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Toward the Total Synthesis of Klaivanolide: Complete Reinterpretation of Its Originally Assigned Structure

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Klaivanolide is an antiparasitic natural product isolated from *Uvaria klaineana*, whose structure was originally assigned as a seven-membered lactone ring. Attempts towards the total synthesis of klaivanolide led us to revise its original structural assignment based on both experimental evidence and spectroscopic data. The isolated compound was revealed to be a known molecule, acetylmelodorinol, originally isolated from *Melodorum fruticosum*. Vibrational circular dichroism simulation of the reassigned structure was also performed to reinvestigate our previous studies on the determination of the absolute configuration of klaivanolide.

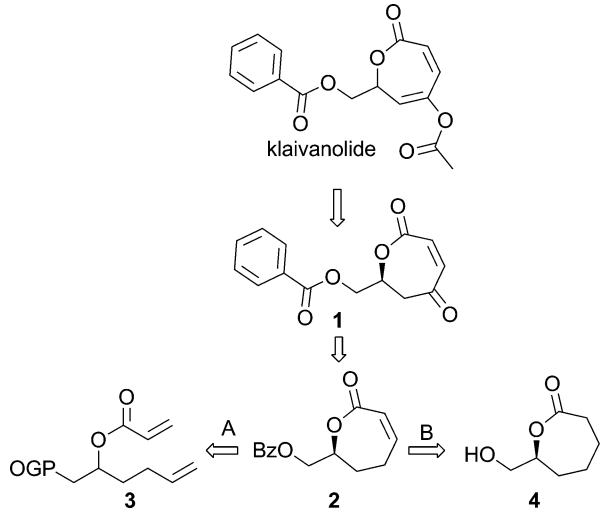
Introduction

Uvaria klaineana, a Gabonese Annonaceae, is a source of promising antiparasitic natural products, and stem extracts of this plant have shown in vitro activities against acari,[1] *Leishmania donovani* promastigote forms, and *Trypanosoma brucei brucei* trypomastigote forms. Bioguided MeOH/CH_2Cl_2 extraction of a sample of *Uvaria klaineana* afforded a crystalline compound that was characterized as a new seven-membered lactone and named klaivanolide.[2] Determination of the absolute configuration of klaivanolide was accomplished by vibrational circular dichroism (VCD) spectroscopy, by analysis of experimental data and density functional theory calculated spectra.[3] Klaivanolide was also isolated from another Annonaceae, *Mitrella mesnyi*,[4] based on the spectroscopic data disclosed in the original report.[2]

Because of the promising antileishmanial activity of the isolated product klaivanolide, we initiated a scientific program with the aim to provide synthetic samples of this molecule and structurally related analogues. Herein we present our synthetic efforts toward the preparation of klaivanolide, which led us to re-assign its structure.

Results and Discussion

To synthesize klaivanolide, we anticipated that the enol acetate moiety in the natural product could derive from ketone **1** (Scheme 1). The carbonyl group could be introduced by a selective allylic oxidation of unsaturated lactone **2**. The enantioenriched lactone (*S*)-**2** could be prepared through two different strategies. The first approach involves a ruthenium-catalyzed ring-closing metathesis (RCM) reaction of diene **3** (Pathway A). The second strategy involves benzoylation of lactone **4** followed by introduction of the unsaturation (Pathway B). Lactone **4** could be prepared through Baeyer–Villiger oxidation and organocatalytic formylation of cyclohexanone as the key steps.



Scheme 1. Retrosynthetic analysis of klaivanolide through Pathways A or B.

Racemic trityl glycidyl ether **5** was used as starting material to test pathway A. Epoxide **5** was opened by allylmagnesium bromide at –30 °C in the presence of CuI to afford dihomoallyl alcohol **6** in 76% yield. Subsequent acryloylation of the hydroxy group gave diene **3** in 80% yield. The key step of this route was a formation of the seven-membered ring by RCM. Nevertheless, previous

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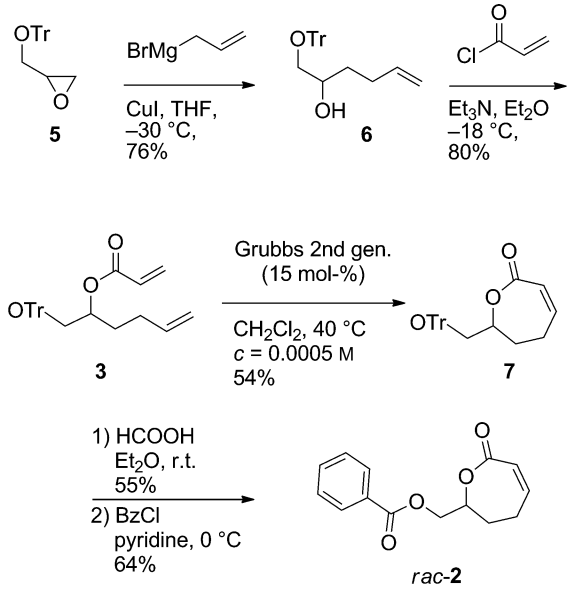
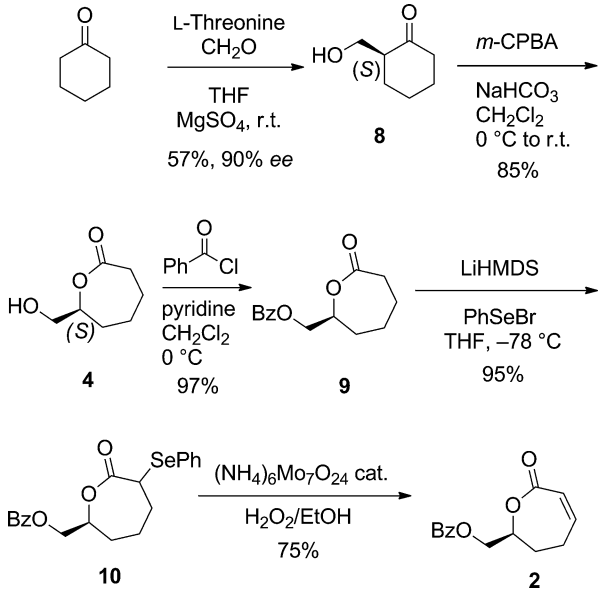
works reported that this transformation is generally difficult,[5] and we observed that dilution is crucial to prevent the formation of polymeric materials. By applying these conditions (5×10^{-4} M) in the presence of 15 mol-% of 2nd-generation Grubbs catalyst, racemic lactone **7** was obtained in moderate yield (55%). The synthesis of racemic compound **2** was then performed in two more steps after hydrolysis of the trityl group[6] and benzoylation (Scheme 2, Pathway A). However, by working on a gram-scale synthesis, the RCM reaction is almost impractical owing to the high catalyst loading, modest yield and high dilution. We turned then our attention to a second strategy to prepare compound **2** more conveniently (Scheme 3, Pathway B).



Scheme 2. Pathway A based on an RCM reaction for the synthesis of klaivanolide.

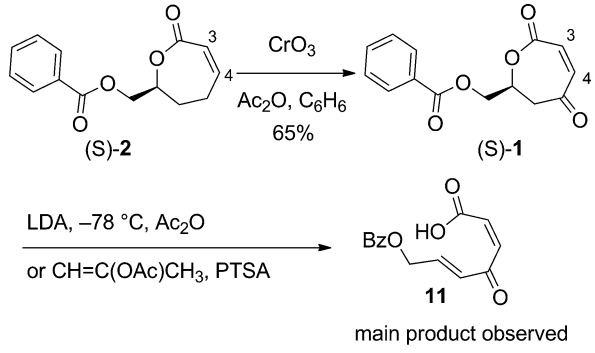


Scheme 3. Pathway B based on an organocatalytic aldol reaction and a Baeyer–Villiger oxidation.

Pathway B began with an organocatalyzed aldol reaction between cyclohexanone and formaldehyde in the presence of threonine in tetrahydrofuran (THF).[7] After 4 d of stirring at room temperature, α-(hydroxymethyl)cyclohexanone (**8**) was isolated in 57% yield and 90% *ee*.[8] The next step was the Baeyer–Villiger oxidation of chiral cyclohexanone **8** with *meta*-chloroperoxybenzoic acid (*m*-CPBA), which gave regioselectively and stereospecifically[9] the expected seven-membered lactone **4** in 85% yield. Subsequent benzoylation of **4** afforded compound **9** in nearly quantitative yield. The unsaturation of the lactone was introduced by a selenoxyelimination in two steps.[10]

First, the lithium enolate of **9** was trapped with phenylselenium bromide to yield selenide **10** (95%). Then, oxidation of **10** with hydrogen peroxide in the presence of ammonium dimolybdate produced the corresponding intermediate selenoxide that underwent spontaneous elimination to afford unsaturated lactone (*S*)-**2** with 75% yield. Pathway B has the advantage of providing efficiently the desired intermediate (*S*)-**2** from cheap reagents (Scheme 3).

The next critical reaction was the introduction of the carbonyl group in the allylic position. Among all the direct or indirect methods that we tested to perform this transformation, only the use of chromic anhydride in combination with acetic anhydride/acetic acid in benzene allowed us to isolate ketone **1**, albeit with a moderate 65% yield.[11] At this point, we expected the synthesis to be almost finished by considering the last step as a simple functional-group transformation. Unfortunately, it was not the case, and whatever the reaction conditions used [propenyl acetate/*p*-toluenesulfonic acid (PTSA), lithium diisopropylamide (LDA)/AcCl], we were not able to obtain or to observe any trace of the supposed structure of klaivanolide (Scheme 4). Indeed, compound **1** is unstable to weakly basic conditions, such as neutral alumina or triethylamine, and moderately stable to silica gel chromatography or aqueous treatment, because the compound has a high tendency to undergo elimination at the β-position of the ketone, driven by the strain in the seven-membered ring to yield compound **11**.



Scheme 4. Endgame and attempts to obtain synthetic klaivanolide. PTSA = *p*-toluenesulfonic acid.

As a result of the observation of the instability of (*S*)-**1** towards various conditions, we questioned that klaivanolide could be isolated by usual extractive techniques on a several hundred milligram scale. We were brought to reinvestigate

the structure reported for klaivanolide, as we understood that such an unstable molecule could hardly be isolated by usual means. A careful look at the ^{1}H NMR spectroscopic data of isolated klavanolide showed that the value of the coupling constant of the ethylene protons in positions 3 and 4 is smaller than expected ($J_{3,4}$ = 5.5 Hz)[2] relative to a classical value of J = 10–11 Hz for a (*Z*) double bond in an acyclic system. In contrast, compound **1** shows a slightly larger coupling constant ($J_{3,4}$ = 12.1 Hz). These differences could be a result of the size of the ring, which distorts the ethylene moiety and changes the corresponding dihedral angle. Figure 1 shows the value of reported coupling constants for vicinal ethylene protons of α,β-unsaturated lactones or cyclic ketones as a function of the ring size and emphasizes that the ring strain has a strong influence on this variable, because cyclobutenone,[12] butenolide,[13] pentenolide,[14] hexenolide,[15] and heptenolide[16] exhibit vicinal coupling constants for ethylene protons of 2.3, 5.8, 9.5, 12.4 and 13.0 Hz, respectively. By comparing vicinal coupling constants of ethylene protons of compound **1** and isolated klaivanolide, 12.1 and 5.5 Hz, respectively, we could postulate that isolated klaivanolide contains a butenolide rather than a hexenolide.

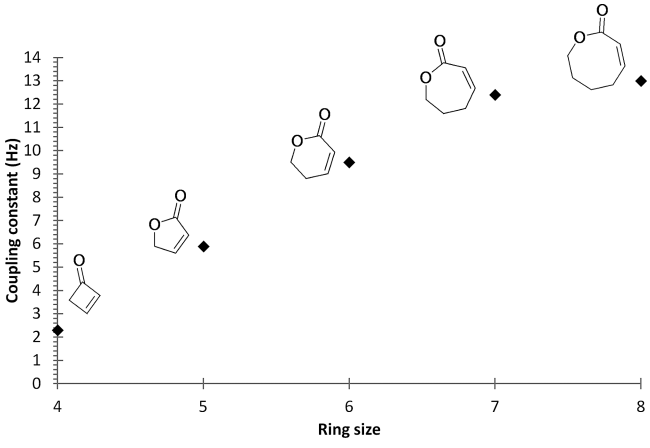


Figure 1. Influence of the ring size on the reported coupling constant of vicinal ethylene protons of α,β-unsaturated cycloesters/ketones.

Reassignment of the structure of klaivanolide led us to propose structure **12**, which is already known in the literature as acetylmelodorinol, originally isolated from *Melodorum fruticosum*[17] and later from other Annonaceae such as *Mitrella kentii*[18] and *Artabotrys madagascaiensis*.[19] Analysis of the NMR spectroscopic data between isolated "klaivanolide" and acetylmelodorinol showed that they are identical. Therefore, we conclude that the isolated compound from *Uvraria klaineana* is not klaivanolide as reported but acetylmelodorinol. (Figure 2).

As a corollary, our previous work on the determination of the absolute configuration by VCD spectroscopy of klaivanolide[3] must be discussed, because the structure was completely revised. We followed the same approach, and a new spectrum was predicted in the density functional theory (DFT) framework and analyzed relative to the previously recorded experimental spectrum.[20] A preliminary conformation sampling on a model of compound **12** was performed by random (Monte-Carlo) torsional search and subsequent minimization with the OPLS[21] molecular mechanics force field. Lowest-energy conformations found were then subjected to geometry optimization at the B3LYP/6-31G* level and yielded 27 unique structures. The six first geometries ranked by ascending energy covered more than 90% of conformational population within the conformational space explored, over a 1.29 kcal/mol energy range (Figure 3). These were retained for VCD calculation at the same level. Overlay of the weighted average theoretical spectrum with previously reported experimental data[3] is plotted in Figure 4. In particular, the spectroscopic signature in the 1290–1180 cm^{-1} band is in good accordance with experimental data, and confirms with a high level of confidence that the absolute configuration for acetylmelodorinol (**12**) isolated from *Uvaria klaineana* at C7 is (*S*).

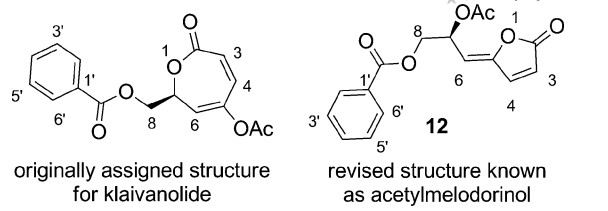


Figure 2. Structure of the originally assigned klaivanolide and revised structure **12** known as acetylmelodorinol.

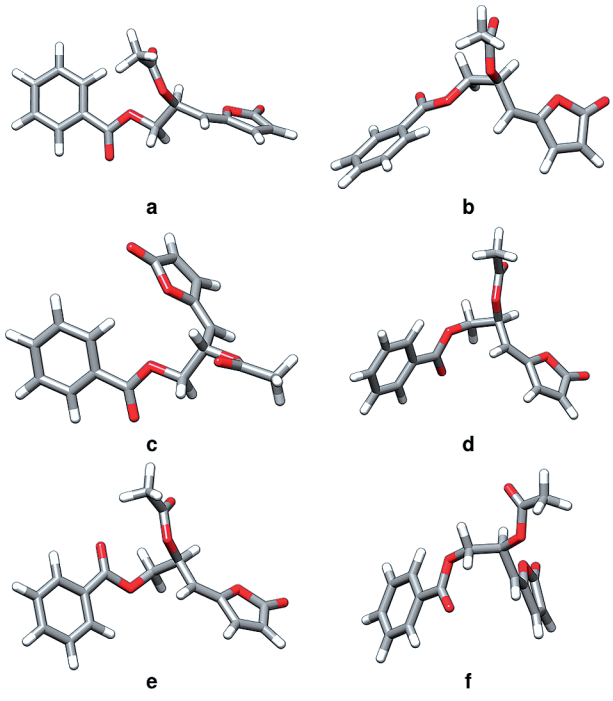


Figure 3. Lowest-energy conformations found for compound **12** at the B3LYP/6-31G* level, sorted by ascending energy (calculated populations: a: 42%, b: 14%, c: 12%, d: 11%, e: 6%, f: 5%).

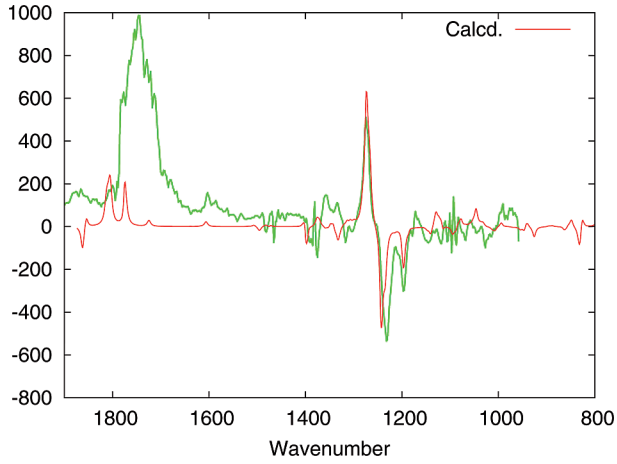


Figure 4. Overlay of an experimental VCD spectrum for acetylmelodorinol (**12**) isolated from *Uvaria klaineana* (in green) with the corresponding (downshifted by 25 cm^{-1}) conformationally weighted spectrum calculated at the B3LYP/6-31G* level (in red).

Conclusions

We discovered that the originally assigned structure of klaivanolide was wrong. The difficulties experienced in the synthesis of this uncommon "natural" seven member-ring product led us to reconsider its structure as a butyrolactone, confirmed by NMR spectroscopy.

We also tried to revise the absolute configuration of "klaivanolide" by VCD spectroscopy, now revised as known acetylmelodorinol (**12**). This work concludes that the theoretical VCD spectrum of klaivanolide reported in our previous communication[3] is very similar to that obtained here for acetylmelodorinol (**12**). This observation can be rationalized by the fact that the VCD phenomenon ensues from infrared absorption properties of functional groups (unsaturation, ester groups) that are identical in both compounds, and is strongly correlated to their relative arrangement around the stereogenic center C7, which remains (*S*) in both structures.

Experimental Section

General Experimental Procedure: Infrared (IR) spectra were recorded with an FTIR apparatus. ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$, and data are reported as follows: chemical shift relative to tetramethylsilane (TMS) with the solvent as an internal standard ($CHCl_3$: δ = 7.26 ppm), multiplicity (br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet or overlap of non-equivalent resonances), and integration. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$, and data are reported as follows: chemical shift relative to TMS with the solvent as an internal standard ($CDCl_3$: δ = 77.0 ppm). HRMS data were recorded by electrospray ionization (ESI). CH_2Cl_2, Et_2O, and toluene were dried by filtration through activated molecular sieves. THF was distilled from sodium/benzophenone ketyl radical. Other reagents or solvents were obtained from commercial suppliers and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel plates visualized either with a UV lamp (254 nm), or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH, $KMnO_4/K_2CO_3$ in H_2O or ammonium molybdate/sulfuric acid in water followed by heating. Flash chromatography was performed with silica gel (230–400 mesh). All the reactions were carried out under N_2 unless specified otherwise.

Acrylate 3: To a solution of compound **6** (3.17 g, 8.88 mmol, 1 equiv.) and triethylamine (17.7 mmol, 2 equiv.) in Et_2O (30 mL) at –20 °C was added dropwise acryloyl chloride (0.9 mL, 11.5 mmol, 1.3 equiv.). After stirring for 1 h, the reaction was quenched by addition of a saturated $NaHCO_3$ aqueous solution. The organic layer was extracted with Et_2O and washed with saturated NH_4Cl aqueous solution and brine. The organic solution was then dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 96:4) to afford compound **3** (1.43 g, 39%). IR (ATR): $\tilde{\nu}$ = 3056, 1724, 1492, 1449, 1405, 1196, 1078, 765, 747, 707, 633 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.43 (m, 6 H), 7.33–7.18 (m, 9 H), 6.46 (dd, *J* = 17.1, 1.8 Hz, 1 H), 6.19 (dd, *J* = 17.1, 10.4 Hz, 1 H), 5.87 (d, *J* = 10.4, 1.8 Hz, 1 H), 5.75 (ddt, *J* = 16.7, 10.4, 6.5 Hz, 1 H), 5.17 (dtd, *J* = 7.6, 5.7, 4.0 Hz, 1 H), 4.94 (dq, *J* = 16.7, 1.5 Hz, 1 H), 4.93 (dq, *J* = 10.4, 1.5 Hz, 1 H), 3.20 (dd, *J* = 9.9, 4.0 Hz, 1 H), 3.14 (dd, *J* = 9.9, 5.7 Hz, 1 H), 2.01 (m, 2 H), 1.85–1.70 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.7, 143.9, 137.6, 130.6, 128.7, 127.8, 127.0, 115.1, 86.4, 72.9, 64.7, 30.1, 29.4 ppm. HRMS (ESI): calcd. for $C_{28}H_{28}O_3Na$ $[M + Na]^+$ 435.1936; found 435.1927.

Racemic Lactone 7: To a solution of compound **3** (621 mg, 1.5 mmol, 1 equiv.) in technical-grade CH_2Cl_2 (3 L), was added 2nd-generation Grubbs catalyst (192.4 mg, 0.226 mmol, 15 mol-%). After the solution had been heated to reflux for 24 h, the solvent was removed by distillation, and the residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 20:80) to afford compound **7** (312.6 mg, 54%). IR (ATR): $\tilde{\nu}$ = 3020, 1696, 1489, 1448, 1397, 1281, 1190, 1091, 1053, 1018, 750, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.46 (m, 6 H), 7.40–7.20 (m, 9 H, Ar), 6.41 (dt, *J* = 12.3, 4.6 Hz, 1 H), 6.00 (dt, *J* = 12.3, 1.9 Hz, 1 H), 4.28 (dddd, *J* = 8.6, 6.1, 5.6, 1.4 Hz, 1 H), 3.46 (dd, *J* = 9.7, 5.6 Hz, 1 H), 3.22 (dd, *J* = 9.7, 6.1 Hz, 1 H), 2.60–2.30 (m, 2 H), 2.20 (br. dt, *J* = 15.4, 5.3 Hz, 1 H), 1.99 (dtd, *J* = 15.4, 8.8, 6.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.0, 143.7, 143.6, 128.6, 127.8, 127.1, 122.2, 86.8, 65.0, 29.4, 29.0 ppm. HRMS (ESI): calcd. for $C_{26}H_{24}O_3Na$ $[M + Na]^+$ 407.1623; found 407.1621.

Benzoylated Lactone 2 from Compound 7: A solution of compound **7** (266 mg, 0.693 mmol) in a mixture of formic acid/Et_2O (1:1; 2 mL, 2 mL) was stirred at room temperature for approximately 3 h, until no starting materiel was left as monitored by TLC. The reaction mixture was then poured carefully into a saturated aqueous solution of $NaHCO_3$, and extracted with 1-butanol (3 ×). The organic layer was dried with $MgSO_4$, filtered, concentrated under vacuum, and the residue purified by flash chromatography on silica gel (CH_2Cl_2/methanol, 99:1) to afford the intermediate unsaturated (hydroxymethyl)caprolactone (53.7 mg, 55%). IR (ATR): $\tilde{\nu}$ = 3500 (br.), 1698, 1452, 1050 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.44 (dt, *J* = 12.3, 4.6 Hz, 1 H), 5.99 (dt, *J* = 12.3, 1.8 Hz, 1 H), 4.39 (tt, *J* = 6.8, 3.5 Hz, 1 H), 3.76 (dd, *J* = 12.1, 6.8 Hz, 2 H), 3.69 (dd, *J* = 12.1, 3.7 Hz, 1 H), 2.60–2.34 (m, 2 H), 2.55 (br. s, 1 H, OH), 2.00 (m, 2 H) ppm. HRMS (ESI): calcd. for $C_7H_{10}O_3Na$ $[M + Na]^+$ 165.0528; found 165.0521. To a solution of the unsaturated (hydroxymethyl)caprolactone (53 mg, 0.373 mmol, 1 equiv.) in pyridine (3 mL) at 0 °C was added benzoyl chloride (65 µL, 0.56 mmol, 1.5 equiv.). The reaction mixture was quenched by addition of a saturated aqueous solution of $NaHCO_3$, the organic layer was extracted with ethyl acetate, washed twice with a satu-

rated copper sulfate aqueous solution and brine. The organic solution was dried with $MgSO_4$, filtered, concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 30:70) to afford racemic compound **2** (59.0 mg, 64%).

Benzoylated Lactone 2 from Compound 10: To a solution of compound **10** (8.0 g, 19.8 mmol, 1 equiv.) and ammonium dimolybdate (50 mg) in EtOH (30 mL) was added dropwise at 0 °C hydrogen peroxide (3.38 mL, 29.7 mmol, 1.5 equiv., 30% in water). After 90 min, the reaction mixture was diluted with water, and the organic layer was extracted with Et_2O, then washed with a sodium thiosulfate aqueous solution, dried with $MgSO_4$, filtered through a pad of silica gel and concentrated under vacuum to afford hexenolide (*S*)-**2** (3.65 g, 75%). $[\alpha]_D^{20}$ = +31.1 (*c* = 2.70, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 1718, 1452, 1271, 1128, 1026, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.05 (dd, *J* = 7.8, 1.3 Hz, 2 H), 7.57 (dt, *J* = 7.8, 1.3 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 6.44 (dt, *J* = 12.1, 4.6 Hz, 1 H), 6.02 (dt, *J* = 12.1, 2.0 Hz, 1 H), 4.65 (m, 1 H), 4.52 (dd, *J* = 11.8, 6.0 Hz, 1 H), 4.47 (dt, *J* = 11.8, 4.7 Hz, 1 H), 2.70–2.40 (m, 2 H), 2.25–2.00 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.4, 166.2, 143.5, 133.3, 129.7, 129.5, 128.4, 75.7, 65.7, 29.0, 28.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}O_4Na$ $[M + Na]^+$ 269.0790; found 269.0788.

(*S*)-Hydroxymethylcyclohexanone 8: To a solution of L-threonine (1.2 g, 10 mmol, 0.1 equiv.) in formaldehyde (8.7 mL, 100 mmol, 1 equiv., 35% wt. in H_2O) was added THF (100 mL) followed by cyclohexanone (20 mL, 200 mmol, 2 equiv.) and $MgSO_4$ (12 g, 100 mmol, 1 equiv.). After 4 d of stirring at room temperature, the reaction mixture was filtered, and the solids were washed with ethyl acetate. Saturated aqueous NH_4Cl solution (50 mL) was added to the filtrate, and the solution was stirred for another 10 min. The organic phase was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with brine (50 mL) and dried with $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure, and the crude product was purified by flash chromatography with silica gel (EtOAc/petroleum ether, 40:60 to 80:20) to afford compound **8** (7.33 g, 57%, 90% *ee*). The enantiomeric excess of product **8** was determined by chiral HPLC analysis of the benzoate derivative[22] (from reaction with benzoyl chloride in pyridine). HPLC (Daicel Chiralcel AD 4.6 × 250 mm; hexanes/*i*PrOH, 90:10 isocratic; flow rate = 1.0 mL/min; λ = 225 nm): t_r = 13.6 [major, (*S*)], 16.9 [minor, (*R*)] min. $[\alpha]_D^{20}$ = +10.1 (*c* = 2.98, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3400 (br.), 1702, 1044 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.77 (dd, *J* = 11.9, 7.5 Hz, 1 H), 3.59 (dd, *J* = 11.9, 4.1 Hz, 1 H), 2.75 (br. s, 1 H, OH), 2.56–2.43 (m, 1 H), 2.43–2.20 (m, 1 H), 2.15–1.97 (m, 2 H), 1.93–1.85 (m, 2 H), 1.76–1.55 (m, 2 H), 1.49–1.36 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 214.8, 62.4, 52.1, 42.0, 29.9, 27.3, 24.5 ppm. HRMS (ESI): calcd. for $C_7H_{12}O_2Na$ $[M + Na]^+$ 151.0730; found 151.0728.

Caprolactone 4: To a solution of compound **8** (1.0 g, 7.8 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) at 0 °C were added solid $NaHCO_3$ (0.98 g, 11.7 mmol, 1.5 equiv.) and *m*-CPBA (1.6 g, 9.37 mmol, 1.2 equiv., 70–75% purity). The reaction mixture was then allowed to reach room temperature and was vigorously stirred for 3 h, then diluted with dichloromethane (20 mL), and quenched by addition of a saturated aqueous sodium thiosulfate solution. The organic layer was extracted with EtOAc (3 ×), and the combined organic phases were dried with $MgSO_4$. After filtration and evaporation of the solvents, purification on silica gel by flash chromatography (EtOAc/petroleum ether, 50:50 to 80:20) afforded compound **4** (960 mg, 85%). $[\alpha]_D^{20}$ = +34.0 (*c* = 3.95, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3400 (br.), 1716, 1185, 1105 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.30 (m, 1 H), 2.80 (br. s, 1 H, OH), 3.66 (dd, *J* = 11.9, 7.4 Hz, 1 H), 3.58 (dd, *J* = 11.9, 4.5 Hz, 1 H), 2.59 (m, 2 H), 1.79–1.98 (m, 3 H), 1.40–1.60 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.6, 80.8, 64.8, 34.6, 30.3, 27.6, 22.7 ppm. HRMS (ESI): calcd. for $C_7H_{12}O_3Na$ $[M + Na]^+$ 167.0679; found 167.0676.

Benzoate 9: To a solution of compound **4** (680 mg, 4.72 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) at 0 °C was added pyridine (1.12 mL, 14.16 mmol, 3 equiv.) followed by benzoyl chloride (995 µL, 7.08 mmol, 1.5 equiv.). After stirring at room temp. for 1 h, the reaction mixture was diluted with ethyl acetate, quenched and washed with a saturated aqueous $NaHCO_3$ solution, washed twice with a saturated copper sulfate aqueous solution and brine. The organic solution was dried with $MgSO_4$, filtered, concentrated under vacuum and the residue purified by flash chromatography on silica gel (EtOAc/petroleum ether, 70:30) to afford benzoate **9** (1.14 g, 97%). $[\alpha]_D^{20}$ = +29.0 (*c* = 3.24, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 1716, 1272, 1096, 711 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.05 (dd, *J* = 7.8, 1.3 Hz, 2 H), 7.57 (dt, *J* = 7.8, 1.3 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 4.65 (dt, *J* = 8.3, 5.7 Hz, 1 H), 4.45 (dd, *J* = 11.6, 6.3 Hz, 1 H), 4.39 (dt, *J* = 11.6, 5.0 Hz, 1 H), 2.73 (br. dd, *J* = 14.2, 7.0 Hz, 1 H), 2.62 (ddd, *J* = 14.2, 12.0, 2.5 Hz, 1 H), 2.15–1.85 (m, 3 H), 1.85–1.45 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.4, 166.2, 133.2, 129.7, 129.6, 128.4, 77.5, 66.4, 34.8, 31.1, 27.9, 22.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{16}O_4Na$ $[M + Na]^+$ 271.0941; found 271.0940.

Phenylselenide 10: To a solution of compound **9** (298 mg, 1.2 mmol, 1 equiv.) in THF (3 mL) was added dropwise lithium bis(trimethylsilyl)amide (1.44 mL, 1.44 mmol, 1.2 equiv., 1 M in THF) at –78 °C. After 30 min of stirring at this temperature, phenylselenyl bromide (1.44 mmol, 1.2 equiv.) was added [prepared from diphenyl diselenide (224 mg, 0.72 mmol, 0.6 equiv.) and bromine (37 µL, 0.72 mmol, 0.6 equiv.) in THF (1 mL)]. The reaction was quenched by the addition of an aqueous HCl solution (1 M, 5 mL), and the organic layer was extracted with ethyl acetate (3 ×). The combined organic layers were washed with a saturated $NaHCO_3$ solution, brine, then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography with silica gel (EtOAc/petroleum ether, 20:80) to afford compound **10** (293 mg, 95%) as a 80:20 mixture of diastereoisomers. $[\alpha]_D^{20}$ = +61.4 (*c* = 2.95, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 1716, 1272, 1096, 711 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.1 (m, 2 H), 7.60 (m, 3 H), 7.48 (m, 2 H), 7.28 (m, 3 H), 5.39 (dt, *J* = 9.9, 4.7 Hz, 0.8 H), 4.70 (dt, *J* = 9.6, 5.1 Hz, 0.2 H), 4.53–4.40 (m, 2 H), 4.30 (dt, *J* = 4.4, 1.4 Hz, 1 H), 2.18 (m, 2 H), 2.09 (m, 1 H), 1.94 (m, 2 H), 1.75 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.5, 166.2, 134.6, 133.2, 129.7, 129.6, 129.4, 128.7, 128.4, 127.7, 77.1, 66.6, 46.6, 31.3 ($^1J_{Se\text{-}C}$ = 115.5 Hz), 28.7, 24.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{20}O_4NaSe$ $[M + Na]^+$ 427.0424; found 427.0419.

4-Oxohexenolide (*S*)-1: To a solution of Ac_2O (2.5 mL) and AcOH (5 mL) at 0 °C was added CrO_3 (812 mg, 8.12 mmol, 4 equiv.) followed by benzene (5 mL). After 15 min, a solution of hexenolide **2** (500 mg, 2.03 mmol, 1 equiv.) in benzene (2 mL) was added dropwise. After 1 h at this temperature, the reaction mixture was poured carefully into a saturated aqueous solution of $NaHCO_3$, and the organic layer was extracted with EtOAc (3 ×). The combined organic extracts were washed with a sodium metabisulfite solution, then dried with $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (short column) with pure EtOAc to afford 4-oxohexenolide **1** (350 mg, 65%). $[\alpha]_D^{20}$ = +11.3 (*c* = 3.56, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 1718, 1269, 1114,

1069, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.05 (m, 1 H), 7.60 (tt, J = 7.3, 1.4 Hz, 1 H), 7.46 (m, 2 H), 6.65 (d, J = 12.5 Hz, 1 H), 6.50 (ddd, J = 12.5, 1.4, 0.5 Hz, 1 H), 5.15 (dddd, J = 10.6, 6.0, 4.7, 1.4 Hz, 1 H), 4.60 (dd, J = 12.0, 6.0 Hz, 1 H), 4.53 (dd, J = 12.0, 4.7 Hz, 1 H), 3.15 (ddd, J = 19.1, 10.6, 0.5 Hz, 1 H), 3.00 (dt, J = 19.1, 1.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 196.1, 166.0, 163.8, 136.7, 130.5, 129.8, 129.1, 128.6, 72.9, 64.5, 45.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{11}O_5$ $[M - H]^-$ 259.0606; found 259.0611: calcd. for $C_{15}H_{14}O_6$ $[(M + MeOH) - H]^-$ 291.0874; found 291.0872.

Molecular Modeling: Coordinates for an arbitrary conformation of acetylmelodorinol (**12**) were subjected to random torsional sampling by using the Monte Carlo Multiple Minima algorithm[23] followed by minimization with the OPLS 2005 force field[24] in vacuo and conjugated gradient algorithm[25] as implemented in MacroModel 9.9.[26] The number of repetitions was set to 10000, and the energy window for saving conformations was set to 5 kcal/mol, which resulted in 45 fully minimized conformations, with a 0.05 kcal mol^{-1} $Å^{-1}$ gradient convergence criterion. Corresponding coordinates were then fully optimized without constraint by using a DFT[27] method with the hybrid Becke-3-parameter-Lee–Yang–Parr exchange-correlation functional[28] and the 6-31G* base[29] as implemented in the Gaussian 09 software package.[30] Vibrational analyses within the harmonic approximation were performed at the same level of theory upon geometrical optimization convergence. Local minima were characterized by the absence of imaginary frequency. Populations were calculated by using Maxwell–Boltzmann statistics. Vibrational rotational strengths within the harmonic approximation were calculated at the same level for the 6 conformations with the lowest free-energy conformations, and used for VCD spectra simulation with a 4 cm^{-1} width at half height.[31] Spectra were plotted with gnuplot.[32] Figures were rendered with UCSF Chimera.[33]

Supporting Information (see footnote on the first page of this article): NMR spectroscopic data for new synthesized compounds **1**–**10**; chiral HPLC data for compound **8**; NMR spectroscopic data of isolated "klaivanolide" and acetylmelodorinol (**12**); computational data for the DFT calculation of acetylmelodorinol (**12**).

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[1] B. Akendengue, E. Ngou-Milama, H. Bourobou-Bourobou, J. Essouma, F. Roblot, C. Gleye, A. Laurens, R. Hocquemiller, P. M. Loiseau, C. Bories, *Phytother. Res.* **2003**, *17*, 364–367.
[2] B. Akendengue, F. Roblot, P. M. Loiseau, C. Bories, E. Ngou-Milama, A. Laurens, R. Hocquemiller, *Phytochemistry* **2002**, *59*, 885–888.
[3] F. J. Devlin, P. J. Stephens, B. Figadère, *Chirality* **2009**, *21*, 48–53.
[4] J.-B. Galle, M. Leti, S. Kim, A. Mandeau, *Biochem. Syst. Ecol.* **2013**, *48*, 9–11.
[5] K. Nakashima, M. Imoto, T. Miki, T. Miyake, N. Fujisaki, S. Fukunaga, R. Mizutani, M. Sono, M. Tori, *Heterocycles* **2002**, *56*, 85–89.
[6] M. Bessodes, D. Komiotis, K. Antonakis, *Tetrahedron Lett.* **1986**, *27*, 579–580.
[7] A. Chen, J. Xu, W. Chiang, C. L. L. Chai, *Tetrahedron* **2010**, *66*, 1489–1495.
[8] The measured enantiomeric excess of **8** was consistent with that reported by Chen et al.; see ref.[7] The enantiomeric excess was measured on the benzoyl derivative.
[9] M. Renz, B. Meunier, *Eur. J. Org. Chem.* **1999**, 737–750.
[10] K. Lal, R. G. Salomon, *J. Org. Chem.* **1989**, *54*, 2628–2632.
[11] a) M. Nakayama, S. Shinke, Y. Matsushita, S. Ohira, S. Hayashi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 184–185; b) F. Busqué, P. Cid, P. de March, M. Figueredo, J. Font, *Heterocycles* **1995**, *40*, 387–399.
[12] X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 11004–11005.
[13] R. Garzelli, S. Samaritani, C. Malanga, *Tetrahedron* **2008**, *64*, 4183–4186.
[14] a) G. Asensio, M. A. Miranda, M. J. Sabater, J. Perez-Prieto, A. Simon-Fuentes, R. Mello, *J. Org. Chem.* **2000**, *65*, 964–968; b) A. D'Annibale, L. Ciaralli, M. Bassetti, C. Pasquini, *J. Org. Chem.* **2007**, *72*, 6067–6074.
[15] S. E. Denmark, N. D. Gould, L. M. Wolf, *J. Org. Chem.* **2012**, *76*, 4260–4336.
[16] E. Fouque, G. Rousseau, J. Seyden-Penne, *J. Org. Chem.* **1990**, *55*, 4807–4817.
[17] a) J. H. Jung, S. Pummangura, C. Chaichantipyuth, C. Patarapanich, P. E. Fanwick, C.-J. Chang, J. L. McLaughlin, *Tetrahedron* **1990**, *46*, 5043; b) J. H. Jung, C.-J. Chang, D. L. Smith, J. L. McLaughlin, S. Pummangura, C. Chaichantipyuth, C. Patarapanich, *J. Nat. Prod.* **1991**, *54*, 500–505; c) P. Tuchinda, J. Udchachon, V. Reutrakul, T. Santisuk, W. C. Taylor, N. R. Famsworth, J. M. Pezzuto, D. Kinghom, *Phytochemistry* **1991**, *30*, 2685–2689.
[18] S. Saadawi, J. Jalil, M. Jasamai, I. Jantan, *Molecules* **2012**, *17*, 4824–4835.
[19] B. T. Murphy, S. Cao, P. J. Brodie, J. S. Miller, F. Ratovoson, C. Birkinshaw, E. Rakotobe, V. E. Rasamison, K. Tendyke, E. M. Suh, D. G. I. Kingston, *Nat. Prod. Res.* **2008**, *22*, 1169–1175.
[20] T. B. Freedman, X. Cao, R. K. Dukor, L. A. Nafie, *Chirality* **2003**, *15*, 743–758.
[21] W. L. Jorgensen, D. S. Maxwell, J. Tirado-Rives, *J. Am. Chem. Soc.* **1996**, *118*, 11225–11236.
[22] S. Ishikawa, T. Hamada, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 12236–12237.
[23] G. Chang, W. Guida, W. C. Still, *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
[24] For a description of the OPLS_2005 parameters, see: J. L. Banks, H. S. Beard, Y. Cao, A. E. Cho, W. Damm, R. Farid, A. K. Felts, T. A. Halgren, D. T. Mainz, J. R. Maple, R. Murphy, D. M. Philipp, M. P. Repasky, L. Y. Zhang, B. J. Berne, R. A. Friesner, E. Gallicchio, R. M. Levy, *J. Comput. Chem.* **2005**, *26*, 1752–1780.
[25] E. Polak, G. Ribière, *Rev. Fr. Inform. Rech. O.* **1969**, *16*, 35–43.
[26] *MacroModel*, version 9.9, Schrödinger, LLC, New York, NY, **2011**.
[27] a) W. Kohn, L. J. Sham, *Phys. Rev.* **1965**, *140*, A1133–A1138; b) P. Hohenberg, W. Kohn, *Phys. Rev.* **1964**, *136*, B864–B871.
[28] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[29] W. J. Hehre, L. Radom, P. v. R. Schleyer, J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley, New York, **1986**.
[30] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell,

J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, Revision A.02. Gaussian, Inc., Wallingford, CT, **2009**.

[31] J. R. Cheeseman, M. J. Frisch, F. J. Devlin, P. J. Stephens, *Chem. Phys. Lett.* **1996**, *252*, 211–220.

[32] T. Williams, C. Kelley, *Gnuplot 4.6: An Interactive Plotting Program*, http://gnuplot.sourceforge.net/, **2012**.

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