.
[b] The enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL CHIRALCEL OD).
[c] The relative stereochemistry was determined by coupling constant analysis of ^{1}H NMR between H-14 and H-15.

Table 2 Optimization of Reaction Precursor for Asymmetric Cyclopropanation



Entry	R	Yield (%) (ee, %)[a,b]	dr[a,c] *trans*/*cis*
1	TIPS (**19**)	**24a** 33 (91) **24b** 21 (58)	1.6:1
2	TES (**20**)	**25a** 33 (77) **25b** 19 (41)	1.7:1
3	Me (**21**)	**26a** 56 (31) **26b** 7.8[d]	7.2:1
4	MEM (**22**)	**27a** 48 (39) **27b** 5.8[d]	8.3:1
5	SEM (**23**)	**28a** 65 (36) **28b** 6.5[d]	10:1

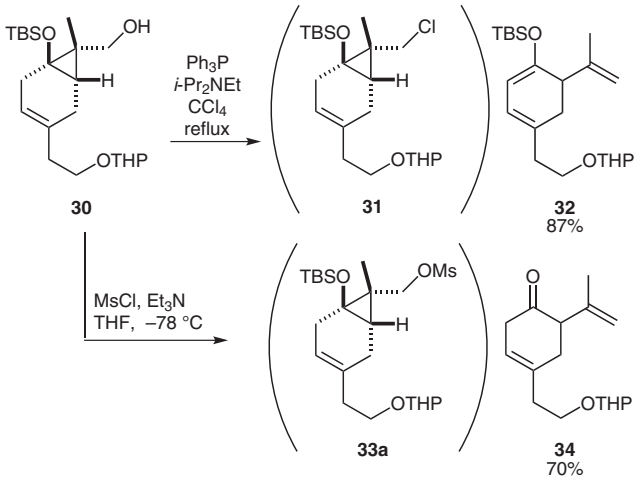
[a] The relative stereochemistry and the enantiomeric excess were determined after the removal of the THP group to corresponding alcohol.
[b] The enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL CHIRALCEL OD).
[c] The relative stereochemistry was determined by coupling constant of ^{1}H NMR between H-14 and H-15.
[d] The enantiomeric excess was not determined.



Scheme 3 Synthesis of **30**

The deoxygenation of the primary hydroxy group in **30** was attempted next by reducing the corresponding chloride **31** or mesylate **33a** (Scheme 4). However, the chlorination or mesylation of **30** gave undesired ring-opened compounds **32** or **34** because of the instability of compound **31** or **33a**.

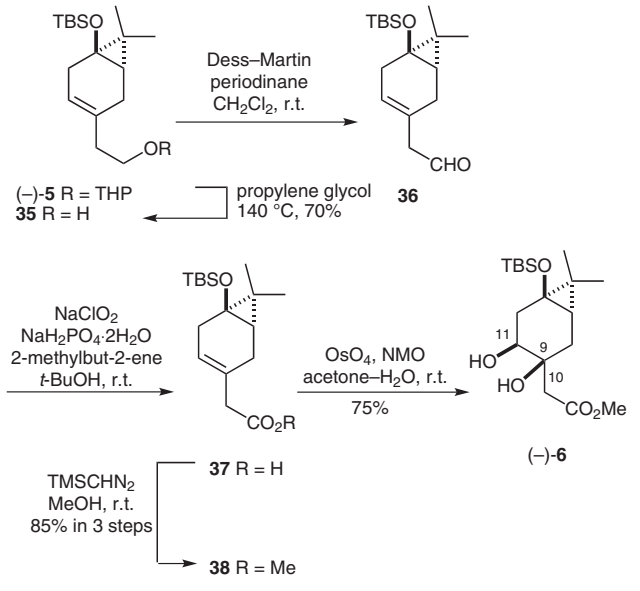
Alternatively, reductive deoxygenation without the isolation of **33a–c** was tried (Table 3). Mesylation of the primary hydroxy group in **30** at –78 °C followed by treatment with $LiAlH_4$ gave the desired compound (–)-**5**



Scheme 4 Introduction of leaving groups in **30**

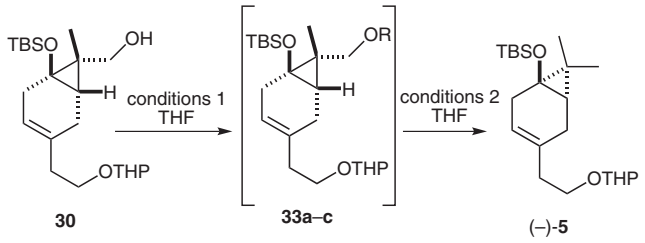
(trace) and undesired ring-opened compounds, such as **32** and **34** (entry 1). In entry 2, compound **30** was transformed into the diphenyl phosphate **33b**,[9] which was then treated with $LiBHEt_3$ to give the desired compound (–)-**5** (ca. 29%) along with the undesired ring-opened compounds. *N*,*N*,*N*′,*N*′-Tetramethylphosphodiamidate **33c**[10] generated in situ from compound **30** was reduced by $LiBHEt_3$ to provide the desired compound (–)-**5** in 74% yield without a ring-opening reaction (entry 3). Compound (–)-**5** is the optically active form of our previous intermediate for an *inside–outside* framework of 13-oxyingenol.[6]

To determine the absolute stereochemistry of the cyclopropane part in (–)-**5** by using a modified Mosher's method,[11] compound (–)-**5** was converted into the MTPA ester **40**.[6] Selective removal of the THP group in (–)-**5** gave alcohol **35**,[12] which was oxidized to carboxylic acid **37** by Dess–Martin oxidation and subsequent Pinnick oxidation. Carboxylic acid **37** was transformed into methyl ester **38**



Scheme 5 Synthesis of diol (–)-**6**[13]

Table 3 Study of Reductive Deoxygenation of Primary Hydroxy Group in **30**[a]



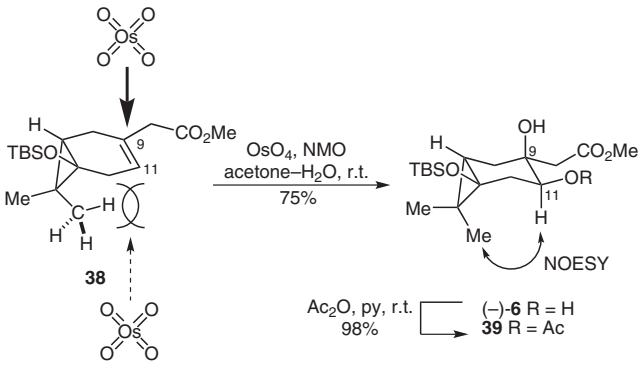
Entry	Conditions 1	**33a–c**	Conditions 2	Yield (%)
1	MsCl, Et_3N, –78 °C	**33a** R = Ms	$LiAlH_4$, –78 °C	trace
2	$(PhO)_2P(O)Cl$, LDA, –78 °C	**33b** R = $P(O)(OPh)_2$	$LiBHEt_3$, –78 °C to r.t.	<29[b]
3	$(Me_2N)_2P(O)Cl$, LHMDS, r.t.	**33c** R = $P(O)(NMe_2)_2$	$LiBHEt_3$, reflux	74

[a] The reaction was conducted with racemic **30**.
[b] This compound contained by-products such as **32** and **34**, which could not be isolated.

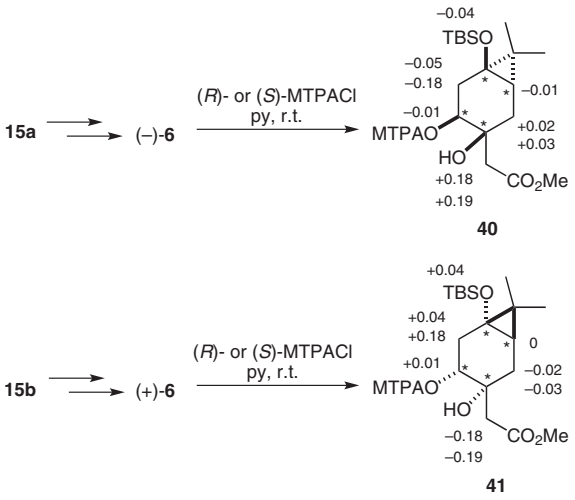
by TMS diazomethane. Dihydroxylation of **38** gave diol (–)-**6** as the sole product because of steric hindrance of the methyl group at the cyclopropane ring (Scheme 5). Diol (–)-**6** was converted into acetate **39**, the NOESY spectrum of which showed the correlation between H-11 and the methyl group at the cyclopropane ring to indicate the relative stereochemistry of acetate **39**, as depicted in Scheme 6.

Esterification of the secondary hydroxy group in diol (–)-**6** afforded the MTPA ester **40**, and the absolute stereochemistry of **40** was determined as depicted in Scheme 7 by the modified Mosher's method. The ester **15b** was also converted into MTPA ester **41** in the same manner, and the absolute stereochemistry of **41** was determined as shown in Scheme 7. Thus, the absolute structures of cyclopropanation products in Table 1 were determined as the structural formulas **15a** and **15b**.

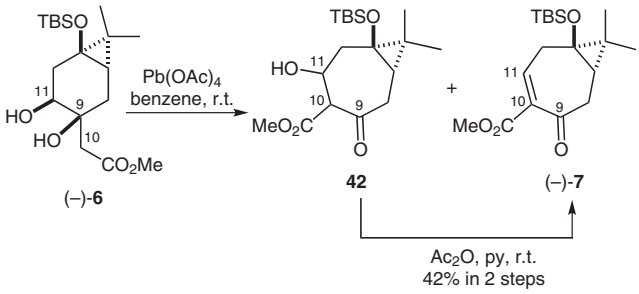
Oxidative cleavage of the diol group in (–)-**6** and a spontaneous intramolecular aldol reaction afforded the seven-membered aldol **42** and the seven-membered enone (–)-**7** (Scheme 8). The former was transformed into the latter by acetylation. This seven-membered enone (–)-**7** is an optically active form of the key intermediate of our previous synthesis of the *inside–outside* framework of 13-oxyingenol in racemic form.[6]



Scheme 6 Diastereoselective dihydroxylation of **38**



Scheme 7 Determination of absolute stereochemistries of cyclopropane part in **15a** and **15b**



Scheme 8 Synthesis of optically active seven-membered enone (–)-**7**[13]

In conclusion, we have achieved the enantioselective synthesis of the key intermediate (–)-**7** of the 13-oxyingenol skeleton by using asymmetric cyclopropanation and reductive deoxygenation as key steps. Efforts toward the total synthesis are currently under way, and the results will be reported elsewhere.

Optical rotations were measured with a Jasco DIP-1000 polarimeter or a Jasco DIP-370 polarimeter. Melting points were recorded on a Yanaco MP-J8 micro melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco FT/IR-230 instrument and only selected peaks are reported. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-EX270 spectrometer, a Bruker Avance 500 spectrometer, or a Bruker Avance 600 spectrometer. The ^{1}H and ^{13}C chemical shifts were referenced to the solvent peaks (δ_H = 7.26 ppm and δ_C = 77.0 ppm in $CDCl_3$). *J* values are given in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. ESI mass spectra were recorded on an Applied Biosystems QStar/Pulsar *i* spectrometer or a Jeol AccuTOFCS JMS-T100CS spectrometer. TLC analyses were conducted on E. Merck precoated silica gel 60 F254 (0.25 mm layer thickness). Fuji Silysia silica gel BW-820 MH (75–200 μm) and FL-60D (45–75 μm) were used for column chromatography, unless otherwise noted. Chiral HPLC was performed on Jasco 880 PU and 875 UV instruments using a DAICEL CHIRALCEL OD, 4.6 mm × 25 cm column. Anhyd benzene, CH_2Cl_2, DCE, DMF, MeOH, THF, and toluene were used as obtained from commercial supplies. Other organic solvents for moisture-sensitive reactions were distilled by standard procedure.

4-[2-(Tetrahydro-*2H*-pyran-2-yloxy)ethyl]phenol (13)

To a suspension of 2-(4-hydroxyphenyl)ethanol (**12**; 10.1 g, 73.7 mmol) in CH_2Cl_2 (260 mL) were added 3,4-dihydropyran (10.0 mL, 111 mmol) and *p*-TsOH·H_2O (139 mg, 733 μmol) at r.t. The mixture was stirred at the same temperature for 2 h, diluted with sat. aq $NaHCO_3$ (50 mL), and extracted with EtOAc (7 × 40 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified twice by column chromatography on silica gel (200 g, hexane–EtOAc, 24:1; FL-60D 100 g, hexane–EtOAc, 7:1 → 5:1) to give **13** (11.4 g, 70%) as a colorless oil.

IR (film): 3600, 3340 (br), 3010, 2950, 2870, 1624, 2495, 2424, 1440, 1355, 1260 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 8.6 Hz, 2 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 5.19–5.13 (m, 1 H), 4.63 (dd, *J* = 3.5, 2.7 Hz, 1 H), 3.91 (dt, *J* = 9.7, 7.3 Hz, 1 H), 3.84–3.76 (m, 1 H), 3.58 (dt, *J* = 9.7, 7.3 Hz, 1 H), 3.53–3.46 (m, 1 H), 2.83 (t, *J* = 7.3 Hz, 2 H), 1.88–1.49 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.2, 130.8, 130.0 (2 C), 115.1 (2 C), 98.8, 68.7, 62.3, 35.3, 30.6, 25.4, 19.4.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_3$ + Na: 245.1154; found: 245.1136.

***tert*-Butyldimethyl{4-[2-(tetrahydro-*2H*-pyran-2-yloxy)ethyl]phenoxy}silane (14)**

To a stirred solution of THP ether **13** (17.6 g, 79.2 mmol) in DMF (270 mL) were added imidazole (13.1 g, 192 mmol) and TBSCl (14.9 g, 98.7 mmol) at 0 °C. The mixture was stirred at r.t. for 2 h, diluted with H_2O (100 mL), and extracted with Et_2O (4 × 60 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, hexane–EtOAc, 25:1) to give **14** (27.0 g, quant) as a colorless oil.

IR (film): 3000, 2950, 2935, 2860, 1610, 2410, 1470, 1260 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.09 (br d, *J* = 8.4 Hz, 2 H), 6.76 (br d, *J* = 8.4 Hz, 2 H), 4.59 (dd, *J* = 3.8, 3.0 Hz, 1 H), 3.90 (dt, *J* = 9.6, 7.3 Hz, 1 H), 3.78–3.69 (m, 1 H), 3.58 (dt, *J* = 9.6, 7.3 Hz, 1 H), 3.48–3.40 (m, 1 H), 2.84 (t, *J* = 7.3 Hz, 2 H), 1.87–1.49 (m, 6 H), 0.98 (s, 9 H), 0.18 (s, 6 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 153.8, 131.7, 129.7 (2 C), 119.7 (2 C), 98.5, 68.5, 62.1, 35.6, 30.7, 25.8 (3 C), 25.5, 19.5, 18.3, –4.3 (2 C).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{32}O_3Si$ + Na: 359.2018; found: 359.2013.

***tert*-Butyldimethyl{4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]cyclohexa-1,4-dienyloxy}silane (4)**

To stirred liquid NH_3 (240 mL) were added a solution of TBS ether **14** (8.04 g, 23.9 mmol) in THF (20 mL), the rinse (THF, 2 × 20 mL) of the flask of TBS ether **14**, THF (36 mL), *t*-BuOH (240 mL), and Li wire (1.10 g, 248 mmol) at –78 °C. The mixture was stirred at reflux for 2 h, and NH_4Cl (120 g) was added. The resultant mixture was stirred at r.t. for 2 h to evaporate NH_3, diluted with H_2O (270 mL), and extracted with hexane (2 × 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (80 g, hexane–EtOAc, 40:1) to give **4** (7.90 g, 99%) as a colorless oil.

IR (film): 3000, 2950, 2935, 2861, 1700, 1660, 2410, 1470, 1380, 1260 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.41 (br s, 1 H), 4.81 (br s, 1 H), 4.58 (dd, *J* = 4.1, 2.7 Hz, 1 H), 3.89–3.78 (m, 2 H), 3.52–3.43 (m, 2 H), 2.76–2.62 (m, 4 H), 2.27 (t, *J* = 7.0 Hz, 2 H), 1.86–1.40 (m, 6 H), 0.91 (s, 9 H), 0.13 (s, 6 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 147.9, 132.2, 119.2, 100.9, 98.7, 66.2, 62.2, 36.8, 31.2, 30.8, 30.3, 25.7 (3 C), 25.5, 19.7, 18.1, –4.3 (2 C).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{34}O_3Si$ + Na: 361.2175; found: 361.2174.

Asymmetric Cyclopropanation; General Procedure

To copper(I) triflate benzene complex (2.0 mol%) was added a solution of chiral aza-semicorrin ligand **18** (2.2 mol%) in DCE (1.3 mL) under an argon atmosphere. The resulting suspension was stirred at r.t. for 1 h. To a stirred solution of enol ether **4** (0.91 mmol) in DCE (7.0 mL) were added the supernatant solution of the greenish suspension prepared as above and 2,2,6,6-tetramethylpiperidine (1.9 mol%). A solution of ethyl diazoacetate (1.0 M in DCE, 4.5 mL, 4.5 mmol) was added slowly to the reaction mixture through a syringe pump over 2.5 h at r.t. After stirring at r.t. for 21 h, the mixture was concentrated, filtered through Florisil (100–200 mesh, 0.5 g, hexane–Et_2O, 1:1), and concentrated. The residual oil was purified by column chromatography on silica gel to give the cyclopropane compounds. The enantiomeric excess was determined by HPLC (DAICEL CHIRALCEL OD) after removal of the THP group to the corresponding alcohol.

Ethyl (1*R*,6*S*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-ene-7-carboxylate (15a)

Yield: 46%; 91% ee; $[\alpha]_D^{27}$ +17.6 (*c* 1.1, $CHCl_3$).

IR (film): 3008, 2950, 2930, 2899, 2858, 1721, 1258, 1211, 1182, 1160 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.26 (br d, *J* = 3.2 Hz, 1 H), 4.56 (br s, 1 H), 4.12 (dq, *J* = 9.9, 7.1 Hz, 1 H), 4.10 (dq, *J* = 9.9, 7.1 Hz, 1 H), 3.83 (t, *J* = 9.4 Hz, 1 H), 3.78–3.72 (m, 1 H), 3.52–3.46 (m, 1 H), 3.39 (dt, *J* = 9.4, 7.1 Hz, 1 H), 2.77–2.72 (m, 1 H), 2.56–2.44 (m, 2 H), 2.26–2.16 (m, 3 H), 2.11–2.07 (m, 1 H), 1.83–1.78 (m, 1 H), 1.77–1.73 (m, 1 H), 1.73–1.67 (m, 1 H), 1.60–1.47 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 0.87 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.2, 131.6 (0.5 C), 131.5 (0.5 C), 119.2 (0.5 C), 119.1 (0.5 C), 98.7 (0.5 C), 98.7 (0.5 C), 66.2 (0.5 C), 66.1 (0.5 C), 62.6, 62.3, 60.3, 37.5 (0.5 C), 37.4 (0.5 C), 33.3, 30.8, 28.5, 28.4, 27.0, 25.7 (3 C), 25.5, 19.7, 18.0, 14.5, –3.5, –3.5.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{40}O_5Si$ + Na: 447.2543; found: 447.2519.

Ethyl (1*S*,6*R*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-ene-7-carboxylate (15b)
Yield: 29%; 52% ee; $[\alpha]_D^{27}$ +10.5 (*c* 0.67, $CHCl_3$).

IR (film): 2952, 2930, 2359, 2341, 1716, 1168, 1030 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.18 (br d, *J* = 4.7 Hz, 1 H), 4.58–4.53 (m, 1 H), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.99–3.92 (m, 1 H), 3.87–3.81 (m, 1 H), 3.78–3.72 (m, 1 H), 3.52–3.46 (m, 1 H), 3.43–3.37 (m, 1 H), 2.86–2.78 (m, 1 H), 2.57–2.47 (m, 2 H), 2.33–2.26 (m, 1 H), 2.24–2.16 (m, 1 H), 2.16–2.08 (m, 1 H), 1.83–1.76 (m, 1 H), 1.81 (d, *J* = 10.5 Hz, 1 H), 1.73–1.65 (m, 1 H), 1.60–1.47 (m, 5 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 0.85 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 168.9, 132.2 (0.5 C), 132.1 (0.5 C), 119.0 (0.5 C), 119.0 (0.5 C), 98.9 (0.5 C), 98.6 (0.5 C), 66.2 (0.5 C), 66.0 (0.5 C), 62.4 (0.5 C), 62.3 (0.5 C), 60.1, 58.1 (0.5 C), 58.0 (0.5 C), 37.5, 30.9, 30.8, 29.4, 26.3 (0.5 C), 26.2 (0.5 C), 25.7 (3 C), 25.5, 24.4, 19.8 (0.5 C), 19.7 (0.5 C), 17.7, 14.3, –3.3, –3.7.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{40}O_5Si$ + Na: 447.2543; found: 447.2532.

***tert*-Butyl (1*R*,6*S*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-ene-7-carboxylate (16a)**
Yield: 44%; 82% ee; $[\alpha]_D^{23}$ +23.1 (*c* 0.72, $CHCl_3$).

IR (film): 3008, 2930, 2858, 1714, 1367, 1221, 1148 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 5.28–5.23 (m, 1 H), 4.60–4.53 (m, 1 H), 3.87–3.68 (m, 2 H), 3.53–3.35 (m, 2 H), 2.81–2.68 (m, 1 H), 2.58–2.37 (m, 2 H), 2.27–2.15 (m, 3 H), 2.04–1.96 (m, 1 H), 1.86–1.49 (m, 7 H), 1.44 (s, 9 H), 0.87 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 131.7, 119.4 (0.5 C), 119.3 (0.5 C), 98.7 (0.5 C), 98.7 (0.5 C), 79.7, 66.1 (0.5 C), 66.1 (0.5 C), 62.2, 62.0 (0.5 C), 62.0 (0.5 C), 37.4 (0.5 C), 37.3 (0.5 C), 33.2, 30.6, 29.2, 28.3, 28.3 (3 C), 26.0, 25.6 (3 C), 25.4, 19.5 (0.5 C), 19.5 (0.5 C), 17.8, –3.6, –3.7.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{44}O_5Si$ + Na: 475.2856; found: 475.2873.

***tert*-Butyl (1*S*,6*R*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-ene-7-carboxylate (16b)**
Yield: 40%; 76% ee; $[\alpha]_D^{23}$ +20.6 (*c* 0.88, $CHCl_3$).

IR (film): 3006, 2930, 2857, 1711, 1257, 1221, 1155 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 5.20–5.13 (m, 1 H), 4.60–4.52 (m, 1 H), 3.65–3.39 (m, 2 H), 3.53–3.33 (m, 2 H), 2.89–2.84 (m, 1 H), 2.60–2.39 (m, 2 H), 2.36–2.03 (m, 3 H), 1.92–1.43 (m, 8 H), 1.38 (s, 9 H), 0.85 (s, 9 H), 0.14 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.1, 132.3 (0.5 C), 132.3 (0.5 C), 119.1 (0.5 C), 119.1 (0.5 C), 98.9 (0.5 C), 98.6 (0.5 C), 80.0, 66.1 (0.5 C), 65.9 (0.5 C), 62.4 (0.5 C), 62.2 (0.5 C), 57.6 (0.5 C), 57.6 (0.5 C), 37.7 (0.5 C), 37.6 (0.5 C), 30.9, 30.7, 30.4, 28.0 (3 C), 26.0 (0.5 C), 26.0 (0.5 C), 25.6 (3 C), 25.5, 23.7 (0.5 C), 23.7 (0.5 C), 19.6 (0.5 C), 19.6 (0.5 C), 17.6, –3.4, –3.9.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{44}O_5Si$ + Na: 475.2856; found: 475.2867.

Ethyl (1*R*,6*S*,7*S*)-4-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1-(triisopropylsilyloxy)bicyclo[4.1.0]hept-3-ene-7-carboxylate (24a)
Yield: 33%; 91% ee; $[\alpha]_D^{25}$ +20.2 (*c* 0.33, $CHCl_3$).

IR (film): 3019, 2945, 2868, 1719, 1209 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.27 (br d, *J* = 4.8 Hz, 1 H), 4.57–4.53 (m, 1 H), 4.17–4.05 (m, 2 H), 3.86–3.79 (m, 1 H), 3.77–3.71 (m, 1 H), 3.53–3.46 (m, 1 H), 3.38 (dt, *J* = 9.6, 7.0 Hz, 1 H), 2.80 (dd, *J* = 17.7, 4.8 Hz, 1 H), 2.57–2.48 (m, 2 H), 2.25–2.16 (m, 3 H), 2.14 (dd, *J* = 5.5, 4.8 Hz, 1 H), 1.85–1.78 (m, 1 H), 1.78–1.74 (m, 1 H), 1.72–1.65 (m, 1 H), 1.59–1.47 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.06–1.04 (m, 21 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.2, 131.5, 119.2, 98.7 (0.5 C), 98.7 (0.5 C), 66.2 (0.5 C), 66.1 (0.5 C), 62.5 (0.5 C), 62.4 (0.5 C), 62.3, 60.3, 37.5, 33.3, 30.7, 29.2, 28.7, 27.4, 25.5, 19.6, 18.2 (3 C), 18.1 (3 C), 14.5, 13.1 (3 C).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{46}O_5Si$ + Na: 489.3012; found: 489.3031.

Ethyl (1*S*,6*R*,7*S*)-4-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1-(triisopropylsilyloxy)bicyclo[4.1.0]hept-3-ene-7-carboxylate (24b)
Yield: 21%; 58% ee; $[\alpha]_D^{25}$ +16.4 (*c* 0.28, $CHCl_3$).

IR (film): 2946, 2868, 1716 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.20 (br s, 1 H), 4.57–4.54 (m, 1 H), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.99–3.93 (m, 1 H), 3.87–3.82 (m, 1 H), 3.78–3.72 (m, 1 H), 3.52–3.46 (m, 1 H), 3.44–3.37 (m, 1 H), 2.93–2.86 (m, 1 H), 2.59–2.49 (m, 2 H), 2.33–2.26 (m, 1 H), 2.26–2.17 (m, 1 H), 2.17–2.09 (m, 1 H), 1.86 (d, *J* = 10.6 Hz, 1 H), 1.83–1.77 (m, 1 H), 1.72–1.67 (m, 1 H), 1.63 (dd, *J* = 10.6, 6.0 Hz, 1 H), 1.58–1.47 (m, 4 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.06–1.03 (m, 21 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 169.0, 131.9, 119.3 (0.5 C), 119.3 (0.5 C), 98.9 (0.5 C), 98.6 (0.5 C), 66.2 (0.5 C), 66.0 (0.5 C), 62.4 (0.5 C), 62.3 (0.5 C), 60.1, 58.0 (0.5 C), 58.0 (0.5 C), 37.5 (0.5 C), 37.5 (0.5 C), 31.1, 30.8, 29.7, 26.5 (0.5 C), 26.4 (0.5 C), 25.5, 25.1, 19.8 (0.5 C), 19.7 (0.5 C), 18.2 (3 C), 18.2 (3 C), 14.3, 12.8 (3 C).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{46}O_5Si$ + Na: 489.3012; found: 489.3016.

Ethyl (1*R*,6*S*,7*S*)-4-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1-(triethylsilyloxy)bicyclo[4.1.0]hept-3-ene-7-carboxylate (25a)
Yield: 33%; 77% ee; $[\alpha]_D^{24}$ +20.7 (*c* 0.69, $CHCl_3$).

IR (film): 3019, 2954, 2877, 1720, 1221, 1185, 1160, 1031 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.26 (br d, *J* = 5.5 Hz, 1 H), 4.55 (br s, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.85–3.80 (m, 1 H), 3.77–3.71 (m, 1 H), 3.52–3.47 (m, 1 H), 3.42–3.36 (m, 1 H), 2.79–2.73 (m, 1 H), 2.55–2.44 (m, 2 H), 2.26–2.16 (m, 3 H), 2.13–2.07 (m, 1 H), 1.83–1.76 (m, 1 H), 1.76–1.73 (m, 1 H), 1.73–1.66 (m, 1 H), 1.60–1.47 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.64 (dq, *J* = 15.7, 7.9 Hz, 3 H), 0.61 (dq, *J* = 15.7, 7.9 Hz, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.3, 131.5 (0.5 C), 131.5 (0.5 C), 119.1 (0.5 C), 119.1 (0.5 C), 98.7 (0.5 C), 98.7 (0.5 C), 66.2 (0.5 C), 66.1 (0.5 C), 62.6, 62.3, 60.2, 37.4 (0.5 C), 37.4 (0.5 C), 33.3, 30.7, 28.7, 28.5 (0.5 C), 28.5 (0.5 C), 27.5, 25.5, 19.6, 14.5, 6.9 (3 C), 5.7 (3 C).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{40}O_5Si$ + Na: 447.2543; found: 447.2520.

Ethyl (1*S*,6*R*,7*S*)-4-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1-(triethylsilyloxy)bicyclo[4.1.0]hept-3-ene-7-carboxylate (25b)
Yield: 19%; 41% ee; $[\alpha]_D^{24}$ +8.0 (*c* 0.53, $CHCl_3$).

IR (film): 2955, 2877, 1716, 1168, 1030 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.18 (br d, *J* = 2.9 Hz, 1 H), 4.58–4.53 (m, 1 H), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.99–3.92 (m, 1 H), 3.87–3.82 (m, 1 H), 3.77–3.72 (m, 1 H), 3.52–3.46 (m, 1 H), 3.43–3.36 (m, 1 H), 2.87–2.81 (m, 1 H), 2.58–2.48 (m, 2 H), 2.33–2.26

(m, 1 H), 2.24–2.17 (m, 1 H), 2.16–2.08 (m, 1 H), 1.83 (d, *J* = 10.7 Hz, 1 H), 1.84–1.77 (m, 1 H), 1.72–1.65 (m, 1 H), 1.62–1.47 (m, 5 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.63 (q, *J* = 8.0 Hz, 6 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 168.9, 132.1 (0.5 C), 132.1 (0.5 C), 119.0 (0.5 C), 119.0 (0.5 C), 98.9 (0.5 C), 98.6 (0.5 C), 66.2 (0.5 C), 66.0 (0.5 C), 62.4 (0.5 C), 62.3 (0.5 C), 60.2, 57.9, 37.5, 31.0, 30.8, 29.4, 26.3 (0.5 C), 26.2 (0.5 C), 25.6 (0.5 C), 25.5 (0.5 C), 24.5, 19.8 (0.5 C), 19.7 (0.5 C), 14.3, 6.9 (3 C), 5.5 (3 C).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{40}O_5Si$ + Na: 447.2543; found: 447.2521.

Ethyl (1*R*,6*S*,7*S*)-1-Methoxy-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-ene-7-carboxylate (26a)

Yield: 56%; 31% ee; $[\alpha]_D^{25}$ +12.4 (*c* 1.1, $CHCl_3$).

IR (film): 3019, 2944, 1717, 1209, 1176, 1031 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.30 (br d, *J* = 5.3 Hz, 1 H), 4.55 (br s, 1 H), 4.16 (dq, *J* = 11.7, 7.1 Hz, 1 H), 4.13 (dq, *J* = 11.7, 7.1 Hz, 1 H), 3.85–3.79 (m, 1 H), 3.77–3.72 (m, 1 H), 3.51–3.46 (m, 1 H), 3.42–3.36 (m, 1 H), 3.27 (s, 3 H), 2.79 (dd, *J* = 17.2, 5.3 Hz, 1 H), 2.57–2.47 (m, 2 H), 2.26–2.17 (m, 4 H), 1.83–1.76 (m, 2 H), 1.72–1.66 (m, 1 H), 1.58–1.47 (m, 4 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.6, 131.7 (0.5 C), 131.7 (0.5 C), 118.4 (0.5 C), 118.3 (0.5 C), 98.7, 67.6, 66.1 (0.5 C), 66.0 (0.5 C), 62.3, 60.4, 54.7, 37.4 (0.5 C), 37.4 (0.5 C), 30.7, 28.3, 28.2 (0.5 C), 28.2 (0.5 C), 28.1, 26.7, 25.5, 19.6, 14.4.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{28}O_5$ + Na: 347.1834; found: 347.1826.

Ethyl (1*R*,6*S*,7*S*)-1-[(2-Methoxyethoxy)methoxy]-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-ene-7-carboxylate (27a)

Yield: 48%; 39% ee; $[\alpha]_D^{26}$ +19.6 (*c* 0.85, $CHCl_3$).

IR (film): 3011, 2944, 1718, 1031 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.27 (m, 1 H), 4.77 (d, *J* = 7.1 Hz, 1 H), 4.74 (d, *J* = 7.1 Hz, 1 H), 4.56–4.53 (m, 1 H), 4.13 (dq, *J* = 10.9, 7.1 Hz, 1 H), 4.10 (dq, *J* = 10.9, 7.1 Hz, 1 H), 3.85–3.80 (m, 2 H), 3.77–3.71 (m, 1 H), 3.67 (ddd, *J* = 9.7, 6.0, 3.7 Hz, 1 H), 3.57–3.53 (m, 2 H), 3.53–3.46 (m, 1 H), 3.41–3.35 (m, 1 H), 3.38 (s, 3 H), 2.83 (dd, *J* = 17.5, 5.5 Hz, 1 H), 2.70–2.65 (m, 1 H), 2.57–2.50 (m, 1 H), 2.28–2.21 (m, 2H), 2.18 (t, *J* = 6.8 Hz, 2 H), 1.86–1.83 (m, 1 H), 1.83–1.76 (m, 1 H), 1.72–1.65 (m, 1 H), 1.60–1.47 (m, 4 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.4, 131.4 (0.5 C), 131.3 (0.5 C), 118.9, 98.7, 94.9, 71.7, 67.6, 67.1, 66.1 (0.5 C), 66.0 (0.5 C), 62.3, 60.5, 59.0, 37.4 (0.5 C), 37.4 (0.5 C), 30.7, 30.7, 28.2 (0.5 C), 28.2 (0.5 C), 28.2, 26.3, 25.5, 19.7, 14.4.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{34}O_7$ + Na: 421.2202; found: 421.2213.

Ethyl (1*R*,6*S*,7*S*)-4-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1-{[2-(trimethylsilyl)ethoxy]methoxy}bicyclo[4.1.0]hept-3-ene-7-carboxylate (28a)

Yield: 65%; 36% ee; $[\alpha]_D^{27}$ +18.1 (*c* 0.20, $CHCl_3$).

IR (film): 3009, 2952, 1717, 1222, 1063, 1029 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.29 (m, 1 H), 4.74 (d, *J* = 7.1 Hz, 1 H), 4.66 (d, *J* = 7.1 Hz, 1 H), 4.57–4.54 (m, 1 H), 4.18–4.08 (m, 2 H), 3.86–3.81 (m, 1 H), 3.79–3.70 (m, 2 H), 3.62–3.56 (m, 1 H), 3.52–3.47 (m, 1 H), 3.43–3.36 (m, 1 H), 2.87–2.82 (m, 1 H), 2.72–2.65 (m, 1 H), 2.58–2.51 (m, 1 H), 2.28–2.23 (m, 2 H), 2.19 (t, *J* = 6.9 Hz, 2 H), 1.87–1.84 (m, 1 H), 1.84–1.76 (m, 1 H), 1.72–1.66 (m, 1 H), 1.60–1.48 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 8.6 Hz, 2 H), 0.01 (s, 9 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.4, 131.3 (0.5 C), 131.3 (0.5 C), 119.0 (0.5 C), 119.0 (0.5 C), 98.8 (0.5 C), 98.8 (0.5 C), 94.3, 67.2, 66.1 (0.5 C), 66.1 (0.5 C), 65.9, 62.4 (0.5 C), 62.4 (0.5 C), 60.5, 37.4 (0.5 C), 37.4 (0.5 C), 31.0, 30.8, 28.3, 28.2 (0.5 C), 28.2 (0.5 C), 26.4, 25.5, 19.7, 18.2, 14.4, –1.3 (3 C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{40}O_6Si$ + Na: 463.2492; found: 463.2492.

(1*R*,6*S*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-7-methyl-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-en-7-yl)methanol (30)

To a stirred solution of LDA (1.10 mmol), prepared from *i*-Pr_2NH (0.17 mL, 1.20 mmol) and *n*-BuLi (1.57 M solution of in hexane, 0.70 mL, 1.10 mmol) in THF (0.75 mL), was added a solution of **15a** [153 mg, 87% purity (contaminated with maleic acid diethyl ester), 313 μmol] in THF (1.5 mL) via cannula at –78 °C. After stirring at –78 °C for 1 h, MeI (0.12 mL, 1.93 mmol) was added. The mixture was stirred at –78 °C for 4 h, diluted with sat. aq NH_4Cl (2 mL), and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–Et_2O, 15:1 → 10:1) to give **29** [137 mg (contaminated with unidentified impurities)] as a colorless oil. A suspension of $LiAlH_4$ (98.6 mg, 2.60 mmol) in THF (7 mL) was heated to reflux over 2 h. To this stirred suspension was added a solution of **29** (130 mg) in THF (4 mL) at 0 °C. After stirring the mixture at 0 °C for 3.5 h, $LiAlH_4$ (254 mg, 5.30 mmol) was added in four portions during 3.5 h to complete the reaction. After stirring the mixture at 0 °C for 1 h, the mixture was diluted with MeOH (4 mL) and sat. aq Na/K tartrate (30 mL), and warmed to r.t. The mixture was stirred at r.t. for 17 h and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified twice by column chromatography on silica gel (0.8 g, hexane–EtOAc, 4:1; 1.0 g, hexane–EtOAc, 6:1 → 2:1) to give **30** (98.9 mg, 80% in 2 steps) as a colorless oil; $[\alpha]_D^{25}$ –23.3 (*c* 0.98, $CHCl_3$).

IR (film): 3462 (br), 2952, 2930, 2858, 1258, 1216, 1134, 1029 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.33 (br s, 1 H), 4.54 (dd, *J* = 5.0, 2.6 Hz, 0.5 H), 4.47 (dd, *J* = 5.9, 3.1 Hz, 0.5 H), 3.94–3.38 (m, 6 H), 2.66–2.57 (m, 1 H), 2.50–2.27 (m, 4 H), 2.26–2.11 (m, 2 H), 1.84–1.77 (m, 1 H), 1.74–1.66 (m, 1 H), 1.60–1.47 (m, 4 H), 1.29 (s, 1.5 H), 1.28 (s, 1.5 H), 0.96–0.90 (m, 1 H), 0.89 (s, 4.5 H), 0.88 (s, 4.5 H), 0.10 (s, 3 H), 0.070 (s, 1.5 H), 0.066 (s, 1.5 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 133.4 (0.5 C), 132.9 (0.5 C), 120.8 (0.5 C), 120.5 (0.5 C), 99.7 (0.5 C), 99.1 (0.5 C), 66.5 (0.5 C), 65.5 (0.5 C), 63.9 (0.5 C), 63.5 (0.5 C), 63.0 (0.5 C), 62.9 (0.5 C), 59.7 (0.5 C), 59.5 (0.5 C), 37.4 (0.5 C), 37.4 (0.5 C), 31.4 (0.5 C), 31.3 (0.5 C), 31.0 (0.5 C), 30.8 (0.5 C), 28.8 (0.5 C), 28.7 (0.5 C), 28.4 (0.5 C), 28.2 (0.5 C), 25.9 (3 C), 25.5 (0.5 C), 25.4 (0.5 C), 25.4 (0.5 C), 24.6 (0.5 C), 20.6 (0.5 C), 20.0 (0.5 C), 18.1 (0.5 C), 18.1 (0.5 C), 18.1 (0.5 C), 18.0 (0.5 C), –3.4 (0.5 C), –3.4 (0.5 C), –3.5 (0.5 C), –3.6 (0.5 C).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{40}O_4Si$ + Na: 419.2594; found: 419.2584.

(1*R*,6*S*)-*tert*-Butyl-7,7-dimethyl-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]bicyclo[4.1.0]hept-3-en-1-yloxy)dimethylsilane [(–)-5]

To a stirred solution of alcohol **30** (15.3 mg, 38.6 μmol) in THF (0.3 mL) was added LHMDS (1.0 M solution of in THF, 420 μL, 420 μmol) at 0 °C. After stirring the mixture at 0 °C for 30 min, bis(dimethylamino)phosphoryl chloride (30.0 μL, 208 μmol) was added. The resulting mixture was stirred at r.t. for 1 h, $LiBHEt_3$ (1.09 M solution of in THF, 700 μL, 763 μmol) was added at r.t., and the mixture was stirred at reflux for 5.5 h. After cooling to r.t., the mixture

was diluted with MeOH (5 mL) and H_2O (5 mL), and extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.8 g, hexane–Et_2O, 40:1 → 20:1) to give (–)-**5** (10.8 mg, 74% in 2 steps) as a colorless oil; $[\alpha]_D^{25}$ –18.3 (*c* 0.87, $CHCl_3$).

IR (film): 2929, 1222 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 5.28 (br s, 1 H), 4.57 (br s, 1 H), 3.90–3.72 (m, 2 H), 3.53–3.36 (m, 2 H), 2.59–2.33 (m, 3 H), 2.21 (t, *J* = 7.0 Hz, 2 H), 1.97–1.89 (m, 1 H), 1.82–1.52 (m, 6 H), 1.14 (s, 3 H), 0.87 (s, 9 H), 0.82 (s, 3 H), 0.72 (d, *J* = 7.3 Hz, 1 H), 0.10 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 132.6 (0.5 C), 132.5 (0.5 C), 120.4 (0.5 C), 120.4 (0.5 C), 98.8, 66.5 (0.5 C), 66.4 (0.5 C), 62.3 (0.5 C), 62.3 (0.5 C), 58.8 (0.5 C), 58.8 (0.5 C), 37.5, 30.9 (0.5 C), 30.8 (0.5 C), 26.7, 26.0 (3 C), 25.6, 25.0, 24.9, 22.4 (0.5 C), 22.4 (0.5 C), 22.1, 19.7 (0.5 C), 19.7 (0.5 C), 18.1, 14.4 (0.5 C), 14.4 (0.5 C), –3.3, –3.6.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{40}O_3Si$ + Na: 403.2644; found: 403.2648.

2-[(1*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-7,7-dimethylbicyclo[4.1.0]hept-3-en-3-yl]ethanol (35)

The bicyclic compound (–)-**5** (34.8 mg, 91.4 μmol) was treated with propylene glycol (0.8 mL). After stirring the mixture at 140 °C for 16 h, propylene glycol (1.0 mL) was added in two portions during 18.5 h to complete the reaction. The reaction mixture was cooled at 0 °C, diluted with H_2O (2 mL), and extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.6 g, hexane–EtOAc, 40:1 → 10:1) to give **35** (19.1 mg, 70%) as a colorless oil; $[\alpha]_D^{25}$ –27.3 (*c* 0.74, $CHCl_3$).

IR (film): 3567 (br), 2956, 2930, 2885, 2858, 1647, 1221 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.34 (br s, 1 H), 3.64 (br t, *J* = 5.8 Hz, 2 H), 2.60–2.53 (m, 1 H), 2.45–2.34 (m, 2 H), 2.23–2.15 (m, 2 H), 1.94–1.88 (m, 1 H), 1.15 (s, 3 H), 0.88 (s, 9 H), 0.82 (s, 3 H), 0.74 (d, *J* = 7.4 Hz, 1 H), 0.098 (s, 3 H), 0.058 (s, 3 H); a signal due to one proton (OH) was not observed.

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 131.8, 121.7, 60.5, 58.7, 40.5, 30.9, 26.5, 25.9 (3 C), 24.4, 22.3, 22.2, 18.1, 14.4, –3.4, –3.6.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}O_2Si$ + Na: 319.2069; found: 319.2085.

Methyl 2-[(1*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-7,7-dimethylbicyclo[4.1.0]hept-3-en-3-yl]acetate (38)

To a stirred solution of alcohol **35** (14.0 mg, 47.2 μmol) in CH_2Cl_2 (0.6 mL) was added Dess–Martin periodinane (87.0 mg, 205 μmol) at r.t. The mixture was stirred at the same temperature for 2.5 h, diluted with half sat. aq $Na_2S_2O_3$ (5 mL) and sat. aq $NaHCO_3$ (3 mL), and extracted with Et_2O (3 × 5 mL). The combined extracts were washed with brine (5 mL) and dried (Na_2SO_4). Removal of the solvent afforded aldehyde **36**, which was used for the next reaction without further purification. To a solution of **36** in *t*-BuOH (0.9 mL) were added 2-methylbut-2-ene (0.12 mL, 1.13 mmol), NaH_2PO_4 (0.71 M solution in H_2O, 0.25 mL 178 μmol), and $NaClO_2$ (13.3 mg, 147 μmol) at r.t. The mixture was stirred at the same temperature for 1.5 h and concentrated to afford an aqueous solution of the crude product. The aqueous solution was diluted with EtOAc (3 mL) and acidified by adding sat. aq NaH_2PO_4 (10 mL) to pH 3. The mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (5 mL) and dried (Na_2SO_4). Removal of the solvent afforded carboxylic acid **37**, which was used for the next reaction without further purification. To a stirred solution of **37** in MeOH (0.3 mL) was added a solution of TMS diazomethane (2.0 M solution in Et_2O, 0.2 mL, 400 μmol) at 0 °C. The mixture was stirred at r.t. for 50 min and concentrated. The residual oil was purified by column chromatography on silica gel (0.7 g, hexane–EtOAc, 100:1) to give **38** (13.0 mg, 85% in 3 steps) as a colorless oil; $[\alpha]_D^{26}$ –18.7 (*c* 0.80, $CHCl_3$).

IR (film): 2953, 2929, 2886, 2858, 1732, 1221 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.39 (br s, 1 H), 3.65 (s, 3 H), 2.93 (s, 2 H), 2.63–2.55 (m, 1 H), 2.46–2.36 (m, 2 H), 1.98–1.92 (m, 1 H), 1.14 (s, 3 H), 0.87 (s, 9 H), 0.84 (s, 3 H), 0.74 (d, *J* = 7.4 Hz, 1 H), 0.10 (s, 3 H), 0.064 (s, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 172.0, 128.9, 123.5, 58.5, 51.7, 42.7, 31.0, 26.5, 25.9 (3 C), 24.8, 22.3 (2 C), 18.1, 14.3, –3.4, –3.6.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{32}O_3Si$ + Na: 347.2018; found: 347.2013.

2-[(1*S*,6*R*)/(1*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-7,7-dimethylbicyclo[4.1.0]hept-3-en-3-yl]ethanol [(±)-35]

The bicyclic compound (±)-**5** (2.68 g, 7.04 mmol) was treated with propylene glycol (25 mL). The mixture was stirred at 100 °C for 15 min. The reaction mixture was cooled at 0 °C, diluted with H_2O (40 mL), and extracted with $CHCl_3$ (3 × 45 mL). The combined extracts were washed with brine (70 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (70 g, hexane–EtOAc, 40:1 → 10:1) to give (±)-**35** (1.80 g, 86%) as a colorless oil.

Methyl 2-[(1*S*,6*R*)/(1*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-7,7-dimethylbicyclo[4.1.0]hept-3-en-3-yl]acetate [(±)-(38)]

To a stirred solution of alcohol (±)-**35** (1.58 g, 5.33 mmol) in CH_2Cl_2 (35 mL) was added Dess–Martin periodinane (2.95 g, 6.96 mmol) at r.t. The mixture was stirred at the same temperature for 40 min, diluted with sat. aq $Na_2S_2O_3$ (20 mL) and sat. aq $NaHCO_3$ (20 mL), and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (40 mL) and dried (Na_2SO_4). Removal of the solvent afforded aldehyde (±)-**36**, which was used in the next reaction without further purification. To a solution of (±)-**36** in *t*-BuOH (40 mL) were added 2-methylbut-2-ene (12.0 mL, 113 mmol), NaH_2PO_4 (0.82 M solution in H_2O, 20 mL, 16.4 mmol), and $NaClO_2$ (1.44 g, 15.9 mmol) at r.t. The mixture was stirred at the same temperature for 1 h and concentrated to afford an aqueous solution of the crude product. The aqueous solution was diluted with EtOAc (20 mL) and acidified by adding aq 1 M HCl to pH 3. The mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent afforded carboxylic acid (±)-**37**, which was used in the next reaction without further purification. To a stirred solution of carboxylic acid (±)-**37** in MeOH (30 mL) was added a solution of TMS diazomethane (2.0 M solution in Et_2O, 14.0 mL, 28.0 mmol) at 0 °C. The mixture was stirred at the r.t. for 10 min and concentrated. The residual oil was purified twice by column chromatography on silica gel (50 g, hexane–EtOAc, 50:1; 90 g, hexane–EtOAc, 100:1) to give (±)-**38** (1.55 g, 90% in 3 steps) as a colorless oil.

Methyl 2-[(1*S*,3*S*,4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-3,4-dihydroxy-7,7-dimethylbicyclo[4.1.0]heptan-3-yl]acetate [(–)-6]

To a stirred solution of methyl ester **38** (12.8 mg, 39.5 μmol) in a 5:1 mixture of acetone and H_2O (0.4 mL) were added *N*-methylmorpholine *N*-oxide (20.8 mg, 178 μmol) and OsO_4 (0.2 M solution in THF, 0.04 mL, 8.0 μmol) at r.t. After stirring at the same temperature for 24.5 h, the mixture was diluted with a solution of $NaHSO_3$ (108 mg) in H_2O (1 mL) and stirred at r.t. for 5.5 h. The mixture was then extracted with EtOAc (3 × 5 mL). The combined EtOAc layers were washed with sat. aq $Na_2S_2O_3$ (2 × 5 mL) and brine (25 × 5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.7 g, hexane–

EtOAc, 40:1 → 5:1) to give diol (–)-**6** (10.6 mg, 75%) as colorless crystals; $[\alpha]_D^{25}$ –3.3 (*c* 0.48, $CHCl_3$); mp 86.0–86.9 °C (EtOAc).

IR (film): 3567 (br), 2954, 2929, 2857, 1714, 1439, 1355, 1254, 1222, 1209 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.55 (br s, 1 H), 3.25 (br s, 1 H), 2.81 (d, *J* = 15.4 Hz, 1 H), 2.42 (dd, *J* = 13.8, 6.8 Hz, 1 H), 2.32 (d, *J* = 15.4 Hz, 1 H), 2.22 (dd, *J* = 15.4, 10.1 Hz, 1 H), 1.97 (d, *J* = 10.1 Hz, 1 H), 1.95 (dd, *J* = 13.8, 10.1 Hz, 1 H), 1.22 (dd, *J* = 15.4, 3.3 Hz, 1 H), 1.11 (s, 3 H), 0.89 (s, 3 H), 0.86 (s, 9 H), 0.68 (dd, *J* = 10.1, 3.3 Hz, 1 H), 0.17 (s, 3 H), 0.13 (s, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 173.7, 72.3, 71.0, 62.7, 51.9, 42.0, 36.0, 31.4, 26.1 (3 C), 24.1, 23.9, 22.5, 18.3, 15.7, –3.2 (2 C).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{34}O_5Si$ + Na: 381.2073; found: 381.2065.

Methyl 2-[(1*S*,3*S*,4*S*,6*R*)/(1*R*,3*R*,4*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-3,4-dihydroxy-7,7-dimethylbicyclo[4.1.0]heptan-3-yl]acetate [(±)-6]

To a stirred solution of methyl ester (±)-**38** (12.9 g, 39.7 mmol) in a 5:1 mixture of acetone and H_2O (85 mL) were added *N*-methylmorpholine *N*-oxide (14.2 g, 120 mmol) and OsO_4 (0.4 M solution in THF, 6.0 mL, 2.4 mmol) at r.t. After stirring at the same temperature for 9 h, the mixture was diluted with a solution of $NaHSO_3$ (4.9 g) in H_2O (50 mL) and stirred at r.t. for 13 h. The mixture was then extracted with EtOAc (4 × 70 mL). The combined EtOAc layers were washed with sat. aq $Na_2S_2O_3$ (2 × 100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (210 g, hexane–EtOAc, 40:1 → 10:1 → 5:1) to give (±)-**6** (12.0 g, 86%) as yellow-brown crystals.

Methyl (1*R*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-8,8-dimethyl-5-oxobicyclo[5.1.0]oct-3-ene-4-carboxylate [(–)-7]

To a stirred solution of diol (–)-**6** (6.5 mg, 18.1 μmol) in benzene (0.3 mL) was added $Pb(OAc)_4$ (12.6 mg, 28.4 μmol) at 0 °C. The mixture was stirred at r.t. for 1.5 h, diluted with sat. aq $NaHCO_3$ (1 mL), and filtered through a pad of Celite. The filtrate was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent afforded a mixture of aldol **42** and enone (–)-**7**, which was used for the next reaction without further purification. The mixture was treated with pyridine (0.4 mL) and Ac_2O (0.1 mL) at r.t. After stirring at r.t. for 3.5 h, the mixture was concentrated to afford an oil. The oil was purified by column chromatography on silica gel (0.5 g, hexane–EtOAc, 20:1 → 10:1) to give (–)-**7** (2.6 mg, 42% in 2 steps) as colorless crystals; $[\alpha]_D^{27}$ –154 (*c* 0.21, $CHCl_3$); mp 98.7–100.5 °C (hexane).

IR (film): 3023, 2955, 2921, 2856, 1731, 1254, 1211 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 8.7, 3.5 Hz, 1 H), 3.81 (s, 3 H), 2.89 (ddd, *J* = 17.5, 8.7, 1.2 Hz, 1 H), 2.84 (dd, *J* = 13.5, 5.9 Hz, 1 H), 2.58 (dd, *J* = 17.5, 3.5 Hz, 1 H), 2.17 (dd, *J* = 13.5, 11.7 Hz, 1 H), 1.21 (s, 3 H), 1.16 (s, 3 H), 0.83 (s, 9 H), 0.83 (m, 1 H), 0.06 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 195.9, 166.7, 150.3, 137.5, 70.5, 52.4, 42.4, 34.1, 30.1, 28.7, 25.9 (3 C), 22.7, 18.4, 17.6, –3.5, –3.6.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{30}O_4Si$ + Na: 361.1811; found: 361.1796.

Methyl (1*R*,7*S*)/(1*S*,7*R*)-(*tert*-Butyldimethylsilyloxy)-8,8-dimethyl-5-oxobicyclo[5.1.0]oct-3-ene-4-carboxylate [(±)-7]

To a stirred solution of diol (±)-**6** (12.0 g, 33.5 mmol) in benzene (250 mL) was added $Pb(OAc)_4$ (18.5 g, 11.3 mmol) at 0 °C. The mixture was stirred at r.t. for 2 h, diluted with sat. aq $NaHCO_3$ (250 mL), and filtered through a pad of Celite. The filtrate was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (2 × 80 mL) and dried (Na_2SO_4). Removal of the solvent afforded a mixture of (±)-**42** and (±)-**7**, which was used in the next reaction without further purification. The mixture was treated with pyridine (150 mL) and Ac_2O (40 mL) at r.t. After stirring at r.t. for 3 h, the mixture was concentrated to afford an oil. The oil was purified by column chromatography on silica gel (200 g, hexane–EtOAc, 30:1 → 10:1) to give (±)-**7** (8.35 g, 74% in 2 steps) as colorless crystals.

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(13) This asymmetric synthesis of seven-membered enone (–)-**7** had a low yield in comparison with our previous approach in racemic form, possibly because of the small reaction scale. The detailed experimental procedures for the seven-membered enone (±)-**7**[6] in multigram scale are given in the experimental section.