Synthesis of Cyclopentenyl Carbocyclic Nucleosides as Potential Antiviral Agents Against Orthopoxviruses and SARS

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A practical and convenient methodology for the synthesis of chiral cyclopentenol derivative (+)-**12a** has been developed as the key intermediate that was utilized for the synthesis of biologically active carbocyclic nucleosides. The selective protection of allylic hydroxyl group followed by the ring-closing metathesis (RCM) reaction with Grubbs catalysts provided (+)-**12a** on a 10 g scale with 52% overall yield from D-ribose (**4**). The key intermediate (+)-**12a** was utilized for the synthesis of unnatural five-membered ring heterocyclic carbocyclic nucleosides. The newly synthesized 1,2,3-triazole analogue (**17c**) exhibited potent antiviral activity (EC_{50} 0.4 μM) against vaccinia virus and moderate activities (EC_{50} 39 μM) against cowpox virus and severe acute respiratory syndrome coronavirus (SARSCoV) (EC_{50} 47 μM). The 1,2,4-triazole analogue (**17a**) also exhibited moderate antiviral activity (EC_{50} 21 μM) against SARSCoV.

Introduction

Neplanocin A (NPA, **1**),[1] a carbocyclic nucleoside isolated from *Ampullariella regularis*, has received a great deal of attention as a potential antiviral or antitumor agents.[2] NPA mediated inhibition of *S*-adenosylhomocysteine hydrolase (AdoHcy-ase) is responsible for its biological activity, which is the key enzyme in the regulation of *S*-adenosyl-L-methionine-(AdoMet-) dependent methylation reactions during mRNA replication cycles.[3] NPA is also a substrate for adenosine kinase as well as adenosine deaminase, and it exhibits cellular toxicity.[4]

On the basis of these interesting biological results, a significant amount of synthetic efforts have been directed toward finding more selective analogues.[5] As part of these efforts, a number of 6′-modified analogues, such as (6′*R*)-6′-*C*-methylneplanocin A (RMNPA, **2a**)[5e] and 6′-homoneplanocin A (HNPA, **2b**),[5i] have been synthesized (Figure 1). 3-Deazaneplanocin A (**2c**)[5d] and its analogue (**2d**)[5a] also showed potent antiviral activity against various viruses, including orthopoxviruses. Our group has reported synthetic methods for NPA and several NPA analogues as well as their antiviral activities.[6] Among the modified NPA analogues, cytosine (**3a**) and fluorocytosine (**3b**) analogues were found to be active against human immunodeficiency virus (HIV), West Nile virus (WNV), and orthopoxviruses.[6]

The syntheses of NPA analogues have utilized a chiral cyclopentenol as the key intermediate, starting from optically pure carbohydrates or tartaric acids by various synthetic methods.[7] Recently, the ring-closing metathesis (RCM) reaction,[8] one of the most powerful methods for the formation of small-sized rings via C−C double bonds, has been employed for the synthesis of disubstituted cyclopentenols.[9] Although a few examples used the RCM reaction as the key synthetic step for the trisubstituted cyclopentenol derivatives, large amounts of expensive Grubbs catalysts were necessary to complete the reaction[10] and its reaction conditions were difficult to control when Schrock's catalysts were used.[11] Herein, we report an efficient and practical method for the synthesis of cyclopentenol (+)-**12a** from D-ribose (**4**) and its utilization for the synthesis of novel biologically active five-membered ring heterocyclic NPA analogues (**17a**−**c**) as potential antiviral agents of biodefense interest.

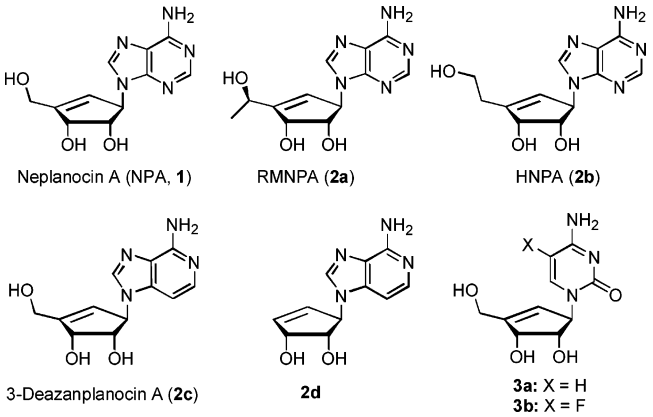

Figure 1. Neplanocin A and its analogues.

Results and Discussion

The chiral intermediate **7a** was synthesized according to modified published procedures[6] as shown in Scheme 1. D-Ribose (**4**) was treated with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid to give isopropylidene derivative **5** in 90% yield, followed by the protection of the primary alcohol with triphenylmethyl chloride (TrCl) to provide **6** in 85% yield. The protected lactol **6a** was reacted with vinylmagnesium bromide to quantitatively give a single diastereomeric diol **7a**, which was subsequently protected with a *tert*-butyldimethylsilyl group (TBDMS) only at the allylic hydroxyl position to afford silyldienol **8a** in 82% yield, which was observed as two conformers in the NMR spectrum as previously observed.[12]

To incorporate another double bond for the RCM reaction, the protected secondary alcohol **8a** was oxidized to the ketone **9a** by Swern oxidation, followed by Wittig reaction with methyltriphenylphosphonium bromide and butyllithium (*n*-BuLi)

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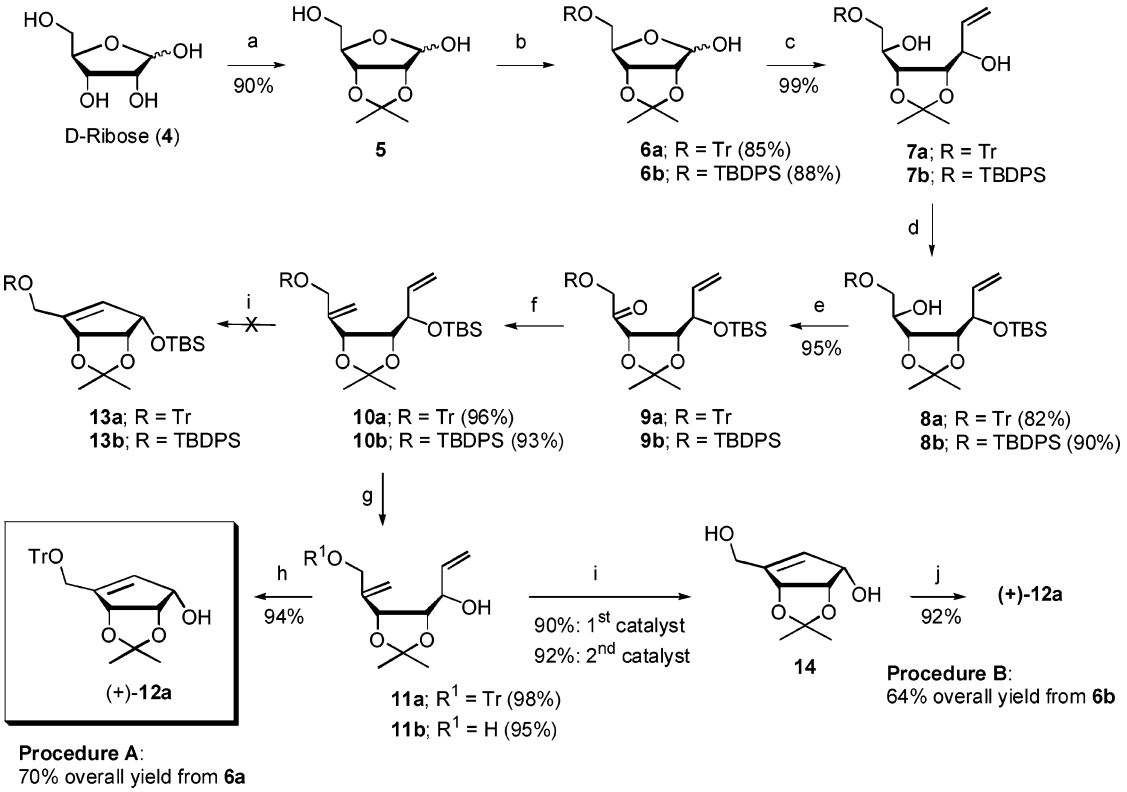
Scheme 1[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane, TsOH·H_2O, acetone, 0 °C → rt, 1 h; (b) (i) TrCl, Et_3N, DMAP, DMF, rt, 48 h (**6a**), (ii) TBDPSCl, imidazole, CH_2Cl_2, 0 °C → rt, 24 h (**6b**); (c) vinylmagnesium bromide, THF, −78 °C → rt, 12 h; (d) TBDMSCl, imidazole, CH_2Cl_2–DMF (10:1 v/v), 0 °C → rt, 24 h; (e) $(COCl)_2$, Et_3N, CH_2Cl_2, −60 °C; (f) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C → rt, 12 h; (g) TBAF, THF, rt, 2−6 h; (h) second-generation Grubbs catalyst, CH_2Cl_2, rt, 24 h; (i) first/second-generation Grubbs catalysts, CH_2Cl_2, rt, 24 h; (j) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 12 h.

in tetrahydrofuran (THF) to provide the diene **10a** in quantitative yield. With the diene **10a** in hand, the RCM reaction was investigated in the presence of 10 or 20 mol % first- or second-generation Grubbs catalysts without success, providing trace amounts of the desired trisubstituted diene **13a** (Scheme 1). The literature search indicated that few RCM reactions with hindered terminal double bonds, as in the case of dienes **10a**, **b**, have been successful with the Grubbs catalysts, due to the significant steric hindrance by bulky groups, the major obstacle of the RCM reaction.[13] Therefore, the silyl group from diene **10a** was removed with tetrabutylammonium fluoride (TBAF) to give the less sterically demanding dienol **11a**, which was successfully converted to cyclopentenol (+)-**12a** with only 2.0 mol % second-generation catalyst in 94% yield (procedure A), whereas a 40.0 mol % first-generation catalyst was required to obtain a similar yield. Thus, this improved procedure was able to provide multigram-scale (10 g) cyclopentenol (+)-**12a** without any major difficulties.

Alternative approaches for the substrate with unprotected dihydroxyl moiety (**11b**) were also investigated to further minimize the amount of Grubbs catalysts in the RCM reaction as shown in Scheme 1 (procedure B). Thus, the dienol **11b** was prepared from **5** following the same route: 2′,3′-protected D-ribose **5** was reacted with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole in CH_2Cl_2 to obtain a silyl lactol **6b** in 90% yield. Grignard reaction of the lactol **6b**, followed by subsequent selective protection with TBDMSCl, Swern oxidation, and Wittig reaction, afforded bis(silyl) diene **10b** in 80% overall yield. Two silyl groups of **10b** were then removed with TBAF to obtain dihydroxydiene **11b** as the substrate for the RCM reaction. The diene **11b** was then cyclized to provide the cyclopentenol **14** with 10.0 mol % first-generation or 5.0 mol % second-generation catalyst in 90% and 92% yield, respectively. The primary alcohol **14** was reacted with TrCl in the presence of Et_3N in CH_2Cl_2 to give the monoprotected cyclopentenol (+)-**12a** in 92% yield. However, considering the required amounts of the RCM catalysts as well as the reaction conditions, we concluded that the procedure A was the preferred method of synthesis for (+)-**12a**. Thus, procedure A was mainly used for the preparation of the key intermediate (+)-**12a** for the desired nucleosides. The overall yield of (+)-**12a** was 70% from compound **6a** (procedure A) and 64% from compound **6b** (procedure B).

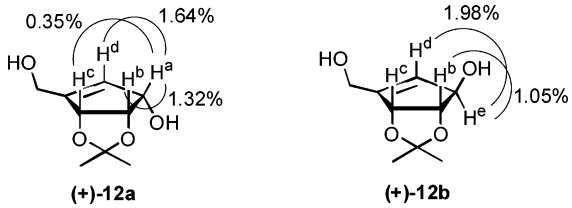
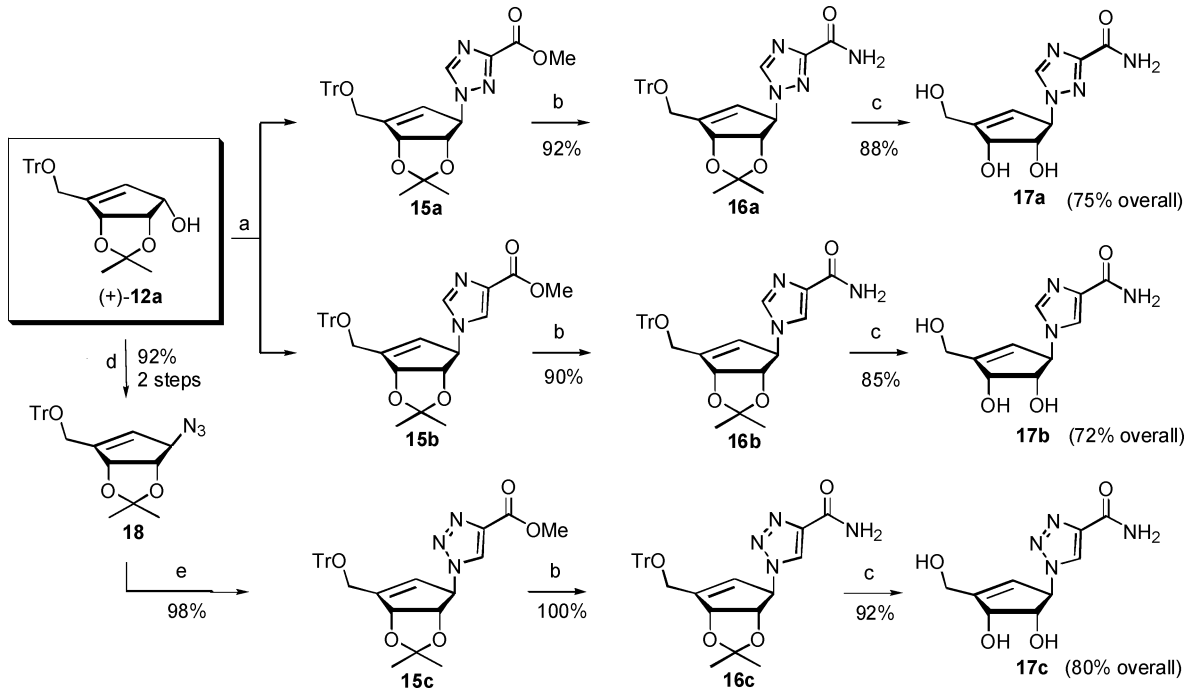


Figure 2. NOE studies of (+)-**12a** and (+)-**12b**.

The stereochemistry of cyclopentenol (+)-**12a** was determined on the basis of ^1H NMR spectra, nuclear Overhauser effect (1D-NOE) and $[\alpha]_D$ value, which were compared to the reported values[14] for (+)-**12a** along with the data of its diastereomer (+)-**12b**, which was readily converted from (+)-**12a** by Mitsunobu reaction.[15] Additionally, 1D-NOE was determined in which a significant interaction between H^a and H^c in (+)-**12a** was observed, whereas the NOE between H^e and H^c was not observed in (+)-**12b** as shown in Figure 2.

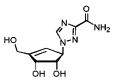
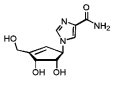
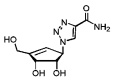
With the chiral (+)-**12a** in hand, Mitsunobu reaction[16] of (+)-**12a** with methyl-1*H*-1,2,4-triazole-3-carboxylate in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine

Scheme 2[a]



[a] Reagents and conditions: (a) (i) DIAD, PPh_3, THF, 0 °C → −78 °C and then rt, 24 h, methyl-*1H*-1,2,4-triazole-3-carboxylate (**15a**); (ii) DIAD, PPh_3, THF, 0 → −78 °C and then rt, 24 h methyl imidazole-4-carboxylate (**15b**). (b) (i) NH_3, MeOH, rt, 24 h for **16a** and **16c**; (ii) NH_3, MeOH, 100 °C, 24 h for **16b**. (c) 1.0 M HCl in ether, MeOH, 0 °C, 2−4 h. (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (ii) NaN_3, DMF, 80 °C, 24 h. (e) methyl propiolate, CuI, Et_3N, THF, rt, 12 h.

Table 1. Antiviral Activities of Five-membered Ring Heterocyclic Carbocyclic Analogues against Vaccinia, Cowpox, SARS, West Nile (WNV), Yellow Fever, and Venezuelan Equine Encephlitis (VEE) Viruses

Compound	Virus	Antiviral activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	Selective Index
 **17a**	Vaccinia	> 300	> 300	0
	Cowpox	> 300	> 300	0
	SARSCoV	21	> 100	> 4.8
	WNV	> 100	> 100	0
	Yellow Fever	> 100	> 100	0
	VEE	> 100	> 100	0
 **17b**	Vaccinia	> 300	> 300	0
	Cowpox	> 300	> 300	0
	SARSCoV	> 100	> 100	0
	WNV	> 100	> 100	0
	Yellow Fever	> 100	> 100	0
	VEE	> 100	> 100	0
 **17c**	Vaccinia	0.4	> 300	> 750
	Cowpox	39	> 300	> 7.7
	SARSCoV	47	> 100	> 2.1
	WNV	> 100	> 100	0
	Yellow Fever	> 100	> 100	0
	VEE	> 100	> 100	0
Cidofovir[a]	Vaccinia	6	< 317	> 52
	Cowpox	15	> 317	> 21
Alferon[a]	SARSCoV	< 100	> 10,000	> 100

[a] Positive control.

(PPh_3) was carried out to obtain the triazole nucleoside **15a** (Scheme 2). The ester **15a** was transformed to the amide **16a** with saturated methanolic ammonia, followed by deprotection of trityl and isopropylidene groups by methanolic hydrogen chloride solution (1.0 M HCl in diethyl ether) to afford the desired nucleoside **17a** in 75% yield in three steps from (+)-**12a**. The regioselectivity of **15a** was determined by comparing the UV data (λ_{max} 204 nm in H_2O) of **17a** with that of ribavirin (λ_{max} 207 nm in H_2O).[17] The other five-membered ring heterocyclic nucleoside **17b** was also prepared from the coupling reactions of (+)-**12a** with methyl imidazole-4-carboxylate by a similar method in 72% yield. The structure of **15b** was identified by 1D-NOE (a correlation between C1′-H and C5-H). The final compound (**17b**) was also compared to the previous reported UV data of an imidazole nucleoside derivative (λ_{max} 235 nm at pH 11).[18] The 1,2,3-triazole derivative (**17c**) was also synthesized by the 1,3-dipolar reaction of methyl propiolate with the azide derivative (**18**), prepared from (+)-**12a** by the reported method.[19] The ester **15c** was converted to the amide **16c** in saturated methanolic ammonia, which was treated with methanolic hydrogen chloride to afford 1,2,3-triazole carbocyclic nucleoside **17c** in 80% overall yield from (+)-**12a**.

Antiviral Activity. The newly synthesized carbocyclic nucleosides (**17a**−**c**) have been evaluated for their antiviral activity against vaccinia, cowpox, severe acute respiratory syndrome (SARS), West Nile (WNV), yellow fever, and Venezuelan equine encephalitis (VEE) viruses, as well as for their cytotoxicity, as summarized in Table 1. While all three carbocyclic nucleosides (**17a**−**c**) did not show any significant antiviral activity against WNV, yellow fever, and VEE viruses, 1,2,4-triazole analogue (**17a**) exhibited moderate antiviral activity [EC_{50} 21 μM, selectivity index (SI) > 4.8] against SARS virus. Interestingly, 1,2,3-triazole analogue (**17c**) exhibited the most potent antiviral activity among the five-membered ring carbocyclic nucleosides (**17a**−**c**) against vaccinia virus with high selectivity (EC_{50} 0.4 μM, SI > 750) and moderate activity against cowpox virus (EC_{50} 39 μM, SI > 7.7) as well as marginal activity against SARS virus (EC_{50} 47 μM, SI > 2.1). However, the imidazole analogue (**17b**) did not show any significant antiviral activity against any of the viruses evaluated. These preliminary in vitro antiviral activities for novel carbocyclic nucleosides warrant additional studies of structure−activity relationships as well as studies of the mode of action, which are in progress in our laboratories.

In summary, an efficient synthetic methodology for the cyclopentenol (+)-**12a**, employing the RCM reaction with the minimum amount of second-generation Grubbs catalyst, has been developed for a multigram scale. Coupling reactions of cyclopentenol (+)-**12a** with appropriate five-membered ring heterocycles provided novel antiviral agents of biodefense interest. 1,2,3-Triazole NPA analogue (**17c**) exhibited the most potent activity against vaccinia (EC_{50} 0.4 μM, SI > 750) along with moderate activities against cowpox (EC_{50} 39 μM, SI > 7.7) and SARSCoV (EC_{50} 47 μM, SI > 2.1).

Experimental Section

NMR spectra were recorded on a 500 MHz Fourier transform spectrometer; chemical shifts are reported in parts per million (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), ddd (doublet of doublets of doublets), and dt (doublet of triplets). Optical rotations were measured by a Jasco DIP-370 digital polarimeter. High-resolution mass spectra (HRMS) were recorded on a Micromass Autospec high-resolution mass spectrometer with electrospray ionization (ESI) in positive mode. Infrared spectra were recorded on an Avatar 360 FT-IR as neat type. Melting points were taken on Mel-Temp II melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel. Purifications were carried out on silica gel (60 Å, 32−63 mm). The data for elemental analysis were provided by Atlantic Microlab Inc., Norcross, GA.

6-Hydroxymethyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (5). To a solution of d-ribose (50.0 g, 0.34 mol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate ($TsOH\cdot H_2O$, 1.90 g, 1.0 mmol) in 500 mL of acetone was added 2,2-dimethoxypropane (38.16 g, 0.37 mol) at 0 °C. The suspension was stirred for 1 h at room temperature until a clear solution was achieved. The solution was then treated with $NaHCO_3$ (0.10 g, 1.20 mmol) and was stirred for an additional 30 min at room temperature. The solid was filtered and the filtrate was adsorbed on silica gel and purified by silica gel column chromatography (hexane/EtOAc = 3:1 to 1:1 v/v) to give compound **5** as a mixture of α- and β-isomers (54.0 g, 0.29 mol) in 90% yield. β-Form: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.65 (d, J = 6.0 Hz, 0.9H), 5.35 (d, J = 6.0 Hz, 0.9H), 4.75 (d, J = 6.0 Hz, 0.9H), 4.52 (d, J = 6.0 Hz, 0.9H), 4.33 (t, J = 2.5 Hz, 0.9H), 4.30 (br s, 0.9H), 3.65 (t, J = 12.0 Hz, 1.8H), 1.43 (s, 2.7H), 1.27 (s, 2.7H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.13, 102.65, 87.56, 86.66, 81.60, 63.41, 26.30, 24.66. α-Form: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.38 (dd, J = 12.0 and 8.0 Hz, 0.1H), 4.87 (t, J = 10.0 Hz, 0.1H), 4.66 (dd, J = 14.0 and 6.0 Hz, 0.1H), 4.59 (dd, J = 14.0 and 8.0 Hz, 0.1H), 4.35 (m, 0.1H), 4.12 (dd, J = 10.0 and 6.0 Hz, 0.1H), 3.67 (br s, 0.2H), 1.52 (s, 0.3H), 1.34 (s, 0.3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 114.12, 89.01, 81.47, 81.09, 79.42, 63.08, 26.70, 25.48.

2,2-Dimethyl-6-(trityloxymethyl)tetrahydrofuro[3,4-*d*][1,3]-dioxol-4-ol (6a). To a solution of compound **5** (15.30 g, 80.46 mmol), a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 0.30 g, 2.41 mmol), and trityl chloride (26.92 g, 96.56 mmol) in 200 mL of anhydrous *N*,*N*-dimethylformamide (DMF) was added Et_3N (12.21 g, 0.12 mol) at room temperature under nitrogen atmosphere. The resulting solution was stirred for 48 h at room temperature and poured into ice water (100 mL). The organic layer was extracted with CH_2Cl_2 (200 mL × 3), washed with saturated aqueous NH_4Cl (100 mL × 2) and water (200 mL), and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1 to 2:1 v/v) to give compound **6a** as a mixture of α- and β-isomers (25.0 g, 58.0 mmol) in 85% yield. β-Form: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.38 (m, 6H), 7.34−7.24 (m, 12H), 5.33 (d, J = 8.5 Hz, 0.8H) 4.79 (d, J = 6.0 Hz, 0.8H), 4.66 (d, J = 6.0 Hz, 0.8H), 4.35 (t, J = 4.0 Hz, 0.8H), 3.95 (d, J = 9.0 Hz, 0.8H), 3.42 (dd, J = 10.0 and 4.0 Hz, 0.8H), 3.34 (dd, J = 10.0 and 4.0 Hz, 0.8H), 1.48 (s, 2.4H), 1.34 (s, 2.4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.83, 128.71, 128.15, 127.54, 112.29, 103.57, 88.25, 87.11, 86.10, 81.96, 65.10, 26.56, 25.14. α-Form: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.38 (m, 1.2H), 7.34−7.24 (m, 2.4H), 5.75 (dd, J = 11.5 and 4.0 Hz, 0.2H), 4.74 (dd, J = 11.5 and 4.0 Hz, 0.2H), 4.58 (d, J = 6.5 Hz, 0.2H), 4.19 (t, J = 3.0 Hz, 0.2H), 4.01 (d, J = 11.5 Hz, 0.2H), 3.45 (dd, J = 10.0 and 3.0 Hz, 0.2H), 3.01 (dd, J = 10.0 and 3.0 Hz, 0.2H), 1.55 (s, 0.6H), 1.37 (s, 0.6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.52, 128.62, 128.03, 127.26, 113.01, 98.02, 87.60, 82.23, 80.15, 79.59, 65.51, 26.21, 24.79.

1-[5-(1-Hydroxy-2-trityloxyethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]prop-2-en-1-ol (7a). To a solution of compound **6a** (23.76 g, 54.94 mmol) in 300 mL of anhydrous THF was added 165 mL of vinylmagnesium bromide (165.0 mmol, 1.0 M of THF) at −78 °C under nitrogen atmosphere. After 1 h, the temperature was raised to room temperature and the reaction mixture was stirred for an additional 6 h and was treated with saturated NH_4Cl solution (100 mL) dropwise at 0 °C, and the resulting solution was poured into iced ether-saturated aqueous NH_4Cl solution (400 mL, 3:1 v/v). The organic layer was separated and the aqueous layer was washed with ether (100 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column (hexane/EtOAc = 10:1 to 3:1 v/v) to give compound **7a** (25.29 g, 54.90 mmol) in quantitative yield. $[\alpha]_D^{27}$ +12.32 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, J = 8.0 Hz, 6H), 7.38 (m, 10H), 6.12 (ddd, J = 17.0, 10.0, and 5.0 Hz, 1H) 5.52 (d, J = 17.0 Hz, 1H), 5.34 (d, J = 10.5 Hz, 1H), 4.41 (s, 2H), 4.22 (dd, J = 10.0 and 5.0 Hz, 1H), 4.13 (dd, J = 10.0 and 5. Hz 0, 1H), 4.04 (m, 1H), 3.65 (d, J = 3.5 Hz, 2H), 3.61 (dd, J = 10.0 and 3.5 Hz, 1H), 3.40 (dd, J = 10.0 and 7.5 Hz, 1H), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.83, 137.61, 128.74, 128.03, 127.28, 116.37, 108.89, 87.15, 80.76, 77.42, 69.96, 69.08, 65.24, 28.07, 25.63; Anal. ($C_{29}H_{32}O_5$) C, H.

1-{5-[1-((*tert*-Butyldimethylsilanyl)oxyl)allyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-2-(trityloxy)ethanol (8a). To a solution of compound **7a** (25.29 g, 54.90 mmol) in 300 mL of anhydrous CH_2Cl_2–DMF solution (10:1 v/v) were added imidazole (11.23 g, 16.50 mmol) and TBDMSCl (10.34 g, 68.64 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 24 h at room temperature and then poured into 500 mL of ether−water solution (1:1 v/v). The organic layer was separated and the aqueous layer was washed with ether (100 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column (hexane/EtOAc = 30:1 v/v) to give compound **8a** as a mixture of two conformers (26.10 g, 45.02 mmol) in 82% yield. ^{1}H NMR

($CDCl_3$, 500 MHz) δ 7.53−7.47 (m, 6H), 7.34−7.23 (m, 9H), 5.93 (m, 1H) 5.35−5.22 (m, 2H), 4.51 (s, 0.8H), 4.34 (m, 0.2H), 4.28 (m, 0.4H), 4.14 (m, 2H), 4.07 (m, 1.6H), 3.74 (s, 0.8H), 3.68 (m, 0.2H), 3.44 (m, 1.2H), 3.25 (m, 0.8H), 1.40 (s, 0.6H), 1.32 (s, 0.6H), 1.29 (s, 2.4H), 1.27 (s, 2.4H), 0.96 (s, 7.2H), 0.86 (s, 1.8H), 0.18 (s, 2.4H), 0.12 (s, 2.4H), 0.11 (s, 0.6H), 0.03 (s, 0.6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.24, 148.64, 142.77, 133.81, 133.68, 132.90, 132.82, 132.64, 132.11, 131.77, 122.95, 120.80, 112.93, 112.13, 92.15, 91.30, 84.95, 82.99, 78.56, 76.31, 74.33, 73.89, 70.32, 70.14, 32.98, 32.77, 30.90, 30.70, 23.22, 23.05, 1.08, 0.60, 0.26, 0.00.

1-{5-[1-((*tert*-Butyldimethylsilanyl)oxyl)allyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-2-(trityloxy)ethanone (9a). To a solution of oxalyl chloride (3.59 g, 41.02 mmol) in 100 mL of anhydrous CH_2Cl_2 was added DMSO (5.82 g, 82.05 mmol) at −60 °C under nitrogen atmosphere, and then the resulting solution was stirred for 10 min. A solution of compound **8a** (19.0 g, 32.82 mmol) in 200 mL of anhydrous CH_2Cl_2 was added to the reaction mixture dropwise over 20 min at −60 °C. After 30 min, Et_3N (16.60 g, 164.09 mmol) was added dropwise over 20 min to the reaction mixture at −60 °C. The mixture was stirred for 1 h at −60 °C and then stirred for 30 min at room temperature. The reaction mixture was treated with 200 mL of water dropwise at 0 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (200 mL × 3). The combined organic layer was washed with brine (200 mL × 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column (hexane/EtOAc = 20:1 to 10:1 v/v) to give compound **9a** (18.0 g, 31.64 mmol) in 95% yield. $[\alpha]_D^{23}$ −14.97 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (m, 6H), 7.39−7.29 (m, 9H), 5.90 (m, 1H) 4.64 (d, *J* = 7.5 Hz, 1H), 4.41 (m, 2H), 4.24 (d, *J* = 18.0 Hz, 1H), 3.95 (d, *J* = 18.0 Hz, 1H), 1.42 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.13, 141.87, 133.31, 133.25, 132.49, 131.69, 122.50, 113.95, 91.71, 87.01, 84.01, 77.67, 74.06, 30.78, 30.63, 29.29, 22.95.

***tert*-Butyl-{1-[2,2-dimethyl-5-(1-(trityloxymethyl)vinyl)-[1,3]-dioxolan-4-yl]allyloxy}dimethylsilane (10a).** To a suspension of Ph_3PCH_3Br (52.63 g, 147.33 mmol) in 100 mL of THF was added 90 mL of *n*-BuLi (140.0 mmol, 1.6 M in hexane) at 0 °C under N_2 atmosphere. After 30 min, a solution of compound **9a** (17.0 g, 29.46 mmol) in 200 mL of THF was added to the reaction mixture at 0 °C. The resulting mixture was stirred for 12 h at room temperature, treated with 50 mL of MeOH and 100 mL of water, and then poured into 300 mL of ether−water solution (2:1 v/v). The organic layer was separated and the aqueous layer was extracted with ether (200 mL × 2). The combined organic layer was washed with brine (20 mL × 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column (hexane/EtOAc = 50:1 to 10:1 v/v) to give compound **10a** (16.02 g, 27.99 mmol) in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (m, 6H), 7.34−7.30 (m, 9H), 5.74 (m, 1H) 5.72 (s, 1H), 5.46 (s, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 4.82 (d, *J* = 5.5 Hz, 1H), 3.98 (m, 2H), 3.79 (d, *J* = 13.5 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.25, 146.08, 142.74, 132.73, 131.98, 131.15, 121.04, 117.65, 112.04, 90.88, 84.73, 82.92, 77.29, 68.84, 30.57, 30.22, 29.15, 22.27, 0.71, 0.01.

1-[2,2-Dimethyl-5-(1-(trityloxymethyl)vinyl)-[1,3]dioxolan-4-yl]prop-2-en-1-ol (11a). A solution of compound **10a** (16.0 g, 27.99 mmol) in 100 mL of THF was treated with 35 mL of TBAF (35.0 mmol, 1.0 M in THF) at room temperature. After being stirred for 2 h, the reaction mixture was adsorbed on silica gel and purified on a silica gel column (hexane/EtOAc = 30:1 v/v) to give compound **11a** (12.52 g, 27.43 mmol) in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (m, 6H), 7.32−7.22 (m, 9H), 5.94 (m, 1H) 5.61 (s, 1H), 5.51 (s, 1H), 5.27 (dt, *J* = 17.0 and 1.5 Hz, 1H), 5.18 (dt, *J* = 11.0 and 1.5 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 3.96 (m, 2H), 3.89 (dd, *J* = 8.0 and 6.0 Hz, 1H), 3.74 (dd, *J* = 24.0 and 13.0 Hz, 2H), 2.22 (d, *J* = 4.0 Hz, 3H), 1.37 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.73, 142.22, 137.73, 128.71, 127.99, 127.25, 116.13, 113.96, 108.23, 87.55, 80.59, 77.95, 70.34, 65.42, 27.18, 25.19.

2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-ol [(+)-12a]: Method A. To a solution of compound **11a** (10 g, 21.90 mmol) in 400 mL of anhydrous CH_2Cl_2 was added second-generation Grubbs catalyst (0.40 g, 0.44 mmol) at room temperature under argon atmosphere. After being stirred for 24 h, the reaction mixture was adsorbed on silica gel and purified on a silica gel column (hexane/EtOAc = 10:1 to 5:1 v/v) to give compound (+)-**12a** (8.82 g, 1.86 mmol) in 94% yield. $[\alpha]_D^{23}$ +33.21 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (m, 6H), 7.29−7.20 (m, 9H), 5.99 (s, 1H) 5.23 (s, 1H), 4.86 (d, *J* = 5.0 Hz, 1H), 4.73 (t, *J* = 5.0 Hz, 1H), 4.57 (m, 1H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.67 (d, *J* = 15.0 Hz, 1H), 2.76 (d, *J* = 10.0 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.95, 143.43, 129.84, 128.63, 127.94, 127.15, 112.52, 87.01, 83.36, 77.93, 73.51, 60.95, 27.83, 26.93.

Method B. To a solution of compound **14** (1.0 g, 5.37 mmol), a catalytic amount of DMAP (0.07 g, 0.54 mmol), and trityl chloride (1.90 g, 6.71 mmol) in 20 mL of anhydrous CH_2Cl_2 was added Et_3N (0.73 g, 6.71 mmol) at room temperature under N_2 atmosphere. After 12 h at room temperature, the reaction mixture was poured into ice water (20 mL). The product was extracted with CH_2Cl_2 (20 mL × 3) from the aqueous layer. The combined solution was washed with saturated aqueous NH_4Cl (10 mL × 2), water (20 mL), and brine (10 mL × 2) and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1 to 4:1 v/v) to give compound **(+)-12a** (2.21 g, 4.94 mmol) in 92% yield. $[\alpha]_D^{22}$ +30.57 (*c* 0.57, $CHCl_3$).

2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-ol ((+)-12b). To a solution of Ph_3P (0.15 g, 1.26 mmol) and DIAD (0.26 g, 1.26 mmol) in 5.0 mL of anhydrous THF were added benzoic acid (0.15 g, 1.26 mmol) and a solution of compound (+)-**12a** (0.36 g, 0.84 mmol) in 10.0 mL of anhydrous THF at 0 °C under N_2 atmosphere. After the suspension overnight at room temperature, the reaction mixture was adsorbed on silica gel and purified on silica gel pad (hexane/EtOAc = 1:2 v/v) to give a crude product with a small amount of DIAD. The crude intermediate was treated with LiOH (0.11 g, 2.52 mmol) in 20 mL of THF−H_2O solution (3:1 v/v) for 12 h at room temperature. The basic solution was neutralized by addition of 1.0 M HCl solution. The product was extracted with ethyl acetate (20 mL × 3) from the aqueous layer. The combined organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1 to 4:1 v/v) to give compound (+)-**12b** (0.30 g, 0.71 mmol) in 84% yield (two steps). $[\alpha]_D^{24}$ +2.44 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (m, 6H), 7.29−7.24 (m, 9H), 5.99 (s, 1H) 5.08 (s, 1H), 4.76 (s, 1H), 4.51 (s, 1H), 3.89 (d, *J* = 15.0 Hz, 1H), 3.71 (d, *J* = 15.0 Hz, 1H), 2.03 (br s, 1H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.26, 143.94, 128.61, 127.88, 127.28, 127.08, 111.89, 86.47, 83.80, 80.01, 70.06, 61.34, 27.49, 26.17.

6-(((*tert*-Butyldiphenylsilanyl)oxy)methyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (6b). To a solution of compound **5** (19.0 g, 99.92 mmol) in 200 mL of anhydrous CH_2Cl_2 were added TBDPSCl (25.60 g, 99.92 mmol) and imidazole (20.21 g, 149.88 mol) at 0 °C under nitrogen atmosphere. The suspension solution was allowed to stir for 24 h at room temperature. The reaction mixture was absorbed on silica gel and then purified by silica gel column chromatography (hexane/EtOAc = 20:1 v/v) to give compound **6b** (40.0 g, 88.20 mmol) in 88% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (m, 4H), 7.47−7.40 (m, 6H), 5.35 (d, *J* = 8.0 Hz, 1H), 4.72 (m, 1H), 4.61 (m, 1H), 4.55 (d, *J* = 10.0 Hz, 1H), 4.28 (s, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 3.65 (d, *J* = 11.0 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.77, 135.60, 130.43, 130.25, 128.14, 128.08, 127.95, 112.15, 103.41, 87.31, 87.09, 81.74, 65.53, 26.95, 26.91, 26.52, 25.02, 19.18. α-Isomer: δ 7.66 (m, 0.8H), 7.47−7.40 (m, 1.2H), 5.62 (d, *J* = 11.0 Hz, 0.2H), 4.78 (m, 0.2H), 4.66 (m, 0.2H),

4.15 (s, 0.2H), 4.11 (m, 0.4H), 3.98 (d, J = 11.0 Hz, 0.2H), 3.82 (m, 0.2H), 3.61 (m, 0.2H), 1.55 (s, 0.6H), 1.39 (s, 0.6H), 1.05 (s, 1.8H).

1-{5-[2-((*tert*-Butyldiphenylsilanyl)oxy)-1-hydroxyethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}prop-2-en-1-ol (7b). To a solution of compound **6b** (36.0 g, 78.90 mmol) in 400 mL of anhydrous THF was added 237 mL of vinylmagnesium bromide (237 mmol, 1.0 M of THF) at −78 °C under nitrogen atmosphere. After 1 h, the temperature was raised to room temperature and the reaction mixture was stirred for an additional 6 h at room temperature. The resulting solution was poured into iced ether-saturated aqueous NH_4Cl solution (400 mL, 3:1 v/v). The organic layer was separated and the aqueous layer was washed with ether (150 mL × 2). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1 to 3:1 v/v) to give compound **7b** (35.64 g, 78.10 mmol) in quantitative yield. $[\alpha]_D^{24}$ +11.05 (*c* 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (m, 4H), 7.48−7.38 (m, 6H), 6.06 (m, 1H), 5.49 (dt, J = 17.0 and 1.5 Hz, 1H), 5.27 (dt, J = 10.0 and 1.5 Hz, 1H), 4.36 (m, 1H), 4.25 (d, J = 3.0 Hz, 1H), 4.12 (dd, J = 10.0 and 5.5 Hz, 1H), 4.05 (dd, J = 10.0 and 5.5 Hz, 1H), 3.92 (m, 2H), 3.77 (m, 1H), 3.42 (d, J = 3.0 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.77, 135.60, 130.43, 130.25, 128.14, 128.08, 127.95, 112.15, 103.41, 87.31, 87.09, 81.74, 65.53, 26.95, 26.91, 26.52, 25.02, 19.18.

1-{5-[1-((*tert*-Butyldimethylsilanyl)oxy)allyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-2-((*tert*-butyldiphenylsilanyl)oxy)ethanol (8b). To a solution of compound **7b** (28.0 g, 61.14 mmol) in 200 mL of anhydrous CH_2Cl_2–DMF solution (10:1 v/v) were added imidazole (12.48 g, 183.45 mmol) and TBDMSCl (10.20 g, 67.50 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 24 h at room temperature and then poured into 600 mL of ether−water solution (1:1 v/v). The organic layer was separated and the aqueous layer was washed with ether (100 mL × 2). The combined organic layer was washed with brine (150 mL × 2), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1 v/v) to give compound **8b** (31.42 g, 55.03 mmol) in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (m, 4H), 7.42−7.33 (m, 6H), 5.90 (m, 1H), 5.25 (dd, J = 16.5 and 11.5 Hz, 2H), 5.27 (dt, J = 10.0 and 1.5 Hz, 1H), 4.28 (t, J = 6.0 Hz, 1H), 4.15 (dd, J = 10.0 and 5.0 Hz, 1H), 4.06 (t, J = 5.0 Hz, 1H), 3.92 (m, 2H), 3.80 (dd, J = 10.0 and 6.0 Hz, 1H), 3.58 (d, J = 5.0 Hz, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.05 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.05, 140.82, 140.75, 138.80, 138.65, 134.59, 134.57, 132.66, 132.60, 123.15, 113.18, 85.07, 81.93, 78.81, 74.76, 70.54, 32.83, 31.90, 31.86, 31.01, 30.74, 24.38, 23.32, 1.32, 0.71.

1-{5-[1-((*tert*-Butyldimethylsilanyl)oxy)allyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-2-((*tert*-butyldiphenylsilanyl)oxy)ethanone (9b). To a solution of oxalyl chloride (1.38 g, 10.95 mmol) in 20 mL of anhydrous CH_2Cl_2 was added DMSO (1.72 g, 21.98 mmol) at −60 °C under nitrogen atmosphere, and then the resulting solution was stirred for 10 min. A solution of compound **8b** (5.0 g, 8.76 mmol) in 50 mL of anhydrous CH_2Cl_2 was added to the reaction mixture dropwise over 15 min at −60 °C. After another 30 min, Et_3N (4.43 g, 43.79 mmol) was added dropwise at −60 °C to the reaction mixture. The mixture was allowed to stir for 30 min at −60 °C and then stirring for 30 min, to the reaction mixture was added 100 mL of cold water, and the aqueous layer was separated and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with brine (50 mL × 2), dried over $MgSO_4$, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/EtOAc = 20:1 to 10:1 v/v) to give compound **9b** (4.74 g, 8.32 mmol) in 95% yield. $[\alpha]_D^{23}$ −22.81 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (m, 4H), 7.40−7.29 (m, 6H), 5.82 (m, 1H), 5.13 (s, 1H), 5.11 (dd, J = 17.0 and 10.0 Hz, 1H), 4.56 (d, J = 7.5 Hz, 1H), 4.51 (d, J = 18.5 Hz, 1H), 4.38 (d, J = 18.5 Hz, 1H), 4.32 (dd, J = 7.5 and 3.5 Hz, 1H), 4.28 (dd, J = 7.0 and 3.5 Hz, 1H), 1.39 (s, 3H), 1.23 (s, 3H), 1.01 (s, 9H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.06, 142.00, 140.10, 140.03, 137.64, 137.31, 134.26, 134.25, 132.19, 132.16, 122.47, 113.74, 86.66, 83.55, 77.95, 73.54, 31.23, 30.89, 30.52, 29.04, 23.77, 22.87, 0.23, 0.00.

4-[1-(((*tert*-Butyldimethylsilanyl)oxy)allyl]-5-[1-((*tert*-butyldiphenylsilanyl)oxy)methyl)vinyl]-2,2-dimethyl-[1,3]dioxolane (10b). To a suspension of Ph_3PCH_3Br (15.54 g, 43.50 mmol) in 50 mL of THF was added 25 mL of *n*-BuLi (1.6 M in hexane) at 0 °C under N_2 atmosphere. After 30 min, a solution of compound **9b** (4.50 g, 7.91 mmol) in 100 mL of THF was added to the reaction mixture at 0 °C. The resulting solution was allowed to stir for 12 h at room temperature, treated with 20 mL of MeOH and 40 mL of water, and then poured into ether−water solution (200 mL, 3:1 v/v). The organic layer was separated and the aqueous layer was washed with ether (100 mL × 2). The collected solution was washed with brine (50 mL × 2), dried over $MgSO_4$, and purified by silica gel column chromatography (hexane/EtOAc = 50:1 to 10:1 v/v) to give compound **10b** (4.17 g, 7.36 mmol) in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (m, 4H), 7.48−7.40 (m, 6H), 5.78 (m, 1H), 5.148 (s, 1H), 5.38 (s, 1H), 5.20 (d, J = 10.0 Hz, 1H), 5.14 (d, J = 17.0 Hz, 1H), 4.80 (d, J = 6.5 Hz, 1H), 4.25 (dd, J = 14.0 and 17.0 Hz, 1H), 4.05 (t, J = 7.5 Hz, 1H), 3.98 (d, J = 6.5 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.12 (s, 9H), 0.85 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.28, 142.91, 139.67, 139.63, 137.59, 137.53, 133.84, 133.81, 131.86, 131.84, 131.82, 121.39, 116.30, 111.92, 84.68, 81.82, 77.46, 69.08, 30.98, 30.81, 30.23, 29.24, 23.42, 22.31, 0.73, 0.00.

1-[5-(1-(Hydroxymethyl(vinyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]prop-2-en-1-ol (11b). To a solution of compound **10b** (0.84 g, 1.48 mmol) in 10 mL of THF was added 4.0 mL of TBAF in THF solution (1.0 M in THF) at room temperature. After being stirred for 2 h, the reaction mixture was adsorbed on silica gel and then purified by silica gel column chromatography (hexane/EtOAc = 2:1 to 1:2 v/v) to give compound **11b** (0.31 g, 1.42 mmol) in 95% yield. $[\alpha]_D^{24}$ −161.30 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.97 (m, 1H), 5.40 (s, 1H), 5.27 (d, J = 17.0 Hz, 1H), 5.25 (s, 1H), 5.19 (d, J = 10.0 Hz, 1H), 4.77 (d, J = 6.0 Hz, 1H), 4.46 (br s, 1H), 4.16 (s, 1H), 3.98 (m, 2H), 3.20 (m, 1H), 1.44 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.35, 138.21, 116.27, 113.09, 107.75, 80.28, 77.74, 69.81, 65.44, 27.51, 25.23, 23.94, 19.67, 13.70.

6-Hydroxymethyl-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxo-4-ol (14): Method A. To a solution of compound **11b** (0.14 g, 0.65 mmol) in 50 mL of anhydrous CH_2Cl_2 was added 0.05 equiv of second-generation Grubbs catalyst (0.028 g, 0.03 mmol) at room temperature under argon atmosphere. After beomg stirred for 24 h, the reaction mixture was adsorbed on silica gel and then purified by silica gel column chromatography (hexane/EtOAc = 1:1 to 1:2 v/v) to give compound **14** (0.11 g, 0.60 mmol) in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.75 (s, 1H), 4.98 (d, J = 5.0 Hz, 1H), 4.79 (dd, J = 5.0 and 6.0 Hz, 1H), 4.57 (m, 1H), 4.31 (dd, J = 14.5 and 33.5 Hz, 2H), 2.87 (d, J = 10.5 Hz, 1H), 2.60 (br s, 1H), 1.45 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.86, 129.95, 112.61, 83.08, 77.89, 73.22, 59.47, 27.55, 26.46.

Method B. To a solution of compound **11b** (0.040 g, 0.187 mmol) in 10 mL of anhydrous CH_2Cl_2 was added 0.10 equiv of first-generation Grubbs catalyst (0.016 g, 0.019 mmol) at room temperature under argon atmosphere. After being stirred for 24 h, the reaction mixture was adsorbed on silica gel and then purified by silica gel column chromatography (hexane/EtOAc = 1:1 to 1:2 v/v) to give compound **14** (0.032 g, 0.171 mmol) in 90% yield.

1-(2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-yl)-1*H*-1,2,4-triazole-3-carboxylic Acid Methyl Ester (15a). To a solution of Ph_3P (0.60 g, 2.10 mmol) in 2.0 mL of anhydrous THF was added 0.35 mL of DIAD at 0 °C under N_2 atmosphere, and the mixture was stirred for 30 min. A solution of compound (+)-**12a** (0.30 g, 0.70 mmol) in 5.0 mL of anhydrous THF was added to the reaction mixture at −78 °C, and stirring continued for an additional 30 min. To the suspension was added methyl 1*H*-1,2,4-triazole-3-carboxylate (0.15 g, 1.05 mmol) at −78

°C, and then the reaction mixture was allowed to stir for 24 h at room temperature. The reaction mixture was adsorbed on silica gel and then purified by silica gel column chromatography (hexane/EtOAc = 2:1 to 1:2 v/v) to give compound **15a** (0.38 g, 0.70 mmol) with a small amount of DIAD. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (s, 1H), 7.45 (m, 6H), 7.30−7.21 (m, 9H), 6.45 (s, 1H) 6.03 (t, J = 2.0 Hz, 1H), 5.27 (d, J = 5.5 Hz, 1H), 4.84 (t, J = 5.5 Hz, 1H), 4.05 (s, 3H), 3.98 (dt, J = 15.5 and 2.0 Hz, 1H), 3.76 (d, J = 15.5 Hz, 1H), 1.42 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.14, 151.22, 143.65, 140.04, 128.55, 128.02, 127.31, 126.39, 121.19, 112.94, 87.39, 84.43, 83.79, 70.42, 61.33, 52.33, 27.45, 26.08.

1-(2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-yl)-1*H*-1,2,4-triazole-3-carboxylic Acid Amide (16a). The crude compound **15a** (0.38 g, 0.70 mmol) was dissolved in 20.0 mL of saturated methanolic ammonia at 0 °C, and then the solution was allowed to stir for 12 h at room temperature. The solvent and ammonia were evaporated under reduced pressure, and then the residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1 v/v) to give compound **16a** (0.34 g, 0.65 mmol) in 92% yield from (+)-**12a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (s, 1H), 7.45 (m, 6H), 7.38 (s, 1H), 7.29−7.21 (m, 9H), 6.70 (s, 1H), 6.34 (s, 1H), 6.06 (s, 1H), 5.28 (d, J = 4.5 Hz, 1H), 4.87 (d, J = 4.5 Hz, 1H), 3.96 (d, J = 15.5 Hz, 1H), 3.74 (d, J = 15.5 Hz, 1H), 1.42 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.86, 151.11, 148.74, 143.83, 128.60, 127.91, 127.12, 123.35, 112.35, 87.14, 84.65, 84.07, 69.38, 61.46, 27.65, 26.37. Anal. ($C_{31}H_{30}N_4O_4 \cdot 0.1H_2O$) C, H, N.

1-(4,5-Dihydroxy-3-hydroxymethylcyclopenten-2-enyl)-1*H*-1,2,4-triazole-3-carboxylic Acid Amide (17a). A solution of compound **16a** (0.20 g, 0.38 mmol) in 5.0 mL of MeOH was treated with 20 mL of 1.0 M HCl in ether solution at 0 °C. The acidic solution was allowed to stir for 2 h at room temperature. The solvents and hydrogen chloride were evaporated under reduced pressure, and then the residue was purified by reverse silica gel column chromatography (distilled water) to give compound **17a** (0.08 g, 0.35 mmol) in 88% yield: mp 177−179 °C; UV (H_2O) λ_{max} 225.0 (ϵ 10 203, pH 11), 204.0 (ϵ 8587, pH 7), 199 (ϵ 9959, pH 2); $[\alpha]_D^{26}$ −146.93 (c 1.00, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 8.13 (s, 1H), 6.44 (d, J = 2.5 Hz, 1H), 5.81 (dd, J = 8.5 and 2.5 Hz, 1H), 4.64 (d, J = 5.5 Hz, 1H), 4.46 (dd, J = 8.5 and 5.5 Hz, 1H), 4.30 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 158.93, 148.98, 148.81, 146.85, 124.70, 77.27, 72.87, 69.69, 58.89. Anal. ($C_9H_{12}N_4O_4 \cdot 0.25H_2O$) C, H, N.

1-(2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-yl)-1*H*-imidazole-4-carboxylic Acid Methyl Ester (15b). Compound **15b** (0.39 g, 0.70 mmol) was synthesized in quantitative yield from (+)-**12a** (0.30 g, 0.70 mmol) and methyl imidazole-4-carboxylate (0.15 g, 1.05 mmol) by following the same procedure as for compound **15a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (s, 1H), 7.47 (m, 6H), 7.33−7.24 (m, 9H), 6.05 (s, 1H) 5.23 (s, 1H), 5.11 (d, J = 5.0 Hz, 1H), 4.53 (t, J = 5.0 Hz, 1H), 4.03 (d, J = 15.0 Hz, 1H), 3.90 (s, 3H), 3.83 (d, J = 15.0 Hz, 1H), 1.41 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.75, 153.57, 150.51, 143.72, 138.61, 128.55, 127.98, 127.25, 122.02, 112.49, 87.26, 85.33, 83.66, 71.82, 66.29, 61.23, 51.78, 27.60, 26.33.

1-(2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-yl)-1*H*-imidazole-4-carboxylic Acid Amide (16b). The crude compound **15b** (0.39 g, 0.70 mmol) was dissolved in 10.0 mL of saturated methanolic ammonia at 0 °C, and then the solution was allowed to stir for 24 h at 100 °C. The solvent and ammonia were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1 v/v to EtOAc) to give compound **16b** (0.33 g, 0.63 mmol) in 90% yield from (+)-**12a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (s, 1H), 7.44 (m, 6H), 7.30−7.21 (m, 9H), 6.69 (s, 1H), 6.06 (d, J = 2.0 Hz, 1H), 5.87 (br s, 2H), 5.27 (d, J = 5.5 Hz, 1H), 4.87 (d, J = 5.5 Hz, 1H), 3.96 (dt, J = 15.5 and 2.0 Hz, 1H), 3.73 (d, J = 15.5 Hz, 1H), 1.42 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.81, 150.11, 148.74, 145.55, 143.83, 128.60, 127.90, 127.12, 123.35, 112.35, 87.14, 84.65, 84.07, 69.38, 61.45, 27.64, 26.37.

1-(4,5-Dihydroxy-3-hydroxymethylcyclopenten-2-enyl)-1*H*-imidazole-4-carboxylic Acid Amide (17b). The solution of compound **16b** (0.25 g, 0.48 mmol) in 6.0 mL of MeOH was treated with 25 mL of 1.0 M HCl in ether solution at 0 °C. The acidic solution was allowed to stir for 3 h at room temperature. The solvents and hydrogen chloride was evaporated under vacuum and the residue was treated with water (20 mL), and then the aqueous layer was washed with EtOAc (10 mL × 5) and concentrated under reduced pressure. The gum-type product was dissolved in ethanol (20 mL) and concentrated. The resulting solid was dried in vacuo for 72 h at room temperature to give compound **17b** (0.10 g, 0.42 mmol) as the HCl salt form in 85% yield. mp 161−163 °C; UV (H_2O) λ_{max} 237.0 (ϵ 2455, pH 11), 204.0, 239 (ϵ 5132, 4034, pH 7), 198 (ϵ 7180, pH 2); $[\alpha]_D^{25}$ −15.43 (c 0.50, CH_3OH); ^{1}H NMR (D_2O, 500 MHz) δ 7.88 (br s, 1H), 7.61 (br d, J = 2.5 Hz, 1H), 5.83 (d, J = 1.5 Hz, 1H), 5.79 (s, 1H), 4.53 (d, J = 5.5 Hz, 1H), 4.21 (s, 2H), 4.06 (t, J = 5.5 Hz, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 163.99, 148.76, 131.90, 124.93, 78.71, 72.81, 65.60, 58.56, 48.80; Anal. ($C_{10}H_{14}N_3O_4 \cdot 1.0HCl \cdot 0.30H_2O$) C, H, N.

4-Azido-2,2-dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxole (18). To a solution of (+)-**12a** (0.35 g, 0.82 mmol) in 20 mL of anhydrous CH_2Cl_2 were added MsCl (0.15 mL, 1.64 mmol) and Et_3N (0.40 mL, 2.86 mmol) at 0 °C under N_2 atmosphere. After the mixture was stirred for 1 h at 0 °C, the reaction mixture was poured into 50 mL of water−CH_2Cl_2 (1:5 v/v) solution. The organic layer was separated and washed with brine (10 mL × 2) and dried over $MgSO_4$. The solution was concentrated and the residue was purified on a short silica gel pad. To the crude product (0.42 g, 0.82 mmol) were directly added 15 mL of anhydrous DMF and NaN_3 (0.44 g, 6.70 mmol) at room temperature under N_2 atmosphere; then the mixture was stirred for 24 h at 80 °C. The reaction mixture was poured into 100 mL of iced ether−water (5: 1 v/v) and then the organic layer was separated and the aqueous layer was washed with ether (25 mL × 2). The collected organic layer was washed with brine (20 mL × 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1 v/v) to give compound **18** (0.34 g, 0.76 mmol) in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (m, 6H), 7.44−7.22 (m, 9H), 6.01 (d, J = 1.5 Hz, 1H), 5.04 (d, J = 5.5 Hz, 1H), 4.58 (d, J = 5.5 Hz, 1H), 4.42 (s, 1H), 3.87 (td, J = 1.5 and 15.0 Hz, 1H), 3.74 (d, J = 15.0 Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.01, 143.84, 128.60, 127.98, 127.21, 122.70, 112.14, 87.21, 84.06, 83.83, 69.99, 61.29, 27.49, 26.22; IR (neat, cm^{-1}) 3072, 2988, 2097, 1265, 1082, 735, 701.

1-(2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-yl)-1*H*-1,2,3-triazole-4-carboxylic Acid Methyl Ester (15c). To a solution of compound **18** (0.18 g, 0.40 mmol) in 10 mL of THF were added CuI (0.76 g, 4.0 mmol), methyl propiolate (0.14 g, 1.60 mmol), and Et_3N (1.22 g, 12.0 mmol) at room temperature under N_2 atmosphere, and then the mixture was stirred for 12 h. The suspension was adsorbed on silica gel and then purified by silica gel column chromatography (hexane/EtOAc = 10:1 to 1:2 v/v) to give compound **15c** (0.21 g, 0.39 mmol) in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (s, 1H), 7.46 (m, 6H), 7.33−7.22 (m, 9H), 6.06 (s, 1H) 5.74 (s, 1H), 5.17 (d, J = 6.0 Hz, 1H), 4.71 (d, J = 6.0 Hz, 1H), 4.03 (d, J = 16.0 Hz, 1H), 3.98 (s, 3H), 3.83 (d, J = 16.0 Hz, 1H), 1.42 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.14, 151.22, 143.65, 140.04, 128.55, 128.02, 127.31, 126.39, 121.19, 112.94, 87.39, 84.43, 83.79, 70.42, 61.33, 52.33, 27.45, 26.08.

1-(2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta-[1,3]dioxol-4-yl)-1*H*-1,2,3-triazole-4-carboxylic Acid Amide (16c). A solution of compound **15c** (0.19 g, 0.36 mmol) in 40 mL of MeOH was bubbled with NH_3 gas at 0 °C for 30 min, and then the solution was allowed to stir for 24 h at room temperature. The solvent and NH_3 were removed under reduced pressure. The solvent was removed under reduced pressure for 24 h at room temperature

to give the product **16c** in quantitative yield (0.19 g, 0.36 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (s, 1H), 7.45 (m, 6H), 7.32−7.21 (m, 9H), 7.19 (d, J = 2.0 Hz, 1H), 6.21 (d, J = 2.0 Hz, 1H), 6.07 (d, J = 1.5 Hz, 1H), 5.74 (s, 1H), 5.18 (d, J = 5.5 Hz, 1H), 4.71 (d, J = 5.5 Hz, 1H), 4.16 (dt, J = 16.0 and 1.5 Hz, 1H), 3.81 (d, J = 16.0 Hz, 1H), 1.41 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.15, 151.12, 143.65, 142.83, 128.55, 128.02, 127.30, 124.78, 121.27, 112.89, 87.33, 84.43, 83.84, 70.37, 61.28, 27.46, 26.13.

1-(4,5-Dihydroxy-3-hydroxymethylcyclopenten-2-enyl)-1*H*-1,2,3triazole-4-carboxylic Acid Amide (17c). Compound **17c** was prepared in 88% yield (0.08 g, 0.33 mmol) from **16c** (0.20 g, 0.38 mmol) following the same procedure as for compound **17a**: mp 178−180 °C; UV (H_2O) λ_{max} 222.0 (ϵ 7041, pH 11), 204.0 (ϵ 6463, pH 7), 199 (ϵ 10 503, pH 2); $[\alpha]_D^{25}$ −127.56 (c = 1.0, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 8.46 (s, 1H), 5.95 (s, 1H), 5.61 (s, 1H), 5.52 (s, 1H), 4.63 (d, J = 5.5 Hz, 1H), 4.30 (m, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 150.63, 125.35, 123.39, 78.24, 73.02, 58.95, 53.86, 48.68; Anal. ($C_9H_{12}N_4O_4 \cdot 0.3H_2O$) C, H, N.

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Supporting Information Available: Elemental analysis data for compounds **7a**, **16a**, and **17a**−**c** and high-resolution mass spectral (HRMS-ES) data for compounds **6a**−**12a**, **12b**, **6b**−**11b**, **14**, **15a**−**17a**, **15b**−**17b**, **15c**, and **16c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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