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An asymmetric total synthesis of (+)-pentalenene

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ABSTRACT

A stereoselective total synthesis of (+)-pentalenene was achieved through the tandem cycloaddition reaction of the allenyl diazo substrate prepared from (+)-citronellal. The initial intramolecular [2+3] cycloaddition reaction between the diazo functionality and the allenyl group produced the trimethylenemethane (TMM) intermediate after immediate loss of nitrogen molecule from the cycloaddition intermediate. Subsequent [2+3] cycloaddition of the TMM with olefin produced the angularly fused triquinane structure stereoselectively.

1. Introduction

Since the isolation of isocomene[1] from natural sources in 1977, angularly fused triquinanes have attracted synthetic chemistry community for their highly congested structural features with diverse substitution patterns (Fig. 1).[2] Various ingenious synthetic strategies have been developed for the construction of this tricyclic structure.[3] Variety of synthetic strategies of the skeleton became a tool for assessments of the complexity derived evaluation of synthetic strategies[4] and eventually became one of the test sets for various measures of ideal synthesis.[5]

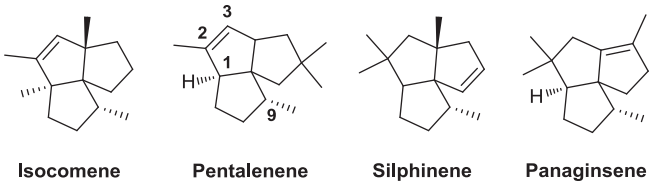
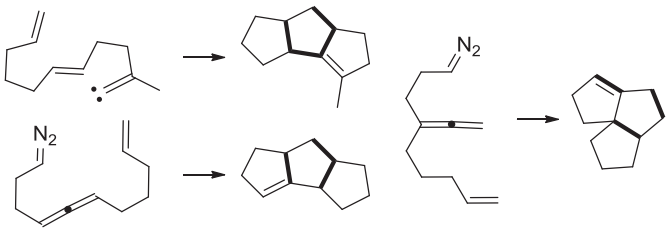


Fig. 1. Angularly fused triquinane natural products.

Pentalenene, a sesquiterpene with tricycle[6.3.0.0]undecane core structure was isolated from *Streptomyces griseochromogenes* by Seto and Yonehara in 1980.[6] A great attention has been drawn to this natural product since it is the representative angular triquinane natural product to test newly developed synthetic methodologies and is the biosynthetic precursor of pentalenolactone, an antibiotic metabolites, produced by several *Streptomyces* species.[7] There have been numerous synthetic efforts of the total and formal synthesis of pentalenene[8] that culminated several total syntheses of the natural product mostly in racemic form except two.[9,12]

Most synthetic approaches toward the linear and angularly fused triquinanes employed sequential annulations to construct the tricyclic ring system by adding one ring at a time. Only few strategies that assembled two or more rings in one-step were reported; thermolytic rearrangemnt,[8e] metal-catalyzed transformation,[8p] squarate ester cascade,[8q] tandem radical cyclization,[10] arene-olefin photocycloaddition,[11] and intramolecular Pauson–Khand reaction.[12]

Recently, we have developed synthetic strategies of constructing the triquinane structures directly from linear substrates through tandem cycloaddition reaction via trimethylenemethane (TMM) intermediates.[13] (Scheme 1) The tandem cycloaddition strategies have been applied to the total synthesis of linearly fused triquinane natural products.[13a,14]



Scheme 1. Tandem cycloaddition routes to triquinanes.

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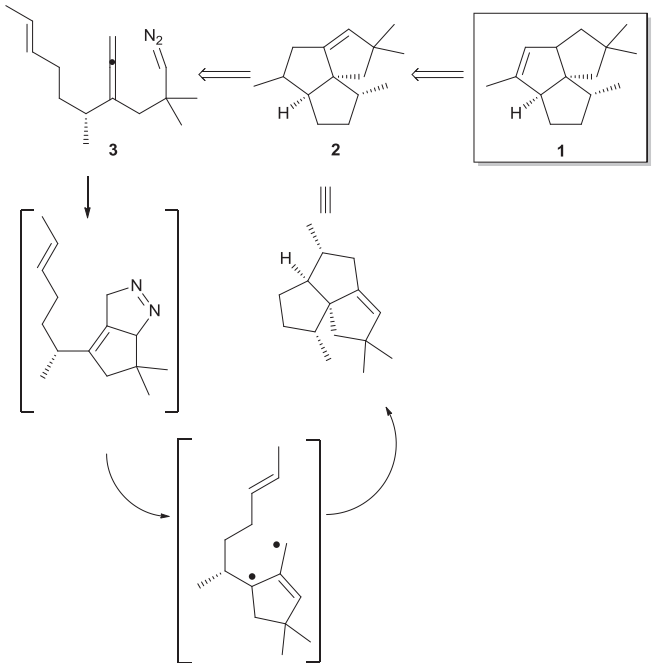
Herein, We report an application of the tandem cycloaddition strategy via TMM diyl [2+3] cycloaddition reaction[13b] to the total synthesis of (+)-pentalenene.

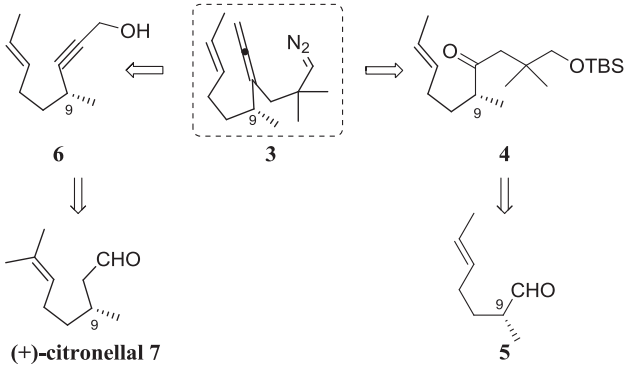
Pentalenene could be synthesized from the isomeric triquinane **2** that would be obtained from the linear precursor **3** through the tandem cycloaddition reaction. The cycloaddition reaction was expected to be stereoselective as the stereochemistry at the C-9 of the substrate was known to control the relative stereochemistry of the triquinane product[15] (Scheme 2).



Scheme 2. Synthetic analysis of pentalenene.

2. Result and discussion

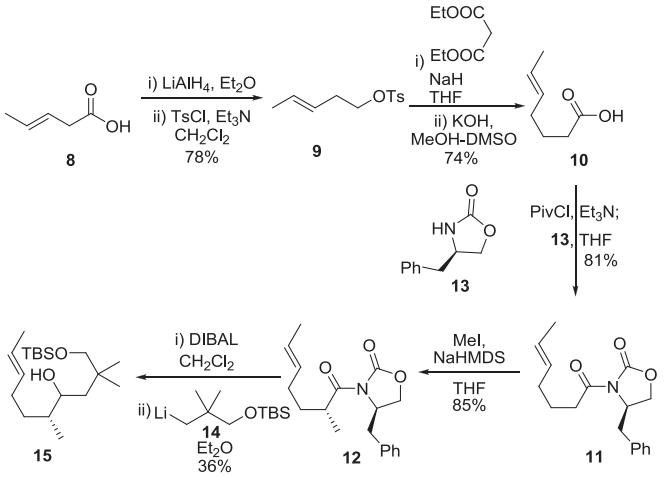
The enantioselective preparation of the cycloaddition precursor **3** was the key to the total synthesis of (+)-pentalenene (Scheme 3). The allenyl compound **3** could be obtained from the corresponding ketone **4** that should be readily synthesized from the aldehyde **5**. The aldehyde **5** would be obtained through an asymmetric alkylation of the corresponding carboxylic acid **8**.



Scheme 3. Synthetic routes to the key intermediate **3**.

Alternatively, the allenyl moiety of **3** could be synthesized from the propargyl alcohol **6** that can be obtained from (+)-citronellal **7** that possesses the desired absolute stereochemistry of the methyl group at C-9 of **7**. Based on our early experience with the racemic synthesis of pentalenene, we first explored the synthetic strategy that was based on the asymmetric alkylation process developed by Evans.[16]

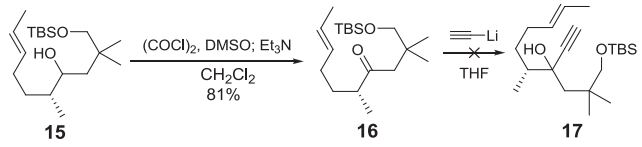
Preparation of the substrate to generate **3** for the tandem cycloaddition started from the synthesis of the carboxylic acid **10** and subsequent asymmetric methylation of the corresponding amide possessing Evans' chiral auxiliary **12** (Scheme 4).



Scheme 4. Preparation of the chiral alcohol **15**. Acronyms and abbreviations: TsCl, *p*-toluenesulphonyl chloride; DMSO, dimethylsulfoxide; PivCl, pivaloyl chloride; NaHMDS, sodium hexamethyldisilazide; THF, tetrahydrofuran; DIBAL, diisobutylaluminum hydride.

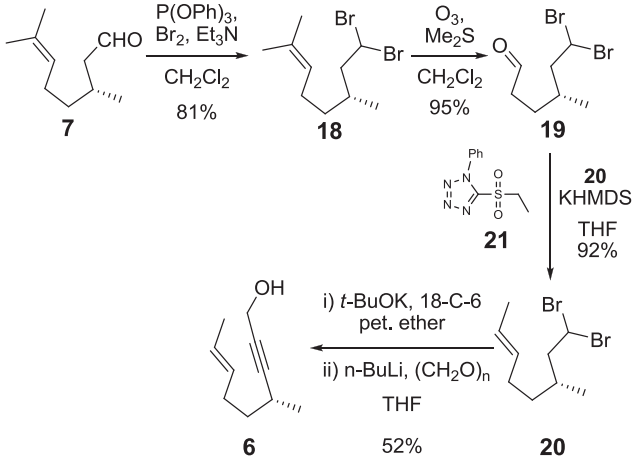
The carboxylic acid **10** was prepared from *trans*-2-pentenoic acid **8** through malonate ester synthesis for the two carbon extension. The carboxylic acid **8** was reduced to the alcohol and activated as the tosylate **9**. Diethyl malonate anion addition to the tosylate **9** followed by decarboxylative hydrolysis produced the desired carboxylic acid **10**. Following the Evans' protocol,[17] chiral amide **10** was prepared by amide formation with chiral oxazolidinone **13** via activation as the mixed anhydride using pivaloyl chloride. Methylation of the enolate of **11** produced the chiral center C-9 stereoselectively[18] and DIBAL reduction furnished the chiral aldehyde **5**. Treating known Li reagent **14**[13b] formed alcohol **15**.

After the Swern's oxidation to form ketone addition of lithiumacetylide to the ketone produced the alkynol **17** as a mixture of diastereomers in trace, and the reaction was sluggish even at room temperature. Due to the low reactivity of the ketone and the long reaction time to form **17**, the enantiomeric purity of the methyl group at the C-9 was lost completely as judged by the optical rotation of the product **17** and the recovered ketone **16** from the reaction (Scheme 5).



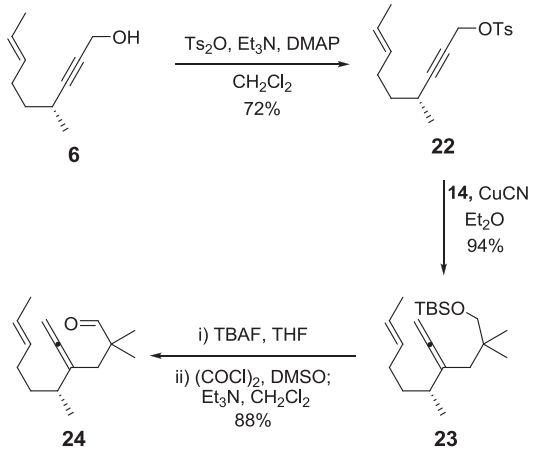
Scheme 5. Synthesis of **17**.

Several efforts to minimize the racemization at the C-9 stereocenter during the acetylide addition reaction were not fruitful. Thus the other synthetic route to **3** was explored starting from (+)-citronellal **7**. Synthesis of **6** from citronellal required the conversion of the aldehyde into the alkyne and deletion of one methyl group (Scheme 6).



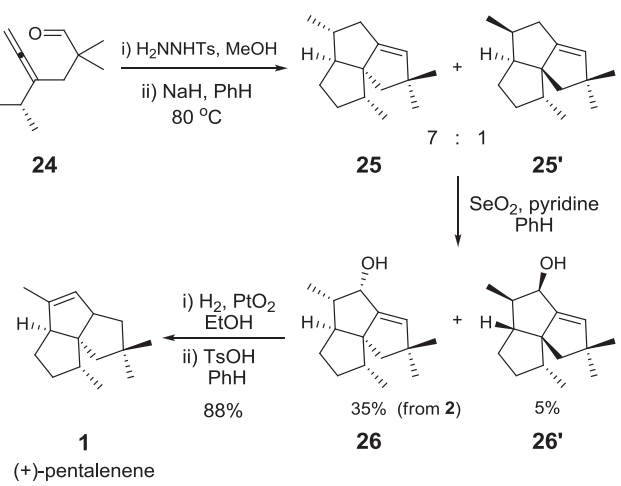
Scheme 6. Synthesis of the propargyl alcohol **6**. Acronyms and abbreviations: KHMDS, potassium hexamethyldisilazide; 18-C-6, 18-crown-6; pet. Ether, petroleum ether.

(*R*)-Citronellal **7** was treated with bromine and triphenylphosphite to convert the aldehyde into the dibromide **18**.[19] At this stage, direct conversion of the trisubstituted olefin of **18** into **20** through olefin metathesis reaction was explored.[20] The reaction of **18** with 2-butene in presence of Grubbs' catalyst did not proceed at all. Even under high pressure of ethylene atmosphere **18** did not undergo metathesis reaction with ethylene. Instead, a two-step protocol of ozonolysis followed by Julia-Kocienski olefination[21] produced the desired olefin **20**. The dibromide of **20** was converted into the corresponding terminal alkyne by the base treatment and subsequent formaldehyde addition to the acetylide anion produced the propargyl alcohol **6**. With the propargyl alcohol **6**, the precursor of the tandem cycloaddition substrate **3** was prepared in a straightforward manner (Scheme 7). The propargylic alcohol was activated as the tosylate **22** and the addition of the cuprate of **14** produced allene **23**. Deprotection of the silyl ether of **23** followed by the oxidation the corresponding alcohol produced **24**, the precursor of the diazo intermediate **3**.



Scheme 7. Synthesis of allenylaldehyde **24**. Acronyms and abbreviations: Ts_2O, *p*-toluenesulphonic anhydride; DMAP, dimethylaminopyridine; TBAF, tetrabutylammonium-fluoride.

With the allenylaldehyde **24** in hand, the tandem cycloaddition of the diazo intermediate **3** was performed following the general two step protocol (Scheme 8). The aldehyde **24** was reacted with tosylhydrazide to form the corresponding hydrazone. The hydrazone was heated to 110 °C in toluene after forming the sodium salt. The diazo intermediate **3** must have been generated and underwent [2+3] cycloaddition reaction with the allene moiety. After losing a nitrogen molecule to form the TMM diyl intermediate, subsequent [2+3] cycloaddition reaction of the TMM diyl with the olefin produced the desired angularly fused triquinane **25** stereoselectively along with its diastereomer **25′** in 7:1 ratio determined by NMR integration. When the reaction temperature was lowered to 80 °C, the reaction proceeded in the same pattern without changing the product ratio. Since the two diastereomers were not separable, the mixture of the diastereomers was subjected to the allylic oxidation using SeO_2 to form the corresponding allylic alcohols **26** and **26′** stereoselectively. The desired isomer **25** was separated and reduction of the olefin followed by acid catalyzed dehydration[8k] afforded (+)-pentalenene. All the spectral data including optical rotation was in complete agreement with the data reported in the literature.[9b]



Scheme 8. Completion of the total synthesis.

3. Conclusion

The tandem cycloaddition reaction of linear substrates to form angularly fused triquinanes was applied to the asymmetric total synthesis of (+)-pentalenene. The asymmetric synthesis was achieved in 6.8% yield with 14 step sequence and thus demonstrated that the tandem cycloaddition route to triquinanes from linear substrates was an efficient and effective strategy for the construction of related natural products and their analogs.

4. Experimental

4.1. General methods

All oxygen or moisture sensitive reactions were carried out in oven dried glassware under a positive pressure of argon. Sensitive liquids and solutions were transferred by syringe or cannula and were introduced through rubber septa through, which a high flow of inert gas was maintained. Unless otherwise stated, reactions were carried out at room temperature. Concentration of solutions was accomplished using a Buchi rotary evaporator with a water aspirator. This was generally followed by removal of residual solvents on a vacuum line held at 0.1–1 Torr.

Unless otherwise noted, all reagents and solvents were used without additional purification. Exceptions include: chromatography grade hexane and ethyl acetate were technical grade and distilled before use; Et_2O and THF were distilled from sodium benzophenone ketyl under nitrogen; triethylamine was distilled from sodium; dichloromethane was distilled from P_2O_5. Benzene and toluene were washed with concentrated sulfuric acid, water, and saturated $NaHCO_3$ solution, and then dried over sodium for

more than 12 h before distillation. Concentration of alkyllithium solutions was determined by titration against diphenylacetic acid.

Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F254 plates. Visualization on TLC was achieved by use of UV light (254 nm), exposure to iodine vapor, or treatment with acidic anisaldehyde or ceric ammonium molybdate stain followed by heating. Flash column chromatography was carried out using Merck 60, 230–400 mesh ASTM. Proton nuclear magnetic resonance spectroscopy (^{1}H NMR) was recorded on Bruker Fourier Transform AM 400 (400 MHz) spectrometers. Chemical shifts were reported in δ units, parts per million (ppm) relative to the singlet as 7.24 ppm for chloroform-*d*. The following abbreviations were used to describe peak patterns when appropriate: b=broad, s=singlet, d=doublet, t=triplet, q=quadraplet, m=multiplet. Coupling constant, *J*, was reported in Hertz unit (Hz). Carbon-13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on Bruker Fourier Transform AM 400 (100 MHz) was fully decoupled by broadband decoupling. Chemical shifts were reported in ppm with the centerline of the triplet for chloroform-*d* set at 77.00 ppm. Mass spectra were obtained on a Jeol JMS 700 high resolution mass spectrometer or JMS 7003 high resolution mass spectrometer using direct insertion probe (DIP), electron impact (EI) (70 eV).

*4.1.1. (E)-Pent-3-enyl 4-methylbenzenesulfonate (**9**).* To a stirred solution of **8** (3 mL, 28.2 mmol) in Et_2O (40 mL) was added Lithium aluminum hydride (1.68 g, 42.1 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was quenched with sequentially addition of water (1.7 mL), 10% NaOH solution (3.4 mL), and water (5.1 mL). The slurry was filtered and the inorganic salts were washed with Et_2O (10 mL×3). The filtrate was concentrated to afford alcohol, which was used without purification.

To a solution of alcohol in CH_2Cl_2 (40 mL) cooled at 0 °C was added triethylamine (7.9 mL, 56.4 mmol) and 4-toluenesulfonyl chloride (10.8 g, 56.4 mmol). The reaction mixture was stirred for overnight at room temperature. The resulting was quenched with saturated NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (20 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (Et_2O/Pentane=1/20) to yield tosylate **9** (5.3 g, 78.2%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=7.9 Hz, 2H), 5.46 (ddt, *J*=15.3, 6.4, 1.4 Hz, 1H), 5.28–5.18 (m, 1H), 3.99 (t, *J*=6.9 Hz, 2H), 2.43 (s, 3H), 2.29 (dt, *J*=6.9, 1.3 Hz, 2H), 1.59 (dq, *J*=6.4, 1.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.6, 133.2, 129.7, 129.0, 127.9, 124.7, 70.0, 32.1, 21.6, 17.9; High resolution mass (ESI): Calculated for $C_{12}H_{16}O_3S$ $[M+Na]^+$: 263.0752, found: 263.0718.

*4.1.2. (E)-Hex-4-enoic acid (**10**).* To a suspension of sodium hydride (34 mg, 60% dispersion in mineral oil, 0.86 mmol) in THF (3 mL) was added diethyl malonate (151 μL, 0.99 mmol) at 0 °C. After stirring for 15 min, tosylate **9** (158 mg, 0.66 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for overnight. The resulting was quenched with NH_4Cl solution (3 mL) and extracted with EtOAc (3 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane=1:20) to yield malonate ester (174.3 mg, 89%).

To a stirred solution of malonate (4.7 g, 20.7 mmol) in methanol (70 mL) was added KOH (2.9 g, 51.7 mmol) and heated to 60 °C for 12 h. Reaction was quenched with HCl solution (10 mL) and extracted with EtOAc (10 mL×3) and followed by dehydration by $MgSO_4$. After solvent was removed by evaporation, DMSO (60 mL) was added and flask was heated to 140 °C for 12 h. Reaction was quenched with NH_4Cl solution (20 mL) and extracted with Et_2O (20×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in reduced pressure, and the residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2=1:30) to yield **10** (2.2 g, 83%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.52–5.31 (m, 2H), 2.34 (q, *J*=7.6 Hz, 2H), 2.13–1.98 (m, 2H), 1.74–1.56 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 130.0, 126.1, 33.1, 31.8, 24.4, 17.9; High resolution mass (ESI): Calculated for $C_7H_{12}O_2$ $[M+K]^+$: 167.0469, found: 167.0430.

*4.1.3. (R,E)-4-Benzyl-3-hept-5-enoyloxazolidin-2-one (**11**).* To a stirred solution of acid **10** (45.6 mg, 0.36 mmol) and triethylamine (60 μL, 0.43 mmol) in THF (2 mL) was added pivaloyl chloride (46 μL, 0.37 mmol) at −78 °C. After the resultant white suspension was stirred for 10 min at −78 °C and 30 min at 0 °C, it was cooled to −78 °C then to it a solution of lithiated oxazolidinone, which was prepared by the addition of *n*-BuLi (156 μL, 0.39 mmol) to a −78 °C to oxazolidone **13** (70 mg, 0.39 mmol) in THF (1 mL) was added via cannula. The reaction mixture was stirred for an additional 30 min at 0 °C and then quenched by addition of aqueous NH_4Cl solution (1 mL). The residue was extracted with CH_2Cl_2 (2 mL×3) and the organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo and further purified by flash column chromatography on silica gel (EtOAc/hexane=1:5) to yield **11** (82.9 mg, 81%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35–7.28 (m, 2H), 7.28–7.25 (m, 1H), 7.22–7.17 (m, 2H), 5.51–5.35 (m, 2H), 4.72–4.62 (m, 1H), 4.21–4.10 (m, 2H), 3.25 (ddd, *J*=25.2, 13.3, 3.4 Hz, 1H), 2.91 (ddd, *J*=11.5, 8.1, 6.8 Hz, 2H), 2.74 (dd, *J*=13.3, 9.6 Hz, 1H), 2.11–2.02 (m, 2H), 1.74 (d, *J*=2.9 Hz, 2H), 1.68–1.59 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 153.4, 135.3, 130.3, 129.4, 129.0, 127.3, 125.9, 66.2, 55.2, 38.0, 34.9, 31.9, 24.1, 18.0.; High resolution mass (ESI): Calculated for $C_{17}H_{21}NO_3$ $[M+Na]^+$: 310.1414, found: 310.1421.

*4.1.4. (R)-4-Benzyl-3-((R,E)-2-methylhept-5-enoyl)oxazolidin-2-one (**12**).* To a stirred solution of **11** (3 g, 10.7 mmol) in THF (40 mL) was added sodium bis(trimethylsilyl)amide (14 mL, 1 M solution in THF, 13.9 mmol) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was treated with methyl iodide (3.4 mL, 53.7 mmol) and stirred for 1 h at −78 °C. The resulting was quenched with NH_4Cl solution (10 mL) and extracted with EtOAc (10 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane=1:5) to yield **12** (2.8 g, 85%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35–7.16 (m, 5H), 5.47–5.30 (m, 2H), 4.70–4.61 (m, 1H), 4.22–4.10 (m, 2H), 3.71 (dt, *J*=13.6, 6.5 Hz, 1H), 3.23 (td, *J*=12.6, 11.9, 3.3 Hz, 1H), 2.75 (ddd, *J*=13.3, 9.6, 3.3 Hz, 1H), 2.11–1.93 (m, 2H), 1.89–1.77 (m, 1H), 1.63–1.55 (m, 3H), 1.45 (ddt, *J*=13.4, 8.5, 6.4 Hz, 1H), 1.21 (td, *J*=7.1, 0.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 152.9, 135.3, 130.5, 129.4, 128.9, 127.3, 125.4, 65.9, 55.3, 37.9, 37.1, 33.1, 30.3, 17.8, 17.4; High resolution mass (ESI): Calculated for $C_{18}H_{23}NO_3$ $[M+Na]^+$: 324.1570, found: 324.1569.

*4.1.5. (5R,E)-1-(tert-Butyldimethylsilyloxy)-2,2,5-trimethyldec-8-en-4-ol (**15**).* To a stirred solution of **12** (73 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added diisobutylaluminum hydride solution 1 M in CH_2Cl_2 (0.5 mL, 0.48 mmol) was added dropwise at −78 °C. After 40 min, saturated aqueous NH_4Cl solution (2 mL) was added and extracted with Et_2O (2 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated with reduced pressure, and the residue was purified by flash column chromatography on silica gel (Et_2O/pentane=1:20) to yield volatile aldehyde **5** (19.5 mg, 64%).

To Li wire (343 mg, 49.5 mmol) in Et_2O (18 mL) was added (3-bromo-2,2-dimethylpropoxy) (*tert*-butyl) dimethyl silane

(4.15 g, 14.1 mmol) in Et_2O (7.5 mL). The reaction mixture was stirred for 40 min. The Li solution was added to a solution of aldehyde **5** (891 mg, 7.1 mmol) in Et_2O (30 mL) at −30 °C. The resulting was quenched with saturated NH_4Cl solution (5 mL) and extracted with Et_2O (5 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane=1:20) to yield alcohol **15** (1.36 g, 56%), which were used for the next step; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.45–5.33 (m, 2H), 3.85–3.61 (m, 1H), 3.60 (s, 1H), 3.43–3.31 (m, 2H), 2.15–1.99 (m, 1H), 1.99–1.86 (m, 1H), 1.60 (ddt, *J*=11.2, 5.7, 1.1 Hz, 3H), 1.58–1.50 (m, 1H), 1.49–1.32 (m, 2H), 1.33–1.23 (m, 1H), 1.14 (m, 1H), 0.89 (d, *J*=0.6 Hz, 9H), 0.87–0.85 (m, 6H), 0.85–0.82 (m, 3H), 0.05 (d, *J*=1.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8, 124.5, 71.8, 70.8, 45.1, 39.1, 34.9, 32.5, 30.6, 27.8, 25.9, 23.5, 18.3, 17.9, 14.2, −5.5; High resolution mass (ESI): Calculated for $C_{19}H_{40}O_2Si$ $[M+Na]^+$: 351.2690, found:351.2686.

*4.1.6. (R,E)-1-(tert-Butyldimethylsilyloxy)-2,2,5-trimethyldec-8-en-4-one (**16**).* To a solution of oxalyl chloride (22.2 μL, 0.25 mmol) in CH_2Cl_2 (0.5 mL) cooled at −78 °C was added diemthylsulfoxide (27.0 μL, 0.38 mmol) dropwise. The reaction mixture was stirred for 10 min and a solution of alcohol (41.7 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was added by cannula. After the solution was stirred for 15 min, triethylamine (70.8 μL, 0.51 mmol) was added, and the reaction mixture was stirred for 10 min and then allowed to warm to room temperature. The resulting was quenched with saturated NH_4Cl solution (1 mL) and extracted with CH_2Cl_2 (2 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo the residue was purified by flash column chromatography on silica gel (EtOAc/hexane=1:30) to yield **16** (32.1 mg, 78%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.38 (tt, *J*=15.5, 8.5 Hz, 2H), 3.33 (d, *J*=1.6 Hz, 2H), 1.95 (dq, *J*=27.2, 7.9, 6.7 Hz, 2H), 1.68 (d, *J*=6.9 Hz, 1H), 1.36–1.22 (m, 2H) 2.54–2.37 (m, 2H), 1.63–1.55 (m, 3H), 1.01 (dd, *J*=8.6, 7.0 Hz, 3H), 0.93 (s, 6H), 0.87 (t, *J*=1.2 Hz, 9H), 0.05 to −0.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.5, 130.7, 125.4, 71.0, 48.1, 46.7, 35.7, 32.6, 30.2, 25.9, 24.5, 24.4, 18.3, 17.9, 16.0, −5.5; High resolution mass (ESI): Calculated for $C_{19}H_{38}O_2Si$ $[M+Na]^+$: 349.2533, found: 349.2572; $[\alpha]_D^{26}$ −22.8 (*c* 0.3, $CHCl_3$).

*4.1.7. (R)-8,8-Dibromo-2,6-dimethyloct-2-ene (**18**).* To a stirred solution of triphenylphosphite ($P(OPh)_3$; 4.9 mL, 18.3 mmol) in dry CH_2Cl_2 (200 mL) maintained at −78 °C was added bromine (Br_2; 0.8 mL, 15.8 mmol) dropwise. Then, freshly distilled triethylamine (5.4 mL, 38.7 mmol) and **7** (2.5 mL, 13.1 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature and stirred for 1.5 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography silica gel (hexane) to give *gem*-dibromide **18** (2.64 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.72 (dd, *J*=5.8, 8.4 Hz, 1H), 5.08 (tdq, *J*=7.2, 3.0,1.5 Hz, 1H), 2.43 (ddd, *J*=14.2, 8.5, 5.5 Hz, 1H), 2.20 (ddd, *J*=14.3, 8.0, 5.8 Hz, 1H), 2.12–1.89 (m, 2H), 1.82–1.72 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.36 (dddd, *J*=13.3, 9.2, 6.4, 5.4 Hz, 1H), 1.21 ppm (dddd, *J*=13.6, 9.2, 7.7,6.2 Hz, 1H), 0.92 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=131.9, 124.2, 52.9, 45.1, 36.3, 32.3, 25.9, 25.3, 18.6, 17.9; High Resolution MS (EI): Calculated for $C_{10}H_{18}Br_2$: 295.9775, found: 295.9773; $[\alpha]_D^{32.2}$ −13.7 (*c* 1.3, $CHCl_3$).

*4.1.8. (R)-6,6-Dibromo-4-methylhexanal (**19**).* A solution of **18** (3.46 g, 11.6 mmol) in CH_2Cl_2 (58 mL) at −78 °C was purged with ozone for 20 min. Then, dimethyl sulfide (SMe_2, 4.3 mL, 58.1 mmol) was added and the reaction mixture was allowed to warm up to room temperature with stirring for 1 h. The mixture diluted with CH_2Cl_2 (30 mL) and saturated NH_4Cl solution (40 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (20 mL×3). Combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel (ethyl acetate/hexane=1:10) to afford aldehyde **19** (1.89 g, 94.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.77 (t, *J*=1.5 Hz, 1H), 5.69 (dd, *J*=5.7, 8.5 Hz, 1H), 2.46 (dtd, *J*=1.6, 6.3, 8.6 Hz, 2H), 2.40 (ddd, *J*=5.4, 8.5, 14.8 Hz, 1H), 2.22 (ddd, *J*=5.7, 7.9, 14.6 Hz, 1H), 1.87–1.60 (m, 2H), 1.57–1.40 (m, 1H), 0.91 ppm (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 52.4, 44.0, 41.2, 32.1, 27.8, 18.3; High Resolution MS (EI): Calculated for $C_7H_{12}Br_2O$: 269.9255, found: 269.9210; $[\alpha]_D^{18.9}$ −8.4 (*c* 1.3, $CHCl_3$).

*4.1.9. (R,E)-8,8-Dibromo-6-methyloct-2-ene (**20**).* 1.0 M solution of potassium hexamethyldisilazide in THF (KHMDS; 10.4 mL, 10.4 mmol) was added at −78 °C over 90 min (syringe pump) to a solution of 5-ethanesulfonyl-1-phenyl-1*H*-tetrazole **21** (2.2 g, 9.2 mmol) and aldehyde **19** (1.9 g, 7.0 mmol) in THF (22 mL) and the mixture was kept for a further 30 min at this temperature. Water was added (5 mL) and the mixture was allowed to warm to room temperature. Additional water (20 mL) and Et_2O (20 mL) were added. The ethereal phase was washed with water (30 mL×3). The aqueous phase was extracted with Et_2O (30 mL×3) and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane) to afford **20** (1.6 g, 80%; *E*/*Z* 85:15); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.70 (ddd, *J*=8.5, 5.7, 2.6 Hz, 1H), 5.49–5.30 (m, 2H), 2.42 (ddt, *J*=14.2, 8.5, 5.3 Hz, 1H), 2.24–2.14 (m, 1H), 2.10–1.90 (m, 2H), 1.81–1.70 (m, 1H), 1.66–1.58 (m, 3H), 1.42–1.31 (m, 1H), 1.21 (dddd, *J*=13.6, 9.3, 7.8, 6.1 Hz, 1H), 0.90 ppm (dd, *J*=8.8, 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=130.8, 125.2, 52.7, 44.8, 35.9, 32.0, 29.6, 18.4, 17.9; High resolution mass (EI): Calculated for $C_9H_{16}Br_2$: 281.9619, found: 281.9621; $[\alpha]_D^{24.3}$ −14.8 (*c* 0.2, $CHCl_3$).

*4.1.10. (R,E)-4-Methylnon-7-en-2-yn-1-ol (**6**).* To a solution of **20** (829.0 mg, 2.0 mmol) in dry petroleum ether (4.5 mL) were added *t*-BuOK (1.0 g, 8.7 mmol) and 18-crown-6 (38.5 mg, 0.1 mmol). The mixture was stirred at 80 °C for 12 h under argon. Water was added to quench the reaction when the mixture was cooled to room temperature, and organic phase was separated and dried over $MgSO_4$, filtered, and concentrated in vacuo (water-pump) carefully to give the alkyne as colorless liquid, which could be directly used in next step. To a stirred solution of the alkyne in THF (3.0 mL) at −78 °C was added 2.24 M solution of *n*-BuLi in hexane (1.3 mL, 2.9 mmol) dropwise over 10 min. The solution was stirred for 1 h, paraformaldehyde (95.8 mg, 3.0 mmol) in THF (1.0 mL) was added by cannula stirred for additional 2 h at −78 °C, and solution was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with saturated NH_4Cl (2 mL). The aqueous phase was extracted with Et_2O (2 mL×3) and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo (water-pump) carefully, and the residue was purified by column chromatography on silica gel (Et_2O/pentane=1:5) to afford propargyl alcohol **6** (230 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.48–5.32 (m, 2H), 4.24 (dd, *J*=5.8, 2.1 Hz, 2H), 2.49–2.39 (m, 1H), 2.18–1.99 (m, 2H), 1.64–1.59 (m, 3H), 1.51–1.37 (m, 2H), 1.14 ppm (dd, *J*=6.9, 5.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.6, 125.4, 90.7, 78.6, 51.4, 36.6, 30.3, 25.3, 20.9, 17.9 ppm; High resolution mass (ESI): Calculated for $C_{10}H_{16}O$ $[M+Na]^+$: 175.1098, Found 175.1062; $[\alpha]_D^{28.6}$ −53.6 (*c* 0.6, $CHCl_3$).

*4.1.11. (R,E)-4-Methylnon-7-en-2-ynyl 4-methylbenzenesulfonate (**22**).* A solution of propargyl alcohol **6** (197 mg, 1.2 mmol) in dry CH_2Cl_2 (2.5 mL) at 0 °C was treated with triethylamine (Et_3N; 330 μL, 2.4 mmol), *p*-toluensulfonic anhydride (Ts_2O; 718.6 mg, 2.1 mmol), and catalytic dimethylaminopyridine (DMAP; 18 mg, 0.1 mmol). The reaction was warmed to room temperature for 12 h,

and the solution was washed with water (2 mL) and brine (2 mL). The aqueous layer was extracted with dichloromethane (2 mL×3). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel (ethyl acetate/hexane=1:20) to afford tosylate **22** (276 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.79 (d, J=8.3 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H), 5.46–5.24 (m, 2H), 4.70 (d, J=2.1 Hz, 2H), 2.42 (s, 3H), 2.36–2.23 (m, 1H), 1.95 (ddt, J=17.7, 13.9, 7.1 Hz, 2H), 1.65–1.54 (m, 3H), 1.32 (qd, J=7.6, 3.3 Hz, 2H), 1.00 ppm (dd, J=6.9, 3.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 133.5, 130.3, 129.7, 128.1, 125.5, 94.5, 72.2, 58.8, 36.1, 30.1, 25.2, 21.6, 20.3, 17.9 ppm; $[\alpha]_D^{33.0}$ −32.8 (c 1.1, $CHCl_3$).

*4.1.12. (R,E)-tert-Butyldimethyl (2,2,5-trimethyl-4-vinylidenedec-8-enyloxy) silane (**23**).* To Li wire (82.3 mg, 11.9 mmol) in dry Et_2O (4 mL) was added 3-(*tert*-butyldimethylsilyloxy)-2,2-dimethylpropan-1-ol (474 mg, 1.7 mmol) in Et_2O (2 mL). The reaction mixture was stirred for 40 min. This solution of the lithiated reagent was cooled to −78 °C, and was added dropwise via syringe pump to a suspension of copper(I) cyanide (CuCN; 121.4 mg, 1.4 mmol) in Et_2O (3.4 mL). The mixture was stirred for 2 min, warmed to 0 °C for 15 min, and recooled to −78 °C. Tosylate **22** (207.6 mg, 0.7 mmol) in Et_2O (1 mL) was added dropwise via cannula and resulting mixture was allowed to stir at −78 °C for 1 h. The reaction mixture was warmed to 0 °C for 10 min then quenched with saturated NH_4Cl solution (3 mL) and extracted with Et_2O (3 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (hexane) to afford allene **23** (245 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.39 (dq, J=4.9, 2.2 Hz, 2H), 4.62 (dq, J=4.4, 2.2 Hz, 2H), 3.25 (d, J=2.1 Hz, 2H), 2.05–1.92 (m, 2H), 1.91–1.84 (m, 3H), 1.64–1.57 (m, 3H), 1.48 (ddt, J=13.6, 8.6, 6.8 Hz, 1H), 1.31–1.17 (m, 1H), 0.97 (dd, J=8.5, 6.8 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 6H), −0.00 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.1, 131.6, 124.6, 105.3, 75.9, 71.2, 39.4, 37.3, 36.6, 35.8, 30.5, 25.9, 24.4, 19.6, 18.3, 17.9, −5.5 ppm; High resolution mass (ESI): Calculated for $C_{21}H_{40}OSi$ $[M+Na]^+$: 359.2746, found: 359.2787; $[\alpha]_D^{26.8}$ −21.8 (c 0.5, $CHCl_3$).

4.1.13. (R,E)-2,2,5-Trimethyl-4-vinylidenedec-8-en-1-ol. To a stirred solution of allene **23** (235 mg, 0.7 mmol) in THF (2.5 mL) was added 1.0 M solution of tetrabutylammoniumfluoride in THF (TBAF; 2.1 mL, 2.1 mmol) at room temperature. After stirring for 5 h, the reaction was quenched with saturated NH_4Cl (2 mL). The aqueous phase was extracted with Et_2O (2 mL×3) and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (ethyl acetate/hexane=1:10) to afford the alcohol (144 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42–5.33 (m, 2H), 4.67–4.66 (m, 2H), 3.33 (s, 2H), 1.97–1.81 (m, 5H), 1.68 (s, 1H), 1.61–1.60 (dd, J=3.4 Hz, J=1.0 Hz, 3H), 1.53–1.44 (m, 1H), 1.30–1.20 (m, 1H), 0.98–0.96 (d, J=6.8 Hz, 3H), 0.89 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.8, 131.4, 124.7, 105.2, 76.3, 71.1, 39.4, 37.0, 36.8, 35.7, 30.3, 24.5, 19.5, 17.9 ppm; High resolution mass (ESI): Calculated for $C_{15}H_{26}O$ $[M+Na]^+$: 245.1881, found: 245.1845; $[\alpha]_D^{30.6}$ −31.6 (c 0.4, $CHCl_3$).

*4.1.14. (E)-2,2,5-Trimethyl-4-vinylidenenedec-8-enal (**24**).* To a solution of oxalyl chloride (79 μL, 0.90 mmol) in CH_2Cl_2 (2 mL) cooled at −78 °C was added dimethylsulfoxide (DMSO; 97 μL, 1.35 mmol) dropwise. The reaction mixture was stirred for 10 min and a solution of the alcohol from 4.1.7 (100 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was added by cannula. After the solution was stirred for 15 min, triethylamine (Et_3N; 251 μL, 1.8 mmol) was added, and the reaction mixture was stirred for 10 min and then allowed to warm to room temperature. The reaction was quenched with saturated NH_4Cl solution (2 mL) and extracted with CH_2Cl_2 (2 mL×3). The organic layer were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane=1:10) to afford aldehyde **24** (96 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.51–9.50 (d, J=2.5 Hz, 1H), 5.41–5.31 (m, 2H), 4.67–4.65 (m, 2H), 2.16–2.15 (t, J=3.0 Hz, 2H), 1.95–1.89 (m, 2H), 1.84–1.79 (m, 1H), 1.61–1.60 (d, J=4.3 Hz, 3H), 1.50–1.41 (m, 1H), 1.29–1.20 (m, 1H), 1.07 (s, 6H) 0.96–0.95 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 206.0, 131.2, 124.8, 104.2, 78.2, 46.3, 38.8, 36.5, 35.3, 30.2, 22.1, 22.1, 19.2, 17.9 ppm; High resolution mass (ESI): Calculated for $C_{15}H_{24}O$ $[M+Na]^+$: 243.1724, found: 243.1713; $[\alpha]_D^{23}$ −30.3 (c 0.3, $CHCl_3$).

*4.1.15. Preparation of the compounds **26** and **26′** from **24**.* To a stirred solution of aldehyde **24** (35 mg, 0.16 mmol) in MeOH (2 mL) was added *p*-toluenesulfonhydrazide (H_2NNHTs; 35 mg, 0.18 mmol) at 0 °C. The reaction mixture was allowed to room temperature and stirred for 2 h. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane=1/4) to afford the *N*-tosyl hydrazone. To a suspension of sodium hydride (7.6 mg, 60% dispersion in mineral oil, 0.19 mmol) in benzene (10 mL) was added a solution of *N*-tosyl hydrazone (61 mg, 0.16 mmol) in benzene (6 mL) at 0 °C. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature. The reaction was quenched with saturated NH_4Cl solution (5 mL) and extracted with Et_2O (5 mL×3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (pentane) to produce a mixture of the angularly triquinanes. A solution of the angular triquinanes, pyridine (39 μL, 0.48 mmol), and selenium dioxide (SeO_2; 27 mg, 0.48 mmol) in benzene (2 mL) was refluxed for 3 h. The mixture was diluted with Et_2O and filtered through a Celite pad, and then the pad was washed with Et_2O. The filtrate and washings were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether=1:4) to afford angularly fused triquinane **26** (12.3 mg, 35%) and **26′** (1.8 mg, 5%). **26**; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.26–5.25 (d, J=2.1 Hz, 1H), 4.71–4.68 (dd, J=8.4 Hz, J=2.0 Hz, 1H), 2.04–2.01 (d, J=13.2 Hz, 1H), 2.00–1.94 (m, 1H), 1.92–1.82 (m, 2H), 1.76–1.71 (m, 1H), 1.61–1.58 (m, 1H), 1.48–1.41 (m, 2H), 1.34–1.19 (m, 2H), 1.11 (s, 3H), 1.09 (s, 3H), 0.95–0.94 (d, J=7.0 Hz, 3H) 0.86–0.84 ppm (d, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2, 129.1, 71.5, 64.1, 57.9, 49.3, 48.7, 47.1, 42.1, 36.0, 32.0, 31.7, 28.6, 17.3, 14.9; High resolution mass (ESI): Calculated for $C_{15}H_{24}NaO$ $[M+Na]^+$: 243.1724, found: 243.1709; $[\alpha]_D^{26.1}$ −6.8 (c 0.1, $CHCl_3$).; **26′**; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.30 (d, J=2.1 Hz, 1H), 4.51 (dd, J=8.5, 1.9 Hz, 1H), 1.92 (d, J=13.0 Hz, 1H), 1.90–1.81 (m, 2H), 1.78–1.66 (m, 3H), 1.45–1.39 (m, 2H), 1.22–1.16 (m, 2H), 1.13 (s, 3H), 1.07 (s, 3H), 0.91 (d, J=7.1 Hz, 3H), 0.84 (d, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ=152.8, 130.4, 72.8, 63.2, 58.6, 58.4, 48.3, 46.3, 45.4, 35.8, 33.1, 32.0, 28.7, 15.4, 15.2; High resolution mass (ESI): Calculated for $C_{15}H_{24}NaO$ $[M+Na]^+$: 243.1724, found: 243.1709; $[\alpha]_D^{27.2}$ −44.7 (c 0.03, $CHCl_3$).

4.1.16. (3aR,4S,5S,5aS,8R,81S)-2,2,5,8-Tetramethyl decahydro cyclopentapentalen-4-ol. A solution of allylic alcohol **26** (6.7 mg, 0.03 mmol) in absolute ethanol (1 mL) with catalytic amount of platinum oxide (PtO_2; 0.7 mg, 10 mol %) was stirred under an atmosphere of hydrogen for 12 h. The catalyst was removed by filtration and the solvent was evaporated to give the crude product, which was purified using flash column chromatography on silica gel (ethyl acetate/hexane=1:10) to afford corresponding alcohol (6.5 mg, 97%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.93–3.91 (t, J=5.2 Hz, 1H) 2.29–2.24 (m, 1H), 1.84–1.63 (m, 7H), 1.49–1.45 (d, J=13.3 Hz, 2H), 1.35–1.28 (m, 2H), 1.21–1.16 (m, 1H), 1.06 (s, 3H), 1.02–1.00 (d, J=7 Hz, 3H), 0.99 (3H, s), 0.87–0.85 ppm (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.2, 65.8, 58.2, 57.2, 48.7, 48.4, 42.5, 41.2, 40.2,

33.8, 30.9, 30.7, 28.4, 17.3, 14.2; High resolution mass (ESI): Calculated for $C_{15}H_{24}O$ $[M+Na]^+$: 243.1725, found: 243.1699; $[\alpha]_D^{25.0}$ +6.2 (*c* 0.05, $CHCl_3$).

*4.1.17. (+)-Pentalenene (**1**).* A solution of the alcohol from 4.1.10 (6 mg, 0.0270 mmol) and *p*-toluenesulfonic acid (TsOH; ca. 0.5 mg) in dry C_6H_6 (2 mL) was heated at reflux for 3 h while part of the solvent was allowed to distilled off. The cooled solution was poured into a saturated $NaHCO_3$ solution, and this was extracted with Et_2O (2 mL×3). The combined solution was dried over $MgSO_4$ and the solvent was removed under carefully controlled vacuum to provide crude product, which was purified using flash column chromatography on silica gel (pentane) to afford (+)-pentalenene **1** (5 mg, 91%); ^1H NMR (400 MHz, $CDCl_3$): δ=5.13 (br s, 1H), 2.66–2.62 (m, 1H), 2.54–2.51 (br d, *J*=9.2 Hz, 1H), 1.82–1.70 (m, 3H), 1.58–1.54 (m, 1H), 1.60 (s, 3H), 1.35–1.21 (m 4H), 1.18–1.13 (dd, *J*=12.5 Hz, *J*=5.1 Hz, 1H), 0.96 (s, 3H), 0.96 (s, 3H), 0.89–0.87 ppm (d, *J*=7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.6, 130.0, 64.7, 62.0, 59.3, 48.9, 46.8, 44.6, 40.5, 33.5, 29.9, 29.1, 27.6, 17.0, 15.5 ppm; IR (neat, cm^{-1}): 3027, 1465, 1377; High Resolution MS (EI): Calculated for $C_{15}H_{24}$: 204.1878; Found: 204.1874; $[\alpha]_D^{26.6}$ +11.7 (*c* 0.07, $CHCl_3$).

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