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Article

Total Synthesis and Anti-Tobacco Mosaic Virus Activity of the Furofuran Lignan (±)-Phrymarolin II and Its Analogues

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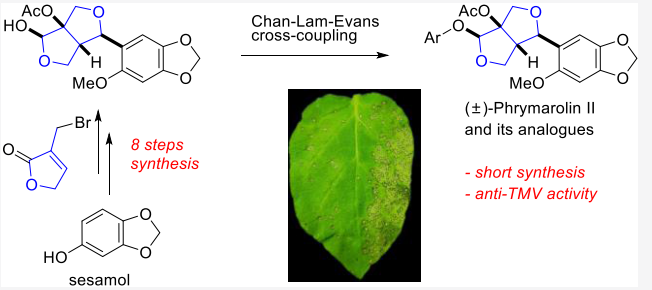
ABSTRACT: Phrymarolin II, a furofuran lignan isolated from *Phryma leptostachya* L., features a 3,7-dioxabicyclo[3.3.0]octane skeleton. Herein, we report an alternative total synthesis of (±)-phrymarolin II (**2**), which was performed in 9 steps from commercially available sesamol. The key steps of the synthesis included a zinc-mediated Barbier-type allylation and a copper-catalyzed anomeric *O*-arylation. Our total synthesis allowed the synthesis of analogues of (±)-phrymarolin II. Most derivatives displayed good to excellent *in vivo* activity against tobacco mosaic virus (TMV). (±)-Phrymarolin II (**2**) and compounds (±)-**31d** and (±)-**31g** exhibited similar or higher activity than commercial ningnanmycin, which indicated that phrymarolin lignans are a promising new class of plant virus inhibitors.



Furofuran lignans containing a 3,7-dioxabicyclo[3.3.0]-octane skeleton are widely distributed in plant species. These lignans are of interest because of their diverse structures and varied biological activities.[1] The plant *Phryma leptostachya* is traditionally used as a traditional Chinese medicine and as a natural insecticide in East Asia. The root of this plant has been shown to possess antiangiogenic, anti-inflammatory, antioxidant, skin-whitening, and insecticidal activity.[2] Phytochemical investigations have shown that lignans are relatively abundant in *P. leptostachya*. At the end of the 1960s, Eiji Taniguchi and Yasuyoshi Oshima isolated phrymarolins I (**1**) and II (**2**) from the root of *P. leptostachya* L.[3] Preliminary biological evaluations showed that these two oxygenated lignans were synergistically active in combination with pyrethrin and sevin. Furthermore, several other furofuran lignans, including phrymarolins III–V (**3**–**5**),[4] leptostachyol acetate (**6**),[5] and haedoxan A (**7**),[6] have been isolated from *P. leptostachya* L. extracts. Furofuran lignans from *P. leptostachya* L. have been proposed as lead compounds for the development of pesticides. However, the poor accessibility of these natural products is a barrier for the further biological evaluations and application in crop protection of these compounds.

Lignans from *P. leptostachya* L., including phrymarolins I–V (**1**–**5**) and haedoxan A (**7**), feature a 3,7-dioxabicyclo[3.3.0]-octane skeleton, which is also present in many other bioactive lignans, including glaberide I (**8**)[7] (zhebeiresinol[8]), salicifoliol (**9**),[9] kachiranol (**10**),[10] samin (**11**),[11] paulownin (**14**),[12] and sesame lignans,[13] such as sesamin (**12**), sesaminol (**13**), sesamolin (**15**), and sesamolinol (**16**). Phrymarolins I (**1**) and II (**2**) have an acetoxy group at the C-1 and a methylenedioxyphenoxy group at C-2. To explore the full potential of this interesting structural class with respect to potential agricultural applications, considerable effort has been devoted to approaches to the synthesis of phrymarolins and related natural products.[14] In 1986, Taniguchi and Ishibashi reported the first racemic synthesis of (±)-phrymarolin II (**2**) and its stereoisomers in 14 steps starting from β-vinyl-γ-butyrolactone (**17**) (Scheme 1a).[15] Using the same strategy, Taniguchi and co-workers synthesized (+)-phrymarolin I (**1**) from (*S*)-(+)-β-vinyl-γ-butyrolactone, which was prepared from the racemate by optical resolution.[16] However, these syntheses required many protection and deprotection steps and gave the products as a mixture. In 1997, the Taniguchi group developed a shorter approach to (+)-phrymarolin I (**1**) from (*R*)-(+)-3-hydroxybutanolide in 11 steps (Scheme 1a).[17] However, this strategy is still rather lengthy and lacks atom economy, particularly because of the low yield (15%) of the acid-catalyzed anomeric *O*-arylation reaction. Therefore, improved methods for phrymarolin syntheses are desirable for further biological evaluation of these compounds. Tobacco mosaic virus (TMV), one of the most destructive plant viruses, seriously affects crop yields and quality, and it is difficult to control. However, to date, few effective anti-TMV agents have been developed. Therefore, there is an urgent and unmet need to develop new, highly effective antiviral agents against TMV. Herein, we describe the racemic total synthesis of (±)-phry-

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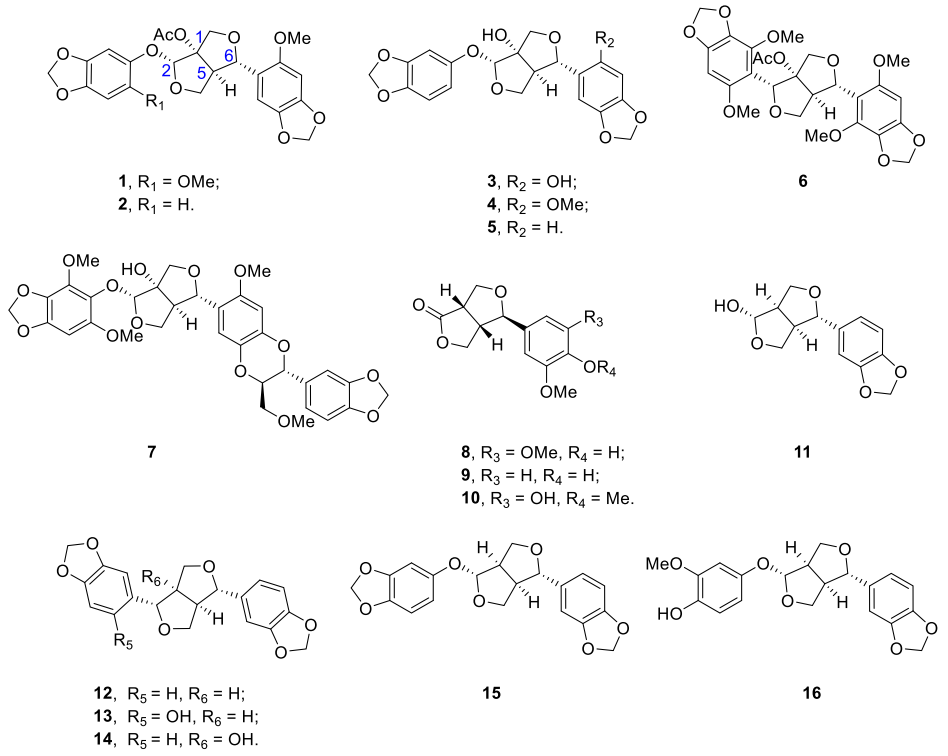
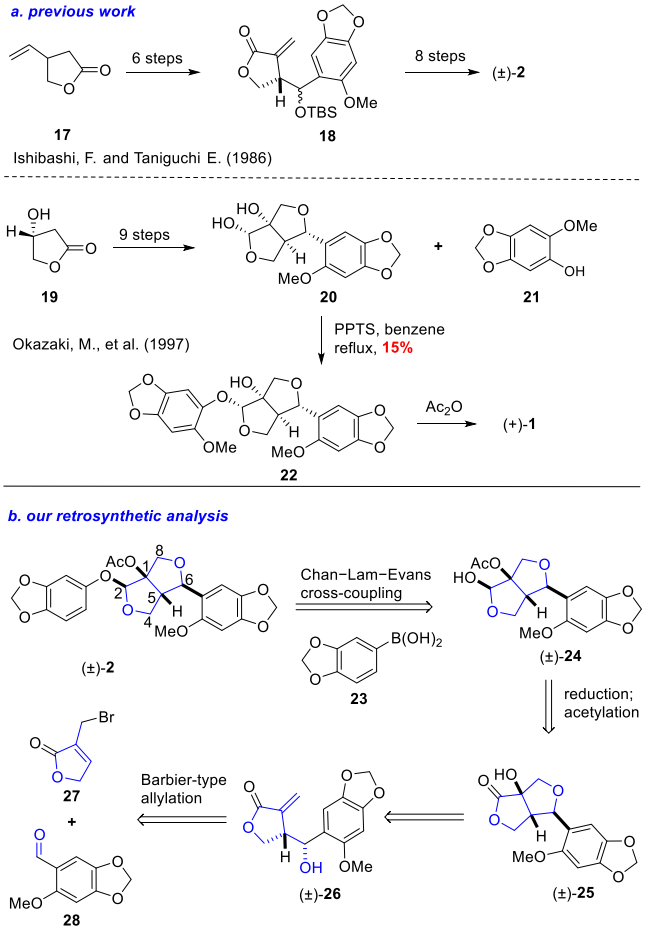
Chart 1



Scheme 1. Strategies for the Synthesis of Phrymarolins I (1) and II (2)



marolin II (**2**) and analogues, which features a zinc-mediated Barbier-type allylation and Chan–Lam–Evans cross-coupling reaction. Furthermore, the anti-TMV activity of the synthesized compounds was investigated.

The Barbier-type addition of 3-bromomethyl-5*H*-furan-2-one (**27**) to aldehydes has been proven to be an efficient method for the construction of a wide variety of *β*-hydroxymethyl-substituted *α*-methylene-*γ*-butyrolactones.[18] This powerful reaction has been used in the total synthesis of natural products.[19] As shown in Scheme 1a, the substituted *α*-methylene-*γ*-butyrolactone **18** was the key intermediate in the first total synthesis of (±)-phrymarolin II (**2**) and (+)-phrymarolin I (**1**).[15,16] Inspired by this synthesis, we investigated application of the Barbier-type allylation reaction in the construction of phrymarolin lignans. The retrosynthetic strategy is outlined in Scheme 1b. The (±)-phrymarolin II (**2**), which could be obtained from the lactol (±)-**24** through glycosidation, was chosen as our initial target molecule. In previously reported phrymarolin syntheses, the *O*-arylation was achieved through a nucleophilic substitution reaction under acidic conditions by treating phenol derivatives with lactol donors. This reaction gave lower yields because of dimerization of the lactol and anomerization of the coupling product. Considering the potential of the Chan–Lam–Evans cross-coupling reaction for the synthesis of *O*-arylglycosides, we expected that this reaction would provide a facile and efficient method to synthesize phrymarolins and analogues. Compound (±)-**24** could be generated from the lactone (±)-**25** by a reduction and acetylation sequence. The lactone (±)-**25** could be derived from the key intermediate *β*-hydroxymethyl-substituted *α*-methylene-*γ*-butyrolactone (±)-**26** via dihydroxylation and acid-catalyzed cyclization reactions. Compound (±)-**26** can be efficiently synthesized via the zinc- or indium-mediated Barbier-type allylation of 6-methoxy-1,3-benzodioxole-5-carbaldehyde (**28**) with 3-bromomethyl-5*H*-furan-2-one

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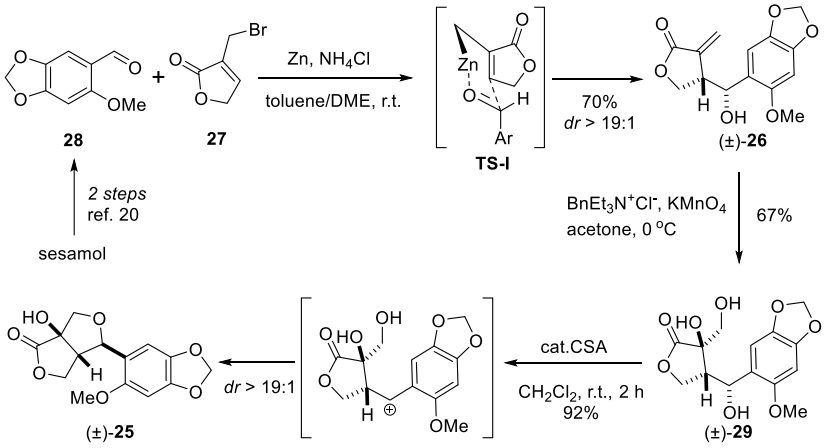
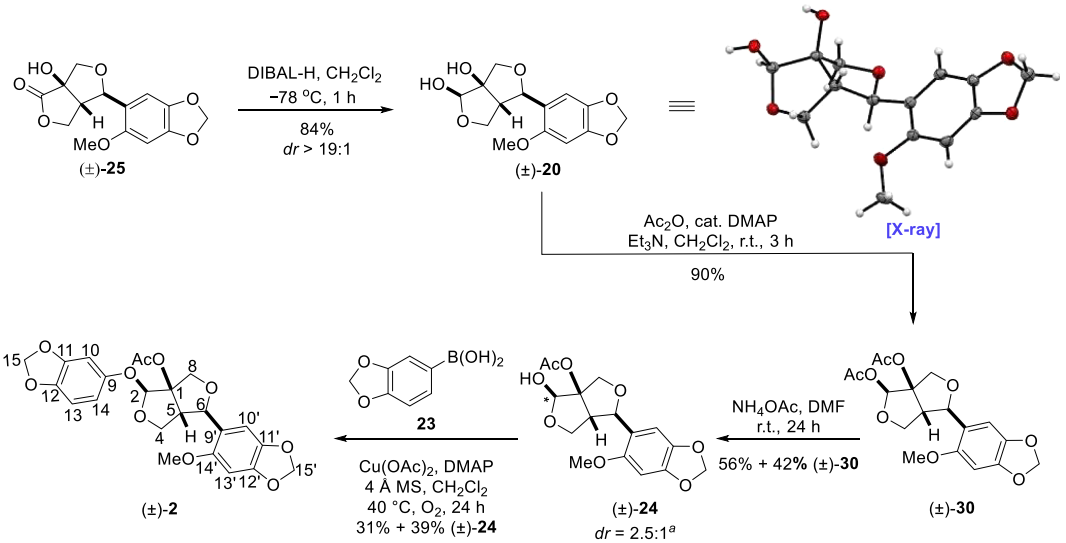
Scheme 2. Synthesis of Lactone (±)-25



Scheme 3. Synthesis of (±)-Phrymarolin II (2)



[a]The ratio between the two anomers was determined by ^{1}H NMR spectroscopy.

(**27**).[18] Compound **27** can be conveniently prepared from the commercially available tulipalin through a one-pot, two-step reaction.[18b]

Our synthetic studies commenced with the preparation of 6-methoxy-1,3-benzodioxole-5-carbaldehyde (**28**). Following the literature procedure,[20] compound **28** was constructed from sesamol in a two-step reaction sequence of *O*-methylation and formylation. Then, the coupling of aldehyde **28** and 3-bromomethyl-5*H*-furan-2-one (**27**) was investigated (Scheme 2). Using zinc with NH_4Cl in a low-polarity solvent [toluene/dimethoxyethane (DME)] resulted in an excellent diastereomeric ratio (*anti*:*syn* > 19:1),[18b,19a] and the desired compound (±)-**26** was obtained in 70% yield. The high regio- and stereoselectivity of this C−C bond-forming step can be explained by the formation of a Felkin−Ahn transition state[18b,19e] (zinc-involved intermediate **TS-I**, Scheme 2). Potassium permanganate, which is less toxic and cheaper than osmium salts, combined with a quaternary ammonium salt was used for the dihydroxylation of compound (±)-**26**. The mild reaction conditions gave the triol (±)-**29** in 67% yield with absolute regioselectivity, which resulted from the exclusive attack of the oxidant at the less-hindered side of the molecule. Transformation of triol (±)-**29** to tetrahydrofuran (±)-**25** was then accomplished by an acid-catalyzed cyclization with a catalytic amount of 10-camphorsulfonic acid (CSA) or *p*-toluenesulfonic acid. The desired diastereomer was predominantly formed (dr > 19:1) at room temperature after 2 h. Epimerization was observed with prolonged reaction times. This result may be explained by the formation of an initial protonation/complexation of the secondary alcohol group at the benzylic position and involvement of the carbonium ion intermediate.[21] The most stable epimer has the substituents in a *trans* position (Scheme 2).

With the synthesis of lactone (±)-**25** in place, the total synthesis of (±)-phrymarolin II (**2**) was attempted (Scheme 3). The selective reduction of (±)-**25** with diisobutylaluminum hydride (DIBAL-H) at −78 °C primarily afforded lactol (±)-**20** in 84% yield (dr > 19:1). The *cis*-fused nature of the ring system, along with the presence of an axial hydroxyl group, may induce the sterically hindered hydride to attack the lactone from the concave (α) face of the molecule.[22] Notably, the 1,2-dioxygenated-3,7-dioxabicyclo[3.3.0]octane skeleton with four continuous stereocenters in (±)-phrymarolin II (**2**) was forged in only 6 steps from commercially available sesamol. The relative stereochemistry of (±)-**20** was confirmed by single-crystal X-ray analysis.[23] With lactol (±)-**20** able to be

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efficiently accessed, we were positioned to install the aryl and acetyl groups. The Chan−Lam−Evans cross-coupling reaction is widely used for the C−O bond formation process with arylboronic acids under copper catalysis.[24] Seeking an arylation method, we were drawn to the recent work by the Messaoudi and Ye groups, who have developed a copper-catalyzed anomeric *O*-arylation of sugar lactols with arylboronic acids.[25] The hydroxyl groups at the C-1 and C-2 positions in the lactol (±)-**20** can react with arylboronic acids to form stable arylboronic esters. Therefore, (±)-**24**, which is required for the selective *O*-arylation reaction of the anomeric OH group, was constructed through a two-step sequence involving acetylation and selective anomeric deacetylation reactions. Compound (±)-**20** was treated with excess Ac_2O and Et_3N in CH_2Cl_2 at room temperature for 1 h to afford the corresponding diacetate (±)-**30** in 90% yield. Next, we investigated the regioselective anomeric deacetylation.[26] A variety of nitrogenous reagents and transition-metal-based Lewis acids were tested; however, in most cases large amounts of either unreacted starting material or the double-deacetylated byproduct were observed. After extensive optimization efforts, we selected NH_4OAc as a mild and economical reagent for the regioselective deacetylation.[26a] Treatment of (±)-**30** with NH_4OAc (2.0 equiv) in dimethylformamide (DMF) resulted in the formation of (±)-**24** (dr = 2.5:1) in 56% yield and recovered diacetate (±)-**30** in 42% yield after 24 h at room temperature. Using a larger excess of NH_4OAc or a longer reaction time did not improve the reaction yield. Finally, we investigated the Chan−Lam−Evans cross-coupling reaction of (±)-**24** using $Cu(OAc)_2$ as the catalyst under different conditions (see the Supporting Information). The optimized conditions [(±)-**24** (1.0 equiv), **23** (3.0 equiv), activated 4 Å molecular sieves, CH_2Cl_2, 40 °C, under O_2 atmosphere for 24 h] provided (±)-phrymarolin II (**2**) in 31% isolated yield (39% recovered (±)-**24** and a trace amount of *epi*-phrymarolin II were also observed). The overall yield of (±)-phrymarolin II (**2**) from 6-methoxy-1,3-benzodioxole-5-carbaldehyde (**28**) was approximately 5.7%. The structure of synthetic (±)-phrymarolin II (**2**) was confirmed by analysis of spectroscopic data. The obtained data were identical to the literature data.[2e]

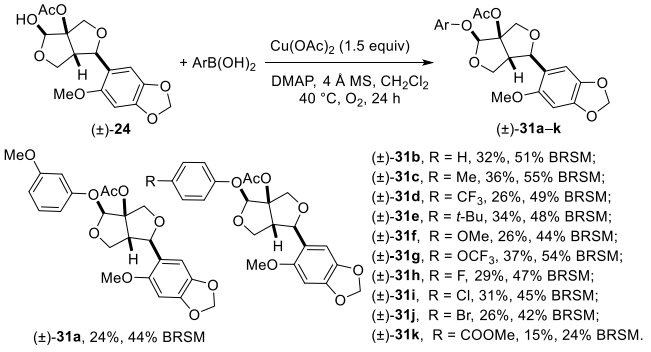
With the key intermediate (±)-**24** in place, the developed synthetic route was then applied to the synthesis of analogues of (±)-phrymarolin II (Scheme 4). The synthesis of (±)-phrymarolin I (**1**) was first attempted. However, the cross-coupling reaction did not give the desired product, which may be because of the severe steric hindrance in the *ortho*-substituted arylboronic acids. Compound (±)-**24** was readily coupled with other arylboronic acids having electron-donating or electron-withdrawing substituents to give the products (±)-**31a−k** in moderate yields. In most cases, the β anomers were separated as the major product by SiO_2 flash chromatography or preparative thin-layer chromatography, and the NMR data of the pure single anomers were obtained.

Many lignans have shown antiviral activity.[27] Therefore, (±)-phrymarolin II (**2**) and its analogues (±)-**31a−k** were tested for anti-TMV activity using the half-leaf method. As shown in Table 1, most of the synthesized compounds exhibited good to excellent *in vivo* anti-TMV activity. (±)-Phrymarolin II (**2**), (±)-**31d**, and (±)-**31g** showed excellent activities, which were similar to that of the commercial ningnanmycin and higher than that of ribavirin and could be considered as promising lead compounds for the development of anti-TMV agents. Compounds (±)-**31a−k** exhibited a viral inactivation effect of 31.6−77.4% at 500 μg/mL and 10.4−31.1% at 100 μg/mL. (±)-Phrymarolin II (**2**) displayed an excellent inactivation effect of 77.4%, a protection effect of 59.2%, and a curative effect of 49.3% at 500 μg/mL. Compounds (±)-**31d** and (±)-**31g** showed inactivation (73.8% and 72.5%, respectively), protection (53.3% and 55.0%, respectively), and curative (43.3% and 44.7%, respectively) activities at 500 μg/mL, which were equivalent to those of the positive control ningnanmycin (75.5%, 52.4%, and 42.1%, respectively). Furthermore, the inactivation effects

Table 1. *In Vivo* Antiviral Activity of (±)-Phrymarolin II (2) and Its Analogues against TMV

compd	concn (μg/mL)	inactivation effect (%)	protection effect (%)	curative effect (%)
(±)-phrymarolin II	500	77.4	59.2	49.3
	100	30.0	35.9	22.3
(±)-**31a**	500	39.5	35.7	28.8
	100	17.5	0	0
(±)-**31b**	500	42.8	29.2	27.9
	100	11.9	0	0
(±)-**31c**	500	62.0	40.5	30.0
	100	25.7	20.5	6.3
(±)-**31d**	500	73.8	53.3	43.3
	100	31.1	30.3	21.5
(±)-**31e**	500	66.5	44.7	38.5
	100	27.3	22.4	17.2
(±)-**31f**	500	46.1	53.4	37.6
	100	16.8	28.9	17.0
(±)-**31g**	500	72.5	55.0	44.7
	100	28.3	29.8	21.1
(±)-**31h**	500	53.3	36.0	32.8
	100	20.3	11.4	13.2
(±)-**31i**	500	45.6	29.8	26.0
	100	17.1	7.3	0
(±)-**31j**	500	41.6	24.8	23.7
	100	16.2	0	0
(±)-**31k**	500	31.6	28.7	24.9
	100	10.4	0	0
ribavirin	500	50.1	38.2	28.3
	100	21.1	19.3	14.0
ningnanmycin	500	75.5	52.4	42.1
	100	33.0	28.7	20.1

Scheme 4. Synthesis of (±)-Phrymarolin II Analogues[a]



[a]Note: DMAP = 4-dimethylaminopyridine, BRSM = based on recovered starting material.

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of compounds(±)-**31c**, (±)-**31e**, and (±)-**31h** (62.0%, 66.5%, and 53.3%, respectively) were higher than that of ribavirin (50.1%) but lower than that of ningnanmycin (75.5%) at 500 μg/mL. Compounds (±)-**31d**, (±)-**31g**, and (±)-**31h** displayed greater inhibitory effects than those of compounds (±)-**31c**, (±)-**31f**, and (±)-**31b**, respectively, which indicated that fluoro-substitution may be favorable for improving the antiviral activity of phrymarolin lignans.

In summary, the racemic total synthesis of (±)-phrymarolin II (**2**) and analogues was achieved in 9 steps from commercially available sesamol. The 3,7-dioxabicyclo[3.3.0]-octane core of the products was constructed by a Barbier-type allylation followed by dihydroxylation and acid-catalyzed condensation reactions. A copper-catalyzed Chan−Lam−Evans cross-coupling reaction was used for anomeric *O*-arylation, which was efficient and provided a suitable platform to access a library of phrymarolin analogues. Our total synthesis enabled the examination of the biological activity of these analogues, which revealed that (±)-phrymarolin II (**2**) and analogues exhibited potent anti-TMV activity. (±)-Phrymarolin II (**2**), (±)-**31d**, and (±)-**31g** displayed similar or more potent antiviral activity than the commercial ningnanmycin. Further studies on the lead optimization and antiviral mechanism of these compounds are currently underway in our laboratories.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed in flame-dried glassware under an argon atmosphere, unless otherwise stated. Dry toluene, CH_2Cl_2, and DMF were obtained by passing these previously degassed solvents through activated alumina columns. All other reagents and solvents were purchased from Sigma-Aldrich, Energy Chemical, or Adamas and used as received. Reactions were monitored by TLC on silica and visualized by UV irradiation and/or staining with *p*-anisaldehyde or basic aqueous $KMnO_4$ developing agents. Qingdao Haiyang silica gel (200−300 mesh) was used for flash column chromatography. NMR spectra were recorded on a Bruker AVANCE III 400 or 500 MHz for ^{1}H NMR (101 or 126 MHz for ^{13}C NMR) in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported with the residual solvent signal used as an internal standard (^{1}H NMR: δ = 7.26 ($CDCl_3$), 2.50 (DMSO-d_6); ^{13}C NMR: δ = 77.16 ($CDCl_3$), 39.52 (DMSO-d_6)). Melting points (mp) are uncorrected and were recorded on a SGWX-4B apparatus. IR spectra were taken on a Thermo Nicolet, Avatar 330 FT-IR spectrometer as thin films and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q Exactive mass spectrometer. X-ray crystallographic analyses were performed on a Bruker APEX-II CCD diffractometer using single crystals.

Compounds 3-bromomethyl-5*H*-furan-2-one (**27**)[18b] and 6-methoxy-1,3-benzodioxole-5-carbaldehyde (**28**)[20] are known compounds, which were prepared by following the literature procedures.

(±)-4-(Hydroxy(6-methoxybenzo[*d*][1,3]dioxol-5-yl)-methyl)-3-methylenedihydrofuran-2(3*H*)-one [(±)-26]. Activated zinc dust (726 mg, 11.1 mmol, 2.0 equiv), NH_4Cl (1.19 g, 22.2 mmol, 4.0 equiv), and aldehyde **28** (1.00 g, 5.55 mmol, 1.0 equiv) were added sequentially to a round-bottom flask. A mixture of toluene and DME (14 mL, v/v = 1:1) was then added, followed by 3-bromomethyl-5*H*-furan-2-one (**27**) (1.18 g, 6.66 mmol, 1.2 equiv). The reaction mixture was stirred vigorously at room temperature for 2 h. The gray to colorless slurry was quenched with saturated NH_4Cl aqueous solution, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give the crude material, which was purified by flash column chromatography (petroleum ether/EtOAc = 2:1) to afford alcohol (±)-**26** (1.08 g, 70% yield) as a white solid. The spectral data were in accordance with the literature:[19a] mp = 104.4−106.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 6.78 (s, 1H), 6.50 (s, 1H), 6.25 (d, *J* = 1.5 Hz, 1H), 5.89 (s, 2H), 5.65 (d, *J* = 0.8 Hz, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 4.16 (d, *J* = 8.8 Hz, 1H), 4.05 (dd, *J* = 9.4, 4.5 Hz, 1H), 3.75 (s, 3H), 3.42−3.33 (m, 1H), 2.89 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$/TMS) δ 171.2, 151.5, 147.9, 141.3, 135.3, 125.0, 121.2, 107.5, 101.4, 94.4, 70.7, 68.2, 56.2, 44.4; IR (KBr): 3456, 2921, 1742, 1661, 1618, 1504, 1481, 1425, 1320, 1192, 1141, 1104, 1020, 930, 818 cm^{-1}.

(±)-3-Hydroxy-4-(hydroxy(6-methoxybenzo[*d*][1,3]dioxol-5-yl)methyl)-3-(hydroxymethyl)dihydrofuran-2(3*H*)-one [(±)-29]. Benzyltriethylammonium chloride (982 mg, 4.31 mmol, 1.2 equiv), $KMnO_4$ (682 mg, 4.31 mmol, 1.2 equiv), and anhydrous acetone (8 mL) were added sequentially to a round-bottom flask, and the mixture was stirred at room temperature for 30 min. Then, the reaction was cooled to 0 °C, and a solution of alcohol (±)-**26** (1.0 g, 3.59 mmol, 1.0 equiv) in acetone (2 mL) was added dropwise over 5 min while the internal temperature was kept below 5 °C. The resulting mixture was then stirred at 0 °C for 30 min (monitored by TLC plates) before it was quenched with a saturated $NaHSO_3$ aqueous solution (5 mL). The mixture was filtered through a pad of Celite, and the residue was washed with acetone. Most of the acetone was removed under reduced pressure to give a crude material that was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (acetone/CH_2Cl_2 = 1:5) to give triol (±)-**29** (0.75 g, 67%) as a white solid: mp = 168.5−169.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.95 (s, 1H), 6.74 (s, 1H), 5.95 (d, *J* = 4.6 Hz, 2H), 5.45 (s, 1H), 5.34 (dd, *J* = 10.1, 5.5 Hz, 1H), 5.20 (t, *J* = 4.5 Hz, 1H), 5.02 (d, *J* = 5.3 Hz, 1H), 4.02 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.75 (dd, *J* = 10.8, 2.5 Hz, 1H), 3.71 (s, 3H), 3.65−3.58 (m, 2H), 2.76 (dd, *J* = 19.8, 10.1 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.5, 150.9, 146.8, 141.0, 124.0, 106.8, 100.9, 94.9, 76.5, 66.1, 63.4, 63.1, 56.6, 51.7; IR (KBr): 3470, 3364, 2899, 1757, 1623, 1486, 1426, 1276, 1217, 1155, 1040, 931, 873, 812 cm^{-1}; HRMS (ESI-ion trap) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}O_8Na$ 335.0737, found 335.0739.

(±)-6a-Hydroxy-4-(6-methoxybenzo[*d*][1,3]dioxol-5-yl)-tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1-one [(±)-25]. To a stirred solution of triol (±)-**29** (903.4 mg, 2.89 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (60 mL) was added D-camphorsulfonic acid (67.1 mg, 0.29 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 2 h and then quenched with a few drops of Et_3N. The mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel flash chromatography (petroleum ether/EtOAc = 2:1) to afford lactone (±)-**25** (0.78 g, 92%) as a white solid: mp = 158.9−160.1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.94 (s, 1H), 6.80 (s, 1H), 6.43 (s, 1H), 5.96 (d, *J* = 6.0 Hz, 2H), 5.02 (d, *J* = 4.7 Hz, 1H), 4.58 (t, *J* = 8.9 Hz, 1H), 4.32 (dd, *J* = 9.6, 4.6 Hz, 1H), 4.00 (dd, *J* = 16.4, 9.8 Hz, 2H), 3.74 (s, 3H), 2.81 (dt, *J* = 8.8, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 177.0, 151.0, 147.1, 140.5, 121.3, 105.5, 101.1, 95.1, 83.1, 82.4, 75.3, 69.9, 56.4, 54.7; IR (KBr): 3406, 2857, 1746, 1505, 1494, 1435, 1229, 1198, 1040, 997, 938 cm^{-1}; HRMS (ESI-ion trap) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}O_7Na$ 317.0632, found 317.0631.

(±)-4-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-1,6a(6*H*)-diol ((±)-20). To a solution of lactone (±)-**25** (500 mg, 1.70 mmol, 1.0 equiv) in CH_2Cl_2 (40.0 mL) at −78 °C was added a solution of DIBAL-H (2.83 mL, 4.25 mmol, 2.5 equiv, 1.5 M in toluene) dropwise over 10 min. The resulting solution was stirred at −78 °C for 1 h and then quenched with MeOH (5 mL). The resulting mixture was stirred at −78 °C for 10 min. After addition of a 20% Rochelle salt aqueous solution (30 mL), the suspension was warmed to room temperature, and the volatile solvents (CH_2Cl_2) were then evaporated under reduced pressure. EtOAc (30 mL) was added to the reaction mixture, which was stirred at room temperature. After the mixture turned clear, it was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/EtOAc =

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1:1) to afford the lactol (±)-**20** (423 mg, 84%) as a white solid: mp = 166.2−167.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6/TMS) δ 6.94 (s, 1H), 6.77 (s, 1H), 6.38 (d, J = 5.2 Hz, 1H), 5.94 (d, J = 8.0 Hz, 2H), 4.94 (s, 1H), 4.92 (d, J = 5.2 Hz, 1H), 4.67 (d, J = 6.2 Hz, 1H), 4.09 (dd, J = 9.0, 7.1 Hz, 1H), 4.00 (d, J = 9.4 Hz, 1H), 3.73−3.68 (m, 1H), 3.71 (s, 3H), 3.48 (d, J = 9.4 Hz, 1H), 2.22 (td, J = 6.7, 2.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.9, 146.7, 140.6, 122.5, 105.7, 100.9, 97.0, 94.9, 91.1, 83.0, 77.6, 68.3, 58.3, 56.4; IR (KBr) 3490, 3371, 2902, 1484, 1430, 1265, 1209, 1167, 1038, 996, 935, 888, 858, 784 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{14}H_{16}O_7Na$ 319.0788, found 319.0787.

(±)-4-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-1,6a(6*H*)-diyl diacetate [(±)-30]. To a stirred solution of lactol (±)-**20** (1.50 g, 5.06 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at room temperature were added sequentially DMAP (74 mg, 0.6 mmol, 0.12 equiv), Ac_2O (1.45 mL, 15.2 mmol, 3.0 equiv), and Et_3N (2.11 mL, 15.2 mmol, 3.0 equiv). The resulting mixture was stirred at room temperature for 3 h before it was quenched with saturated $NaHCO_3$ aqueous solution (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (CH_2Cl_2/EtOAc = 3:1) to afford the diacetate (±)-**30** (1.72 g, 90%) as a white solid: mp = 185.1−187.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.02 (s, 1H), 6.51 (s, 1H), 6.49 (s, 1H), 5.92 (s, 2H), 4.84 (d, J = 7.2 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.16 (dd, J = 9.4, 6.8 Hz, 1H), 4.07 (dd, J = 9.4, 2.0 Hz, 1H), 3.82 (d, J = 11.2 Hz, 1H), 3.76 (s, 3H), 2.79 (t, J = 6.6 Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.5, 169.2, 151.5, 147.7, 141.5, 121.1, 106.3, 101.4, 96.2, 95.7, 94.3, 82.8, 75.8, 69.5, 56.7, 56.3, 21.1, 20.9; IR (KBr) 2851, 1737, 1509, 1485, 1466, 1427, 1248, 1099, 1039, 975, 934 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{18}H_{20}O_9Na$ 403.1000, found 403.0999.

(±)-4-Hydroxy-1-(6-methoxybenzo[*d*][1,3]dioxol-5-yl)-dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-24]. To a stirred solution of diacetate (±)-**30** (0.8 g, 2.10 mmol, 1.0 equiv) in anhydrous DMF (20 mL) was added NH_4OAc (324 mg, 4.21 mmol, 2.0 equiv). The resulting mixture was stirred at room temperature for 24 h. Then, the reaction was quenched with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O and brine and dried over anhydrous $MgSO_4$. After filtration, the extract was concentrated and the residue was purified by silica gel flash chromatography (acetone/CH_2Cl_2/petroleum ether = 1:25:25 → CH_2Cl_2/EtOAc = 3:1) to afford recovered diacetate (±)-**30** (335 mg, 42%) and lactol (±)-**24** (395 mg, 56%, 96% BRSM) as a white solid and a mixture of anomers: dr = 2.5:1; mp = 150.4−153.0 °C; major anomer: ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.02 (s, 1H), 6.51 (s, 1H), 5.92 (s, 2H), 5.63 (s, 1H), 4.83 (d, J = 7.1 Hz, 1H), 4.54 (d, J = 11.1 Hz, 1H), 4.33−4.24 (m, 1H), 3.99 (dd, J = 9.2, 1.7 Hz, 1H), 3.78−3.77 (m, 1H), 3.76 (s, 3H), 2.76 (t, J = 6.9 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 171.4, 151.6, 147.6, 141.5, 121.4, 106.4, 101.4, 97.3, 97.2, 94.4, 82.8, 75.8, 68.1, 56.5, 56.4, 21.3; IR (KBr) 3352, 2905, 1741, 1507, 1430, 1373, 1238, 1194, 1037, 929, 858 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{16}H_{18}O_8Na$ 361.0894, found 361.0893.

General Procedure for the Synthesis of (±)-Phrymarolin II (2) and Its Analogues [(±)-31a−k]. To a flame-dried flask were added sequentially $Cu(OAc)_2$ (120.8 mg, 0.67 mmol, 1.5 equiv), DMAP (108.3 mg, 0.89 mmol, 2.0 equiv), and activated 4 Å molecular sieves (450 mg). CH_2Cl_2 (9 mL) was added, and the suspension was stirred for 5 min. Boronic acid (1.33 mmol, 3.0 equiv) was then added, and the reaction mixture was stirred for 5 min. Finally, lactol (±)-**24** (150 mg, 0.44 mmol, 1.0 equiv) was added, and the resulting mixture was stirred at 40 °C under an O_2 atmosphere. After 24 h, the reaction mixture was filtered through Celite (eluting with EtOAc and CH_2Cl_2), and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (EtOAc/CH_2Cl_2 = 1:20 → 1:10 → 1:0) to give recovered lactol (±)-**24** and the crude product, which was further purified by preparative thin-layer chromatography (EtOAc/petroleum ether = 3:20) to afford the desired pure single anomer.

(±)-Phrymarolin II (2): 66.0 mg (31% yield, 51% BRSM) as a white solid; mp = 160.1−161.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.05 (s, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.58 (s, 1H), 6.52 (s, 1H), 6.49 (dd, J = 8.6, 2.2 Hz, 1H), 5.93 (s, 2H), 5.91 (s, 2H), 5.70 (s, 1H), 4.87 (d, J = 7.1 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.29 (dd, J = 9.2, 7.0 Hz, 1H), 4.06 (dd, J = 9.2, 1.9 Hz, 1H), 3.81 (d, J = 11.3 Hz, 1H), 3.77 (s, 3H), 2.84 (t, J = 7.0 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 151.9, 151.5, 148.1, 147.6, 143.4, 141.5, 121.4, 110.5, 108.1, 106.4, 103.1, 101.41, 101.37, 101.3, 96.5, 94.3, 83.0, 75.7, 68.7, 56.6, 56.3, 21.2; IR (KBr) 2907, 1742, 1631, 1503, 1485, 1428, 1371, 1241, 1180, 1033, 932, 859 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{23}H_{22}O_{10}Na$ 481.1105, found 481.1107.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(3-methoxyphenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31a]: 46.4 mg (24% yield, 44% BRSM) as a white solid: mp = 104.0−106.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.20−7.15 (m, 1H), 7.06 (s, 1H), 6.65−6.57 (m, 3H), 6.52 (s, 1H), 5.93 (s, 2H), 5.88 (s, 1H), 4.88 (d, J = 7.1 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.28 (dd, J = 9.3, 6.8 Hz, 1H), 4.06 (dd, J = 9.2, 1.9 Hz, 1H), 3.85 (d, J = 11.1 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.87 (t, J = 6.5 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.8, 160.8, 157.9, 151.5, 147.6, 141.5, 130.0, 121.4, 109.8, 108.5, 106.4, 103.9, 101.6, 101.4, 96.6, 94.4, 83.0, 75.8, 68.9, 56.6, 56.3, 55.4, 21.2; IR (KBr) 2922, 1741, 1593, 1486, 1240, 1194, 1150, 1039, 936, 863 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ calcd for $C_{23}H_{24}O_9Na$ 467.1313, found 467.1313.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-phenoxydihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31b]: 58.5 mg (32% yield, 51% BRSM) as a white solid: mp = 170.3−171.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.29 (d, J = 8.8 Hz, 2H), 7.07−7.00 (m, 4H), 6.53 (s, 1H), 5.94 (s, 2H), 5.87 (s, 1H), 4.89 (d, J = 7.0 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.29 (dd, J = 9.3, 6.9 Hz, 1H), 4.06 (dd, J = 9.2, 2.1 Hz, 1H), 3.85 (d, J = 11.1 Hz, 1H), 3.77 (s, 3H), 2.87 (t, J = 7.0 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 156.8, 151.6, 147.6, 141.5, 129.6 (2C), 122.9, 121.4, 117.8 (2C), 106.4, 101.8, 101.4, 96.6, 94.4, 83.0, 75.8, 68.8, 56.7, 56.4, 21.2; IR (KBr) 2900, 1735, 1599, 1500, 1484, 1427, 1374, 1252, 1221, 1188, 1086, 1038, 938, 860 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{22}H_{22}O_8Na$ 437.1207, found 437.1207.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(*p*-tolyloxy)-dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31c]. 68.0 mg (36% yield, 55% BRSM) as a white solid: mp = 146.3−146.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.10−7.04 (m, 3H), 6.92 (d, J = 8.1 Hz, 2H), 6.53 (s, 1H), 5.93 (s, 2H), 5.81 (s, 1H), 4.88 (d, J = 7.0 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.29 (dd, J = 9.2, 6.8 Hz, 1H), 4.05 (dd, J = 9.3, 1.7 Hz, 1H), 3.84 (d, J = 11.2 Hz, 1H), 3.77 (s, 3H), 2.86 (t, J = 6.9 Hz, 1H), 2.29 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 154.7, 151.5, 147.6, 141.5, 132.3, 130.1 (2C), 121.4, 117.8 (2C), 106.4, 102.1, 101.4, 96.6, 94.3, 83.0, 75.8, 68.7, 56.7, 56.3, 21.2, 20.8; IR (KBr) 2903, 2851, 1736, 1613, 1509, 1481, 1462, 1424, 1317, 1223, 1189, 1159, 1040, 937, 815 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{23}H_{24}O_8Na$ 451.1363, found 451.1363.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(4-(trifluoromethyl)phenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31d]: 56.2 mg (26% yield, 49% BRSM) as a white solid: mp = 127.3−128.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.54 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 7.06 (s, 1H), 6.53 (s, 1H), 5.94 (s, 3H), 4.89 (d, J = 7.0 Hz, 1H), 4.61 (d, J = 11.1 Hz, 1H), 4.25 (dd, J = 9.3, 6.8 Hz, 1H), 4.09 (dd, J = 9.3, 1.9 Hz, 1H), 3.86 (d, J = 11.2 Hz, 1H), 3.77 (s, 3H), 2.88 (t, J = 6.5 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 159.1, 151.5, 147.7, 141.5, 127.0 (q, J = 3.8 Hz, 2C), 124.9 (q, J = 32.9 Hz), 124.4 (q, J = 272.8 Hz), 121.2, 117.4 (2C), 106.4, 101.4, 101.3, 96.5, 94.4, 83.1, 75.8, 69.2, 56.6, 56.3, 21.1; IR (KBr) 2919, 1735, 1615, 1505, 1484, 1429, 1329, 1204, 1161, 1070, 1005, 937, 862 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{23}H_{21}F_3O_8Na$ 505.1081, found 505.1081.

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(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(4-(*tert*-butyl)-phenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31e]: 71.2 mg (34% yield, 48% BRSM) as a white solid: mp = 151.2−153.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.31−7.28 (m, 2H), 7.06 (s, 1H), 6.95 (d, J = 7.5 Hz, 2H), 6.53 (s, 1H), 5.93 (s, 2H), 5.86 (s, 1H), 4.89 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.31−4.25 (m, 1H), 4.05 (d, J = 9.1 Hz, 1H), 3.85 (d, J = 11.2 Hz, 1H), 3.77 (s, 3H), 2.87 (t, J = 6.9 Hz, 1H), 2.13 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 154.4, 151.6, 147.6, 145.6, 141.5, 126.4 (2C), 121.4, 117.1 (2C), 106.5, 101.7, 101.4, 96.6, 94.4, 83.0, 75.8, 68.7, 56.7, 56.3, 34.3, 31.6 (3C), 21.2; IR (KBr) 2960, 1739, 1511, 1484, 1428, 1371, 1248, 1187, 1116, 1024, 932, 872, 830 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{26}H_{30}O_8Na$ 493.1833, found 493.1834.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(4-methoxy-phenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31f]: 51.0 mg (26% yield, 44% BRSM) as a white solid: mp = 126.1−128.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.06 (s, 1H), 6.96 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 6.53 (s, 1H), 5.93 (s, 2H), 5.73 (s, 1H), 4.88 (d, J = 7.0 Hz, 1H), 4.61 (d, J = 11.1 Hz, 1H), 4.31 (dd, J = 9.2, 6.8 Hz, 1H), 4.06 (d, J = 9.1 Hz, 1H), 3.82 (d, J = 11.1 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.86 (t, J = 6.8 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 155.5, 151.5, 150.8, 147.6, 141.5, 121.4, 119.5(2C), 114.7(2C), 106.4, 102.9, 101.4, 96.6, 94.3, 83.0, 75.8, 68.6, 56.7, 56.3, 55.8, 21.3; IR (KBr) 2897, 2863, 1733, 1508, 1485, 1427, 1376, 1245, 1211, 1040, 937, 868, 829, 783 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{23}H_{24}O_9Na$ 467.1313, found 467.1314.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(4-(trifluoro-methoxy)phenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31g]: 82.0 mg (37% yield, 54% BRSM) as a white solid: mp = 120.2−122.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.14 (d, J = 8.5 Hz, 2H), 7.06−7.01 (m, 3H), 6.53 (s, 1H), 5.94 (s, 2H), 5.84 (s, 1H), 4.88 (d, J = 7.0 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.30−4.23 (m, 1H), 4.08 (d, J = 9.3 Hz, 1H), 3.84 (d, J = 11.2 Hz, 1H), 3.77 (s, 3H), 2.87 (t, J = 6.9 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 155.2, 151.5, 147.7, 144.4 (q, J = 1.8 Hz), 141.5, 122.5 (2C), 121.2, 120.6 (q, J = 256.8 Hz), 118.7 (2C), 106.4, 102.0, 101.4, 96.5, 94.3, 83.0, 75.7, 68.9, 56.6, 56.3, 21.2; IR (KBr) 2901, 2856, 1731, 1630, 1503, 1465, 1428, 1377, 1253, 1222, 1192, 1164, 1083, 1033, 1008, 930, 867 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{23}H_{21}FO_9Na$ 521.1030, found 521.1030.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(4-fluoro-phenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31h]: 56.2 mg (29% yield, 47% BRSM) as a white solid: mp = 106.5−107.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.05 (s, 1H), 7.00−6.94 (m, 4H), 6.53 (s, 1H), 5.94 (s, 2H), 5.76 (s, 1H), 4.88 (d, J = 7.0 Hz, 1H), 4.61 (d, J = 11.1 Hz, 1H), 4.29 (dd, J = 9.1, 7.0 Hz, 1H), 4.07 (dd, J = 9.3, 2.0 Hz, 1H), 3.82 (d, J = 11.1 Hz, 1H), 3.77 (s, 3H), 2.86 (t, J = 7.0 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 158.7 (d, J = 240.8 Hz), 152.9 (d, J = 2.4 Hz), 151.5, 147.7, 141.5, 121.4, 119.5 (d, J = 8.2 Hz, 2C), 116.1 (d, J = 23.1 Hz, 2C), 106.4, 102.7, 101.4, 96.6, 94.4, 83.0, 75.8, 68.8, 56.6, 56.4, 21.2; IR (KBr): 2925, 1742, 1622, 1505, 1428, 1372, 1246, 1202, 1074, 1025, 934, 833, 791 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{22}H_{21}FO_8Na$ 455.1113, found 455.1112.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(4-chloro-phenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31i]: 62.0 mg (31% yield, 45% BRSM) as a white solid: mp = 146.3−147.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.25−7.22 (m, 2H), 7.05 (s, 1H), 6.97−6.94 (m, 2H), 6.53 (s, 1H), 5.94 (s, 2H), 5.81 (s, 1H), 4.88 (d, J = 7.1 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.26 (dd, J = 9.3, 6.9 Hz, 1H), 4.07 (d, J = 9.3 Hz, 1H), 3.83 (d, J = 11.1 Hz, 1H), 3.77 (s, 3H), 2.86 (t, J = 6.9 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 155.4, 151.5, 147.7, 141.5, 129.6 (2C), 128.0, 121.3, 119.2 (2C), 106.4, 102.0, 101.4, 96.6, 94.4, 83.0, 75.8, 68.9, 56.6, 56.3, 21.2; IR (KBr) 2901, 1740, 1488, 1427, 1373, 1283, 1190, 1076, 1038, 934, 866, 826 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{22}H_{21}ClO_8Na$ 471.0817, found 471.0819.

(±)-1-(6-Methoxybenzo[*d*][1,3]dioxol-5-yl)-4-(4-bromo-phenoxy)dihydro-1*H*,3*H*-furo[3,4-*c*]furan-3a(4*H*)-yl acetate [(±)-31j]: 57.0 mg (26% yield, 42% BRSM) as a white solid: mp = 145.5−147.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.38 (d, J = 7.5 Hz, 2H), 7.05 (s, 1H), 6.90 (d, J = 7.5 Hz, 2H), 6.52 (s, 1H), 5.93 (s, 2H), 5.81 (s, 1H), 4.87 (d, J = 6.9 Hz, 1H), 4.60 (d, J = 11.0 Hz, 1H), 4.30−4.20 (m, 1H), 4.07 (d, J = 9.2 Hz, 1H), 3.83 (d, J = 11.1 Hz, 1H), 3.77 (s, 3H), 2.85 (t, J = 7.0 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 155.9, 151.5, 147.7, 141.5, 132.5 (2C), 121.3, 119.6 (2C), 115.4, 106.4, 101.9, 101.4, 96.5, 94.3, 83.0, 75.7, 68.9, 56.6, 56.3, 21.2; IR (KBr): 2901, 1739, 1485, 1424, 1374, 1284, 1284, 1073, 1038, 1007, 936, 866, 822 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{22}H_{21}BrO_8Na$ 515.0312, found 515.0314.

(±)-Methyl-4-((6a-acetoxy-4-(6-methoxybenzo[*d*][1,3]-dioxol-5-yl)tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1-yl)oxy)-benzoate [(±)-31k]: 31.0 mg (15% yield, 24% BRSM) as a white solid: mp = 164.0−165.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.98 (d, J = 7.7 Hz, 1H), 7.09−6.99 (m, 3H), 6.53 (s, 1H), 5.96 (s, 1H), 5.94 (s, 2H), 4.89 (d, J = 7.0 Hz, 1H), 4.61 (d, J = 11.1 Hz, 1H), 4.24 (dd, J = 9.3, 6.9 Hz, 1H), 4.08 (d, J = 9.2 Hz, 1H), 3.89 (s, 3H), 3.92−3.82 (m, 1H), 3.77 (s, 3H), 2.87 (t, J = 7.0 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$/TMS) δ 170.9, 166.8, 160.3, 151.5, 147.7, 141.5, 131.6 (2C), 124.4, 121.2, 116.8 (2C), 106.4, 101.4, 101.0, 96.5, 94.3, 83.0, 75.7, 69.1, 56.6, 56.3, 52.1, 21.2; IR (KBr): 2927, 2854, 1738, 1720, 1606, 1507, 1483, 1428, 1374, 1282, 1249, 1172, 1104, 1071, 1015, 938, 862, 771 cm^{-1}; HRMS (ESI-ion trap) m/z [M + Na]$^+$ calcd for $C_{24}H_{24}O_{10}Na$ 495.1262, found 495.1262.

Antiviral Assays. TMV (U1 strain) was obtained from the Key Laboratory of Botanical Pesticide R&D of Northwest A&F University, China. TMV multiplication and purification were performed as described by Gooding and Hebert.[28] The anti-TMV activities of the target compounds (±)-**2** and (±)-**31a**−**k** at concentrations of 100 and 500 μg/mL were evaluated by the half-leaf method in three modes (inactivation effect, curative effect, and protection effect *in vivo*). Commercial ribavirin and ningnanmycin were used as controls.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.1c00763.

X-ray crystallographic data for (±)-**20** and spectral data of synthetic compounds (PDF)

X-ray crystallographic data for (±)-**20** (CIF)

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Notes

The authors declare no competing financial interest.

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