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Total Synthesis of Cristatic Acid Based on Late-Stage Decarboxylative Allylic Migration and Biomimetic Aromatization of a Diketo Dioxinone

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A fifteen-step synthesis of methyl cristatate is described. *tert*-Butyl-[(*E*)-6-iodo-3-methylhex-2-enyloxy)]diphenylsilane, synthesized from geraniol, was coupled with 2-(diethoxymethyl)-4-lithiofuran and transformed – by acetal hydrolysis, Wittig olefination, and desilylation – into a sesquiterpene furan alcohol. This alcohol was converted into methyl cristatate by sequential condensation with carbonyldiimidazole and the enolate dianion derived from 2,2-dimethyl-6-(2-oxopropyl)-4*H*-1,3-dioxin-4-one and subsequent Pd^0-catalyzed decarboxylative allylic migration, biomimetic aromatization, and transesterification with methanol.

Introduction

Terpene resorcylates exhibit an interesting array of biological activities and are widely found in nature (a selection of examples is shown in Figure 1).[1] Among them, cristatic acid (**6**), isolated from the fruiting bodies of the higher mushroom *Albatrellus cristatus* in 1981, exhibits a broad range of biological properties, including antibiotic activity against Gram-positive bacteria.[1o] In addition, it was found to have strong hemolytic activity and inhibitory effects against cells of the ascites form of the Ehrlich carcinoma.[2]

Most resorcylate natural product syntheses depend on the use of 6-alkylated derivatives of 2,4-dihydroxybenzoate esters as the starting materials.[2b,3] These approaches involve derivatization of this aromatic building block and usually require the use of protecting groups, which can be problematic to cleave chemoselectively at the end. This is especially true for cristatic acid (**6**) due to the sensitive nature of the furan moiety. Joullié's synthesis can be taken as an illustration of this major difficulty: only one of the two MOM protecting groups could be removed from methyl di-*O*-MOM-cristatate.[4] Fürstner circumvented this problem by using a SEM {[2-(trimethylsilyl)ethoxy]methyl} protecting group.[2b]

As an alternative strategy to solve these issues, we have developed a flexible approach based on extending the methods of Harris, Hyatt, and Boeckman, which involve late-stage aromatization from diketo-dioxinone precursors.[5] This strategy has been utilized efficiently for the syntheses of several biologically active resorcylate natural products.[6]

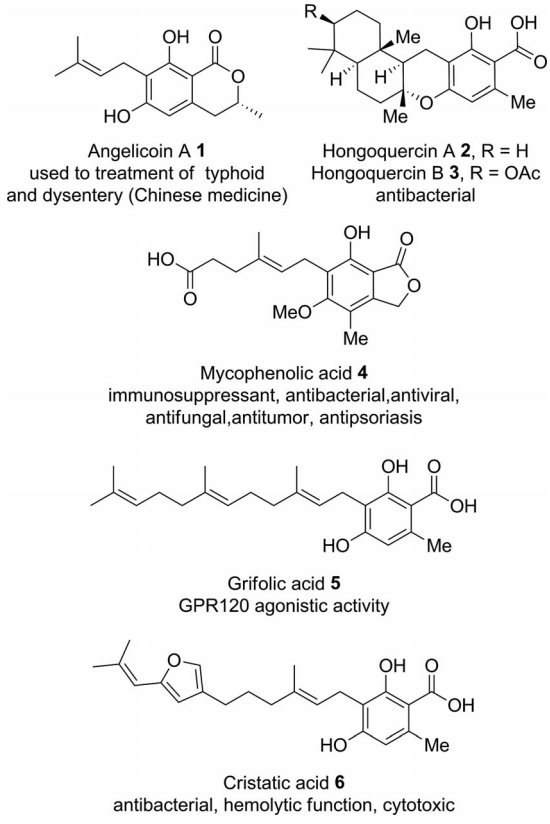

Figure 1. Angelicoin A (**1**), hongoquercins **2** and **3**, mycophenolic acid (**4**), grifolic acid (**5**), and cristatic acid (**6**).

Recently, we discovered that allylic dioxinone diketo esters readily undergo palladium(0)-catalyzed regiospecific allylic migration followed by cesium-carbonate-mediated aromatization.[7] Here we report the extension of this methodology to the synthesis of methyl cristatate.

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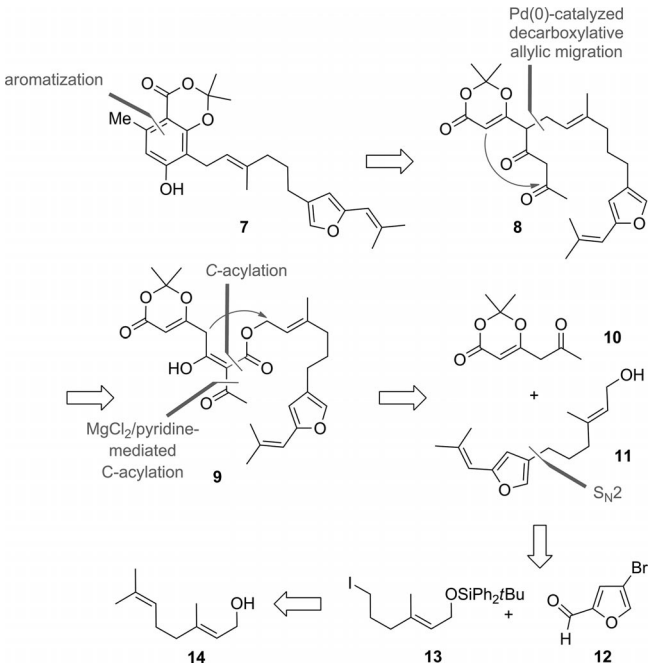
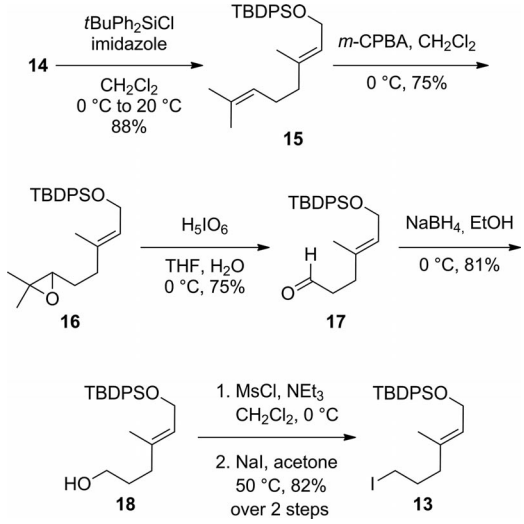
The retrosynthetic analysis is outlined in Scheme 1 with disassembly of the resorcylate **7**, which should be available (in a forward direction) through a late-stage regioselective palladium(0)-catalyzed decarboxylative allylic migration and aromatization of diketo-dioxinone **9**, via the dioxinone diketo ester **8**.[7] Dioxinone diketo ester **9** should be available through two successive *C*-acylations of keto dioxinone **10** with acetyl chloride and with an activated carbonate ester derivative of alcohol **11**.[6c,6d,6f,8] In turn, alcohol **11** should be available from bromofuran **12** and iodide **13**, which should be easily derived from geraniol (**14**).



Scheme 1. Retrosynthetic analysis.

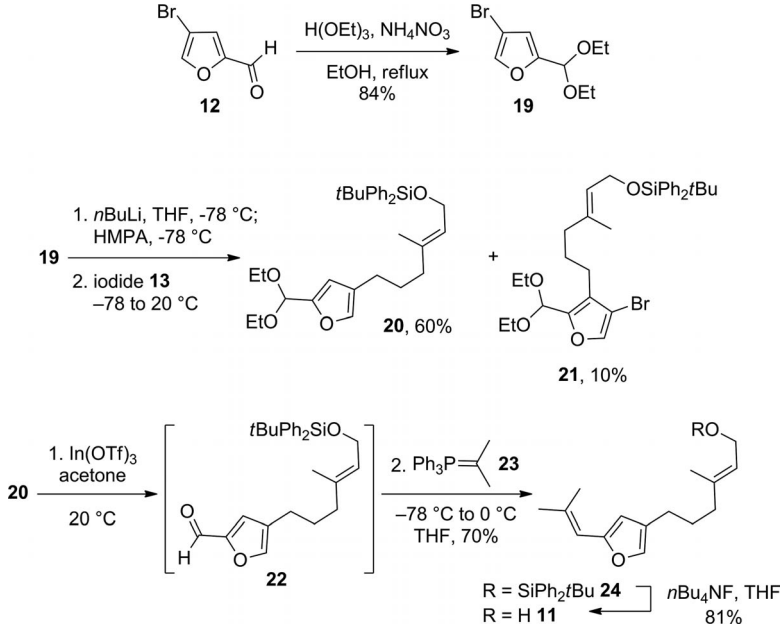
Results and Discussion

Geraniol (**14**) was protected under modified Corey's conditions to provide silyl ether **15** (Scheme 2).[9] Selective epoxidation and oxidative cleavage (*m*-CPBA, H_5IO_6) gave aldehyde **17**,[10] which was reduced with sodium borohydride, and the derived alcohol was converted into iodide **13** by mesylation and iodide displacement. This sequence was successfully scaled up to provide 34 g of iodide **13** (starting from 25 mL of geraniol, 147 mmol) with a 50% yield over six steps and after only one final purification by chromatography.



Scheme 2. Synthesis of iodide **13** from geraniol (**14**).

In order to link the furan moiety to the geraniol-derived side chain **13** (Scheme 3), the commercially available sensitive 4-bromofuran-2-carbaldehyde (**12**) was protected as acetal **19** under mild conditions (NH_4NO_3, EtOH).[4] At-



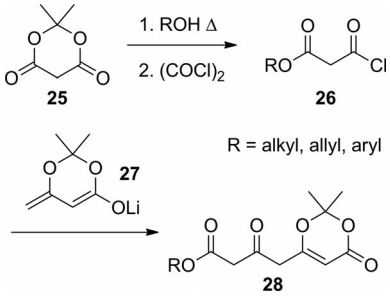
Scheme 3. Synthesis of the allylic alcohol **11**.

tempted lithiation/halogen exchange with bromide **19**, addition to the aldehyde **17**, and reduction of the derived secondary alcohol proved inefficient (<10%).

Fortunately, though, treatment of the lithiofuran derived from bromide **19** with iodide **13** gave furan **20** (Scheme 3, 60%) accompanied by bromofuran **21** (10%). There was clearly competition between lithium/bromide exchange and C2-lithiation assisted by the precomplexation of *n*BuLi by the acetal. After optimization, introduction of HMPA after the addition of *n*BuLi was found to be essential for obtaining furan **20** as the major product. Indeed, introduction of HMPA prior to *n*BuLi furnished only bromofuran **21** (73%).[11] Utilization of DMPU or *N*,*N*′-dimethylimidazolidin-2-one as substitutes for HMPA did not improve the yield of furan **20** (24% and 33% yields, respectively).[12]

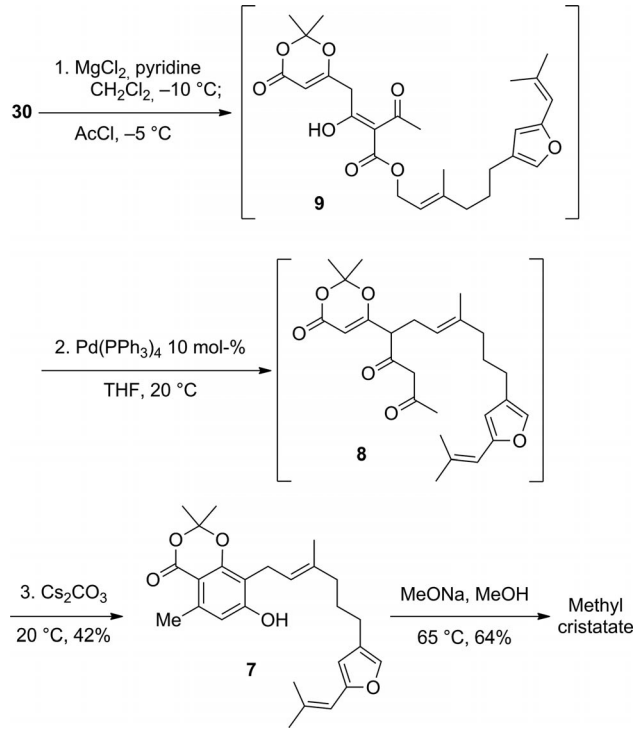
Indium-triflate-catalyzed deprotection of the diethyl acetal **20** was clean (93%).[13] The resulting aldehyde **22** (Scheme 3) was directly condensed with isopropylidenetriphenylphosphorane, giving the alkene **24**. Finally, deprotection of this product with tetrabutylammonium fluoride gave allylic alcohol **11**.

Attempted synthesis of the dioxinone keto ester **30** (Scheme 5, below) by the known[5f,6a,6b,6e,7b,7c,7d,14] thermal retro-Diels–Alder reaction of Meldrum's acid in the presence of alcohol **11**, subsequent treatment of the resulting malonate half ester with oxalyl chloride, and condensation with the enolate **27** (Scheme 4) failed on account of the high instability of the delicate furan unit towards acid chloride formation.



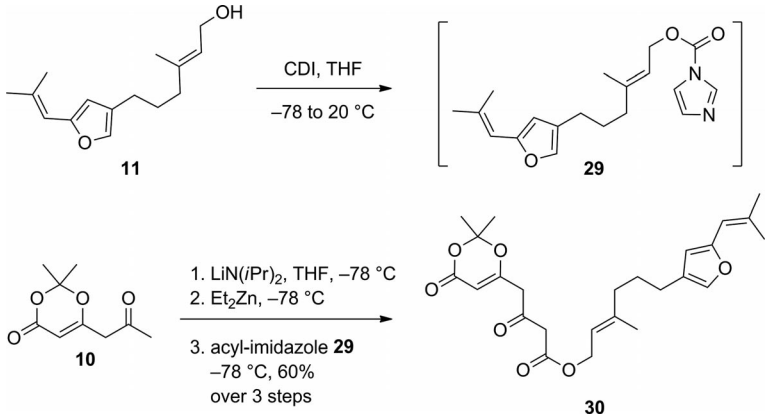
Scheme 4. General pathway to dioxinone keto esters **28**.

In consequence, we developed a milder alternative procedure. Treatment of alcohol **11** with excess *N*,*N*-carbonyldiimidazole (3 equiv.) at –78 °C to room temperature cleanly gave the imidazolecarboxylate **29** (Scheme 5). This compound was directly used to acylate the zinc dienolate derived from keto-dioxinone **10**, to give dioxinone keto ester **30**.[6c,6d,6f,8] This was subjected to our key aldol and aromatization sequence, leading to isopropylidene-protected β-resorcylate **7** (Scheme 6).



Scheme 6. Completion of the synthesis of methyl cristatate.

A regioselective $MgCl_2$-mediated Claisen condensation of dioxinone **30** with acetyl chloride gave the dioxinone diketo ester **9** (Scheme 6), which was not isolated but was subjected to a sequence consisting of palladium(0)-catalyzed regioselective decarboxylative allyl migration, in situ Cs_2CO_3-mediated cyclisation, and aromatization.[7] All of



Scheme 5. Synthesis of dioxinone keto ester **30**; CDI = *N*,*N*-carbonyldiimidazole.

these reactions were compatible with the sensitive isobutylene-substituted furan. Finally, the synthesis of the furanyl terpenoid resorcylate in its methyl ester form was completed by isopropylidene cleavage with sodium methoxide in hot methanol (Scheme 6).

Conclusions

In conclusion, we have completed the synthesis of methyl cristatate with a 2.7% overall yield and in 15 linear steps (six purifications by chromatography) from inexpensive geraniol (**14**). Our late-stage decarboxylative allylic migration, cyclization, and aromatization sequence leading to protected β-resorcylate from dioxinone diketo ester **7** proved to be general, mild, and practical. The synthesis of intermediate **13** was adjusted from our previous approach because of the high sensitivity of the 2-isobutenylfuran unit to acidic conditions.

Experimental Section

General Methods: All reactions were carried out in oven-dried glassware under dry N_2 or Ar unless otherwise stated. The following reaction solvents were distilled under N_2: THF over Na/Ph_2CO, MeOH over Na, and CH_2Cl_2, pyridine, and Et_3N from CaH_2. H_2O refers to redistilled H_2O. Other solvents and all reagents were obtained from commercial suppliers and, if purity was >98%, used as obtained. NaI was recrystallized from Me_2CO. Isopropyltriphenylphosphonium iodide was recrystallized three times from PhMe; the crystals were washed with diethyl ether and dried under vacuum. Cs_2CO_3 was oven-dried at 120 °C overnight. Flash column chromatography was performed with Merck silica gel 60, particle size 40–63 mm (eluents are given in parentheses). "Hexanes" refers to petroleum spirit of boiling range 40–60 °C. Thin layer chromatography (TLC) was performed on pre-coated aluminum-backed plates (Merck Kieselgel 60 F_{254}); visualization was accomplished under UV light (254 nm) and/or by staining with aqueous potassium permanganate or vanillin followed by gentle heating with a heat gun. ^{1}H NMR and ^{13}C NMR spectra were recorded by operating at 400 or 500 MHz and at 100 or 125 MHz, respectively, with chemical shifts (δ) quoted in parts per million (ppm) and referenced to the residual $CDCl_3$ solvent peak (δ_H = 7.26, δ_C = 77.16 ppm). Coupling constants (J) are quoted in Hertz (Hz) to the nearest 0.1 Hz.

***tert*-Butyl-[(*E*)-3,7-dimethylocta-2,6-dienyloxy]diphenylsilane (15):** Imidazole (1.3 g, 19.02 mmol, 1.1 equiv.) and *t*$BuPh_2SiCl$ (5 mL,19.02 mmol, 1.1 equiv.) were added at 0 °C with stirring to geraniol (**14**, 2.7 g, 17.3 mmol, 1.0 equiv.) in CH_2Cl_2 (90 mL), and the mixture was allowed to warm to 20 °C. After 12 h, H_2O (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (2× 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (EtOAc/hexanes 1:9 to 2:8) to afford silyl ether **15** (6 g, 88%) as a colorless oil. R_f = 0.8 (EtOAc/hexanes 2:8). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.71–7.68 (m, 4 H), 7.44–7.35 (m, 6 H), 5.40–5.36 (m, 1 H), 5.12–5.08 (m, 1 H), 4.22 (d, J = 8.0 Hz, 2 H), 2.09–1.96 (m, 4 H), 1.68 (d, J = 0.5 Hz, 3 H), 1.61 (s, 3 H), 1.43 (s, 3 H), 1.04 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 137.0, 135.6 (4 C), 135.2 (2 C), 134.1, 131.5 (2 C), 129.5 (4 C), 124.1, 124.0 (2 C), 61.2, 39.5, 26.8 (3 C), 26.4, 25.7, 19.2, 17.7, 16.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1473, 1428, 1379, 1110, 1056, 822 cm^{-1}. HRMS (CI) calcd. for $C_{26}H_{40}NO_2Si$ $[M + NH_4]^+$ 426.2828; found 426.2842.

***tert*-Butyl-[(*E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enyloxy]-diphenylsilane (16):**[10] *m*-CPBA (3.6 g, 15.83 mmol, 1.2 equiv.) in CH_2Cl_2 (50 mL) was added dropwise with stirring at 0 °C to alkene **15** (5.2 g, 13.2 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL). After 2 h, the mixture was filtered and $Ca(OH)_2$ (4.2 g, 56.76 mmol, 4.3 equiv.) was added. After 1 h stirring, the mixture was filtered, concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 3:7) to afford epoxide **16** (4 g, 75%) as a colorless oil. R_f = 0.65 (Et_2O/pentane 3:7). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.70–7.67 (m, 4 H), 7.44–7.35 (m, 6 H), 5.43–5.39 (m, 1 H), 4.22 (d, J = 6.0 Hz, 2 H), 2.71 (t, J = 5.0 Hz, 1 H), 2.19–2.03 (m, 2 H), 1.71–1.59 (m, 2 H), 1.46 (s, 3 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 136.1, 135.6 (4 C), 134.0 (2 C), 129.5 (2 C), 127.6 (4 C), 124.6, 64.0, 61.0, 58.4, 36.1, 27.2, 26.8 (2 C), 24.9, 19.2, 18.7, 16.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1473, 1428, 1378, 1112, 1057, 823 cm^{-1}. HRMS (ESI) calcd. for $C_{26}H_{36}O_2NaSi$ $[M + Na]^+$ 431.2382; found 431.2369.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-4-enal (17):[10] H_5IO_6 (4.14 g, 19.51 mmol, 2.0 equiv.) in H_2O (20 mL) was added with stirring at 0 °C to epoxide **16** (4 g, 9.76 mmol, 1.0 equiv.) in THF (32 mL). After 30 min, saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with Et_2O (2× 200 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 3:7) to give aldehyde **17** (2 g, 60%) as a colorless oil. R_f = 0.60 (Et_2O/pentane 3:7). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 9.75 (t, J = 1.0 Hz, 1 H), 7.69–7.67 (m, 4 H), 7.42–7.36 (m, 6 H), 5.40–5.37 (m, 1 H), 4.22 (d, J = 6.0 Hz, 2 H), 2.50 (td, J = 6.0, 1.0 Hz, 2 H), 2.30 (t, J = 6.0 Hz, 2 H), 1.45 (s, 3 H), 1.04 (s, 9 H). ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 202.2, 135.6 (2 C), 134.9, 133.9 (4 C), 129.6 (2 C), 127.6 (4 C), 125.0, 60.9, 41.8, 31.5, 26.8 (3 C), 19.1, 16.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1722, 1472, 1428, 1390, 111, 1069, 822 cm^{-1}. MS (CI) $[M + NH_4]^+$ requires 340; found 340; $[M + H]^+$ requires 323; found 323.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-4-en-1-ol (18): $NaBH_4$ (330 mg, 8.67 mmol, 2.0 equiv.) was added with stirring at 0 °C to aldehyde **17** (1.6 g, 4.34 mmol, 1.0 equiv.) in EtOH (80 mL). After 3 h, the mixture was concentrated (rotary evaporator) and saturated aqueous $NaHCO_3$ (100 mL) was added. The mixture was extracted with EtOAc (2× 200 mL), and the combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 2:1) to give alcohol **18** (1.3 g, 81%) as a colorless oil. R_f = 0.55 (Et_2O/pentane 2:1). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 7.70–7.68 (m, 4 H), 7.44–7.36 (m, 6 H), 5.43–5.40 (m, 1 H), 4.22 (d, J = 7.0 Hz, 2 H), 4.63 (m, J = 6.0 Hz, 2 H), 2.05 (t, J = 6.0 Hz, 2 H), 1.69–1.63 (m, 2 H), 1.46 (s, 3 H), 1.28 (t, J = 6.0 Hz, 1 H), 1.04 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 136.8, 135.6 (2 C), 134.0 (4 C), 129.5 (2 C), 127.6 (4 C), 124.4, 62.7, 61.0, 35.7, 30.5, 26.8 (3 C), 19.1, 16.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3343, 1473, 1428, 1112, 1052, 998, 823 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{36}NO_2Si$ $[M + NH_4]^+$ 386.2515; found 386.2517.

***tert*-Butyl-[(*E*)-6-iodo-3-methylhex-2-enyloxy]diphenylsilane (13):** Et_3N (6.3 mL, 45.52 mmol, 2.0 equiv.), followed by MsCl (2.1 mL, 27.3 mmol, 1.2 equiv.), were added with stirring at 0 °C to alcohol **18** (8.4 g, 22.76 mmol, 1.0 equiv.) in CH_2Cl_2 (115 mL). After 45 min, saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was extracted with CH_2Cl_2 (2× 100 mL). The combined organic layers were successively washed with aqueous HCl (1 M, 100 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated (ro-

tary evaporator). The product was used directly without further purification. NaI (4.438 g, 29.6 mmol, 1.3 equiv.) was added with stirring to the crude methanesulfonate in Me_2CO (200 mL). The mixture was heated at 50 °C for 18 h and concentrated (rotary evaporator). A 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (100 mL) was added, and the mixture was extracted with Et_2O (2× 100 mL). The organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 1:99) to give iodide **13** (9.2 g, 84% over two steps) as a colorless oil. R_f = 0.90 (Et_2O/pentane 1:9). ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 7.72–7.71 (m, 4 H), 7.46–7.39 (m, 6 H), 5.46–5.43 (m, 1 H), 4.25 (d, J = 6.0 Hz, 2 H), 3.14 (t, J = 7.0 Hz, 2 H), 2.08 (t, J = 7.0 Hz, 2 H), 1.91 (quin., J = 7.0 Hz, 2 H), 1.44 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 135.6, 134.9 (2 C), 133.9 (4 C), 129.5 (2 C), 127.6 (4 C), 125.4, 61.0, 39.8, 31.3, 26.8 (3 C), 19.1, 16.1, 6.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1427, 1388, 1217, 1110, 1051, 823 cm^{-1}. HRMS (CI) calcd. for $C_{23}H_{35}NOSiI$ $[M + NH_4]^+$ 496.1533; found 496.1542.

4-Bromo-2-(diethoxymethyl)furan (19):[4] NH_4NO_3 (3 mg, 0.032 mmol, 0.05 equiv.) was added with stirring to aldehyde **12** (0.1 g, 0.63 mmol, 1.0 equiv.) in EtOH (3.15 mL), and the mixture was heated to reflux. After 2 h, the solution was cooled to 20 °C and concentrated (rotary evaporator). Brine (50 mL) was added and the mixture was extracted with Et_2O (2× 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 1:49) to afford bromofuran **19** (120 mg, 77%) as a pale yellow oil. R_f = 0.90 (Et_2O/pentane 1:9). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.40 (d, J = 0.5 Hz, 1 H), 6.47 (d, J = 0.5 Hz, 1 H), 5.49 (s, 1 H), 3.66–3.54 (m, 4 H), 1.23 (t, J = 8.0 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 152.8, 140.5, 111.6, 100.0, 95.8, 61.4 (2 C), 15.1 (2 C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3147, 1737, 1372, 1320, 1218, 1138, 1050, 923, 898, 790 cm^{-1}. HRMS (EI) calcd. for $C_9H_{13}O_3Br$ $[M + H]^+$ 248.0048; found 248.0041.

***tert*-Butyl-{(*E*)-6-[5-(diethoxymethyl)furan-3-yl]-3-methylhex-2-enyloxy}diphenylsilane (20) and {(*E*)-6-[4-Bromo-2-(diethoxymethyl)-furan-3-yl]-3-methylhex-2-enyloxy}(*tert*-butyl)diphenylsilane (21):** *n*BuLi (0.9 mL, 1.2 M in hexanes, 1.09 mmol, 2.0 equiv.) was added dropwise with stirring at –78 °C to bromofuran **19** (270 mg, 1.09 mmol, 2.0 equiv.) in THF (4 mL). After 5 min, HMPA (0.25 mL, 1.417 mmol, 2.6 equiv.) was added dropwise and stirring continued for 30 min. Iodo-olefin **13** (261 mg, 0.55 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise, and the resulting solution was allowed to warm to 20 °C. After 18 h, saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with Et_2O (2× 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 1:29 to 3:27) to afford furan **20** (175 mg, 60%) as a clear gum and bromofuran **21** (32 mg, 10%) as a clear oil.

Furan 20: R_f = 0.70 (Et_2O/pentane 1:9). ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 7.71–7.69 (m, 4 H), 7.42–7.36 (m, 6 H), 7.17 (d, J = 0.5 Hz, 1 H), 6.30 (br. s, 1 H), 5.50 (s, 1 H), 5.40–5.37 (m, 1 H), 4.24 (d, J = 6.0 Hz, 2 H), 3.67–3.58 (m, 4 H), 2.35 (t, J = 7.0 Hz, 2 H), 2.00 (d, J = 7.0 Hz, 2 H), 1.63 (quin. J = 7.0 Hz. 2 H), 1.44 (s, 3 H), 1.25 (t, J = 8.0 Hz, 6 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 151.8, 138.6, 136.7, 135.6 (4 C), 134.1 (2 C), 129.5 (2 C), 127.6 (4 C), 125.5, 124.4, 109.4, 96.4, 61.3 (2 C), 61.1, 38.9, 27.7, 26.8 (3 C), 24.3, 19.2, 19.2, 15.15 (2 C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 1683, 1461, 1427, 1361, 1109, 1051, 1005, 822 cm^{-1}. HRMS (ESI) calcd. for $C_{32}H_{44}O_5NaSi$ $[M + Na]^+$ 559.2856; found 599.2856.

Bromofuran 21: R_f 0.75 (Et_2O/pentane 1:9). ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 7.70–7.68 (m, 4 H), 7.41–7.36 (m, 6 H), 6.38 (s, 1 H), 5.45 (s, 1 H), 5.40–5.38 (m, 1 H), 4.22 (d, J = 6.0 Hz, 2 H), 3.65–3.54 (m, 4 H), 2.59 (t, J = 7.0 Hz, 2 H), 1.99 (t, J = 7.0 Hz, 2 H), 1.72 (quin, J = 7.0 Hz, 2 H), 1.42 (s, 3 H), 1.22 (t, J = 8.0 Hz, 6 H), 1.04 (s, 9 H). ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 152.8, 150.1, 136.2, 135.6 (4 C), 134.0 (2 C), 129.5 (2 C), 127.6 (4 C), 124.7, 111.8, 96.3, 96.0, 61.3 (2 C), 61.1, 38.7, 26.8 (3 C), 25.7, 25.6, 19.2, 16.1, 15.1 (2 C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3457, 1725, 1436, 1368, 1217, 1111, 1092, 900 cm^{-1}. HRMS (ESI) calcd. for $C_{32}H_{43}O_4NaSiBr$ $[M + Na]^+$ 621.2012; found 621.2013.

***tert*-Butyl-{3-methyl-6-[(*E*)-5-(2-methylprop-1-enyl)furan-3-yl]hex-2-enyloxy}diphenylsilane (24):** $In(OTf)_3$ (51 mg, 0.09 mmol, 0.1 equiv.) was added with stirring to (diethoxymethyl)furan **20** (500 mg, 0.91 mmol, 1.0 equiv.) in Me_2CO (18.2 mL). After 5 min, saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (2× 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator) to afford aldehyde **22** (380 mg, 93%) as a colorless oil. The product was used directly without further purification. *n*BuLi (0.35 mL, 1.2 M in hexanes, 0.42 mmol, 1.2 equiv.) was added dropwise with stirring at –78 °C to isopropyltriphenylphosphonium iodide (182 mg, 0.42 mmol, 1.2 equiv.) in THF (3.5 mL), giving an orange solution. After 30 min at 0 °C the color had turned deep red, the mixture was recooled to –78 °C, and crude aldehyde **22** (141 mg, 0.32 mmol, 1.0 equiv.) in THF (0.5 mL) was added dropwise. After the mixture had been kept for 30 min at 0 °C, saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (2× 40 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 2:98) to afford alkene **24** (120 mg, 70%) as a colorless oil. R_f = 0.95 (Et_2O/pentane 1:9). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.72–7.70 (m, 4 H), 7.44–7.38 (m, 6 H), 7.11 (s, 1 H), 6.07 (s, 1 H), 6.04 (s, 1 H), 5.40 (t, J = 6.0 Hz, 1 H), 4.25 (d, J = 6.0 Hz, 2 H), 2.37 (t, J = 8.0 Hz, 2 H), 2.02 (t, J = 8.0 Hz, 2 H), 2.00 (s, 3 H), 1.91 (s, 3 H), 1.65 (quin. J = 8.0 Hz, 2 H), 1.45 (s, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 153.7, 136.8, 135.6 (4 C), 134.8 (2 C), 134.1 (2 C), 129.5 (2 C), 127.6 (4 C), 126.4, 124.4, 114.6, 108.7, 61.13, 38.9, 27.9, 27.0, 26.9 (3 C), 24.4, 20.1, 19.2, 16.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1472, 1428, 1261, 1111, 1059, 823 cm^{-1}. HRMS (CI) calcd. for $C_{31}H_{41}O_2Si$ $[M + H]^+$ 473.2876; found 473.2874.

3-Methyl-6-[5-((*E*)-2-methylprop-1-enyl)furan-3-yl]hex-2-en-1-ol (11): nBu_4NF in THF (1 M, 0.18 mL, 0.18 mmol, 1.5 equiv.) was added dropwise with stirring to silyl ether **24** (60 mg, 0.12 mmol, 1.0 equiv.) in THF (0.6 mL). After 18 h, saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with Et_2O (2× 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (Et_2O/pentane 1:1) to afford alcohol **11** (25 mg, 81%) as a colorless gum. R_f = 0.42 (Et_2O/pentane 1:1). ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 7.12 (s, 1 H), 6.06 (s, 1 H), 6.03 (s, 1 H), 5.45–5.42 (m, 1 H), 4.17 (d, J = 6.0 Hz, 2 H), 2.37 (t, J = 8.0 Hz, 2 H), 2.08 (t, J = 8.0 Hz, 2 H), 1.99 (s, 3 H), 1.90 (s, 3 H), 1.74–1.66 (m, 2 H), 1.69 (s, 3 H) 1.40 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 153.7, 139.5, 136.8, 134.7, 126.3, 123.6, 114.5, 108.7, 59.4, 39.1, 27.9, 27.0, 24.6, 20.1, 16.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3453 (br.) 1739, 1441, 1366, 1217, 1229, 1206, 985 cm^{-1}. HRMS (EI) calcd. for $C_{15}H_{22}O_2$ $[M + H]^+$ 234.1620; found 234.1635.

3-Methyl-6-[5-((*E*)-2-methylprop-1-enyl)furan-3-yl]hex-2-enyl 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (30): Alcohol **11** (200 mg, 0.85 mmol) in THF (6 mL) was added with stirring at –78 °C to *N*,*N*′-carbonyldiimidazole (413 mg,

2.55 mmol) in THF (11 mL) and the mixture was allowed to warm to room temperature overnight. H_2O (50 mL) was added and the mixture was extracted with AcOEt (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator) to leave the crude imidazole carbonate, which was used without further purification. 2,2-Dimethyl-6-(2-oxopropyl)-4*H*-1,3-dioxin-4-one (**10**, 344 mg, 1.87 mmol, 2.2 equiv.) in THF (2 mL) was added at –78 °C to freshly prepared $LiN(iPr)_2$ (3.88 mmol, 4.5 equiv.) in THF (5 mL). After 10 min, the mixture had solidified and was allowed to warm to –40 °C and left for 1 h. Et_2Zn in hexanes (1 M, 3.9 mL, 3.9 mmol, 4.6 equiv.) was added and, after 20 min, the mixture was cooled to –78 °C and the crude imidazole carboxylate **29** in THF (3 mL) was added dropwise. After the system had been kept at –78 °C for 45 min, saturated aqueous NH_4Cl (5 mL) was added slowly. The solution was allowed to warm to room temperature, after which H_2O (40 mL) was added and the pH was adjusted to about 3 with aqueous HCl (1 M, 5 mL). After separation, the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (AcOEt/hexanes 3:7) to give dioxinone keto ester **30** containing 20% of the corresponding enol (228 mg, 60% over two steps) as a light yellow oil. R_f = 0.44 (AcOEt/hexanes 4:6). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) of the dioxinone keto ester: δ = 7.11 (s, 1 H), 6.05 (s, 1 H), 5.38 (s, 1 H), 5.36 (m, 1 H), 4.68 (d, J = 7.2 Hz, 2 H), 3.53 (s, 2 H), 3.51 (s, 2 H), 2.38 (t, J = 7.5 Hz, 2 H), 2.09 (t, J = 7.4 Hz, 2 H), 1.98 (s, 3 H), 1.90 (s, 3 H), 1.72–1.67 (m, 11 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 195.7, 166.4, 163.6, 160.5, 153.7, 143.4, 136.8, 135.0, 126.1, 117.6, 114.5, 108.6, 107.4, 97.1, 62.6, 49.1, 47.0, 38.9, 27.8, 27.0, 25.0 (2 C), 24.4, 20.1, 16.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1722, 1639, 1390, 1375, 1272, 1253, 1203, 1016 cm^{-1}. HRMS (ES) calcd. for $C_{25}H_{33}O_7$ $[M + H]^+$ 445.2226; found 445.2229.

7-Hydroxy-2,2,5-trimethyl-8-{(*E*)-3-methyl-6-[5-(2-methylprop-1-enyl)furan-3-yl]hex-2-enyl}-4*H*-benzo[*d*][1,3]dioxin-4-one (7): $MgCl_2$ (82 mg, 0.86 mmol, 2 equiv.) and (after 5 min and 30 min, respectively) pyridine (0.93 mL, 1.16 mmol, 2.7 equiv.) and subsequently AcCl (0.37 mL, 0.52 mmol, 1.2 equiv.) were added dropwise with stirring at –10 °C and –5 °C (AcCl) to dioxinone keto ester **13** (192 mg, 0.43 mmol) in CH_2Cl_2 (5 mL). After 30 min, saturated aqueous NH_4Cl (25 mL) and CH_2Cl_2 (25 mL) were added. After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator) to leave crude dioxinone, which was used without further purification. The crude dioxinone diketo ester **9** in THF (5 mL) was degassed by bubbling argon through the solution for 15 min. $Pd(PPh_3)_4$ (24 mg, 0.022 mmol, 0.05 equiv.) was added and the mixture was stirred at room temperature for 70 h. Dry Cs_2CO_3 (420 mg, 1.29 mmol, 3 equiv.) was added and the mixture was further stirred for 15 h. H_2O (5 mL) and AcOEt (25 mL) were added and the pH was adjusted to about 5 with aqueous HCl (0.1 M, 20 mL). After phase separation, the aqueous phase was extracted with AcOEt (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (AcOEt/hexanes 2:8) to afford the cristatic acid derivative **7** (77 mg, 42% over two steps) as a yellow oil. R_f = 0.52 (AcOEt/hexanes 3:7). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.08 (s, 1 H), 6.97 (br. s, 1 H), 6.49 (s, 1 H), 6.04 (s, 1 H), 6.01 (s, 1 H), 5.21 (t, J = 7.2 Hz, 2 H), 3.33 (t, J = 7.5 Hz, 2 H), 2.60 (s, 3 H), 2.36 (t, J = 7.5 Hz, 2 H), 2.05 (t, J = 7.4 Hz, 2 H), 1.97 (s, 3 H), 1.89 (s, 3 H), 1.80 (s, 3 H), 1.72–1.67 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 161.7, 160.4, 156.2, 153.7, 142.6, 137.0, 136.8, 134.8, 126.3, 121.4, 114.5, 113.6, 113.3, 108.7, 104.9 (×2), 39.2, 28.1, 27.0, 25.7 (×2), 24.4, 22.0, 21.8, 20.1, 16.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1692, 1607, 1592, 1294, 1276, 1208, 1166, 1107, 1042, 908, 730 cm^{-1}. HRMS (ES): calcd. for $C_{26}H_{33}O_5$ $[M + H]^+$ 425.2328; found 425.2322.

Methyl 2,4-Dihydroxy-6-methyl-3-{(*E*)-3-methyl-6-[5-(2-methylprop-1-enyl)furan-3-yl]hex-2-enyl}benzoate, Methyl Cristatate: Freshly prepared NaOMe [from Na (6 mg), 0.26 mmol, 10 equiv.] in MeOH (1 mL) was added to solid dioxinone resorcylate **7** (11 mg, 0.026 mmol). The mixture was heated at 65 °C in a sealed tube for 20 h. Aqueous HCl (0.1 M, 15 mL) and AcOEt (20 mL) were added. After phase separation, the aqueous layer was extracted with AcOEt (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed (AcOEt/hexanes 15:85) to afford methyl cristatate (6.6 mg, 64%) as a colorless oil. R_f = 0.42 (AcOEt/hexanes 2:8). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 12.13 (s, 1 H), 7.10 (s, 1 H) 6.25 (s, 1 H), 6.05 (s, 1 H), 6.02 (m, 1 H), 5.72 (s, 1 H), 5.32 (t, J = 7.2 Hz, 1 H), 3.94 (s, 3 H), 3.45 (d, J = 7.3 Hz, 2 H), 2.48 (s, 3 H), 2.37 (t, J = 7.5 Hz, 2 H), 2.09 (t, J = 7.5 Hz, 2 H), 1.98 (s, 3 H) 1.90 (s, 3 H) 1.83 (s, 3 H), 1.69 (multiplet, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 172.6, 162.6, 159.2, 153.7, 140.9, 138.6, 136.8, 134.8, 126.3, 121.8, 114.5, 111.4, 111.3, 108.7, 105.2, 51.8, 39.2, 28.1, 27.0, 24.4, 24.1, 22.0, 20.1, 16.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1651, 1620, 1455, 1419, 1378, 1272, 1195, 908, 730 cm^{-1}. HRMS (ES): calcd. for $C_{24}H_{31}O_5$ $[M + H]^+$ 399.2171; found 399.2186.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for **7**, **11**, **13**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **24**, **30** and methyl cristatate.

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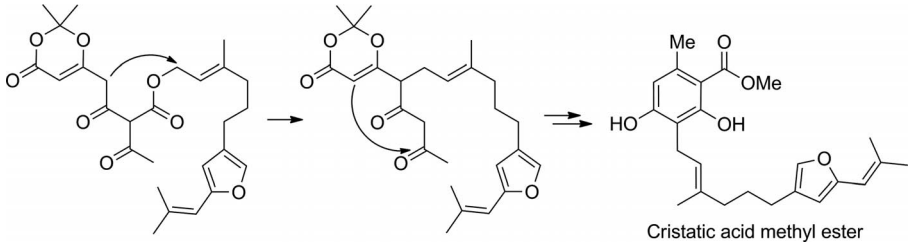
Natural Product Synthesis



The terpenoid resorcylate methyl cristate was synthesized by use of a regioselective Claisen condensation reaction to give a dioxinone diketo ester that subsequently underwent Pd^0-catalyzed allylic migration and biomimetic aromatization.

Keywords: Natural products / Total synthesis / Medicinal chemistry / Biomimetic synthesis / Terpenoids

