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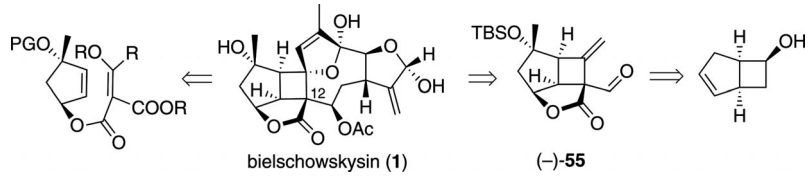

Various photocycloaddition precursors have been designed to study both biomimetic and non-biomimetic [2 + 2] cycloadditions to form the bicyclo[3.2.0]heptane core of the marine diterpenoid bielschowskysin. Additionally, an optimized thermal approach to aldehyde (–)-**55** is described.

J.-B. Farcet, M. Himmelbauer, J. Mulzer* **1–21**

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Photochemical and Thermal [2 + 2] Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin

Jean-Baptiste Farcet,[a] Martin Himmelbauer,[a] and Johann Mulzer*[a]

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A bicyclic core fragment of the marine diterpenoid bielschowskysin has been synthesized. First, a large library of precursors for a photochemical [2 + 2] cycloaddition was prepared and tested, but with limited success. In the end, a thermal [2 + 2] cycloaddition followed by appropriate regio- and stereocontrolled functionalization efficiently gave access to the desired bicyclo[3.2.0]heptane core. An optimized route to this remarkable molecular structure is presented.

Introduction

Furanocembranoids are diterpenoids that have, to date, been isolated exclusively from marine sources, in particular from gorgonian corals. The combination of significant bioactivity and interesting architectural structures has aroused the interest of the scientific community over the last decade. Notwithstanding their wide structural diversity, all members seem to be related and have biogenetic interconnections.[1] Although bielschowskysin (**1**) has an uncommon bicyclo[3.2.0]heptane core,[2] it probably originates from an intramolecular [2 + 2] cycloaddition of an "ordinary" diterpenoid precursor.[3]

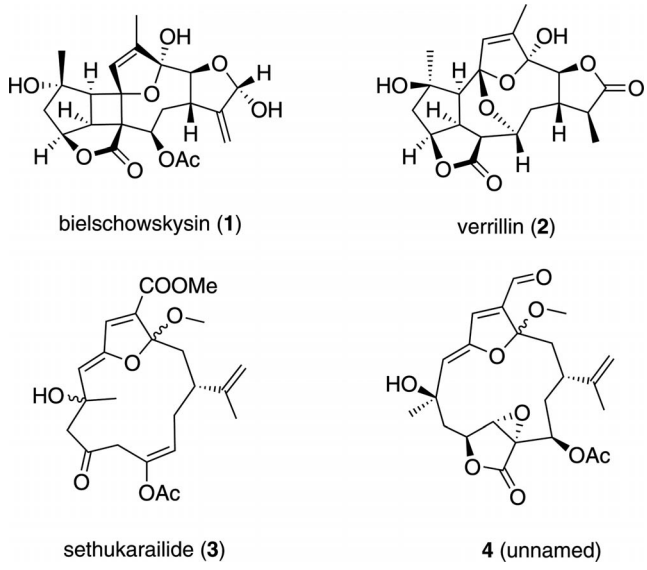
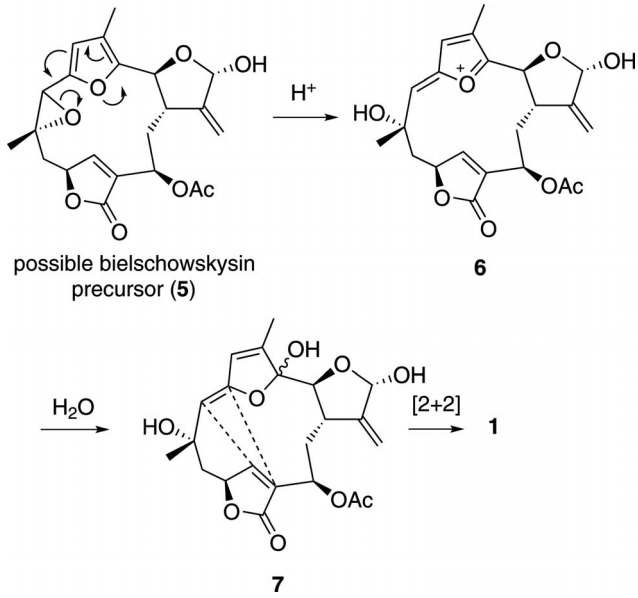


Figure 1. Furanocembranoid family members.

It has been suggested that *exo* enol ethers or known cembranoids such as sethukarailide (**3**) or unnamed compound **4** are stable key intermediates in the biosynthesis of more complex polycyclic diterpenes.[1] These metabolites could undergo transannular additions to form a furan-2(5*H*)-one moiety en route to more complex furanocembranoids such as bielschowskysin (**1**) and verrillin (**2**; Figure 1).

To design a biomimetic route to bielschowskysin (**1**), we investigated the suitability of a nucleophilic insertion into the furan ring of **5** as a potential precursor in the biosynthesis of bielschowskysin (Scheme 1). However, before starting with the construction of the complex and fully substituted furanocembranoid macrocycle, it seemed reasonable to test



Scheme 1. Biosynthesis of bielschowskysin.

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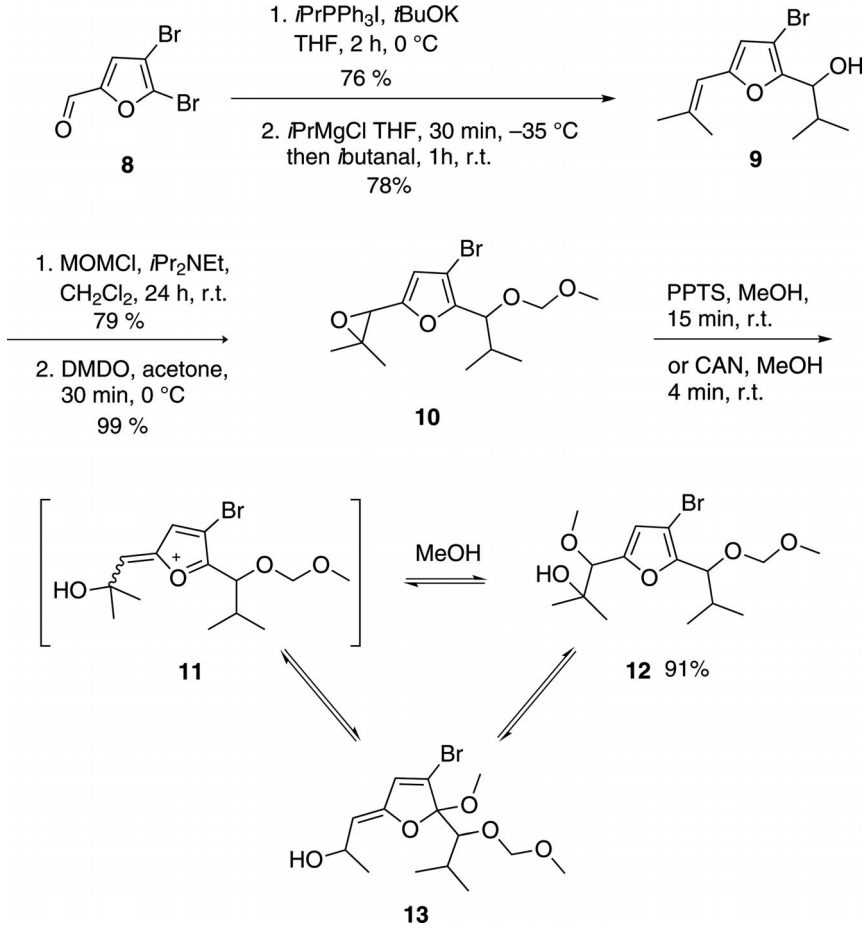


Scheme 2. Synthesis of a test system. CAN = ceric ammonium nitrate.

the cycloaddition in a model system. Epoxide **10** was chosen as a model for the reactivity of **5** (Scheme 2).

Results and Discussion

To prepare alcohol **9**, Wittig olefination of known aldehyde **8**[4] was used to generate a trisubstituted double bond. This was followed by regioselective halogen–metal exchange with isopropylmagnesium chloride (*i*PrMgCl) and addition of the resulting intermediate to isobutyraldehyde to form secondary alcohol **9**. The hydroxy group was protected as a methoxymethyl (MOM) ether to mimic the acetal group in the target molecule. When a solution of dimethyldioxirane (DMDO) was added, oxirane **10** was the only product formed. By stirring **10** in methanol in presence of pyridinium *para*-toluenesulfonate (PPTS), compound **12** was isolated as single product after work-up and chromatographic purification (Scheme 2). This was not surprising, as Pattenden and co-workers have already reported the formation of intermediate **13** and its rapid isomerization into **12**.[5]

The lability of intermediate **13** discouraged us from pursuing this approach further. Instead, we considered the photo-[2 + 2] cycloaddition of enoate **14**, which could be accessed from known enantiomerically pure prostaglandin precursor (–)-**15**, readily available from furfuryl alcohol[6] (Figure 2).

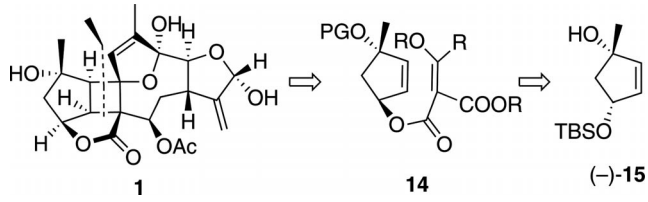


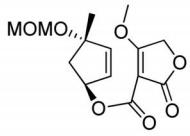
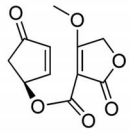
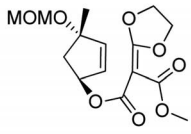
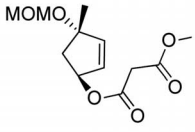
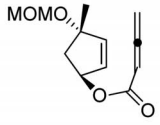
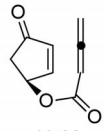
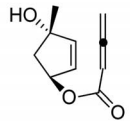
Figure 2. Retrosynthesis based on photo-[2 + 2] cycloaddition.

A protection–deprotection sequence was used to convert (–)-**15** into (+)-**16**, whose esterification with known carboxylic acid **17**[7] under Mitsunobu conditions[8] delivered ester (–)-**18**. However, the desired photo-cyclization to cyclobutane **19** was not observed under various photochemical activation conditions (Table 1, entry 3). Instead, malonate (–)-**20** was isolated in moderate yield (Scheme 3).

Next, we envisaged that compound (–)-**27**, containing a push–pull system, could be a suitable precursor for the photo-[2 + 2] reaction. Hence, mixed ester **22** was formed quantitatively from potassium malonate **21**[9] and methyl 2-bromoacetate. Tetronic acid derivative **23** was obtained as

crystalline tetrabutyl ammonium salt from **22** upon treatment with TBAF in THF. Methylation followed by debenzylation gave carboxylic acid **25** in an excellent overall yield (Scheme 4). As the Mitsunobu protocol failed to deliver ester (–)-**27** directly from alcohol (+)-**16** and carboxylic acid **25**, the desired inversion was effected in a two-step pro-

Table 1. Screening of [2 + 2] cyclization substrates and conditions.

Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions[a]
1	 **(-)-27** 66% from **(–)-26** and **25**	decomposition	**A**, **B**, **C**, **F**, **G**, **H**
2	 **(-)-30** 72% from **(–)-29**[b] and **25**	decomposition	**A**, **B**
3	 **(-)-18** (81%, 99% b.r.s.m.) from **(+)-16** and **17**	 **(-)-20** 46%	**A**, **B**, **C**, **F**, **G**, **H**
4	 **(-)-32** 87% from **(+)-16** and **31**[b]	decomposition	**A**, **B**, **D**, **F**, **I**, **J**
5	 **(-)-33** 60% from **(–)-29**[b] and **31**[b]	decomposition	**A**, **B**, **C**, **D**, **J**
6	 **(-)-35** 35% from **(–)-34**[b] and **31**[b]	decomposition	**A**, **B**

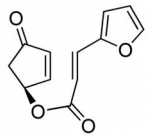
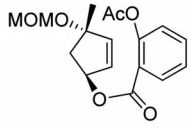
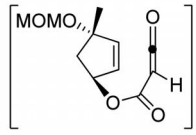
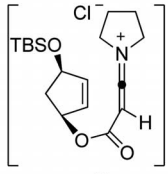
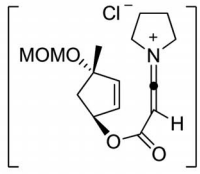
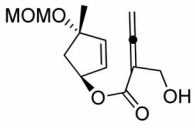
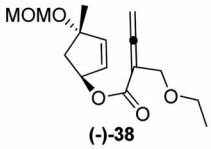
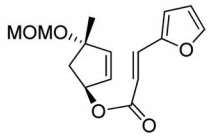
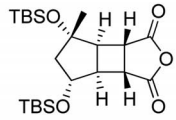
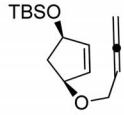
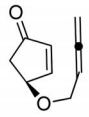
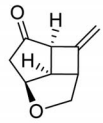
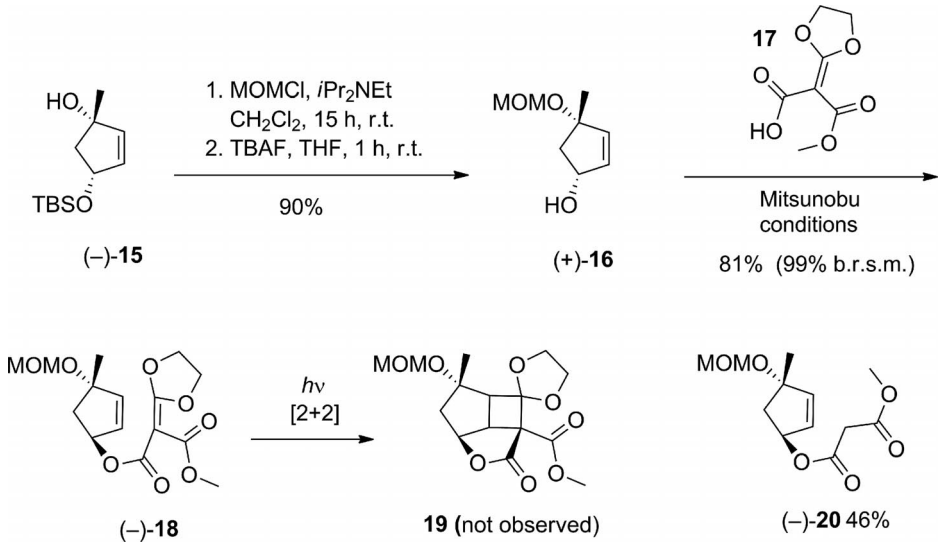
Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions[a]
10	 **(-)-41** 71% from **(–)-29**[b] and **39**[b]	starting material recovered + decomposition	**A**, **B**, **F**
11	 **(-)-42** 52%, 97% b.r.s.m. from **(+)-16** and aspirin	starting material recovered + decomposition	**A**, **B**, **C**, **E**
12	 **43** [c] from **(–)-26** and suboxide	no reaction, then decomposition	**J**
13	 **46** [c] from **(–)-45**[b]	no reaction, then decomposition	**K**
14	 **48** [c] from **(–)-26** and **47**[b]	no reaction, then decomposition	**K**

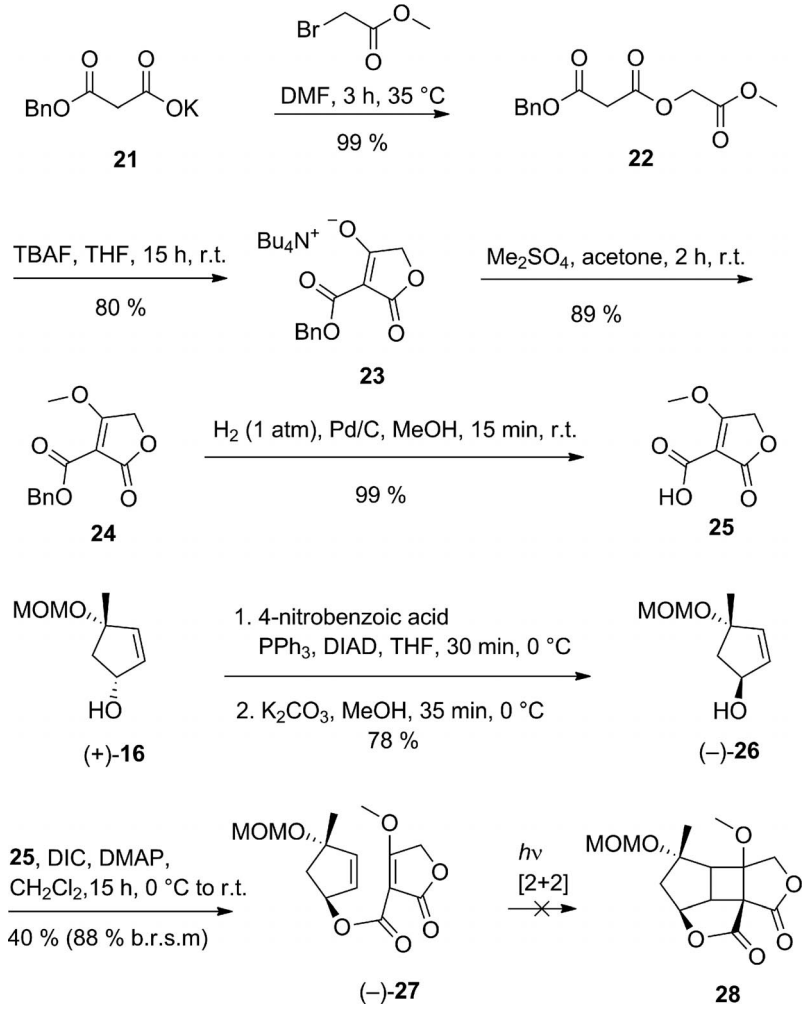
Table 1. *(continued)*.

Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions[a]
7	 **(-)-36** 62% from *para*-formaldehyde and **(–)-32**	decomposition	**A, B, F, G, H**
8	 **(-)-38** 58% from **(+)-16** and **37**[b]	starting material recovered + decomposition	**A, B, C, D, E, F, G, I**
9	 **(-)-40** 99% from **(+)-16** and **39**[b]	starting material recovered + decomposition	**A, B, F**
15	Intermolecular reaction from **(–)-49**[b] and maleic anhydride	 **(-)-50** 58%	**A**
16	 **(+)-51** 83%, 2 steps from **(+)-44**[b] and propargyl bromide	no reaction, then decomposition	**A, B, D, F, H**
17	 **(+)-52** 29%, 3 steps from **(+)-44**[b] and propargyl bromide	 **(+)-53** 60%	**G**

[a] Irradiation conditions: A: UV-A lamps 8 × 16 W, acetone, B: UV-B lamps 8 × 16 W, acetone/CH_2Cl_2, 1:1, C: Sun lamp 750 W, duran filter, pentane/CH_2Cl_2, 1:1, D: Sun lamp 750 W, duran filter, acetone, E: Sun lamp 750 W, quartz filter, pentane/CH_2Cl_2, 1:1, F: Sun lamp 750 W, quartz filter, acetone, G: UV-B lamp 2 × 16 W, quartz filter, Et_2O, H: UV-B lamp 2 × 16 W, quartz filter, Et_2O + cat. $Cu(OTf)_2$, I: Sun lamp 750 W, quartz filter, Et_2O + cat. $Cu(OTf)_2$, J: THF, 0 °C 90 min, then room temp. 6 h, K: DCE, room temp. 6 h, then reflux 2 h. [b] For preparation and characterization, see Supporting Information. [c] Formed in situ, not isolated.



Scheme 3. Synthesis of [2 + 2] precursor (–)-**18**. TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl; b.r.s.m. = based on recovered starting material.

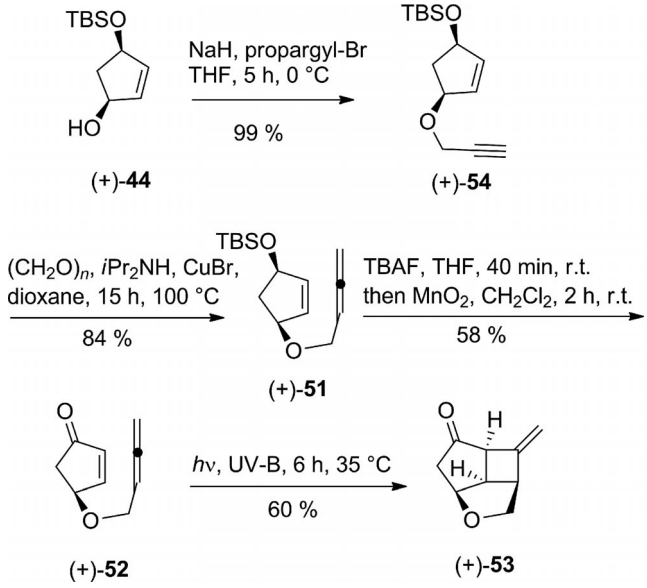


Scheme 4. Synthesis of [2 + 2] precursor (–)-**27**. DIAD = diisopropyl azodicarboxylate; DIC = *N*,*N*′-diisopropylcarbodiimide; DMAP = 4-dimethyl aminopyridine.

cedure to give (–)-**26** in good yield. Carbodiimide-mediated esterification eventually gave [2 + 2] precursor (–)-**27**. Unfortunately, this substrate only underwent decomposition under photo-cyclization conditions, and polycycle **28** was not formed (Scheme 4 and Table 1, entry 1). Nevertheless, a broad screening of potential photo-[2 + 2] substrates under various irradiation conditions was initiated (Table 1).

When enone (–)-**30** (Table 1, entry 2) was used to promote a stepwise ionic mechanism via zwitterionic intermediates, decomposition occurred after a few minutes of UV irradiation (conditions A and B). Similarly, irradiation of buta-2,3-dienoic esters (–)-**32**, (–)-**33**, (–)-**35**, (–)-**36**, and (–)-**38** led to the formation of complex product mixtures, none of which contained the desired tricycle (Table 1, entries 4–8). Furylacrylic esters (–)-**40** and (–)-**41** (Table 1, entries 9 and 10) were more stable to irradiation, but under various conditions (conditions A, B, and F) only the starting material was recovered. Substituted phenyl ester (–)-**42** (Table 1, entry 11) did not lead to cycloaddition, even after a prolonged irradiation time. Our attention turned to thermally driven [2 + 2] cycloadditions, but no product was detected when ketene **43** or ketene iminium salts **46** and **48** (Table 1, entries 12–14) were stirred at room temperature or even heated to reflux.

On reviewing these results, we suspected that cycloaddition could have been prevented not only by electronic effects, but also by conformational issues. Hence, an intermolecular cycloaddition was performed between alkene (–)-**49** and an excess of maleic anhydride (Table 1, entry 15) in acetone under UV-A irradiation (conditions A). Tricycle (–)-**50** was formed as a single isomer in satisfactory yield. Next, the carbonyl group was exchanged for a methylene group to give more flexibility to the allenic side-chain. Thus, alcohol (+)-**44**[6] was alkylated with propargyl bromide in quantitative yield. A Searles–Crabbé reaction[10] gave desired allene (+)-**51**, which was unreactive to photoirradiation (conditions A, B, D, F, H, Table 1, entry 16, Scheme 5). However, when (+)-**51** was converted into enone (+)-**52** by TBAF deprotection and oxidation of the allylic alcohol, irradiation of (+)-**52** with UV-B light led to tricycle (+)-**53** as a volatile liquid in good overall yield (Table 1, entry 17, Scheme 5).



Scheme 5. Synthesis of polycycle (+)-**53**.

From this screening, we concluded that precursors with a carbonyl group in the position α to the reacting double bond were unsuitable for intramolecular [2 + 2] photocyclization under various conditions. Nevertheless, an intermolecular cycloaddition seemed possible. More interestingly, we showed that an intramolecular cycloaddition between homoallenic ether and enone indeed gave tricyclic core (+)-**53**. While further investigations to elaborate this intermediate were underway, we capitalized on the abundant non-photochemical availability of functionalized bicyclo[3.2.0] systems such as (+)-**56**.[11] This compound was used in a stereocontrolled synthesis of a fully substituted western fragment (–)-**55**[2d] of bielschowskysin (**1**), including its all-carbon quaternary center (Figure 3). Here, we disclose the full details of this route, as well as optimized procedures for nine steps of the sequence.

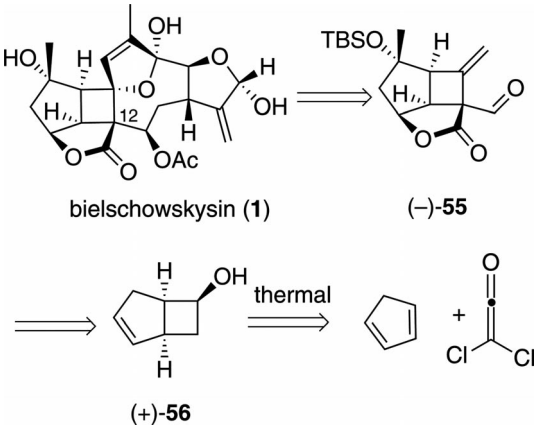
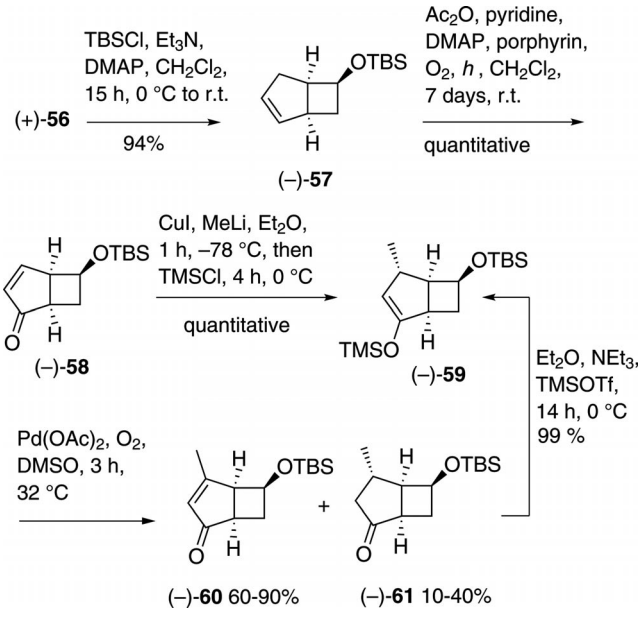


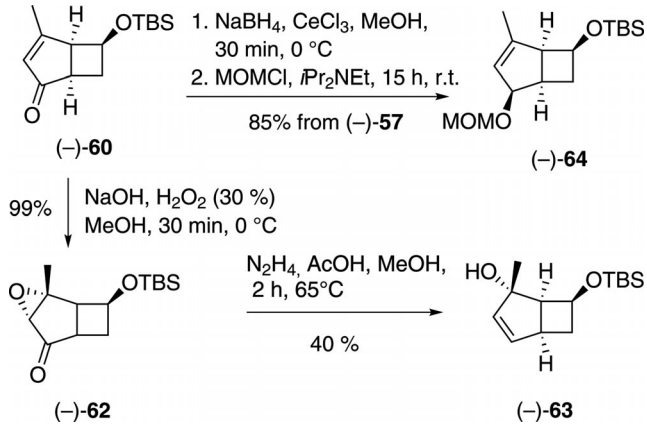
Figure 3. Retrosynthesis based on a non-photochemical approach.

Our synthesis started with TBS protection of enantiomerically enriched (+)-**56**, which was obtained in a four-step sequence from commercially available racemic material,[11] to give (–)-**57**. To functionalize the five-membered ring, photooxygenation[12] with molecular oxygen in the presence of acetic anhydride and base was chosen. This oxidation was exceptionally easy to carry out, even on a molar scale, and produced α,β-unsaturated ketone (–)-**58** with high regioselectivity (isomeric ratio: 20:1). Conjugate addition of dimethyl cuprate and trapping of the enolate with trimethylsilyl chloride (TMSCl) gave enol ether (–)-**59**, which was used in a Saegusa–Ito oxidation[13] to provide enone (–)-**60**. The success of this oxidation crucially depended on the use of dimethyl sulfoxide (DMSO) as solvent and molecular oxygen as co-oxidant. Otherwise, the reaction was difficult to scale up and suffered from inconsistent yields. Moreover, TMS enol ether (–)-**59** was prone to desilylation to form undesired ketone (–)-**61**. It was shown that this side-reaction was highly dependent on the batch of palladium(II) acetate used and, on a larger scale, the ratio of products (–)-**60** and (–)-**61** was not reproducible. However, it was possible to recover (–)-**61** by chromatography, and to reconvert it into (–)-**59** in quantitative yield. This procedure led to a 10% increase in the overall yield (Scheme 6).



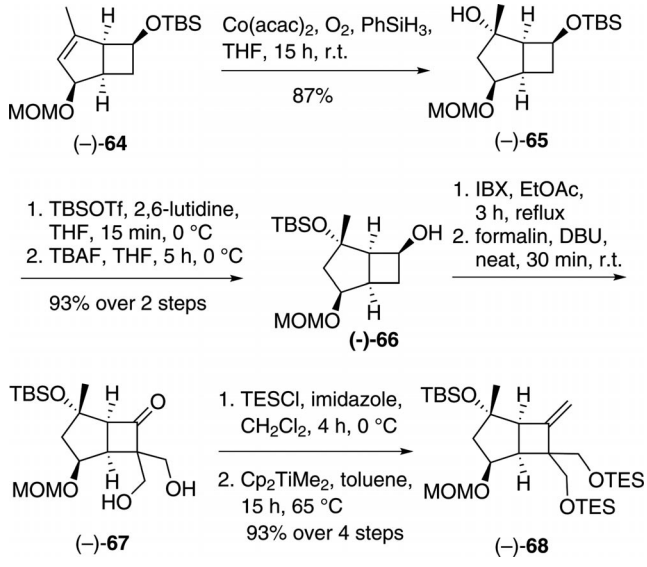
Scheme 6. Synthesis of enone (–)-**60**. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

Taking advantage of the "open-book" geometry of bicycle (–)-**60**, the enone was epoxidized diastereoselectively under Scheffer–Weitz conditions.[14] No conditions could be found for the opening of epoxide (–)-**62** to install the required tertiary alcohol. For instance, a Wharton transposition[15] did provide allylic alcohol (–)-**63**, but it turned out to be highly unstable and impractical for the synthesis. Alternatively, the carbonyl group was reduced diastereoselectively under Luche conditions,[16] and the product was protected with a MOM group to give compound (–)-**64**. This sequence could be carried out in 85% overall yield from (–)-**57** (Scheme 7).



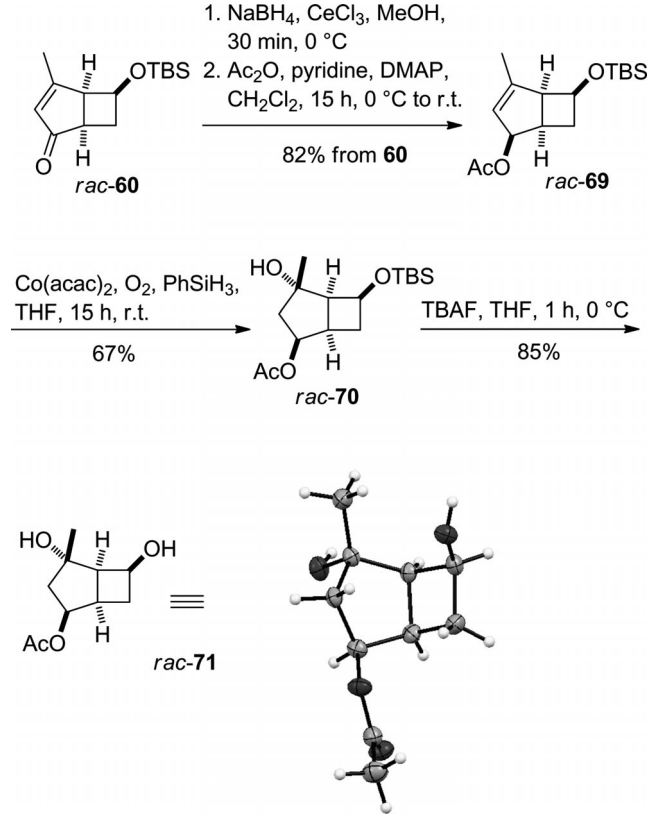
Scheme 7. Synthesis of enone (–)-**63** and (–)-**64**.

Molecular oxygen, a catalytic amount of a cobalt complex, and phenylsilane promoted the Mukaiyama–Isayama oxidation–reduction–hydration sequence[17] in a regio- and stereoselective manner, leading to tertiary alcohol (–)-**65**. The yield could be increased from 64 to 87% by using a 24 h aqueous workup, a time that presumably allowed the peroxide intermediate to rearrange and hydrolyse completely. After an optimized protection–deprotection sequence, the five-membered ring in bicycle (–)-**66** was appropriately substituted, and the installation of the quaternary center could be envisaged (Scheme 8). Oxidation with 2-iodoxybenzoic acid (IBX) smoothly formed the ketone, which underwent a double aldol reaction with formalin to deliver key intermediate (–)-**67**. Triethylsilyl (TES) protection of the two primary alcohols and Petasis' olefination gave (–)-**68** (Scheme 8). The four-step sequence from (–)-**66** to (–)-**68** was performed with a single final purification step, and allowed a quick and high-yielding substitution of the bicycle.



Scheme 8. Synthesis of olefin (–)-**68**. acac = acetylacetonate; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Cp = cyclopentadiene.

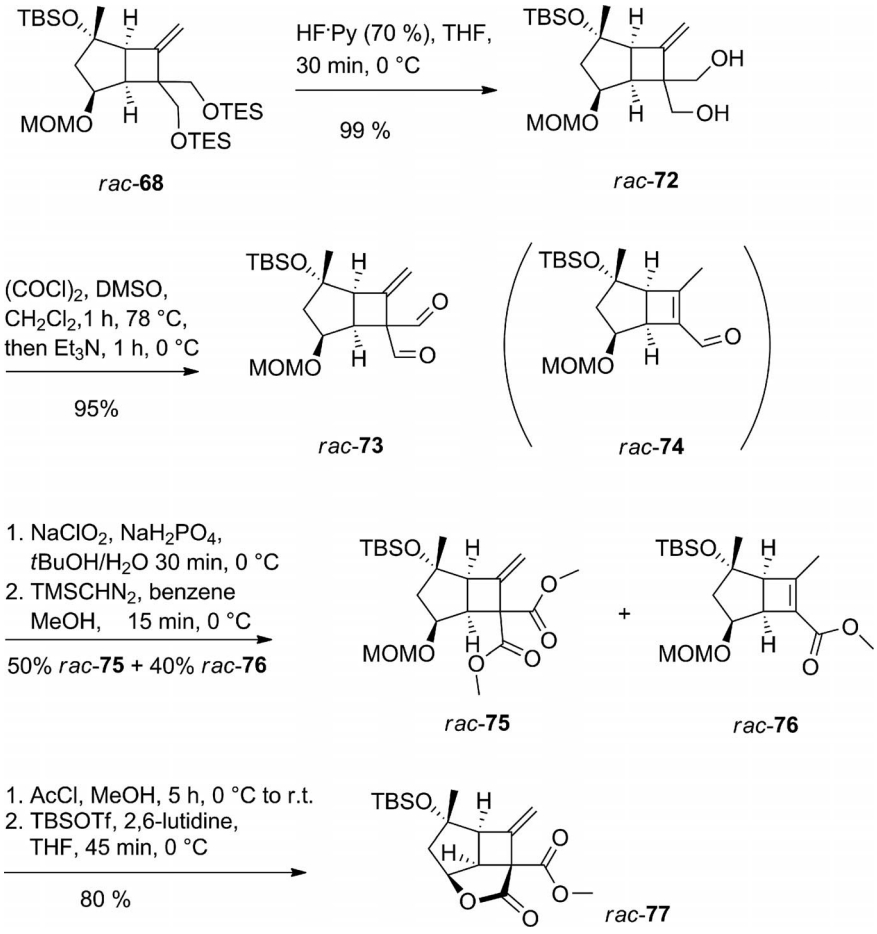
To assign the relative configuration by single crystal diffraction, racemic crystalline acetoxy diol *rac*-**71** was prepared by an analogous sequence (Scheme 9).[18]



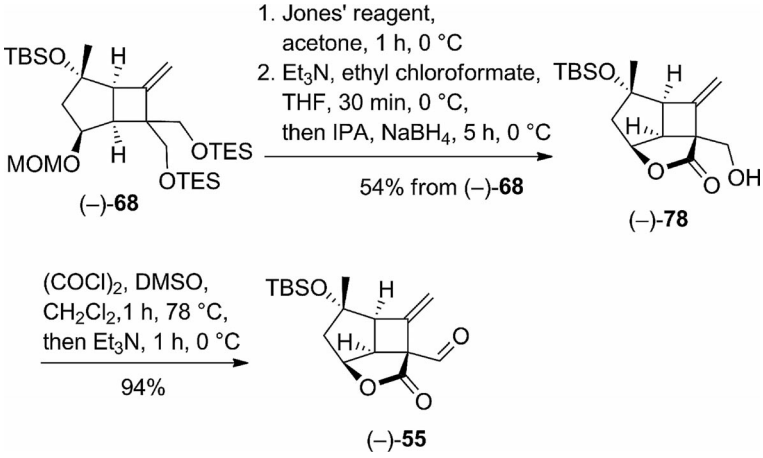
Scheme 9. Synthesis and X-ray structure of *rac*-**71**.

To form lactone *rac*-**77**, the two TES protecting groups were removed to give diol *rac*-**72**. Subsequent Swern oxidation led to dialdehyde *rac*-**73** in excellent yield. However, during evaporation of the volatiles at bath temperatures >30 °C, a decarbonylation with concomitant double-bond shift was observed, which led exclusively to compound *rac*-**74**. Similarly, Pinnick oxidation of crude dialdehyde *rac*-**73** and subsequent esterification of the product with trimethylsilyl diazomethane ($TMSCHN_2$) gave dimethyl ester *rac*-**75** and decarboxylated methyl ester *rac*-**76** as a nearly 1:1 mixture. Gratifyingly, dimethyl ester *rac*-**75** could be transformed into lactone *rac*-**77** in good yield (Scheme 10).

After some experimentation, an optimized cascade reaction was developed to create the tricyclic core of bielschowskysin directly from (–)-**68**. Thus, under the acidic conditions of the Jones' reagent, deprotection of the two TES protecting groups was followed by oxidation of the resulting diol to the dicarboxylic acid. Concomitantly, the MOM protecting group was removed, and lactonization of the resulting alcohol with the *cis* carboxy group occurred spontaneously. Without purification, the free carboxylic acid was transformed into a mixed carbonate with ethyl chloroformate, and this product was reduced with $NaBH_4$ to give alcohol (–)-**78** in 54% overall yield over eight transformations (>92% each) starting from (–)-**68**. Swern oxidation gave desired aldehyde (–)-**55** (Scheme 11).



Scheme 10. Synthesis of bicyclo[3.2.0]heptane lactone *rac*-**77**.



Scheme 11. Synthesis of aldehyde (–)-**55**. Jones' reagent = CrO_3, H_2SO_4 in water; IPA = isopropyl alcohol.

Conclusions

After screening various substrates to obtain the bicyclo[3.2.0]heptane core of bielschowskysin by [2 + 2] photocycloaddition, we developed a stereoselective and optimized scalable non-photochemical route to aldehyde (–)-**55** [>30% overall yield from known alcohol (+)-**56**]. This tricyclic building block bears promising functional groups for connection with an eastern fragment and completion of the total synthesis of bielschowskysin.

Experimental Section

General Remarks: All moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under a slight argon overpressure. All solvents (except dichloromethane and methanol) were purchased as the highest available grade from Sigma–Aldrich, Acros Organics, or Fischer Chemicals. Anhydrous dichloromethane was purified by filtration through alumina under argon immediately before use. Methanol was heated at reflux for several hours over sodium and then distilled. NEt_3, iPr_2NEt, and 2,6-lutidine were distilled from CaH_2 before use. All other reagents were used as received from Sigma–Aldrich, Acros Organics, Fischer Chemicals, TCI, or ABCR, unless otherwise stated. Preparative column chromatography was performed with silica gel 60 from Merck (0.040–0.063 μm, 240–400 mesh). NMR spectra were measured with Bruker AV400, DRX400, or DRX600 spectrometers. Chemical shifts are given in ppm and are referenced to the solvent residual peaks ($CDCl_3$: ^1H, δ = 7.26 ppm; ^{13}C, δ = 77.16 ppm). Infrared spectra were recorded as thin films of pure products on an ATR-unit with a Bruker Vertex 70 instrument. High-resolution mass spectra were measured with a Bruker MaXis (ESI-TOF) instrument at a resolution of 10000. A P341 Perkin–Elmer polarimeter equipped with in a 10 cm cell and a Na lamp (589 nm) was used for the measurement of optical rotation.

1-[3-Bromo-5-(2-methylprop-1-en-1-yl)furan-2-yl]-2-methylpropan-1-ol (9): Potassium *tert*-butoxide (5.7 g, 51.0 mmol) was added in one portion to a solution of isopropyl(triphenyl)phosphonium iodide (2.5 g, 56.7 mmol) in THF (200 mL) at 0 °C. 4,5-Dibromofuran-2-carbaldehyde (**8**; 7.20 g, 28.4 mmol) in THF (50 mL) was added rapidly to the prepared solution. The mixture was stirred at 0 °C for 60 min, after which TLC indicated complete consumption of the starting material. Water (300 mL) was then added. The dark solution was filtered through a pad of Celite, and the phases were separated. The aqueous phase was extracted with EtOAc (2× 150 mL). The combined organic extracts were washed with brine (50 mL) and dried with $MgSO_4$. SiO_2 (25 g) was added to the solution before it was concentrated under reduced pressure. The material was purified by column chromatography (SiO_2, hexane) to give a light yellow oil (6.03 g, 76%) that darkened within a few hours. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.20 (s, 1 H), 5.95 (m, J = 1.1 Hz, 1 H), 1.94 (s, 3 H), 1.90 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 155.6, 138.3, 120.2, 113.1, 111.9, 102.8, 27.0, 20.2 ppm. HRMS (EI): calcd. for $C_8H_8OBr_2$ $[M]^+$ 277.8942; found 277.8940. IR: $\tilde{\nu}$ = 1780, 1553, 1440, 1267, 1205, 951, 935, 925, 788, 586 cm^{-1}. R_f (hexane/EtOAc, 20:1): 0.93.

A solution of dibromoalkene (5.3 g, 19.1 mmol) in THF (200 mL) was cooled to –35 °C. A solution of isopropylmagnesium chloride (2 M in ether; 11.5 mL, 23.0 mmol) was added slowly, and the resulting solution was stirred at the same temperature for 60 min. Freshly distilled isobutanal (2.28 mL, 24.8 mmol) was added, and the reaction mixture was stirred for 4 h at –35 °C, and then it was allowed to warm to room temp. over 3 h. NH_4Cl (saturated aq.; 40 mL) was added, and the aqueous phase was extracted with EtOAc (3× 45 mL). The combined organic extracts were washed with brine (20 mL) and dried with $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography (SiO_2, hexane/EtOAc, 20:1) to give **9** (4.07 g, 78%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.15 (s, 1 H), 6.00–5.97 (m, 1 H), 4.41 (dd, J = 5.5, J = 8.3 Hz, 1 H), 2.21–2.09 (m, 1 H), 1.95 (s, 3 H), 1.91 (d, J = 4.6 Hz, 1 H), 1.90 (s, 3 H), 1.09 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 153.1, 149.7, 137.6, 113.9, 110.6, 99.3, 71.7, 33.8, 27.2, 20.4, 19.1, 18.6 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}O_2Br$ $[M]^+$ 272.0412; found 272.0413. IR: $\tilde{\nu}$ = 3370, 2963, 2872, 1468, 1384, 1142, 1013, 844, 633, 537 cm^{-1}. R_f (hexane/EtOAc, 10:1): 0.21.

3-Bromo-5-(3,3-dimethyloxiran-2-yl)-2-[1-(methoxymethoxy)-2-methylpropyl]furan (10): MOMCl (3.77 mL, 41.7 mmol) was added dropwise to a solution of alcohol **9** (3.8 g, 13.9 mmol) in DIPEA (10 mL) and CH_2Cl_2 (20 mL) at 0 °C. A few crystals of NaI were added, and the solution was stirred for 1 h at 0 °C, and then for a further 20 h at room temp. Water (100 mL) and EtOAc (100 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (3× 50 mL), and the combined organic extracts were washed with brine (30 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc, 20:1) to give the MOM-protected alkene (3.47 g, 79%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.15 (s, 1 H), 6.02–5.98 (m, 1 H), 4.55 (d, J = 6.8 Hz, 1 H), 4.50 (d, J = 6.9 Hz, 1 H), 4.34 (d, J = 8.9 Hz, 1 H), 3.36 (s, 3 H), 2.31–2.17 (m, 1 H), 1.95 (s, 3 H), 1.90 (s, 3 H), 1.11 (d, J = 6.6 Hz, 3 H), 0.79 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 153.5, 147.8, 137.6, 114.0, 110.3, 101.7, 94.5, 74.8, 55.8, 32.3, 27.2, 20.4, 19.7, 18.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}O_3Br$ $[M]^+$ 316.0674; found 316.0665. IR: $\tilde{\nu}$ = 2959, 1471, 1386, 1154, 1098, 1032, 971, 923, 784, 561 cm^{-1}. R_f (hexane/EtOAc, 10:1): 0.43.

A solution of dimethyldioxirane (2.8 mL, 0.13 mmol) was added to a magnetically stirred solution of the MOM-protected alkene (40 mg, 0.13 mmol) in acetone (1.3 mL) at 0 °C. After 30 min at 0 °C, the solvent was removed to give pure oxide **10** (42 mg, 99%) as a 1:1 mixture of diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.25 and 6.24 (2 d, J = 0.5 Hz, 1 H), 4.56–4.50 (m, 2 H), 4.33 (d, J = 9.0 Hz, 1 H), 3.71 and 3.70 (2 s, 1 H), 3.36 and 3.34 (2 s, 3 H), 2.28–2.17 (m, 1 H), 1.44 and 1.43 (2 s, 3 H), 1.30 (s, 3 H), 1.10 (2 d, J = 6.5 Hz, 3 H), 0.79 and 0.76 (2 d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 151.3, 150.3, 111.8 and 111.7, 100.8, 94.7 and 94.6, 74.9, 61.7 and 61.7, 58.7 and 58.6, 55.9 and 55.8, 32.3, 24.2, 19.7 and 19.6, 18.7, 18.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{25}O_5BrNa$ $[M + MeOH + Na]^+$ 387.0783; found 387.0796. IR: $\tilde{\nu}$ = 2977, 2871, 1676, 1461, 1370, 1099, 1010, 979, 840, 653 cm^{-1}. R_f (hexane/EtOAc, 5:1): 0.34.

1-{4-Bromo-5-[1-(methoxymethoxy)-2-methylpropyl]furan-2-yl}-1-methoxy-2-methylpropan-2-ol (12)

Procedure A: PPTS (1 mg) was added to a solution of epoxide **10** (26 mg, 0.08 mmol) in MeOH (0.8 mL), and the solution was stirred at room temp. for 15 min. The reaction mixture was quenched with water (1.5 mL) and extracted with EtOAc (3× 5 mL). The combined organic extracts were washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified over a short column (SiO_2, hexane/EtOAc, 4:1) to give undesired tertiary alcohol **12** (26 mg, 91%) as a 1:1 mixture of diastereoisomers.

Procedure B: Ceric ammonium nitrate (90 mg, 0.16 mmol) was added to a solution of epoxide **10** (13.6 mg, 0.04 mmol) in MeOH (2.7 mL). The reaction mixture was stirred for 4 min before being cautiously quenched with sodium hydrogen carbonate (saturated aq.; 2 mL). The mixture was diluted with water (5 mL) and EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (2× 20 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give undesired tertiary alcohol **12** (13.5 mg, 91%) as a 1:1 mixture of diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.36 and 6.34 (2 s, 1 H), 4.55 (d, J = 3.8 Hz, 1 H), 4.52 (s, 1 H), 4.34 and 4.32 (2 d, J = 4.0 Hz, 1 H), 3.99 and 3.96 (2 s, 1 H), 3.35 and

3.34 (2 s, 3 H), 3.32 and 3.30 (2 s, 3 H), 2.45 (br. s, 1 H), 2.29–2.18 (m, 1 H), 1.19 and 1.18 (2 s, 3 H), 1.17 and 1.14 (2 s, 3 H), 1.11 and 1.09 (2 d, J = 3.8 Hz, 3 H), 0.78 and 0.76 (2 d, J = 2.6 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 152.8 and 152.4, 150.2 and 150.1, 112.9 and 112.2, 100.9 and 100.7, 94.8 and 94.7, 84.6 and 84.4, 75.2 and 75.0, 72.7, 57.9 and 57.7, 55.8, 32.3 and 32.2, 26.1 and 26.0, 24.6 and 24.4, 19.6, 18.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{25}O_5BrNa$ $[M + Na]^+$ 387.0783; found 387.0797. IR: $\tilde{\nu}$ = 3466, 2981, 2877, 2401, 1370, 1137, 1098, 1035, 779, 597 cm^{-1}. R_f (hexane/EtOAc, 1:1): 0.42.

(1*R*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-enol [(+)-16]: iPr$_2$NEt (757 μL, 4.33 mmol) and MOMCl (225 μL, 2.96 mmol) were added to a stirred solution of tertiary alcohol (–)-**15** (450 mg, 1.97 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred at room temp. until the reaction was complete (after 24 h, only traces of starting material remained). After slow addition of NH_4Cl (saturated aq.; 0.5 mL), the mixture was diluted with water (25 mL) and EtOAc (35 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (2× 60 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO_2, hexane/EtOAc, 20:1) to give methoxy methyl ether (434 mg, 81%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (dd, J = 1.0, J = 5.6 Hz, 1 H), 5.78 (dd, J = 1.9, J = 5.6 Hz, 1 H), 4.75 (d, J = 7.0 Hz, 1 H), 4.71–4.66 (m, 1 H), 4.65 (d, J = 7.0 Hz, 1 H), 3.35 (s, 3 H), 2.28 (dd, J = 7.1, J = 13.8 Hz, 1 H), 2.92 (dd, J = 4.5, J = 13.8 Hz, 1 H), 1.33 (s, 3 H), 0.89 (s, 9 H), 0.07 (2 s, 6 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 138.2, 135.8, 91.9, 86.1, 75.0, 55.2, 47.9, 27.4, 26.0 (3 C), 18.3, –4.5 (2 C) ppm. HRMS (ESI): calcd. for $C_{13}H_{25}O_3Si$ $[M – CH_3]^+$ 257.1573; found 257.1572. IR: $\tilde{\nu}$ = 2930, 2858, 1365, 1255, 1100, 1039, 836, 632, 534, 504 cm^{-1}. $[\alpha]_D^{20}$ = + 7.2 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.57.

Methoxy methyl ether (381 mg, 1.40 mmol) was dissolved in THF (9 mL), and TBAF (1 M in THF; 1.82 mL, 1.82 mmol) was added at 0 °C. The resulting solution was stirred at room temp. for 1 h. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexane/EtOAc, 5:1) to give free alcohol (+)-**16** (205 mg, 93%) as a colorless oil. Alternatively, the crude methoxy methyl ether could be used directly to give the product in 90% yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (dd, J = 2.4, J = 5.5 Hz, 1 H), 5.74 (d, J = 5.6 Hz, 1 H), 4.91 (d, J = 7.6 Hz, 1 H), 4.64–4.58 (m, 1 H), 4.59 (d, J = 7.7 Hz, 1 H), 3.39 (s, 3 H), 3.11 (d, J = 9.6 Hz, 1 H), 2.24 (dd, J = 7.4, J = 15.0 Hz, 1 H), 2.00 (dd, J = 2.3, J = 14.9 Hz, 1 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 138.1, 137.3, 92.0, 86.5, 75.6, 55.0, 46.9, 27.6 ppm. HRMS (EI): calcd. for $C_7H_{11}O_3$ $[M – CH_3]^+$ 143.0708; found 143.0712. IR: $\tilde{\nu}$ = 3402, 2972, 2891, 1444, 1354, 1220, 1144, 1091, 1035, 773 cm^{-1}. $[\alpha]_D^{20}$ = +115.7 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.11.

1-[(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl] 3-Methyl 2-(1,3-Dioxolan-2-ylidene)malonate [(–)-18]: Triphenylphosphane (318 mg, 1.2 mmol) was dissolved in THF (3 mL), and the solution was cooled to 0 °C. DIAD (236 μL, 1.2 mmol) was added very slowly, and the mixture was stirred for 30 min. At this stage, a milky precipitate formed. Acid **17** (226 mg, 1.2 mmol) was added in one portion, and then a solution of alcohol (+)-**16** (95 mg, 0.60 mmol) in THF (0.5 mL) was added dropwise at 0 °C. The mixture was stirred at the same temperature for 20 h. Water (15 mL) was added, and the aqueous phase was extracted with EtOAc (3× 20 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (SiO_2, hexane/EtOAc, 5:1 to 0:1) to give recovered starting material (+)-**16** (18 mg, 19%) and ester (–)-**18** (160 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 2 H), 5.83 (dd, J = 2.9, J = 7.2 Hz, 1 H), 4.67 (d, J = 7.3 Hz, 1 H), 4.60 (s, 4 H), 4.59 (d, J = 7.3 Hz, 1 H), 3.73 (s, 3 H), 3.35 (s, 3 H), 2.54 (dd, J = 7.2, J = 14.6 Hz, 1 H), 1.88 (dd, J = 2.9, J = 14.6 Hz, 1 H), 1.47 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.5, 165.5, 165.0, 141.6, 132.4, 92.0, 87.5, 80.9, 78.8, 67.8, 67.7, 55.2, 51.8, 44.1, 27.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_8Na$ $[M + Na]^+$ 351.1056; found 351.1048. IR: $\tilde{\nu}$ = 2926, 1724, 1686, 1471, 1304, 1270, 1084, 1031, 983, 954 cm^{-1}. $[\alpha]_D^{20}$ = – 131.8 (c = 1.11, $CHCl_3$). R_f (EtOAc): 0.23.

(1*R*,4*R*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl Methyl Malonate [(–)-20]: Ester (–)-**18** (13 mg, 0.04 mmol) was dissolved in degassed Et_2O (4 mL) in a quartz vial. One crystal of $Cu(OTf)_2$ was added, and the mixture was irradiated with two 16 W UV-B lamps (Irradiation conditions H) at room temp. for 50 min. The solution was diluted with ice (15 g) and NH_4OH (0.5 mL), and extracted with EtOAc. The organic phase was washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (SiO_2, hexane/EtOAc, 1:1 to 1:2) to give undesired (–)-**20** (6 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03 (dd, J = 5.7, J = 1.0 Hz, 1 H), 5.96 (dd, J = 5.7, J = 2.1 Hz, 1 H), 5.83–5.77 (m, 1 H), 4.66 (d, J = 7.4 Hz, 1 H), 4.57 (d, J = 7.4 Hz, 1 H), 3.74 (s, 3 H), 3.36 (s, 2 H), 3.34 (s, 3 H), 2.56 (dd, J = 7.3, J = 14.7 Hz, 1 H), 1.85 (dd, J = 3.1, J = 14.7 Hz, 1 H), 1.47 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.1, 166.5, 142.3, 131.7, 92.1, 87.3, 80.1, 55.3, 52.6, 44.1, 41.6, 27.2 ppm. HRMS (ESI): calcd. for $C_{12}H_{18}O_6Na$ $[M + Na]^+$ 281.1001; found 281.1003. IR: $\tilde{\nu}$ = 2920, 2852, 1736, 1439, 1349, 1275, 1144, 1029, 641, 597 cm^{-1}. $[\alpha]_D^{20}$ = –95.6 (c = 0.09, $CHCl_3$). R_f (EtOAc): 0.61.

Benzyl (2-Methoxy-2-oxoethyl) Malonate (22): Methyl bromoacetate (2.61 mL, 28.4 mmol) was added dropwise to a suspension of monopotassium carboxylate **21** (6.00 g, 25.8 mmol) in DMF (51 mL) at 35 °C. The mixture was stirred for 1 h. The solvent was removed (water bath at 55 °C), and the residue was partitioned between water (100 mL) and toluene (100 mL). The phases were separated, and the aqueous phase was extracted with toluene (100 mL). The organic phases were combined, washed with brine (50 mL), dried with $MgSO_4$, and concentrated to give analytically pure malonate **22** (6.87 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.38 (m, 5 H), 5.20 (s, 2 H), 4.67 (s, 2 H), 3.76 (s, 3 H), 3.54 (s, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.6, 165.8, 165.7, 135.2, 128.6, 128.5, 128.3, 67.4, 61.3, 52.3, 41.0 ppm. HRMS (EI): calcd. for $C_{13}H_{14}O_6$ $[M]^+$ 266.0790; found 266.0784. IR: $\tilde{\nu}$ = 1755, 1737, 1383, 1337, 1274, 1214, 1145, 633, 535, 498 cm^{-1}. R_f (hexane/EtOAc, 1:1): 0.40.

Tetrabutylammonium 4-[(Benzyloxy)carbonyl]-5-oxo-2,5-dihydrofuran-3-olate (23): TBAF (1 M in THF; 19.3 mL, 19.3 mmol) was slowly added to a solution of malonate **22** (3.43 g, 12.9 mmol) in THF (26 mL) at 0 °C. The resulting solution was stirred at room temp. for 15 h. The reaction mixture was concentrated, and the residue was heated to reflux in EtOAc (50 mL). The suspension was cooled to room temp. The precipitate was filtered off and washed with cold EtOAc (20 mL). After drying under high vacuum, **23** (4.89 g, 80%) was obtained as pure white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 7.3 Hz, 2 H), 7.29–7.23 (m, 2 H), 7.21–7.15 (m, 1 H), 5.24 (s, 2 H), 4.19 (s, 2 H), 3.18–3.10 (m, 8 H), 1.59–1.48 (m, 8 H), 1.40–1.19 (m, 8 H), 0.95 (t, J = 7.4 Hz, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 193.6, 176.5, 164.8, 138.9, 128.2 (2 C), 127.2 (2 C), 126.9, 85.0, 70.4, 63.4, 58.8

(4 C), 24.0 (4 C), 19.8 (4 C), 13.7 (4 C) ppm. HRMS (ESI): calcd. for $C_{12}H_9O_5$ [M – NBu_4]$^-$ 233.0450; found 233.0452. IR: $\tilde{\nu}$ = 2959, 2873, 1742, 1684, 1634, 1432, 1056, 736, 698, 609 cm^{-1}, m.p. 151–153 °C. R_f (hexane/EtOAc, 1:1): 0.00.

Benzyl 4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylate (24): Ammonium salt **23** (2.0 g, 4.20 mmol) was dissolved in THF (21 mL). Dimethyl sulfate (0.42 mL, 4.41 mmol) was added at room temp., and the mixture was stirred for 2 h before further dimethyl sulfate (1 equiv.) was added. Stirring was continued for a further 3 h, and then the mixture was concentrated under reduced pressure. The residue was filtered through a chromatography column (SiO_2, hexane/EtOAc, 1:1 to 0:1) to give methylated product **24** (928 mg, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.40 (m, 2 H), 7.40–7.27 (m, 3 H), 5.30 (s, 2 H), 4.75 (s, 2 H), 4.06 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 182.5, 168.6, 160.8, 135.8, 128.7 (2 C), 128.3, 128.2 (2 C), 97.2, 66.7, 65.1, 59.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{12}O_5Na$ [M + Na]$^+$ 271.0582; found 271.0583. IR: $\tilde{\nu}$ = 1768, 1709, 1623, 1478, 1411, 1338, 1262, 1066, 1025, 606 cm^{-1}, m.p. 172–173 °C. R_f (EtOAc): 0.28.

4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylic Acid (25): Benzyl ester **24** (928 mg, 3.74 mmol) was dissolved in MeOH (75 mL), and Pd (5% on C; 50 mg) was added under Ar. Then a gentle flow of H_2 (1 atm) was bubbled through the solution for 60 min at room temp. The heterogeneous mixture was filtered through a Celite pad and concentrated to give carboxylic acid **25** (587 mg, 99%) as a white solid that turned pale yellow after a few days. ^{1}H NMR (400 MHz, [D_4]methanol): δ = 5.06 (s, 2 H), 4.15 (s, 3 H) ppm. ^{13}C NMR (400 MHz, [D_4]methanol): δ = 187.7, 172.9, 163.7, 96.3, 66.7, 60.4 ppm. HRMS (EI): calcd. for $C_6H_4O_4$ [M – H_2O]$^+$ 140.0110; found 140.0108. IR: $\tilde{\nu}$ = 2921, 1748, 1615, 1464, 1285, 1145, 1087, 1059, 903, 701 cm^{-1}, m.p. 157–159 °C. R_f (EtOAc): 0.05.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-enol [(–)-26]: Secondary alcohol (+)-**16** (133 mg, 0.84 mmol), triphenylphosphane (662 mg, 2.52 mmol), and *p*-nitrobenzoic acid (821 mg, 2.52 mmol) were dissolved in THF (4 mL), and the solution was cooled to 0 °C under Ar. DIAD (480 µL, 2.44 mmol) was added slowly, and the mixture was stirred for 40 min. The mixture was diluted with EtOAc (50 mL) and water (30 mL), and the aqueous phase was extracted with EtOAc (30 mL). The combined organic extracts were washed with $NaHCO_3$ (15 mL) and brine (2× 20 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was then purified by flash chromatography (SiO_2, hexane/EtOAc, 7:1) to give the *para*-nitrobenzoic ester (218 mg, 84%) as a clear semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31–8.22 (m, 2 H), 8.22–8.14 (m, 2 H), 6.11 (dd, *J* = 0.7, *J* = 5.6 Hz, 1 H), 6.09 (dd, *J* = 2.0, *J* = 5.6 Hz, 1 H), 6.05–6.00 (m, 1 H), 4.66 (dd, *J* = 35.9, *J* = 7.4, 2 Hz), 3.37 (s, 3 H), 2.69 (dd, *J* = 14.7, *J* = 7.2 Hz, 1 H), 1.99 (dd, *J* = 14.8, *J* = 3.2 Hz, 1 H), 1.54 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 164.6, 150.7, 142.6, 135.9, 131.7, 130.8 (2 C), 123.7 (2 C), 92.1, 87.3, 80.5, 55.3, 44.3, 27.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}O_6NNa$ [M + Na]$^+$ 330.0954; found 330.0961. IR: $\tilde{\nu}$ = 1721, 1608, 1528, 1340, 1271, 1143, 1102, 1031, 842, 720 cm^{-1}. $[\alpha]_D^{20}$ = +158.4 (*c* = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 5:1): 0.14.

The *p*-nitrobenzoic ester (205 mg, 0.67 mmol) was dissolved in MeOH (13 mL), and the solution was cooled to 0 °C. K_2CO_3 (92 mg, 0.67 mmol) was added in one portion, and the mixture was stirred for 35 min before being quenched with NH_4Cl. Almost all of the organic solvent was removed under reduced pressure, and EtOAc (20 mL) was added. The aqueous phase was removed and extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (2× 10 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc, 2:1) to give alcohol (–)-**26** (86 mg, 82%) as a colorless oil. Alternatively the crude product from the Mitsunobu reaction could be used, which gave the product in 78% yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 (dd, *J* = 5.6, *J* = 1.9 Hz, 1 H), 5.86 (dd, *J* = 5.6, *J* = 1.2 Hz, 1 H), 5.03–4.96 (m, 1 H), 4.59 (dd, *J* = 31.7, *J* = 7.3 Hz, 2 H), 3.33 (s, 3 H), 2.53 (dd, *J* = 14.4, *J* = 7.0 Hz, 1 H), 1.68 (dd, *J* = 14.3, *J* = 3.9 Hz, 1 H), 1.67 (br. s, 1 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 138.9, 137.0, 92.0, 87.8, 76.4, 55.2, 47.8, 27.8 ppm. HRMS (ESI): calcd. for $C_7H_{11}O_3$ [M – CH_3]$^+$ 143.0708; found 143.0712. IR: $\tilde{\nu}$ = 3371, 2932, 1449, 1356, 1143, 1091, 1030, 918, 634, 537 cm^{-1}. $[\alpha]_D^{20}$ = –99.4 (*c* = 1.05, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.45.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylate [(–)-27]: Secondary alcohol (–)-**26** (40 mg, 0.25 mmol) and carboxylic acid **25** (96 mg, 0.61 mmol) were dissolved in CH_2Cl_2 (5.1 mL), and the mixture was cooled to 0 °C. DIC (47 µL, 0.30 mmol) was added, followed by DMAP (6 mg, 0.05 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp., and stirring was continued overnight. The volatiles were removed, and the residue was purified by column chromatography (SiO_2, hexane/EtOAc, 1:1 to 1:2) to give starting material (–)-**26** (22 mg, 55%) and ester (–)-**27** (30 mg, 40%, 88% based on recovered starting material) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08–6.00 (m, 2 H), 5.89 (dt, *J* = 7.2, *J* = 2.2 Hz, 1 H), 4.74 (s, 2 H), 4.64 (dd, *J* = 34.3, *J* = 7.3 Hz, 2 H), 4.11 (s, 3 H), 3.35 (s, 3 H), 2.58 (dd, *J* = 14.6, *J* = 7.2 Hz, 1 H), 1.96 (dd, *J* = 14.7, *J* = 3.0 Hz, 1 H), 1.51 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 181.7, 168.5, 160.9, 142.4, 131.8, 97.6, 92.1, 87.4, 79.7, 65.0, 59.9, 55.3, 44.1, 27.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_7Na$ [M + Na]$^+$ 321.0950; found 321.0951. IR: $\tilde{\nu}$ = 2931, 1771, 1709, 1626, 1413, 1264, 1143, 1028, 632, 538 cm^{-1}. $[\alpha]_D^{20}$ = –140.6 (*c* = 0.55, $CHCl_3$). R_f (EtOAc): 0.22.

(*S*)-4-Oxocyclopent-2-en-1-yl 4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylate [(–)-30]: Secondary alcohol (–)-**29** (40 mg, 0.41 mmol) and carboxylic acid **25** (77 mg, 0.49 mmol) were dissolved in CH_2Cl_2/MeCN (3:1; 4 mL), and the mixture was cooled to 0 °C. DIC (76 µL, 0.49 mmol) was added, followed by DMAP (10 mg, 0.08 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp., and stirring was continued overnight. The volatiles were removed, and the residue was purified by column chromatography (SiO_2, hexane/EtOAc, 2:1 to 0:1) to give starting material (–)-**29** (4 mg, 10%) ester (–)-**30** (88 mg, 78%) as a white solid that turned yellow on contact with air. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 2.4, *J* = 5.7 Hz, 1 H), 6.36 (dd, *J* = 1.3, *J* = 5.7 Hz, 1 H), 5.99 (m, 1 H), 4.81 (s, 2 H), 4.12 (s, 3 H), 2.87 (dd, *J* = 6.3, *J* = 18.8 Hz, 1 H), 2.44 (dd, *J* = 2.2, *J* = 18.8 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 204.7, 183.5, 168.1, 160.3, 158.7, 137.5, 96.6, 72.7, 64.9, 59.8, 41.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{10}O_6Na$ [M + Na]$^+$ 261.0375; found 261.0377. IR: $\tilde{\nu}$ = 1766, 1711, 1619, 1479, 1409, 1341, 1261, 1066, 1026, 794 cm^{-1}. $[\alpha]_D^{20}$ = 106.8 (*c* = 0.50, $CHCl_3$), m.p. 148–149 °C. R_f (EtOAc): 0.25.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl Buta-2,3-dienoate [(–)-32]: Triphenylphosphane (935 mg, 3.57 mmol) was dissolved in THF (30 mL), and the solution was cooled to 0 °C. DIAD (702 µL, 3.57 mmol) was added very slowly, and the mixture was stirred for 30 min. At this stage, a milky precipitate formed. Allenic acid **31** (300 mg, 3.57 mmol) was added in one portion, and a solution of alcohol (+)-**16** (470 mg, 2.97 mmol) in THF (5 mL) was then added dropwise at 0 °C. The mixture was stirred at the same temperature for 2 h. Water (45 mL) was added, and the re-

sulting mixture was extracted with EtOAc (3× 80 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography (SiO_2, hexane/EtOAc, 6:1) to give ester (–)-**32** (580 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (dd, J = 0.8, J = 5.7 Hz, 1 H), 5.96 (dd, J = 2.1, J = 5.7 Hz, 1 H), 5.82–5.76 (m, 1 H), 5.60 (t, J = 6.5 Hz, 1 H), 5.20 (d, J = 6.6 Hz, 2 H), 4.61 (dd, J = 7.3, J = 33.4 Hz, 2 H), 3.33 (s, 3 H), 2.55 (dd, J = 7.3, J = 14.6 Hz, 1 H), 1.84 (dd, J = 3.3, J = 14.7 Hz, 1 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 216.0, 165.7, 141.7, 132.2, 92.0, 88.14, 87.3, 79.4, 79.3, 55.2, 44.2, 27.2 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}O_4$ [M – CH_3]$^+$ 209.0814; found 209.0808. IR: $\tilde{\nu}$ = 2929, 1714, 1450, 1350, 1256, 1163, 1144, 1032, 632, 535 cm^{-1}. $[\alpha]_D^{20}$ = –187.3 (c = 1.04, $CHCl_3$). R_f (hexane/EtOAc, 4:1): 0.22.

(*S*)-4-Oxocyclopent-2-en-1-yl Buta-2,3-dienoate [(–)-33]: Alcohol (–)-**29** (100 mg, 1.02 mmol) and carboxylic acid **31** (103 mg, 1.22 mmol) were dissolved in CH_2Cl_2 (5.1 mL), and the mixture was cooled to 0 °C. DIC (189 μL, 1.22 mmol) was added, followed by DMAP (41 mg, 0.20 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp. and stirring was continued overnight. The volatiles were removed, and the residue was purified by chromatography column (SiO_2, hexane/EtOAc, 1:1 to 1:2) to give ester (–)-**33** (100 mg, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd, J = 2.5, J = 5.8 Hz, 1 H), 6.33 (dd, J = 1.2, J = 5.7 Hz, 1 H), 5.92–5.89 (m, 1 H), 5.64 (t, J = 6.5 Hz, 1 H), 5.24 (d, J = 6.5 Hz, 2 H), 2.83 (dd, J = 6.3, J = 18.6 Hz, 1 H), 2.36 (dd, J = 2.3, J = 18.7 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 216.4, 204.8, 165.2, 158.9, 137.2, 87.5, 79.8, 72.5, 41.1 ppm. HRMS (ESI): calcd. for $C_9H_8O_3$ [M]$^+$ 164.0473; found 164.0475. IR: $\tilde{\nu}$ = 3451, 2927, 2856, 1713, 1659, 1442, 1362, 1231, 1184, 1102 cm^{-1}. $[\alpha]_D^{20}$ = –132.54 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.48.

(1*S*,4*S*)-4-Hydroxy-4-methylcyclopent-2-en-1-yl Buta-2,3-dienoate [(–)-35]: Triphenylphosphane (172 mg, 0.66 mmol) was dissolved in THF (6.6 mL), and the solution was cooled to 0 °C. DIAD (129 μL, 0.66 mmol) was added very slowly, and the mixture was stirred for 30 min. At this stage a milky precipitate formed. Allenic acid **31** (55 mg, 0.66 mmol) was added in one portion, and a solution of alcohol (–)-**34** (75 mg, 0.66 mmol) in THF (1 mL) was then added dropwise at 0 °C. The mixture was stirred at the same temperature for 2 h. Water (25 mL) was added, and the resulting mixture was extracted with EtOAc (3× 30 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography (SiO_2, hexane/EtOAc, 2:1) to give ester (–)-**35** (41 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (dd, J = 0.9, J = 5.5 Hz, 1 H), 5.90 (dd, J = 2.3, J = 5.5 Hz, 1 H), 5.85–5.80 (m, 1 H), 5.60 (t, J = 6.6 Hz, 1 H), 5.21 (d, J = 6.6 Hz, 2 H), 2.38 (dd, J = 7.1, J = 14.6 Hz, 1 H), 1.98 (dd, J = 3.1, J = 14.6 Hz, 1 H), 1.91 (br. s, 1 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 215.9, 165.6, 143.6, 130.8, 88.0, 82.1, 79.3 (2 C), 46.6, 28.6 ppm. HRMS (ESI): calcd. for $C_{10}H_{12}O_3$ [M]$^+$ 180.0786; found 180.0783. IR: $\tilde{\nu}$ = 3407, 1970, 1942, 1707, 1348, 1256, 1164, 1086, 854, 631 cm^{-1}. $[\alpha]_D^{20}$ = –130.3 (c = 0.95, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.26.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 2-(Hydroxymethyl)buta-2,3-dienoate [(–)-36]: A solution of DABCO (predried under vacuum for 30 min; 5 mg, 0.04 mmol) in THF (0.5 mL) was added dropwise to a suspension of paraformaldehyde (predried under vacuum at 50 °C for 30 min; 33 mg, 1.12 mmol) in THF (1 mL) at –10 °C, and then a solution of ester (–)-**32** (50 mg, 0.22 mmol) in THF (0.5 mL) was added to the mixture. The reaction mixture was allowed to warm to room temp. and stirred for 7 h. The reaction was quenched by the addition of NH_4Cl (saturated aq.; 3 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3× 5 mL). The combined organic extracts were washed with brine (5 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, hexane/EtOAc, 3:1) gave product (–)-**36** (35 mg, 62%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03 (dd, J = 0.7, J = 5.6 Hz, 1 H), 5.97 (dd, J = 2.1, J = 5.7 Hz, 1 H), 5.84–5.80 (m, 1 H), 5.21 (t, J = 2.1 Hz, 1 H), 4.62 (dd, J = 7.2, J = 33.8 Hz, 2 H), 4.31 (t, J = 1.8 Hz, 2 H), 3.34 (s, 3 H), 2.55 (dd, J = 7.2, J = 14.6 Hz, 1 H), 2.48 (br. s, 1 H), 1.85 (dd, J = 3.1, J = 14.7 Hz, 1 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 213.3, 166.7, 142.1, 132.0, 100.0, 92.1, 87.3, 80.5, 79.6, 61.1, 55.3, 44.2, 27.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}O_5$ [M]$^+$ 239.0919; found 239.0906. IR: $\tilde{\nu}$ = 3220, 2930, 1713, 1449, 1361, 1214, 1142, 1091, 1030, 631 cm^{-1}. $[\alpha]_D^{20}$ = –172.0 (c = 0.27, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.29.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 2-(Ethoxy Methyl)buta-2,3-dienoate [(–)-38]: Secondary alcohol (+)-**16** (100 mg, 0.63 mmol), triphenylphosphane (232 mg, 0.88 mmol), and carboxylic acid **37** (180 mg, 1.26 mmol) were dissolved in THF (6.3 mL), and the solution was cooled to 0 °C under Ar. DIAD (174 μL, 0.88 mmol) was slowly added, and the mixture was stirred for 30 min. The mixture was diluted with EtOAc (30 mL) and water (15 mL), and the aqueous phase was extracted with EtOAc (30 mL). The combined organic extracts were washed with $NaHCO_3$ (15 mL) and brine (2× 15 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was then purified by flash column chromatography (SiO_2, hexane/EtOAc, 8:1) to give ester (–)-**38** (104 mg, 58%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (dd, J = 0.7, J = 5.6 Hz, 1 H), 5.98 (dd, J = 2.0, J = 5.6 Hz, 1 H), 5.82–5.78 (m, 1 H), 5.21 (t, J = 2.2 Hz, 2 H), 4.62 (dd, J = 7.4, J = 32.4 Hz, 2 H), 4.18 (t, J = 2.1 Hz, 2 H), 3.53 (q, J = 7.0 Hz, 2 H), 3.34 (s, 3 H), 2.53 (dd, J = 7.2, J = 14.6 Hz, 1 H), 1.85 (dd, J = 3.1, J = 14.6 Hz, 1 H), 1.46 (s, 3 H), 1.20 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 214.6, 165.8, 141.7, 132.0, 98.3, 91.9, 87.2, 79.5, 79.2, 67.2, 66.0, 55.1, 44.1, 27.0, 15.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}O_5Na$ [M + Na]$^+$ 305.1365; found 305.1359. IR: $\tilde{\nu}$ = 2975, 2873, 1967, 1710, 1371, 1259, 1143, 1091, 1031, 535 cm^{-1}. $[\alpha]_D^{20}$ = –115.9 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.29.

(*E*)-(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 3-(Furan-2-yl)acrylate [(–)-(40)]: Secondary alcohol (+)-**16** (100 mg, 0.63 mmol), triphenylphosphane (249 mg, 0.95 mmol), and carboxylic acid **39** (131 mg, 0.95 mmol) were dissolved in THF (4.2 mL), and the solution was cooled to 0 °C under Ar. DIAD (187 μL, 0.95 mmol) was slowly added, and the mixture was stirred for 20 min. The mixture was diluted with EtOAc (20 mL) and water (15 mL), and the aqueous phase was extracted with EtOAc (40 mL). The combined organic extracts were washed with $NaHCO_3$ (10 mL) and brine (2× 20 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 6:1) to give ester (–)-**40** (175 mg, 99%) as a crystalline product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 1.6 Hz, 1 H), 7.40 (d, J = 15.7 Hz, 1 H), 6.60 (d, J = 3.5 Hz, 1 H), 6.46 (dd, J = 1.8, J = 3.4 Hz, 1 H), 6.28 (d, J = 15.7 Hz, 1 H), 6.03–5.99 (m, 2 H), 5.89–5.84 (m, 1 H), 4.63 (dd, J = 7.3, J = 32.9 Hz, 2 H), 3.35 (s, 3 H), 2.60 (dd, J = 7.3, J = 14.7 Hz, 1 H), 1.88 (dd, J = 3.3, J = 14.6 Hz, 1 H), 1.50 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 166.9, 151.1, 144.9, 141.6, 132.5, 131.3, 116.0, 114.9, 112.4, 92.1, 87.4, 78.8, 55.3, 44.3,

27.3 ppm. HRMS (EI): calcd. for $C_{15}H_{18}O_5$ $[M]^+$ 278.1154; found 278.1097. IR: $\tilde{\nu}$ = 2930, 1706, 1638, 1448, 1302, 1259, 1209, 1163, 1110, 1032 cm^{-1}. $[\alpha]_D^{21}$ = –242.9 (c = 1.50, $CHCl_3$), m.p. 74–75 °C, R_f (hexane/EtOAc, 3:1): 0.31.

(*S*,*E*)-4-Oxocyclopent-2-en-1-yl 3-(Furan-2-yl)acrylate [(–)-(41)]: Secondary alcohol (–)-**29** (500 mg, 5.10 mmol) and carboxylic acid **39** (845 mg, 6.12 mmol) were dissolved in CH_2Cl_2 (25.5 mL), and the solution was cooled to 0 °C. DIC (947 μL, 6.12 mmol) was added, followed by DMAP (201 mg, 1.02 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp., and stirring was continued overnight. The volatiles were removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexane/EtOAc, 6:1 to 4:1) to give ester (–)-**41** (788 mg, 71%) as a white crystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, J = 2.5, J = 5.8 Hz, 1 H), 7.48 (d, J = 1.4 Hz, 1 H), 7.44 (d, J = 15.7 Hz, 1 H), 6.64 (d, J = 3.5 Hz, 1 H), 6.47 (dd, J = 1.8, J = 3.4 Hz, 1 H), 6.64 (dd, J = 1.3, J = 5.8 Hz, 1 H), 6.29 (d, J = 15.7 Hz, 1 H), 5.98–5.94 (m, 1 H), 2.86 (dd, J = 6.5, J = 18.8 Hz, 1 H), 2.39 (dd, J = 2.2, J = 18.8 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 204.9, 166.3, 159.1, 150.6, 15.1, 137.0, 132.1, 115.5, 114.5, 112.4, 71.9, 41.1 ppm. HRMS (EI): calcd. for $C_{12}H_{10}O_4$ $[M]^+$ 218.0579; found 218.0562. IR: $\tilde{\nu}$ = 2933, 1708, 1635, 1479, 1353, 1282, 1207, 1156, 1016, 753 cm^{-1}. $[\alpha]_D^{21}$ = –243.1 (c = 4.00, $CHCl_3$), m.p. 80–81 °C, R_f (hexane/EtOAc, 3:1): 0.21.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 2-Acetoxybenzoate [(–)-42]: Secondary alcohol (+)-**16** (100 mg, 0.63 mmol), triphenylphosphane (199 mg, 0.76 mmol), and 2-acetoxybenzoic acid (137 mg, 0.76 mmol) were dissolved in THF (6.3 mL), and the solution was cooled to 0 °C under Ar. DIAD (149 μL, 0.76 mmol) was added slowly, and the mixture was stirred for 40 min. The mixture was diluted with EtOAc (30 mL) and water (15 mL), and the aqueous phase was extracted with EtOAc (50 mL). The combined organic extracts were washed with $NaHCO_3$ (25 mL) and brine (2× 40 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was then purified by flash column chromatography (SiO_2, hexane/EtOAc, 6:1) to give ester (–)-**42** (106 mg, 52%) and recovered starting material (45 mg, 45%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, J = 1.8, J = 7.9 Hz, 1 H), 7.54 (dt, J = 1.7, J = 7.8 Hz, 1 H), 7.29 (dt, J = 1.2, J = 7.7 Hz, 1 H), 7.08 (dd, J = 1.2, J = 8.1 Hz, 1 H), 6.07–6.02 (m, 2 H), 5.98–5.93 (m, 1 H), 4.63 (dd, J = 7.4, J = 34.5 Hz, 2 H), 3.35 (s, 3 H), 2.64 (dd, J = 7.3, J = 14.9 Hz, 1 H), 2.32 (s, 3 H), 1.92 (dd, J = 3.4, J = 14.8 Hz, 1 H), 1.51 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.7, 164.4, 150.7, 142.0, 133.9, 132.3, 131.9, 126.1, 123.9, 123.6, 92.1, 87.3, 79.5, 55.3, 44.3, 27.3, 21.2 ppm. HRMS (EI): calcd. for $C_{17}H_{20}O_6Na$ $[M + Na]^+$ 343.1158; found 343.1184. IR: $\tilde{\nu}$ = 2932, 1770, 1717, 1607, 1368, 1289, 1191, 1029, 961, 915 cm^{-1}. $[\alpha]_D^{20}$ = –147.5 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.32.

Ketene 43: Et_3N (14 μL, 0.10 mmol) was added to a solution of alcohol (–)-**26** (15 mg, 0.09 mmol) in THF (0.5 mL) at 0 °C. After 15 min at this temperature, the resulting clear reaction mixture was slowly added to a pre-formed solution of suboxide at 0 °C [Ketene preparation: A solution of malonyl dichloride (18 μL, 0.19 mmol) in THF (0.5 mL) was treated with iPrEt$_2$N (35 μL, 0.21 mmol) dropwise at 0 °C. The reaction mixture was kept at this temperature for 30 min, resulting in an orange suspension]. The resulting suspension was stirred at the same temperature for 90 min, and then it was allowed to warm to room temp. After 6 h, no starting material was left, as indicated by TLC. Water (5 mL) and then EtOAc (5 mL) were added to the reaction mixture. The mixture was extracted with EtOAc (3× 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure. Column chromatography (SiO_2, EtOAc) of the resulting yellow oil led neither to the recovery of starting material nor to the isolation of the desired cyclization product or ketene **43**.

Ketene Iminium Ion 46: A solution of amide (–)-**45** (48 mg, 0.14 mmol) and collidine (19 μL, 0.14 mmol) in DCE (2.0 mL) was treated with a solution of triflic anhydride (25 μL, 0.15 mmol) in CH_2Cl_2 (0.5 mL) at room temp. The reaction mixture was stirred at this temperature for 6 h. As no reaction was indicated by TLC, the reaction vessel was sealed with a stopper and heated to reflux for an additional 2 h. Water (5 mL) and then CH_2Cl_2 (5 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried over $MgSO_4$. After evaporation of the volatiles, flash column chromatography (SiO_2, EtOAc) did not result in isolation of the desired cylization product or **46**.

Ketene Iminium Ion 48: A solution of alcohol (–)-**26** (30 mg, 0.19 mmol), acid **47** (33 mg, 0.21 mmol), and DMAP (3 mg, 0.02 mmol) in CH_2Cl_2 (1.9 mL) was treated with DIC (35 μL, 0.23 mmol) dropwise at 0 °C under an Ar atmosphere. The resulting pale beige suspension was allowed to warm to room temp. and stirred for 24 h. As TLC indicated full consumption of the starting material, ammonium chloride (saturated aq.; 5 mL) was added to the reaction mixture. After extraction with CH_2Cl_2 (3× 10 mL), $MgSO_4$ was added to the combined organic extracts. Filtration followed by removal of the volatiles resulted in a pale yellow oil, which was purified by column chromatography (SiO_2, EtOAc) to give the desired amide (56 mg, quant. yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.01 (dd, J = 5.6, J = 0.9 Hz, 1 H), 5.97 (dd, J = 5.6, J = 2.0 Hz, 1 H), 5.80 (m, 1 H), 4.65 (d, J = 7.3 Hz, 1 H), 4.57 (d, J = 7.3 Hz, 1 H), 3.49 (t, J = 6.8 Hz, 2 H), 3.43 (t, J = 6.8 Hz, 2 H), 3.36 (s, 2 H), 3.33 (s, 3 H), 2.55 (dd, J = 14.7, J = 7.2 Hz, 1 H), 1.96 (m, 2 H), 1.91–1.84 (m, 3 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.6, 164.4, 142.0, 132.0, 92.1, 87.3, 79.8, 55.3, 47.3, 46.1, 44.1, 42.7, 27.2, 26.2, 24.6 ppm. HRMS (EI): calcd. for $C_{15}H_{23}NNaO_5$ $[M + Na]^+$ 320.1474; found 320.1473. IR: $\tilde{\nu}$ = 2973, 2881, 1736, 1646, 1442, 1344, 1259, 1144, 1032, 750 cm^{-1}. $[\alpha]_D^{20}$ = –97.7 (c = 0.60, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.19.

A solution of amide (56 mg, 0.19 mmol) and collidine (26 μL, 0.19 mmol) in DCE (2.0 mL) was treated with a solution of triflic anhydride (34 μL, 0.21 mmol) in CH_2Cl_2 (0.5 mL) at room temp. The reaction mixture was stirred at this temperature for 6 h. As no reaction was indicated by TLC, the reaction vessel was sealed with a stopper and heated to reflux for an additional 2 h. Water (5 mL) and then CH_2Cl_2 (5 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried over $MgSO_4$. After evaporation of the volatiles, flash column chromatography (SiO_2, EtOAc) did not result in isolation of the desired cyclization product or **48**.

Anhydride (–)-50: A quartz vial of 1 cm diameter was charged with cyclopentene (–)-**49** (20 mg, 0.06 mmol), maleic anhydride (29 mg, 0.29 mmol), a magnetic stirrer bar and acetone (6.0 mL). The vial was sealed with a rubber septum and equipped with an argon balloon. The reaction vessel was placed in an ultrasound bath, and the reaction mixture was degassed by passing a gentle stream of argon through the solution. After 30 min, the quartz vial was placed 1 cm in front of 8 × 16 W UV-A lamps, and irradiated for

a period of 8 h. After full consumption of the cyclopentene, as judged by TLC, the solvent was removed under reduced pressure. The colorless semi-solid was purified by column chromatography (SiO_2, hexane/EtOAc, 10:1) to give desired tricycle (–)-**50** (15 mg, 58%) as a colorless oil, which partially crystallized upon storage in the fridge. During purification by chromatography, as well as upon dissolving and storing in $CDCl_3$, partial hydrolysis of the anhydride functionality was observed, resulting in a small amount of impurity in the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (dt, J = 10.7, J = 7.0 Hz, 1 H), 3.56 (dd, J = 6.5, J = 2.6 Hz, 1 H), 3.51 (dd, J = 6.5, J = 3.0 Hz, 1 H), 2.87 (dt, J = 6.7, J = 2.7 Hz, 1 H), 2.62 (dd, J = 6.1, J = 3.0 Hz, 1 H), 2.00 (dd, J = 12.7, J = 6.6 Hz, 1 H), 1.86 (m, 1 H), 1.52 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 173.9, 173.4, 76.7, 70.2, 51.6, 45.7, 44.5, 38.9, 35.9, 29.8, 29.4, 26.0 (3 C), 25.9 (3 C), 18.2, –2.2, –2.3, –4.7, –4.8 ppm. HRMS (EI): calcd. for $C_{23}H_{44}NaO_6Si_2$ [M + MeOH + Na]$^+$ 495.2574; found 495.2592. $[\alpha]_D^{20}$ = –127.8 (c = 0.75, $CHCl_3$). IR: $\tilde{\nu}$ = 2973, 2879, 1875, 1834, 1642, 1601, 1332, 1269, 1144, 834 cm^{-1}. R_f (hexane/EtOAc, 6:1): 0.58.

***tert*-Butyldimethyl{[(1*R*,4*S*)-4-(prop-2-yn-1-yloxy)cyclopent-2-en-1-yl]oxy}silane [(+)-54]:** A solution of (+)-**44** (1.00 g, 4.66 mmol) in THF (3.5 mL) was added to a suspension of NaH (450 mg, 18.66 mmol) in THF (3.5 mL) at 0 °C. The mixture was allowed to warm to room temp., and after the evolution of H_2 had subsided, the mixture was cooled again to 0 °C. Propargyl bromide (80 wt.-% in toluene; 1.51 mL, 13.99 mmol) was then slowly added, and the reaction mixture was stirred overnight while it warmed to room temp. The reaction was quenched with water (10 mL) and extracted with EtOAc (3× 20 mL). The combined organic extracts were washed with brine (15 mL) and water (15 mL), and dried with $MgSO_4$, and the solvent was removed in vacuo. Purification by chromatography column (SiO_2, hexane/EtOAc, 15:1) gave (+)-**54** (1.38 g, 99%) as a slightly viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97–5.90 (m, 2 H), 4.67 (m, 1 H), 4.56 (m, 1 H), 4.17 (dd, J = 2.4, J = 4.1 Hz, 2 H), 2.69 (td, J = 7.2, J = 13.4 Hz, 1 H), 2.41 (t, J = 2.4 Hz, 1 H), 1.60 (td, J = 5.3, J = 13.4 Hz, 1 H), 0.98 (s, 9 H), 0.83 (s, 3 H), 0.79 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 138.0, 132.2, 81.2, 80.4, 74.8, 74.0, 55.6, 41.2, 25.9 (3 C), 18.1, –4.6 (2 C) ppm. HRMS (EI): calcd. for $C_{10}H_{15}O_2Si$ [M – tBu]$^+$ 195.0841; found 195.0841. IR: $\tilde{\nu}$ = 2955, 2931, 2857, 1372, 1253, 1081, 1059, 905, 837, 777 cm^{-1}. $[\alpha]_D^{20}$ = +32.7 (c = 1.05, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.48.

{[(1*R*,4*S*)-4-(Buta-2,3-dien-1-yloxy)cyclopent-2-en-1-yl]oxy}(tert-butyl)dimethylsilane [(+)-51]: Paraformaldehyde (416 mg, 13.85 mmol), DIPA (1.0 mL, 7.13 mmol), and CuBr (331 mg, 2.31 mmol) were sequentially added to a solution of alkyne (+)-**54** (1.17 g, 4.38 mmol) in dioxane (30 mL). The reaction mixture was heated at reflux overnight. After the reaction was complete (TLC monitoring), the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 1:0 to 20:1) to give (+)-**51** (1.04 g, 84%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94–5.87 (m, 2 H), 5.25 (d, J = 6.8 Hz, 1 H), 4.78 (td, J = 2.5, J = 6.6 Hz, 1 H), 4.66 (m, 1 H), 4.42 (m, 1 H), 4.05 (m, 1 H), 2.67 (td, J = 7.2, J = 13.2 Hz, 1 H), 1.58 (td, J = 5.6, J = 13.2 Hz, 1 H), 0.89 (s, 9 H), 0.08 (s, 1 H), 0.08 (s, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 209.2, 137.5, 132.7, 88.2, 81.1, 75.6, 74.9, 66.3, 41.5, 25.9 (3 C), 18.2, –4.6 (2 C) ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_2SiNa$ [M + Na]$^+$ 289.1600; found 289.1592. IR: $\tilde{\nu}$ = 2955, 2931, 2857, 1368, 1253, 1079, 940, 905, 837, 777 cm^{-1}. $[\alpha]_D^{20}$ = +10.4 (c = 0.85, $CHCl_3$). R_f (hexane/EtOAc, 15:1): 0.49.

(*S*)-4-(Buta-2,3-dien-1-yloxy)cyclopent-2-enone [(+)-52]: Compound (+)-**51** (500 mg, 1.88 mmol) was dissolved in THF (2 mL), and TBAF (1 M in THF; 2.40 mL, 2.40 mmol) was added at room temp. After TLC had indicated an almost complete conversion, CH_2Cl_2 (12 mL) was added. Then MnO_2 (4.89 g, 56.25 mmol) was added, and stirring was continued overnight at room temp. The mixture was filtered through Celite, and, after gentle evaporation of the solvent in vacuo, the residue was purified by column chromatography (SiO_2, pentane/Et_2O, 2:1) to give (+)-**52** (164 mg, 58%) as a volatile greenish-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, J = 2.3,. J = 5.7 Hz, 1 H), 6.26 (dd, J = 1.4, J = 5. 7 Hz, 1 H), 5.26 (t, J = 6.8 Hz, 1 H), 4.83 (td, J = 2.4, J = 6.6 Hz, 2 H), 4.78 (m, 1 H), 4.16–4.09 (m, 2 H), 2.69 (dd, J = 5.9, J = 18.3 Hz, 1 H), 2.33 (dd, J = 2.3, J = 18.3 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 209.5, 205.8, 161.0, 135.8, 87.5, 76.5, 76.1, 67.7, 41.8 ppm. HRMS (ESI): calcd. for $C_9H_{10}O_2Na$ [M + Na]$^+$ 150.0681; found 150.0699. IR: $\tilde{\nu}$ = 2926, 2856, 1719, 1351, 1184, 1105, 1074, 996, 849, 792 cm^{-1}. $[\alpha]_D^{20}$ = +5.14 (c = 1.23, $CHCl_3$). R_f (Pentane/Et_2O, 2:1) : 0.20.

(3a*S*)-1-Methylenehexahydro-3-oxacyclobuta[cd]pentalen-5(1a1*H*)-one [(+)-53]: Enone (+)-**52** (30 mg, 0.21 mmol) was dissolved in diethyl ether (6 mL). The solution was irradiated with UV-B light under 2 × 16 W lamps (Irradiation conditions G) in a quartz vial for 6 h. After TLC indicated partial conversion, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (pentane/Et_2O, 2:1) to give (+)-**53** (18 mg, 60%) as a volatile liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.16 (m, 1 H), 5.00 (m, 1 H), 4.66 (t, J = 5.7 Hz, 1 H), 4.00 (d, J = 9.1 Hz, 1 H), 3.70 (dd, J = 4.2, J = 9.1 Hz, 1 H), 3.61–3.56 (m, 1 H), 3.49–3.44 (m, 1 H), 3.38–3.34 (m, 1 H), 2.70 (d, J = 18.2 Hz, 1 H), 2.54 (ddd, J = 0.6, J = 5.0, J = 18.2 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 214.1, 145.2, 111.7, 79.3, 73.9, 51.8, 48.7, 48.3, 42.7 ppm. HRMS (EI): calcd. for $C_9H_{10}O_2$ [M]$^+$ 150.0681; found 150.0692. IR: $\tilde{\nu}$ = 2965, 2831, 1747, 1291, 1114, 1056, 1001, 943, 819, 732 cm^{-1}. $[\alpha]_D^{21}$ = +12.1 (c = 0.90, $CHCl_3$). R_f (pentane/Et_2O, 2:1): 0.14.

[(1*S*,5*R*,6*S*)-Bicyclo[3.2.0]hept-2-en-6-yloxy](*tert*-butyl)dimethylsilane [(–)-57]: TBSCl (9.36 g, 59.0 mmol) was added to a solution of alcohol (+)-**56** (5.00 g, 45.4 mmol) in anhydrous CH_2Cl_2 (91 mL) at 0 °C under Ar, and then Et_3N (10.1 mL, 72.6 mmol) and DMAP (277 mg, 2.30 mmol) were added. The reaction mixture was allowed to warm to room temp. overnight. NH_4Cl (saturated aq.; 50 mL) was added. The mixture was diluted with CH_2Cl_2 (50 mL), washed in sequence with HCl (0.5 M; 40 mL), water (40 mL), and brine (2× 50 mL), and dried with $MgSO_4$. The volatile materials were removed under reduced pressure to give a crude product. Purification by column chromatography (SiO_2, hexane) gave protected alcohol (–)-**57** (9.52 g, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.75 (m, 2 H), 4.51–4.44 (m, 1 H), 3.14–3.04 (m, 1 H), 2.92–2.80 (m, 2 H), 2.64–2.54 (m, 1 H), 2.36–2.26 (m, 1 H), 1.64–1.56 (m, 1 H), 0.88 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 134.6, 133.0, 65.6, 44.1, 40.8, 39.1, 31.5, 26.0 (3 C), 18.3, –4.7 (2 C) ppm. HRMS (EI): calcd. for $C_9H_{15}OSi$ [M – tBu]$^+$ 167.0892; found 167.0890. IR: $\tilde{\nu}$ = 2930, 2857, 1709, 1471, 1254, 1125, 1004, 879, 837, 777 cm^{-1}. $[\alpha]_D^{22}$ = –0.2 (c = 1.0, $CHCl_3$). R_f (hexane): 0.49.

(1*R*,5*R*,6*S*)-6-[(*tert*-butyldimethylsilyl)oxy]bicyclo[3.2.0]hept-3-en-2-one [(–)-58]: A solution of alkyne (–)-**57** (9.36 g, 41.7 mmol), acetic anhydride (4.34 mL, 45.9 mmol), pyridine (1.69 mL, 20.9 mmol), DMAP (305 mg, 2.50 mmol), and tetraphenylporphyrin (25.6 mg, 41.7 μmol) in CH_2Cl_2 (52 mL) was irradiated with a halogen lamp (500 W) for 7 d under vigorous stirring while O_2 was bubbled con-

tinuously through the solution. The mixture was diluted with CH_2Cl_2 (100 mL), washed in sequence with $NaHCO_3$ (saturated aq.; 50 mL), water (50 mL), $CuSO_4$ (saturated aq.; 50 mL), and brine (50 mL), and dried with $MgSO_4$. The volatile materials were removed under reduced pressure to give crude enone (–)-**58** (10.0 g, 100%) as a dark red oil containing <5% of starting material. An aliquot was purified by column chromatography (SiO_2, hexane/EtOAc, 5:1) for analytical purposes. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dd, J = 2.8, J = 5.6 Hz, 1 H), 6.39 (dd, J = 1.1, J = 5.6 Hz, 1 H), 4.58 (q, J = 7.7 Hz, 1 H), 3.68–3.62 (m, 1 H), 2.84–2.74 (m, 1 H), 2.60–2.52 (m, 1 H), 1.84–1.76 (m, 1 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 212.3, 162.7, 136.8, 65.3, 49.4, 36.9, 35.4, 25.8 (3 C), 18.1, –4.7, –4.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{22}O_2Si$ 238.1389; found 238.1389. IR: $\tilde{\nu}$ = 2953, 2857, 1706, 1252, 1183, 1122, 949, 870, 837, 777 cm^{-1}. $[\alpha]_D^{25}$ = –179.5 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 5:1): 0.25.

Optimized Procedure for TMS Enol Ether (–)-59

Procedure A, From Enone (–)-58: MeLi (1.6 M in Et_2O; 336 mL, 503 mmol) was slowly added to a suspension of CuI (47.9 g, 252 mmol) in anhydrous Et_2O (840 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min and then cooled to –78 °C. A solution of enone (–)-**58** (60.0 g, 252 mmol) in Et_2O (100 mL) was slowly added to the solution over 25 min. The mixture was stirred for 1 h at –78 °C and then warmed quickly to 0 °C. TMSCl (39.9 mL, 315 mmol) was rapidly added, followed immediately by Et_3N (43.8 mL, 315 mmol). The mixture was stirred for 16 h at 0 °C and then ether (300 mL) and water (300 mL) were slowly added. The organic phase was extracted with NH_4OH (10% aq.; 3× 100 mL), water (3× 150 mL), and brine (200 mL), dried with $MgSO_4$, and filtered. The volatiles were removed to give pure TMS enol ether (–)-**59** (82.2 g, quantitative).

Procedure B, From Ketone (–)-61: TMSOTf (17.2 mL, 95.1 mmol) and Et_3N (23.2 mL, 166 mmol) were slowly added to a suspension of ketone (–)-**61** (12.1 g, 47.6 mmol) in anhydrous Et_2O (237 mL) at 0 °C. The mixture was stirred for 16 h at 0 °C and then $NaHCO_3$ (saturated aq.; 500 mL) was added. The aqueous phase was extracted with Et_2O (2× 250 mL), and the combined organic extracts were washed with water (2× 150 mL) and brine (200 mL), dried with $MgSO_4$, and filtered. The volatiles were removed to give pure TMS enol ether (–)-**59** (15.4 g, 99%).

Optimized Procedure for Enone (–)-60: Crude TMS enol ether (–)-**59** (82.2 g, 252 mmol) was dissolved in DMSO (840 mL), and the solution was warmed to 32 °C and saturated with oxygen by bubbling gas through the solution for 10 min. Under an O_2 atmosphere, $Pd(OAc)_2$ (28.2 g, 126 mmol) was added in one portion. After 3 h, the reaction mixture was filtered through Celite (10 cm thick). The filtrate was diluted with EtOAc (400 mL), and the filtration through Celite (10 cm thick) was repeated. A mixture of water (200 mL) and crushed ice (200 g) was added with vigorous agitation. After separation of the phases, the organic phase was washed with water (2× 100 mL). The combined aqueous phases were extracted with EtOAc (3× 200 mL). The organic extracts were combined, washed with water (3× 100 mL) and brine (100 mL), dried with $MgSO_4$, and concentrated under reduced pressure. NMR analysis showed a 4:1 mixture of enone (–)-**60** and ketone (–)-**61**. Compounds (–)-**60** and (–)-**61** were separated by column chromatography (hexane/EtOAc, 20:1 then 5:1) to give ketone (–)-**61** (12.1 g, 19%) and enone (–)-**60** (51.4 g, 81%). Data for enone (–)-**60**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09 (s, 1 H), 4.61 (q, J = 7.7 Hz, 1 H), 3.50–3.44 (m, 1 H), 2.79–2.69 (m, 1 H), 2.59–2.52 (m, 1 H), 2.19 (s, 3 H), 1.81–1.73 (m, 1 H), 0.85 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 211.9, 177.4, 132.3, 65.2, 51.9, 38.2, 34.9, 25.7 (3 C), 19.9, 17.9, –4.77, –5.05 ppm. HRMS (ESI): calcd. for $C_{14}H_{24}O_2Si$ [M]$^+$ 252.1546; found 252.1548. IR: $\tilde{\nu}$ = 2929, 2857, 1698, 1613, 1253, 1183, 1117, 955, 838, 778 cm^{-1}. $[\alpha]_D^{20}$ = –238.0 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.32.

Data for ketone (–)-**61**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (q, J = 7.2 Hz, 1 H), 2.85–2.73 (m, 2 H), 2.73–2.55 (m, 2 H), 2.55–2.45 (m, 1 H), 2.00–1.90 (m, 2 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 220.9, 64.6, 50.9, 47.2, 39.6, 36.3, 27.3, 25.9 (3 C), 21.6, 18.1, –4.6, –4.9 ppm. HRMS (EI): calcd. for $C_{13}H_{23}O_2Si$ [M – CH_3]$^+$ 239.1467; found 239.1465. IR: $\tilde{\nu}$ = 2954, 2857, 1735, 1252, 1187, 1118, 949, 887, 837, 777 cm^{-1}. $[\alpha]_D^{25}$ = –96.4 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 4:1): 0.24.

(1*R*,2*R*,4*R*,6*R*,8*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-3-oxatricyclo[4.2.0.02,4]octan-5-one [(–)-62]: Enone (–)-**60** (150 mg, 0.59 mmol) was dissolved in MeOH (6.1 mL), and the solution was cooled to –20 °C. NaOH (1 M aq.; 179 µL, 0.179 mmol) was added, followed by the dropwise addition of hydrogen peroxide (30 wt.-%; 750 µL). The reaction mixture was allowed to warm to 0 °C. After 1 h at this temperature, the reaction was quenched with HCl (0.5 M aq.; 2 mL) and $Na_2S_2O_3$ (saturated aq.; 5 mL). The solution was diluted with water (40 mL) and EtOAc (60 mL), the phases were separated, and the aqueous phase extracted with EtOAc (60 mL). The combined organic extracts were washed with brine (40 mL), dried with $MgSO_4$, filtered and concentrated. The crude product (160 mg, 99%) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.49–4.40 (m, 1 H), 3.35 (s, 1 H), 3.17 (t, J = 6.8 Hz, 1 H), 2.75–2.64 (m, 1 H), 2.60–2.53 (m, 1 H), 1.77 (ddt, J = 1.1, J = 4.1, J = 12.8 Hz, 1 H), 1.63 (s, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 211.0, 65.9, 64.2, 63.8, 47.4, 38.8, 35.2, 25.8 (3 C), 18.0, 16.8, –4.6, –5.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{24}O_3SiNa$ [M + Na]$^+$ 291.1392; found 291.1383. IR: $\tilde{\nu}$ = 2931, 2587, 1743, 1399, 1254, 1124, 1070, 922, 834, 776 cm^{-1}. $[\alpha]_D^{22}$ = –32.8 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 5:1): 0.45.

(1*R*,2*S*,5*S*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2-methylbicyclo-[3.2.0]hept-3-en-2-ol [(–)-63]: $N_2H_4{\cdot}H_2O$ (27 µL, 0.56 mmol) and AcOH (80 µL, 1.40 mmol) were added to a solution of epoxide (–)-**62** (75 mg, 0.28 mmol) in MeOH (3 mL) at 0 °C. After 5 min at this temperature, TLC showed no remaining starting materials, and the hydrazine intermediate and a new product spot had appeared. The mixture was stirred for a further 15 min. The mixture was then heated to reflux for 2 h. Then water (5 mL) was added. The solution was neutralized with $NaHCO_3$ and extracted with EtOAc (3× 15 mL). The combined organic extracts were washed with brine (15 mL) and dried with $MgSO_4$. Removal of the solvent by rotary evaporation and purification by flash column chromatography (hexane/EtOAc, 6:1) gave tertiary alcohol (–)-**63** (29 mg, 40%) as an unstable colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (dd, J = 2.4, J = 5.3 Hz, 1 H), 5.80 (d, J = 5.3 Hz, 1 H), 4.58–4.48 (m, 1 H), 3.09–3.00 (m, 1 H), 2.91–2.83 (m, 1 H), 2.59–2.49 (m, 1 H), 1.62 (s, 3 H), 1.56–1.44 (m, 2 H), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 140.0, 136.7, 85.4, 65.8, 54.7, 39.2, 38.6, 29.7, 25.8 (3 C), 24.1, –3.6, –4.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{26}O_2SiNa$ [M + Na]$^+$ 277.1600; found 277.1583. IR: $\tilde{\nu}$ = 2998, 2787, 1319, 1124, 1099, 1021, 977, 902, 874, 736 cm^{-1}. $[\alpha]_D^{20}$ = –5.9 (c = 1.2, $CHCl_3$). R_f (hexane/EtOAc, 5:1): 0.17.

Alkene (–)-64: Cerium chloride heptahydrate (5.79 g, 15.6 mmol) was added to a stirred solution of enone (–)-**60** (3.27 g, 13.0 mmol)

in MeOH (65 mL) at room temp. After 5 min, the mixture was cooled to 0 °C, and $NaBH_4$ (539 mg, 14.3 mmol) was added portionwise. The reaction mixture was stirred at 0 °C until the starting material had been completely consumed (30 min). The reaction was quenched by the addition of acetic acid (1:1 in water; 5 mL). Water (100 mL) and EtOAc (150 mL) were added, and the heterogeneous mixture was extracted with EtOAc (4× 80 mL). The organic phase was washed with water (2× 75 mL) and brine (2× 50 mL). The combined organic extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure to give crude allylic alcohol (3.30 g, quantitative) as a viscous oil.

The crude alcohol (3.30 g, 12.9 mmol) was dissolved in CH_2Cl_2 (43 mL), and iPr_2NEt (6.78 mL, 38.9 mmol) and MOMCl (2.45 mL, 32.3 mmol) were added at 0 °C. The reaction mixture was stirred at room temp. for 15 h. After the addition of water (100 mL) and CH_2Cl_2 (150 mL), the organic phase was washed with $NaHCO_3$ (5% aq.; 75 mL) and brine (3× 60 mL), then dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 20:1) to give alkene (–)-**64** (3.29 mg, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (br. s, 1 H), 4.80 (dq, J = 1.7, J = 7.1 Hz, 1 H), 4.62 (d, J = 6.7 Hz, 1 H), 4.57 (d, J = 6.7 Hz, 1 H), 4.27 (q, J = 7.7 Hz, 1 H), 3.36 (s, 3 H), 3.19 (br. s, 1 H), 2.55–2.45 (m, 1 H), 2.32–2.22 (m, 1 H), 2.20–2.11 (m, 1 H), 1.83 (br. s, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 144.0, 127.4, 96.3, 85.0, 65.4, 55.6, 55.3, 32.3, 31.7, 26.0 (3 C), 18.2, 17.1, –4.5, –4.8 ppm. HRMS (ESI): calcd. for $C_{16}H_{30}O_3Si$ Na $[M + Na]^+$ 321.1862; found 321.1866. IR: $\tilde{\nu}$ = 2929, 2857, 2361, 2342, 1375, 1254, 1122, 1042, 835, 776 cm^{-1}. $[\alpha]_D^{24}$ = 81.4 (c = 1.1, $CHCl_3$). R_f (hexane/EtOAc, 5:1): 0.55.

Optimized Procedure for Alcohol (–)-65: $Co(acac)_2$ (741 mg, 2.88 mmol) was added to a solution of alkene (–)-**64** (8.60 g, 28.8 mmol) in THF (300 mL) in a 2 L flask at room temp. The reaction mixture was then saturated with O_2 (40 min), and then $PhSiH_3$ (14.2 mL, 115 mmol) was added over 45 min using a syringe pump, while a gentle flow of O_2 was blown 5 cm above the well-stirred solution. The O_2 flow was reduced, and stirring was maintained for 15 h at room temp. The reaction mixture was diluted with EtOAc (250 mL), water (100 mL), and saturated $NaHCO_3$ (100 mL), and stirred for a further 24 h. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3× 200 mL). The aqueous phase was saturated with solid NaCl and further extracted with EtOAc (2× 200 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 3:1) to give tertiary alcohol (–)-**65** (7.93 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.60 (d, J = 6.4 Hz, 1 H), 4.57 (d, J = 6.4 Hz, 1 H), 4.48–4.36 (m, 2 H), 3.34 (s, 3 H), 2.69–2.55 (m, 2 H), 2.29–2.20 (m, 1 H), 2.18–2.09 (m, 1 H), 2.08–1.96 (m, 2 H), 1.49 (s, 3 H), 1.24 (br. s, 1 H), 0.88 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 96.1, 79.7, 78.9, 64.7, 55.5, 55.4, 44.5, 33.5, 30.3, 26.0 (3 C), 25.5, 18.2, –4.6, –5.0 ppm. HRMS (EI): calcd. for $C_{16}H_{32}O_4SiNa$ $[M + Na]^+$ 339.3968; found 339.3964. IR: $\tilde{\nu}$ = 3405, 2955, 2884, 2362, 1254, 1132, 1044, 869, 867, 777 cm^{-1}. $[\alpha]_D^{24}$ = –1.73 (c = 1.1, $CHCl_3$). R_f (hexane/EtOAc, 2:1): 0.25.

Optimized Procedure for Alcohol (–)-66: Alcohol (–)-**65** (18.3 g, 57.8 mmol) was dissolved in THF (290 mL), and the solution was cooled to 0 °C. 2,6-Lutidine (26.9 mL, 231 mmol) and then TBSOTf (26.6 mL, 116 mmol) were rapidly added to the reaction vessel, and the mixture was stirred at 0 °C for 15 min. The reaction was quenched by the addition of $NaHCO_3$ (150 mL), and the mixture was diluted with water (100 mL) and diethyl ether (200 mL). The phases were separated, and the aqueous phase was extracted with diethyl ether (2× 150 mL). The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 15:1) to give the di-TBS-protected alcohol (25.5 g, quantitative) contaminated with TBS-OH and 2,6-lutidine. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61 (d, J = 6.6 Hz, 1 H), 4.57 (d, J = 6.6 Hz, 1 H), 4.45–4.32 (m, 2 H), 3.34 (s, 3 H), 2.70–2.63 (m, 1 H), 2.70–2.54 (m, 1 H), 2.28–2.17 (m, 1 H), 2.07–1.97 (m, 3 H), 1.48 (s, 3 H), 0.88 (s, 9 H), 0.83 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 96.3, 82.2, 79.7, 65.0, 55.9, 55.5, 45.6, 33.7, 30.3, 26.0 (3 C), 25.9 (3 C), 24.9, 18.2, 18.1, –2.0, –2.2, –4.6, –5.0 ppm. HRMS (ESI): calcd. for $C_{22}H_{46}O_4SiNa$ $[M + Na]^+$ 453.2832; found 453.2813. IR: $\tilde{\nu}$ = 2929, 2856, 1253, 1108, 1076, 1043, 1001, 939, 832, 772 cm^{-1}. $[\alpha]_D^{24}$ = –9.3 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 5:1): 0.61.

The crude residue was dissolved in THF (116 mL), and the solution was cooled to 0 °C. Then, TBAF (1 M in THF; 69.6 mL, 69.6 mmol) was added over 15 min. The reaction mixture was allowed to warm slowly to room temp. overnight, and then the volatiles were removed under reduced pressure at 30 °C. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 3:1) to give alcohol (–)-**66** (17.1 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.60 (d, J = 6.6 Hz, 1 H), 4.57 (d, J = 6.6 Hz, 1 H), 4.53–4.42 (m, 1 H), 4.40–4.31 (m, 1 H), 3.33 (s, 3 H), 2.69–2.57 (m, 2 H), 2.35–2.25 (m, 1 H), 2.11–1.97 (m, 3 H), 1.68 (d, J = 3.7 Hz, 1 H), 1.50 (s, 3 H), 0.82 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 96.3, 81.9, 79.6, 65.0, 55.5, 55.4, 45.9, 33.7, 28.9, 25.8 (3 C), 24.9, 18.1, –2.0, –2.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{32}O_4SiNa$ $[M + Na]^+$ 339.1968; found 339.1961. IR: $\tilde{\nu}$ = 3444, 2930, 2856, 1461, 1252, 1107, 1036, 995, 832, 772 cm^{-1}. $[\alpha]_D^{20}$ = –34.8 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.30.

Optimized Procedure for Diol (–)-67: Alcohol (–)-**66** (8 g, 25.3 mmol) was dissolved in EtOAc (168 mL), and IBX (14.1 g, 50.6 mmol) was added to the solution. The heterogeneous mixture was heated to reflux for 3 h and then cooled to room temp. Hexane (150 mL) was added, and stirring was continued for 15 min. The suspension was filtered through a Celite pad (3 cm), and the filtrate was concentrated to give the ketone (7.90 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65 (s, 2 H), 4.63–4.55 (m, 1 H), 4.43–4.37 (m, 1 H), 3.35 (s, 3 H), 3.19–3.11 (m, 1 H), 3.10–3.00 (m, 1 H), 2.95–2.86 (m, 1 H), 2.15 (ddd, J = 1.9, J = 6.4, J = 13.0 Hz, 1 H), 1.63 (dd, J = 11.1, J = 13.0 Hz, 1 H), 1.38 (s, 3 H), 0.84 (s, 9 H), 0.10 (s, 36 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 209.1, 96.5, 79.5, 78.9, 76.0, 55.7, 45.3, 45.2, 31.4, 25.8 (3 C), 24.5, 18.0, –2.2, –2.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{30}O_4SiNa$ $[M + Na]^+$ 337.1811; found 337.1804. IR: $\tilde{\nu}$ = 2929, 2856, 1777, 1253, 1147, 1109, 1042, 833, 773, 696 cm^{-1}. $[\alpha]_D^{20}$ = –151.6 (c = 1.4, $CHCl_3$). R_f (hexane/EtOAc, 2:1): 0.55.

DBU (11.2 mL, 75.4 mmol) was slowly added to a solution of crude ketone (7.90 g, 25.1 mmol) in formalin (65 mL). A cold water bath was used to avoid a slight increase of temperature. The water bath was then warmed to 30 °C, and the solution was stirred vigorously for a further 30 min. The reaction mixture was diluted with water (120 mL) and EtOAc (200 mL), and the aqueous phase was extracted with EtOAc (6× 80 mL). The combined organic extracts were washed with brine (40 mL), dried with $MgSO_4$, and concentrated under reduced pressure to give diol (–)-**67** (10.1 g, quantitative) contaminated with polymethylene ether derivatives. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79–4.70 (m, 3 H), 4.11 (d, J = 12.9 Hz,

1 H), 3.92 (d, J = 11.2 Hz, 1 H), 3.87–3.78 (m, 2 H), 3.49 (d, J = 9.6 Hz, 1 H), 3.42 (dd, J = 2.0, J = 7.5 Hz, 1 H), 3.39 (s, 3 H), 3.20 (t, J = 7.7 Hz, 1 H), 2.83 (br. s, 1 H), 2.28 (ddd, J = 2.0, J = 6.5, J = 12.6 Hz, 1 H), 1.71 (t, J = 12.3 Hz, 1 H), 1.42 (s, 3 H), 0.85 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 210.0, 97.3, 80.6, 80.0, 71.5, 71.4, 67.3, 61.9, 55.9, 46.9, 39.8, 25.8 (3 C), 24.5, 18.1, 0.0, –0.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{34}O_6SiNa$ $[M + Na]^+$ 397.2022; found 397.2022. IR: $\tilde{\nu}$ = 3416, 2929, 2856, 1766, 1254, 1153, 1109, 1001, 835, 774 cm^{-1}. $[\alpha]_D^{25}$ = –91.6 (c = 1.05, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.25.

Optimized Procedure for Alkene (–)-68: Imidazole (8.55 g, 126 mmol) was added to a solution of crude diol (–)-**67** (10.1 g, 25.1 mmol) in CH_2Cl_2 (251 mL) at 0 °C, and then neat TESCl (9.28 mL, 55.3 mmol) was added. The resulting mixture was allowed to warm slowly to room temp. overnight before it was quenched with $NaHCO_3$ (saturated aq.; 120 mL). The aqueous phase was extracted with CH_2Cl_2 (2× 80 mL). The combined organic extracts were washed with water (3× 90 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated under reduced pressure to give the desired ketone (17.2 g, quantitative) contaminated with TES-OH. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80–4.72 (m, 1 H), 4.71 (d, J = 6.6 Hz, 1 H), 4.56 (d, J = 6.6 Hz, 1 H), 3.98 (d, J = 10.5 Hz, 1 H), 3.91 (d, J = 10.5 Hz, 1 H), 3.86 (d, J = 9.3 Hz, 1 H), 3.81 (d, J = 9.3 Hz, 1 H), 3.36 (s, 3 H), 3.27 (dd, J = 2.0, J = 7.6 Hz, 1 H), 3.12 (t, J = 7.6 Hz, 1 H), 2.11 (ddd, J = 2.2, J = 6.4, J = 12.6 Hz, 1 H), 1.76 (t, J = 12.3 Hz, 1 H), 1.41 (s, 3 H), 0.95 (t, J = 8.0 Hz, 9 H), 0.94 (t, J = 8.0 Hz, 9 H), 0.84 (s, 9 H), 0.62–0.53 (m, 12 H), 0.09 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 212.3, 96.0, 79.4, 78.4, 73.0, 71.3, 65.0, 60.2, 55.3, 47.7, 39.0, 25.8 (6 C), 24.7, 18.1, 6.9 (3 C), 4.5 (6 C), –2.3, –2.6 ppm. HRMS (ESI): calcd. for $C_{30}H_{62}O_6Si_3Na$ $[M + Na]^+$ 625.3752; found 625.3740. IR: $\tilde{\nu}$ = 2954, 2877, 1772, 1461, 1085, 1046, 1003, 834, 805, 740 cm^{-1}. $[\alpha]_D^{25}$ = –113.6 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.75.

Cp_2TiMe_2 (19 wt.-% in toluene; 54.7 mL, 42.7 mmol) was mixed with the carbonyl compound (17.2 g, 25.1 mmol) and the mixture was stirred under argon at 65 °C for 3 d. The mixture was diluted with hexane (150 mL), stirred for 30 min, and then cooled in the fridge overnight. The resulting yellow-orange precipitate was removed by filtration (two or three filtrations were required), and the filtrate was concentrated. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 20:1) to give alkene (–)-**68** (14.2 g, 94%, 93% over 4 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (d, J = 2.7 Hz, 1 H), 4.82 (d, J = 2.1 Hz, 1 H), 4.69 (d, J = 6.4 Hz, 1 H), 4.60–4.52 (m, 1 H), 4.49 (d, J = 6.4 Hz, 1 H), 3.96 (d, J = 10.1 Hz, 1 H), 3.87 (d, J = 9.3 Hz, 1 H), 3.84 (d, J = 10.2 Hz, 1 H), 3.40 (d, J = 9.3 Hz, 1 H), 3.33 (s, 3 H), 3.01–2.96 (m, 1 H), 2.86 (t, J = 7.2 Hz, 1 H), 2.00–1.86 (m, 2 H), 1.38 (s, 3 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.84 (s, 9 H), 0.54 (q, J = 7.9 Hz, 6 H), 0.54 (q, J = 7.9 Hz, 6 H), 0.09 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 155.2, 112.1, 97.6, 83.5, 80.2, 68.5, 64.3, 57.9, 57.5, 54.9, 48.4, 45.1, 28.5 (3 C), 26.4, 20.3, 9.2 (3 C), 9.2 (3 C), 6.9 (3 C), 6.9 (3 C), 0.0, –0.1 ppm. HRMS (ESI): calcd. for $C_{31}H_{64}O_5Si_3Na$ $[M + Na]^+$ 623.3959; found 623.3952. IR: $\tilde{\nu}$ = 2954, 2878, 1461, 1253, 1072, 1046, 1004, 836, 773, 742 cm^{-1}. $[\alpha]_D^{25}$ = –60.5 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 40:1): 0.26.

Acetate *rac*-69: Cerium chloride heptahydrate (1.24 g, 3.33 mmol) was added to a stirred solution of crude enone *rac*-**60** (700 mg, 2.77 mmol) in MeOH (14 mL) at room temp. After 5 min, the mixture was cooled to 0 °C, and $NaBH_4$ (115 mg, 3.05 mmol) was added portionwise. The reaction mixture was stirred at 0 °C until the starting material had been completely consumed (30 min). The reaction was quenched by the addition of a few drops of acetic acid (50% aq.) to reach neutral pH. Water (30 mL) and EtOAc (50 mL) were added, and the heterogeneous mixture was extracted with EtOAc (4× 20 mL). The combined organic extracts were washed with water (2× 15 mL) and brine (2× 15 mL), and dried with $MgSO_4$. The solvent was removed under reduced pressure to give the crude allylic alcohol as a viscous oil.

Acetic anhydride (394 μL, 4.15 mmol), pyridine (448 μL, 5.54 mmol), and 4-(dimethylamino)pyridine (34 mg, 0.28 mmol) were added to a solution of the crude alcohol (705 mg, 2.77 mmol) in CH_2Cl_2 (28 mL) at 0 °C. The solution was allowed to warm to room temp. overnight. The mixture was diluted with CH_2Cl_2 (12 mL), washed in sequence with $NaHCO_3$ (saturated aq.; 15 mL), water (15 mL), and brine (10 mL), and dried with $MgSO_4$. The volatile materials were removed by evaporation to give the crude product. Purification over a short column (SiO_2, hexane/EtOAc, 20:1) gave acetate *rac*-**69** (673 mg, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66–5.61 (m, 1 H), 5.41 (br. s, 1 H), 4.29 (q, J = 7.7 Hz, 1 H), 3.22 (t, J = 6.6 Hz, 1 H), 2.77–2.65 (m, 1 H), 2.17–2.09 (m, 2 H), 2.03 (s, 3 H), 1.88–1.84 (m, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.3, 146.2, 125.4, 82.65, 65.14, 55.18, 31.99, 31.49, 26.00 (3 C), 21.11, 18.21, 17.16, –4.61, –4.81 ppm. HRMS (EI): calcd. for $C_{16}H_{28}O_3Si$ Na $[M + Na]^+$ 319.1705; found 319.1678. IR: $\tilde{\nu}$ = 2929, 2858, 1735, 1372, 1242, 1123, 1021, 872, 836, 777 cm^{-1}. R_f (hexane/EtOAc, 5:1): 0.54.

Alcohol *rac*-70: $Co(acac)_2$ (18 mg, 67 μmol) was added to a solution of acetate *rac*-**69** (100 mg, 0.34 mmol) in THF (6 mL). The reaction mixture was then saturated with O_2 (20 min), and then $PhSiH_3$ (166 μL, 1.35 mmol) was added over 15 min. Stirring was continued under a static O_2 atmosphere for 15 h at room temp. The reaction mixture was then diluted with EtOAc (15 mL), washed with $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 5:1) to give tertiary alcohol *rac*-**70** (71 mg, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34–5.26 (m, 1 H), 4.48–4.40 (m, 1 H), 2.85–2.77 (m, 1 H), 2.66–2.59 (m, 1 H), 2.30–2.15 (m, 2 H), 2.13–2.06 (m, 1 H), 2.03 (s, 3 H), 1.94–1.86 (m, 1 H), 1.50 (s, 3 H), 1.18 (br. s, 1 H), 0.89 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.0, 79.6, 76.3, 64.7, 55.1, 43.6, 33.4, 30.2, 26.0 (3 C), 25.2, 21.2, 18.2, –4.7, –4.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{30}O_4SiNa$ $[M + Na]^+$ 337.1811; found 337.1821. IR: $\tilde{\nu}$ = 3420, 2930, 2857, 1737, 1374, 1250, 1131, 1041, 837, 778 cm^{-1}. R_f (hexane/EtOAc, 1:1): 0.48.

Diol *rac*-71: TBAF (1 M in THF; 159 μL, 0.16 mmol) was added to a stirred solution of alcohol *rac*-**70** (50 mg, 0.16 mmol) in THF (2 mL) at 0 °C. The solution was allowed to warm to room temp., and after stirring for 1 h, the reaction was quenched by the addition of $NaHCO_3$ (saturated aq.; 10 mL). The mixture was diluted with water (30 mL) and Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2× 20 mL). The organic phases were combined, dried with Na_2SO_4, filtered, and concentrated to give a colorless oil. This residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 1:1) to give diol *rac*-**71** (27 mg, 85%), which crystallized from $CHCl_3$ as a colorless plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.31 (dt, J = 7.1, J = 10.4 Hz, 1 H), 4.53 (q, J = 8.1 Hz, 1 H), 2.90–2.80 (m, 1 H), 2.66–2.58 (m, 1 H), 2.38–2.27 (m, 1 H), 2.24–2.10 (m, 2 H), 2.03 (s, 3 H), 1.99–1.90 (m, 1 H), 1.64 (br. s, 1 H), 1.53 (s, 3 H), 1.33 (br. s, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.0, 79.4, 76.2,

64.7, 54.6, 43.7, 33.2, 28.7, 25.6, 21.2 ppm. HRMS (EI): calcd. for $C_{10}H_{16}O_4Na$ [M + Na]$^+$ 223.0946; found 223.0937. IR: $\tilde{\nu}$ = 3367, 2925, 1714, 1377, 1264, 1173, 1107, 1039, 853, 612 cm^{-1}, m.p. 117–120 °C. R_f (EtOAc): 0.40.

{(1*R*,2*S*,4*S*,5*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(methoxymethoxy)-2-methyl-7-methylenebicyclo[3.2.0]heptane-6,6-diyl}dimethanol [(–)-72]: HF (70% in pyridine; 269 μL, 9.22 mmol) was slowly added to a solution of (–)-**68** (277 mg, 0.46 mmol) in THF (3 mL) in a teflon vial at 0 °C. The mixture was stirred for 30 min at the same temperature, after which time TLC analysis indicated a clean conversion. The reaction was carefully quenched with $NaHCO_3$ (saturated aq.; 10 mL) and the mixture was extracted with EtOAc (3× 30 mL). The combined organic extracts were washed with water (30 mL) and brine (50 mL), dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (SiO_2, hexane/EtOAc, 2:1) to give diol (–)-**72** (170 mg, 99%) as a viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.88 (d, J = 1.9 Hz, 1 H), 4.83 (d, J = 2.5 Hz, 1 H), 4.71 (d, J = 6.6 Hz, 1 H), 4.69 (d, J = 6.6 Hz, 1 H), 4.64–4.55 (m, 1 H), 4.05 (d, J = 11.9 Hz, 1 H), 3.80 (dd, J = 3.1, J = 11.1 Hz, 1 H), 3.77–3.63 (m, 3 H), 3.37 (s, 3 H), 3.20 (br. d, J = 7.0 Hz, 1 H), 3.07–2.98 (m, 2 H), 2.12 (ddd, J = 1.4, J = 6.4, J = 13.4 Hz, 1 H), 1.86 (t, J = 12.0 Hz, 1 H), 1.37 (s, 3 H), 0.84 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 151.0, 108.8, 97.1, 81.6, 80.8, 71.7, 65.7, 55.9, 55.1, 52.2, 45.6, 43.9, 25.8 (3 C), 24.0, 18.1, –2.2, –2.3 ppm. HRMS (ESI): calcd. for $C_{19}H_{36}O_5SiNa$ [M + Na]$^+$ 395.2230; found 395.2219. IR: $\tilde{\nu}$ = 3435, 2929, 1462, 1372, 1253, 1151, 1106, 1034, 835, 772 cm^{-1}. $[\alpha]_D^{20}$ = –64.4 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 2:1): 0.12.

Dialdehyde *rac*-73: DMSO (118 μL, 0.1.66 mmol) was added to a solution of oxalyl chloride (70 μL, 0.83 mmol) in CH_2Cl_2 (0.8 mL) at –78 °C. The solution was stirred at –78 °C for 20 min. Compound *rac*-**72** (50 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL) was then added slowly to the reaction mixture. The solution was stirred at –78 °C for 1 h. Et_3N (290 μL, 2.08 mmol) was added to the mixture, and stirring was continued at –78 °C for 15 min and then at 0 °C for 1 h. The reaction was quenched with NH_4Cl (5 mL), and the aqueous phase was extracted with EtOAc (2× 25 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure (water bath temperature: 30 °C) to give pure dialdehyde *rac*-**73** (29 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.88 (s, 1 H), 9.61 (s, 1 H), 5.30 (dd, J = 1.6, J = 2.0 Hz, 1 H), 5.21 (dd, J = 1.5, J = 2.7 Hz, 1 H), 4.63 (dt, J = 6.8, J = 11.3 Hz, 1 H), 4.57 (d, J = 6.5 Hz, 1 H), 4.54 (d, J = 6.5 Hz, 1 H), 3.75 (t, J = 7.3 Hz, 1 H), 3.29 (s, 3 H), 3.07–3.03 (m, 1 H), 2.15 (ddd, J = 1.4, J = 6.7, J = 12.7 Hz, 1 H), 1.82 (dd, J = 11.6, J = 12.5 Hz, 1 H), 1.42 (s, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 196.4, 194.6, 141.4, 115.8, 96.6, 82.0, 79.0, 71.3, 56.4, 46.2, 44.3, 25.8 (3 C), 23.6, 18.1, 8.8, –2.2, 2.3 ppm. HRMS (EI): calcd. for $C_{19}H_{32}O_5SiNa$ [M + Na]$^+$ 391.1917; found 391.1903. IR: $\tilde{\nu}$ = 2929, 2855, 1728, 1700, 1254, 1153, 1109, 1042, 835, 774 cm^{-1}. R_f (hexane/EtOAc, 2:1): 0.38.

Aldehyde *rac*-74: While trying to synthesize *rac*-**73**, undesired product *rac*-**74** was formed almost quantitatively if the concentration of the organic phases was done in a water bath warmer than 30 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 4.80 (d, J = 6.8 Hz, 1 H), 4.55 (d, J = 6.8 Hz, 1 H), 4.36–4.28 (m, 1 H), 3.58–3.52 (m, 1 H), 3.34 (s, 3 H), 2.86–2.81 (m, 1 H), 2.12 (t, J = 1.4 Hz, 3 H), 2.02 (ddd, J = 1.7, J = 3.4, J = 12.9 Hz, 1 H), 1.83 (dd, J = 10.6, J = 12.8 Hz, 1 H), 1.37 (s, 3 H), 0.86 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 186.2, 162.6, 140.4, 95.8, 78.0, 74.0, 59.0, 55.4, 44.5, 43.9, 25.8 (3 C), 25.6, 18.2, 15.4, –2.1, –2.1 ppm. HRMS (EI): calcd. for $C_{18}H_{32}O_4SiNa$ [M + Na]$^+$ 363.1968; found 363.1962. IR: $\tilde{\nu}$ = 2928, 2855, 1678, 1254, 1150, 1101, 1040, 918, 860, 772 cm^{-1}. R_f (hexane/EtOAc, 2:1): 0.49.

Dimethyl Ester *rac*-75: A solution of dialdehyde *rac*-**73** (40 mg, 0.11 mmol) and 2-methylbutene (300 μL) in *t*BuOH (1.4 mL) was cooled to 0 °C, then a solution of $NaClO_2$ (122 mg, 1.09 mmol) and NaH_2PO_4 (180 mg, 1.30 mmol) in water (1 mL) was added. The mixture was stirred for 30 min. The solution was diluted with NH_4Cl (aq.; 15 mL) and extracted with Et_2O (2× 30 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, and concentrated. The crude dicarboxylic acid was dissolved in benzene/MeOH (3:2; 2 mL), and then $TMSCHN_2$ (2 M in Et_2O; 200 μL, 0.40 mmol) was added slowly at 0 °C. The solution was stirred at this temperature for 2 h, and then it was allowed to warm to room temp. overnight. After concentration, the residue was purified by column chromatography (SiO_2, hexane/EtOAc, 15:1) to give an inseparable mixture (39 mg) containing dimethyl ester *rac*-**75** (23 mg, 50%) and methyl ester *rac*-**76** (16 mg, 40%). Data for *rac*-**75**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.37 (dd, J = 0.8, J = 2.7 Hz, 1 H), 5.21 (dd, J = 0.9, J = 2.1 Hz, 1 H), 4.68–4.60 (m, 1 H), 4.58 (d, J = 6.6 Hz, 1 H), 4.46 (d, J = 6.6 Hz, 1 H), 3.83 (t, J = 7.4 Hz, 1 H), 3.74 (s, 3 H), 3.67 (s, 3 H), 3.32 (s, 3 H), 3.10–3.04 (m, 1 H), 2.12 (t, J = 12.0 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.42 (s, 3 H), 0.84 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.1, 169.3, 143.6, 115.4, 95.8, 81.3, 77.1, 59.2, 58.1, 56.4, 53.2, 52.3, 44.9, 44.2, 25.8 (3 C), 23.7, 18.1, –2.2, –2.3 ppm. HRMS (EI): calcd. for $C_{21}H_{36}O_7SiNa$ [M + Na]$^+$ 451.2128; found 451.2143. R_f (hexane/EtOAc, 5:1): 0.28.

Data for *rac*-**76**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.83 (d, J = 6.9 Hz, 1 H), 4.53 (d, J = 6.9 Hz, 1 H), 4.34 (dt, J = 6.7, J = 10.4 Hz, 1 H), 3.71 (s, 3 H), 3.51–3.46 (m, 1 H), 3.34 (s, 3 H), 2.76–2.73 (m, 1 H), 2.04 (t, J = 1.3 Hz, 3 H), 2.00–1.91 (m, 1 H), 1.86 (dd, J = 10.5, J = 12.8 Hz, 1 H), 1.34 (s, 3 H), 0.85 (s, 9 H), 0.10 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.3, 159.8, 131.5, 95.5, 73.6, 59.1, 55.5, 55.2, 51.0, 44.4, 43.7, 25.8 (3 C), 23.7, 18.2, 16.1, –2.0, –2.1 ppm. HRMS (EI): calcd. for $C_{19}H_{34}O_5SiNa$ [M + Na]$^+$ 391.2073; found 391.2083. R_f (hexane/EtOAc, 5:1): 0.28.

Lactone *rac*-77: AcCl (10 drops) was added to an ice-cold solution of dimethyl ester *rac*-**75** (54 mg, 0.12 mmol) in MeOH (6.3 mL). The resulting solution was stirred at the same temperature for 5 h, and then allowed to warm to room temp. to be stirred for a further 40 h. The mixture was concentrated and purified by column chromatography (SiO_2, hexane/EtOAc, 2:1) to give the tricycle (30 mg, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.63 (dd, J = 1.9, J = 2.8 Hz, 1 H), 5.36–5.29 (m, 2 H), 3.89 (dd, J = 6.5, J = 8.3 Hz, 1 H), 3.83 (s, 3 H), 3.31–3.26 (m, 1 H), 2.48 (ddd, J = 1.7, J = 7.8, J = 15.2 Hz, 1 H), 2.05 (dd, J = 5.0, J = 15.1 Hz, 1 H), 1.45 (s, 3 H), 1.30 (br. s, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.1, 167.1, 141.3, 117.3, 83.3, 82.4, 57.5, 53.4, 48.5, 46.9, 29.9, 24.3 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}O_5Na$ [M + Na]$^+$ 261.0739; found 261.0738. IR: $\tilde{\nu}$ = 3498, 2928, 1771, 1734, 1437, 1302, 1227, 1156, 1030, 906 cm^{-1}. R_f (EtOAc): 0.42.

The tricycle (30 mg, 0.13 mmol) was dissolved in THF (1.2 mL), and the solution was cooled to 0 °C. Lutidine (59 μL, 0.50 mmol) and then TBSOTf (58 μL, 0.25 mmol) were added to the reaction vessel, and the mixture was stirred for a further 45 min at 0 °C. The reaction was quenched by the addition of water (5 mL), and diluted with additional sodium hydrogen carbonate (aq.; 3 mL) and diethyl ether (30 mL). The phases were separated, and the aqueous

phase was extracted with diethyl ether (2× 20 mL). The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 10:1) to give lactone *rac*-**77** (36 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (dd, J = 1.8, J = 2.8 Hz, 1 H), 5.31–5.24 (m, 2 H), 3.82 (s, 3 H), 3.79 (dd, J = 6.6, J = 8.5 Hz, 1 H), 3.31–3.26 (m, 1 H), 2.48 (ddd, J = 1.7, J = 7.8, J = 14.7 Hz, 1 H), 1.94 (dd, J = 5.5, J = 14.7 Hz, 1 H), 1.42 (s, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.3, 167.3, 141.7, 117.0, 84.6, 83.6, 58.3, 57.9, 53.4, 49.3, 47.1, 25.7 (3 C), 23.3, 18.0, –2.3 (2 C) ppm. HRMS (EI): calcd. for $C_{18}H_{28}O_5SiNa$ [M + Na]$^+$ 375.1604; found 375.1613. IR: $\tilde{\nu}$ = 2954, 2857, 1779, 1734, 1254, 1151, 1038, 990, 836, 775 cm^{-1}. R_f (hexane/EtOAc, 5:1): 0.34.

Alcohol (–)-78: Cold Jones reagent (2.5 M in water; 665 μL, 1.66 mmol) was added to a stirred cooled (water/ice bath, 0 °C) solution of alkene (–)-**68** (100 mg, 0.17 mmol) in acetone (3.3 mL). Stirring was continued for 40 min. The excess of the Jones reagent was quenched by the addition of IPA (1.5 mL). The suspension was stirred for 5 min at 0 °C and for 10 min at room temp. The clear greenish supernatant was decanted, and the remaining green solid residue was extracted with EtOAc (5× 15 mL). The combined organic extracts were washed with brine (2× 5 mL) and dried with Na_2SO_4. The volatiles were removed to give the crude carboxylic acid.

A solution of the crude carboxylic acid in THF (3.7 mL) was stirred at 0 °C under Ar while Et_3N (43 μL, 0.31 mL) was added. The solution was stirred for 30 min, and then ethyl chloroformate (40 μL, 0.40 mmol) was added. The reaction mixture became cloudy as it was stirred at 0 °C for 1.5 h. At this point, IPA (1 mL) was added, followed by $NaBH_4$ (30 mg, 0.79 mmol) 5 min later. The mixture was stirred at 0 °C for 5 h, then it was diluted with Et_2O (20 mL), treated dropwise with HCl (5% aq.; 2 mL), and poured into a mixture of Et_2O (30 mL) and HCl (1% aq.; 20 mL). The aqueous phase was extracted with Et_2O (2× 20 mL), and the combined organic extracts were washed with $NaHCO_3$ (saturated aq.; 2× 20 mL) and brine (20 mL), dried with Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 4:1) to give primary alcohol (–)-**78** (29 mg, 54%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.31 (dd, J = 1.4, J = 2.8 Hz, 1 H), 5.23 (dt, J = 5.5, J = 8.2 Hz, 1 H), 5.18 (dd, J = 1.6, J = 2.1 Hz, 1 H), 4.00 (dd, J = 7.1, J = 11.9 Hz, 1 H), 3.84 (dd, J = 5.6, J = 11.7 Hz, 1 H), 3.45 (dd, J = 6.0, J = 8.2 Hz, 1 H), 3.22–3.17 (m, 1 H), 2.47 (ddd, J = 1.9, J = 7.9, J = 14.6 Hz, 1 H), 2.23 (t, J = 6.4 Hz, 1 H), 1.94 (dd, J = 5.5, J = 14.6 Hz, 1 H), 1.42 (s, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 177.0, 144.9, 114.5, 84.9, 84.0, 63.4, 57.1, 55.6, 49.3, 44.8, 25.7 (3 C), 23.2, 18.0, –2.3, –2.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{28}O_4SiNa$ [M + Na]$^+$ 347.1655; found 347.1648. IR: $\tilde{\nu}$ = 3446, 2930, 2856, 1764, 1252, 1153, 1047, 988, 835, 774 cm^{-1}. $[\alpha]_D^{20}$ = –52.3 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.20.

Aldehyde (–)-55: DMSO (16 μL, 0.22 mmol) was added to a solution of oxalyl chloride (9 μL, 0.11 mmol) in CH_2Cl_2 (0.6 mL) at –78 °C. The solution was stirred for 20 min at –78 °C, then alcohol (–)-**78** (18 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL) was slowly added to the reaction mixture. The solution was stirred for 1 h at –78 °C. Et_3N (46 μL, 0.33 mmol) was added, and stirring was continued for 15 min at –78 °C and then for 1 h at 0 °C. The reaction was quenched with NH_4Cl (5 mL) and extracted with EtOAc (2× 20 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, hexane/EtOAc, 3:1) gave aldehyde (–)-**55** (17 mg, 94%) as an amorphous white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (s, 1 H), 5.44 (t, J = 2.5 Hz, 1 H), 5.30 (t, J = 2.3 Hz, 1 H), 5.26 (dd, J = 5.7, J = 8.0 Hz, 1 H), 3.80 (dd, J = 6.2, J = 8.1 Hz, 1 H), 3.25–3.21 (m, 1 H), 2.52 (ddd, J = 1.8, J = 7.8, J = 14.8 Hz, 1 H), 1.96 (dd, J = 5.6, J = 14.8 Hz, 1 H), 1.43 (s, 3 H), 0.83 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 192.5, 171.8, 142.7, 116.2, 84.8, 84.2, 63.6, 57.8, 49.3, 42.7, 25.7 (3 C), 23.1, 18.0, –2.3 (2 C) ppm. HRMS (ESI): calcd. for $C_{17}H_{26}O_4SiNa$ [M + Na]$^+$ 345.1498; found 345.1490. IR: $\tilde{\nu}$ = 2931, 2856, 1768, 1721, 1253, 1145, 1047, 987, 836, 775 cm^{-1}. $[\alpha]_D^{22}$ = –87.6 (c = 0.7, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.28.

Supporting Information (see footnote on the first page of this article): Preparation/characterization of (–)-**29**, **31**, (–)-**34**, **37**, **39**, (+)-**44**, (–)-**45**, **47**, and (–)-**49**. Copies of ^{1}H and ^{13}C NMR spectra for compounds: **9**, **10**, **12**, (+)-**16**, (–)-**18**, (–)-**20**, **22**, **23**, **24**, **25**, (–)-**26**, (–)-**27**, (–)-**30**, (–)-**32**, (–)-**33**, (–)-**35**, (–)-**36**, (–)-**38**, (–)-**40**, (–)-**41**, (–)-**42**, (–)-**50**, (+)-**54**, (+)-**51**, (+)-**52**, (+)-**53**, (–)-**57**, (–)-**58**, (–)-**60**, (–)-**61**, (–)-**62**, (–)-**63**, (–)-**64**, (–)-**65**, (–)-**66**, (–)-**67**, (–)-**68**, *rac*-**69**, *rac*-**70**, *rac*-**71**, (–)-**72**, *rac*-**73**, *rac*-**74**, *rac*-**75**, *rac*-**76**, *rac*-**77**, (–)-**78**, (–)-**55**.

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[18] CCDC-884126 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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