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SPECIAL FEATURE: ARTICLE

Sequential *exo*-mode oxacyclizations for the synthesis of the CD substructure of brevenal

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Abstract

We describe a novel strategy for synthesizing the CD bicyclic ether substructure of the fused polycyclic ether natural product brevenal. This product arises from a three-step sequence beginning with (1) regio- and diastereoselective iodoetherification of an acyclic diene-diol, followed by (2) alkene metathesis with an epoxyalkene synthon, concluding with (3) palladium-catalyzed cycloisomerization. Despite the modest yield and long reaction period for the cycloisomerization step, these studies provide valuable insights into the nature of byproducts generated and the mechanisms by which they form. This work demonstrates a portion of a larger synthetic strategy for constructing the pentacyclic core of brevenal from an acyclic precursor.

Introduction

Brevenal (**1**, Fig. 1) is a fused polycyclic ether natural product produced by *Karenia brevis*, a dinoflagellate indigenous to the Gulf of Mexico [1, 2]. Remarkably, the same marine organism also produces a host of structurally related but substantially larger compounds known as brevetoxins, or "red tide toxins" [3]. Brevenal binds to the same sodium ion channels as brevetoxins, while exerting no toxic effects [4, 5]. Thus, brevenal tempers the neurotoxic effects of brevetoxin, making it a potential remedy for those exposed to brevetoxins. Brevenal may have additional beneficial applications for treating the symptoms of cystic fibrosis [6]. The literature describes several syntheses of brevenal [7–9], in which the seven-membered ring ethers arise from well-developed methods, namely oxidative lactonizations of 1,6-diols [10], dehydrative cyclizations of hydroxyacids and hydroxyacetals [11], intramolecular allylations of γ-alkoxyallylstannanes with α-acetoxy ethers [12], ring-closing metathesis [13] and olefinic ester cyclizations [14].

Our recent approach to the synthesis of brevenal has featured a sequence of stereo- and regioselective oxacyclizations of hydroxyalkenes [15, 16]. Prior to our research in this area, these transformations were not well-developed for preparing six- and seven-membered cyclic ethers, especially from structurally complex substrates. We have envisioned that stereoselective intramolecular addition of the C18-hydroxyl onto the alkene terminus (C23) of an epoxyalkene **2** will form the oxepane D ring of brevenal, with the expected product **3** bearing a side-chain corresponding to the chiral tertiary alcohol at C26 of the E ring of brevenal (Fig. 2).

In this Article, we describe the synthesis of the brevenal CD substructure by this strategy, building on our recently reported cycloisomerizations of model compounds **4** and **6** (Fig. 3) [17]. For these transformations:

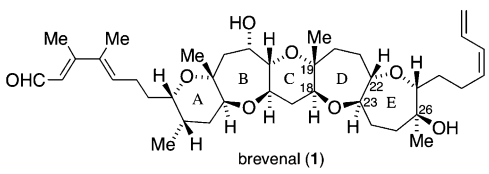

Fig. 1 Structure of brevenal (**1**)

Dedication This work celebrates the breadth, the quality, and the impact of Prof. Samuel Danishefsky's contributions to the science of natural products synthesis, and honors his thoughtful mentorship of the corresponding author.

Electronic supplementary material The online version of this article (https://doi.org/10.1038/s41429-018-0124-1) contains supplementary material, which is available to authorized users.

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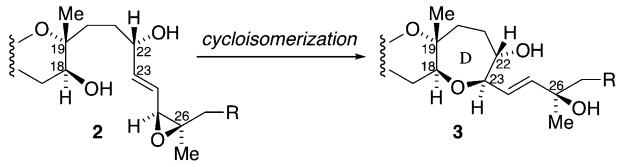


Fig. 2 Proposed synthetic approach to the D ring of brevenal (**2** → **3**)

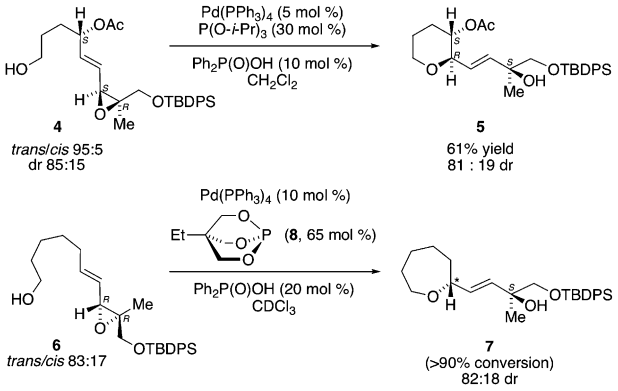


Fig. 3 Stereoselective cycloisomerizations of epoxyalkenes **4** and **6** require dual catalysis with palladium and a Brønsted acid

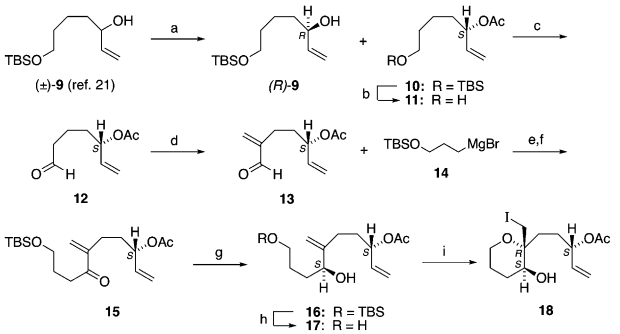
- the best results have required dual catalysis with palladium and a Brønsted acid, such as diphenylphosphinic acid, to promote epoxide opening;
- the acetate ester of **4** suppresses a significant side-reaction occurring with the corresponding allylic alcohol, arising from palladium-catalyzed hydride migration;
- the epoxyalkene of **4** is chemoselectively activated in preference to the allylic acetate;
- the stereochemistry of the newly formed carbon-oxygen bond in the pyran **5** arises from the chirality of the epoxide and also the *trans*- or *cis*-geometry of the alkene; and
- the bicyclic trimethylol phosphite ligand (**8**) [18, 19] increases the rate of cycloisomerization of the epoxyalkene substrate **6** leading to the oxepane **7**, relative to triisopropyl phosphite (P(O-*i*-Pr)$_3$).

Although the stereochemical assignment of the major diastereomer of **7** is not yet confirmed, the chirality depicted at the starred center of **7** is consistent with our results from other (*R,R*)-epoxy-*trans*-alkene substrates [17].

Results

Synthesis of epoxyalkene substrate 21

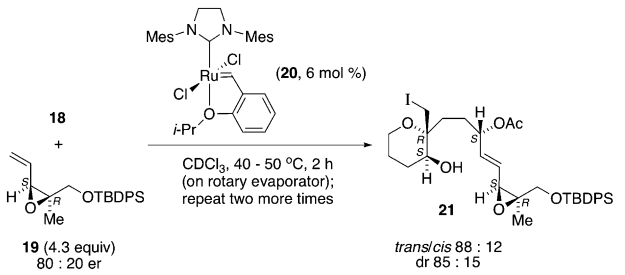
To test the proposed conversion of epoxyalkene **2** into the D-ring of **3** (Fig. 2), we prepared a substrate with stereochemistry identical to the allylic acetate and epoxyalkene of



Scheme 1 Preparation of tetrahydropyranyl alcohol **18**. Conditions: (a) *Candida antarctica* lipase (CAL-B, 4% by mass), isopropenyl acetate (1.7 equiv), K_3PO_4 (1.07 equiv), toluene, 20 °C, 3.25 h: (*R*)-**9**, 50% yield, 96:4 er; **10**, 49% yield, 97:3 er); (b) acetyl chloride (30 mol%), methanol, 0–20 °C, 20 min, 98% yield; (c) $Cu(MeCN)_4OTf$ (5 mol%), 2,2′-bipyridine (bpy, 5 mol%), 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO, 5 mol%), *N*-methylimidazole (NMI, 10 mol%), acetonitrile, air, 20 °C, 12 h, 75% yield; (d) *N,N*-dimethylmethyleneiminium iodide (2.1 equiv), triethylamine (3.1 equiv), dichloromethane, 20 °C, 2 h, 62% yield; (e) tetrahydrofuran, −78 °C, 15 min, satd. aq. NH_4Cl quench, 68% yield (+21% recovered **13**); (f) $Cu(MeCN)_4OTf$ (15 mol %), 4,4′-dimethoxy-2,2′-bipyridine (MeObpy, 10 mol%), 9-azabicyclo [3.3.1]nonane *N*-oxyl (ABNO, 2 mol%), NMI (20 mol%), acetonitrile, air, 20 °C, 48 h, 88% yield; (g) (*R*)-2-methyl-CBS-oxazaborolidine (1.1 equiv), borane-THF (1.06 equiv), tetrahydrofuran, −40 °C, 1.5 h, 56% yield, 96:4 dr; (h) acetyl chloride (2.6 equiv), methanol, 0 °C, 10 min; (i) iodine (3.4 equiv), sodium bicarbonate (7.8 equiv), tetrahydrofuran, 0–20 °C, 1.5 h, 93% yield (2 steps).

4 (Fig. 3), tethered to a tetrahydropyranyl alcohol with relative stereochemistry matching C18 and C19 in the C-ring of brevenal. Our synthesis began with enzyme-catalyzed resolution [20] of the known racemic alcohol **9** [21] to provide the allylic acetate **10** with high enantioselectivity (Scheme 1). We then constructed the C-ring from the primary alcohol of **11**, beginning with Stahl oxidation [22] and *alpha*-methylenation [23] of aldehyde **12** to introduce the 1,1-disubstituted alkene of enal **13**. Addition of the Grignard reagent **14** [24] to the enal **13** was compatible with the acetate ester, but afforded a mixture of allylic alcohol diastereomers. However, Stahl oxidation [25] to the enone **15** followed by Corey-Bakshi-Shibata reduction [26] set the chiral center of the allylic alcohol **16** with high diastereoselectivity. Iodine-promoted cycloetherification of diene-diol **17** produced the desired pyranyl alcohol **18**, structurally corresponding to our precedents for stereoinduction from the chiral allylic alcohol in the tether [15, 16]. Moreover, the six-membered ring of **18** formed without competition from oxacyclization of the secondary alcohol with the monosubstituted alkene [27].

We completed the substrate synthesis by cross-metathesis of compound **18** with the chiral non-racemic (*S,R*)-epoxyalkene synthon **19** [17] to provide the substrate **21** (Scheme 2). The best results for the cross-metathesis step arose from adding Hoveyda-Grubbs catalyst **20** and solvent



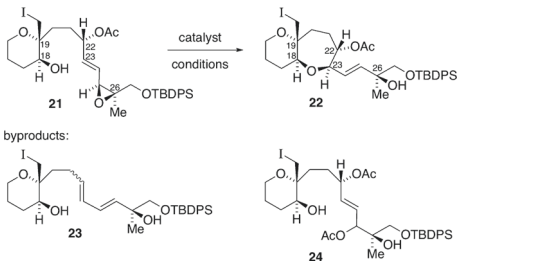
Scheme 2 Synthesis of epoxyalkene tethered to tetrahydropyranyl alcohol, compound **21**

to a mixture of alkenes **18** and **19**, then concentrating the reaction solution at slightly elevated temperature on a rotary evaporator to remove the ethylene byproduct from the reaction headspace, and repeating this process two more times.

Palladium-catalyzed cycloisomerization of epoxyalkene substrate 21

We expected that the tetrahydropyran ring tethered to the epoxyalkene of **21** would limit degrees of freedom relative to the simple substrate **6** initially studied for oxepane synthesis. This might be advantageous if the two separated chiral networks at C18-C19 and C22-C26 readily adopted a conformation with the C18 alcohol in proximity to C23 on the reactive face of the proposed palladium π-allyl reactive intermediate, but could be disastrous for our synthetic plan if such a conformation was disfavored. Initial experiments were not promising: compound **21** did not initially react under palladium catalysis at room temperature in $CDCl_3$, and upon gently heating the reaction mixture, we observed the dienyl diol **23** as the only new product (Table 1, entry 1), without any indication of oxepane formation. Upon repeating this experiment with the trimethylol phosphite ligand **8** in place of P(O-*i*-Pr)$_3$ (entry 2), several new species appeared after 18 h at room temperature, including bisacetate **24**, presumably incorporating the acetate lost in the elimination process leading to dienyl diol **23**. Although most of the substrate **21** was still present, the ^{1}H NMR spectrum showed one additional minor product, later determined to be bicyclic polyether **22**. Compound **22** gradually increased in quantity over six days (entry 3) in proportion to the slow consumption of epoxyalkene **21** and progressive accumulation of byproducts **23** and **24**. After 21 days (entry 4), epoxyalkene **21** was no longer visible in the ^{1}H NMR spectrum of the reaction mixture. Compounds **22**, **23**, and **24** were isolated by preparative thin layer chromatography (entry 5), enabling complete structural assignments by extensive NMR characterization.

Table 1 Cycloisomerization of epoxyalkene **21** to bicyclic **22**, and byproducts **23**–**24**



entry	catalyst	conditions	products[a] 21	22	23	24
1	$Pd(PPh_3)_4$ (10 mol %) $P(O\text{-}i\text{-}Pr)_3$ (120 mol %) $Ph_2P(O)OH$ (20 mol %)	$CDCl_3$, 20 °C 30 min; then 45 °C, 1.5 h	64%	not observed	36%	not observed
2	$Pd(PPh_3)_4$ (10 mol %) trimethylol phosphite (**8**, 65 mol %) $Ph_2P(O)OH$ (20 mol %)	$CDCl_3$, 20 °C: after 18 h	80%	3%	8%	9%
3[b]		after 6 d	29%	10%	30%	31%
4[b]		after 21 d	not observed	18%	47%	35%
5[b]		isolated[c]	--	8%[c]	25%[c,d]	29%[c]

[a] Relative percentages of reactant **21** and products were determined by ^{1}H NMR integration of the *tert*-butyl resonances of the TBDPS protective group of each species. [b] Entries 3 - 5 are simply the continuation of the entry 2 experiment, over extended time. [c] These are isolated yields of chromatographically purified compounds. [d] Dienyl diol **23** was isolated as an inseparable mixture of (*E*,*E*) and (*Z*,*E*)-isomers (68 : 32 ratio).

Discussion

Structure characterization

We relied extensively on NMR methods to unambiguously assign the bicyclic product **22**. In particular, ^{1}H–^{1}H COSY and 1D-TOCSY analyses showed two large, independent spin systems (Fig. 4), establishing connectivity for much of the six-membered ring, as well as linking the seven-membered ring with the side chain alkene. NOESY correlations confirmed the 1,3-syn relationship of H_g and H_i of the oxepane, in addition to identifying the tertiary alcohol hydrogen as H_o. The coupling constant between H_f and H_g was approximately 1.3–1.5 Hz, indicating that the major conformation in solution did not orient these hydrogens anti to each other. Instead, the small coupling constant suggested a dihedral angle close to ~ 90°. The nOe correlation between H_f and H_g, in addition to the deshielding of H_f (5.02 ppm) was consistent with a conformation that placed H_f in a pseudo-equatorial orientation. ^{13}C–^{1}H HMBC spectroscopy linked the independent spin systems, notably:

- three-bond coupling for C_H–H_i, supporting ring-closing to the oxepane;
- another three-bond coupling for C_A–H_f, verifying the location of the acetate; and

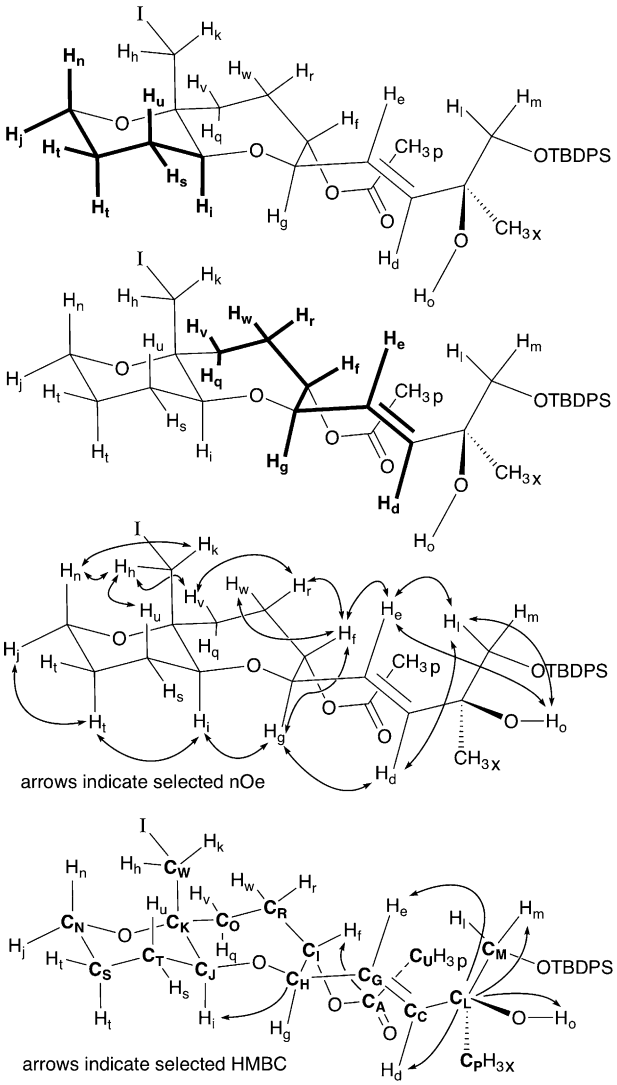


Fig. 4 NMR correlations observed in the bicyclic compound **22**

- several two-bond and three-bond correlations of C_L with H_d, H_e, H_m, and particularly C_L–H_o, confirming the presence and location of the tertiary alcohol.

The dienyl diol **23** was isolated as an inseparable mixture of (*E,E*) and (*Z,E*)-diene isomers (68:32 ratio). The isomers were distinguishable by 1D-TOCSY spectroscopy, so that ^{1}H–^{1}H COSY and NOESY assignments were made for each 1,3-diene isomer within this mixture (Fig. 5).

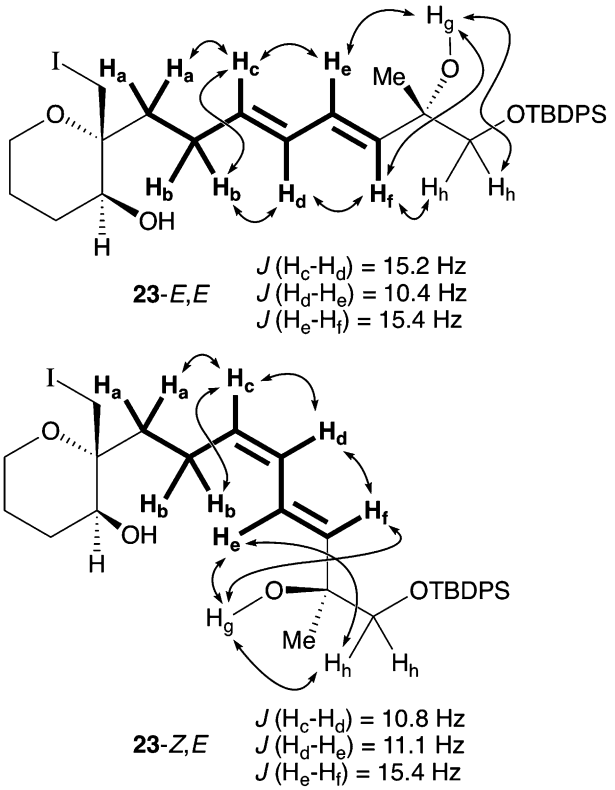


Fig. 5 NMR correlations for characterizing (*E,E*) and (*Z,E*)-isomers of dienyl diol byproduct **23**. Bold regions denote diene-linked spin systems; arrows indicate selected nOe

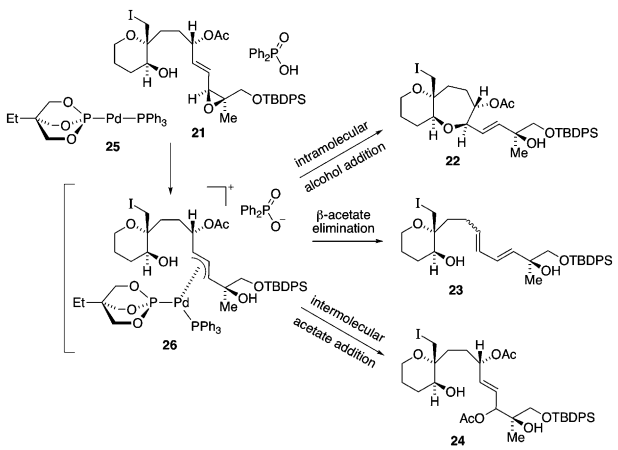


Fig. 6 Mechanistic proposal for the formation of product **22** and byproducts **23** and **24**

Mechanism

Although the formation of the bicyclic product **22** from epoxyalkene **21** required an extremely long reaction time and proceeded with modest yield, the generation of byproducts **23** and **24** is consistent with our overall mechanistic hypothesis (Fig. 6). Structure **25** represents a Pd-ligand complex with the trimethylol phosphite (**8**) and triphenylphosphine ligands, although the relative stoichiometry of the phosphite and phosphine ligands in the reactive catalyst is unknown. We propose that Pd η^3-π-allyl intermediate **26** forms upon protonation of the epoxide of **21**, with addition of Pd-ligand complex **25** onto the face anti- to the epoxide oxygen. Intramolecular addition of the alcohol nucleophile then occurs onto the π-allyl ligand on the face anti- to Pd, to produce the observed diastereomer **22**.

The 1,3-diene byproduct **23** involves the loss of the allylic acetate, in a process analogous to the palladium-catalyzed *beta*-eliminations of 2-ene-1,4-diol-derived dicarbonates to form 1,3-dienes [28–30]. This literature transformation and our observed formation of the diene byproduct **23** requires formal oxidation to Pd(II), which presumably is reduced to Pd(0) by excess phosphite ligand, maintaining a catalytic cycle for this transformation [28]. The *beta*-elimination to form the diene byproduct **23** also provides a source of acetate, which may add to the Pd π-allyl intermediate **26** in competition with the distant secondary alcohol, to produce the diacetate byproduct **24**.

The bicyclic trimethylol phosphite ligand **8** is essential for cycloisomerization of **21** to the bicyclic product **22**. The reduced cone angle of the bicyclic phosphite **8** (cone angle 101°) [31] with respect to P(O-*i*-Pr)$_3$ (cone angle 130°) may better enable nucleophilic addition of sterically hindered alcohols, or alcohols separated from the epoxyalkene by longer tethers. The ^{31}P chemical shift of the phosphorus in bicyclic phosphite ligand **8** is −90.1 ppm, whereas in P(O-*i*-Pr)$_3$ it is −137.5 ppm [31]. As the phosphorus in trimethylol phosphite **8** is more deshielded than in P(O-*i*-Pr)$_3$, the bicyclic phosphite ligand **8** may increase the electrophilicity of the η^3-π-allyl intermediate **26**.

Conclusion

We have developed an effective synthetic route for the epoxyalkene-containing substrate **21**, leading to the CD substructure of brevenal **22**. As the cycloisomerization step forming the seven-membered ring of product **22** proceeded in modest yield, we do not currently have sufficient material to attempt subsequent steps. Nonetheless, knowing the identity of byproducts has suggested some avenues for improving selectivity in favor of oxepane formation. As the bicyclic product **22** contains a side-chain with the oxygen substituents necessary for cycloetherification to the E ring of brevenal, we foresee melding an optimized version of this approach with our previously disclosed synthetic strategy for the ABC substructure [15]. Our long-term goal is a sequential oxacyclization synthesis of the pentacyclic core of brevenal from an acyclic precursor.

Experimental procedure

General methods

Proton and carbon NMR spectra were recorded on INOVA-400 (400 MHz), VNMRS 400 (400 MHz), INOVA-600 (600 MHz), or a BRUKER 600 (600 MHz) instrument equipped with cryogen probe. NMR spectra were taken in solutions of deuterated chloroform ($CDCl_3$) with the residual chloroform (7.27 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). All diastereomer and *trans:cis* ratios were determined by NMR integration of isolated peaks with an uncertainty of ± 2%. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; dq, doublet of quartet; tt, triplet of triplet; tdd, triplet of doublet of doublet; m, multiplet. IR spectra were collected on a Nicolet iS10 from Thermo Scientific and reported in units of cm^{-1}. Mass spectra (high resolution ESI and APCI) were recorded on a Thermo LTQ (linear quadrupole ion trap) FTMS (Fourier transform mass spectrometer) based on ion cyclotron resonance mass spectrometry (ICR-MS). Optical rotations were measured using a Perkin-Elmer 341 polarimeter (concentration in g/100 mL). Thin layer chromatography (TLC) was performed on pre-coated glass-backed plates purchased from Whatman (silica gel 60F254; 0.25 mm thickness). Preparative TLC was conducted with pre-coated glass-backed plates purchased from Analtech (20 × 20 cm, Silica gel GF UV254, 1.0 mm thickness). Flash column chromatography utilized silica gel 60 (230–400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven dried or flame dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were dried with 4 Å molecular sieves purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF titrator from Denver instruments. All reagents, catalysts, and solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification.

Allylic acetate 10

To a solution of the known allylic alcohol **9** [21] (17.3 g, 70.8 mmol) in toluene (175 mL) was added K_3PO_4 (16.9 g, 76 mmol), isopropenyl acetate (12 mL, 120 mmol) and *Candida antarctica* lipase (CAL-B resin, 733 mg). The mixture was stirred at rt for 3.25 h, whereupon an NMR aliquot showed ~ 50% conversion to the acetate. The reaction mixture was filtered through a pad of Celite with diethyl ether (Et_2O). The solution was concentrated by rotary evaporation and chromatographed eluting with 5/95 ethyl acetate (EtOAc)/hexanes–20/80 EtOAc/hexanes–EtOAc to give the (*S*)-acetate **10** as a clear oil (9.87 g, 34.5 mmol, 49% yield, er 97:3 by analysis of the Mosher esters following acetate hydrolysis), and (*R*)-alcohol **9** as a yellow oil (8.62 g, 35.3 mmol, 50% yield, er 96:4 by analysis of the Mosher esters). The spectra and optical rotation of **10** matched the literature values [32]. HRMS (NSI) calculated for $C_{15}H_{31}O_3Si^+$ $[M+H]^+$ 287.20370, found 287.20405; IR

(CH_2Cl_2): 2951, 2930, 2858, 1741, 1472, 1371, 1238, 1099, 835, 775 cm^{-1}; $[\alpha]_D^{20}$ −2.6 (*c* 1.3, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 5.78 (ddd, $J = 17.3$, 10.6, 6.4 Hz, 1H), 5.25–5.22 (m, 2H), 5.17 (dt, $J = 10.5$, 1.2 Hz, 1H), 3.61 (t, $J = 6.4$ Hz, 2H), 2.07 (s, 3H), 1.70–1.57 (m, 2H), 1.56–1.50 (m, 2H), 1.43–1.33 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.56, 136.76, 116.80, 75.02, 63.10, 34.17, 32.72, 26.17, 21.66, 21.46, 18.56, −5.07.

For Mosher ester analysis [33], a small portion of **10** was hydrolyzed with K_2CO_3 in methanol, then concentrated and filtered through a small plug of silica gel to give the (*S*)-alcohol **9**. Mosher ester derivatives were prepared by dissolving the alcohol in dry $CDCl_3$ (1.2 mL), adding d_5-pyridine (12 drops, from a freshly opened ampule) to this solution, then partitioning the mixture between two new NMR tubes, sparged with argon. To each tube was added one drop (as dispensed from a short Pasteur pipette using thumb pressure) of one enantiomer of α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl). The NMR tubes were inverted several times to mix and then allowed to stand for 24 h before NMR analysis (Fig. 7).

Primary alcohol 11

To a cooled (0 °C) solution of crude silyl ether **10** (7.91 g, 27.6 mmol) in methanol (MeOH, 100 mL) was added acetyl chloride (AcCl, 0.6 mL, 8.4 mmol). After 20 min the starting material was consumed (TLC analysis), and the reaction mixture was quenched with satd. aq. $NaHCO_3$ (20 mL). The solution was concentrated in vacuo to remove the methanol. The aqueous layer was then extracted with Et_2O (5 × 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and concentrated by rotary evaporation to give a yellow oil. Flash chromatography eluting with 50/50 Et_2O/hexanes–75/25 Et_2O/hexanes–Et_2O delivered primary alcohol **11** as a yellow oil (4.67 g, 27.2 mmol, 98% yield). HRMS (NSI) calculated for $C_9H_{17}O_3^+$ $[M+H]^+$ 173.11722 found 173.11714; IR (CH_2Cl_2): 3412, 3088, 2939, 2865, 1736, 1647, 1373, 1240, 1021 cm^{-1}; $[\alpha]_D^{20}$ −8.3 (*c* 1.00, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 5.78 (ddd, $J = 17.2$, 10.6, 6.5 Hz, 1H), 5.27–5.23 (m, 2H), 5.18 (dt, $J = 10.5$, 1.2 Hz, 1H), 3.65 (t, $J = 6.5$ Hz, 2H), 2.07 (s, 3 H), 1.72–1.56 (m, 4H), 1.46–1.38 (m, 2H), 1.29 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.61, 136.64, 116.96, 74.88, 62.93, 34.17, 32.63, 21.58, 21.47.

Aldehyde 12

To a solution of primary alcohol **11** (4.69 g, 27.2 mmol) in acetonitrile (MeCN, 150 mL) was added Stahl 1° alcohol oxidation solution (7 mL of a MeCN solution containing 0.2 M in TEMPO, 0.2 M in bpy, and 0.4 M in NMI) followed by $Cu(MeCN)_4OTf$ (512 mg, 1.4 mmol). The resulting red solution was stirred vigorously while open to air for 12 h whereupon it turned green, indicating completion. The mixture was concentrated by rotary evaporation, the resulting oil was filtered through a plug of silica gel with Et_2O and the eluant concentrated to give the aldehyde **12** as an orange oil (3.50 g, 20.6 mmol, 75% yield). HRMS (NSI) calculated for $C_9H_{15}O_3^+$ $[M+H]^+$ 171.10157, found 171.10153; IR (CH_2Cl_2): 3087, 2940, 2725, 1732, 1646, 1372, 1237, 1020 cm^{-1}; $[\alpha]_D^{20}$ −7.1 (*c* 1.13, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 9.77 (t, $J = 1.5$ Hz, 1H), 5.78 (ddd, $J = 17.2$, 10.7, 6.4 Hz, 1H), 5.28–5.23 (m, 2H), 5.19 (dt, $J = 10.5$, 1.1 Hz, 1H), 2.48 (tdd, $J = 6.7$, 3.1, 1.5 Hz, 2H), 2.08 (s, 3H), 1.72–1.62 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 202.06, 170.50, 136.24, 117.26, 74.40, 43.64, 33.64, 21.41, 17.81.

Enal 13

To a solution of aldehyde **12** (3.33 g, 19.6 mmol) in CH_2Cl_2 (70 mL) at room temperature was added Et_3N (8.5 mL, 61 mmol) followed by *N*,*N*-dimethylmethyleneiminium iodide (7.51 g, 40.6 mmol). The reaction was stirred for 2 h whereupon the starting aldehyde was consumed (TLC analysis). The mixture was quenched with satd. aq. $NaHCO_3$ (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. Flash chromatography eluting with 25/75 Et_2O/Hexanes gave the enal **13** as a pale yellow oil (2.20 g, 12.1 mmol,

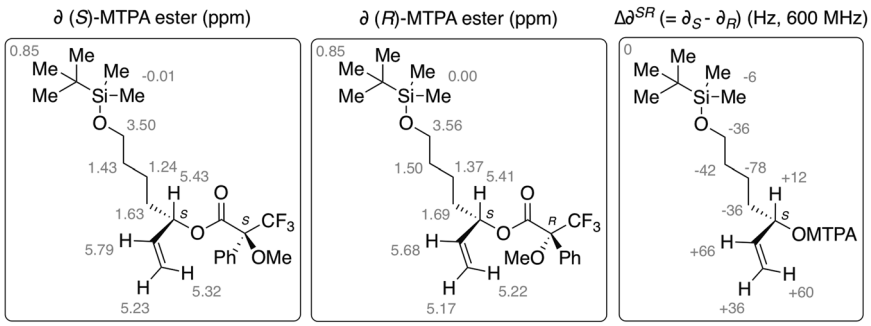


Fig. 7 Analysis of MTPA esters from (*S*)-allylic alcohol **9**

62% yield). HRMS (NSI) calculated for $C_{10}H_{15}O_3^+$ [M+H]$^+$ 183.10157, found 183.10144; IR (CH_2Cl_2): 3088, 2933, 2821, 2702, 1735, 1688, 1647, 1629, 1431, 1372, 1236, 1022, 958 cm^{-1}; $[\alpha]_D^{20}$ −1.7 (*c* 1.14, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.55 (s, 1H), 6.29 (t, *J* = 1.4 Hz, 1H), 6.04 (s, 1H), 5.78 (ddd, *J* = 17.1, 10.6, 6.4 Hz, 1H), 5.26 (d, *J* = 17.2 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 5.20 (d, *J* = 10.6 Hz, 1H), 2.37–2.23 (m, 2H), 2.08 (s, 3H), 1.86–1.74 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 194.55, 170.48, 149.45, 136.15, 134.58, 117.39, 74.20, 32.20, 23.82, 21.41.

Preparation of Grignard reagent 14

To an oven dried 100 mL round bottomed flask equipped with a new stir bar was added Mg turnings (788 mg, 32.4 mmol). (Note: Mg turnings should be shiny, without black MgO on the surface; it is advisable to clean them with conc. HCl prior to use). The flask was purged with argon (× 3) whereupon tetrahydrofuran (THF, 30 mL) was added, followed by 1 M diisobutylaluminum hydride (DIBAL) in hexanes (0.15 mL, 0.15 mmol) (Note: DIBAL serves both to dry the THF and to activate the Mg surface) [34]. The reaction mixture was stirred at rt for 20 min whereupon 1,2-dibromoethane was added (0.05 mL), followed by the dropwise addition of (3-bromopropoxy)-*tert*-butyldimethylsilane (3.2 mL, 13.8 mmol) over 25 min, the surface of the flask not exceeding 34 °C as observed by thermal camera (SeekThermal^{TM} Thermal Camera for iPhone). After aging for 2 h, the solution was black. Removal of a small (0.1 mL) aliquot of the solution, quenching it with CD_3OD and NMR analysis showed the solution to have been ~ 33% Grignard (the rest of the material being dimerized bromide or elimination products).

Enone 15

A solution of the aldehyde **13** (846 mg, 4.6 mmol) in THF (20 mL) was cooled to −78 °C. The entire solution of the Grignard reagent **14** (30 mL, as prepared above) was slowly added down the side of the flask via syringe. After 5 min, TLC showed almost complete conversion to the alcohol product. After 15 min, the reaction mixture was quenched at −78 °C with the addition of satd. aq. NH_4Cl (10 mL) by syringe. After warming to rt, more satd. aq. NH_4Cl (40 mL) was added. The aqueous layer was extracted with Et_2O (3 × 50 mL), the combined organics washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography eluting with 1/100 MeOH CH_2Cl_2 to 3/100 MeOH/CH_2Cl_2 gave allylic alcohol **16** as an inseparable 1:1 mixture with its diastereomer, as a clear oil (1.12 g, 3.1 mmol, 68% yield). Aldehyde **13** was also recovered (180 mg, 0.98 mmol, 21% yield). The mixture of product **16** and its diastereomer was characterized: HRMS (NSI) calculated for $C_{19}H_{37}O_4Si^+$ [M+H]$^+$ 357.24556, found 357.24498; IR (CH_2Cl_2): 3446, 3084, 2952, 2929, 2885, 2857, 1740, 1645, 1472, 1372, 1239, 1098, 1023, 835, 775 cm^{-1}; $[\alpha]_D^{20}$ −1.3 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.79 (apparent dddd, *J* = 17.2, 10.6, 6.5, 0.9 Hz, 1H (0.9 Hz because of two diastereomers), 5.29–5.24 (m, 2H), 5.19 (dq, *J* = 10.5, 1.2 Hz, 1H), 5.08 (tt, *J* = 2.2, 1.1 Hz, 1H), 4.86 (quintet, *J* = 1.4 Hz, 1H), 4.10–4.08 (m, 1H), 3.67 (t, *J* = 5.8 Hz, 2H), 2.64 (s, 1H), 2.14 (tdd, *J* = 16.1, 10.6, 5.7 Hz, 1H), 2.08 (apparent d, *J* = 0.7 Hz, 3H (both diastereomers)), 2.02 (tdd, *J* = 16.8, 10.7, 6.2 Hz, 1H), 1.89–1.74 (m, 2H), 1.75–1.68 (m, 1H), 1.65–1.54 (m, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.60, 170.55, 151.09, 150.98, 136.53, 136.50, 117.17, 117.13, 110.10, 109.94, 75.28, 75.09, 74.78, 74.69, 63.55, 33.11, 33.02, 32.71, 32.69, 29.19, 27.21, 26.93, 26.16, 25.87, 21.47, 18.55, −5.15. To a solution of alcohol **16** and its diastereomer (349 mg, 0.98 mmol) in MeCN (5 mL) was added Stahl 2° alcohol oxidation solution (15 mL of a MeCN solution containing 0.002 M in ABNO, 0.01 M in ^{MeO}bpy and 0.02 M in NMI) followed by $Cu(MeCN)_4OTf$ (68 mg, 0.18 mmol). The reaction was stirred open to air for 2 days, and concentrated by rotary evaporation. The resulting residue was filtered through a plug of SiO_2 with Et_2O and the eluant concentrated by rotary evaporation to give nearly pure enone **15** (305 mg, 0.86 mmol, 88% yield). HRMS (NSI) calculated for $C_{19}H_{35}O_4Si^+$ [M + H]$^+$ 355.22991, found 355.22970; IR (CH_2Cl_2): 3090, 2953, 2929, 2857, 1737, 1678, 1472, 1372, 1236, 1097, 1021, 836, 776 cm^{-1}; $[\alpha]_D^{20}$ + 1.6 (*c* 1.13, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.06 (s, 1H), 5.79 (ddd, *J* = 17.4, 10.8, 6.7 Hz, 1H), 5.76 (t, *J* = 1.8 Hz, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 3.64 (t, *J* = 6.1 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.36–2.27 (m, 2H), 2.08 (s, 3H), 1.83 (dt, *J* = 13.7, 6.7 Hz, 2H), 1.79–1.69 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 201.80, 170.53, 148.07, 136.35, 124.53, 117.17, 74.42, 62.37, 34.19, 33.04, 27.69, 26.84, 26.14, 25.86, 21.44, −5.12.

Allylic alcohol 16

To a flask charged with THF (5 mL) was added *R*-2-methyl-CBS-oxazaborolidine (0.53 mL, 1 M in toluene, 0.53 mmol) followed by BH_3•THF (0.51 mL, 1 M in THF, 0.51 mmol). The mixture was stirred at room temperature for 1 h before cooling to −40 °C. A solution of enone **15** (174 mg, 0.48 mmol) in THF (5 mL) was added dropwise. After 1.5 h the reaction was complete (TLC analysis) and was quenched by the addition of MeOH (0.4 mL). Following concentration, the resulting residue was chromatographed to give allylic alcohol **16** (96 mg, 0.27 mmol, 56% yield). ^{1}H NMR (600

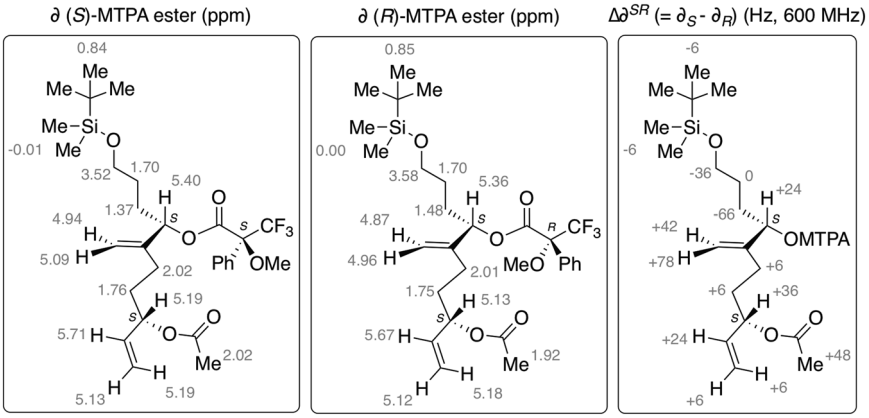


Fig. 8 Analysis of MTPA esters from (*S*)-allylic alcohol **16**

MHz, $CDCl_3$): δ 5.80 (ddd, $J = 17.2$, 10.6, 6.5 Hz, 1H), 5.28 (q, $J = 6.6$ Hz, 1H), 5.26 (dt, $J = 17.3$, 1.2 Hz, 1H), 5.19 (dt, $J = 10.6$, 1.2 Hz, 1H), 5.08 (quintet, $J = 1.0$ Hz, 1H), 4.86 (q, $J = 1.4$ Hz, 1H), 4.10 (dd, $J = 7.3$, 3.2 Hz, 1H), 3.67 (t, $J = 5.8$ Hz, 2H), 2.67 (d, $J = 3.6$ Hz, 1H), 2.13 (ddd, $J = 15.8$, 10.1, 5.8 Hz, 1H), 2.08 (s, 3H), 2.03 (ddd, $J = 15.9$, 10.5, 5.6 Hz, 1H), 1.88–1.77 (m, 2H), 1.74–1.69 (m, 1H), 1.64–1.56 (m, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

The major allyl alcohol stereocenter was determined to be *S* by analysis of the corresponding Mosher esters (Fig. 8), which also revealed a dr of 96:4.

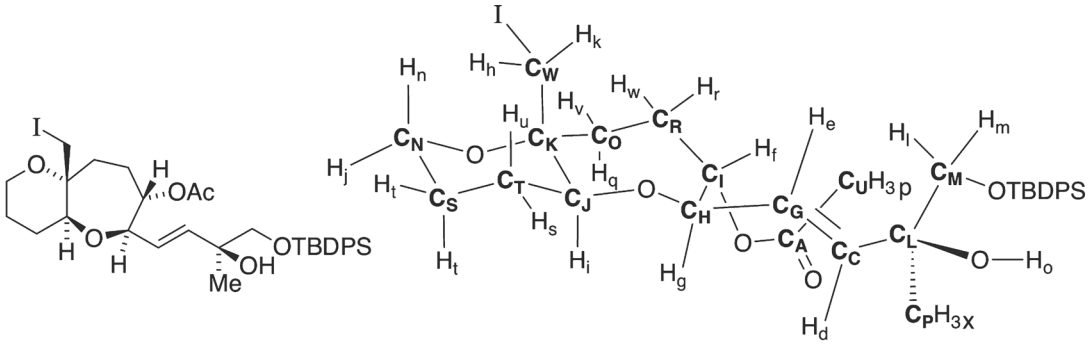
Iodomethyl-tetrahydropyranyl alcohol 18

To a cooled (0 °C) solution of **16** (96 mg, 0.27 mmol) in MeOH (3 mL) was added acetyl chloride (3–5 drops, ~ 0.05 mL, ~ 0.7 mmol). The reaction mixture was stirred for 10 min and then quenched with solid $NaHCO_3$ (47 mg). Filtration and concentration by rotary evaporation gave the diene diol **17**, which was carried on to the next step without further purification. To a 0 °C solution of the diene diol **17** in THF (5 mL) was added $NaHCO_3$ (180 mg, 2.1 mmol) followed by I_2 (235 mg, 0.93 mmol). After 1.5 h, the reaction was complete (TLC analysis) and was quenched with satd. aq. $Na_2S_2O_3$ (2 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics dried over $MgSO_4$ and concentrated to give iodomethyl-tetrahydropyranyl alcohol **18** (93 mg, 0.25 mmol, 93% yield, 2 steps). ^{1}H NMR (600 MHz; $CDCl_3$): δ 5.80 (ddd, $J = 17.2$, 10.7, 6.4 Hz, 1H), 5.30–5.24 (m, 2H), 5.21 (d, $J = 10.5$ Hz, 1H), 3.79 (ddd, $J = 7.7$, 5.9, 4.0 Hz, 1H), 3.61 (ddd, $J = 11.6$, 6.8, 4.5 Hz, 1H), 3.53 (ddd, $J = 11.8$, 7.8, 4.0 Hz, 1H), 3.47 (d, $J = 10.9$ Hz, 1H), 3.40 (d, $J = 10.9$ Hz, 1H), 2.10 (s, 3H), 1.91 (ddt, $J = 12.8$, 8.2, 4.3 Hz, 1H), 1.83 (d, $J = 6.1$ Hz, 1H), 1.80–1.63 (m, 6 H), 1.54–1.47 (m, 1H).

Tetrahydropyranyl alcohol-epoxyalkene substrate 21

To a solution of allylic acetate **18** (93 mg, 0.25 mmol) and (*S,R*)-epoxyalkene **19** [17] (385 mg, 1.1 mmol) in $CDCl_3$ (5 mL) was added Hoveyda Grubbs II catalyst (**20**, 10 mg, 0.016 mmol). The mixture was concentrated on a rotary evaporator with water bath temperature at 50 °C for 2 h. ^{1}H NMR analysis of an aliquot of the reaction mixture showed 27% conversion to the desired product **21**, with 46% of the epoxyalkene having dimerized. To increase conversion to the cross-metathesis product **21**, another portion of catalyst (10 mg) was added with $CDCl_3$ (5 mL). After concentrating on the rotary evaporator for another 2 h, ^{1}H NMR analysis of an aliquot indicated 48% conversion to the desired product **21**, and 86% of the epoxyalkene having dimerized. Thus one additional portion of catalyst (10 mg) was added with $CDCl_3$, and the reaction mixture was concentrated on the rotary evaporator for two more hours (6 h total). ^{1}H NMR analysis of an aliquot of the reaction mixture showed 80% conversion to the cross-metathesis product **21**, with 89% of epoxyalkene **19** having dimerized. Column chromatography of the resulting oil eluting with 60/40 Et_2O/Hexanes gave tetrahydropyranyl alcohol-epoxyalkene **21** as a brown oil (104 mg, 0.15 mmol, 60% yield, *E*/*Z* 88:12, dr of *E* 85:15 (± 2)) containing an additional 10 mg of the starting acetate **18**. HRMS (APCI) calculated for $C_{33}H_{46}IO_6Si^+$ $[M+H]^+$ 693.21029, found 693.20889; IR (CH_2Cl_2) 3459, 3070, 3048, 2931, 2858, 1736, 1471, 1428, 1372, 1237, 1112, 1085, 1020, 824, 742, 703 cm^{-1}; $[\alpha]_D^{20}$ −0.8 (*c* 0.883, CH_2Cl_2); ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.71–7.65 (m, 4H), 7.46–7.38 (m, 6H), 5.78 (ddd, $J = 15.6$, 6.5, 0.9 Hz, 1H), 5.53 (ddd, $J = 15.6$, 6.9, 1.1 Hz, 1H), 5.23 (q, $J = 6.0$ Hz, 1H), 3.69–3.65 (m, 3H), 3.55–3.46 (m, 2H), 3.42 (d, $J = 10.9$ Hz, 1H), 3.32 (d, $J = 10.9$ Hz, 1H), 3.28 (d, $J = 6.4$ Hz, 1H), 2.03 (s, 3H), 1.93–1.43 (m, 11H), 1.26 (s, 1H), 1.07 (s, 9H);^{13}C NMR (151 MHz, $CDCl_3$): δ 170.49, 135.87, 135.78, 134.21, 133.54, 133.33, 129.98,

Table 2 Correlation analysis of NMR data for bicyclic compound **22**



^{13}C	Shift (ppm)	^{1}H	Shift (ppm)	Multi–plicity	Couplings (Hz)	COSY correlations	HMBC correlations	NOESY correlations
A	170.05	none	–	–	–	–	H_f	–
B_2	135.56	a_4	7.68–7.65	m	–	H_{c4}	H_{a4}, H_{b2}, H_{c4}	H_{c4}, H_l, H_m, H_{y9}
B'_2	135.61						H_{a4}, H_{b2}, H_{c4}	
C	135.25	d	5.83	dd	15.7, 1.6	H_e, H_g	H_e, H_g, H_l, H_m, H_o	H_f, H_g, H_l
D	132.86	none	–	–	–	–	H_{a4}, H_{c4}	–
D'	132.97	none	–	–	–	–	H_{a4}, H_{c4}	–
E_2	129.86	b_2	7.48–7.45	m	–	H_{c4}	H_{a4}, H_{c4}	H_{c4}
F_4	127.8	c_4	7.43–7.40	m	–	H_{a4}, H_{b2}	H_{a4}, H_{b2}, H_{c4}	H_{a4}, H_{b2}
G	127.44	e	5.74	dd	15.7, 4.8	H_d, H_g	H_d, H_g	H_f, H_g, H_l, H_o
H	82.01	g	4.23	dt	4.8, 1.5	H_e, H_d, H_f	H_d, H_e, H_f, H_i, H_r	H_d, H_e, H_f, H_i
I	76.97	f	5.02	dt	7.0, 1.3	H_r, H_g, H_w	H_r, H_v	H_d, H_e, H_g, H_r, H_w
J	76.08	i	3.73	dd	11.7, 5.0	H_u, H_s	not observed	H_g, H_s, H_{t2}
K	75.44	none	–	–	–	–	H_h, H_r, H_v	–
L	72.86	none	–	–	–	–	H_d, H_e, H_l, H_m, H_o	–
M	70.93	l	3.53	d	9.7	H_m	not observed	H_d, H_e, H_m, H_o
		m	3.51	d	9.6	H_l		H_d, H_e, H_l, H_o
N	60.35	j	3.66	ddd	12.3, 4.5, 1.5	H_n, H_{t2}	not observed	H_h, H_k, H_n, H_{t2}
		n	3.38	td	11.9, 3.3	H_j, H_{t2}		H_h, H_j, H_k, H_{t2}
O	32.84	q	1.99	dd	13.3, 5.2	H_v, H_r, H_w	H_f, H_h, H_r	H_h, H_k, H_v
		v	1.62–1.58	m	–	H_q, H_r, H_w		H_h
P	30.32	x_3	1.46	s	–	none	not observed	not observed
Q_3	26.83	y_9	1.09	s	–	none	not observed	H_{a4}
R	26.76	r	1.87	td	13.2, 6.4	H_w, H_f, H_q	not observed	H_f, H_w
		w	1.54–1.49	m	–	H_f, H_q, H_r, H_v		H_f, H_k
S	25.13	t_2	1.75–1.55	m	–	H_j, H_n, H_s	not observed	H_i, H_j
T	21.96	s	1.84	dd	13.1, 4.0	H_u, H_i, H_{t2}	H_t	H_i, H_{t2}, H_u
		u	1.65–1.57	m	–	H_i, H_s, H_{t2}		H_h
U	21.35	p_3	2.14	s	–	none	not observed	not observed
V	19.33	none	–	–	–	–	not observed	–
W	10.19	h	3.81	dd	11.8, 2.2	H_k, $\mathbf{H_v}^*$	H_v, H_q	H_k, H_n, H_u, H_v
		k	3.58	d	11.9	H_h		H_h, H_n, H_w
	(OH)	o	2.63	s	–	none		H_e, H_l, H_2O

*** denotes W coupling**

129.97, 127.98, 127.94, 127.18, 75.54, 73.60, 68.05, 65.26, 63.26, 63.12, 61.54, 29.57, 27.64, 27.32, 26.98, 22.68, 21.44, 20.08, 19.50, 10.85.

Bicyclic CD substructure 22

Epoxyalkene **21** (15.3 mg, 0.022 mmol) was combined with $Pd(PPh_3)_4$ (2.8 mg, 0.0025 mmol), trimethylolpropane phosphite (**8**, 2.5 mg, 0.016 mmol) and diphenylphosphinic acid (0.9 mg, 0.004 mmol) in $CDCl_3$ (0.7 mL) in a clean NMR tube. The solution was monitored by NMR analysis at several time points. Extensive 2-dimensional NMR analysis after 21 days indicated the presence of the bicyclic product **22**. Preparative thin layer chromatography (eluting with Et_2O) allowed for isolation of **22** as a colorless film (1.2 mg, 0.0017 mmol, 8% yield), as well as 1,3-diene byproducts **23** (3.5 mg, 0.0055 mmol, 25% yield) and diacetate **24** (4.8 mg, 0.0064 mmol, 29% yield).

Data for 22

HRMS (APCI, negative ion mode) calculated for $[M-H]^-$ $C_{33}H_{44}IO_6Si^-$ 691.19573, found 691.19320; IR (CH_2Cl_2) 3361, 3312, 2952, 2921, 1737, 1659, 1633, 1468, 1390, 1260, 1088, 1019, 800, 702 cm^{-1}; $[\alpha]_D^{20}$ −4.0 (*c* 0.100, CH_2Cl_2); ^1H NMR (600 MHz; $CDCl_3$): δ 7.68–7.65 (m,4H), 7.48–7.45 (m, 2H), 7.43–7.40 (m, 4H), 5.83 (dd, $J = 15.7$, 1.6 Hz, 1H), 5.74 (dd, $J = 15.7$, 4.8 Hz, 1H), 5.02 (dt, $J = 7.0$, 1.3 Hz, 1H), 4.23 (dt, $J = 4.8$, 1.5 Hz, 1H), 3.81 (dd, $J = 11.8$, 2.2 Hz, 1H), 3.73 (dd, $J = 11.7$, 5.0 Hz, 1H), 3.66 (ddd, $J =$ 12.3, 4.5, 1.5 Hz, 1H), 3.58 (d, $J = 11.9$ Hz, 1H), 3.53 (d, $J =$ 9.7 Hz, 1H), 3.51 (d, $J = 9.6$ Hz, 2H), 3.38 (td, $J = 11.9$, 3.3 Hz, 1H), 2.63 (s, 1H), 2.14 (s, 3H), 1.99 (dd, $J = 13.3$, 5.2 Hz, 1H), 1.87 (td, $J = 13.2$, 6.4 Hz, 1H), 1.84 (dd, $J = 13.1$, 4.0 Hz, 1H), 1.75–1.55 (m, 2H), 1.65–1.57 (m, 1H), 1.62–1.58 (m, 1H), 1.54–1.49 (m, 1H), 1.46 (s, 1H), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.05, 135.56, 135.61, 135.25, 132.86, 132.97, 129.86, 127.8, 127.44, 82.01, 76.97, 76.08, 75.44, 72.86, 70.93, 60.35, 32.84, 30.32, 26.83, 26.76, 25.13, 21.96, 21.35, 19.33, 10.19.

Table 2 provides correlation analysis of NMR data for bicyclic compound **22**, including HMQC (^1H–^{13}C; ^1J), COSY (^1H–^1H; ^2J,^3J,^4J), HMBC (^1H–^{13}C; ^2J,^3J) and NOESY experiments.

Data for 23

HRMS (NSI) calculated for $C_{31}H_{42}IO_3Si^+$ $[M–OH]^+$ 617.19424, found 617.19670; IR (CH_2Cl_2): 3423, 3071, 3048, 2929, 2857, 1735 (weak), 1691, 1671, 1472, 1428, 1112, 1085, 823, 741, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.69–7.64 (m, 4H), 7.47–7.43 (m, 2H), 7.42–7.38 (m, 4H), 6.64 (ddd, $J = 15.4$, 11.1, 1.1 Hz, 1H, (*Z*,*E*)), 6.27 (dd, $J = 15.4$, 10.4 Hz, 1H, (*E*,*E*)), 6.07 (dd, $J = 15.2$, 10.4 Hz, 1H, (*E*,*E*)), 6.00 (t, $J = 10.9$ Hz, 1H, (*Z*,*E*)), 5.71 (dt, J = 14.8, 7.2 Hz, 1H, (*E*,*E*)), 5.67 (d, $J = 15.3$ Hz, 1H, (*Z*,*E*)), 5.57 (d, $J = 15.5$ Hz,1H, (*E*,*E*)), 5.46 (dt, $J = 10.7$, 7.5 Hz, 1H, (*Z*,*E*)), 3.82 (ddd, $J = 7.4$, 6.5, 3.8 Hz, 1H), 3.66–3.62 (m, 1 H), 3.57–3.54 (m, 1 H), 3.53–3.46 (m, 3H), 3.41 (apparent dd, $J = 10.9$, 1.1 Hz, 1H), 2.69 (s, 1H, (*Z*,*E*)), 2.64 (s, 1H, (*E*,*E*)), 2.31–2.08 (m, 2 H), 1.96–1.66 (m, 5H), 1.54–1.47 (m,1H), 1.27 (apparent d, $J = 3.2$ Hz, 3H), 1.07 (app. d, $J = 0.8$ Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 137.91, 137.88, 135.90, 135.83, 135.55, 135.47, 134.03, 133.96, 133.33, 133.22, 131.44, 130.40, 130.07, 130.04, 129.32, 128.82, 128.02, 127.99, 127.98, 127.96, 124.40, 124.39, 73.46, 73.20, 71.36, 71.34, 68.04, 61.67, 61.64, 29.92, 29.89, 27.61, 27.57, 27.11, 27.05, 25.69, 24.51, 22.58, 22.48, 20.98, 20.92, 19.56, 10.99, 10.90. (Note: Many double peaks were present in the ^{13}C NMR spectrum due to presence of both *E*,*E* and *Z*,*E* stereoisomers).

Data for 24

HRMS (NSI) calculated for $C_{35}H_{48}IO_7Si^+$ $[M–OH]^+$ 735.22085, found 735.22098; IR (CH_2Cl_2): 3468, 3071, 3049, 2929, 2857, 1737, 1665, 1428, 1371, 1234, 1085, 1022, 973, 824, 741, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.66–7.62 (m, 4 H), 7.48–7.44 (m, 2H), 7.43–7.38 (m, 4H), 5.80 (ddd, $J = 15.7$, 6.4, 0.9 Hz, 1H), 5.66 (ddd, $J = 15.7$, 6.9, 1.2 Hz, 1H), 5.36 (dd, $J = 6.4$, 1.0 Hz, 1H), 5.23 (q, $J = 6.6$ Hz, 1H), 3.76 (dt, $J = 8.8$, 4.6 Hz, 1H), 3.61–3.58 (m, 1H), 3.58 (d, $J =$ 10.1 Hz, 1H), 3.52 (d, $J = 11.0$ Hz, 1H), 3.51–3.45 (m, 1H), 3.46 (d, $J = 10.1$ Hz, 1H), 3.35 (d, $J = 11.0$ Hz, 1H), 2.59 (s, 1H), 2.30 (d, $J = 6.0$ Hz, 1H), 2.04 (s, 3H), 2.00 (s, 3H), 1.89 (dt, $J = 12.7$, 6.1 Hz, 1H), 1.80–1.71 (m, 3H), 1.70–1.59 (m, 2H), 1.55–1.48 (m, 2H), 1.12 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.45, 170.25, 135.88, 135.81, 133.07, 132.89, 132.84, 130.17, 130.16, 128.07, 128.04, 127.77, 75.97, 75.70, 73.94, 73.80, 67.91, 67.67, 61.49, 29.93, 27.57, 27.51, 27.11, 23.12, 21.53, 21.38, 19.99, 19.47, 11.57.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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