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Total Synthesis of the Resorcyclic Acid Lactone Spiroketal Citreoviranol

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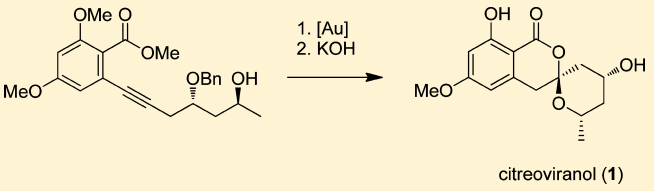
Supporting Information

ABSTRACT: The first total synthesis of resorcyclic acid lactone spiroketal citreoviranol (**1**) is described. The synthesis was completed in nine steps and via Sonogashira cross-coupling, gold-catalyzed cyclization, and an unusual base-induced ketalization. The relative and absolute stereochemistry of citreoviranol was unambiguously confirmed using 2D NMR spectroscopy and X-ray crystallography.



INTRODUCTION

Citreoviranol (**1**) was isolated from the mycelium of the fungus *Penicillium citreoviride* in 1988 by Yamamura et al.[1] It is structurally related to the resorcyclic acid lactone (RAL) family of natural products (Figure 1). The RALs are bioactive

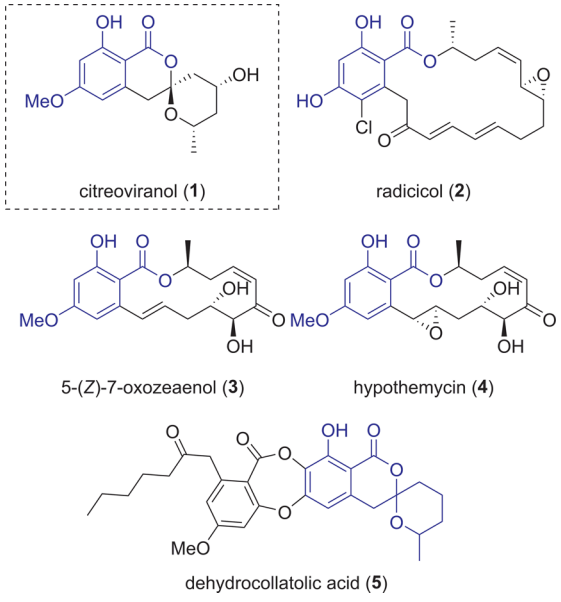
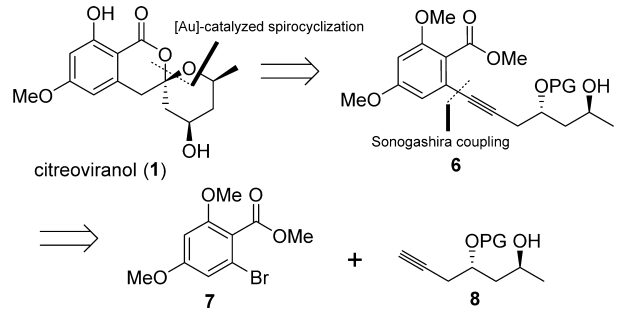


Figure 1. Resorcyclic acid lactone natural products.

polyketide metabolites produced by a range of fungal strains that have been shown to possess potent bioactivity against neurodegenerative diseases and cancer.[2] For instance, radicicol (**2**) is a potent HSP90 inhibitor (IC_{50} = 20 nM), 5-(*Z*)-7-oxozeaenol (**3**) inhibits TAK-1 (IC_{50} = 8.1 nM), and hypothemycin (**4**) inhibits MAP kinase (IC_{50} = 17−90 nM).

Aside from the characteristic resorcylic acid lactone motif, citreoviranol (**1**) also contains a unique 6,6-spiroketal lactone.

Scheme 1. Retrosynthetic Analysis of Citreoviranol (1)



This substructure has only been found in one other natural product, dehydrocollatolic acid (**5**) (Figure 1).[3] While RALs have been shown to have potential therapeutic value, neither citreoviranol (**1**) nor dehydrocollatolic acid (**5**) has been tested for biological activity. In addition, there have been no previous syntheses of the 6,6-spiroketal lactone ring system rendering these natural products attractive synthetic targets.

Gold catalysis has emerged as a mild and efficient tool to construct complex heterocycles in the past decade, and its use is often favored due to its high atom economy and high functional group tolerance.[4] We were therefore interested to apply this methodology to the unprecedented spiroketal lactone ring system present in citreoviranol (**1**). Consequently, our retrosynthetic strategy hinged on the gold-catalyzed cyclization of alkynol **6**, the product of Sonogashira coupling of bromide **7** and alkyne **8** (Scheme 1).

RESULTS AND DISCUSSION

Initial attention focused on the preparation of Sonogashira coupling partners, bromide **7** and alkyne **8**. Following literature procedures,[5] synthesis of bromide **7** was achieved

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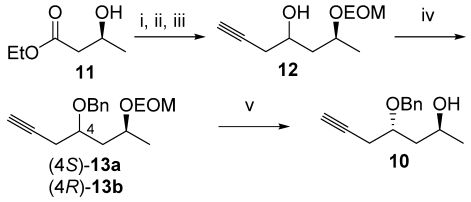
Scheme 2. Synthesis of Bromide 7[a]

[a]Reagents and conditions: (i) $POCl_3$, DMF, rt, 30 min, then 100 °C, 4 h, 80%; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (5:1), rt, 15 min; (iii) K_2CO_3, MeI, DMF, 80 °C, 15 min, 75% over two steps.

Scheme 3. Synthesis of Alkyne 10[a]



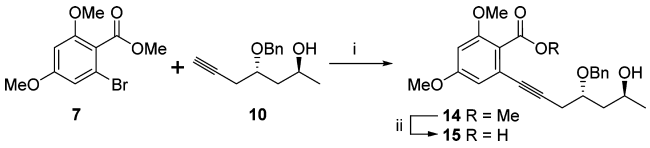
[a]Reagents and conditions: (i) EOMCl, DIPEA, CH_2Cl_2, 0 °C, 1 h then rt, 16 h, 98%; (ii) DIBAL, CH_2Cl_2, −78 °C, 1 h, 95%; (iii) propargyl bromide, Zn, THF, 0 °C, 1 h, 75%, *anti*/*syn*, 2:1; (iv) **12**, NaH, THF, 0 °C, 40 min then BnBr, TBAI (10 mol %), 60 °C, 1 h, **13a** (54%), **13b** (38%); (v) **13a**, *p*TSA (20 mol %), EtOH, 60 °C, 5 h, 98%.

via Vilsmeier−Haack formylation of 3,5-dimethoxybromobenzene (**9**), followed by Pinnick oxidation and subsequent methylation to afford bromide **7** in 60% yield over three steps (Scheme 2).

Synthesis of alkyne coupling partner **10** was readily achieved over five steps (Scheme 3). After protection of ethyl (*S*)-3-hydroxybutyrate (**11**) as the corresponding ethoxymethyl ether, treatment with DIBAL afforded the desired aldehyde in 92% yield over two steps, which upon addition of propargyl zinc bromide at 0 °C yielded alkyne **12** in 75% yield as a 2:1 diastereomeric mixture. Disappointingly, despite screening a range of temperatures (0 °C, −40 °C, −78 °C), Lewis acids ($BF_3{\cdot}Et_2O$, $TiCl_4$, $MgBr_2$), and protecting groups (EOM, PMB), attempts to optimize the diastereoselectivity of this reaction proved fruitless. However, subsequent benzyl protection of the mixture enabled separation of the *anti* and *syn* diastereomers **13a** and **13b**.[6] Cleavage of the ethoxymethyl ether in *anti*-isomer **13a** then afforded the desired Sonogashira coupling partner **10**.

Pleasingly, despite the use of an electron-rich bromide coupling partner, the Sonogashira cross-coupling of bromide **7** with alkyne **10** proceeded smoothly, using the copper-free Sonogashira conditions previously employed by our group and others[7] (Scheme 4). Optimization of the reaction conditions

Scheme 4. Sonogashira Coupling and Saponification for the Formation of 15[a]

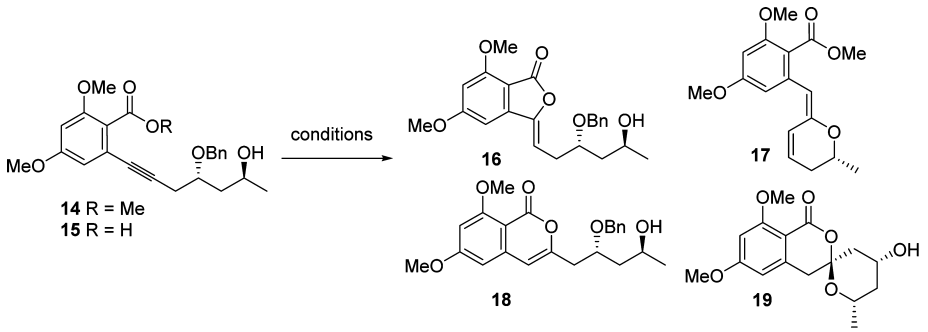


[a]Reagents and conditions: (i) $Pd(OAc)_2$ (10 mol %), dtbpf (15 mol %), K_2CO_3, NMP, 80 °C, 30 min, 70%; (ii) aq. KOH (2 M), MeOH, reflux, 4.5 h, 80%.

provided alkyne **14** in a reliable 67% yield within 30 min at 80 °C. Saponification of methyl ester **14** then afforded carboxylic acid **15** in a 78% yield.

With cyclization precursor **15** in hand, the key gold-catalyzed spirocyclization was attempted. The use of $AuClPPh_3$ as the catalyst in the presence of a silver cocatalyst ($AgSbF_6$)[8] or base (K_2CO_3, Et_3N) resulted in 5-*exo*-dig cyclization of alkynol acid **15** to the undesired isobenzofuranone **16** (entries 1−3, Table 1). $PdCl_2$-catalyzed

Table 1. Metal-Catalyzed Cyclization of 14 and 15[a]



entry	R	[M][b]	additive[c] [Ag]/base/acid	solvent, *T*	time (h)	yield[d] 16	17	18
1	H	$AuClPPh_3$	$AgSbF_6$	CH_2Cl_2, rt	16	33	0	0
2	H	$AuClPPh_3$	K_2CO_3	CH_3CN, rt	48	15	0	0
3	H	$AuClPPh_3$	K_2CO_3/Et_3N	THF, rt	16	25	0	0
4	H	$PdCl_2$	Et_3N	CH_3CN, rt	2	50	0	0
5	Me	$AuClPPh_3$	$AgSbF_6$	THF, reflux	3.5	0	50	0
6	Me	AuCl	$AgSbF_6$, PPTS	THF, 50 °C	16	0	trace	trace
7	Me	$AuClPPh_3$	$AgSbF_6$, PPTS	THF, 50 °C	1	0	0	30
8	Me	$AuCl_3$	$AgSbF_6$, PPTS	THF, 50 °C	0.5	0	0	75

[a]All reactions carried out on racemic starting material with 2:1 dr with stereochemistry retained in all entries. [b]10 mol % catalyst. [c]10 mol % [Ag] additive except entry 8 (30 mol %). [d]Isolated yield (%).

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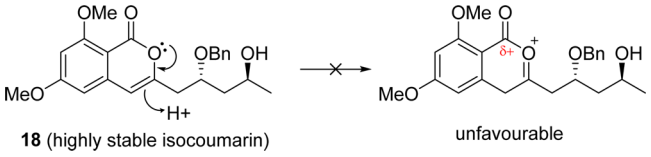
Scheme 5. Proposal for Inability to Form an Oxonium Ion Intermediate



cyclization of alkynol acid **15** also resulted in the formation of isobenzofuranone **16** (entry 4, Table 1). Exposure of alkynol ester **14** to $AuClPPh_3$ in the presence of $AgSbF_6$ yielded the elimination product, dihydropyran **17** (entry 5, Table 1). Based on the conditions reported by Trost et al.[9] that avoided formation of elimination products on a similar substrate, we next attempted the cyclization of **14** using AuCl in the presence of PPTS, cocatalyzed by $AgSbF_6$. A trace quantity of the 6-*endo*-dig cyclization product, isocoumarin **18**, was observed together with elimination product **17** (entry 6, Table 1). Changing the gold catalyst to $AuClPPh_3$ yielded 30% of isocoumarin **18** with no elimination product observed (entry 7, Table 1). Disappointingly, despite extensive screening no evidence for cyclization to the desired spiroketal **19** was observed. However, further optimization of the formation of isocoumarin **18**, which constitutes a potential precursor to spiroketal **19** resulted in a 75% yield using $AuCl_3$ in the presence of PPTS and $AgSbF_6$ (entry 8, Table 1).

Following the successful preparation of isocoumarin **18**, we screened conditions for its conversion to spiroketal lactone **19**. A number of Brønsted acids returned either starting material **18** or degradation products. The inability to form the spiroketal product was rationalized as being due to the unfavorable electronics associated with the formation of the required oxonium ion (Scheme 5). It is postulated an oxonium ion is unlikely to form next to a carbonyl carbon which carries a partial positive charge.

Attempts to reduce the isocoumarin to the dihydroisocoumarin and perform an oxidative radical cyclization were also unsuccessful.[10] Surprisingly, however, when isocoumarin **18** was subjected to 1 M KOH for 1 h followed by acidic workup formation of spiroketal lactone **19** was observed as a 2:1 mixture of epimers **19a** and **19b** (suggesting substitution of the OBn) in modest yield (Scheme 6). Occasionally, trace quantities of 6′*R*-spiroketals **19c** and **19d** were observed upon aq. citric acid workup.[11]

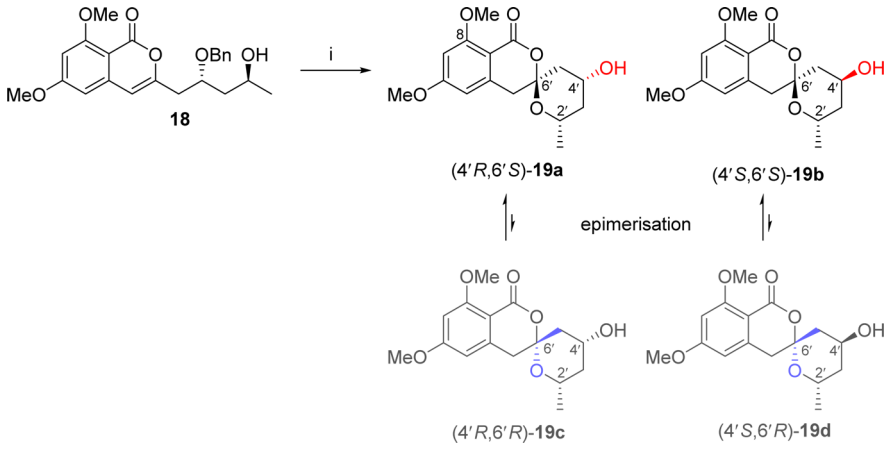
The stereochemical assignments of **19a**, **19b**, and **19c** were achieved by NMR spectroscopy (Figures 2−3). Observation of a 1,3-diaxial NOE correlation between H2′ and H4′ in **19a** shown in Figure 2 established that the substituents on the tetrahydropyran ring are positioned equatorially, *syn* to each other (conversely, the NOE correlation between H2′ and H4′ for *anti*-epimer **19b** is absent). The NOE correlations of H4b with $H5'_{ax}$ and $H5'_{eq}$ of **19a** suggested that the tetrahydropyran ring adopts the chair conformation represented below (conversely, the NOE correlation between H4 and $H2'_{ax}$, $H4'_{ax}$ and $H5'_{eq}$ of **19c** suggests it adopts the ring-flipped chair conformation). The requirement that H2′ and H4′ adopt axial positions on the required chair conformation established that the spiroketal center in isomer **19a** exhibits the *S*-configuration. This assignment was also further confirmed by subsequent conversion to the natural product citreoviranol (**1**) upon selective demethylation of the 8-methyl ether

The absence of a NOE correlation between H2′ and H4′ in spiroketal **19b** suggested that it is the 2′,4′-*anti* isomer (also confirmed by chemical shift data discussed later). The NOESY spectrum of **19b** exhibited correlations between H4′ and both of the H3′ and H5′ protons (equatorial and axial), suggesting that H4′ is positioned equatorially. NOE correlations between H4b with $H5'_{ax}$ and $H5'_{eq}$ are also present in **19b** suggesting that the tetrahydropyran ring also adopts the same chair conformation as **19a** represented in Figure 2. This combination of structural features (**19b** being the *anti*-epimer, H4′ is equatorial, and adoption of the required chair conformation) implies that the spiroketal center also adopts the *trans*-diaxial *S*-configuration.

The *anti*-configuration of **19b** was also confirmed by the changes in chemical shift observed for H2′ and H4′ due to the inversion of C4′ relative to **19a**. The ^1H NMR spectrum of **19b** showed a characteristic downfield chemical shift for H2′ at 4.38 ppm due to the additional 1,3-diaxial oxygen interaction with C4′−OH and a distinctive upfield shift for the H4′ at 4.17 ppm due to the absence of a 1,3-diaxial interaction with the lactone oxygen (Figure 3).[12]

The stereochemical assignment of **19c** was also achieved by NMR spectroscopy. A 1,3-diaxial NOE correlation between

Scheme 6. Synthesis of 8-Methylcitreoviranol 19a and Its *anti*-Epimer 19b[a]



[a]Reagents and conditions: (i) aq. 1 M KOH, dioxane, rt, 1 h, then 1 M HCl, **19a** (20%), **19b** (16%).

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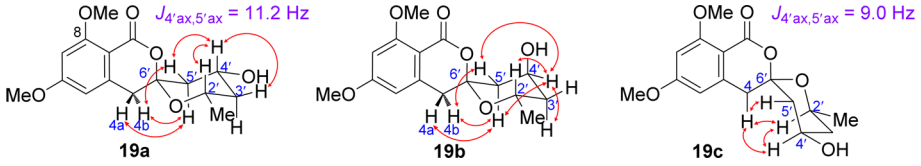


Figure 2. NOE correlations of H4′ and H4 in **19a**, **19b**, and **19c**.

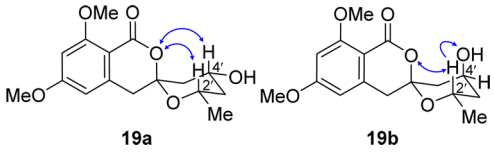


Figure 3. 1,3-Diaxial interactions in **19a** and **19b**.

H2′ and H4′ of **19c** shown in Figure 2 indicates that the substituents on the tetrahydropyran ring are positioned equatorially, *syn* to each other. The observed NOE correlations of H4 with $H2'_{ax}$, $H4'_{ax}$, and $H5'_{eq}$ suggest that the tetrahydropyran ring adopts a chair conformation as depicted in Figure 2. These structural features require the *R*-configuration at the spiroketal center.

A proposed mechanism for the spiroketalization of **18** to **19** is shown in Scheme 7. During the cyclization, the secondary benzyl ether of ketone intermediate (**i**) is eliminated and conjugate addition of hydroxide to α,β-unsaturated ketone (**ii**) with poor stereocontrol affords a mixture of C-4′ epimeric alcohols (**iii**). Spirocyclization of hemiketal (**iv**) affords spiroketal lactone **19a** and its C4′-epimer **19b**. The spiroketal product **19** was only formed upon acidic workup, and attempts to isolate any intermediates using a neutral workup were unsuccessful.

Final selective demethylation of **19a** with BCl_3 afforded citreoviranol (**1**), completing the first total synthesis of the natural product. Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) for the synthetic sample of citreoviranol (**1**) were in full agreement with those reported for the natural product. The key 1,3-diaxial NOE correlation observed between H2′ and H4′ supported assignment of *syn*-stereochemistry between these two protons. The NOESY spectrum for synthetic citreoviranol (**1**) exhibited correlations between H4b and $H5'_{ax}$ and $H5'_{eq}$ suggesting that the tetrahydropyran ring adopts the chair conformation represented below (Scheme 8).

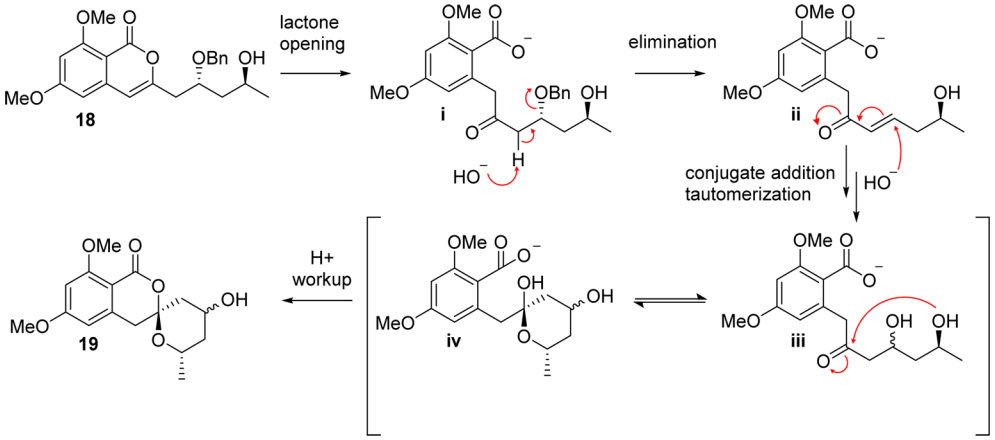
The relative stereochemistry and chair conformation for synthetic citreoviranol (**1**) were also confirmed by X-ray crystallography.[13] Notably while the $[\alpha]_D$ values of synthetic and natural citreoviranol were not in close agreement (synthetic: $[\alpha]_D^{24}$ −78.0 (*c* 0.20 in $CHCl_3$), lit.:[1] $[\alpha]_D^{30}$ −147 (*c* 0.196 in $CHCl_3$), use of chiral HPLC confirmed that the enantiopurity of the synthetic sample was 95% by comparison to a racemic synthetic sample.

In summary the first total synthesis of citreoviranol (**1**) has been accomplished in nine steps from readily available starting materials. The synthesis features a Sonogashira cross-coupling, gold catalyzed cyclization, and an unprecedented base-induced ketalization. The absolute stereochemistry of the natural product was confirmed by extensive NMR experiments and X-ray crystallography. Future work will involve biological testing of this unique molecule to probe its therapeutic value.

EXPERIMENTAL SECTION

General Procedures. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard techniques. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl. CH_2Cl_2 was freshly distilled from calcium hydride. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as the visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Silica gel (60, 230−400 mesh) was used for flash column chromatography. NMR spectra were recorded at room temperature in $CDCl_3$ solution on either a spectrometer operating at 500 MHz for ^{1}H nuclei and 125 MHz for ^{13}C nuclei or a spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million on the δ scale, and coupling constants, *J*, are in hertz. Multiplicities are reported as "s" (singlet), "br s" (broad singlet), "d" (doublet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet), and "m" (multiplet). NMR

Scheme 7. Proposed Mechanism for Spiroketalization of Isocoumarin 18



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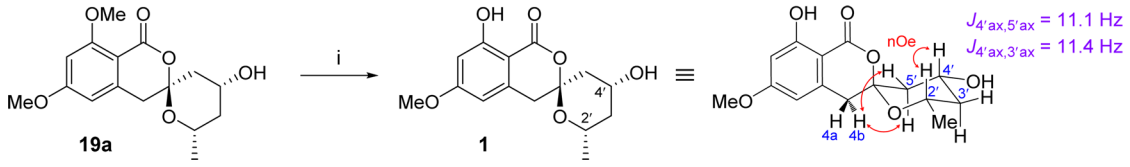
Scheme 8. Selective Demethylation to Citreoviranol (1)[a]



[a]Reagents and conditions: (i) BCl_3, CH_2Cl_2, −78 °C then rt, 30 min, 84%.

spectra are calibrated at 7.26 for ^{1}H NMR and 77.0 for ^{13}C NMR. Where distinct from those due to the major diastereomer, resonances due to minor diastereomers are denoted by an asterisk. ^{1}H and ^{13}C NMR resonances were assigned using a combination of DEPT 135, COSY, HSQC, HMBC, and NOESY spectra. Infrared (IR) spectra were recorded using a thin film on a composite of zinc selenide and diamond crystal on an FT-IR system transform spectrometer. Melting points are uncorrected. High resolution mass spectrometry (HRMS) was performed using a spectrometer operating at a nominal accelerating voltage of 70 eV or a TOF-Q mass spectrometer.

*2-Bromo-4,6-dimethoxybenzaldehyde (**S1**).* To a stirred solution of 3,5-dimethoxybromobenzene (**9**) (8.00 g, 36.8 mmol) in DMF (17.2 mL, 221 mmol) at 0 °C was added $POCl_3$ (10.3 mL, 110 mmol) dropwise. The resultant mixture was stirred at rt for 30 min, then heated to 100 °C, and continued stirring for 4 h. The reaction mixture was poured onto crushed ice (100 mL), warmed to rt, and left to sit at rt for 16 h. The crystals were collected by filtration and recrystallized from 3:1 hexanes−EtOAc (100 mL) to afford **S1** (7.2 g, 80%) as yellow crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H, CHO), 6.77 (d, J = 2.4 Hz, 1H, ArH), 6.43 (d, J = 2.2 Hz, 1H, ArH), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 164.4, 163.6, 127.3, 116.9, 111.6, 98.1, 56.1, 55.8; mp 150−152 °C. The spectroscopic data were in agreement with those reported in the literature.[5]

*Methyl 2-Bromo-4,6-dimethoxybenzoate (**7**).* To a stirred mixture of **S1** (4.00 g, 16.3 mmol), $NaClO_2$ (6.30 g, 65.3 mmol), and NaH_2PO_4 (2.94 g, 24.5 mmol) was added a solution of *t*-BuOH/H_2O (5:1, 66 mL), followed by 2-methyl-2-butene (10.4 mL, 97.9 mmol). The resultant mixture was stirred at rt for 15 min, and then the reaction was quenched with 2 M HCl (15 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with sat. aq NaCl (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* yielding acid **S2** as a yellow solid (4.46 g), which was used directly in the next step. To a stirred mixture of crude acid **S2** (4.46 g) and K_2CO_3 (3.38 g, 24.5 mmol) in DMF (160 mL) was added MeI (1.52 mL, 24.5 mmol) dropwise. The resultant mixture was warmed to 80 °C and then stirred for 45 min, and then the reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with water (100 mL) and then sat. aq. NaCl (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 hexanes−EtOAc) afforded **7** (3.37 g, 75% over 2 steps) as an off-white solid: IR (neat) ν_{max} 2951, 1722, 1597, 1566, 1432, 1265, 1219, 1145, 1100, 1000, 943 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, J = 2.0 Hz, 1H, ArH), 6.40 (d, J = 2.1 Hz, 1H, ArH), 3.91 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 161.6, 158.3, 120.5, 118.9, 108.9, 98.0, 56.0, 55.7, 52.5; HRMS (ESI+) for $C_{10}H_{11}BrNaO_4$ $[M + Na]^+$ requires 296.9733, found 296.9737; mp 42−43 °C.

*(S)-Ethyl 3-(Ethoxymethoxy)butanoate (**S3**).* To a stirred solution of ethyl (*S*)-3-hydroxybutyrate (**11**) (1.00 g, 7.57 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DIPEA (9.84 mL, 56.8 mmol) followed by dropwise addition of EOMCl (1.54 mL, 16.6 mmol). The resultant mixture was stirred at 0 °C for 1 h and warmed to rt for 16 h, and then the reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with 0.5 M aq citric acid solution (3 × 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (6:1 pentane−Et_2O) afforded **S3** (1.41 g, 98%) as a colorless oil: $[\alpha]_D^{22}$ +8.0 (*c* 1.01 in $CHCl_3$); IR (neat) ν_{max} 2977, 1735, 1447, 1378, 1298, 1256, 1195, 1172, 1096, 1029 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.71 (ABq, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 7.1 Hz, 2H, OCH_2O), 4.20−4.12 (m, 1H, H-3), 4.13 (q, J = 7.2 Hz, 2H, CH_2CH_3), 3.58 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.49 (ABX, $\Delta\delta_{AB}$ = 0.18, J_{AB} = 15.2, J_{AX} = 7.6, J_{BX} = 5.6 Hz, 2H, H-2), 1.26 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.24 (d, J = 6.2 Hz, 3H, H-4), 1.20 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 93.8, 70.2, 63.2, 60.4, 42.4, 20.5, 15.0, 14.2; HRMS (ESI+) for $C_9H_{18}NaO_4$ $[M + Na]^+$ requires 213.1097, found 213.1105.

*(S)-3-(Ethoxymethoxy)butanal (**S4**).* To a stirred solution of **S3** (1.32 g, 6.93 mmol) in CH_2Cl_2 (75 mL) at −78 °C was added DIBAL-H (1 M in toluene, 7.62 mL, 7.62 mmol) dropwise over 1 h. The reaction was quenched by the addition of MeOH (10 mL) at −78 °C followed by sat. aq. potassium sodium tartrate (100 mL). The resultant mixture warmed to rt and continued stirring vigorously for 1 h. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 pentane−Et_2O) afforded **S4** (957 mg, 95%) as a colorless oil: $[\alpha]_D^{23}$ +31.7 (*c* 1.02 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (dd, J = 2.7, 1.8 Hz, 1H, CHO), 4.71 (ABq, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 7.2 Hz, 2H, OCH_2O), 4.26 (dqd, J = 12.4, 6.3, 4.9 Hz, 1H, H-3), 3.58 (ABX$_3$, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 9.6, J_{AX} = 7.1, J_{BX} = 7.1 Hz, 2H, CH_2CH_3), 2.58 (ABXY, $\Delta\delta_{AB}$ = 0.15, J_{AB} = 16.4, J_{AX} = 7.5, J_{AY} = 2.7, J_{BX} = 4.9, J_{BY} = 1.8 Hz, 2H, H-2), 1.27 (d, J = 6.3 Hz, 3H, H-4), 1.20 (t, J = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 93.6, 68.5, 63.4, 20.6, 15.0. The spectroscopic data were in agreement with those reported in the literature.[14]

*(4S,6S)-6-(Ethoxymethoxy)hept-1-yn-4-ol (**12**).* To a stirred suspension on zinc powder (2.04 g, 31.2 mmol) in THF (10 mL) at 0 °C was added propargyl bromide (2.78 mL, 31.2 mmol). The mixture was stirred for 1.5 h, and then a solution of **S4** (2.28 g) in THF (6 mL) was added dropwise. The resultant mixture was stirred at 0 °C for 15 min, and then the reaction was quenched with sat. aq. NH_4Cl (50 mL). The solid residue was removed by filtration, and 2 M HCl (5 mL) was added to the filtrate. The filtrate was extracted with EtOAc (3 × 100 mL), and the combined organic extracts were washed with sat. aq NaCl (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (5:1 PE−EtOAc) afforded a diastereotopic mixture of **12** (2.18 g, 75%, dr = 2:1) as a yellow oil: IR (neat) ν_{max} 3451, 3296, 2974, 1378, 1139, 1097, 1027 cm^{-1}; ^{1} H NMR (400 MHz, $CDCl_3$) δ 4.78−4.66 (m, 2H, OCH_2O), 4.07−3.90 (m, 2H, H-4, H-6), 3.68−3.52 (m, 2H, CH_2CH_3), 243−2.31 (m, 2H, H-3), 2.03−2.01 (m, 1H, H-1), 1.81−1.68 (m, 2H, H-5), 1.23−1.19 (m, 6H, H-7, CH_2CH_3); ^{13} C NMR (100 MHz, $CDCl_3$) δ 93.8, 92.9*, 81.0, 80.9, 73.1*, 71.1, 70.4, 70.3*, 69.5*, 66.5, 63.7*, 63.6, 42.8*, 42.5, 27.1, 27.1*, 20.3, 20.3*, 15.0*, 15.0; HRMS (ESI+) for $C_{10}H_{18}NaO_3$ $[M + Na]^+$ requires 209.1148, found 209.1153. *denotes *syn*-isomer.

*(4S,6S)-4-Benzyloxy-6-(ethoxymethoxy)hept-1-yne (**13a**) and (4R,6S)-4-Benzyloxy-6-(ethoxymethoxy)hept-1-yne (**13b**).* NaH

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(60% in mineral oil, 600 mg, 15.1 mmol) was washed twice with hexanes and dried *in vacuo*. To a stirred solution of NaH in THF (12 mL) at 0 °C was added a solution of **12** (936 mg, 5.02 mmol) in THF (5.0 mL). The mixture was stirred for 40 min, and then BnBr (1.20 mL, 10.0 mmol) was added dropwise followed by TBAI (185 mg, 0.50 mmol). The resultant mixture was heated to 60 °C and stirred for 1 h. The mixture was then cooled to 0 °C, and the reaction was quenched by the addition of water (5 mL) and EtOAc. The organic layer was separated, and then the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography on silica (20:1 hexanes−Et_2O) afforded **13a** (757 mg, 54%) and **13b** (526 mg, 38%) as pale yellow oils: **13a**: $[\alpha]_D^{22}$ +62.8 (*c* 1.00 in $CHCl_3$); IR (neat) ν_{max} 3293, 2973, 1455, 1377, 1111, 1071, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H, Bn), 4.64 (ABq, $\Delta\delta_{AB}$ = 0.11, J_{AB} = 7.0 Hz, 2H, OCH_2O), 4.59 (ABq, $\Delta\delta_{AB}$ = 0.21, J_{AB} = 11.2 Hz, 2H, OCH_2Ar), 3.97−3.89 (m, 1H, H-6), 3.83−3.77 (m, 1H, H-4), 3.59 (ABX$_3$, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 9.5, J_{AX} = 7.1, J_{BX} = 7.1 Hz 2H, OCH_2CH_3), 2.49 (d, *J* = 2.7 Hz, 1H, H-3$_a$), 2.47 (d, *J* = 2.7 Hz, 1H, H-3$_b$), 2.02 (t, *J* = 2.7 Hz, 1H, H-1), 1.77 (ABXY, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 14.5, J_{AX} = 9.4, J_{AY} = 3.2, J_{BX} = 9.4, J_{BY} = 3.3 Hz, 2H, H-5), 1.20 (d, *J* = 6.2 Hz, 3H, H-7), 1.18 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.4, 127.9, 127.7, 70.8, 70.3, 63.3, 42.8, 24.0, 21.3, 15.1; HRMS (ESI+) for $C_{17}H_{24}NaO_3$ $[M + Na]^+$ requires 299.1618, found 299.1621. **13b**: $[\alpha]_D^{25}$ −10.6 (*c* 1.04 in $CHCl_3$); IR (neat) ν_{max} 3307, 2973, 1455, 1377, 1111, 1071, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H, Bn), 4.68 (ABq, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 7.1 Hz, 2H, OCH_2O), 4.59 (ABq, $\Delta\delta_{AB}$ = 0.14, J_{AB} = 11.7 Hz, 2H, OCH_2Ar), 3.90−3.83 (m, 1H, H-6), 3.68 (ddt, *J* = 6.8, 5.7, 5.6 Hz, 1H, H-4), 3.59−3.54 (m, 2H, OCH_2CH_3), 2.51 (dd, *J* = 5.4, 2.7 Hz, 2H, H-3), 2.03−1.96 (m, 1H, H-5$_a$), 2.01 (t, *J* = 2.7 Hz, 1H, H-1), 1.79−1.72 (m, 1H, H-5$_b$), 1.19 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.16 (d, *J* = 6.2 Hz, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.3, 127.8, 127.6, 93.3, 80.9, 74.2, 71.1, 70.2, 70.2, 63.3, 41.2, 23.7, 20.3, 15.1; HRMS (ESI+) for $C_{17}H_{24}NaO_3$ $[M + Na]^+$ requires 299.1618, found 299.1624.

*(2S,4S)-4-(Benzyloxy)hept-6-yn-2-ol (**10**).* To a stirred solution of **13a** (104 mg, 0.37 mmol) in EtOH (2 mL) was added PTSA (14 mg, 0.75 mmol). The resultant solution was stirred at 60 °C for 6 h and then diluted by the addition of EtOAc (10 mL) and water (2 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (5:1 hexanes−EtOAc) afforded **10** (81 mg, 98%) as a yellow oil: $[\alpha]_D^{22}$ +67.4 (*c* 1.02 in $CHCl_3$); IR (neat) ν_{max} 3416, 3295, 2965, 2915, 1497, 1455, 1352, 1091, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H, Bn), 4.62 (ABq, $\Delta\delta_{AB}$ = 0.17, J_{AB} = 11.5 Hz, 2H, OCH_2Ar), 4.12−4.05 (m, 2H, H-2), 3.90−3.84 (m, 1H, H-4), 2.52 (ABXY, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 16.8, J_{AX} = 4.9, J_{AY} = 2.7, J_{BX} = 7.2, J_{BY} = 2.6 Hz, 2H, H-5), 2.03 (t, *J* = 2.7 Hz, 1H, H-7), 1.78 (ABXY, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 14.5, J_{AX} = 7.8, J_{AY} = 2.9, J_{BX} = 9.0, J_{BY} = 3.6 Hz, 2H, H-3), 1.19 (d, *J* = 6.3 Hz, 3H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.5, 128.0, 127.9, 80.8, 74.7, 71.6, 70.4, 64.4, 42.2, 23.7, 23.5; HRMS (ESI+) for $C_{14}H_{18}NaO_2$ $[M + Na]^+$ requires 241.1199, found 241.1200.

*(2S,4S)-Heptane-2,4-diol (**S5**).* To a stirred solution of **10** (50 mg, 0.23 mmol) in MeOH (2 mL) was added Pd/C (10 wt %, 24 mg, 0.023 mmol). Hydrogen gas was bubbled through the mixture for 30 min. The reaction mixture was filtered through Celite, washed with MeOH, and concentrated *in vacuo* to afford **S5** (27 mg, 92%) as a colorless oil: $[\alpha]_D^{26}$ +16.7 (80% de, *c* 1.03 in $CHCl_3$), lit.[15] $[\alpha]_D^{22}$ −21.7 (*c* 1.15 in $CHCl_3$); IR (neat) ν_{max} 3343, 2961, 2932, 1458, 1376, 1148, 1120, 1055, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (d, *J* = 4.8 Hz, 1H, H-2), 3.92 (br s, 1H, H-4), 3.07 (d, *J* = 2.6 Hz, 1H, OH), 2.96 (d, *J* = 3.8 Hz, 1H, OH), 1.56 (dd, *J* = 5.8, 5.5 Hz, 2H, H-3), 1.53−1.30 (m, 4H, H-5 and H-6), 1.21 (d, *J* = 6.4 Hz, 3H, H-1), 0.91 (t, *J* = 7.1 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.9, 65.3, 44.0, 39.5, 23.4, 18.9, 14.0; HRMS (ESI+) for $C_7H_{16}NaO_2$ $[M + Na]^+$ requires 155.1043, found 155.1037. The spectroscopic data were in agreement with those reported in the literature.[15]

*(2S,4S)-4-(Benzyloxy)-7-(3,5-dimethoxy-2-(methylcarboxy)-phenyl)hept-6-yn-2-ol (**14**).* To a stirred mixture of **7** (280 mg, 1.02 mmol), $Pd(OAc)_2$ (21 mg, 0.093 mmol), dtbpf (66 mg, 0.14 mmol), and K_2CO_3 (639 mg, 4.63 mmol) was added NMP (6 mL). The reaction mixture was degassed over 5 min by bubbling a stream of argon through the mixture. A solution of **10** (202 mg, 0.93 mmol) in NMP (4 mL) was added dropwise, heated to 80 °C, and then continued stirring for 2 h. The resultant mixture was filtered through a short plug of silica and washed with EtOAc. The filtrate was washed with water (3 × 100 mL), sat. aq. NaCl (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (2:1 hexanes−EtOAc) afforded **14** (268 mg, 70%) as a yellow oil: $[\alpha]_D^{21}$ +27.1 (*c* 1.04 in $CHCl_3$); IR (neat) ν_{max} 3493, 2940, 1729, 1597, 1578, 1455, 1229, 1269, 1204, 1161, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H, Bn), 6.53 (d, *J* = 2.2 Hz, 1H, ArH), 6.42 (d, *J* = 2.2 Hz, 1H, ArH), 4.64 (ABq, $\Delta\delta_{AB}$ = 0.15, J_{AB} = 11.6 Hz, 2H, OCH_2Ar), 4.13−4.05 (m, 1H, H-2), 3.95−3.89 (m, 1H, H-4), 3.86 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.72 (ABX, $\Delta\delta_{AB}$ = 0.18, J_{AB} = 16.9, J_{AX} = 4.8, J_{BX} = 7.8 Hz, 2H, H-5), 2.38 (br s, 1H, OH), 1.84−1.81 (m, 2H, H-3), 1.22 (d, *J* = 6.3 Hz, 3H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 161.3, 157.8, 138.0, 128.5, 127.9, 123.5, 119.1, 108.1, 99.3, 90.2, 79.8, 75.3, 71.7, 64.6, 56.0, 55.5, 52.4, 42.7, 24.6, 23.9; HRMS (ESI+) for $C_{24}H_{28}NaO_6$ $[M + Na]^+$ requires 435.1778, found 435.1780. dtbpf = 1,1′-bis-(di-*tert*-butylphosphino)-ferrocene.

*(2S,4S)-4-(Benzyloxy)-7-(3,5-dimethoxy-2-(carboxy)phenyl)hept-6-yn-2-ol (**15**).* To a stirred solution of **14** (8 mg, 0.020 mmol) in MeOH (0.50 mL) was added 2 M KOH (0.5 mL), followed by stirring under reflux for 4 h and being quenched with 1 M HCl (1 mL). The aqueous layer was extracted with Et_2O (5 mL), washed with sat. aq NaCl (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:2 hexanes−EtOAc) afforded **15** (6.2 mg, 80%) as a white oil: IR (neat) ν_{max} 3395, 2965, 2928, 1707, 1596, 1577, 1455, 1418, 1337, 1228, 1203, 1163, 1110, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H, Bn), 6.56 (d, *J* = 2.2 Hz, 1H, ArH), 6.43 (d, *J* = 2.2 Hz, 1H, ArH), 4.60 (ABq, $\Delta\delta_{AB}$ = 0.13, J_{AB} = 11.5 Hz, 2H, OCH_2Ar), 4.16−4.06 (m, 1H, H-2), 3.99−3.91 (m, 1H, H-4), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.69 (ABX, $\Delta\delta_{AB}$ = 0.37, J_{AB} = 16.8, J_{AX} = 3.9, J_{BX} = 9.2 Hz, 2H, H-5), 1.90 (2H, ABXY, $\Delta\delta_{AB}$ = 0.36, J_{AB} = 14.6, J_{AX} = 9.8, J_{AY} = 2.4, J_{BX} = 9.1, J_{BY} = 2.5 Hz, H-5), 1.25 (d, *J* = 6.3 Hz, 3H, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.3, 161.6, 158.0, 138.2, 128.5, 127.9, 127.8, 124.8, 108.5, 99.2, 91.6, 80.6, 75.6, 71.8, 65.3, 56.1, 55.6, 43.0, 24.8 23.8; HRMS (ESI+) for $C_{23}H_{27}O_6$ $[M + H]^+$ requires 399.1802, found 399.1801.

*(Z)-3-(3-(Benzyloxy)-5-hydroxyhexylidene)-5,7-dimethoxy-3H-2-benzofuran-1-one (**16**).* To a stirred solution of **15** (20 mg, 0.050 mmol) in THF (1 mL) was added Et_3N (25 μL, 0.18 μmol) followed by $PdCl_2$ (0.89 mg, 5.0 μmol). The reaction mixture was stirred at rt for 1 h, and then the solvent was removed *in vacuo*. Purification by flash column chromatography on silica (1:1 hexanes−EtOAc, 1% Et_3N) afforded **16** (10 mg, 50%) as a yellow oil: IR (neat) ν_{max} 3455, 2925, 1751, 1601, 1495, 1455, 1431, 1335, 1207, 1158, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ* 7.38−7.28 (m, 5H, Bn), 6.63 (d, *J* = 1.7 Hz, 1H, ArH), 6.44 (d, *J* = 1.7 Hz, 1H, ArH), 5.60 (dd, *J* = 8.3, 7.2 Hz, 1H, H-1), 4.63 (ABq, $\Delta\delta_{AB}$ = 0.21, *J* = 11.5, 2H, OCH_2Ar), 4.03−3.97 (m, 1H, H-5), 3.96−3.89 (m, 1H, H-3), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.88−2.68 (m, 2H, H-2), 1.83−1.54 (m, 2H, H-4), 1.14 (d, *J* = 6.2 Hz, 3H, H-6); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H, Bn), 6.60 (d, *J* = 1.7 Hz, 1H, ArH), 6.43 (d, *J* = 1.7 Hz, 1H, ArH), 5.57 (t, *J* = 7.85 Hz, 1H, C=CH), 4.62 (ABq, $\Delta\delta_{AB}$ = 0.12, *J* = 11.3 Hz, 2H, OCH_2Ar), 4.16−4.06 (m, 1H, H-5), 3.96−3.89 (m, 1H, H-3), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.88−2.68 (m, 2H, H-2), 1.83−1.54 (m, 2H, H-4), 1.18 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 167.0, 166.9, 2 × 164.8, 2 × 159.3, 147.1*, 146.8, 143.5, 143.4*, 138.0, 137.5, 2 × 128.6*, 2 × 128.5, 2 × 128.1, 2 × 128.0, 128.0*, 127.9, 2 × 105.7, 104.1, 103.2*, 100.1, 100.0, 94.9, 94.9, 78.4*, 75.4, 71.3, 70.9*, 67.5*, 64.7, 2 × 56.1, 56.0*, 56.0*, 42.7*, 42.5, 29.7, 29.3*, 23.7, 23.5*; HRMS (ESI+) for $C_{23}H_{26}NaO_6$ $[M + Na]^+$ requires 421.1622, found 421.1620. *denotes minor isomer.

*6-(3,5-Dimethoxy-2-(methylcarboxy)benzylidene)-2-methyl-3,6-dihydro-2H-pyran (**17**).* To a stirred solution of **14** (20 mg, 0.050 mmol) in THF (1 mL) was added $AuClPPh_3$ (2.4 mg, 5.0 μmol) followed by $AgSbF_6$ (1.7 mg, 5.0 μmol). The reaction mixture was stirred at 60 °C for 3.5 h, and then the solvent was removed *in vacuo*. Purification by flash column chromatography on silica (4:1 hexanes−EtOAc, 1% Et_3N) afforded **17** (10 mg, 50%) as a yellow oil: IR (neat) ν_{max} 2925, 1726, 1631, 1593, 1578, 1456, 1422, 1394, 1325, 1295, 1269, 1237, 1205, 1156, 1100, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 2.2 Hz, 1H, ArH), 6.30 (d, J = 2.2 Hz, 1H, ArH), 6.07−6.04 (m, 1H, H-5), 6.00−5.95 (m, 1H, H-4), 5.26 (s, 1H, HC═C) 4.18−4.10 (m, 1H, H-2), 3.89 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.25−2.24 (m, 2H, H-3), 1.43 (d, J = 6.2 Hz, 3H, 2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 160.9, 157.5, 152.3, 135.7, 126.9, 125.6, 110.0, 104.8, 103.5, 96.9, 71.4, 55.9, 55.2, 52.2, 31.7, 21.1; HRMS (ESI+) for $C_{17}H_{20}NaO_5$ $[M + Na]^+$ requires 327.1203, found 327.1213.

*3-((2R,4S)-2-(Benzyloxy)-4-hydroxypentyl)-6,8-dimethoxy-1H-isochromen-1-one (**18**).* To a stirred solution of **14** (135 mg, 0.33 mmol) in THF (3.5 mL) was added PPTS (8.22 mg, 0.033 mmol) followed by $AuCl_3$ (9.93 mg, 0.033 mmol) and $AgSbF_6$ (34 mg, 0.098 mmol). The reaction mixture was heated to 50 °C for 1 h, and then the solvent was removed *in vacuo*. Purification by flash column chromatography on silica (1:2 hexanes−EtOAc) afforded **18** (93 mg, 72%) as a yellow oil: $[\alpha]_D^{21}$ −21.0 (c 0.85 in $CHCl_3$); IR (neat) ν_{max} 3470, 2930, 1710, 1664, 1600, 1570, 1456, 1373, 1166, 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27−7.21 (m, 5H, Bn), 6.44 (d, J = 2.3 Hz, 1H, ArH), 6.31 (d, J = 2.3 Hz, 1H, ArH), 6.16 (s, 1H, H-4), 4.55 (s, 2H, OCH_2Ar), 4.20−4.15 (m, 1H, H-4′), 4.12−4.06 (m, 1H, H-2′), 3.95 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.73 (ABX, $\Delta\delta_{AB}$ = 0.18, J_{AB} = 14.4, J_{AX} = 7.1, J_{BX} = 5.7 Hz, 2H, H-1′), 1.70 (ABXY, $\Delta\delta_{AB}$ = 0.08, J_{AB} = 14.6, J_{AX} = 9.3, J_{AY} = 3.7, J_{BX} = 7.1, J_{BY} = 2.6 Hz, 2H, H-3′), 1.18 (d, J = 6.3 Hz, 3H, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 163.2, 159.2, 155.4, 142.0, 137.7, 128.4, 128.0, 127.8, 105.3, 103.0, 99.7, 98.4, 74.5, 72.1, 64.5, 56.2, 55.6, 42.3, 38.5, 23.7; HRMS (ESI+) for $C_{23}H_{26}NaO_6$ $[M + Na]^+$ requires 421.1622, found 421.1607.

*(2′S,4′R,6′S)-Spiro[6,8-dimethoxyisochroman-1-one-3,6′-2′-methyloxan-4′-ol] (**19a**) and (2′S,4′S,6′S)-Spiro[6,8-dimethoxyisochroman-1-one-3,6′-2′-methyloxan-4′-ol] (**19b**).* To a stirred solution of **18** (25 mg, 63 μmol) in dioxane (1.0 mL) was added KOH (1 M, 1.0 mL, 1.0 mmol). The resultant solution was stirred at rt for 1 h, and then the reaction was quenched with HCl (1 M, 1.0 mL) and EtOAc (2 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 2 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:9 hexanes−EtOAc) afforded a mixture of **19a** (3.0 mg, 20%) and **19b** (2.4 mg, 16%) as colorless oils: **19a**: $[\alpha]_D^{26}$ −77.4 (c 0.23 in $CHCl_3$); IR (neat) ν_{max} 3428, 2923, 1702, 1603, 1582, 1459, 1325, 1263, 1220, 1160, 1068, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (d, J = 2.3 Hz, 1H, ArH), 6.31 (d, J = 2.2 Hz, 1H, ArH), 4.38 (tt, J = 11.2, 4.8 Hz, 1H, H-4′), 4.08 (dqd, J = 11.5, 6.3, 2.1 Hz, 1H, H-2′), 3.93 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.08 (ABq, $\Delta\delta_{AB}$ = 0.19, J_{AB} = 16.3 Hz, 2H, H-4), 2.37 (ddd, J = 12.7, 4.8, 1.9 Hz, 1H, H-5′$_a$), 2.04−1.99 (m, 1H, H-3′$_a$), 1.47 (dd, J = 12.7, 11.2 Hz, 1H, H-5′$_b$), 1.28 (m, 1H, H-3′$_b$), 1.09 (d, J = 6.3 Hz, 3H, 2′-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 163.1, 160.9, 141.1, 105.9, 104.9, 102.4, 97.7, 66.9, 63.7, 56.2, 55.5, 42.8, 41.8, 40.0, 21.3; HRMS (ESI+) for $C_{16}H_{20}NaO_6$ $[M + Na]^+$ requires 331.1152, found 331.1144. **19b**: $[\alpha]_D^{26}$ −76.3 (c 0.097 in $CHCl_3$); IR (neat) ν_{max} 3442, 2923, 1716, 1604, 1583, 1459, 1324, 1265, 1221, 1159, 1082, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (d, J = 2.3 Hz, 1H, ArH), 6.30 (d, J = 2.0 Hz, 1H, ArH), 4.41−4.35 (m, 1H, H-2′), 4.18−4.16 (m, 1H, H-4′), 3.93 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.05 (ABq, $\Delta\delta_{AB}$ = 0.27, J_{AB} = 16.2 Hz, 2H, H-4), 2.25 (ddd, J = 14.5, 2.2, 2.2 Hz, 1H, H-5′$_a$), 1.92−1.87 (m, 1H, H-3′$_a$), 1.81 (dd, J = 14.5, 3.9 Hz, 1H, H-5′$_b$), 1.50−1.45 (ddd, J = 14.0, 12.0, 3.0 Hz, 1H, H-3′$_b$), 1.09 (d, J = 6.3 Hz, 3H, 2′-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 163.3, 159.8, 141.2, 105.5, 105.0, 102.7, 97.6, 64.3, 62.6, 56.2, 55.5, 40.1, 39.2, 39.1, 21.3; HRMS (ESI+) for $C_{16}H_{20}NaO_6$ $[M + Na]^+$ requires 331.1152, found 331.1148.

*(2′S,4′R,6′R)-Spiro[6,8-dimethoxyisochroman-1-one-3,6′-2′-methyloxan-4′-ol] (**19c**).* To a stirred solution of **18** (33 mg, 83 μmol) in dioxane (1.5 mL) was added KOH (1 M, 1.5 mL, 1.5 mmol). The resultant solution was stirred at rt for 1 h, and then the reaction was quenched with citric acid solution (0.5 M, 1.0 mL) and EtOAc (2 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 2 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:9 hexanes−EtOAc) afforded **19c** (1.9 mg, 7.4%) as a colorless oil and an inseparable mixture of **19a** and **19d** (2:1, 2.2 mg, 6.7%) as a colorless oil: **19c**: $[\alpha]_D^{23}$ −64.3 (c 0.014 in $CHCl_3$); IR (neat) ν_{max} 3430, 2924, 1709, 1605, 1459, 1430, 1327, 1262, 1203, 1163, 1068, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.41 (d, J = 2.3 Hz, 1H, ArH), 6.27 (d, J = 2.3 Hz, 1H, ArH), 4.05−4.00 (m, 1H, H-4′), 3.93 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.68−3.62 (m, 1H, H-2′), 3.10 (ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 16.2 Hz, 2H, H-4), 2.28 (ddd, J = 13.1, 5.1, 1.2 Hz, 1H, H-5′$_a$), 2.08−2.02 (m, 1H, H-3′$_a$), 1.81 (dd, J = 13.1, 9.0 Hz, 1H, H-5′$_b$), 1.50−1.43 (m, 1H, H-3′$_b$), 1.15 (d, J = 6.2 Hz, 3H, 2′-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 163.1, 160.4, 106.5, 104.9, 101.9, 97.6, 68.1, 56.2, 55.5, 42.6, 40.9, 36.85, 21.9; HRMS (ESI+) for $C_{16}H_{20}NaO_6$ $[M + Na]^+$ requires 331.1152, found 331.1153. **19d**: Tentatively identified as (2′*S*,4′*S*,6′*R*)-isomer based on ^1H NMR; however, it was not possible to obtain full characterization of the trace amount present in the mixture.

*(2′S,4′R,6′S)-Spiro[6,8-dimethoxyisochroman-1-one-3,6′-2′-methyloxan-4′-ol] (**1**).* To a stirred solution of **19a** (3.0 mg, 9.9 μmol) in CH_2Cl_2 (0.50 mL) at −78 °C was added BCl_3 (10 μL). The resultant mixture was stirred at rt for 15 min, and then the reaction was quenched with ice (0.5 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 1 mL). The combined organic extracts were washed with sat. aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:1 hexanes−EtOAc) afforded **1** (2.4 mg, 84%) as a white solid: $[\alpha]_D^{24}$ −78.0 (c 0.20 in $CHCl_3$), lit.[1] $[\alpha]_D^{30}$ −147 (c 0.196 in $CHCl_3$); IR (neat) ν_{max} 3410, 2926, 1664, 1626, 1584, 1508, 1440, 1363, 1232, 1157, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H, ArOH), 6.36 (d, J = 2.2 Hz, 1H, ArH), 6.26−6.26 (m, 1H, ArH), 4.40 (tt, J = 11.2, 4.7 Hz, 1H, H-4′), 4.11−4.05 (m, 1H, H-2′), 3.82 (s, 3H, OCH_3), 3.10 (2H, ABq, $\Delta\delta_{AB}$ = 0.15, J_{AB} = 16.4 Hz, H-4), 2.41 (ddd, J = 12.9, 4.8, 1.9 Hz, 1H, H-5′$_a$), 2.07−2.02 (m, 1H, H-3′$_a$), 1.51 (dd, J = 12.9, 11.1 Hz, 1H, H-5′$_b$), 1.28 (q, J = 11.4 Hz, 1H, H-3′$_b$), 1.13 (d, J = 6.3 Hz, 3H, 2′CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 166.0, 164.4, 138.9, 107.1, 104.6, 100.9, 99.3, 67.4, 63.6, 55.5, 42.7, 41.7, 38.8, 21.2; HRMS (ESI+) for $C_{15}H_{18}NaO_6$ $[M + Na]^+$ requires 317.0996, found 317.0986; mp 71−73 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01503.

^1H and ^{13}C NMR spectra for all compounds, ORTEP structure for citreoviranol (**1**) (PDF)

Crystal data for **1** (CIF)

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Notes

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