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First Total Synthesis and Assignment of the Stereochemistry of Crispatenine

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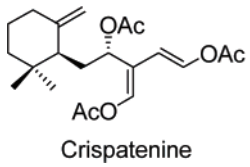
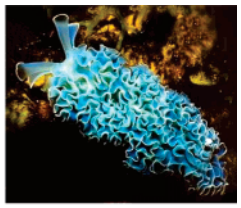


Crispatenine



The first racemic and enantioselective synthesis of crispatenine **1** has been achieved, which involved a few steps, enabling the assignment of the absolute and relative configurations.

Introduction

Marine algae of the order Caulerpales are known for their chemical defense against predators by producing secondary metabolites. The majority of these often acyclic compounds are sesquiterpenoids and diterpenoids. The terminal 1,4-diacetoxybutadiene moiety is a functional group common to most of these metabolites. Nowadays, more than 30 toxins with this moiety have been isolated from the Udoteaceae and Caulerpaceae families such as caulerpenyne **A** and dihydrorhipocephaline **B** (Figure 1).[1] The 1,4-diacetoxybutadiene moiety represents an acetylated bis-enol form of the 1,4-dialdehyde system, to which a high degree of biological activity is generally attributed. Indeed, some of the metabolites containing this moiety have been implicated in chemical defense against grazing fishes and invertebrates in herbivore-rich tropical waters,[2] and this has, for example, been proposed to explain the proliferation from Italy to Spain of *Caulerpa taxifolia* a tropical green seaweed accidentally introduced in the Mediterranean sea.

Chemical studies from different Caribbean areas on *Tridachia* (= *Elysia*) *crispata* led to describe a series of polypropionates most likely biosynthesized *de novo* and accordingly to successful experiments with the Mediterranean *Elysia viridis*[3] and the Pacific *Placobranchus ocellatus*.[4] Surprisingly, Venezualan specimens of *Elysia crispata*, which average four times larger than the Mexican individuals, contain crispatenine **1**,[5] a sesquiterpene, possessing a 1,4-diacetoxybutadiene moiety, isomer of a metabolite **C** isolated from the alga *Caulerpa ashmedii*[6] and onchidal **D**, together (Figure 1) with the typical polypropionate metabolites. Crispatenine **1** could be envisaged as the masked form of the aldehyde onchidal **D**, analogously with caulerpenyne **A**, the protected form of the more reactive oxytoxin-1 **E**. Interestingly, the co-occurrence in a population of a *Elysia crispata* from Venezuela of both crispatenine **1** and onchidal **D** (caulerpa-derived metabolites), in addition to several polypropionates, is intriguing because two different metabolite pathways (biosynthesis of polypropionates and biotransformation of dietary sesquiterpenoid) seem to be active and could be considered as the conjunction between different groups of sacoglossans displaying different secondary metabolite pathways.[7]

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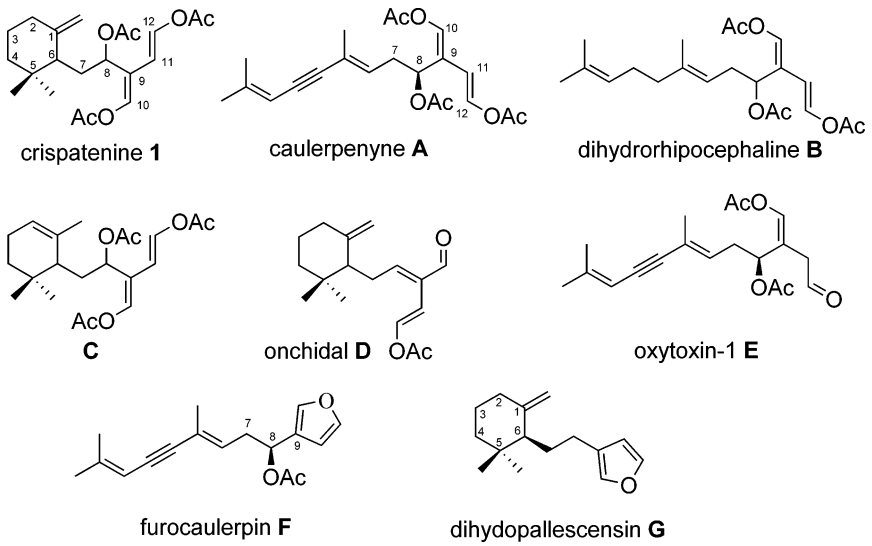

FIGURE 1. Examples of terpenoid natural product.

To our knowledge, no synthetic route toward **1** has yet been published, and although the structure of **1** was confidently elucidated by NMR, mass, IR, and UV spectroscopies, the absolute and relative configurations of crispatenine **1** remain unknown.

Consequently, in order to continue our efforts in the synthesis of terpenoids possessing a terminal 1,4-diacetoxybutadiene moiety[8] and to provide material for more extensive biological evaluation toward, for example, the tubulin network, along with access to novel analogues, we have undertaken total synthesis of crispatenine **1**. It was envisaged that an enantioselective synthesis starting from a well chosen chiral building block would allow us to determinate the absolute and relative configuration of the two stereocenters.

Results and Discussion

Racemic Synthesis. In order to validate our chosen synthetic route, a racemic synthesis was first chosen. The main structural features of **1** are a terminal 1,4-diacetoxybutadiene moiety, an exocyclic double bond, and two unknown chiral centers. Our strategy for synthesizing **1** is outlined in the Scheme 1 and called for the initial preparation of two fragments west and east. We considered that the assembly of the complete carbon skeleton of **1** could be obtained through a coupling reaction between the vinylstannane **4** (east fragment) (tin−lithium exchange) derived from butynediol and the aldehyde **3** (west fragment).

Synthesis of the key vinyl fragment **4** (Scheme 2) began by a palladium-catalyzed hydrostannation[9] of but-2-yn-1,4-diol, giving the (*E*)-vinyltin reagent **5**, in which the more accessible alcohol function could be selectively protected as the *tert*-butyldimethylsilyl ether in 64% yield over two steps.[10]

Synthesis of the known western fragment **3** was achieved using Matsui's procedure over four steps from methylcyclohexanone (Scheme 2).[11] First, methylcyclohexanone was converted into hydroxymethylene cyclohexanone **6** by an improved method of Bailey's procedure. The crude alcohol **6** was next converted into the vinyl ether **7**. Reduction of crude ether **7** using sodium borohydride followed by acidic treatment yielded an aldehyde which was subjected to another reduction with sodium borohydride to give the desired alcohol **8** in 36% yield from methylcyclohexanone. Finally a Claisen reaction at 220 °C in the presence of ethyl vinyl ether and pivalic acid gave γ-homocyclogeranial **3** in 49% yield (18% over four steps).

The construction of the core carbon framework was next achieved through coupling of the two fragments **4** and γ-homocyclogeranial (±)-**3** (Scheme 3). The coupling reaction between west segment (±)-**3** and the carbanion generated by the tin−lithium exchange reaction on the east fragment **4** gave a 1/1 mixture of (±)-**9** and (±)-**9′** in moderate yield (58%), which could be separated by flash chromatography on silica gel. An X-ray crystal structure of (±)-**9**,[12] the first diastereoisomer eluted from flash chromatography, allowed us to attribute the (*S*,*S*) or (*R*,*R*) configuration (Figure 2). The stereochemistry of some natural products, isolated from Caulerpa algae (with or without the 1,4-diacetoxybutadiene moiety) have been previously reported. For example, the (8*S*) configuration was assigned for caulerpenyne **A**[13] and furocaulerpin **F** (Figure 1).[14]

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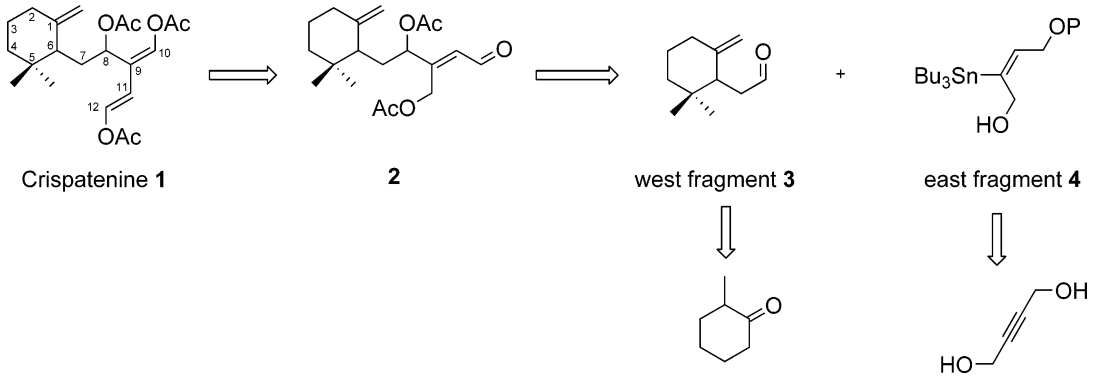
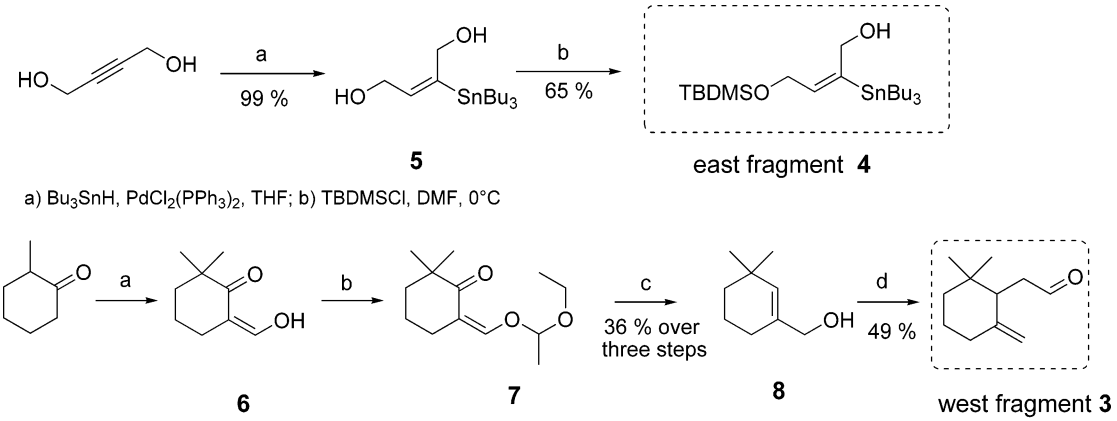
SCHEME 1. Retrosynthetic Scheme of (±)-Crispatenine 1



SCHEME 2. Synthesis of East and West Fragments



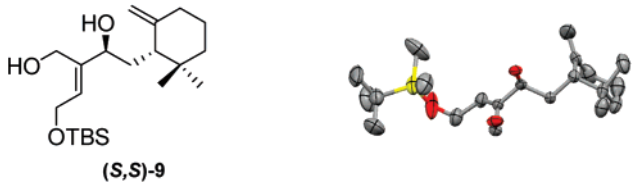


FIGURE 2. X-ray structure of (±)-**9**.

Moreover, dihydopallescensin **G** (Figure 1),[15] which has the same cyclic structure as crispatenine and a furan ring, and which can arise from hydrolysis of the diacetoxybutadiene moiety, has a stereocenter with a (6*S*) configuration. By analogy with these examples of natural products, we can propose that the configurations of the two chiral centers of **1** are (6*S*) and (8*S*).

Consequently, we decided to pursue the synthesis of (±)-**1** from the diol (±)-**9** (Scheme 3). Esterification of diol (±)-**9** using standard conditions afforded diacetate (±)-**10** in 90% yield. Deprotection of the silyl ether function with HF−pyridine[16] furnished the desired alcohol (±)-**11** in 76% yield. Oxidation of the alcohol with Dess−Martin periodinane[17] gave the aldehyde (±)-**2** in 89% yield. In order to complete the synthesis and generate the diacetoxybutadiene moiety, we employed conditions developed in our group[8b] (NEt_3, DMAP, Ac_2O at 80 °C), and the target was obtained in 90% yield as a 47/53 mixture of two racemic diasteromers (±)-**1** and *iso*-(±)-**1**. The data of the synthetic (±)-crispatenine (±)-**1** were in excellent agreement with those reported in the literature which confirms our prediction.[5] Crispatenine isomer **12** was also obtained (63%, over four steps from **9′**) using the same conditions described above.

To confirm without ambiguity the stereochemistry of **1**, we undertook an enantioselective total synthesis of crispatenine **1**.

Enantioselective Synthesis. We chose as our starting point the known Karahana lactone[18] which was readily transformed in four steps into the chiral aldehyde (+)-**3** (Scheme 4).[19] Reduction of the enantiopure Karahana lactone with DIBAL-H gave a mixture of diastereomeric lactols **13** (and the opened aldehydic form) in 95% yield.[20] Exposure of the crude mixture of products **13** to an excess of α-methoxy methyl triphenyl phosphorane[21] afforded **14** as a mixture of stereomers in 82% yield. Barton−McCombie deoxygenation[22] of **14** was achieved *via* the corresponding xanthate, which was reduced smoothly with tri-*n*-butyltin hydride to provide **15** in an overall yield of

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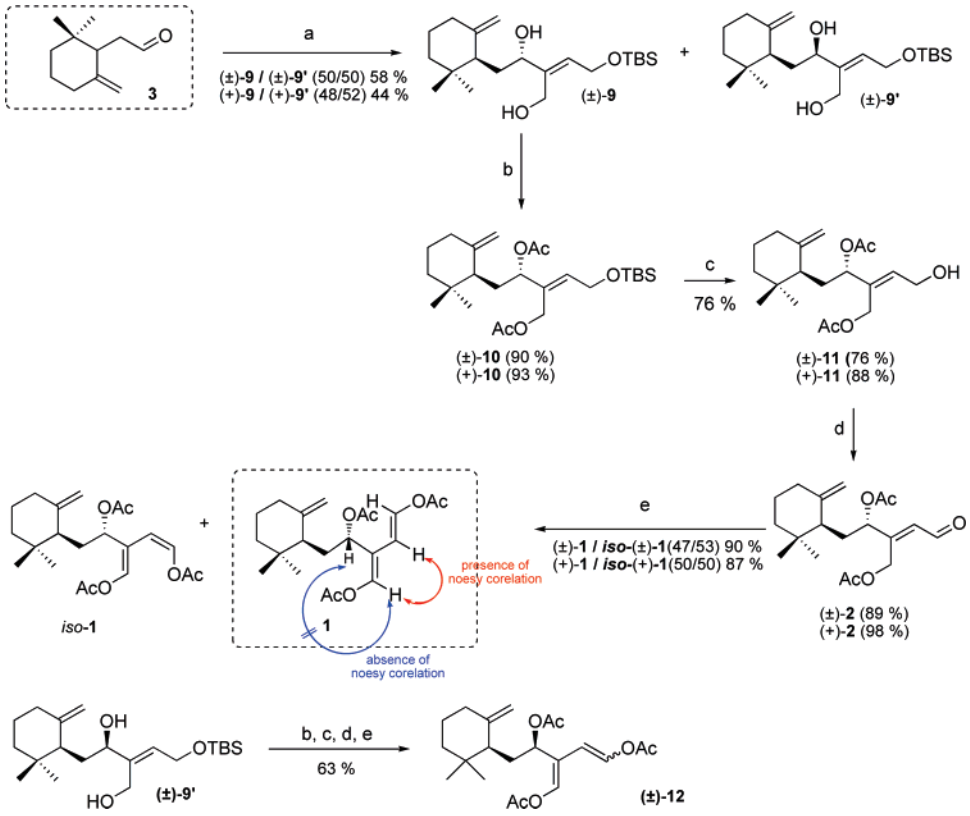
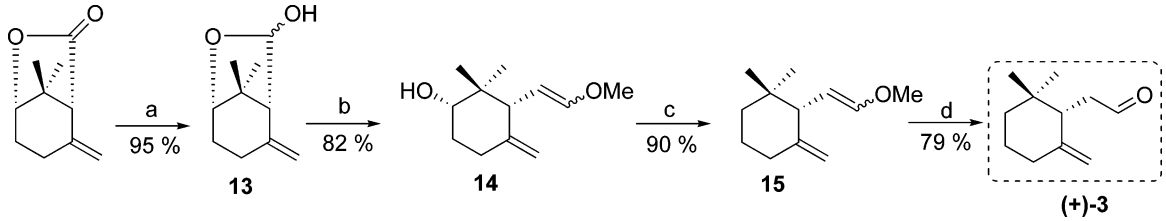
SCHEME 3. Synthesis of 1[a]



[a] (a) (*i*) MeLi.LiBr, (*ii*) 4 −78 °C; (b) Ac_2O, DMAP, pyridine; (c) HF•pyridine, THF; (d) Dess−Martin periodinane, CH_2Cl_2; (e) Ac_2O, DMAP, NEt_3, 80 °C.

SCHEME 4. Enantioselective Synthesis of West Fragment (+)-3[a]



[a] (a) DIBAL-H, toluene, 70 °C; (b) $Ph_3P^+CH_2OMeCl^-$, *n*-BuLi, THF, rt; (c) (*i*) NaH, CS_2, MeI, rt, THF; (*ii*) $HSnBu_3$, cat. AIBN, toluene, reflux; (d) 1 M HCl/THF:1/2, rt, THF.

90% for the two steps. Subsequent hydrolysis at 0 °C with 1 M HCl (THF/H_2O) gave γ-homocyclogeranial (+)-**3**, $[\alpha]^{25}_D$ +31 (*c* 1.0, $CHCl_3$)/lit[23] $[\alpha]^{20}_D$ +29.0 (*c* 0.35, CH_2Cl_2), in 79% yield.

With the enantiopure aldehyde (+)-**3** in hand, the synthesis of (+)-crispatenine was achieved following the same synthetic sequence described above. Thus, coupling of the two fragments west and east was achieved *via* the cross-coupling reaction between (+)-**3** and the carbanion generated by tin−lithium exchange reaction on **4**, which gave diol (+)-**9** and (+)-**9′** in moderate yield (44%). At this stage, the two hydroxyl groups of (+)-**9** were protected as acetates, and desilylation of (+)-**10** by the HF−pyridine complex provided (+)-**11**. The primary hydroxyl group was next oxidized by Dess−Martin periodinane, furnishing in 80% yield over three steps the enantiopure aldehyde (+)-**2**. Subjected to a mixture of 3 equiv. of acetic anhydride, 1 equiv. of dimethylaminopyridine, and triethylamine at 80 °C, (+)-**2** led, in 87% yield, to a 1/1 mixture of enantiopure crispatenine (+)-**1** and its isomer *iso*-(+)-**1.** Moreover, the mixture (+)-**1** and *iso*-(+)-**1** could be separated by semipreparative HPLC to give (+)-**1**, *iso*-(+)-**1** in enantiomeric pure form. The specific rotation ($[\alpha]^{20}_D$ +5.2 (*c* 0.5, $CHCl_3$)) was comparable in magnitude and exhibited the same sign as the natural product ($[\alpha]_D$ +5.0 (*c* 2.1, $CHCl_3$)).[5] The configuration of the diacetoxybutadiene moiety and the structure of (+)-**1** were also confirmed by NOESY experiments (Scheme 3). This enantioselective synthesis confirmed our prediction for the absolute configuration of the two chiral centers of **1** and allowed us to firmly assign the absolute configuration of natural crispatenine **1**.

In conclusion, a racemic and an enantioselective synthesis of crispatenine **1** were achieved for the first time with the assignment of the absolute and relative configurations.

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Experimental Section

γ-Homocyclogeranial ((+)-3). To a solution of **15** (200 mg, 1.11 mmol) in THF (13 mL) at 0 °C was added dropwise a 1 M HCl solution (13 mL). The reaction mixture was allowed to warm to rt. After 12 h, the solution was diluted in ether, poured into water, quenched by a saturated solution of $NaHCO_3$, and extracted by ether. The combined organic extracts were washed with water, dried, filtered and concentrated. The residue was purified by flash chromatography (light petroleum−Et_2O, 98/2 to 95/5) to give pure aldehyde (+)-**3** ($[\alpha]^{25}_D$ +31.0 (*c* 1.0, $CHCl_3$)) in 79% yield. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.78 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.25−1.66 (m, 4H, 2 × CH_2), 2.0−2.09 (m, 1H, C*H*$_2$), 2.15−2.23 (m, 1H, C*H*$_2$), 2.41−2.50 (m, 3H, CH_2 and CH), 4.52 (br s, 1H, CH_2), 4.80 (br s, 1H, CH_2), 9.64 (t, 1H, *J* = 2.2 Hz, CH).

2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethylidene]-4-(2,2-dimethyl-6-methylene-cyclohexyl)-butane-1,3-diol ((±)-9 and (±)-9′ or (+)-9 and (+)-9′). To a solution of **(±)-3** or **(+)-3** (800 mg, 1.63 mmol) in THF (25 mL), under argon, at −35 °C, was added dropwise MeLi•LiBr (2.2 M in Et_2O, 1.35 mL, 2.98 mmol). The solution was kept at −35 °C for 2 h, and then **4** (226 mg, 1.36 mmol) was added. The solution was kept at −35 °C for 3 h and quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate, and then the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by flash chromatography (petroleum ether−Et_2O, 7/3 to 1/1) to give a 1/ 1 separated mixture of (±)-**9** and (±)-**9′** in 58% yield or a 48/52 separated mixture of (+)-**9** ($[\alpha]^{22}_D$ +0.8 (*c* 1, $CHCl_3$)) and (+)-**9′** ($[\alpha]^{20}_D$ +41.4 (*c* 3.5, $CHCl_3$)) in 44% yield. (±)-**9** or (+)-**9** was recrystallized in 1/1/1 acetonitrile/Et_2O/pentane. mp = 84 °C (for (±)-**9** and (+)-**9**). **9**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H, 2 × CH_3), 0.83 (s, 3H, CH_3), 0.90 (s, 9H, 3 × CH_3), 0.93 (s, 3H, CH_3), 1.19−1.28 (m, 1H, C*H*$_2$), 1.41−1.43 (m, 1H, C*H*$_2$), 1.45−1.75 (m, 4H, 2 × CH_2), 2.03−2.11 (m, 3H, CH_2 and CH), 2.31 (br s, 1H, OH), 2.95 (s, 1H, OH), 4.11 (br d, 1H, *J* = 9.8 Hz, CH), 4.19 (s, 2H, CH_2), 4.28 (br d, 1H, *J* = 6.0 Hz, CH_2), 4.62 (br s, 1H, CH), 4.82 (br s, 1H, CH), 5.66 (t, 1H, *J* = 6.0 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ - 5.1 (2 × CH_3), 18.4 (C), 23.8 (CH_2), 26.0 (3 × CH_3), 26.4 (CH_3), 28.4 (CH_3), 32.6 (CH_2), 33.1 (CH_2), 34.8 (C), 36.2 (CH_2), 49.9 (CH), 58.9 (CH_2), 59.7 (CH_2), 73.9 (CH), 109.7 (CH_2), 127.6 (CH), 143.7 (C), 149.6 (C); *m*/*z* (ESI+) 386 $[M + NH_4]^+$; HMRS found 369.2820 $[M + H]^+$, $C_{21}H_{41}O_3Si$ requires 369.2819; anal. calcd $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94 found C, 68.39; H, 11.07. **9′**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H, 2 × CH_3), 0.81 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.89 (s, 9H, 3 × CH_3), 1.16−1.24 (m, 1H, C*H*$_2$), 1.39−1.57 (m, 3H, CH_2 and C*H*$_2$), 1.65−1.72 (m, 1H, CH), 1.74−1.84 (m, 2H, CH_2), 1.96−2.03 (m, 1H, C*H*$_2$), 2.14−2.25 (m, 1H, C*H*$_2$), 2.95 (s, 1H, OH), 3.21 (s, 1H, OH), 4.13 (t, 1H, *J* = 6.9 Hz, CH), 4.20 (s, 2H, CH_2), 4.27 (d, 1H, *J* = 6.0 Hz, CH_2), 4.62 (br s, 1H, CH), 4.79 (br s, 1H, CH), 5.60 (t, 1H, *J* = 6.0 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1 (2 × CH_3), 18.4 (C), 23.8 (CH_2), 26.0 (3 × CH_3), 26.2 (CH_3), 28.2 (CH_3), 32.2 (CH_2), 32.8 (CH_2), 35.1 (C), 36.5 (CH_2), 51.2 (CH), 58.2 (CH_2), 59.5 (CH_2), 76.9 (CH), 109.6 (CH_2), 130.4 (CH), 141.0 (C), 150.2 (C); *m*/*z* (ESI+) 386 $[M + NH_4]^+$; HMRS found 369.2810 $[M + H]^+$, $C_{21}H_{41}O_3Si$ requires 369.2819.

Acetic Acid 2-Acetoxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-1-(2,2-dimethyl-6-methylene-cyclohexylmethyl)-but-2-enyl Ester (10). A solution of (±)-**9** or (+)-**9** (105 mg, 0.28 mmol), acetic anhydride (0.11 mL, 1.14 mmol), DMAP (1.7 mg), and pyridine (4 mL) was stirred for 12 h. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with ethyl ether. The combined organic layers were washed with saturated aqueous $CuSO_4$ solution and water, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (petroleum ether−Et_2O, 8/2) to give (±)-**10** in 90% yield or (+)-**10** ($[\alpha]^{22}_D$ +2.0 (*c* 1, $CHCl_3$)) in 93% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H, 2 × CH_3), 0.82 (s, 3H, CH_3), 0.87 (m, 9H, 3 × CH_3), 0.91 (s, 3H, CH_3), 1.17−1.26 (m, 1H, C*H*$_2$), 1.35−1.59 (m, 3H, CH_2 and C*H*$_2$), 1.62−1.67 (m, 1H, C*H*$_2$), 1.75−1.81 (m, 1H, C*H*$_2$), 1.84−1.89 (m, 1H, CH), 1.94−2.09 (m, 2H, CH_2), 2.01 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 4.27 (d, 2H, *J* = 5.8 Hz, CH_2), 4.48 (br s, 1H, CH), 4.56 (d, 1H, *J* = 12.5 Hz, CH), 4.63 (d, 1H, *J* = 12.5 Hz, CH), 4.78 (br s, 1H, CH), 5.02 (br d, 1H, *J* = 10.8 Hz, CH), 5.76 (t, 1H, *J* = 5.8 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ - 5.1 (2 × CH_3), 18.4 (C), 20.9 (CH_3), 21.1 (CH_3), 23.6 (CH_2), 26.0 (3 × CH_3), 26.5 (CH_3), 28.3 (CH_3), 31.8 (CH_2), 32.2 (CH_2), 34.5 (C), 36.0 (CH_2), 50.1 (CH), 59.7 (CH_2), 60.2 (CH_2), 74.2 (CH), 110.2 (CH_2), 132.9 (CH), 134.5 (C), 148.1 (C), 170.3 (C), 170.7 (C); *m*/*z* (ESI+) 470 $[M + NH_4]^+$; HMRS found 470.3296 $[M + NH_4^+]$, $C_{25}H_{48}NO_5Si$ requires 470.3296

Acetic Acid 2-Acetoxymethyl-1-(2,2-dimethyl-6-methylene-cyclohexylmethyl)-4-hydroxy-but-2-enyl Ester (11) To a solution of (±)-**10** or (+)-**10** (105 mg, 0.23 mmol) in THF (3.5 mL) was added an excess of HF•pyridine (0.212 mL). The mixture was stirred at room temperature and monitored by TLC. After disappearance of the starting material, the solution was concentrated and then purified by flash chromatography (petroleum ether−Et_2O, 1/1) to give (±)-**11** in 76% yield or (+)-**11** ($[\alpha]^{22}_D$ +4.9 (*c* 1, $CHCl_3$)) in 88% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 1.17−1.24 (m, 1H, C*H*$_2$), 1.34−1.43 (m, 1H, C*H*$_2$), 1.46−1.56 (m, 2H, CH_2) , 1.60−1.65 (m, 1H, C*H*$_2$), 1.74−1.80 (m, 1H, C*H*$_2$), 1.83−1.90 (m, 1H, CH), 1.96−2.08 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.39 (s, 1H, OH), 4.21 (d, 2H, *J* = 6.8 Hz, CH_2), 4.48 (br s, 1H, CH), 4.65 (s, 2H, CH_2), 4.79 (br s, 1H, CH), 5.00 (br d, 1H, *J* = 11.0, CH), 5.86 (t, 1H, *J* = 6.8 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_3), 21.2 (CH_3), 23.5 (CH_2), 26.5 (CH_3), 28.3 (CH_3), 31.9 (CH_2), 32.1 (CH_2), 34.5 (C), 35.9 (CH_2), 50.1 (CH), 58.4 (CH_2), 60.0 (CH_2), 74.1 (CH), 110.2 (CH_2), 131.2 (CH), 136.6 (C), 148.1 (C), 170.5 (C), 171.1 (C); *m*/*z* (ESI+) 356 $[M + NH_4]^+$; HMRS found 356.2430 $[M + NH_4^+]$, $C_{19}H_{34}NO_5$ requires 356.2431.

Acetic Acid 2-Acetoxymethyl-1-(2,2-dimethyl-6-methylene-cyclohexylmethyl)-4-oxo-but-2-enyl Ester (2). To a solution of (±)-**11** or (+)-**11** (0.059 g, 0.17 mmol) in CH_2Cl_2 (4.5 mL), under argon, at 0 °C, was added Dess−Martin periodinane (0.089 g, 0.21 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After disappearance of the starting material, the mixture was poured into a saturated aqueous solution of $Na_2S_2O_3$/$NaHCO_3$ (10 mL, 1/1) and shaken vigorously for 5 min. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (petroleum ether−Et_2O, 7/3) to give (±)-**2** in 89% yield or (+)-**2**. ($[\alpha]^{22}_D$ +8.8 (*c* 1, $CHCl_3$)) in 98% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.19−1.28 (m, 1H, C*H*$_2$), 1.36−1.45 (m, 1H, C*H*$_2$), 1.51−1.59 (m, 2H, CH_2) , 1.74−1.78 (m, 2H, CH_2), 1.94−2.12 (m, 3H, CH_2 and CH), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 4.53 (br s, 1H, CH), 4.83 (br s, 1H, CH), 5.05−5.09 (m, 3H, CH_2 and CH), 6.07 (d, 1H, *J* = 7.4 Hz, CH), 10.07 (d, 1H, *J* = 7.4 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (CH_3), 20.9 (CH_3), 23.4 (CH_2), 26.9 (CH_3), 28.2 (CH_3), 31.7 (CH_2), 31.8 (CH_2), 34.6 (C), 35.6 (CH_2), 50.2 (CH), 59.8 (CH_2), 72.8 (CH), 110.8 (CH_2), 127.9 (CH), 147.7 (C), 157.1 (C), 170.2 (C), 170.3 (C), 190.5 (CH); *m*/*z* (ESI+) 354 $[M + NH_4]^+$; HMRS found 354.2276 $[M + NH_4^+]$, $C_{19}H_{32}NO_5$ requires 354.2274.

(1*S*,3*R*)-3-((*E*)-2-Methoxy-vinyl)-2,2-dimethyl-4-methylene-cyclohexanol (*E*-14) and (1*S*,3*R*)-3-((*Z*)-2-Methoxy-vinyl)-2,2-dimethyl-4-methylene-cyclohexanol (*Z*-14). (+)-Karahana lactone (600 mg, 3.60 mmol) was dissolved in 40 mL of anhydrous toluene, and a 1 M toluene solution of diisobutylaluminium hydride (7.2 mL, 7.20 mmol) was added dropwise at −70 °C under an argon atmosphere. The reaction mixture was stirred for 45 min at this temperature, quenched with Na_2SO_4•$10H_2O$ (4 g) and Celite (5 g), and allowed to rise to rt. Filtration through a pad of $MgSO_4$,

concentration, and purification by flash chromatography (petroleum ether−Et_2O, 8/2 to 3/7) gave, in the same spot, a 1:1:0.5 mixture (^{1}H NMR determination) of lactols **13** and aldehyde **13′** in 95% yield as a clear oil. To a suspension of (methoxymethyl)-triphenylphosphonium chloride (3.35 g, 9.76 mmol) in THF (30 mL) at −18 °C was added a 1.6 M *n*-butyllithium in hexane solution (6.00 mL, 9.60 mmol). The dark red mixture was allowed to stir for 3 h at 0 °C. A solution of the mixture **13** and **13′** (400 mg, 2.38 mmol) in THF (7 mL) was added dropwise. After the reaction mixture was stirred overnight at rt, the solution was diluted in ether and poured into water. The aqueous layer was extracted with ether, and the combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (petroleum ether−Et_2O, 9/1 to 2/8) afforded in 82% yield a 20:3 mixture of *E* and *Z* isomers of **14**. ^{1}H NMR of *E*-**14** (300 MHz, $CDCl_3$) δ 0.72 (s, 3H), 0.98 (s, 3H), 1.42−1.57 (m, 2H), 1.78−1.87 (m, 1H), 2.05−2.16 (m, 1H), 2.26 (br d, J = 10.4 Hz, 1H), 2.35−2.42 (m, 1H), 3.44 (dd, J = 11.2, 4.4 Hz, 1H), 3.57 (s, 3H), 4.67 (br s, 1H), 4.77−4.84 (m, 2 × 1H), 6.24 (d, J = 12.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 26.3 (CH_3), 31.3 (CH_2), 33.4 (CH_2), 40.4 (C), 51.0 (CH), 56.2 (CH_3), 77.8 (CH), 100.4 (CH), 109.4 (CH_2), 148.6 (CH) 149.2 (C); Anal. Calcd for $C_{12}H_{20}O_2$ (*E* + *Z* mixture) C, 73.43; H, 10.27. Found: C, 73.69; H, 10.23.

(*S*)-2-((*E*)-2-Methoxy-vinyl)-1,1-dimethyl-3-methylene-cyclohexane (*E*-15) and (*S*)-2-((*Z*)-2-Methoxy-vinyl)-1,1-dimethyl-3-methylene-cyclohexane (*Z*-15). To a suspension of sodium hydride (141 mg, 2.94 mmol, 50% dispersion) in THF (6 mL) at 0 °C was added a solution of *E*- and *Z*-**14** (287 mg, 1.46 mmol) and carbon disulfide (355 μL, 5.88 mmol) in THF (8 mL). The reaction mixture was stirred for 1.5 h at rt and iodomethane (735 μL, 11.80 mmol) was added at 0 °C. The reaction mixture was stirred overnight at rt, diluted in ether, and carefully poured into water. After extraction with ether, the combined organic phases were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford in 98% yield the corresponding xanthate. This mixture was used in the next step without further purification. To a solution of xanthate (411 mg, 1.43 mmol) in toluene (10 mL) was added a solution of tri-*n*-butyltin hydride (690 μL, 2.60 mmol) and a catalytic amount of AIBN in toluene (10 mL) under an argon atmosphere. The reaction mixture was stirred under reflux for 1 h, cooled, and concentrated. The oily residue was purified by flash chromatography (petroleum ether−Et_2O, 10/0 to 95/5) to give **15** (*E*/*Z* : 20/3) in 90% yield. ^{1}H NMR of *E*-**15** (300 MHz, $CDCl_3$) δ 0.76 (s, 3H), 0.89 (s, 3H), 1.22−1.36 (m, 1H), 1.43−1.62 (m, 3H), 1.96−2.09 (m, 1H), 2.24−2.35 (m, 2H), 3.55 (s, 3H), 4.61 (br s, 1H), 4.72 (br s, 1H), 4.83 (dd, J = 12.5, 10.2 Hz, 1H), 6.23 (d, J = 12.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (CH_3), 23.6 (CH_2), 29.9 (CH_3), 35.1 (C) 35.5 (CH_2), 39.6 (CH_2), 53.1 (CH), 56.2 (CH_3), 101.9 (CH), 108.2 (CH_2), 148.0 (CH) 151.3 (C); Anal. Calcd for $C_{12}H_{20}O$ (*E* + *Z* mixture): C, 79.95; H, 11.18. Found: C, 80.22; H, 11.21.

Crispatenine (1). In a dry Schlenk tube, a solution of (±)-**2** or (+)-**2** (30 mg, 0.089 mmol), DMAP (11 mg, 0.089 mmol), NEt_3 (0.67 mL), and acetic anhydride (0.025 mL, 0.27 mmol) was stirred under argon at 80 °C and monitored by TLC. After disappearance of the starting material, the mixture was concentrated under vacuum. The crude product was then purified by flash chromatography (petroleum ether−Et_2O, 8/2) to give a mixture (47/53 *E*,*Z*/*Z*,*Z*) of two isomers (±)-**1** and *iso*-(±)-**1** in 90% yield or a mixture (1/1 *E*,*Z*/*Z*,*Z*) of (+)-**1** ([α]$^{20}_D$ +5.2 (*c* 0.5, $CHCl_3$)) and *iso*-(+)-**1** in 87% yield. *m*/*z* (ESI+) 396 $[M + NH_4]^+$; ^{1}H NMR of **1** (500 MHz, $CDCl_3$) δ 0.84 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.18−1.28 (m, 1H, CH_2), 1.38−1-44 (m, 1H, CH_2), 1.49−1.60 (m, 4H, 2 × CH_2), 1.92−1.97 (br d, 1H, J = 11.5 Hz, CH), 2.03−2.11 (m, 2H, CH_2), 2.06 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 4.56 (br s, 1H, CH), 4.83 (br s, 1H, CH), 5.68 (br d, 1H, J = 11.3 Hz, CH), 5.78 (d, 1H, J = 12.6 Hz, CH), 7.17 (s, 1H, CH), 7.60 (d, 1H, J = 12.6 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (CH_3), 20.8$_3$ (CH_3), 21.0 (CH_3), 23.7 (CH_2), 26.2 (CH_3), 28.4 (CH_3), 30.5 (CH_2), 32.4 (CH_2), 34.7 (C), 36.2 (CH_2), 49.8 (CH), 68.8 (CH), 109.7 (CH), 110.0 (CH_2), 121.0 (C), 133.1 (CH), 136.9 (CH), 148.2 (C), 167.2 (C), 168.0 (C), 170.2 (C); HMRS found 396.2380 $[M + NH_4^+]$, $C_{21}H_{34}NO_6$ requires 396.2380. ^{1}H NMR of *iso*-**1** (300 MHz, $CDCl_3$) δ 0.84 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.18−1.28 (m, 1H, CH_2), 1.38−1.58 (m, 4H, CH_2 and 2 × CH_2), 1.88−1.99 (m, 2H, CH and CH_2), 2.03 (s, 3H, CH_3), 2.05−2.14 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 4.56 (br s, 1H, CH), 4.83 (br s, 1H, CH), 5.15 (d, 1H, J = 7.4 Hz, CH), 5.70−5.76 (m, 1H, CH), 7.21 (d, 1H, J = 7.4 Hz, CH), 7.78 (s, 1H, CH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 23.7 (CH_2), 26.2 (CH_3), 28.5 (CH_3), 30.9 (CH_2), 32.5 (CH_2), 34.7 (C), 36.3 (CH_2), 49.8 (CH), 68.7 (CH), 103.7 (CH), 109.8 (CH_2), 119.1 (C), 135.1 (CH), 136.5 (CH), 148.4 (C), 167.3 (C), 167.5 (C), 170.2 (C); HMRS found 396.2380 $[M + NH_4^+]$, $C_{21}H_{34}NO_6$ requires 396.2380.

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Supporting Information Available: Synthesis procedures of known compounds (±)-**3**, (±)-**4**, (±)-**5**, (±)-**6**, (±)-**7**, (±)-**8**, copies of ^{1}H NMR and ^{13}C NMR spectra, and CIF file of (±)-**9** are available free of charge via the Internet at http://pubs.acs.org.

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