Construction of Polycyclic Ring Systems Fused to Cyclobutane by Cascade Reactions of Formyl α,β-Unsaturated Esters

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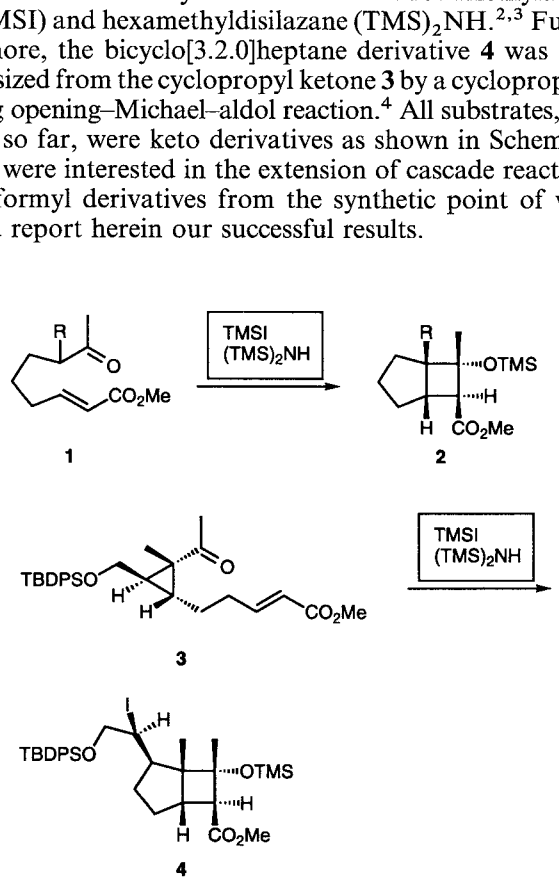
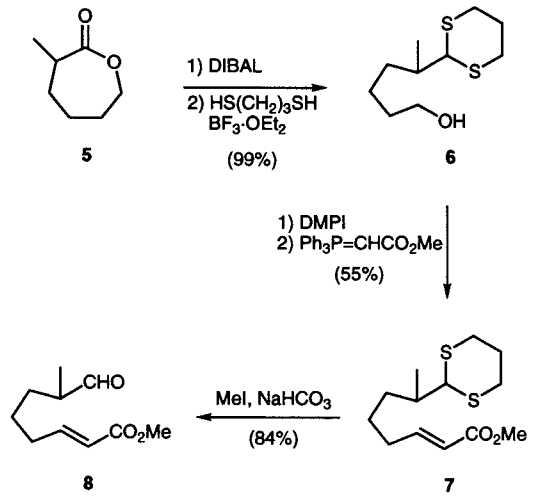
The intramolecular Michael–aldol reaction of methyl 7-formyloct-2-enoate (**8**) using iodotrimethylsilane (TMSI) and hexamethyldisilazane $(TMS)_2NH$ produced the separable diastereoisomeric mixture of bicyclo[3.2.0]heptanes **9** and **10**. Treatment of the α,β-unsaturated ester **19** possessing a formylcyclopropane function under the same reaction conditions caused cyclopropane ring opening–Michael–aldol reaction to give the bicyclo[3.2.0]heptane **22**. The filifolone derivative **31** was synthesized starting from **19** via **22**.

Recently, we developed new methodologies for the construction of polycyclic ring systems fused to cyclobutane by cascade reactions.[1,2] For example, bicyclo[3.2.0]heptanes **2** were produced by the intramolecular Michael–aldol reaction of the keto α,β-unsaturated esters **1**, which was carried out by the action of iodotrimethylsilane (TMSI) and hexamethyldisilazane $(TMS)_2NH$.[2,3] Furthermore, the bicyclo[3.2.0]heptane derivative **4** was synthesized from the cyclopropyl ketone **3** by a cyclopropane ring opening–Michael–aldol reaction.[4] All substrates, tested so far, were keto derivatives as shown in Scheme 1. We were interested in the extension of cascade reactions to formyl derivatives from the synthetic point of view and report herein our successful results.



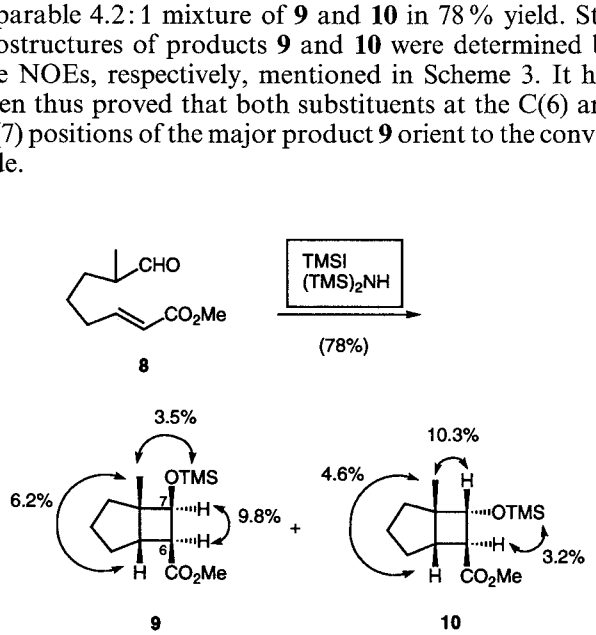
Scheme 1

The formyl α,β-unsaturated ester **8** was prepared from the lactone **5**[5] as described in Scheme 2. Namely, **5** was converted to **6** in two steps involving reduction with diisobutylaluminum hydride (DIBAL) and thioacetalization. Oxidation of **6** with the Dess-Martin periodinane (DMPI),[6] followed by the Wittig reaction of the resulting aldehyde, provided **7**, the deprotection of which furnished **8**.



Scheme 2

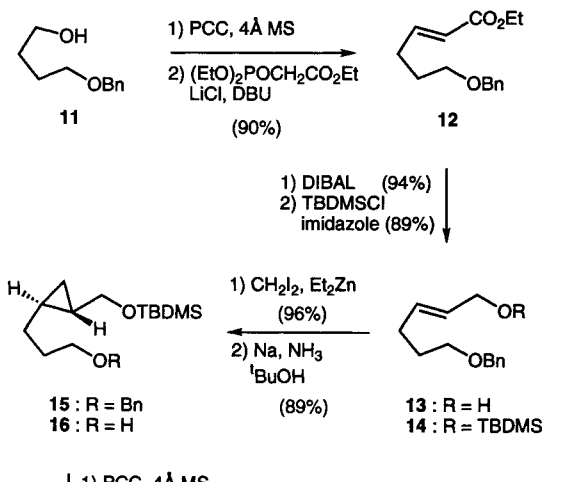
Reaction of **8** with 1.2 molar equivalents of TMSI in the presence of 1.5 molar equivalents of $(TMS)_2NH$ in 1,2-dichloroethane at room temperature gave rise to the desired intramolecular Michael–aldol reaction to afford a separable 4.2:1 mixture of **9** and **10** in 78% yield. Stereostructures of products **9** and **10** were determined by the NOEs, respectively, mentioned in Scheme 3. It has been thus proved that both substituents at the C(6) and C(7) positions of the major product **9** orient to the convex side.



Scheme 3

The formylcyclopropane **19** was synthesized from **11**[7] according to Scheme 4. Oxidation of **11**, followed by the Emmons reaction under Masamune's conditions,[8] gave the (*E*)-unsaturated ester **12**, which was reduced with DIBAL to give **13**. The construction of the cyclo-

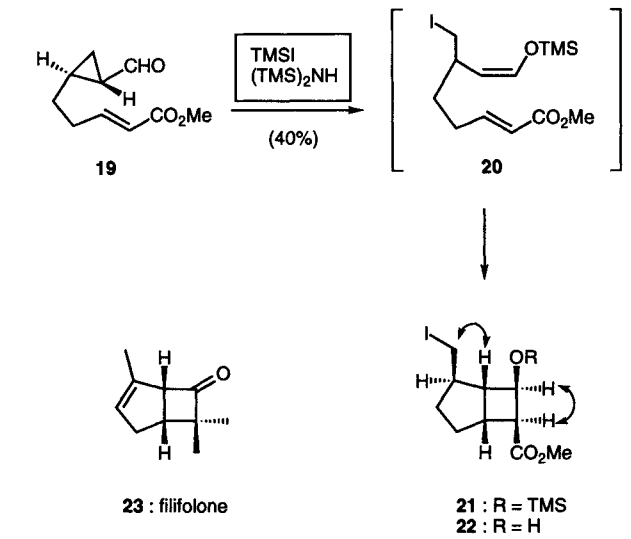
propane ring starting with **13** resulted in poor yield. After protection of the hydroxyl group with *tert*-butyldimethylsilyl (TBDMS) group, reaction of **14** with diiodomethane and diethylzinc[9] provided **15** in the excellent yield. After the debenzylation of **15**, oxidation of the resulting **16** with pyridinium chlorochromate (PCC) in the presence of 4 Å molecular sieves (MS), followed by the Wittig reaction, gave **17**. Removal of the TBDMS group of **17** with tetrabutylammonium fluoride and the successive oxidation of **18** with tetrapropylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMO),[10] provided **19**.



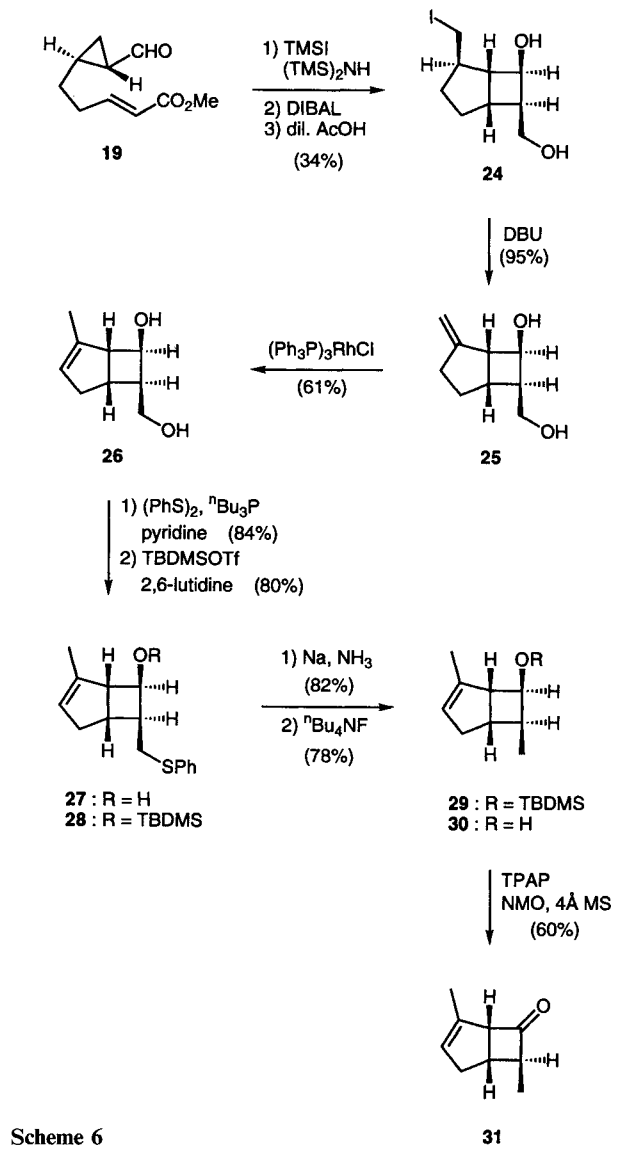
Scheme 4

Treatment of **19** with TMSI in the presence of $(TMS)_2NH$ in 1,2-dichloroethane as described (vide infra) caused the cleavage of the cyclopropane ring to afford **20**, which was cyclized in situ to **21**. Enolic structure (*Z*)-**20** was assigned to the intermediate, since the olefinic hydrogens at the silyl enol ether part were observed at $\delta = 6.28$ as doublet with $J = 7.1$ Hz and $\delta = 4.23$ as double doublet with $J = 8.5$ and 7.1 Hz, respectively. After chromatographic purification on silica gel, **22** was obtained in 40 % yield from **19**. It is noteworthy that the β-hydroxy ester **22** is isolated as a stable compound. The stereostructure of **22** was determined by the observation of NOEs in the NOESY spectrum depicted in Scheme 5.

The bicyclic compound **22**, produced by the above cascade reaction, possesses all carbon units of filifolone **(23)**[11] except one carbon at the C(6) position. Therefore, the transformation of **22** into the filifolone derivative **31** was investigated as shown in Scheme 6. The diol **24** was synthesized in three successive steps from **19**. The elimination of hydroiodide from **24** was carried out by reaction



Scheme 5



Scheme 6

with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Isomerization of **25** to **26** was performed with $(Ph_3P)_3RhCl$[12] in hot ethanol. The primary hydroxyl group of **26** was selectively converted to the sulfide by treatment with phenyl disulfide in the presence of tributylphosphine in pyridine.[13] After protection of the secondary hydroxyl group of **27** with TBDMS group, the desulfurization of the resulting **28** with sodium in liquid ammonia provided **29**, the TBDMS group of which was removed with tetrabutylammonium fluoride to give **30**. Oxidation of **30** with TPAP in the presence of NMO[10] produced **31**. It was revealed that the introduction of the methyl group at C(6) position of **31** was difficult.

In conclusion, it has been made clear that two cascade reactions, the intramolecular Michael–aldol reaction and the cyclopropane ring opening–Michael–aldol reaction, are applicable to formyl α,β-unsaturated esters.

Ratio of solvent mixtures is based on v/v. All new compounds gave satisfactory elemental analyses: C ± 0.41, H ± 0.43 or HRMS values: ± 0.0032 amu.

5-Methyl-6,6-(trimethylenedithio)hexan-1-ol (6):
To a stirred solution of **5**[5] (485 mg, 3.8 mmol) in anhydr. CH_2Cl_2/DME (1:1, 15 mL) was added a 0.93 M solution of DIBAL in hexane (4.5 mL, 4.2 mmol) at −78 °C, and the mixture was stirred for 50 min at −78 °C. After addition of Et_2O (80 mL) and H_2O (4.5 mL), the mixture was stirred for 1.5 h at r.t., and then filtered through Celite. After drying ($MgSO_4$), the filtrate was evaporated to give the crude hemiacetal, which was used in the next reaction without purification.

A mixture of the above product, propane-1,3-dithiol (1.1 mL, 11.4 mmol) and $BF_3 \cdot OEt_2$ (2.3 mL, 19 mmol) in anhydr. CH_2Cl_2 (15 mL) was stirred for 20 min at r.t. After dilution with Et_2O, the resulting mixture was treated with H_2O (3 mL) during 5 min. The organic solution was washed with 10% aq NaOH and brine, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel with Et_2O/hexane (1:1) as eluent to afford **6** (822 mg, 99%) as a yellow oil.

IR (neat): $\nu = 3350\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.15$ (d, $J = 4.0$ Hz, 1H), 3.66 (t, $J = 6.6$ Hz, 2H), 2.98–2.81 (m, 4H), 2.18–2.08 (m, 1H), 1.94–1.75 (m, 2H), 1.70–1.51 (m, 3H), 1.50–1.28 (m, 4H), 1.09 (d, $J = 7.0$ Hz, 3H).

HRMS: *m/z* calc. for $C_{10}H_{20}OS_2$ 220.0988, found 220.0971.

Methyl (2*E*)-7-Methyl-8,8-trimethylenedithiooct-2-enoate (7):
To a mixture of DMPI[6] (500 mg, 1.2 mmol) in anhydr. CH_2Cl_2 (5 mL) was added under cooling with ice a solution of **6** (200 mg, 0.91 mmol) in anhydr. CH_2Cl_2 (1 mL), and the mixture was stirred for 30 min at r.t. After addition of Et_2O, sat. $NaHCO_3$ and 0.1 N aq $Na_2S_2O_3$, the mixture was stirred for 10 min at r.t. The organic layer was washed with H_2O, brine, and dried ($MgSO_4$). Evaporation of the solvents gave the crude aldehyde, which was subjected to the following reaction without purification.

A solution of the above product and $Ph_3P{=}CHCO_2Me$ (395 mg, 1.2 mmol) in MeCN (6 mL) was stirred for 15 h at r.t. Evaporation of the solvent gave a residue, which was chromatographed on silica gel. Elution with Et_2O/hexane (1:5) provided **7** (138 mg, 55%) as a colorless oil.

IR (neat): $\nu = 1730, 1660\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.97$ (dt, $J = 15.8$, 7.3 Hz, 1H), 5.83 (dt, $J = 15.8$, 1.1 Hz, 1H), 4.12 (d, $J = 4.4$ Hz, 1H), 3.73 (s, 3H), 2.92–2.82 (m, 4H), 2.25–2.16 (m, 2H), 2.15–2.06 (m, 1H), 1.92–1.76 (m, 2H), 1.69–1.57 (m, 1H), 1.55–1.29 (m, 3H), 1.09 (d, $J = 7.0$ Hz, 3H).

HRMS: *m/z* calc. for $C_{13}H_{22}O_2S_2$ 274.1060, found 274.1028.

Methyl (2*E*)-7-Formyloct-2-enoate (8):
A mixture of **7** (413 mg, 1.5 mmol), $NaHCO_3$ (630 mg, 7.5 mmol), and MeI (0.93 mL, 15 mmol) in MeCN/H_2O (8:1, 13.5 mL) was stirred for 7 h at 40 °C. After dilution with Et_2O, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give a residue, which was subjected to silica gel chromatography. Elution with Et_2O/hexane (1:2) yielded **8** (232 mg, 84%) as a yellow oil.

IR (neat): $\nu = 1730, 1725, 1660\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.61$ (d, $J = 1.5$ Hz, 1H), 6.95 (dt, $J = 14.3$, 7.0 Hz, 1H), 5.85 (dt, $J = 14.3$, 1.1 Hz, 1H), 3.73 (s, 3H), 2.42–2.29 (m, 1H), 2.28–2.17 (m, 2H), 1.82–1.67 (m, 1H), 1.62–1.22 (m, 3H), 1.11 (d, $J = 7.3$ Hz, 3H).

HRMS: *m/z* calc. for $C_{10}H_{16}O_3 + H$ 185.1177, found $M^+ + H$ 185.1163.

(±)-(1*S,5*R**,6*S**,7*R**)- and (1*S**,5*R**,6*S**,7*S**)-6-Methoxycarbonyl-1-methyl-7-(trimethylsiloxy)bicyclo[3.2.0]heptanes (9 and 10):**
TMSI (0.21 mL, 1.5 mmol) was added to a stirred solution of **8** (232 mg, 1.3 mmol) and $(TMS)_2NH$ (0.4 mL, 1.9 mmol) in anhydr. $ClCH_2CH_2Cl$ (5.5 mL) under cooling with ice. The mixture was stirred for 10 min at the same temperature and for 9 h at r.t. After dilution with Et_2O, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with Et_2O/hexane (1:10) provided a 4.2:1 mixture of **9** and **10** (252 mg, 78%), which were separated by HPLC using a 4.6 × 250 mm column of Dynamax Microsorb silica (5 μm) with Et_2O/hexane (1:25, 1 mL/1 min) as eluent.

9:

IR (neat): $\nu = 1735\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.98$ (d, $J = 8.4$ Hz, 1H), 3.66 (s, 3H), 2.78 (dd, $J = 8.4$, 4.8 Hz, 1H), 2.62 (br t, $J = 5.5$ Hz, 1H), 1.85–1.73 (m, 1H), 1.69–1.38 (m, 4H), 1.29–1.18 (m, 1H), 1.09 (s, 3H), 0.05 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.8$, 71.9, 51.3, 50.4, 48.8, 41.2, 39.8, 31.5, 26.3, 19.0, −0.20.

HRMS: *m/z* calc. for $C_{13}H_{24}O_3Si$ 256.1493, found 256.1482.

10:

IR (neat): $\nu = 1735\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.03$ (d, $J = 6.2$ Hz, 1H), 3.68 (s, 3H), 2.37 (t, $J = 6.2$ Hz, 1H), 2.12–2.01 (m, 2H), 1.83–1.73 (m, 2H), 1.67–1.55 (m, 3H), 1.15 (s, 3H), 0.08 (s, 9H).

^{13}C NMR (125 MHz, C_6D_6): $\delta = 174.4$, 73.5, 51.0, 49.9, 43.8, 32.7, 32.3, 30.4, 26.6, 25.8, −0.03.

HRMS: *m/z* found 256.1477.

Ethyl (2*E*)-6-Benzyloxyhex-2-enoate (12):
To a solution of **11**[7] (10 g, 56 mmol) in anhydr. CH_2Cl_2 (200 mL) were added at r.t. 4 Å MS (22 g) and PCC (14.4 g, 67 mmol), and the mixture was stirred for 1.5 h at r.t. After dilution with Et_2O, the mixture was filtered through silica gel. Evaporation of the filtrate gave the crude aldehyde, which was used in the next reaction without further purification.

After a mixture of LiCl (2.8 g, 67 mmol), $(EtO)_2POCH_2CO_2Et$ (13.4 mL, 67 mmol), and DBU (9.1 mL, 61 mmol) in anhydr. MeCN (150 mL) had been stirred for 30 min at r.t., to the resulting mixture was added a solution of the above aldehyde in anhydr. MeCN (30 mL). After stirring for 1 h, evaporation of the solvent gave a residue, which was chromatographed on silica gel. Elution with Et_2O/hexane/CH_2Cl_2 (1:10:1) provided **12** (12.4 g, 90%) as a colorless oil.

IR (neat): $\nu = 1720, 1650\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.38–7.28$ (m, 5H), 6.96 (dt, $J = 15.4$, 7.0 Hz, 1H), 5.82 (dt, $J = 15.4$, 1.5 Hz, 1H), 4.50 (s, 2H), 4.18 (q, $J = 7.3$ Hz, 2H), 3.49 (t, $J = 6.2$ Hz, 2H), 2.32 (ddd, $J = 13.9$, 7.0, 1.5 Hz, 2H), 1.78 (dd, $J = 7.0$, 6.2 Hz, 2H), 1.29 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 148.2, 138.4, 128.2, 127.41, 127.36, 121.6, 72.8, 69.2, 59.9, 28.8, 28.2, 14.2.

HRMS: *m/z* calc. for $C_{15}H_{20}O_3$ 248.1411, found 248.1410.

(2*E*)-6-(Benzyloxy)hex-2-en-1-ol (13):
To a stirred solution of **12** (10 g, 40 mmol) in anhydr. CH_2Cl_2 (200 mL) was slowly added a 0.93 M solution of DIBAL in hexane (95 mL, 89 mmol) at − 78 °C. After stirring for 1 h at − 78 °C, Et_2O and H_2O (95 mL) were added. After stirring for 2 h at r.t., the mixture was filtered through Celite, and the filtrate was dried ($MgSO_4$). Evaporation of the solvent gave a residue, which was purified by chromatography on silica gel. Elution with EtOAc/hexane (1:2) provided **13** (7.8 g, 94%) as a colorless oil.

IR (neat): ν = 3350 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5H), 5.72–5.54 (m, 2H), 4.49 (s, 2H), 4.03 (d, J = 4.0 Hz, 2H), 3.47 (t, J = 6.6 Hz, 2H), 2.12 (dd, J = 12.8, 6.6 Hz, 2H), 1.92 (br s, 1H), 1.70 (t, J = 7.7 Hz, 2H).

HRMS: *m/z* calc. for $C_{13}H_{18}O_2$ 206.1306, found 206.1294.

(2*E*)-6-(Benzyloxy)-1-(*tert*-butyldimethylsiloxy)hex-2-ene (14):
A mixture of **13** (1.59 g, 77 mmol), imidazole (7.9 g, 116 mmol), and TBDMSCl (14 g, 93 mmol) in anhydr. DMF (250 mL) was stirred for 8 h at r.t. The mixture was partitioned between H_2O and Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was chromatographed on silica gel with Et_2O/hexane (1:5) as eluent to afford **14** (21.9 g, 89%) as a colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5H), 5.69–5.48 (m, 2H), 4.49 (s, 2H), 4.11 (d, J = 4.8 Hz, 2H), 3.47 (t, J = 6.6 Hz, 2H), 2.13 (dd, J = 14.3, 7.0 Hz, 2H), 1.70 (t, J = 7.0 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H).

HRMS: *m/z* calc. for $C_{19}H_{32}O_2Si - C_4H_9$ 263.1466, found $M^+ - t$-Bu 263.1480.

***trans*-2-(3-Benzyloxypropyl)-1-[(*tert*-butyldimethylsiloxy)methyl)]-cyclopropane (15):**
CH_2I_2 (6.4 mL, 79 mmol) was slowly added to a stirred 1 M solution of Et_2Zn in hexane (47 mL, 47 mmol) in anhydr. $ClCH_2CH_2Cl$ (170 mL) under cooling with ice, and the mixture was stirred for 30 min at the same temperature. After addition of a solution of **14** (10.1 g, 32 mmol) in anhydr. $ClCH_2CH_2Cl$ (30 mL), the mixture was stirred for 1 h at the same temperature. After dilution with Et_2O, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with Et_2O/hexane (1:30) gave **15** (10.1 g, 96%) as a colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5H), 4.50 (s, 2H), 3.52–3.48 (m, 1H), 3.51 (t, J = 6.6 Hz, 2H), 3.44 (dd, J = 10.6, 6.6 Hz, 1H), 1.71 (t, J = 7.0 Hz, 2H), 1.41–1.24 (m, 2H), 0.89 (s, 9H), 0.80–0.69 (m, 1H), 0.62–0.52 (m, 1H), 0.34 (dt, J = 8.1, 4.8 Hz, 1H), 0.25 (dt, J = 8.4, 4.8 Hz, 1H), 0.04 (s, 6H).

HRMS: *m/z* calc. for $C_{20}H_{34}O_2Si - C_4H_9$ 277.1622, found $M^+ - t$-Bu 277.1613.

***trans*-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-(3-hydroxypropyl)cyclopropane (16):**
To a stirred solution of **15** (10.1 g, 30.2 mmol), *t*-BuOH (1 mL), and anhydr. THF (10 mL) in anhydr. NH_3 (500 mL) was added portionwise Na (1.0 g, 45.3 mmol). After stirring for 40 min, followed by addition of NH_4Cl (400 mg), NH_3 was evaporated to give a residue, which was taken up in EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with EtOAc/hexane (1:4) as eluent yielded **16** (6.6 g, 89%) as a colorless oil.

IR (neat): ν = 3350 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.70 (br dd, J = 11.7, 5.9 Hz, 2H), 3.63 (dd, J = 10.6, 5.9 Hz, 1H), 3.30 (dd, J = 10.6, 7.0 Hz, 1H), 1.72–1.63 (m, 3H), 1.52–1.43 (m, 1H), 1.20 (dt, J = 13.9, 7.3 Hz, 1H), 0.90 (s, 9H), 0.84–0.74 (m, 1H), 0.69–0.58 (m, 1H), 0.35 (dt, J = 8.4, 4.8 Hz, 1H), 0.26 (dt, J = 8.4, 4.8 Hz, 1H), 0.05 (s, 6H).

HRMS: *m/z* calc. for $C_{13}H_{28}O_2Si - C_4H_9$ 187.1153, found $M^+ - t$-Bu 187.1142.

***trans*-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-[(3*E*)-4-(methoxycarbonyl)but-3-enyl]cyclopropane (17):**
A mixture of **16** (6.1 g, 25 mmol), 4 Å MS (10.3 g), and PCC (6.9 g, 32 mmol) in anhydr. CH_2Cl_2 (120 mL) was stirred for 1 h at r.t. After dilution with Et_2O, the mixture was filtered through silica gel. Evaporation of the filtrate provided the crude aldehyde, which was subjected to the following reaction without further purification.

A mixture of the above product and $Ph_3P{=}CHCO_2Me$ (10 g, 30 mmol) in MeCN (100 mL) was stirred for 16 h at r.t. After evaporation of the solvent, the residue was purified by chromatography on silica gel with Et_2O/hexane (1:5) as eluent to afford **17** (5.7 g, 77%) as a colorless oil.

IR (neat): ν = 1720, 1650 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.99 (dt, J = 15.8, 7.0 Hz, 1H), 5.82 (dt, J = 15.8, 1.5 Hz, 1H), 3.72 (s, 3H), 3.48 (dd, J = 10.6, 6.2 Hz, 1H), 3.42 (dd, J = 10.6, 6.6 Hz, 1H), 2.28 (ddd, J = 14.3, 7.3, 1.5 Hz, 2H), 1.48–1.32 (m, 2H), 0.89 (s, 9H), 0.82–0.72 (m, 1H), 0.66–0.54 (m, 1H), 0.38 (dt, J = 8.4, 4.8 Hz, 1H), 0.27 (dt, J = 8.4, 5.1 Hz, 1H), 0.04 (s, 6H).

HRMS: *m/z* calc. for $C_{16}H_{30}O_3Si - C_4H_9$ 241.1259, found $M^+ - t$-Bu 241.1235.

***trans*-1-Hydroxymethyl-2-[(3*E*)-4-(methoxycarbonyl)but-3-enyl]cyclopropane (18):**
A solution of **17** (5.7 g, 19 mmol) in THF (110 mL) was stirred with a 1 M THF solution of Bu_4NF (23 mL, 23 mmol) for 1 h at r.t. After dilution with EtOAc, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with EtOAc/hexane (1:1) as eluent afforded **18** (3.2 g, 91%) as a colorless oil.

IR (neat): ν = 3370, 1715, 1650 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.00 (dt, J = 15.4, 7.0 Hz, 1H), 5.84 (dt, J = 15.4, 1.5 Hz, 1H), 3.73 (s, 3H), 3.44 (d, J = 7.2 Hz, 2H), 2.31 (ddd, J = 14.6, 8.1, 1.5 Hz, 2H), 1.58 (br s, 1H), 1.42 (ddd, J = 14.3, 8.1, 1.1 Hz, 2H), 0.92–0.81 (m, 1H), 0.70–0.58 (m, 1H), 0.41 (dt, J = 8.4, 4.4 Hz, 1H), 0.38–0.31 (m, 1H).

HRMS: *m/z* calc. for $C_{10}H_{16}O_3 + H$ 185.1177, found $M^+ + H$ 185.1206.

***trans*-2-[(3*E*)-4-(Methoxycarbonyl)but-3-enyl]cyclopropanecarbaldehyde (19):**
To a stirred solution of **18** (3.2 g, 17 mmol) in anhydr. CH_2Cl_2 (60 mL) were added at r.t. 4Å MS (4.1 g), NMO (4.1 g, 35 mmol), and TPAP[10] (305 mg, 0.87 mmol), and the mixture was stirred for 20 min at r.t. After dilution with Et_2O, the mixture was filtered through silica gel to remove the catalyst. Evaporation of the filtrate gave a residue, which was purified by chromatography on silica gel. Elution with Et_2O/hexane (2:1) provided **19** (2.57 g, 81%) as a yellow oil.

IR (neat): ν = 1715, 1710, 1680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.05 (d, J = 5.1 Hz, 1H), 6.95 (dt, J = 15.7, 6.6 Hz, 1H), 5.84 (dt, J = 15.7, 1.5 Hz, 1H), 3.73 (s, 3H), 2.32 (ddd, J = 14.7, 7.3, 1.5 Hz, 2H), 1.72–1.63 (m, 1H), 1.58–1.46 (m, 3H), 1.36–1.28 (m, 1H), 0.98–0.92 (m, 1H).

HRMS: *m/z* calc. for $C_{10}H_{14}O_3 + H$ 183.1020, found $M^+ + H$ 183.1000.

(±)-(1*R,2*R**,5*R**,6*S**,7*R**)-2-Iodomethyl-6-(methoxycarbonyl)bicyclo[3.2.0]heptan-7-ol (22):**
To a stirred solution of **19** (45 mg, 0.25 mmol) and $(TMS)_2NH$ (80 µL, 0.37 mmol) in anhydr. $ClCH_2CH_2Cl$ (1.2 mL) was added TMSI (40 µL, 0.30 mmol) under cooling with ice. The mixture was stirred for 17 h at r.t. After dilution with Et_2O, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with Et_2O/hexane (1:30) as eluent gave **22** (31 mg, 40%) as a yellow oil.

IR (neat): ν = 3450, 1720 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.03 (ddd, J = 8.5, 7.9, 4.3 Hz, 1 H), 3.71 (s, 3 H), 3.25 (d, J = 8.5 Hz, 1 H), 3.01 (dd, J = 9.8, 7.3 Hz, 1 H), 2.96–2.90 (m, 2 H), 2.57 (dd, J = 6.7, 3.1 Hz, 1 H), 2.42 (dd, J = 14.6, 7.3 Hz, 1 H), 1.91–1.76 (m, 3 H), 1.59–1.55 (m, 2 H).

HRMS: m/z calc. for $C_{10}H_{15}IO_3$ + H 311.0142, found M^+ + H 311.0150.

(±)-(1*R,2*R**,5*R**,6*R**,7*R**)-6-Hydroxymethyl-2-(iodomethyl)bicyclo[3.2.0]heptan-7-ol (24):**

By utilizing the same procedure as above, **19** (910 mg, 5 mmol) was treated with TMSI (0.85 mL, 6 mmol) and $(TMS)_2NH$ (1.6 mL, 7.5 mmol) in anhydr. $ClCH_2CH_2Cl$ (17 mL) to afford the crude **21**. To a solution of the product in anhydr. CH_2Cl_2 (20 mL) was slowly added a 0.93 M solution of DIBAL in hexane (11.8 mL, 11 mmol) at −78 °C, and the mixture was stirred for 1 h at −78 °C. After addition of Et_2O (25 mL) and H_2O (11.8 mL), followed by stirring for 2 h at r.t., the mixture was filtered through Celite. After drying ($MgSO_4$), evaporation of the solvent gave the crude alcohol, which was used in the following reaction without purification.

A mixture of the above product and AcOH/H_2O/THF (3:1:1, 10 mL) was stirred for 1 h at r.t. Concentration of the reaction mixture under a reduced pressure gave a residue, which was subjected to chromatography on silica gel. Elution with EtOAc/hexane (1:1) afforded **24** (483 mg, 34%) as a colorless oil.

IR (neat): ν = 3370 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (dd, J = 8.1, 4.0 Hz, 1 H), 3.92 (dd, J = 11.0, 7.0 Hz, 1 H), 3.85 (dd, J = 11.0, 4.0 Hz, 1 H), 3.00 (d, J = 7.7 Hz, 1 H), 2.99 (d, J = 8.1 Hz, 1 H), 2.58–2.35 (m, 6 H), 2.19–2.11 (m, 1 H), 1.95–1.68 (m, 2 H), 1.54–1.45 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.7, 62.7, 54.1, 47.8, 44.6, 34.5, 32.4, 29.0, 11.5.

HRMS: m/z calc. for $C_9H_{15}IO_2 - H_2O$ 263.9977, found $M^+ - H_2O$ 264.0010.

(±)-(1*R,5*R**,6*R**,7*R**)-6-Hydroxymethyl-2-methylenebicyclo[3.2.0]heptan-7-ol (25):**

A mixture of **24** (1.4 g, 5 mmol) and DBU (3.7 mL, 25 mmol) in anhydr. benzene (25 mL) was heated for 8 h under reflux. After dilution with EtOAc, the mixture was washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with EtOAc/hexane (1:1) as eluent provided **25** (730 mg, 95%) as a colorless oil.

IR (neat): ν = 3375 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.87 (br s, 1 H), 4.86 (br s, 1 H), 4.18–4.12 (m, 1 H), 3.95 (br dd, J = 10.6, 7.3 Hz, 1 H), 3.87 (br dd, J = 10.6, 4.4 Hz, 1 H), 2.90 (br d, J = 7.7 Hz, 1 H), 2.75–2.63 (m, 2 H), 2.54–2.43 (m, 1 H), 2.40–2.23 (m, 3 H), 1.82–1.69 (m, 1 H), 1.67–1.54 (m, 1 H).

HRMS: m/z calc. for $C_9H_{14}O_2$ + 155.1071, found M^+ + 155.1093.

(±)-(1*S,5*R**,6*R**,7*R**)-6-(Hydroxymethyl)-2-methylbicyclo[3.2.0]hept-2-en-7-ol (26):**

A mixture of **25** (230 mg, 1.5 mmol) and $(Ph_3P)_3RhCl$ (138 mg, 0.15 mmol) in anhydr. EtOH (4 mL) was heated for 72 h under reflux. After cooling, the mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which was chromatographed on silica gel. Elution with EtOAc/hexane (1:2) provided **26** (141 mg, 61%) as a yellow oil.

IR (neat): ν = 3375 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.34 (br s, 1 H), 4.22–4.20 (m, 1 H), 3.90–3.88 (m, 2 H), 2.90 (br s, 1 H), 2.82 (dd, J = 14.3, 6.1 Hz, 1 H), 2.64–2.48 (m, 2 H), 2.28 (t, J = 5.7 Hz, 1 H), 2.19–2.08 (m, 2 H), 1.76 (br s, 3 H).

HRMS: m/z calc. for $C_9H_{14}O_2$ 154.0993, found 154.0972.

(±)-(1*S,5*R**,6*S**,7*R**)-2-Methyl-6-[(phenylthio)methyl]bicyclo[3.2.0]hept-2-en-7-ol (27):**

A mixture of **26** (118 mg, 0.77 mmol), Bu_3P (0.57 mL, 2.3 mmol), and $(PhS)_2$ (501 mg, 2.3 mmol) in anhydr. pyridine (2.5 mL) was heated for 6 h under reflux. After dilution with Et_2O, the mixture was washed with 10% aq NaOH, H_2O, and brine, dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel with Et_2O/hexane (1:3) as eluent gave **27** as a yellow oil.

IR (neat): ν = 3440 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.15 (m, 5 H), 5.29 (br s, 1 H), 4.18 (dd, J = 5.9, 0.7 Hz, 1 H), 3.22 (dd, J = 12.5, 10.3 Hz, 1 H), 3.08 (dd, J = 12.5, 6.6 Hz, 1 H), 2.92–2.84 (m, 1 H), 2.70 (dd, J = 14.3, 7.3 Hz, 1 H), 2.58–2.46 (m, 1 H), 2.32–2.21 (m, 1 H), 2.13 (br s, 1 H), 2.07 (br s, 1 H), 1.74 (br s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5, 136.2, 129.4, 129.0, 126.1, 126.0, 76.7, 55.8, 44.4, 40.8, 38.8, 33.2, 14.5.

HRMS: m/z calc. for $C_{15}H_{18}OS$ 246.1077, found 246.1106.

(±)-(1*S,5*R**,6*S**,7*R*)-7-(*tert*-Butyldimethylsiloxy)-2-methyl-6-[(phenylthio)methyl]bicyclo[3.2.0]hept-2-ene (28):**

To a stirred solution of **27** (223 mg, 0.91 mmol) and 2,6-lutidine (0.2 mL, 1.8 mmol) in anhydr. CH_2Cl_2 (4 mL) was added at r.t. TBDMSOTf (0.3 mL, 1.4 mmol). After stirring for 3 h, the mixture was partitioned between H_2O and Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was chromatographed on silica gel. Elution with Et_2O/hexane (1:5) provided **28** (261 mg, 80%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.08 (m, 5 H), 5.26 (br s, 1 H), 4.10 (d, J = 6.6 Hz, 1 H), 3.17 (dd, J = 12.5, 7.3 Hz, 1 H), 3.02 (dd, J = 12.5, 8.8 Hz, 1 H), 2.85–2.78 (m, 1 H), 2.67 (dd, J = 14.3, 7.0 Hz, 1 H), 2.57–2.45 (m, 1 H), 2.27 (t, J = 7.0 Hz, 1 H), 2.05 (br d, J = 16.1 Hz, 1 H), 1.72 (br s, 3 H), 0.91 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

HRMS: m/z calc. for $C_{21}H_{32}OSSi$ 360.1941, found 360.1961.

(±)-(1*R,5*S**,6*S**,7*S**)-7-(*tert*-Butyldimethylsiloxy)-2,6-dimethylbicyclo[3.2.0]hept-2-ene (29):**

To a stirred solution of **28** (260 mg, 0.72 mmol) and THF (2 mL) in anhydr. NH_3 (15 mL) was added portionwise Na (33 mg, 1.4 mmol) during 1 h. After addition of NH_4Cl (30 mg), followed by evaporation of NH_3, the residue was taken up into Et_2O. The extract was washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by chromatography on silica gel. Elution with Et_2O/pentane (1:100) provided **29** (149 mg, 82%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.29 (br s, 1 H), 4.01 (d, J = 6.6 Hz, 1 H), 2.86–2.79 (m, 1 H), 2.54–2.39 (m, 2 H), 2.18–2.04 (m, 2 H), 1.75 (br s, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.09 (s, 6 H).

HRMS: m/z calc. for $C_{15}H_{28}OSi$ 252.1908, found 252.1935.

(±)-(1*R,5*S**,6*S**,7*S**)-2,6-Dimethylbicyclo[3.2.0]hept-2-en-7-ol (30):**

A solution of **29** (40 mg, 0.16 mmol) in THF (1 mL) was stirred with 1 M THF solution of Bu_4NF (0.20 mL, 0.20 mmol) for 1 h at r.t. After dilution with Et_2O, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with Et_2O/pentane (1:5) provided **30** (17 mg, 78%) as a colorless oil.

IR (neat): ν = 3350 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.31 (br s, 1 H), 4.06 (d, J = 6.6 Hz, 1 H), 2.84 (br s, 1 H), 2.55–2.43 (m, 2 H), 2.19–2.04 (m, 2 H), 1.79 (br s, 1 H), 1.75 (br s, 3 H), 1.04 (d, J = 7.3 Hz, 3 H).

HRMS: m/z calc. for $C_9H_{14}O$ 138.1044, found 138.1030.

(±)-(1*R,5*S**,6*S**)-2,6-Dimethylbicyclo[3.2.0]hept-2-en-7-one (31):**

To a stirred solution of **30** (8 mg, 0.06 mmol) in anhydr. CH_2Cl_2 (0.5 mL) were added at r.t. 4 Å MS (14 mg), NMO (14 mg, 0.12 mmol) and TPAP[10] (1 mg, 3 μmol), and the mixture was stirred for 45 min at r.t. After dilution with Et_2O, the mixture was filtered through silica gel. Evaporation of the filtrate afforded a residue, which was chromatographed on silica gel with Et_2O/pentane (1:10) as eluent to provide **31** (4.7 mg, 60%) as a yellow oil.

IR (neat): ν = 1760, 1650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.43 (br s, 1 H), 3.98 (br s, 1 H), 3.05–2.92 (m, 1 H), 2.87–2.72 (m, 1 H), 2.53–2.32 (m, 2 H), 1.76 (br s, 3 H), 1.19 (d, J = 7.3 Hz, 3 H).

HRMS: m/z calc. for $C_9H_{12}O$ 136.0888, found 136.0886.

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