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SHORT COMMUNICATION

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Total Synthesis and Configurational Validation of (+)-Violapyrone C

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Gold(I)-catalyzed intramolecular 6-*endo-dig* cyclization of *tert*-butyl ynoates afforded α-pyrone cores of violapyrones. Moreover, this reaction was successfully applied to the stereospecific syntheses of (+)- and (–)-violapyrone C, which allowed the absolute configuration of natural (+)-violapyrone C to be assigned by comparison of the optical rotations. This first total synthesis, which proceeded in 22 % yield over 10 steps from (*S*)-(–)-2-methylbutanol, features silver(I) oxide promoted monobenzylation of 1,4-butanediol, Wittig olefination, Claisen condensation, Corey–Fuchs reaction, and gold(I)-catalyzed α-pyrone synthesis.

Introduction

Violapyrones constitute a family of nine 3,4,6-trisubstituted α-pyrone derivatives first reported by Huang and coworkers (Figure 1).[1] These chemical entities were isolated from the fermentation broth of *Streptomyces violascens* (YIM100525) obtained from *Hylobates hoolock* feces.[1] Very recently, (+)-violapyrone C along with the two new members violapyrones H and I were identified in our laboratory from the mass culture of actinomycete *Streptomyces* sp. 112CH148 associated with crown-of-thorns starfish, *Acanthaster planci*, collected from Chuuk, Micronesia.[2]

Although violapyrones contain relatively simple alkyl chains at the C6 position of the core α-pyrone scaffold, the absolute configuration at C11 of violapyrone C (**1**) has yet to be validated. In addition to moderate antibacterial activities originally reported by Huang and co-workers,[1] violapyrone C showed cytotoxicity against a panel of six human tumor cell lines.[2a] Moreover, in an assay with the use of HCT116 human colon cancer cells stably expressing a luciferase reporter construct under the control of a hypoxia response element (HCT116-HRE-Luc), it was revealed that (+)-violapyrone C has inhibitory effect on the HIF (hypoxia-inducible factor) pathway, which is related to tumor progression, invasion, and metastasis.[2b] Therefore, ensuing material supply is in urgent need for further biomedical study. Herein, we report the gold(I)-catalyzed efficient synthesis of the α-pyrone skeleton and its application to the total synthesis and configurational validation of (+)-violapyrone C.

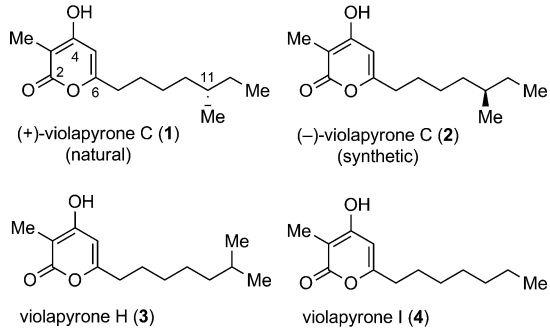

Figure 1. Violapyrones.

Results and Discussion

Although protocols for α-pyrone synthesis by 6-*endo-dig* intramolecular cyclization are already known, either undesirable extra steps (e.g., hydrolysis) or harsh reaction conditions are required.[3] Owing to its alkynophilic character and high functional group compatibility, in addition to its many other advantages, gold as a catalyst has been at the center of rapid development over the past decade.[4,5] Recently, the successful application of (SPhos)AuNTf$_2$ (SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, Tf = trifluoromethylsulfonyl) to the synthesis of 4-hyroxy-2-pyrones under exceptionally mild conditions was reported.[3a] We imagined that treatment of β-keto esters with an appropriate catalyst would form α-pyrones. In our retrosynthetic analysis of violapyrone C (Scheme 1), the key step is the gold-catalyzed 6-*endo-dig* cyclization of β-keto ester **17** to

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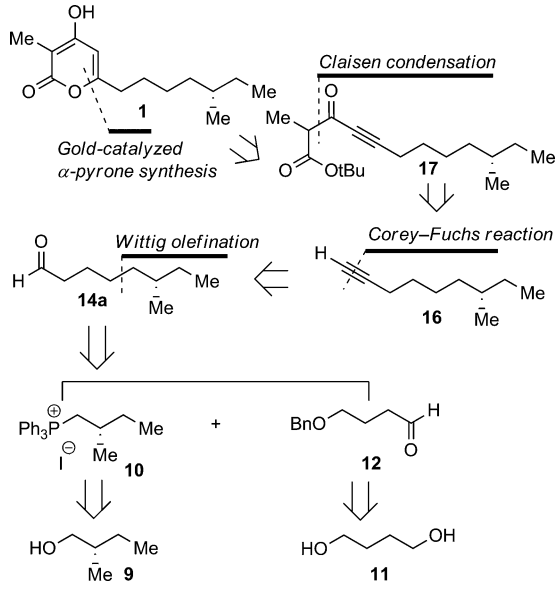
form the α-pyrone core leading to violapyrone C. To access the key intermediate, β-keto ester **17**, it is necessary to introduce an ester group directly to propargylic intermediate **16** through the acetylide anion, followed by Claisen condensation. Further analysis suggested that installation of a C≡C bond to intermediate **16** could be achieved by Corey–Fuchs reaction of aldehyde **14a**, which in turn would be prepared by Wittig olefination between phosphonium iodide salt **10** and aldehyde **12**. In principle, these two Wittig reagents would be accessible in a few steps from (*S*)-(–)-2-methyl-1-butanol (**9**) and 1,4-butanediol (**11**, Scheme 1).

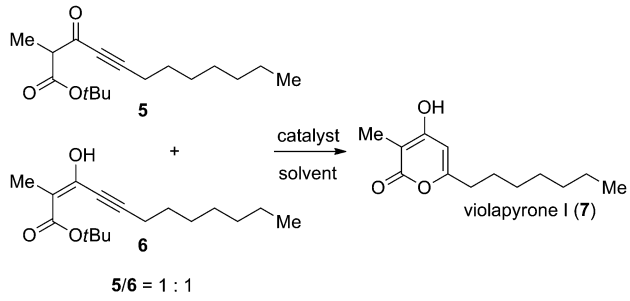


Scheme 1. Retrosynthetic analysis of violapyrone C.

To prove the concept, an inseparable mixture of β-keto ester **5** and tautomer **6** was applied as a model system for this transformation (Table 1).[6] Although preliminary test reactions with various transition-metal catalysts suffered from low conversion efficiency and poor yields, as evaluated by ^{1}H NMR spectroscopy (Table 1, entries 1–5), significant catalytic conversions were noticed in reactions with gold(I) catalyst **8** {[bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold(I) (2:1) toluene adduct} (Table 1, entries 6–8). Further investigation in a 4:1 mixture of AcOH/MeCN at room temperature provided **7** in 69% yield (Table 1, entry 9). Moreover, if $MeNO_2$ was used instead of MeCN, the reaction improved and gave desired **7** in 73% yield (Table 1, entry 10).

Consequently, the above reaction was considered to be applicable to the synthesis of violapyrone C. Our synthesis began with transformation of readily available (*S*)-(–)-2-methyl-1-butanol (**9**) into corresponding iodide **9a** (not shown) by using imidazole, iodine, and triphenylphosphine in CH_2Cl_2 (83% yield, Scheme 2).[7] Subsequent treatment of iodide **9a** with triphenylphosphine in toluene at reflux furnished desired phosphonium iodide **10** in 82% yield (Scheme 2).[8] The coupling partner of phosphonium iodide **10** in the ensuing Wittig olefination, that is, aldehyde **12**,

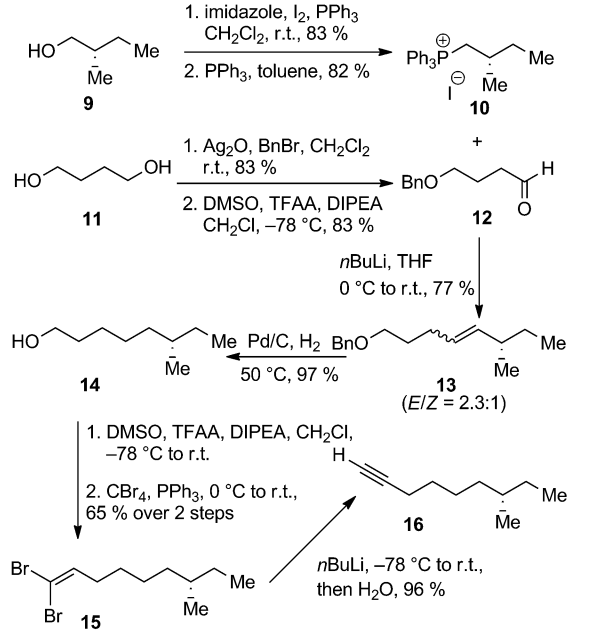
Table 1. Screening of the reaction conditions.[a]



Entry	Cat. (10 mol-%)	Solvent	Conv. [%][b]
1[c]	$PdCl_3$	AcOH/$MeNO_2$ (4:1)	11
2[c]	Ag_2CO_3	AcOH/$MeNO_2$ (4:1)	34
3[c]	$InCl_3$	AcOH/$MeNO_2$ (4:1)	trace
4[c]	$Sc(OTf)_3$	AcOH/$MeNO_2$ (4:1)	trace
5[c]	$AuCl_3$	AcOH/$MeNO_2$ (4:1)	23
6[d]	**8**[e]	toluene	91
7[d]	**8**[e]	CH_2Cl_2	86
8[d]	**8**[e]	THF	82
9[f]	**8**[e]	AcOH/MeCN (4:1)	100 (69)[g]
10[f]	**8**[e]	AcOH/$MeNO_2$ (4:1)	100 (73)[g]

[a] The reactions were performed under a N_2 atmosphere at room temperature. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction quenched after 44 h. [d] Reaction quenched after 20 h. [e] [Bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)-gold(I) (2:1) toluene adduct was used. [f] Reaction was complete in 15 h. [g] The value in parentheses indicates the yield of the isolated product.

was prepared by silver(I) oxide promoted monobenzylation of readily available 1,4-butanediol (**11**) in the presence of Ag_2O and benzyl bromide in CH_2Cl_2 to afford primary alcohol **11a** (not shown, 83% yield);[9] this was followed by



Scheme 2. Synthesis of terminal alkyne **16**.

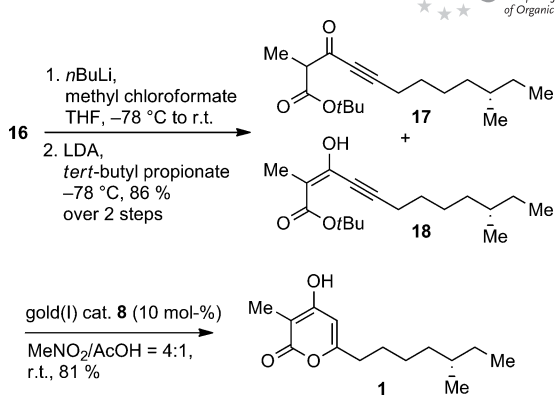
Swern oxidation with trifluoroacetic anhydride (TFAA) and DMSO (83% yield, Scheme 2).[10] Wittig olefination between phosphonium iodide **10** and aldehyde **12** by using *n*-butyllithium provided desired olefin **13** (*E*/*Z* = 2.3:1) in 77% yield (Scheme 2).[8]

Notably, if olefin **13** was subjected to hydrogenation conditions in the presence of a palladium catalyst, reduction of the C=C bond and deprotection of the benzyl group were concurrently triggered to afford primary alcohol **14** in 97% yield (Scheme 2). Swern oxidation of primary alcohol **14** with DMSO, TFAA, and *N*,*N*-diisopropylethylamine (DIPEA) provided corresponding aldehyde **14a** (not shown).[10]

Corey–Fuchs reaction for the one-carbon homologation of aldehyde **14a** to corresponding terminal alkyne **16** was accomplished by homologation to dibromoolefin **15** with carbon tetrabromide and triphenylphosphine in CH_2Cl_2 (65% overall), followed by sequential lithium–halogen exchange with *n*-butyllithium and elimination (96% yield, Scheme 2).[11]

With propargylic intermediate **16** in hand, our attention was now directed towards installation of the β-keto ester moiety in key intermediate **17**. Introduction of an ester group to terminal alkyne **16** was successfully achieved by generation of the acetylic anion by using *n*-butyllithium and subsequent treatment with methyl chloroformate to provide corresponding methyl ynoate **16a** (not shown).[12] As precedented in the model system (for **5** and **6**), Claisen condensation with LDA (lithium diisopropylamide) and *tert*-butyl propionate afforded an inseparable mixture of desired β-keto ester **17** along with tautomer **18** in a 1:1 ratio (86% yield, Scheme 3).[3a] We were now poised to complete the synthesis by gold-catalyzed 6-*endo*-*dig* intramolecular cyclization. Thus, treatment of a mixture of **17** and **18** from the above reaction with catalyst **8** in $MeNO_2$ provided **1** in 81% yield (Scheme 3).

In parallel to the synthesis of **1**, the synthesis of the enantiomer of **1** was sought to validate the absolute configuration of (+)-violapyrone C. Thus, Swern oxidation of primary alcohol **19** provided aldehyde **19a** (not shown). Similar to the previously described synthesis, transformation of aldehyde **19a** (not shown) into corresponding terminal alkyne **21** was achieved by Corey–Fuchs reaction (Scheme 4). Introduction of an ester functional group to terminal alkyne **21** was accomplished by treatment of terminal alkyne **21** with *n*-butyllithium and methyl chloroformate to provide corresponding ynoate **22** in 95% yield (Scheme 4). Completion of **2** relied on Claisen condensation of ynoate **22** by using LDA and *tert*-butyl propionate to afford β-keto ester **19**, which was followed by formation of the α-pyrone by using gold(I) catalyst **8** (10 mol-%) in $MeNO_2$ to provide desired enantiomer **2** in 52% yield over two steps (Scheme 4).

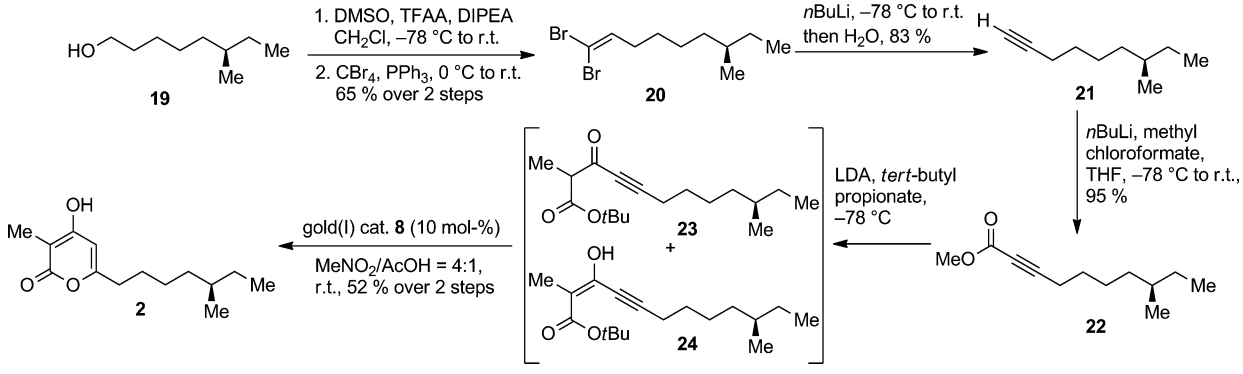


Scheme 3. Completion of the total synthesis.

With synthetic samples of **1** (22% yield overall) and **2** (27% yield overall) in hand, we were able to assign the absolute configuration of (+)-violapyrone C. As expected, the ^1H NMR and ^{13}C NMR spectra of the two synthetic samples were indistinguishable to those of natural (+)-violapyrone C obtained from actinomycete *Streptomyces* sp. 112CH148. Ultimately, the optical rotations of these three compounds were compared [natural violapyrone C: $[\alpha]_D$ = +50.0 (*c* = 0.1, MeOH); compound **1**: $[\alpha]_D$ = +49.0 (*c* = 0.1, MeOH); compound **2**: $[\alpha]_D$ = –53.0 (*c* = 0.1, MeOH)] to confirm that synthetic **1** was (+)-violapyrone C and **2** was its enantiomer (Figure 2).[13]

Conclusions

In conclusion, we described the efficient first total synthesis of (+)-violapyrone C and its enantiomer. The synthe-



Scheme 4. Synthesis of (–)-violapyrone C.

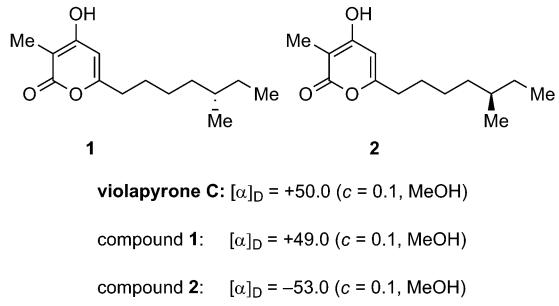


Figure 2. Optical rotations (in MeOH) of synthetic compounds **1** and **2** and natural violapyrone C.

sis route features the silver(I) oxide promoted monobenzylation of 1,4-butanediol, Wittig olefination, Claisen condensation, Corey–Fuchs reaction, and the gold-catalyzed synthesis of α-pyrone by 6-*endo*-*dig* cyclization. Furthermore, our total synthesis of (+)-violapyrone C confirms the structure and absolute configuration of natural (+)-violapyrone C.

Experimental Section

General: All reactions were performed under an atmosphere of nitrogen unless otherwise indicated. Anhydrous dichloromethane (CH_2Cl_2), toluene, acetonitrile (MeCN), dimethyl sulfoxide (DMSO), nitromethane ($MeNO_2$), and tetrahydrofuran (THF) were directly used from commercial sources. The concentration of *n*BuLi was titrated by using (–)-menthol and 1,10-phenanthroline. All other reagents were used without further purification. All workup, wash, and chromatographic solvents were distilled. Sodium sulfate (Na_2SO_4) was anhydrous. Thin-layer chromatography (TLC) was used to monitor the progress of the reactions by cospotting with the starting materials. *p*-Anisaldehyde (1350 mL absolute ethanol, 50 mL concentrated H_2SO_4, 37 mL *p*-anisaldehyde) was utilized as a common TLC visualizing solution. Flash chromatographic purifications were performed by using silica gel (230–400 mesh). The ^1H NMR and ^{13}C NMR spectroscopic data were recorded with a Varian 500-NMR in [D_1]chloroform as the solvent and are described in parts per million (ppm) from residual chloroform [δ =7.24 (for ^1H) and 77.23 ppm (for ^{13}C)]. Mass spectra were performed by using a Surveyor MSQ Benchtop LC–MS (Thermo Finnigan) and a 6128 Quadrupole LC–MS (Agilent Technologies) in KIOST.

(*S*)-{[(6-Methyloct-4-en-1-yl)oxy]methyl}benzene (13): A mixture of phosphonium iodide **10** (2.3 g, 5.00 mmol) and THF was cooled to 0 °C, and a solution of *n*BuLi (1.85 M in hexanes, 2.7 mL, 5.00 mmol) was added. After the mixture was stirred at room temperature for 30 min, a solution of aldehyde **12** (1.2 g, 6.50 mmol, 1.3 equiv.) in THF (5.0 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h, saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with pentane, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (CH_2Cl_2/pentane = 5:95 to 15:85) to give **13** [892.1 mg, 3.84 mmol, 77%; 2.3:1 mixture of (*E*)/(*Z*) isomers]. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.34 (d, *J* = 4.1 Hz, 4 H), 7.26–7.29 (m, 1 H), 5.29–5.34 (m, 1 H), 5.11–5.16 (t, *J* = 10.3 Hz, 1 H), 4.50 (s, 2 H), 3.47–3.49 (t, *J* = 6.5 Hz, 2 H), 2.33–2.36 (m, 1 H), 2.07–2.16 (m, 2 H), 1.65–1.71 (m, 2 H), 1.17–1.35 (m, 2 H), 0.92–0.93 (d, *J* = 6.6 Hz, 3 H), 0.82–0.85 ppm (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 137.0, 136.97, 128.5, 127.92, 127.88, 127.82, 127.81, 127.7, 73.10, 73.07, 70.1, 70.0, 38.6, 33.5, 30.4, 30.2, 30.1, 29.9, 29.3, 24.3, 21.2, 20.6, 12.2, 12.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{23}O$ $[M - H]^-$ 231.1749; found 231.1768.

(*S*)-6-Methyloctan-1-ol (14): A mixture of olefin **13** (656.0 mg, 2.82 mmol) and 10% Pd/C (27.0 mg, 9.0 mol-%) was stirred under an atmosphere of hydrogen at 50 °C for 45 h. Upon completion of the reaction, the catalyst was removed by filtration through a pad of Celite, and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:20 to 1:5) to give **14** (395.9 mg, 2.74 mmol, 97%). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.60–3.62 (t, *J* = 6.6 Hz, 2 H), 1.52–1.57 (m, 2 H), 1.22–1.32 (m, 7 H), 1.06–1.12 (m, 2 H), 0.81–0.84 (t, *J* = 7.5 Hz, 3 H), 0.81–0.83 ppm (d, *J* = 7.8 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 63.3, 36.8, 34.5, 33.0, 29.7, 27.1, 26.3, 19.4, 11.6 ppm. HRMS (ESI): calcd. for $C_9H_{20}O$ $[M]^+$ 144.1514; found 144.0677.

(*S*)-1,1-Dibromo-7-methylnon-1-ene (15): TFAA (427.3 μL, 3.07 mmol, 3.0 equiv.) was added dropwise to a solution of DMSO (436.6 μL, 6.15 mmol, 6.0 equiv.) in CH_2Cl_2 at –78 °C. After stirring at –78 °C for 10 min, a solution of **14** (147.7 mg, 1.02 mmol) in CH_2Cl_2 (4.0 mL) was added dropwise. The resultant cloudy mixture was stirred at –78 °C for 1 h. DIPEA (892.4 μL, 5.12 mmol, 5.0 equiv.) was added slowly, and the mixture was warmed to room temperature for 2 h. The mixture was diluted with EtOAc and quenched with H_2O. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:40) to give **14a** (123.5 mg, 0.87 mmol, 85%). A solution of carbon tetrabromide (575.9 mg, 1.74 mmol, 2.0 equiv.) in CH_2Cl_2 was stirred at room temperature, and the solution was cooled in an ice bath. Triphenylphosphine (911.0 mg, 3.47 mmol, 4.0 equiv.) was added at 0 °C, and the mixture was stirred for 1 h. A solution of **14a** (123.5 mg, 0.87 mmol) in CH_2Cl_2 (1.0 mL) was added to this mixture. The solution was warmed to room temperature and stirred for 18 h. The mixture was diluted with CH_2Cl_2 and quenched with H_2O. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (100% pentane) to give **15** (200.5 mg, 0.67 mmol, 65% over 2 steps). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.35–6.38 (t, *J* = 7.0 Hz, 1 H), 2.05–0.10 (q, 2 H), 1.38–1.39 (m, 2 H), 1.25–1.30 (m, 5 H), 1.07–1.13 (m, 2 H), 0.83–0.85 (t, *J* = 7.2 Hz, 3 H), 0.83–0.84 ppm (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.1, 88.7, 36.5, 34.5, 33.3, 29.7, 28.4, 26.8, 19.4, 11.6 ppm. HRMS (ESI): calcd. for $C_{10}H_{19}Br_2$ $[M + H]^+$ 296.9853; found 296.9890.

(*S*)-7-Methylnon-1-yne (16): Dibromoolefin **15** (755.5 mg, 2.53 mmol) was dissolved in THF under an atmosphere of N_2 and cooled to –78 °C. The solution was treated with *n*BuLi (1.85 M in hexanes, 5.9 mL, 10.90 mmol) and then stirred. After 1 h, the mixture was warmed to room temperature and stirred. After 3 h, the mixture was treated with H_2O, extracted with pentane, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (100% pentane) to give **16** (337.3 mg, 2.44 mmol, 96%). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.15–2.18 (dt, *J* = 7.2 Hz, 2 H), 1.91–1.92 (t, *J* = 2.7 Hz, 1 H), 1.46–1.53 (m, 2 H), 1.25–1.44 (m, 5 H), 1.06–1.14 (m, 2 H), 0.82–0.85 (t, *J* = 6.8 Hz, 3 H), 0.82–0.84 ppm (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 85.0, 68.3, 36.2, 34.5, 29.7, 29.0, 26.5, 19.4, 18.6, 11.6 ppm. HRMS (ESI): calcd. for $C_{10}H_{17}$ $[M - H]^-$ 137.1330; found 137.1341.

(10S)-*tert*-Butyl 2,10-Dimethyl-3-oxododec-4-ynoate (17): *n*BuLi (1.85 M in hexanes, 142.6 μL, 0.2638 mmol) was added to a cold solution (–78 °C) of terminal alkyne **16** (22.8 mg, 0.16 mmol) in THF under an atmosphere of N_2. The resulting mixture was stirred for 40 min and methyl chloroformate was added. The mixture was allowed to warm to room temperature. The mixture was diluted with diethyl ether and quenched with H_2O. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:30) to give **16a** (31.3 mg, 0.16 mmol, quantitative). *tert*-Butyl propionate (59.7 μL, 0.39 mmol, 3.0 equiv.) was added dropwise to a stirred solution of LDA (2.0 M in THF, 1.31 mmol, 10.0 equiv.) at –78 °C. The mixture was stirred at this temperature for 30 min before **16a** (25.8 mg, 0.13 mmol) was slowly introduced; stirring was continued at –78 °C for 2 h. The mixture was diluted with diethyl ether and quenched with saturated aqueous solution of NH_4Cl. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:35) to give **17** (34.3 mg, 0.12 mmol, 86% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.27 (s, 1 H), 3.40–3.44 (q, 1 H), 2.39–2.41 (t, J = 7.0 Hz, 2 H), 2.34–2.37 (t, J = 7.1 Hz, 2 H), 1.81 (s, 3 H), 1.55 (m), 1.48 (s, 9 H), 1.45 (s, 9 H), 1.25–1.32 (m), 1.07–1.12 (m), 0.82–0.85 (t, J = 7.0 Hz, 6 H), 0.82–0.84 ppm (d, J = 6.6 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.8, 173.2, 169.0, 152.1, 104.5, 100.1, 96.8, 82.0, 81.9, 79.7, 75.3, 56.1, 49.9, 36.2, 36.1, 34.5, 34.4, 29.624, 29.617, 28.6 28.4, 28.32, 28.27, 28.22, 28.19, 28.17, 28.09, 28.0, 26.6, 26.6, 19.7, 19.4, 19.34, 19.26, 14.0, 13.6, 13.0, 11.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{29}O_3$ $[M - H]^-$ 293.2117; found 293.2127.

(*S*)-4-Hydroxy-3-methyl-6-(5-methylheptyl)-2*H*-pyran-2-one (1): A solution of gold(I) catalyst **8** (9.2 mg, 0.01 mmol, 10.0 mol-%) and **17** (34.3 mg, 0.12 mmol) in $MeNO_2$/AcOH (4:1) was stirred for 20 h at room temperature. The mixture was diluted with EtOAc and quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:4 to 1:2) to give **1** (22.5 mg, 0.09 mmol, 81%). ^{1}H NMR (500 MHz, CD_3OD): δ = 5.99 (s, 1 H), 2.47 (t, J = 7.6 Hz, 2 H), 1.85 (s, 3 H), 1.62 (m, 2 H), 1.36 (m, 2 H), 1.33 (m, 2 H), 1.32 (m, 1 H), 1.15 (m, 2 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.87 ppm (d, J = 6.5 Hz, 3 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 169.3, 168.2, 165.0, 101.3, 99.0, 37.5, 35.7, 34.4, 30.7, 28.4, 27.6, 19.7, 11.9, 8.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{22}O_3$ $[M]^-$ 238.1569; found 238.1564.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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[13] For a comparison of the ^{1}H NMR and ^{13}C NMR spectra of synthetic **1** and **2** and natural violapyrone C, see: Table S2 in the Supporting Information.

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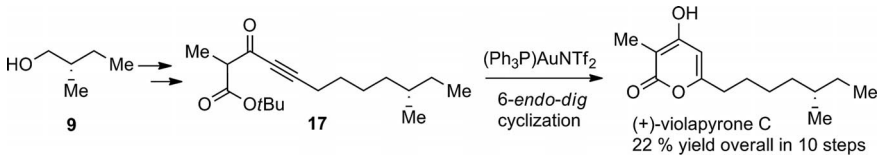
Total Synthesis



The total synthesis of (+)-violapyrone C is accomplished through gold(I)-catalyzed 6-*endo-dig* cyclization, silver(I) oxide promoted monobenzylation, Wittig olefination, and Corey–Fuchs reaction [22% yield over 10 steps from readily available (*S*)-(–)-2-methylbutanol]. The absolute configuration of natural (+)-violapyrone C is determined; Tf = trifluoromethylsulfonyl.

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Total Synthesis and Configurational Validation of (+)-Violapyrone C

Keywords: Total synthesis / Natural products / Oxygen heterocycles / Gold / Wittig reactions

