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Application of the Chemo- and Enantioselective Cyclopropanation of Polyenes to the Total Synthesis of (+)-Bicyclohumulenone.

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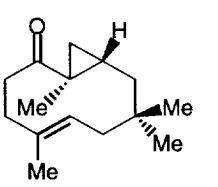
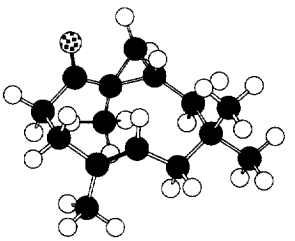
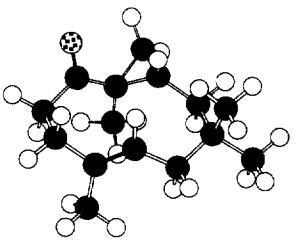
Abstract: The chemo- and enantioselective cyclopropanation of a monoprotected bis(allylic alcohol) using a chiral dioxaborolane-derived ligand and $Zn(CH_2I)_2$ was used as a key step in the total synthesis of (+)-bicyclohumulenone. The synthesis of this important perfume component was efficiently accomplished in 16 steps from diethyl 3,3-dimethylglutarate in 9% overall yield.

(+)-Bicyclohumulenone (**1**) is a novel humulane-type sesquiterpene that was isolated in 1979 by Matsuo and coworkers from the liverwort, *Plagiochila siophila*.[1] This novel skeleton, displaying a unique cyclodecenone ring fused with a cyclopropane has attracted some attention in the past few years. For example, its unique wood-like aroma reminiscent of the odors of vetiver, patchouli, cedar wood, and other related fragrances, has made it an attractive compound in the perfume industry.[2]



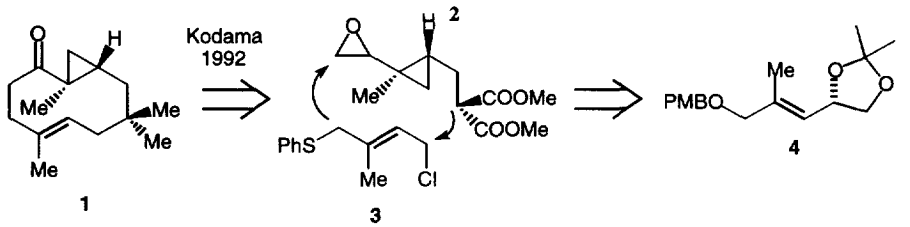
(+)-Bicyclohumulenone (**1**)





Two racemic and one enantioselective syntheses have been reported thus far. The racemic syntheses relied on a biomimetic transannular cyclization of humulene 9,10-epoxide[3] or on a stereoselective cyclopropanation of a 10-membered macrocyclic enone.[4] The only enantioselective synthesis was reported in 1992 by Kodama.[5] The macrocyclic ring closure was achieved by an intramolecular epoxide opening reaction with the α-sulfenyl carbanion (Scheme 1). The macrocyclization precursor was obtained by the alkylation of the substituted malonate derivative **2** and chloride **3**. The synthesis of the chiral cyclopropane in **2** was elaborated by the diastereoselective cyclopropanation of the protected allylic alcohol **4** which is readily available from 1,2-*O*-isopropylidene glyceraldehyde. The total synthesis was achieved in 18 steps from the protected glyceraldehyde.

Scheme 1

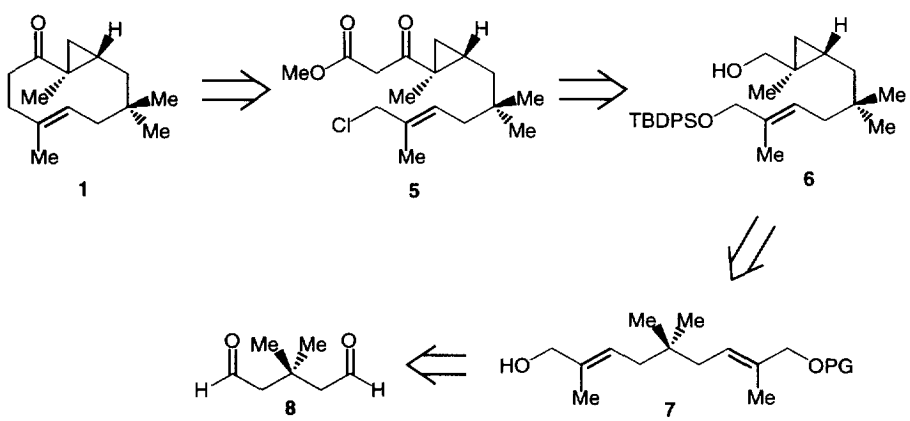


In this paper, we report an efficient total synthesis of (+)-bicyclohumulenone that relies on a bidirectional chain synthesis[6] of the 10-membered ring precursor and on a chemo- and an enantioselective cyclopropanation of a monoprotected bis(allylic alcohol).

Retrosynthetic analysis

Our retrosynthetic analysis is shown in Scheme 2. We elected to close the macrocyclic ketone by an intramolecular alkylation of the β-ketoester enolate derived from chloride **5**. This chloride was further simplified by dismantling into **6**, which could be derived from a chemo- and enantioselective cyclopropanation[7] of the monoprotected bis(allylic alcohol) **7** using the chiral dioxaborolane ligand developed in our laboratories. The corresponding diol could be elaborated from dialdehyde **8** by a bidirectional chain synthesis.

Scheme 2

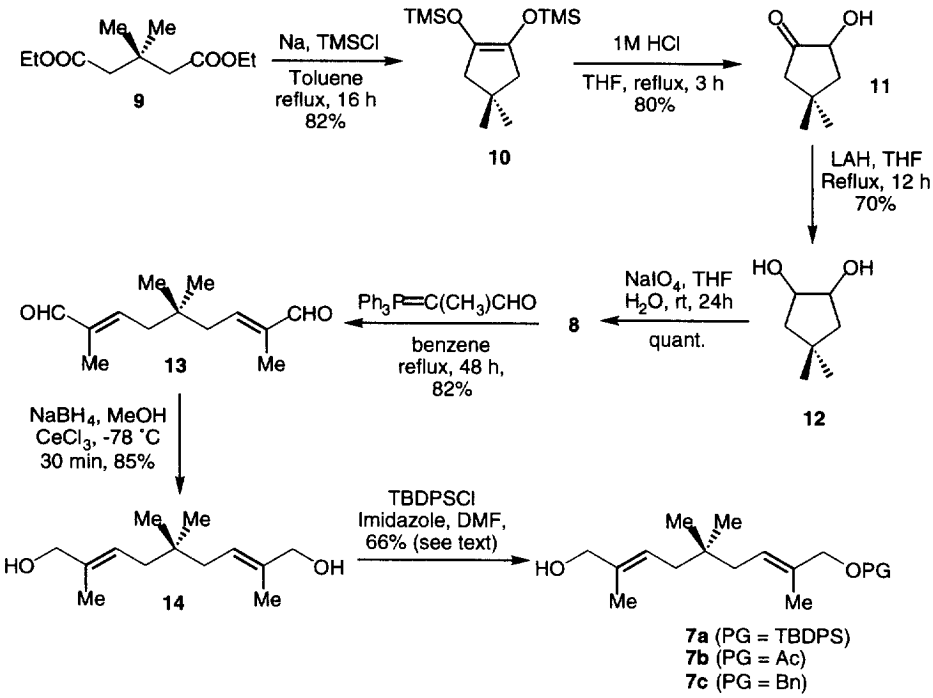


Synthesis of the monoprotected diol 7

At the outset of this project, we felt that 3,3-dimethylglutaraldehyde could be easily prepared from the diester **9**. However, all our attempts to convert diethyl glutarate to the corresponding dialdehyde **8** failed under a variety of reducing conditions. The longer, but more reliable synthesis of 3,3-dimethylglutaraldehyde (**8**) reported by Fraenkel was used.[8] Diethyl glutarate was converted to the bis TMS protected α-hydroxy enol ether by the acyloin condensation in 82% yield. Hydrolysis followed by LAH reduction and oxidative cleavage of the diol produced the requisite dialdehyde. Dialdehyde **8** was

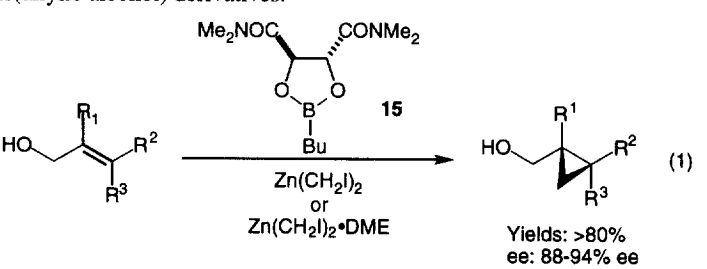
submitted to the double olefination reaction using excess (triphenylphosphoranylidene)propionaldehyde[9] to produce (*E*,*E*)-dialdehyde **13** as a single olefinic isomer in 82% yield.[10] Double Luche reduction[11] produced the required diol **14** in 85% yield. The monoprotection as a TBDPS ether[12] was accomplished in 50% yield and the remaining unreacted diol was recycled to produce an additional 16% of the desired alcohol **7a**.

Scheme 3



Chemo- and enantioselective cyclopropanation of alcohol 15

With monoprotected diol **7a** in hand, the chemo- and enantioselective cyclopropanation reaction could be performed. At the outset of this project, it was not clear whether or not, the enantioselective cyclopropanation of allylic alcohols developed in our laboratories (eq 1)[13] could be applied to monoprotected bis(allylic alcohol) derivatives.



It is well-established that basic groups such as alcohols, zinc alkoxides, or ethers can exert a strong directing effect in the iodomethylzinc-derived cyclopropanation reaction.[14] However, our initial fear was that the two oxygenated groups could possibly compete for reagent complexation and delivery giving a non-chemoselective reaction (Figure 1).

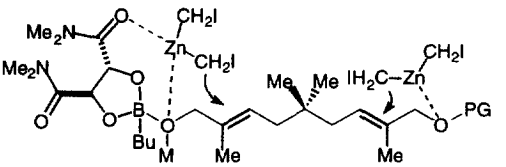
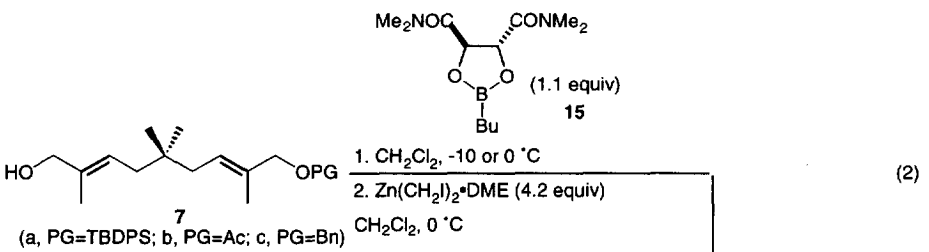


Figure 1

Several substrates with different protecting groups were prepared and were submitted to the asymmetric cyclopropanation conditions to test the feasibility of this transformation.

The monoacetate derivative, the monobenzyl ether, and the mono-TBDPS ether were all prepared under standard conditions and were treated with 1.0 equiv of the chiral dioxaborolane ligand **15** and excess bis(iodomethyl)zinc. Quite surprisingly, all three compounds reacted smoothly with the zinc reagent to produce quantitative conversion to the monocyclopropane derivative. The enantiomeric excesses were measured by ^{1}H NMR of their corresponding Mosher's ester derivatives and were determined to be 85-87%. The high chemoselectivity is probably a reflection of the much greater basicity of the amide group (in **15**) compare to that of the ether oxygen of **7**.



PG	Conversion	Ratio mono:bis	ee
R = TBDPS (**6a,7a**)	>95%	>20 : 1	87%
R = Ac (**6b,7b**)	>95%	>20 : 1	85%
R = Bn (**6c,7c**)	>95%	>20 : 1	86%

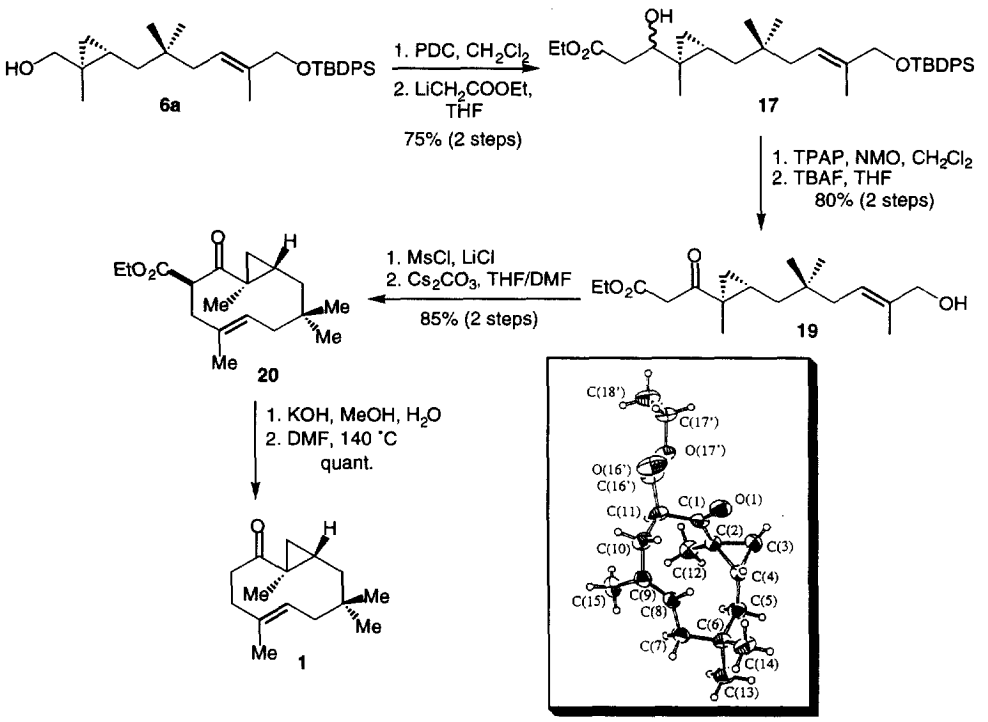
For compatibility reasons, the synthesis of (+)-bicyclohumulenone was then pursued with the TBDPS ether derivative **6a**.

Completion of the synthesis of (+)-Bicyclohumulenone

With compound **6a** in hand, the synthesis of the macrocyclization precursor could be tackled. PDC oxidation of the cyclopropylmethanol derivative produced aldehyde **16** which was treated with the anion derived from ethyl acetate to afford the β-hydroxyester **17** as a 1:1 mixture of diastereomers in 75%

overall yield for the 2 steps. Oxidation using Ley's reagent[15] followed by desilylation using tetrabutylammonium fluoride afforded the desired alcohol **19** in 80% yield. Conversion of the allylic alcohol into the corresponding chloride **5** was accomplished with MsCl and LiCl. The macrocyclization was smoothly achieved under high dilution conditions (4 x 10^{-3}M) using Cs_2CO_3[16] as the base in a mixture of THF/DMF to produce **20** in a satisfying 85% yield for the two steps. This material crystallized nicely from chloroform to give single crystals suitable for X-ray crystallographic analysis. The X-ray crystal structure of **20**, shown in Scheme 4, unambiguously confirmed the stereochemistry of the cyclopropanation reaction. The synthesis of (+)-bicyclohumulenone was then completed by a 2-step decarboxylation sequence of the ester side-chain. Saponification and thermal decarboxylation of the potassium carboxylate produced (+)-bicyclohumulenone in quantitative yield. The synthetic material was identical in all respects (^{1}H, ^{13}C NMR, IR, mp, MS) to authentic material. The $[\alpha]_D$ of the synthetic material was found to be +50.5° (*c* 0.83, $CHCl_3$) which correlates well with Kodama's value (+43.8°)[5] or with natural bicyclohumulenone (+60.0°).[1]

Scheme 4



In conclusion, the enantioselective synthesis of (+)-bicyclohumulenone was efficiently accomplished in 16 steps and 9% overall yield from commercially available ethyl 3,3-dimethylglutarate.

Experimental section

(2*E*,7*E*)-2,5,5,8-Tetramethyl-nona-2,7-dien-1,9-dial (13): To a solution of 3,3-dimethylpentanedial **8** (3.1 g, 24 mmol) in benzene (400 mL) was added the 2-(triphenylphosphoranylidene)propionaldehyde (28 g, 80 mmol). The mixture was heated under reflux for 24 h. The solvent was then removed under reduced pressure and the product was purified by flash chromatography (20% EtOAc/hexanes) to afford the desired dialdehyde **13** (4.1 g, 82%) as a colorless oil: R_f 0.31 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 2H, C*H*O), 6.40 (t, *J* = 7.7 Hz, 2H, C*H*=C), 2.15 (d, *J* = 7.7 Hz, 4H, CH_2CH=), 1.52 (s, 6H, CH_3C=), 0.84 (s, 6H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 150.2, 140.8, 40.8, 35.5, 26.6, 9.2.

(2*E*,7*E*)-2,5,5,8-Tetramethyl-nona-2,7- dien-1,9-diol (14): To a solution of dialdehyde **13** (2.9 g, 14 mmol) in CH_3OH (50 mL) at -78 °C was added $CeCl_3$•$7H_2O$ (8.4 g, 30 mmol). The reaction was stirred for 15 min and $NaBH_4$ (2.1 g, 56 mmol) was slowly added in small portions and the resulting mixture was stirred at -78 °C for 30 min. The reaction was diluted with EtOAc and quenched with water. The organic layer was washed with 10% aq. HCl, sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% EtOAc/hexanes) to produce the desired diol **14** (2.5 g, 85%) as a colorless oil: R_f 0.24 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (t, *J* = 6.5 Hz, 2H, C*H*=C), 3.96 (s, 4H, CH_2OH), 2.58 (bs, 2H, O*H*), 1.91 (d, *J* = 6.5 Hz, 4H, CH_2CH=), 1.60 (s, 6H, CH_3C=), 0.85 (s, 6H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 122.7, 68.8, 39.6, 35.0, 26.9, 13.7; IR (neat) 3380, 3000-2900, 1770, 1750, 1700 1010 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{23}O_2$ (M^+-H): 235.1698, found 235.1690.

(2*E*,7*E*)-2,5,5,8-Tetramethyl-9-(*t*-butyldiphenylsilyloxy)-2,7-nonadien-1-ol (7a): To a solution of diol **14** (1.0 g, 4.7 mmol) in anhydrous DMF (50 mL) was added imidazole (400 mg, 5.9 mmol) and TBDPSCl (1.25 mL, 4.7 mmol). The reaction mixture was stirred at rt for 45 min and then diluted with EtOAc. The organic layer was washed with 10% aq. HCl, sat. aq. $NaHCO_3$, and sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford the monoprotected diol **7a** (1.0 g, 50%). The remaining diol was resubmitted to these conditions to produce an additional 16% of the desired monosilyl ether **7a**: R_f 0.33 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.71 (m, 4H, C$H_{arom.}$), 7.45-7.37 (m, 6H, C$H_{arom.}$), 5.61 (t, *J* = 6.5 Hz, 1H, C*H*=C), 5.53 (t, *J* = 6.5 Hz, 1H, C*H*=C), 4.12 (s, 2H, CH_2OSi), 4.05 (s, 2H, CH_2OH), 2.00 (d, *J* = 6.5 Hz, 4H, C=CCH_2), 1.68 (s, 3H, CH_3C=C), 1.62 (s, 3H, CH_3C=C), 1.10 (s, 9H, *t*-Bu), 0.92 (s, 6H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 135.3, 134.9, 133.9, 129.5, 127.6, 123.0, 120.9, 69.2, 69.0, 39.6, 39.5, 35.3, 26.9, 26.8, 26.6, 19.3, 13.9, 13.7; IR (neat) 3400, 3110-3090, 3000-2900, 1765 cm^{-1}.

(+)-(2*S*,3*S*,7*E*)-2,5,5,8-Tetramethyl-2,3-methano-9-(*t*-butyldiphenylsilyloxy)-7-nonen-1-ol (6a): To a solution of DME (500 μL, 4.9 mmol) and Et_2Zn (500 μL, 4.9 mmol) in anhydrous CH_2Cl_2 at 0 °C was slowly added CH_2I_2 (780 μL, 9.8 mmol). The reaction was stirred at 0 °C for 15 min and at rt for an additional 30 min. This homogenous solution was slowly added to a preformed solution containing the allylic alcohol **7a** (350 mg, 1.28 mmol) and the (*R*,*R*)-dioxaborolane **15**[13] (520 mg, 1.16 mmol) in CH_2Cl_2 (8 mL) that was precooled to 0 °C. The reaction was warmed to rt and stirred for 1 h. The reaction was

diluted with EtOAc and quenched with sat. aq. NH_4Cl. The organic layer was washed with 10% aq. HCl, 2.5 M aq. NaOH, sat. aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was then purified by flash chromatography (20% EtOAc/hexanes) to produce the desired alcohol **6a** (470 mg, 88%). A small sample was converted into its Mosher's ester[17] and it was shown to be 87% ee by integration of the signals at 4.01 ppm (major) and 3.94 ppm (minor) (400 MHz, C_6D_6): R_f 0.33 (20% EtOAc/hexanes); $[\alpha]_D$ + 8.3° (*c* 2.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.71 (m, 4H, $CH_{arom.}$), 7.47-7.37 (m, 6H, CH_{arom}), 5.61 (t, *J* = 7.7 Hz, 1H, C*H*=C), 4.12 (s, 2H, CH_2OSi), 3.42 (d *J* = 11 Hz, 1H, CH_2OH), 3.34 (d, *J* = 11 Hz, 1H, CH_2OH), 2.04 (d, *J* = 7.7 Hz, 2H, CH_2C=), 1.63 (s, 3H, CH_3C=), 1.52-1.46 (m, 2H, $CH_2C_{cyclopropyl}$), 1.14 (s, 3H, $CH_3C_{cyclopropyl}$), 1.10 (s, 9H, *t*-Bu), 0.963 (s, 3H, $(CH_3)_2C$), 0.965 (s, 3H, $CH_3)_2C$), 0.69-0.60 (m, 2H, $CH_{cyclopropyl}$), 0.01 (t, *J* = 4 Hz, 1H, $CH_{cyclopropyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.2, 133.9, 129.5, 127.6, 121.0, 72.6, 69.0, 40.7, 39.7, 34.8, 26.99, 26.95, 26.8, 21.3, 19.3, 17.5, 17.3, 15.6, 13.7; IR (Film) 3350 (br), 3060, 3040, 2960, 2920, 2840, 1420, 1100 cm^{-1}; HRMS calcd for $C_{30}H_{44}O_2Si$ (M^+-H): 463.3032., found: 463.3055.

(2*S*,3*S*,7*E*)-2,5,5,8-Tetramethyl-2,3-methano-9-(*t*-butyldiphenylsilyloxy)-7-nonen-1-al (16): To a solution of alcohol **6a** (1.0 g, 2.15 mmol) in anhydrous CH_2Cl_2 (22 mL) was added 4 Å molecular sieves (1.16 g), Celite (1.16 g) and PDC (1.16 g, 3.2 mmol). The reaction was stirred at rt for 16 h. The mixture was then filtered through celite and the clear solution was concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/hexanes) to produce the aldehyde **16** as a colorless oil (990 mg, 100%): R_f 0.52 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H, C*H*O), 7.71-7.66 (m, 4H, CH_{arom}), 7.45-7.36 (m, 6H, CH_{arom}), 5.60-5.56 (t, *J* = 7.7 Hz, 1H, C*H*=C), 4.09 (s, 2H, CH_2OR), 2.05 (d, *J* = 7.7 Hz, 2H, CH_2CH=), 1.59 (s, 3H, CH_3C=), 1.50 (m, 2H, $CH_2CH_{cyclopropyl}$), 1.35 (m, 1H, $CH_{cyclopropyl}$), 1.15 (m, 1H, $CH_{cyclopropyl}$), 1.21 (s, 3H, $CH_3C_{cyclopropyl}$), 1.07 (s, 9H, *t* -Bu), 0.96 (s, 3H, $(CH_3)_2C$), 0.95 (s, 3H, $(CH_3)_2C$), 0.64 (dd, *J* = 5.6, 3.6 Hz, 1H, $CH_{cyclopropyl}$); ^{13}C NMR ($CDCl_3$) δ 202.7, 135.57, 135.54, 133.8, 129.5, 127.5, 120.2, 68.8, 39.7, 39.6, 34.7, 31.0, 27.0, 26.9, 26.8, 20.9, 20.8, 19.2, 13.7, 11.2.

Ethyl (3*R*,4*S*,5*S*,9*E*)- and (3*S*,4*S*,5*S*,9*E*)-3-hydroxy-4,7,7,10-tetramethyl-4,5-methano-11-(*t*-butyldiphenylsilyloxy)-9-nonenoate (17): To a solution of diisopropylamine (800 μL, 5.7 mmol) in anhydrous THF (20 mL) at -78 °C was added BuLi (2.75 mL, 6.88 mmol, 2.5M in hexanes). The reaction was warmed to 0 °C for 15 min and then recooled to -78 °C. To the LDA solution at -78 °C was added EtOAc (500 μL, 5.12 mmol). The mixture was warmed to 0 °C, stirred for 1 h and this enolate solution was added to a solution of aldehyde **16** (800 mg, 1.73 mmol) in THF (15 mL) at -78 °C. The reaction was stirred at -78 °C for 15 min after which time it was diluted with EtOAc and quenched with sat. aq. NH_4Cl. The organic layer was washed with 10% aq. HCl, sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford the desired alcohol **17** (700 mg, 75 %) as a 1 : 1 mixture of diastereoisomers. (3*S*)-**17**:[18] R_f0.29 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.71 (m, 4H, $CH_{arom.}$), 7.46-7.36 (m, 6H, $CH_{arom.}$), 5.61 (t, *J* = 6.8 Hz, 1H, C*H* =C), 4.18 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.12 (s, 2H, CH_2OSi), 3.31 (dd, *J* = 9.5, 3.5 Hz, 1H, $CH_2CH(OH)$), 2.50 (dd, *J* = 15.8, 9.4 Hz, 1H, $CH_2CH(OH)$), 2.50 (dd, *J* = 15.8, 3.5 Hz, 1H, $CH_2CH(OH)$), 2.04 (d, *J* = 7.6 Hz, 2H, CH_2CH=), 1.62 (s,

3H, CH_3C=), 1.49 (dd, J = 13.9, 4.3 Hz, 1H, $CH_2CH_{cyclopropyl}$), 1.29 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.31-1.25 (m, 1H, $CH_2CH_{cyclopropyl}$), 1.10 (s, 9H, t-Bu), 1.05 (s, 3H, $CH_3C_{cyclopropyl}$), 0.95 (s, 3H, $(CH_3)_2C$), 0.94 (s, 3H, $(CH_3)_2C$), 0.74 (dd, J = 8.8, 4.2 Hz, 1H, $CH_{cyclopropyl}$), 0.67 (m, 1H, $CH_{cyclopropyl}$), 0.08 (t, J = 5 Hz, 1H, $CH_{cyclopropyl}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 135.5, 135.2, 133.9, 129.5, 127.6, 120.8, 76.1, 68.9, 60.6, 40.4, 39.7, 38.8, 34.7, 27.04, 26.97, 26.8, 22.7, 19.6, 19.2, 16.8, 14.1, 13.7, 12.4; IR (neat) 3500, 1730 cm^{-1}.

(3*R*)-**17**: R_f 0.38 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.70 (m, 4H, $CH_{arom.}$), 7.46-7.36 (m, 6H, $CH_{arom.}$), 5.60 (t, J = 6.7 Hz, 1H, CH_2CH =), 4.18 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.11 (s, 2H, CH_2OSi), 3.37 (dd, J = 8.2, 4.6 Hz, 1H, $CH_2CH(OH)$), 2.59-2.56 (m, 2H, $CH_2CH(OH)$), 2.05-2.02 (m, 2H, CH_2CH=), 1.62 (s, 3H, CH_3C=), 1.51 (dd, J = 13.9, 4.9 Hz, 1H, $CH_2C_{cyclopropyl}$), 1.29 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.35-1.25 (m, 1H, $CH_2C_{cyclopropyl}$), 1.08 (s, 9H, t-Bu), 1.03 (s, 3H, $CH_3C_{cyclopropyl}$), 0.96 (s, 3H, $(CH_3)_2C$), 0.95 (s, 3H, $(CH_3)_2C$), 0.88 (m, 1H, $CH_{cyclopropyl}$), 0.63 (dd, J = 8.8, 4.4 Hz, 1H, $CH_{cycloproyl}$), -0.03 (dd, J = 5.4, 4.8 Hz, 1 H, $CH_{cyclopropyl}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 135.5, 135.1, 134.0, 129.5, 127.5, 121.0, 76.1, 69.0, 60.6, 40.9, 39.7, 38.7, 34.8, 26.9, 26.9, 26.8, 22.6, 19.2, 19.0, 17.3, 14.0, 13.7, 12.6; IR (neat) 3500, 1730 cm^{-1}.

Ethyl (4*S*,5*S*,9*E*)-3-oxo-4,7,7,10-tetramethyl-4,5-methano-11-(*t*-butyldiphenylsilyloxy)-9-nonenoate (18): To a solution of alcohols **17** (374 mg, 0.68 mmol) in CH_2Cl_2 (1.36 mL) was added molecular sieves 4 Å (340 mg), NMO (120 mg, 1.02 mmol) and TPAP (12 mg, 0.034 mmol). The heterogeneous mixture was stirred vigourously at rt for 30 min and filtered through Celite. The organic layer was concentrated under reduced pressure and purified by flash chromatography (20% EtOAc/hexanes) to produce the β-keto ester **18** (300 mg, 80%) as a colorless oil: R_f 0.46 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.68 (m, 4H, $CH_{arom.}$), 7.46-7.35 (m, 6H, $CH_{arom.}$), 5.57 (t, J = 6.5 Hz, 1H, CH_2CH=), 4.20 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.09 (s, 2H, CH_2OSi), 3.53 (d, J = 14 Hz, 2H, $C(O)CH_2C(O)$), 3.48 (d, J = 14 Hz, 2H, $C(O)CH_2C(O)$), 2.0 (d, J =7.5 Hz, 2H, CH_2CH=), 1.59 (s, 3H, CH_3C=), 1.42-1.30 (m, 1H, $CH_{cyclopropyl}$), 1.32 (s, 3H, $CH_3C_{cyclopropyl}$), 1.28 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.07 (s, 9H, t-Bu), 1.06-0.87 (m, 1H, $CH_{cyclopropyl}$), 0.94 (s, 3H, $(CH_3)_2C$), 0.93 (s, 3 H, $(CH_3)_2C$), 0.5 (dd, J = 6.5, 3.8 Hz, 1H, $CH_{cyclopropyl}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 167.6, 135.6, 135.5, 133.8, 129.5, 127.6, 120.4, 68.9, 61.1, 45.8, 40.5, 39.6, 34.8, 30.3, 26.9, 26.9, 26.8, 26.1, 25.6, 19.3, 14.5, 14.1, 13.7; IR (neat) 2980-2870, 1750, 1700 cm^{-1}.

Ethyl (4*S*,5*S*,9*E*)-3-oxo-4,7,7,10-tetramethyl-4,5-methano-11-hydroxy-9-nonenoate (19): To a solution of silyl ether **18** (580 mg, 1.06 mmol) in THF (10 mL) was added TBAF (1.6 mL, 1.6 mmol, 1.0 M in THF). The reaction was stirred at rt for 5 h and diluted with EtOAc. The organic layer was washed with 10% aq. HCl, sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by flash chromatography (50% EtOAc/hexanes) afforded the desired alcohol **19** (326 mg, 100%) as a colorless oil: R_f 0.37 (50% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (t, J = 6.3 Hz, 1H, CH_2CH=), 4.16 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.99 (s, 2H, CH_2OH), 3.47 (s, 2H, $C(O)CH_2C(O)$), 1.97 (d, J = 7.5 Hz, 2H, CH_2CH=), 1.90 (bs, 1H, OH), 1.62 (s, 3H, CH_3C=), 1.54-1.49 (m, 2H, $CH_2CH_{cyclopropyl}$), 1.44-1.39 (m, 1H, $CH_{cyclopropyl}$), 1.30 (s, 3H, $CH_3C_{cyclopropyl}$), 1.24 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.05 (dd, J = 13.6, 8.2 Hz, 1H, $CH_{cyclopropyl}$),

0.9 (s, 6H, $(CH_3)_2C$), 0.46 (dd, J = 6.8, 3.8 Hz, 1H, $CH_{cyclopropyl}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 167.6, 136.4, 122.2, 68.9, 61.2, 45.7, 40.5, 39.7, 34.6, 30.3, 26.9, 26.8, 26.1, 25.6, 14.5, 14.0, 13.8; IR (neat) 3450, 2960-2880, 1740, 1680 cm^{-1}. HRMS calcd for $C_{18}H_{31}O_4$ (M^++H): 311.2222, found: 311.2236.

(1*S*,3*R*,5*E*,10*S*)-3-Carbethoxy-1,5,8,8-tetramethylbicyclo[8. 1. 0]-5-undecen-2-one (20): To a solution of allylic alcohol **19** (75 mg, 0.24 mmol) in DMF (400 μL) was added *sym*-collidine (38 μL, 0.29 mmol) and LiCl (12 mg, 0.29 mmol). The reaction was cooled to 0 °C and MsCl (28 μL, 0.36 mmol) was added. The mixture was stirred at 0 °C for 3 h and then EtOAc was added. The organic layer was washed with H_2O, sat. aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to produce the allylic chloride that was used directly in the next step. A solution of the crude allylic chloride in THF (7.5 mL) was added to a solution of Cs_2CO_3 (469 mg, 1.44 mmol) in a mixture of DMF (30 mL) and THF (22.5 mL) at 75 °C over 4 h. After the addition was completed, the mixture was heated under reflux for an additional 2 h. The reaction was cooled to rt and diluted with ether. The organic layer was washed successively with H_2O, sat. aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. A subsequent purification by flash chromatography (10% EtOAc/hexanes) afforded the macrocyclic ketoester **20** (60 mg, 85%) as a colorless oil that crystallized from $CDCl_3$ to give crystals suitable for X-ray crystallographic analysis: R_f 0.43 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (d, J = 10.4 Hz, 1H, CH_2CH=), 4.20-4.10 (m, 3H, $CO_2CH_2CH_3$, C(O)CHC(O)), 2.44 (d, J = 7.5 Hz, 2H, CH_2CH=), 2.10 (dd, J = 15, 10.5 Hz, 1H, CH_2C=), 1.89-1.85 (m, 2H), 1.76 (s, 3H, CH_3C=), 1.48 (dd, J = 13.8, 1.9 Hz, 1H, CH_2CH=), 1.24 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.23 (s, 3H, $(CH_3)C_{cyclopropyl}$), 1.16-1.04 (m, 2H, $CH_{cyclopropyl}$), 1.08 (s, 3H, $(CH_3)_2C$), 0.97 (s, 3H, $(CH_3)_2C$), 0.38 (t, J = 3.5 Hz, 1H, $CH_{cyclopropyl}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 170.1, 127.7, 127.0, 60.9, 52.5, 41.7, 40.9, 39.3, 34.6, 34.4, 33.7, 33.8, 26.4, 24.9, 17.4, 16.3, 14.0; IR (neat) 3000-2900, 1750, 1690 cm^{-1}; HRMS calcd for $C_{18}H_{29}O_3$ (M^++H): 293.2117, found: 293.2129.

(+)-Bicyclohumulenone (1): To the β-ketoester **20** (34 mg, 0.12 mmol) in a mixture of H_2O (0.22 mL) and CH_3OH (0.44 mL) was added KOH (6 mg, 0.24 mmol). The reaction was stirred at rt for 1 h. The mixture was then diluted with DMF (6 mL) and heated at 140 °C for 30 min. The reaction was then cooled to rt and diluted with EtOAc. The organic layer was washed with 10% aq. HCl, sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes) to produce the (+)-bicyclohumulenone (**1**) as a white solid (25 mg, 100%): mp 75-76 °C (lit.:[1] 76 °C); R_f 0.47 (20% EtOAc/hexanes); $[\alpha]_D$ + 50.5° (*c* 0.83, $CHCl_3$), lit.[1] $[\alpha]_D$ + 60.0° ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, J = 10.7 Hz, 1H, CH_2CH=), 3.13 (m, 1H, $CH_2C(O)$), 2.27-2.06 (m, 4H, $CH_2C(O)$, CH_2C=), 1.87-1.78 (m, 2H, CH_2), 1.75 (s, 3H, CH_3C=), 1.47 (dd, J = 14, 1.9 Hz, 1H, CH_2), 1.17 (s, 3H, $CH_3C_{cyclopropyl}$), 1.13- 1.00 (m, 2H, $CH_{cyclopropyl}$), 1.08 (s, 3H, $(CH_3)_2C$), 0.97 (s, 3H, $(CH_3)_2C$), 0.26 (dd, J = 7.2, 3.3 Hz, 1H, $CH_{cyclopropyl}$); ^{13}C NMR ($CDCl_3$) δ 215.7, 130.1, 125.3, 40.8, 39.4, 39.5, 38.5, 34.5, 34.3, 33.8, 32.3, 25.4, 24.9, 17.1, 16.6.

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