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Approach to a New Dihydrofuran-Fused Cyclic System by a Remarkable Switching of *endo*/*exo* Selectivity of a [4+2] Cycloaddition Reaction

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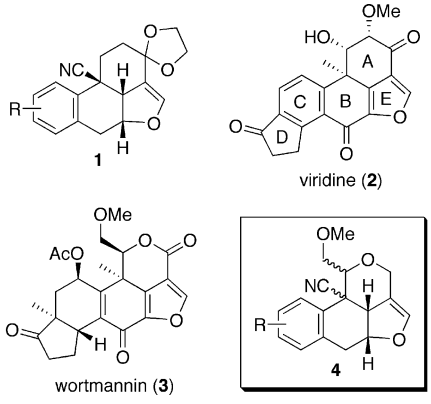
An efficient synthesis of a new class of dihydrofuran-fused tetracyclic compounds, possessing a 2-oxa-furano-steroidal framework, has been achieved by successive electrocyclic reactions of benzocyclobutene derivatives. It has been revealed that the stereoselectivity of a key intramolecular [4+2] cycloaddition reaction can be controlled by installation of a bulky silyl substituent onto the furan ring resulting in the formation of the *exo* adducts, the opposite selectivity to that observed in our past related studies. Preliminary examinations of the bioactivities of the synthesized compounds have been performed and have revealed that they have potential as anti-influenza agents.

Introduction

Furan-fused polycyclic systems are widely found in natural compounds and known to exhibit significant biological activities, including antifungal, antibiotic, antiviral, and anti-inflammatory.[1] In the course of our model studies on the synthesis of furan-fused polyketides, halenaquinone, and xestoquinone,[2] we found that dihydrofuran-fused tetracyclic compounds, represented by general structure **1**, exert notable antiproliferative effects against viruses, including influenza A and B.[3] More recently, we also reported that this class of compounds can enhance hyperthermia-induced apoptosis in human lymphoma U937 cells.[4] Novel structural characteristics make them a promising lead compound for the discovery of a new type of therapeutic agent. In addition, these compounds form a partial framework (A, B, C, and E rings) of furano-steroids, exemplified by viridine (**2**)[1b,5] and wortmannin (**3**),[1a,6] and thus represent a new motif for advanced drug design and discovery. As a part of structure–activity relationship (SAR) studies of the dihydrofuran-fused compounds **1**, we undertook the synthesis of new analogous compounds **4**, which possess a 2-oxa-furano-steroidal framework and a methoxymethyl substituent, as found in the wortmannin structure. During the synthetic study we encountered a high degree of *exo* selectivity in the key intramolecular [4+2] cycloaddition of *o*-quinodimethane due to the influence of a bulky silyl group, unlike our previous synthesis of **1** (exclusive *endo* selectivity).[2,3] In this paper, we describe a concise synthesis of compounds **4** based on successive electrocyclic reactions of benzocyclobutene derivatives containing a furyl substructure and an interesting switching of stereoselectivity of the reaction by variation of the substituents.



Results and Discussion

Readily available 5-methoxybenzocyclobutene-1-carbonitrile (**5**)[7] was deprotonated by LDA and then exposed to Weinreb amide **6**[8] to yield an acylated product **7** in 69% yield. Reduction of the ketone with sodium borohydride in MeOH produced the corresponding alcohol **8** as a diastereomeric mixture (ca. 1:1) which was allowed to react with 3-(bromomethyl)furan in the presence of sodium hydride to afford furylmethyl ether **9**. This compound was heated in refluxing *o*-dichlorobenzene (180 °C) with a view to preparing the target ring system **11** by intramolecular

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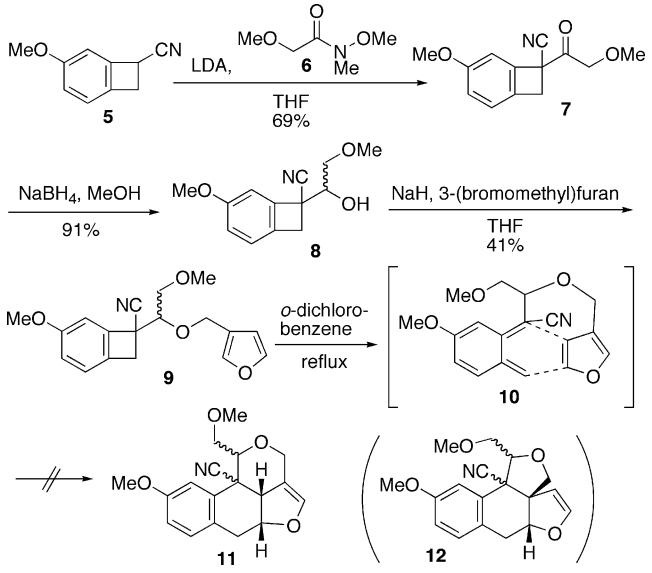
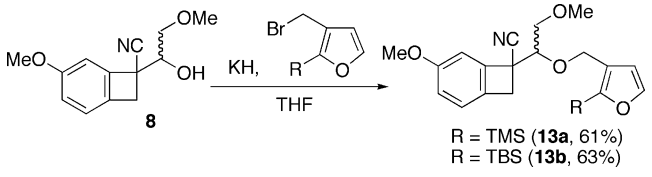
[4+2] cycloaddition of intermediate *o*-quinodimethane **10**. However, instead an inseparable mixture of many products was formed (Scheme 1). These disappointing results are probably due to the multiplicity of possible reactions of the intermediate **10**, including the formation of 5-5-6-fused compound **12**. In fact, the formation of **12** was suggested by careful ^{1}H NMR analysis of the crude reaction mixture. This undesirable side-product clearly arises from the cycloaddition of **10** to the 2,3-double bond of the furan moiety (and not the 4,5-double bond). To circumvent this problem, a bulky and removable silyl group was preinstalled onto the 2-position of the furan ring. Thus, silylated furylmethyl ethers **13a** and **13b** were synthesized from **8** according to the foregoing method, by using known silylated (bromomethyl)furan derivatives[9] as the reagents (Scheme 2).

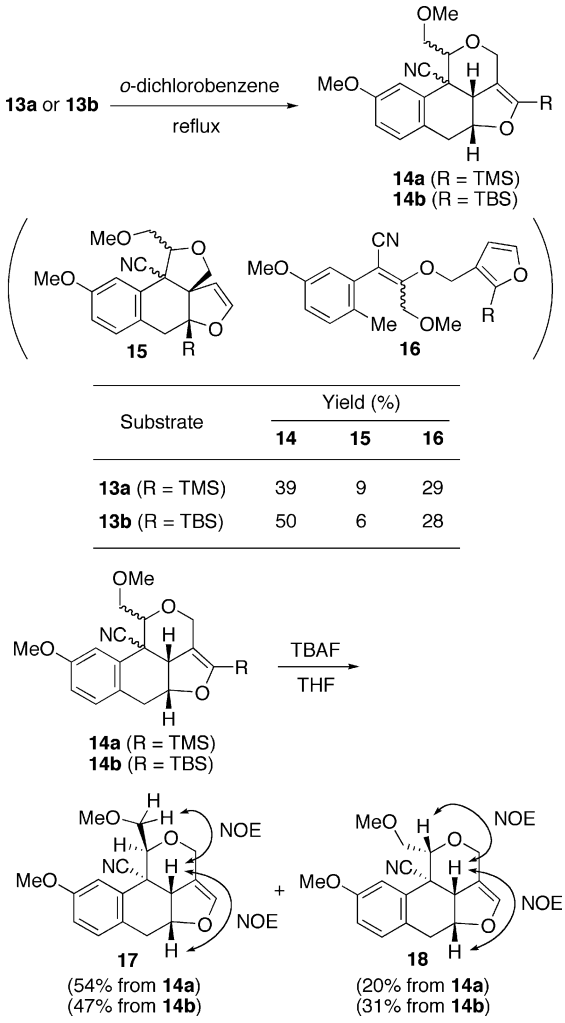


Scheme 1.



Scheme 2.

Gratifyingly, the thermal reaction of compound **13a** was cleaner in comparison with the case of the non-silylated substrate **9**, and the required tetracyclic adduct **14a** could be isolated as a mixture of two stereoisomers, along with the side-products **15** and **16**, in the yields indicated in Scheme 3. The ring-opened olefin product **16** may be formed by [1,5] sigmatropic rearrangement of the *o*-quinodimethane intermediate (probably a geometric isomer of **10**), as previously discussed.[10] Furthermore, **14b** was synthesized in a higher yield than **14a**. Although the two isomers of **14b**, as well as those of **14a**, were inseparable at this stage, chromatographic separation was achieved after desilylation by treatment with TBAF. Thus, the diastereomers **17** and **18** were successfully isolated from both **14a** and **14b** as single isomers (Scheme 3).



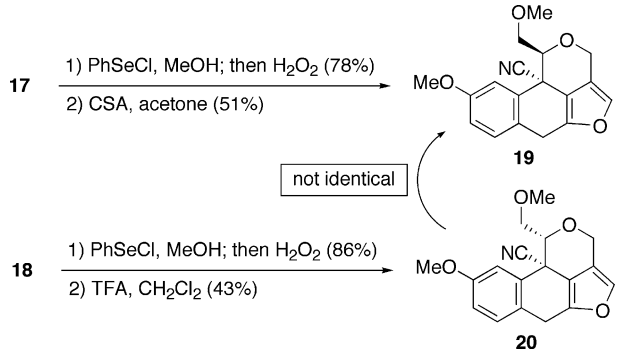
Substrate	Yield (%)		
	14	**15**	**16**
13a (R = TMS)	39	9	29
13b (R = TBS)	50	6	28

Scheme 3.

The relative configurations of the methoxymethyl group and hydrogen atoms on the dihydrofuran ring were unambiguously determined by NOE experiments (indicated in Scheme 3) for each compound, whereas the configuration of the cyano group remained unclear. For compound **17**, however, the cyano group could be converted into a formyl group by DIBAL reduction (although it did not work well for **18**), and observation of an NOE between the formyl proton and the adjacent hydrogen suggested a *trans* relationship between the cyano group and the methoxymethyl group in compound **17**.

To determine the configuration of the cyano group of **18**, both **17** and **18** were transformed into aromatized furan derivatives **19** and **20**, respectively, through a three-step oxidation sequence (Scheme 4).[2b] The dihydrofuran part of each was phenylselenenylated in the presence of MeOH followed by *syn* elimination via a selenoxide to give a 2-methoxy-2,5-dihydrofuran structure which was treated with CSA or TFA to furnish the aromatized products **19** and **20**.

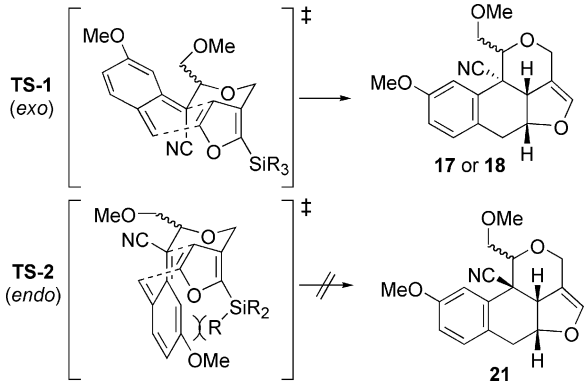
Comparison of various spectroscopic data revealed that these compounds were stereoisomers and, therefore, there is a *cis* relationship between the cyano and methoxymethyl groups in compound **20** (and inevitably in **18**).



Scheme 4.

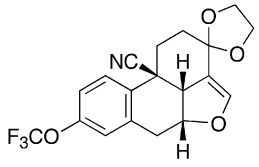
These stereochemical investigations revealed that the only difference between the two isomers **17** and **18** was the relative configuration of the methoxymethyl group. This implies that the intramolecular [4+2] cycloaddition proceeded via an *exo* transition state (**TS-1**) in which the cyano group is oriented inwards in the *o*-quinodimethane (Scheme 5).[11] In our previous studies on the synthesis of dihydrofuran-fused compounds **1**, the exclusive formation of all-*cis*-fused cycloadducts was observed in all cases. This stereochemical outcome should involve an *endo* transition state (**TS-2**) probably as a result of preferable secondary interactions between orbitals.[2,3] In the present case, however, an unfavorable steric repulsion between the trialkylsilyl group and the aromatic ring may disfavor **TS-2**, impeding the formation of **21**. Consequently, the selective formation of **17** and **18** possessing a common tetracyclic core with the same stereochemistry was achieved. These results clearly suggest that a silyl group introduced onto the furan ring can act as a traceless regulator of the stereoselectivity of the formation of the furan-fused tetracyclic system. Namely, substrates possessing the silyl group are a suitable choice when requiring *exo* adducts, whereas *endo* adducts are usually formed without such sterically demanding substituents. It is important to note that both the installation and removal of stereocontrolling silyl groups are quite easily performed on the furan ring.

The bioactivities of the new type of dihydrofuran-fused compounds **17** and **18** were briefly examined with a focus on anti-influenza virus activity. These compounds possess quite a different molecular shape in a stereochemical sense from compounds **1**, which have previously been reported as antivirus agents,[3] because of the different stereochemistry at the ring fusion. Whereas compounds **1** have the all-*cis*-fused system, which enforces a rigid cage-type conformation, compounds **17** and **18** are likely to have a rather planar conformation. In spite of such a dissimilarity, these compounds exhibited potent antivirus activity against the influenza A virus comparable to that of the trifluoromethylated derivative **22**, the most potent and promising compound in our previous study (Table 1).[3b] All three compounds suppressed the virus proliferation to around 50% of the control experiment (without drug treatment).[12] These findings will provide a new perspective for the SAR considerations of the dihydrofuran-fused tetracyclic compounds.



Scheme 5.

Table 1. Inhibitory effects of compounds **17**, **18**, and **22** on the growth of influenza A/aichi/2/68 virus in MDCK cells at 10 μM concentration.[a]



22 (positive control)

Compound	Virus yield (% of control)
17	54.4 ± 6.2
18	47.8 ± 10.1
22	52.5 ± 6

[a] Data shown are the means ± SD of three experiments.

Conclusions

In this study we have succeeded in the concise synthesis of dihydrofuran-fused tetracyclic compounds with a 2-oxafurano-steroid-like framework. The synthesis requires only five steps from the starting benzocyclobutene **5** and a number of analogues bearing various substituents would be accessible through the present synthetic pathway. In addition, the introduction of a bulky silyl group onto the furan moiety could control the stereochemical outcome of a Diels–Alder reaction, in contrast to our past syntheses of all-*cis*-fused ring systems such as **1**. A thorough investigation of the biological profiles of compounds **17** and **18** is underway and will be reported in due course.

Experimental Section

General Remarks: All nonaqueous reactions were carried out under argon. Reagents were purchased from commercial sources and used as received. Anhydrous solvents were prepared by distillation over CaH_2 or purchased from commercial sources. ^1H and ^{13}C NMR

spectra were obtained with a Varian UNITY plus 500 instrument using the chloroform peak as the internal reference. Mass spectra were measured with a JEOL D-200 or AX 505 mass spectrometer using the electron-impact ionization method (EI, 70 eV). IR spectra were recorded with a JASCO FT/IR-460Plus spectrometer. Column chromatography was carried out by employing Cica Silica Gel 60 (spherical, neutral, 40–50 μm or 63–210 μm). Compound **5** was prepared according to the reported method.[7]

5-Methoxy-1-(2-methoxy-1-oxoethyl)benzocyclobutene-1-carbonitrile (7): 5-Methoxybenzocyclobutene-1-carbonitrile (**5**) (1.0 g, 6.28 mmol) in dry THF (2 mL) was added to a stirred solution of LDA (6.91 mmol) in dry THF (20 mL), prepared from diisopropylamine and *n*BuLi, at –78 °C. After stirring for 10 min, Weinreb amide **6** (920 mg, 6.91 mmol) in dry THF (2 mL) was added to the reaction mixture and stirred at –78 °C for 1 h. The reaction was quenched with a saturated NH_4Cl aqueous solution and the aqueous mixture was extracted with AcOEt. The organic layer was dried with $MgSO_4$ and evaporated to leave a residue which was purified by chromatography on silica gel (AcOEt–hexane, 1:1) to afford **7** (1.0 g, 69%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, J = 7.9 Hz, 1 H), 6.92 (dd, J = 7.9, 2.0 Hz, 1 H), 6.86 (d, J = 2.0 Hz, 1 H), 4.36 (s, 2 H), 3.90 (d, J = 14 Hz, 1 H), 3.79 (s, 3 H), 3.64 (d, J = 14 Hz, 1 H), 3.52 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0, 160.5, 139.3, 133.8, 125.1, 117.8, 117.5, 107.9, 75.3, 59.8, 55.7, 49.5, 39.6 ppm. IR (neat): $\tilde{\nu}$ = 2238, 1735 cm^{-1}. MS (EI): m/z = 231 $[M]^+$. HRMS (EI): calcd. for $C_{13}H_{13}NO_3$ 231.0985 $[M]^+$; found 231.0985.

1-(1-Hydroxy-2-methoxyethyl)-5-methoxybenzocyclobutene-1-carbonitrile (8): Sodium borohydride (27 mg, 0.72 mmol) was added to a stirred solution of the ketone **7** (166 mg, 0.72 mmol) in MeOH (3 mL) at 0 °C and the mixture was stirred at the same temperature for 1 h. After the reaction was complete, the mixture was diluted with water and then extracted with AcOEt. The organic layer was dried with $MgSO_4$ and evaporated to leave a residue which was purified by chromatography on silica gel (AcOEt/hexane, 1:1) to afford the alcohol **8** (153 mg, 91%) as colorless plates (a 1:1 mixture of diastereomers); M.p. 93–95 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.09–7.03 (m, 1 H), 6.92–6.88 (m, 2 H), 4.01–3.98 (m, 1 H), 3.80 (s, 3 H), 3.75–3.39 (m, 4 H), 3.46 (s, 3 H), 2.76–2.58 (m, 1 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 160.1, 141.5, 133.7, 133.2, 125.1, 124.6, 120.0, 117.4, 117.2, 108.3, 107.8, 73.7, 73.4, 72.8, 72.4, 59.3, 55.6, 45.0, 40.1, 38.8 ppm. IR (KBr): $\tilde{\nu}$ = 3431, 2230 cm^{-1}. MS (EI): m/z = 233 $[M]^+$. HRMS (EI): calcd. for $C_{13}H_{15}NO_3$ 233.1052 $[M]^+$; found 233.1053.

General Procedure for the Synthesis of Furylmethyl Ethers 9, 13a, and 13b: An excess amount of sodium hydride or potassium hydride was suspended in dry THF and the alcohol **8** (1 mmol) and 3-bromomethylfuran derivatives (1.1 mmol) were added successively to the suspension at –35 °C. After stirring at –35 °C for 0.5 h and 0 °C for an additional 2 h, water was added to the reaction mixture and the resultant aqueous solution was extracted with Et_2O. The organic layer was dried with $MgSO_4$ and evaporated to leave a residue which was purified by chromatography on silica gel (CH_2Cl_2/hexane, 1:1) to afford the ether **9** (128 mg, 41%), **13a** (222 mg, 61%), or **13b** (270 mg, 63%) as a colorless oil (a 1:1 mixture of diastereomers).

Data for Compound 9: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.39–7.38 (m, 2 H), 7.04–6.75 (m, 3 H), 6.38–6.36 (m, 1 H), 4.67–4.47 (m, 2 H), 3.78–3.31 (m, 11 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 160.1, 143.5, 143.4, 142.4, 141.2, 140.7, 133.8, 133.1, 124.8, 124.6, 122.0, 121.7, 117.4, 117.1, 110.5, 110.3, 108.1, 107.8, 79.8, 78.5, 73.5, 73.4, 65.0, 64.5, 59.4, 59.3, 55.6, 55.5, 45.1, 45.0, 40.1, 39.6 ppm. IR (neat): $\tilde{\nu}$ = 2235 cm^{-1}. MS (EI): m/z = 313 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{19}NO_4$ 313.1306 $[M]^+$; found 313.1306.

Data for Compound 13a: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 1 H), 7.05–7.02 (m, 1 H), 6.90–6.76 (m, 2 H), 6.43–6.33 (m, 1 H), 4.73–4.69 (m, 1 H), 4.55–4.47 (m, 1 H), 3.79–3.38 (m, 11 H), 0.28 and 0.25 (s, 9 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 160.0, 146.3, 142.3, 141.2, 133.8, 133.1, 131.7, 131.6, 124.7, 124.6, 117.4, 117.0, 111.4, 111.2, 108.0, 107.9, 80.0, 78.8, 73.5, 73.4, 65.6, 65.2, 59.4, 59.3, 55.6, 55.5, 45.1, 45.0, 40.0, 39.6, –1.11, –1.17 ppm. IR (neat): $\tilde{\nu}$ = 2236 cm^{-1}. MS (EI): m/z = 385 $[M]^+$. HRMS (EI): calcd. for $C_{21}H_{27}NO_4Si$ 385.1709 $[M]^+$; found 385.1703.

Data for Compound 13b: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.59–7.56 (m, 1 H), 7.05–7.02 (m, 1 H), 6.91–6.76 (m, 2 H), 6.46–6.33 (m, 1 H), 4.74–4.68 (m, 1 H), 4.51–4.44 (m, 1 H), 3.81–3.38 (m, 11 H), 0.88 and 0.87 (s, 9 H), 0.26–0.22 (m, 6 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 160.0, 155.5, 155.3, 146.5, 142.4, 141.3, 133.8, 133.0, 132.8, 124.7, 124.6, 120.2, 120.0, 117.4, 117.0, 111.2, 111.1, 108.0, 107.9, 80.2, 79.1, 73.5, 73.4, 65.8, 65.5, 59.3, 59.2, 55.5, 55.4, 45.1, 45.0, 39.9, 39.6, 26.3, 17.3, 15.2, –5.77, –5.86, –5.90 ppm. IR (neat): $\tilde{\nu}$ = 2230 cm^{-1}. MS (EI): m/z = 427 $[M]^+$. HRMS (EI): calcd. for $C_{24}H_{33}NO_4Si$ 427.2179 $[M]^+$; found 427.2213.

General Procedure for the Thermal Reaction of Compounds 13a and 13b. Formation of the Tetracyclic Compounds 14a and 14b: A solution of the substrate **13a** or **13b** (0.2 mmol) in *o*-dichlorobenzene (2 mL) was refluxed for 2 h. After disappearance of the starting material on TLC, the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel (Et_2O/hexane, 1:2) to afford compound **14a** (30 mg, 39%) or **14b** (43 mg, 50%) as a colorless oil (an inseparable mixture of two diastereomers).

Data for Compound 14a: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.17–7.11 (m, 1 H), 7.03–6.80 (m, 2 H), 5.20–4.98 (m, 1 H), 4.58–4.34 (m, 2 H), 4.18–4.00 (m, 3 H), 3.83–3.78 (m, 4 H), 3.50 and 3.46 (s, 3 H), 3.25–2.95 (m, 2 H), –0.10 and –0.16 (s, 9 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 159.6, 158.8, 158.3, 158.2, 132.7, 131.4, 131.1, 130.8, 128.0, 126.7, 120.4, 119.8, 115.2, 114.7, 114.0, 113.9, 112.8, 82.0, 78.7, 78.6, 74.6, 73.0, 70.9, 65.1, 60.1, 59.4, 59.1, 56.2, 55.5, 41.6, 41.5, 33.8, 32.7, –2.16, –2.23 ppm. IR (neat): $\tilde{\nu}$ = 2230 cm^{-1}. MS (EI): m/z = 385 $[M]^+$. HRMS (EI): calcd. for $C_{21}H_{27}NO_4Si$ 385.1709 $[M]^+$; found 385.1725.

Data for Compound 14b: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.16–7.11 (m, 1 H), 7.00–6.78 (m, 2 H), 5.21–5.06 (m, 1 H), 4.60–3.88 (m, 5 H), 3.82–3.76 (m, 4 H), 3.49 (s, 3 H), 3.38–3.00 (m, 2 H), 0.56 and 0.48 (s, 9 H), –0.09 and –0.10 (s, 6 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 159.1, 158.5, 157.2, 133.0, 131.5, 131.3, 131.1, 128.2, 127.1, 120.2, 119.8, 116.0, 115.1, 115.0, 114.1, 113.3, 112.6, 82.2, 78.9, 78.6, 74.6, 73.0, 71.0, 65.7, 60.3, 59.4, 59.1, 56.1, 55.6, 55.5, 49.1, 41.6, 40.5, 33.7, 32.8, 26.3, 25.9, 25.8, 16.3, 16.0, –5.46, –5.80, –6.66, –6.69 ppm. IR (neat): $\tilde{\nu}$ = 2231 cm^{-1}. MS (EI): m/z = 427 $[M]^+$. HRMS (EI): calcd. for $C_{24}H_{33}NO_4Si$ 427.2179 $[M]^+$; found 427.2157.

Desilylation of Compounds 14a and 14b. Formation of 17 and 18: Tetra-*n*-butylammonium fluoride in 0.2 mL of THF (2 equiv.) was added to a stirred solution of compound **14a** or **14b** (0.1 mmol) in dry THF (1 mL) at room temperature. After completion of the reaction (1 h), the reaction mixture was diluted with water and the aqueous solution was extracted with Et_2O which was then dried with $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (AcOEt/hexane, 3:2). Two isomeric products were separated to afford compound **17** (17 mg, 54% from **14a**, 15 mg, 47% from **14b**) or **18** (6 mg, 20% from **14a**, 10 mg, 31% from **14b**) as colorless needles.

Data for Compound 17: M.p. 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, J = 8.1 Hz, 1 H), 7.03 (d, J = 2.6 Hz, 1 H), 6.86 (dd, J = 8.1, 2.6 Hz, 1 H), 6.06 (t, J = 1.7 Hz, 1 H), 5.17 (td, J = 3.8, 10 Hz, 1 H), 4.70 (dd, J = 7.7, 2.7 Hz, 1 H), 4.49 (dd, J = 13, 1.7 Hz, 1 H), 4.21 (d, J = 13 Hz, 1 H), 4.19–4.11 (m, 1 H), 4.04 (d, J = 10 Hz, 1 H), 3.90 (dd, J = 11, 2.7 Hz, 1 H), 3.80 (s, 3 H), 3.49 (s, 3 H), 3.17 (dd, J = 15, 3.8 Hz, 1 H), 3.04 (dd, J = 15, 3.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 142.8, 132.6, 131.1, 126.8, 120.2, 114.0, 112.8, 104.7, 79.2, 77.4, 72.7, 70.8, 59.7, 58.8, 55.6, 40.5, 32.9 ppm. IR (KBr): $\tilde{\nu}$ = 2229 cm^{-1}. MS (EI): m/z = 313 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{19}NO_4$ 313.1314 $[M]^+$; found 313.1316.

Data for Compound 18: M.p. 179–181 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, J = 7.7 Hz, 1 H), 6.87–6.83 (m, 2 H), 5.97 (s, 1 H), 5.28 (td, J = 3.5, 10 Hz, 1 H), 4.36 (d, J = 12 Hz, 1 H), 4.18–4.11 (m, 3 H), 4.06 (dd, J = 6.4, 2.1 Hz, 1 H), 3.84–3.79 (m, 4 H), 3.50 (s, 3 H), 3.29 (dd, J = 16, 3.0 Hz, 1 H), 3.12 (dd, J = 16, 2.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3, 143.4, 131.3, 131.2, 127.4, 119.7, 115.4, 112.9, 104.4, 82.4, 79.3, 74.8, 64.6, 59.4, 55.5, 54.1, 41.5, 33.6 ppm. IR (KBr): $\tilde{\nu}$ = 2226 cm^{-1}. MS (EI): m/z = 313 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{19}NO_4$ 313.1314 $[M]^+$; found 313.1323.

Transformation of Compounds 17 and 18 into the Aromatized Compounds 19 and 20: Phenylselenenyl chloride (0.27 mmol) was added to a stirred solution of the substrate **17** or **18** (0.25 mmol) in anhydrous MeOH (3 mL) at 0 °C and the mixture was stirred for 2.5 h. The reaction was quenched with a saturated $NaHCO_3$ solution, the aqueous mixture was extracted with AcOEt, and then the combined organic layers were washed with brine. After drying with $MgSO_4$, the solvent was evaporated to leave a residue which was subjected to silica gel column chromatography (AcOEt/hexane, 1:1). The selenenylated product thus obtained was dissolved in THF (2 mL) and 30% H_2O_2 was added to the solution at 0 °C. After continuous stirring for 1 h, the reaction mixture was diluted with a saturated $NaHCO_3$ solution, extracted with AcOEt, and dried. Evaporation of the solvent followed by column chromatography on silica gel (AcOEt/hexane, 1:1) gave an intermediate, a 2-methoxy-2,5-dihydrofuran derivative, in 78% (66 mg from **17**) or 86% yield (73 mg from **18**), respectively. These intermediates were treated with organic acid at room temperature for 15 h (CSA in acetone or TFA in CH_2Cl_2). After washing with a saturated $NaHCO_3$ solution followed by column chromatography (AcOEt/hexane, 1:1), the aromatized product **19** (30 mg, 51%) or **20** (30 mg, 43%) was isolated.

Data for Compound 19: Colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2 H), 7.17 (s, 1 H), 6.91 (dd, J = 8.5, 2.7 Hz, 1 H), 5.18 (d, J = 15 Hz, 1 H), 4.82 (dd, J = 15, 1.4 Hz, 1 H), 4.26 (dd, J = 16, 2.5 Hz, 1 H), 4.12–3.88 (m, 3 H), 3.84 (s, 3 H), 3.72–3.69 (m, 1 H), 3.59 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 149.5, 134.7, 132.4, 131.3, 127.4, 119.7, 117.5, 115.6, 114.5, 114.2, 80.1, 74.2, 63.4, 60.0, 55.7, 41.0, 28.6 ppm. IR (neat): $\tilde{\nu}$ = 2230 cm^{-1}. MS (EI): m/z = 311 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{17}NO_4$ 311.1158 $[M]^+$; found 311.1143.

Data for Compound 20: Colorless needles; m.p. 178–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.21 (m, 2 H), 7.00 (d, J = 2.7 Hz, 1 H), 6.93 (dd, J = 8.5, 2.7 Hz, 1 H), 5.14 (dd, J = 15, 1.4 Hz, 1 H), 5.03–5.00 (m, 1 H), 4.85 (dd, J = 15, 1.4 Hz, 1 H), 4.09–3.92 (m, 2 H), 3.85 (s, 3 H), 3.24 (s, 3 H), 3.06–3.03 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 149.3, 135.1, 131.6, 131.1, 126.5, 121.2, 116.8, 115.2, 112.5, 111.9, 76.1, 67.5, 59.4, 58.1, 55.8, 40.2, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 2229 cm^{-1}. MS (EI): m/z = 311 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{17}NO_4$ 311.1158 $[M]^+$; found 311.1165.

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

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[11] We suppose that the *o*-quinodimethane intermediate, having an outward-oriented cyano group, would be largely transformed into compound **16** by the [1,5]-sigmatropic rearrangement pathway.

[12] The virus yields as a percent of the control were estimated by a plaque titration method. Details of the experimental conditions for the assay are described in ref.[3b]

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