Design, Synthesis and Antifungal Activity of the Novel Water-Soluble Prodrug of Antifungal Triazole CS-758

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CS-758 was selected as a candidate for clinical trials, but since its water-solubility was insufficient for an injectable formulation, phosphoryl ester prodrugs were designed. In this study, the synthesis and evaluation of these injectable prodrugs are described. Phosphoryl ester 17h was soluble in water, and was stable in both water and in a solid state. 17h was converted to CS-758 in human liver microsome and was also converted to CS-758 in rats after intravenous (i.v.) administration with good conversion speed and efficiency. 17h (i.v.) reduced the viable cell counts in kidneys in a murine hematogenous *Candida albicans* infection model and in lungs in a murine pulmonary *Aspergillus fumigatus* infection model, wherein the effects were comparable to or slightly superior to that of CS-758 (*per os*).

Key words water-soluble prodrug; phosphate ester; antifungal azole; CS-758

There is a great medical need for an injectable antifungal agent with a broad spectrum for the treatment of severe deep mycoses of hospitalized patients.[1—4] Currently, injectable antifungal azoles, fluconazole (FLCZ), fosfluconazole[5] and voriconazle[6] are available for parenteral use, but they have limitations in terms of antifungal spectra and safety, respectively. Most of the azoles under development have a broader spectrum but cannot be administered parenterally because of low water-solubility.[7—10] There have been some efforts to overcome this problem by using a prodrug approach.[11—14]

Previously, we identified CS-758[15—17] which has a broad antifungal spectrum covering *Aspergillus* spp., FLCZ-resistant *Candida* spp. and has a good safety profile, including low drug–drug interaction. Since the water solubility of CS-758 was, however, too low for a parenteral formulation, we conducted a study on a prodrug of CS-758 which should have sufficient water solubility and efficient bioconversion.

CS-758 has two obvious functional groups, namely the tertiary hydroxy and the triazole groups, with the possibility of being linked to a pro-moiety. It is known that water-soluble prodrugs can be readily accessed by alkylating a triazole ring with halomethyl acetate derivatives to give a quaternary ammonium salt prodrug.[12,14,18] Phosphonooxymethy ether of ravuconazole has also been reported[13] (Fig. 1).

However, the prodrugs in these classes liberate an equivalent amount of formaldehyde or quinone methide *in vivo* when cleaved. Consequently, we focused our efforts on identifying a suitable, safe, polar group with which we could functionalize CS-758 on the tertiary hydroxy group and recently reported the novel prodrug **1**[19] of CS-758 (Fig. 2).

Compound **1** had good water solubility, and its *in vivo* efficacy was comparable to or slightly superior to efficacy of CS-758, but there was some room for improvement in both the conversion speed and the conversion efficiency. We thought that the slow conversion speed of **1** to CS-758 was due to steric hindrance of the tertiary hydroxy group and planned the general concept of prodrugs (cascade type prodrugs) illustrated in Chart 1.

In these prodrugs, two auxiliary units, a self-cleavable linker and a solubilizing part, were lined up to be linked to the parent prodrug CS-758. First, the solubilizing part of the prodrug could be rapidly hydrolyzed by an esterase to generate an unstable intermediate, and then it would undergo a

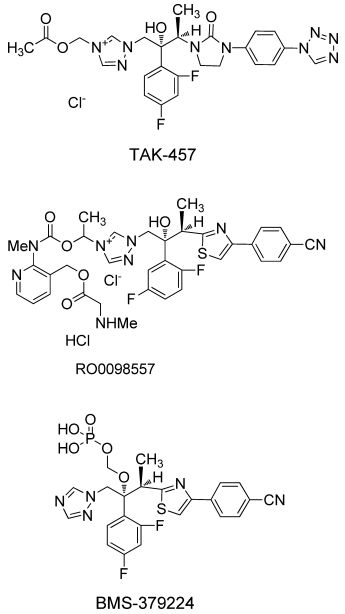

Fig. 1. Structural Formulas of Prodrugs of Triazole Antifungal Agents

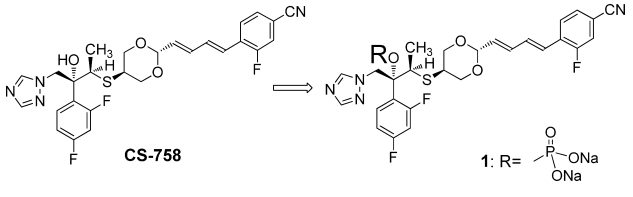

Fig. 2. Structural Formulas of CS-758 and the Prodrug of CS-758 (**1**)

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rapid and spontaneous intra-molecular cyclization to release CS-758 and a lactone.[20)]

In this paper, we describe the design and synthesis of water-soluble prodrugs of CS-758, and their physicochemical and biological properties.

First, we designed and synthesized the prodrug **2**. We chose a 4-hydroxybutyrate moiety as the self-cleavable linker and a phosphoric acid ester moiety as the solubilizing part because phosphoric acid ester has good water solubility and dephosphorylation is a familiar enzyme response. 4-Hydroxybutyrate ester afforded by dephosphorylation was expected to afford a lactone and the parent drug CS-758. The synthesis of compound **2** is shown in Chart 2.

Sodium 4-hydroxybutyrate **4** was reacted with 4-methoxybenzyl chloride to afford 4-methoxybenzyl ester **5**. As the ester **5** was unstable, **5** was used for the next step without further purification. **5** was phosphorylated by using the procedure developed by Fraser–Reid[21)] to give the phosphoryl ester **6**. The 4-methoxybenzyl (PMB) group of **6** was removed using trifluoroacetic acid (TFA) and anisole to obtain the carboxylic acid **7**, which was treated with oxalyl chloride in CH_2Cl_2 to afford the corresponding acid chloride **8**. Though the tertiary hydroxy group of CS-758 was almost unreactive with acid chlorides because of its steric hindrance, the sodium alkoxide form of CS-758, which was generated from CS-758 and NaH in tetrahydrofuran (THF), could be reacted with acid chloride **8** at room temperature to afford the desired ester **9** in 63% yield. Removal of two allyl groups of **9** was accomplished by the use of tetrakis(triphenylphosphine)palladium and pyrrolidine in CH_2Cl_2 to afford the desired compound as a pyrrolidinium salt. The salt was purified with a C-18 reverse phase column, and then the counter ion was exchanged using Dowex 50W×8 (Na form) to give sodium salt **2**.

The pharmacokinetic (PK) profile after intravenous (i.v.) bolus administration of **2** to rats at a dose of 2 mg (CS-758 equivalent)/kg is shown in Fig. 3. As expected, compound **2** disappeared from plasma within 1 h and rapid formation of dephosphorylated intermediate alcohol was observed by HPLC identification. Though the intermediate alcohol disappeared from plasma rapidly and formation of CS-758 was

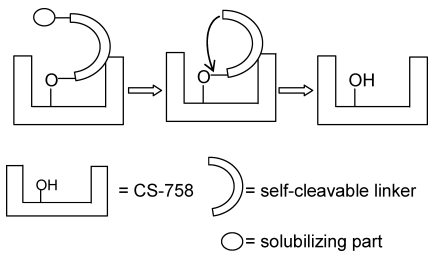


Chart 1. General Concept of Cascade-Type Prodrugs

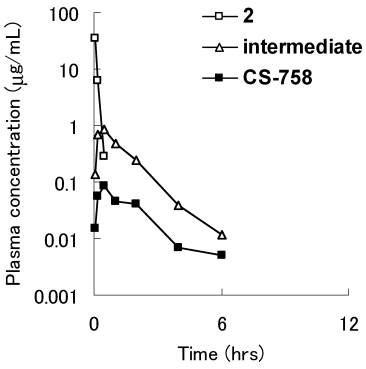
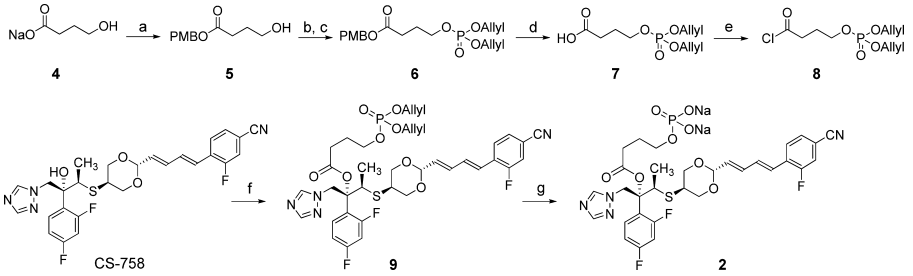
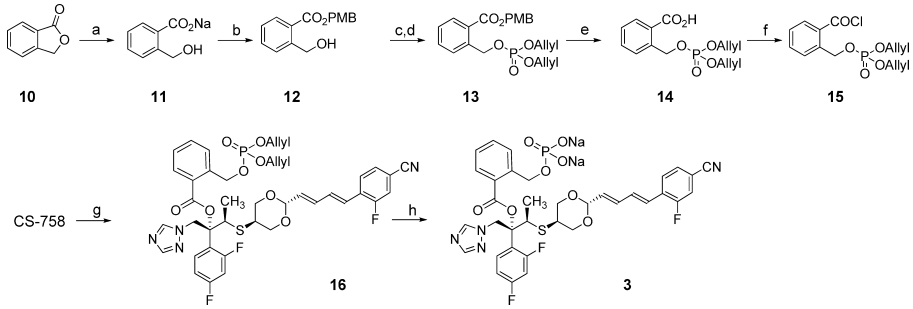


Fig. 3. Plasma Level of CS-758 and Intermediate Alcohol after i.v. Administration of **2** to Rats at a Dose of 2 mg (CS-758 Equivalent)/kg (Average of Three Rats)



Reagents and conditions: (a) 4-(MeO)BnCl, DMF, 80 °C; (b) *i*-$Pr_2NP(OAllyl)_2$, 1*H*-tetrazole, CH_2Cl_2; (c) *t*-BuOOH, CH_2Cl_2; (d) TFA, anisole; (e) $(COCl)_2$, cat. DMF, CH_2Cl_2; (f) NaH, **8**, THF; (g) $Pd(PPh_3)_4$, pyrrolidine, CH_2Cl_2, then Dowex 50W×8 (Na form).

Chart 2. Synthesis of **2**



Reagents and conditions: (a) NaOH aq., MeOH, THF; (b) 4-(MeO)BnCl, DMF, 80 °C; (c) *i*-$Pr_2NP(OAllyl)_2$, 1*H*-tetrazole, CH_2Cl_2; (d) *t*-BuOOH, CH_2Cl_2; (e) TFA, anisole; (f) $(COCl)_2$, cat. DMF, CH_2Cl_2; (g) NaH, **15**, THF; (h) $Pd(PPh_3)_4$, pyrrolidine, CH_2Cl_2, then Dowex 50W×8 (Na form).

Chart 3. Synthesis of **3**

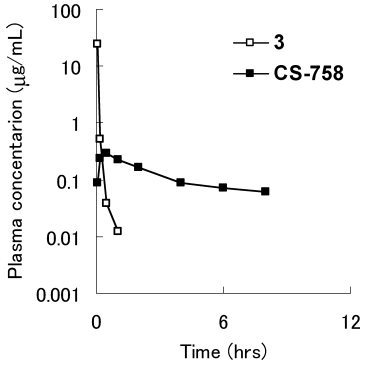


Fig. 4. Plasma Level of CS-758 after i.v. Administration of **3** to Rats at a Dose of 2 mg (CS-758 Equivalent)/kg (Average of Three Rats)

observed, the conversion efficiency was 3.4% and there are some room for improvement.

We assumed that conformational restriction of linker part might hasten intra-molecular cyclization of the intermediate alcohol and high conversion efficiency might be achieved. On the basis of this supposition, we designed compound **3**, which employs a 2-(hydroxymethyl)benzoyl moiety as the self-cleavable linker and a phosphoric acid ester moiety as the solubilizing part.

Compound **3** was synthesized in a similar manner to **2**. The phthalide ring in **10** was opened by treatment with 1 eq of NaOH to afford sodium salt **11**. The sodium salt **11** was treated with 4-methoxybenzyl chloride to give the unstable hydroxy ester **12**. The ester **12** was treated with diallyl diisopropylphosphoramidite in the presence of 1*H*-tetrazole and oxidized successively with *tert*-butyl hydroperoxide to give the corresponding phosphate **13**. The 4-methoxybenzyl group of **13** was removed by TFA and the afforded carboxylic acid **14** was treated with oxalyl chloride to give acid chloride **15**. The oxide anion prepared from CS-758 was esterified with **15** to afford ester **16** and the desired compound **3** was afforded by deprotection of the phosphoryl group.

The PK profile after i.v. bolus administration of **3** to rats at a dose of 2 mg (CS-758 equivalent)/kg is shown in Fig. 4. Compound **3** was converted to CS-758 rapidly and dephosphorylated intermediate alcohol was not observed in plasma. Thus, the conformational restriction had a distinct effect on the conversion rate of intermediate alcohols to drug CS-758.

Compared with **1**,[19] the conversion speed of **3** to CS-758 was improved. In the case of **3**, maximum drug concentration time (T_{max}) is 0.5 h, whereas T_{max} was 1.3 h in the case of **1**. The conversion efficiency (BA)[22] of compound **3** to CS-758 was 28.7%.

Aiming to further improve the conversion efficiency, we decided to continue modifying compound **3**, as shown in Fig. 5. We expected that certain steric effects or electric effects in the linker part might improve the conversion efficacy and conversion speed. In compounds **17a**—**i**, substituents were introduced to the benzene ring of the linker part and in compounds **17j** and **k**, the linker benzene ring was replaced by a naphthalene or furanyl ring. These compounds were synthesized as follows.

Compounds **17a**—**d**, **h** and **i** were synthesized in a similar manner starting from corresponding phthalide derivatives (Chart 4).

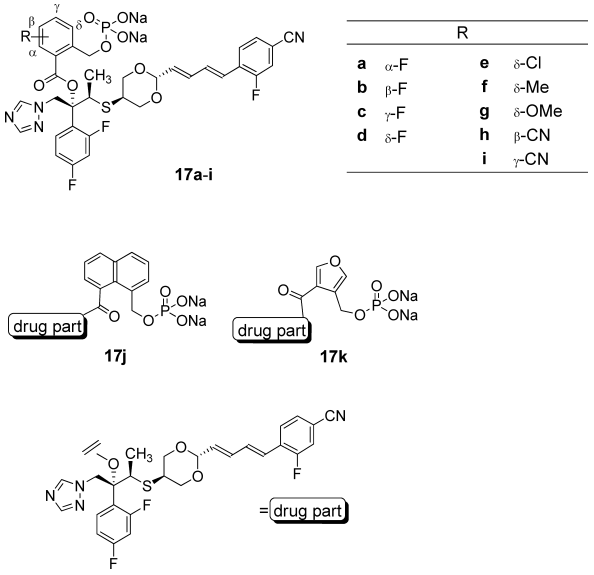


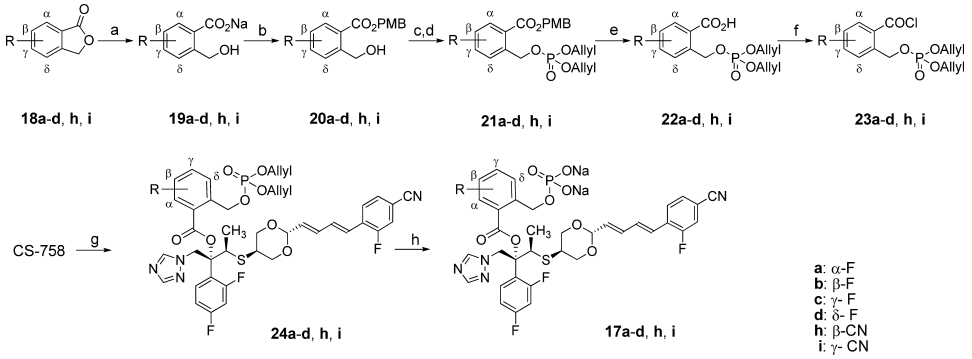
Fig. 5. Structural Formulas of Compounds **17a**—**k**

Table 1. Conversion of Compounds **3**, and **17a**—**k** to CS-758 in Human Plasma and Liver Microsome

Compd.	Human plasma[a]		Human liver microsome[a]	
	30 min	120 min	30 min	120 min
3	−	−	±	+
17a	−	−	+	++
17b	−	−	+	+
17c	−	−	±	±
17d	−	−	++	++
17e	−	−	±	+
17f	−	−	±	+
17g	−	−	+	+
17h	−	−	++	++
17i	−	−	++	++
17j	−	−	±	+
17k	−	−	+	++

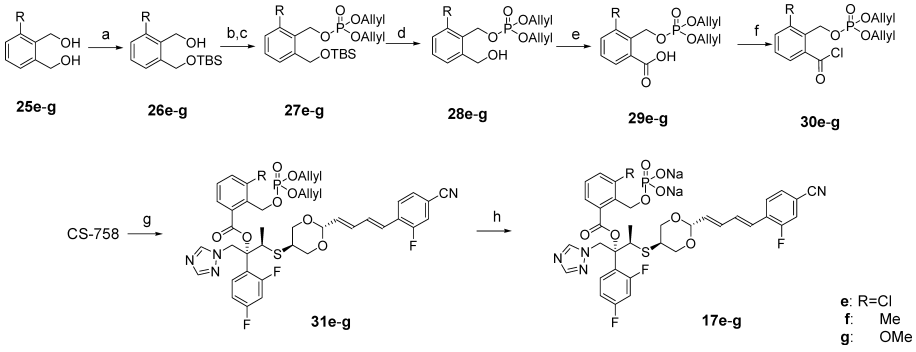
a) −, no detetction or very low formation of CS-758 (conversion yield: <20%); ±, low formation of CS-758 (conversion yield: 20—40%); +, middle formation of CS-758 (conversion yield: 40—70%); ++, high formation of CS-758 (conversion yield: >70%).

Compounds **17e**—**g** were synthesized as depicted in Chart 5. Diols **25e**—**g** were reacted with 1 eq of *tert*-butylchlorodimethylsilane (TBSCl) in THF at 0 °C to afford isomers **26e**—**g** preferentially. The structure of **26e**—**g** was determined by measuring the nuclear Overhauser effect (NOE) in the ^{1}H-NMR spectrum. Phosphorylation of **26e**—**g** with diallyl diisopropylphosphoramidite and successive oxidation with *tert*-butyl hydroperoxide gave phosphate esters **27e**—**g**. The silyl group of **27e**—**g** was removed with tetrabutylammonium fluoride in THF and the following oxidization with Jones reagent afforded carboxylic acids **29e**—**g**. Acid chlorides **30e**—**g** were reacted with the sodium alkoxide form of CS-758 to give **31e**—**g**. Removal of the two allyl groups in **31e**—**g** was accomplished by use of bis(triphenylphosphine)dichloropalladium and tri(*n*-butyl)tin hydride in dichloromethane. The sodium salt **17e**—**g** was prepared by treatment with sodium hydrogen carbonate and purified by C-18 reverse-phase column chromatography. **17j** and **17k** were synthesized in a manner similar to the synthesis of



Reagents and conditions: (a) NaOH aq., MeOH, THF; (b) 4-(MeO)BnCl, DMF, 80 °C; (c) *i*-$Pr_2NP(OAllyl)_2$, 1*H*-tetrazole, CH_2Cl_2; (d) *t*-BuOOH, CH_2Cl_2; (e) TFA, anisole; (f) $(COCl)_2$, cat. DMF, CH_2Cl_2; (g) NaH, **23a**—**d**, **h**, **i**, THF; (h) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnH, CH_2Cl_2, then $NaHCO_3$ aq.

Chart 4. Synthesis of **17a**—**d**, **h** and **i**



Reagents and conditions: (a) TBSCl, imidazole, THF; (b) *i*-$Pr_2NP(OAllyl)_2$, 1*H*-tetrazole, CH_2Cl_2; (c) *t*-BuOOH, CH_2Cl_2; (d) TBAF, THF, r.t.; (e) Jones reagent, acetone; (f) $(COCl)_2$, cat. DMF, CH_2Cl_2; (g) NaH, **30e**—**g**, THF; (h) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnH, CH_2Cl_2, then $NaHCO_3$ aq.

Chart 5. Synthesis of **17e**—**g**

17e—**g** (Charts 6, 7).

Compounds **17a**—**k** were incubated with human plasma or with human liver microsome and the conversion of these compounds to CS-758 was determined. The results are summarized in Table 1.

Compounds **17a**—**k** were not converted to CS-758 in human plasma, but these compounds were converted to CS-758 effectively in human liver microsome. In compounds **17a**—**d**, which had a F atom on the benzene ring, **17a** and **17d** were superior. The steric effect of the F atoms which are situated in α-position or δ-position on the benzene ring (position number shown in Chart 4) might hasten second spontaneous cleavage of the –O–CH_2–Ar–C(=O)– linker. Compounds **17e**—**g**, which have a substituent on the δ-position of benzene ring gave favorable results, but the conversion speed and conversion efficiency of these compounds were inferior to **17d**. In these compounds, **17h** and **17i** which had CN group at β-position or γ-position on the benzene ring afforded best results. The electron-withdrawing group on the benzene ring might hasten cyclization of the –O–CH_2–Ar–C(=O)– group. Also a compound with a furan ring in the linker part (**17k**) and a compound with a naphthalene ring in the linker part (**17j**) showed good results.

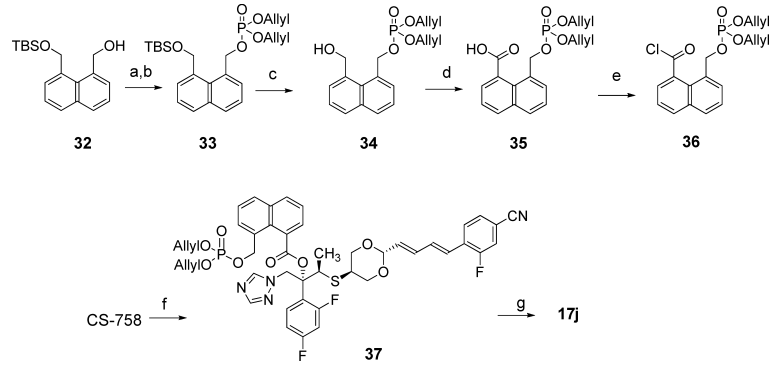
The disappearance of **17h** and **17i**, and the formation of CS-758 after incubation with human liver microsome are shown in Figs. 6 and 7, respectively. These compounds were converted to CS-758 within 1 h with excellent conversion efficacy.

The *in vivo* conversion of **17h** and **17i** to CS-758 upon i.v. administration to rats (2 mg of CS-758 equivalent/kg) is shown in Figs. 8 and 9, respectively. When **17h** was administered to rats, CS-758 was quickly formed (T_{max}; 0.7 h) and a high concentration of CS-758 was observed (C_{max}; 0.512 μg/ml). CS-758 was eliminated slowly ($t_{1/2}$; 5.7 h) and the BA of CS-758 was almost quantitative (94.4%). Interestingly, when **17i** was administered to rats, **17i** was eliminated from plasma within 1 h. But the conversion efficiency of **17i** was far less than that of **17h**. The reason for this large difference between **17h** and **17i** in the conversion to CS-758 was undefined.

The *in vivo* efficacies of the prodrug **17h** (i.v. administration) and CS-758 (oral administration) were evaluated in a hematogenous *C. albicans* infection model in mice (Fig. 10) and in a pulmonary *A. fumigatus* infection model in mice (Fig. 11). In the hematogenous *C. albicans* infection model, i.v.-administered prodrug **17h** exhibited high activity which was almost equal to or slightly better than that of orally administered CS-758. In a pulmonary aspergillosis model in mice, the efficacy of iv-administered **17h** was superior to that of orally administered CS-758.

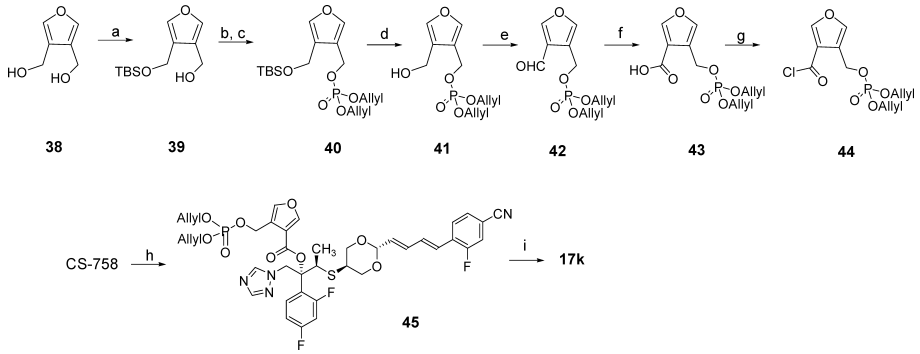
Furthermore compound **17h** had good water solubility (>30 mg/ml in water) and sufficient stability in solution at around neutral conditions. **17h** was also stable in solid state as an amorphous salt.

In summary, we developed a widely applicable prodrug technique for the solubilization of compounds having a hydroxy group. We identified the phosphoryl ester prodrug **17h**, which showed potent antifungal activity against both hematogenous candidasis and pulmonary aspergillosis in



Reagents and conditions: (a) *i*-$Pr_2NP(OAllyl)_2$, 1*H*-tetrazole, CH_2Cl_2; (b) *t*-BuOOH, CH_2Cl_2; (c) TBAF, THF, r.t.; (d) Jones reagent, acetone; (e) $(COCl)_2$, cat. DMF, CH_2Cl_2; (f) NaH, **36**, THF; (g) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnH, CH_2Cl_2, then $NaHCO_3$ aq.

Chart 6. Synthesis of **17j**



Reagents and conditions: (a) TBSCl, imidazole, THF; (b) *i*-$Pr_2NP(OAllyl)_2$, 1*H*-tetrazole, CH_2Cl_2; (c) *t*-BuOOH, CH_2Cl_2; (d) TBAF, AcOH, THF, r.t.; (e) MnO_2, CH_2Cl_2; (f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, (g) $(COCl)_2$, cat. DMF, CH_2Cl_2; (h) NaH, **44**, THF; (i) $Pd(PPh_3)_4$, pyrrolidine, CH_2Cl_2, then Dowex 50W×8 (Na form).

Chart 7. Synthesis of **17k**

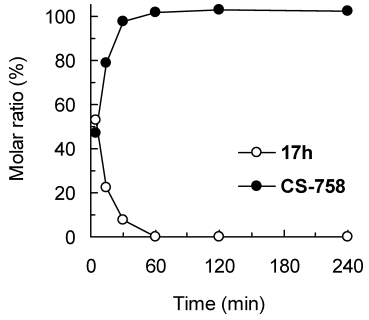


Fig. 6. Conversion of **17h** (○) to CS-758 (●) in Human Liver Microsome

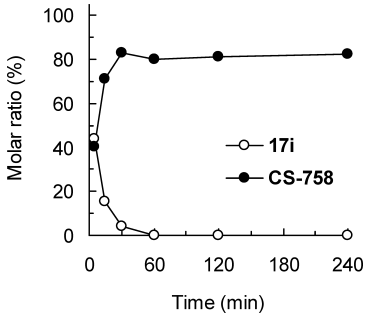


Fig. 7. Conversion of **17i** (○) to CS-758 (●) in Human Liver Microsome

mice *via* i.v. administration. Because there are few injectable antifungal azole agents with a broad spectrum, **17h** could be a promising drug for the treatment of fungal infections.

Experimental

^{1}H-NMR spectra were recorded either on a Varian Mercury 400 (400 MHz) or a Varian Mercury 500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. MS and high-resolution MS (HR-MS) were recorded either on a JEOL HX-100, a SX-102A or a JMS-AX-505H mass spectrometer. Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT-IR 8900 spectrometer. Optical rotations were measured on a JASCO P-1030 polarimeter.

4-Methoxybenzyl 4-{[Bis(allyloxy)phosphoryl]oxy}butanoate (6) To a suspension of a sodium 4-hydroxybutyrate (630 mg, 5.00 mmol) in *N*,*N*-dimethylformamide (DMF) (3.5 ml) was added 4-methoxybenzyl chloride (783 mg, 5.00 mmol), and the mixture was heated at 80 °C for 3 h. Water and EtOAc were added to the mixture and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure to give a crude product of **5** as an oil. The crude oil of **5** was dissolved in CH_2Cl_2 (5 ml), and tetrazole (700 mg, 10 mmol) and diallyl diisopropylphosphoramidite (1.5 g, 6.1 mmol) were added at 0 °C. The mixture was stirred at room temperature for 30 min, and methanol (0.1 ml) was added to the mixture. The mixture was stirred for 5 min at room temperature and *tert*-butyl hydroperoxide (*ca.* 5 M nonane solution, 1.5 ml, *ca.* 7.5 mmol) was added to the solution at 0 °C followed by stirring the mixture at room temperature for 30 min. Saturated $NaHCO_3$ solution and an aqueous solution of sodium thiosulfate were added to the mixture, and the mixture was stirred for 10 min. The product was extracted with EtOAc and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give an oily residue. The residue was subjected to chromatography on silica gel (30 g) column (EtOAc : hexane = 2 : 3—1 : 1) to give **6** (1.55 g, 81% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.01 (2H, quint, J=7 Hz), 2.47 (2H, t, J=7 Hz), 3.81 (3H, s), 4.10 (2H, q, J=7 Hz), 4.50—4.55 (4H, m), 5.06 (2H, s), 5.25 (2H, br d, J=10 Hz), 5.36 (2H, br d, J=17 Hz), 5.93 (2H, ddt, J=17, 10, 5 Hz), 6.84 (2H, d, J=9 Hz), 7.29 (2H, d, J=9 Hz). IR (neat) cm^{-1}: 1731, 1613, 1516, 1464, 1254. MS *m*/*z* (FAB):

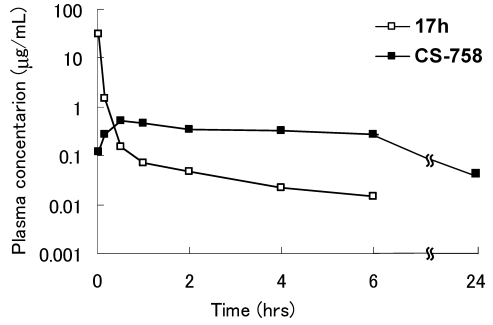


Fig. 8. Plasma Level of CS-758 after i.v. Administration of **17h** to Rats at a Dose of 2 mg (CS-758 Equivalent)/kg (Average of Three Rats)

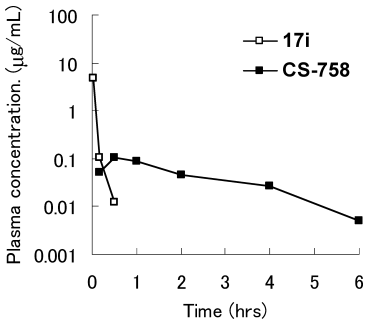


Fig. 9. Plasma Level of CS-758 after i.v. Administration of **17i** to Rats at a Dose of 2 mg (CS-758 Equivalent)/kg (Average of Three Rats)

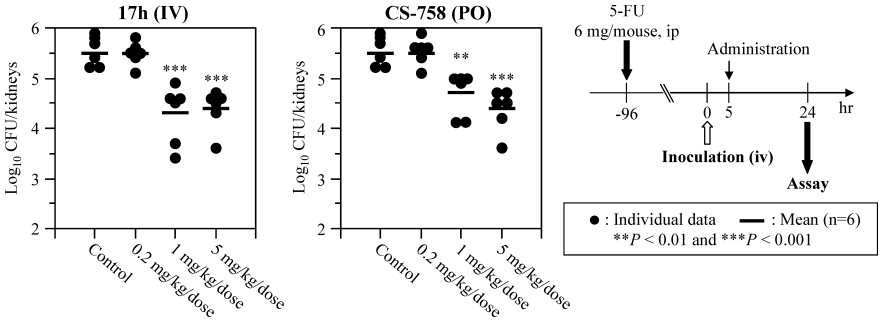


Fig. 10. *In Vivo* Efficacy of Compound **17h** (i.v.) against Murine Intravenous Infection with *C. albicans* SANK51486 Compared with That of CS-758 (*p. o.*)

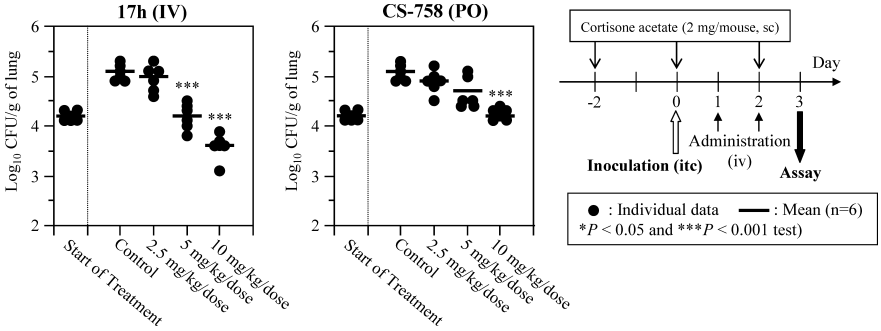


Fig. 11. *In Vivo* Efficacy of Compound **17h** (i.v.) against Murine Intratracheal Infection with *A. fumigatus* TIMM1776 Compared with That of CS-758 (*p. o.*)

385 (M^++1).

4-{[Bis(allyloxy)phosphoryl]oxy}butanoic Acid (7) To a mixture of **6** (700 mg, 1.82 mmol) and anisole (0.7 ml) was added TFA (3 ml) at room temperature. The mixture was stirred at room temperature for 15 min, then diluted with toluene (5 ml), and the solvent was distilled off under reduced pressure to give crude product of **7** as a pale yellow oil. The crude oil of **7** was used for the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.03 (2H, quint, J=7 Hz), 2.51 (2H, t, J=7 Hz), 4.16 (2H, q, J=7 Hz), 4.55—4.60 (4H, m), 5.29 (2H, br d, J=10 Hz), 5.39 (2H, br d, J=17 Hz), 5.94 (2H, ddt, J=17, 10, 5 Hz), 11.29 (1H, br s).

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 4-{[Bis(allyloxy)phosphoryl]oxy}butanoate (9) DMF (0.05 ml) and oxalyl chloride (350 mg, 2.76 mmol) were added to the solution of **7** in CH_2Cl_2 (3.5 ml) and the mixture was stirred at room temperature for 1 h, then toluene was added, and the mixture was concentrated under reduced pressure to afford **8** as a crude material. Sodium hydride (55% dispersion in mineral oil; 80 mg, 1.83 mmol) was added to the solution of CS-758 (936 mg, 1.73 mmol) in THF (10 ml) at room temperature. The mixture was stirred for 3 h. The obtained suspended mixture was cooled to 0 °C, and the crude material of **8** was added to the mixture. The mixture was stirred at room temperature for 30 min. After cooling, the mixture was partitioned between EtOAc and an aqueous solution of ammonium chloride, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The oily residue was purified by chromatography on silica gel (30 g) (EtOAc : methanol=1 : 0—10 : 1) to afford **9** (862 mg, 63% yield) as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, dd, J=7, 2 Hz), 1.90—2.10 (2H, m), 2.46 (1H, dt, J=17, 7 Hz), 2.57 (1H, dt, J= 17, 7 Hz), 3.04 (1H, tt, J=11, 5 Hz), 3.52 (2H, t, J=11 Hz), 3.90 (1H, q, J=7 Hz), 4.12 (2H, q, J=7 Hz) 4.15—4.25 (2H, m), 4.55—4.60 (4H, m), 5.00 (1H, d, J=4 Hz), 5.27 (2H, d, J=11 Hz), 5.35 (2H, s), 5.38 (2H, d, J=17 Hz), 5.85 (1H, dd, J=15, 4 Hz), 5.90—6.00 (2H, m), 6.58 (1H, dd, J=16, 11 Hz), 6.74 (1H, d, J=15 Hz), 6.85—6.95 (3H, m), 7.30—7.45 (3H, m), 7.57 (1H, t, J=8 Hz), 7.90 (1H, s), 7.92 (1H, s). IR (KBr) cm^{-1}: 2233, 1741, 1615, 1600, 1504. MS *m/z* (FAB): 789 (M^++1).

Disodium 4-{[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}-4-oxobutyl Phosphate (2) Pyrrolidine (644 mg, 9.06 mmol) was added to the solution of **9** (350 mg, 0.453 mmol), tetrakis(triphenylphosphine)palladium (5 mg, 0.0043 mmol), and triphenylphosphine (5 mg, 0.019 mmol) in CH_2Cl_2 (3 ml) at room temperature under N_2 atomsphere. After the reaction mixture was stirred for 1 h, it was diluted with toluene and the solvent was distilled off under reduced pressure. The residue was purified by reverse phase column chromatography using Cosmosil 75 C18-PREP (water : methanol=1 : 0—4 : 6). The concentrated eluates were passed through an ion exchange column of Dowex 50W×8 (Na form). The collected fractions were concentrated under reduced pressure and lyophilized to afford **2** (233 mg, 64% yield) as an amorphous colorless solid. ^{1}H-NMR (400 MHz, D_2O) δ: 1.13 (3H, d, J=7 Hz), 1.68 (2H, quint, J=7 Hz), 2.35—2.50 (2H, m), 2.87 (1H, m), 3.43 (1H, t, J=12 Hz), 3.46 (1H, t, J=12 Hz), 3.55—3.65 (3H, m), 3.95—4.05 (2H, m),

4.97 (1H, d, J=4 Hz), 5.13 (1H, d, J=15 Hz), 5.26 (1H, d, J=15 Hz), 5.65 (1H, dd, J=15, 5 Hz), 6.42 (1H, dd, J=15, 10 Hz), 6.64 (1H, d, J=16 Hz), 6.80—6.90 (3H, m), 7.25—7.35 (3H, m), 7.51 (1H, t, J=7 Hz), 7.82 (1H, s), 8.13 (1H, s). IR (KBr) cm^{-1}: 3432, 2231, 1740, 1615, 1599, 1503, 1418, 1387, 1276, 1257, 1142. MS *m/z* (FAB): 753 (M^++1). *Anal.* Calcd for $C_{31}H_{30}F_3N_4O_8PSNa_2 \cdot 3H_2O$: C, 46.16; H, 4.50; N, 6.95; Na, 5.70. Found: C, 46.41; H, 4.83; N, 7.04; Na, 5.37.

4-Methoxybenzyl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)benzoate (13) An aqueous solution (4.8 ml) of sodium hydroxide (0.56 g, 10 mmol) was added to a solution of phthalide (1.34 g, 10 mmol) in THF (30 ml). After the reaction mixture was stirred at room temperature for 3 h, the solution was concentrated under reduced pressure, and the residue was dried using a vacuum pump to give **11** as a crude material. 4-Methoxybenzyl chloride (2.04 g, 13 mmol) was added to the solution of the crude material of **11** in DMF (30 ml), and, and then the mixture was stirred at 80 °C for 1 h. After cooling the mixture, a saturated NH_4Cl solution was added to the mixture, and the product was extracted with EtOAc. The organic layer was washed with water and then with brine, and the solvent was distilled off under reduced pressure to afford crude product of **12** as the residue. The residue was dissolved in CH_2Cl_2 (70 ml), and tetrazole (1.4 g, 20 mmol) and diallyl diisopropylphosphoramidite (2.45 g, 10 mmol) were added at 0 °C, then the mixture was stirred at room temperature for 30 min, and methanol (0.1 ml) was added to the mixture. The mixture was stirred for 5 min further, and *tert*-butyl hydroperoxide (*ca.* 5 M nonane solution, 4.6 ml, *ca.* 23 mmol) was added at 0 °C followed by stirring the mixture at room temperature for 30 min. Saturated $NaHCO_3$ solution and an aqueous solution of sodium thiosulfate were added to the mixture, and the mixture was stirred for 10 min and then partitioned between EtOAc and water. The organic layer was washed successively with saturated $NaHCO_3$ solution, saturated NH_4Cl solution, and an aqueous solution of sodium chloride, and then dried over anhydrous $MgSO_4$, and the solvent was distilled off under reduced pressure to give an oily residue. The residue was chromatographed on silica gel (EtOAc : hexane=2 : 3—1 : 1) to give **13** (1.76 g, 40% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (3H, s), 4.57 (4H, m), 5.24 (2H, d, J=10.3 Hz), 5.28 (2H, s), 5.35 (2H, d, J=19.0 Hz), 5.55 (2H, d, J=6.6 Hz), 5.93 (2H, ddd, J= 18.0, 10.3, 5.2 Hz), 6.92 (2H, d, J=8.8 Hz), 7.35—7.38 (1H, m), 7.38 (2H, d, J=8.8 Hz), 7.56 (1H, m), 7.69 (1H, d, J=7.3 Hz), 8.01 (1H, d, J=6.6 Hz). MS *m/z* (FAB): 433 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)benzoic Acid (14) In a similar manner to **7**, **14** was obtained from **13** in quantitative yield as a colorless oil. The crude product of **14** was used for the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.60—4.63 (4H, m), 5.27 (2H, d, J=10.2 Hz), 5.28 (2H, d, J=16.9 Hz), 5.63 (2H, d, J=7.3 Hz), 5.95 (ddd, J=16.9, 10.2, 5.3 Hz), 7.41—7.45 (1H, m), 7.60—7.63 (1H, m), 7.69—7.71 (1H, m), 8.10 (1H, d, J=8.1 Hz).

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)benzoate (16) In a similar manner to **9**, **16** was obtained from **14** and CS-758 in 76% yield as a colorless amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (3H, dd, J=7, 2 Hz), 3.05 (1H, tt, J=11, 5 Hz), 3.50 (1H, t, J=11 Hz), 3.53 (1H, t, J=11 Hz), 4.01 (1H, q, J=7 Hz), 4.10—4.20 (2H, m), 4.50—4.60 (4H, m), 4.99 (1H, d, J=4 Hz), 5.24 (2H, br d, J=10 Hz), 5.34 (2H, br d, J=18 Hz), 5.40—5.55 (4H, m), 5.71 (1H, dd, J=15, 4 Hz), 5.85—6.00 (2H, m), 6.57 (1H, dd, J=15, 11 Hz), 6.73 (1H, d, J=15 Hz), 6.85—6.95 (3H, m), 7.34 (1H, dd, J=10, 1 Hz), 7.35—7.45 (3H, m), 7.57 (1H, t, J=8 Hz), 7.62 (1H, td, J=7, 1 Hz), 7.72 (1H, d, J=8 Hz), 7.76 (1H, d, J=9 Hz), 7.90 (1H, s), 7.91 (1H, s). IR (KBr) cm^{-1}: 2231, 1724, 1615, 1504. MS *m/z* (FAB): 837 (M^++1).

Disodium 2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)benzyl Phosphate (3) In a similar manner to **2**, **3** was obtained from **16** in 76% yield as a colorless amorphous solid. ^{1}H-NMR (400 MHz, D_2O) δ: 1.27 (3H, d, J=7 Hz), 2.95 (1H, m), 3.40 (1H, t, J=11 Hz), 3.45 (1H, t, J=11 Hz), 3.79 (1H, q, J=7 Hz), 3.93 (1H, m), 4.05 (1H, m), 4.90 (1H, dd, J=16, 7 Hz), 4.95 (1H, d, J=5 Hz), 5.03 (1H, dd, J=16, 7 Hz), 5.35 (1H, d, J=15 Hz), 5.44 (1H, br d, J=15 Hz), 5.67 (1H, m), 6.34 (1H, m), 6.68 (1H, br d, J=15 Hz), 6.85—7.00 (3H, m), 7.20—7.30 (1H, m), 7.30—7.45 (3H, m), 7.50—7.65 (3H, m), 7.76 (1H, d, J=8 Hz), 7.84 (1H, s), 8.23 (1H, s). IR (KBr) cm^{-1}: 3414, 2231, 1722, 1615, 1503, 1418, 1387, 1275, 1257, 1205, 1139. MS *m/z* (FAB): 801 (M^++1). *Anal.* Calcd for $C_{35}H_{30}F_3N_4O_8PSNa_2 \cdot 4H_2O$: C, 48.17; H, 4.39; N, 6.24; Na, 5.27. Found: C, 47.94; H, 4.31; N, 6.39; Na, 5.07.

4-Methoxybenzyl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-6-fluorobenzoate (21a) In a similar manner to **13**, **21a** was obtained from **18a** in 24% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.81 (3H, s), 4.49—4.54 (4H, m), 5.22—5.35 (6H, m), 5.33 (2H, dd, J=17, 1 Hz), 5.90 (2H, ddt, J=17, 11, 5 Hz), 6.91 (2H, d, J=9 Hz), 7.10 (1H, t, J=8 Hz), 7.32 (1H, d, J=8 Hz), 7.39 (2H, d, J=9 Hz), 7.43 (1H, td, J=8.6 Hz). IR ($CHCl_3$) cm^{-1}: 1727, 1614, 1516, 1465, 1268, 1114, 1034. MS *m/z* (FAB): 451 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-6-fluorobenzoic Acid (22a) In a similar manner to **7**, **22a** was obtained from **21a** in quantitative yield as a colorless oil. The crude product of **22a** was used for the next step without further purification.

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-6-fluorobenzoate (24a) In a similar manner to **9**, **24a** was obtained from CS-758 and **22a** in 51% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43 (3H, dd, J=7, 1 Hz), 3.05 (1H, tt, J=11, 5 Hz), 3.44 (1H, t, J=11 Hz), 3.51 (1H, t, J=11 Hz), 3.98 (1H, q, J=7 Hz), 4.08 (1H, ddd, J=11, 5, 2 Hz), 4.18 (1H, ddd, J=11, 5, 2 Hz), 4.53—4.59 (4H, m), 4.96 (1H, d, J=4 Hz), 5.24 (2H, dt, J=10, 1 Hz), 5.31—5.40 (4H, m), 5.44 (1H, d, J=15 Hz), 5.56 (1H, dd, J=15, 3 Hz), 5.83 (1H, dd, J=15, 4 Hz), 5.93 (2H, ddt, J=16, 10, 6 Hz), 6.55 (1H, dd, J=15, 11 Hz), 6.73 (1H, d, J=16 Hz), 6.88—6.98 (2H, m), 6.93 (1H, dd, J=16, 11 Hz), 7.11 (1H, td, J=8, 1 Hz), 7.34 (1H, dd, J=10, 1 Hz), 7.40 (1H, dd, J=8, 1 Hz), 7.48—7.59 (4H, m), 7.88 (1H, s), 7.89 (1H, s). IR ($CHCl_3$) cm^{-1}: 2233, 1727, 1614, 1504, 1277, 1140, 1034. MS *m/z* (FAB): 855 (M^++1).

Disodium 2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-3-fluorobenzyl Phosphate (17a) To a solution of **24a** (650 mg, 0.76 mmol) in CH_2Cl_2 (20 ml), dichlorobis(triphenylphosphine)palladium (16.0 mg, 0.023 mmol) was added at room temperature. To this mixture, tri(*n*-butyl)tin hydride (786.7 mg, 2.70 mmol) was added over 10 min and stirred for 30 min. Hexane, methanol, saturated $NaHCO_3$ solution were added to the mixture, and the aqueous layer was concentrated to afford crude residue. The residue was purified by reverse phase column chromatography using Cosmosil 75 C18-PREP (Nacalai Tesque, Inc.; 15 g) (water : methanol=4 : 6—3 : 7). The collected fractions were concentrated under reduced pressure and lyophilized to afford **17a** (440.5 mg, 71% yield) as an amorphous colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.39 (3H, dd, J=7, 1 Hz), 3.06 (1H, tt, J=11, 5 Hz), 3.25 (1H, t, J=11 Hz), 3.49 (1H, t, J=11 Hz), 3.94 (1H, ddd, J=11, 5, 2 Hz), 4.10 (1H, q, J=7 Hz), 4.15 (1H, ddd, J=11, 5, 2 Hz), 4.95 (1H, d, J=4 Hz), 5.03 (1H, dd, J=15, 5 Hz), 5.27 (1H, dd, J=15, 5 Hz), 5.52 (1H, dd, J=15, 3 Hz), 5.62 (1H, d, J=15 Hz), 5.83 (1H, dd, J=15, 4 Hz), 6.54 (1H, dd, J=15, 11 Hz), 6.79 (1H, d, J=16 Hz), 6.99—7.15 (4H, m), 7.50—7.58 (3H, m), 7.62 (1H, td, J=8, 6 Hz), 7.79 (1H, t, J=8 Hz), 7.88 (1H, d, J=8 Hz), 8.00 (1H, s), 8.33 (1H, s). IR (KBr) cm^{-1}: 2231, 1724, 1614, 1504, 1278, 1257, 1140, 1113, 1055, 975. MS *m/z* (FAB): 819 (M^++1). $[\alpha]_D^{25}$ +56.4° (c=1.02, MeOH).

4-Methoxybenzyl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-5-fluorobenzoate (21b) In a similar manner to **13**, **21b** was obtained from **18b** in 27% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (3H, s), 4.53—4.58 (4H, m), 5.25 (2H, dq, J=10, 1 Hz), 5.28 (2H, s), 5.35 (2H, dq, J=17, 1 Hz), 5.49 (2H, d, J=7 Hz), 5.93 (2H, ddt, J=17, 10, 5 Hz), 6.92 (2H, d, J=8 Hz), 7.25 (1H, td, J=8, 3 Hz), 7.38 (2H, d, J=8 Hz), 7.66 (1H, dd, J=8, 5 Hz), 7.69 (1H, dd, J=9, 3 Hz). IR ($CHCl_3$) cm^{-1}: 1719, 1516, 1272, 1031, 989. MS *m/z* (FAB): 451 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-5-fluorobenzoic Acid (22b) In a similar manner to **7**, **22b** was obtained from **21b** in quantitative yield as a colorless oil. The crude product of **22b** was used for the next step without further purification.

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-5-fluorobenzoate (24b) In a similar manner to **9**, **24b** was obtained from CS-758 and **22b** in 56% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (3H, dd, J=7, 2 Hz), 3.03 (1H, tt, J=11, 4 Hz), 3.53 (1H, t, J=11 Hz), 3.53 (1H, t, J=11 Hz), 4.00 (1H, q, J=7 Hz), 4.15—4.20 (2H, m), 4.54—4.58 (4H, m), 5.00 (1H, d, J=4 Hz), 5.24 (2H, dd, J=10, 1 Hz), 5.35 (2H, dd, J=18, 1 Hz), 5.40—5.49 (4H, m), 5.85 (1H, dd, J=15, 4 Hz), 5.92 (2H, ddt, J=18, 10, 5 Hz), 6.58 (1H, dd, J=15, 11 Hz), 6.73 (1H, d, J=16 Hz), 6.90—7.00 (3H, m), 7.29—7.38 (3H, m), 7.40 (1H, dd, J=8, 1 Hz), 7.53—7.60 (2H, m), 7.69 (1H, dd, J=9, 6 Hz), 7.90 (1H, s), 7.93 (1H, s). IR ($CHCl_3$) cm^{-1}: 2233, 1728, 1615, 1504, 1276, 1139, 1025. MS *m/z* (FAB): 855 (M^++1).

Disodium 2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-4-fluorobenzyl Phosphate (17b) In a similar manner to **17a**, **17b** was obtained from **24b** in 13% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.41 (3H, dd, J=7, 1 Hz), 3.02 (1H, tt, J=11, 5 Hz), 3.49 (1H, t, J=11 Hz), 3.54 (1H, t, J=11 Hz), 4.04 (1H, q, J=7 Hz), 4.08 (1H, ddd, J=11, 5, 2 Hz), 4.17 (1H, ddd, J=11, 5, 2 Hz), 5.02 (1H, d, J=5 Hz), 5.18 (1H, dd, J=16, 6 Hz), 5.30 (1H, dd, J=16, 6 Hz), 5.51 (1H, dd, J=15, 3 Hz), 5.59 (1H, d, J=15 Hz), 5.86 (1H, dd, J=15, 5 Hz), 6.58 (1H, dd, J=15, 11 Hz), 6.79 (1H, d, J=15 Hz), 7.03—7.13 (3H, m), 7.33 (1H, td, J=9, 3 Hz), 7.43 (1H, dd, J=10, 3 Hz), 7.49—7.58 (3H, m), 7.79 (1H, t, J=8 Hz), 7.99 (1H, s), 8.10 (1H, dd, J=9, 6 Hz), 8.36 (1H, s). IR (KBr) cm^{-1}: 2231, 1727, 1614, 1503, 1275, 1199, 1140, 1052, 975. MS *m*/*z* (FAB): 819 (M^++1). $[\alpha]_D^{25}$ +22.8° (c=0.94, MeOH).

4-Methoxybenzyl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-4-fluorobenzoate (21c) In a similar manner to **13**, **21c** was obtained from **18c** in 46% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (3H, s), 4.58—4.61 (4H, m), 5.26 (2H, s), 5.26 (2H, dq, J=11, 1 Hz), 5.38 (2H, dq, J=17, 1 Hz), 5.54 (2H, d, J=7 Hz), 5.95 (2H, ddt, J=17, 11, 5 Hz), 6.91 (2H, d, J=9 Hz), 7.02 (1H, td, J=9.2 Hz), 7.37 (2H, d, J=9 Hz), 7.43 (1H, dd, J=10, 2 Hz), 8.06 (1H, dd, J=9, 6 Hz). IR ($CHCl_3$) cm^{-1}: 1714, 1613, 1590, 1516, 1261, 1120, 1031. MS *m*/*z* (FAB): 451 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-4-fluorobenzoic Acid (22c) In a similar manner to **7**, **22c** was obtained from **21c** in quantitative yield as a colorless oil. The crude product of **22c** was used for the next step without further purification.

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-4-fluorobenzoate (24c) In a similar manner to **9**, **24c** was obtained from CS-758 and **22c** in 55% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (3H, dd, J=7, 2 Hz), 3.03 (1H, tt, J=11, 5 Hz), 3.50 (1H, t, J=11 Hz), 3.53 (1H, t, J=11 Hz), 4.01 (1H, q, J=7 Hz), 4.10—4.20 (2H, m), 4.57—5.61 (4H, m), 4.99 (1H, d, J=4 Hz), 5.26 (2H, dt, J=10, 1 Hz), 5.37 (2H, dt, J=17, 1 Hz) 5.41—5.52 (4H, m), 5.84 (1H, dd, J=15, 4 Hz), 5.95 (2H, ddt, J=17, 10, 5 Hz), 6.57 (1H, dd, J=15, 11 Hz), 6.74 (1H, d, J=15 Hz), 6.89—6.94 (2H, m), 6.94 (1H, dd, J=15, 11 Hz), 7.06 (1H, td, J=8, 3 Hz), 7.26—7.41 (3H, m), 7.46 (1H, dd, J=10, 3 Hz), 7.57 (1H, t, J=8 Hz), 7.81 (1H, dd, J=8, 6 Hz), 7.89 (1H, s), 7.89 (1H, s). IR ($CHCl_3$) cm^{-1}: 2232, 1721, 1614, 1590, 1504, 1275, 1140, 1028. MS *m*/*z* (FAB): 855 (M^++1).

Disodium 2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-5-fluorobenzyl Phosphate (17c) In a similar manner to **17a**, **17c** was obtained from **24c** in 64% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.41 (3H, dd, J=7, 1 Hz), 3.04 (1H, tt, J=11, 4 Hz), 3.48 (1H, t, J=11 Hz), 3.54 (1H, t, J=11 Hz), 4.05 (1H, q, J=7 Hz), 4.08 (1H, ddd, J=11, 4, 2 Hz), 4.17 (1H, ddd, J=11, 4, 2 Hz), 5.03 (1H, d, J=5 Hz), 5.20 (1H, dd, J=17, 5 Hz), 5.34 (1H, dd, J=17, 5 Hz), 5.50 (1H, dd, J=15, 3 Hz), 5.58 (1H, d, J=15 Hz), 5.87 (1H, dd, J=15, 5 Hz), 6.58 (1H, dd, J=15, 11 Hz), 6.80 (1H, d, J=15 Hz), 6.98—7.05 (3H, m), 7.10 (1H, dd, J=15, 11 Hz), 7.48—7.54 (3H, m), 7.77—7.81 (2H, m), 7.87 (1H, dd, J=10, 3 Hz), 7.96 (1H, s), 8.31 (1H, s). IR (KBr) cm^{-1}: 2231, 1724, 1613, 1503, 1256, 1140, 1117, 1051, 977. MS *m*/*z* (FAB): 819 (M^++1). $[\alpha]_D^{25}$ +28.3° (c=0.86, MeOH).

4-Methoxybenzyl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-fluorobenzoate (21d) In a similar manner to **13**, **21d** was obtained from **18d** in 31% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (3H, s), 4.49—4.53 (4H, m), 5.22 (2H, d, J=10, 1 Hz), 5.31 (2H, s), 5.33 (2H, d, J=17, 1 Hz), 5.52 (2H, dd, J=7, 1 Hz), 5.91 (2H, ddt, J=17, 10, 5 Hz), 6.91 (2H, d, J=8 Hz), 7.25 (1H, dt, J=1,8 Hz), 7.37—7.42 (1H, m), 7.39 (2H, d, J=8 Hz), 7.72 (1H, d, J=8 Hz). IR ($CHCl_3$) cm^{-1}: 1724, 1516, 1462, 1272, 1171, 1029. MS *m*/*z* (FAB): 451 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-fluorobenzoic acid (22d) In a similar manner to **7**, **22d** was obtained from **21d** in quantitative yield as a colorless oil. The crude product of **22d** was used for the next step without further purification.

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-fluorobenzoate (24d) In a similar manner to **9**, **24d** was obtained from CS-758 and **22d** in 55% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (3H, dd, J=7, 2 Hz), 3.03 (1H, tt, J=12, 5 Hz), 3.46 (1H, t, J=12 Hz), 3.51 (1H, t, J=12 Hz), 3.99 (1H, q, J=7 Hz), 4.09 (1H, ddd, J=12, 5, 2 Hz), 4.18 (1H, ddd, J=12, 5, 2 Hz), 4.44—4.56 (4H, m), 4.97 (1H, d, J=4 Hz), 5.21 (2H, d, J=10 Hz), 5.31 (2H, d, J=17 Hz), 5.43—5.54 (4H, m), 5.83 (1H, dd, J=15, 4 Hz), 5.89 (2H, ddt, J=17, 10, 5 Hz), 6.55 (1H, dd, J=15, 11 Hz), 6.73 (1H, d, J=15 Hz), 6.87—6.93 (3H, m), 7.29—7.35 (2H, m), 7.39—7.49 (4H, m), 7.57 (1H, t, J=8 Hz), 7.93 (1H, s), 8.00 (1H, s). IR ($CHCl_3$) cm^{-1}: 2233, 1732, 1504, 1462, 1276, 1141, 1023, 991. MS *m*/*z* (FAB): 855 (M^++1).

Disodium 2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-6-fluorobenzyl Phosphate (17d) In a similar manner to **17a**, **17d** was obtained from **24d** in 75% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.43 (3H, dd, J=7, 1 Hz), 2.98 (1H, tt, J=11, 5 Hz), 3.48 (1H, t, J=11 Hz), 3.53 (1H, t, J=11 Hz), 4.03 (1H, q, J=7 Hz), 4.05 (1H, ddd, J=11, 5, 2 Hz), 4.14 (1H, ddd, J=11, 5, 2 Hz), 5.00 (1H, d, J=4 Hz), 5.25 (1H, dd, J=12, 5 Hz), 5.32 (1H, ddd, J=12, 5, 2 Hz), 5.52 (1H, dd, J=15, 3 Hz), 5.69 (1H, d, J=15 Hz), 5.84 (1H, dd, J=15, 4 Hz), 6.56 (1H, dd, J=15, 10 Hz), 6.78 (1H, d, J=15 Hz), 7.00—7.13 (2H, m), 7.09 (1H, dd, J=15, 10 Hz), 7.34 (1H, t, J=9 Hz), 7.42 (1H, td, J=8, 5 Hz), 7.49—7.54 (2H, m), 7.62—7.70 (2H, m), 7.78 (1H, t, J=8 Hz), 7.96 (1H, s), 8.70 (1H, s). IR (KBr) cm^{-1}: 2230, 1731, 1614, 1504, 1275, 1142, 1048, 975. MS *m*/*z* (FAB): 819 (M^++1). $[\alpha]_D^{25}$ +5.4° (c=0.91, MeOH).

4-Methoxybenzyl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-5-cyanobenzoate (21h) In a similar manner to **13**, **21h** was obtained from **18h** in 15% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.83 (3H, s), 4.57—4.61 (4H, m), 5.27 (2H, dd, J=11, 1 Hz), 5.29 (2H, s), 5.37 (2H, dd, J=17, 1 Hz), 5.58 (2H, d, J=7 Hz), 5.94 (2H, ddt, J=17, 11, 5 Hz), 6.94 (2H, d, J=9 Hz), 7.38 (2H, d, J=9 Hz), 7.83 (1H, dd, J=8, 1 Hz), 7.87 (1H, d, J=8 Hz), 8.30 (1H, d, J=1 Hz). IR ($CHCl_3$) cm^{-1}: 2236, 1722, 1516, 1255, 1175, 1031. MS *m*/*z* (FAB): 458 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-5-cyanobenzoic Acid (22h) In a similar manner to **7**, **22h** was obtained from **21h** in quantitative yield as a colorless oil. The crude product of **22h** was used for the next step without further purification.

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-5-cyanobenzoate (24h) In a similar manner to **9**, **24h** was obtained from CS-758 and **22h** in 23% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (3H, dd, J=7, 2 Hz), 3.02 (1H, tt, J=12, 5 Hz), 3.54 (1H, t, J=12 Hz), 3.55 (1H, t, J=12 Hz), 4.00 (1H, q, J=7 Hz), 4.14—4.19 (2H, m), 4.58—4.61 (4H, m), 5.01 (1H, d, J=4 Hz), 5.26 (2H, dd, J=10, 1 Hz), 5.36 (2H, d, J=17 Hz), 5.47 (2H, s), 5.52 (2H, d, J=7 Hz), 5.87 (1H, dd, J=15, 4 Hz), 5.94 (2H, ddt, J=17, 10, 6 Hz), 6.58 (1H, dd, J=15, 11 Hz), 6.73 (1H, d, J=16 Hz), 6.90—7.00 (3H, m), 7.31—7.37 (2H, m), 7.40 (1H, dd, J=8, 1 Hz), 7.57 (1H, t, J=8 Hz), 7.88—7.92 (4H, m), 8.18 (1H, s). IR (KBr) cm^{-1}: 2232, 1731, 1615, 1504, 1276, 1142, 1027. MS *m*/*z* (FAB): 862 (M^++1).

Disodium 4-Cyano-2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)benzyl Phosphate (17h) In a similar manner to **17a**, **17h** was obtained from **24h** in 39% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.41 (3H, dd, J=7, 1 Hz), 3.04 (1H, tt, J=11, 5 Hz), 3.48 (1H, t, J=11 Hz), 3.54 (1H, t, J=11 Hz), 4.01 (1H, q, J=7 Hz), 4.05 (1H, ddd, J=11, 5, 2 Hz), 4.18 (1H, ddd, J=11, 5, 2 Hz), 5.01 (1H, d, J=4 Hz), 5.25 (1H, dd, J=18, 6 Hz), 5.39 (1H, dd, J=18, 5 Hz), 5.52 (1H, dd, J=15, 3 Hz), 5.58 (1H, d, J=15 Hz), 5.90 (1H, dd, J=15, 4 Hz), 6.58 (1H, dd, J=15, 11 Hz), 6.79 (1H, d, J=16 Hz), 7.02—7.12 (3H, m), 7.50—7.54 (3H, m), 7.78 (1H, t, J=8 Hz), 7.93 (1H, dd, J=8, 2 Hz), 8.01 (2H, s), 8,31 (1H, d, J=8 Hz), 8.40 (1H, s). IR (KBr) cm^{-1}: 3423, 2232, 1729, 1615, 1504, 1141, 1054, 976. MS *m*/*z* (FAB): 826 (M^++1). $[\alpha]_D^{25}$ +31.2° (c=0.73, MeOH).

4-Methoxybenzyl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-4-cyanobenzoate (21i) In a similar manner to **13**, **21i** was obtained from **18i** in 26% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (3H, s), 4.58—4.62 (4H, m), 5.29 (2H, dd, J=10, 1 Hz), 5.29 (2H, s), 5.39 (2H, dd, J=17, 1 Hz), 5.53 (2H, d, J=7 Hz), 5.96 (2H, ddt, J=17, 10, 5 Hz), 6.92 (2H, d, J=9 Hz), 7.37 (2H, d, J=9 Hz), 7.65 (1H, dd, J=8, 2 Hz), 8.00 (1H, br s), 8.09 (1H, d, J=8 Hz). IR ($CHCl_3$) cm^{-1}: 2237, 1721, 1613, 1516, 1266, 1031, 990. MS *m*/*z* (FAB): 458 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-4-cyanobenzoic Acid (22i) In a similar manner to **7**, **22i** was obtained from **21i** in quantitative yield as a colorless oil. The crude product of **22i** was used for the next step without further purification.

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-4-cyanobenzoate (24i) In a similar manner to **9**, **24i** was obtained from CS-758 and crude **22i** in 54% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43 (3H, dd, J=7, 2 Hz), 3.01 (1H, tt, J=11, 5 Hz), 3.48 (1H, t, J=11 Hz), 3.52 (1H, t, J=11 Hz), 4.01 (1H, q, J=7 Hz), 4.09 (1H, ddd, J=11, 5, 2 Hz), 4.17 (1H, ddd, J=11, 5, 2 Hz), 4.56—4.62 (4H, m), 4.99 (1H, d, J=4 Hz), 5.29 (2H, d, J=11 Hz), 5.38 (2H, dd, J=17, 1 Hz), 5.45—5.50 (4H, m), 5.83 (1H, dd, J=15, 4 Hz), 5.95 (2H, ddt, J=17, 11, 5 Hz), 6.56 (1H, dd, J=15, 10 Hz), 6.75 (1H, d, J=16 Hz), 6.93—6.96 (2H, m), 6.94 (1H, dd, J=16, 10 Hz), 7.33—7.39 (2H, m), 7.40 (1H, dd, J=8, 1 Hz), 7.58 (1H, t, J=8 Hz), 7.69 (1H, dd, J=8, 1 Hz), 7.82 (1H, d, J=8 Hz), 7.87 (1H, s), 7.91 (1H, s), 8.03 (1H, s). IR ($CHCl_3$) cm^{-1}: 2235, 1729, 1616, 1504, 1277, 1141, 1028, 991. MS *m*/*z* (FAB): 862 (M^++1).

Disodium 5-Cyano-2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)benzyl Phosphate (17i) In a similar manner to **17a**, **17i** was obtained from **24i** in 79% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.40 (3H, dd, J=7, 1 Hz), 3.02 (1H, tt, J=11, 5 Hz), 3.45 (1H, t, J=11 Hz), 3.53 (1H, t, J=11 Hz), 4.00 (1H, q, J=7 Hz), 4.02 (1H, ddd, J=11, 5, 2 Hz), 4.16 (1H, ddd, J=11, 5, 2 Hz), 5.01 (1H, d, J=4 Hz), 5.21 (1H, dd, J=17, 5 Hz), 5.36 (1H, dd, J=17, 6 Hz), 5.55 (2H, s), 5.86 (1H, dd, J=15, 4 Hz), 6.57 (1H, dd, J=15, 11 Hz), 6.80 (1H, d, J=15 Hz), 7.02—7.08 (2H, m), 7.10 (1H, dd, J=15, 11 Hz), 7.49—7.58 (3H, m), 7.66 (1H, dd, J=8, 1 Hz), 7.80 (1H, t, J=8 Hz), 7.83 (1H, d, J=8 Hz), 7.96 (1H, s), 8.37 (1H, s), 8.50 (1H, s). IR (KBr) cm^{-1}: 3422, 2232, 1731, 1615, 1503, 1276, 1257, 1140, 1053, 977. MS *m*/*z* (FAB): 826 (M^++1). $[\alpha]_D^{25}$ +31.7° (c=0.97, MeOH).

[2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-chlorophenyl]methanol (26e) Imidazole (1.19 g, 17.5 mmol) and *tert*-butylchlorodimethylsilane (2.64 g, 17.5 mmol) were added to a solution of 3-chloro-1,2-benzenedimethanol (**25e**, 3.02 g, 17.5 mmol) in THF (40 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was poured into ice-water and the aqueous water was extracted with EtOAc. The combined organic layer was washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc : hexane=1 : 5) to afford **26e** (3.69 g, 73% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.13 (6H, s), 0.92 (9H, s), 2.93 (1H, t, J=7 Hz), 4.83 (2H, s), 4.86 (2H, d, J=7 Hz), 7.19—7.25 (2H, m), 7.37 (1H, dd, J=8, 2 Hz). IR ($CHCl_3$) cm^{-1}: 2959, 2931, 1732, 1257, 1049, 839. MS *m*/*z* (FAB): 287 (M^++1).

Diallyl 2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-chlorobenzyl Phosphate (27e) Tetrazole (2.23 g, 31.9 mmol) and diallyl diisopropylphosphoramidite (3.91 g, 16.0 mmol), were added to the solution of **26e** (3.66 g, 12.8 mmol) in CH_2Cl_2 at 0 °C. The mixture was warmed to room temperature, then stirred for 30 min, and methanol (0.1 ml) was added. The mixture was stirred for 5 min further, and *tert*-butyl hydroperoxide (*ca.* 80% di-*tert*-butylperoxide solution, 1.8 g, *ca.* 16 mmol) was added at 0 °C followed by stirring the mixture at room temperature for 30 min. Saturated $NaHCO_3$ solution and saturated $Na_2S_2O_3$ solution were added to reaction mixture and the reaction mixture was stirred for 10 min. Water and EtOAc were added to the reacton mixture. The combined organic layer was washed with water and brine, and then dried over $MgSO_4$, and the solvent was distilled off under reduced pressure to give an oily residue. The residue was chromatographed on silica gel (EtOAc : hexane=1 : 5—2 : 3) to give **27e** (4.52 g, 79% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.11 (6H, s), 0.94 (9H, s), 4.51—4.55 (4H, m), 4.88 (2H, s), 5.23 (2H, br d, J=10 Hz), 5.30 (2H, d, J=7 Hz), 5.34 (2H, dq, J=17, 1 Hz), 5.91 (2H, ddt, J=17, 10, 5 Hz), 7.28—7.34 (2H, m), 7.44 (1H, d, J=7 Hz). IR ($CHCl_3$) cm^{-1}: 2956, 2931, 1259, 1018, 989, 839. MS *m*/*z* (FAB): 447 (M^++1).

Diallyl 2-Chloro-6-(hydroxymethyl)benzyl Phosphate (28e) Tetrabutylammonium fluoride (1 N THF solution; 10 ml, 10 mmol) was added to a solution of **27e** (4.41 g, 9.87 mmol) in THF (50 ml). The mixture was stirred at room temperature for 40 min. Water and EtOAc were added to the mixture and the organic layer was separated. The organic layer was washed with brine, dried and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (EtOAc : hexane=1 : 1—3 : 1) to afford **28e** (2.71 g, 83% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.49 (1H, t, J=6 Hz), 4.47—4.51 (4H, m), 4.78 (2H, d, J=6 Hz), 5.23 (2H, br d, J=10 Hz), 5.33 (2H, br d, J=18 Hz), 5.40 (2H, d, J=9 Hz), 5.89 (2H, ddt, J=18, 10, 6 Hz), 7.32 (1H, t, J=8 Hz), 7.37—7.40 (2H, m). IR ($CHCl_3$) cm^{-1}: 3608, 1732, 1268, 1028, 987. MS *m*/*z* (FAB): 333 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-chlorobenzoic Acid (29e) To a solution of **28e** (2.62 g, 7.88 mmol) in acetone (25 ml) was added Jones reagent (*ca.* 32 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. Then 2-propanol (1 ml) was added to the reaction mixture. The insoluble material was filtered off, and then the filtrate was concentrated under reduced pressure to give an oily residue. The residue was purified by flash chromatography on silica gel (EtOAc : CH_2Cl_2=1 : 10—1 : 1) to afford **29e** (2.065 g, 76% yield) as a pale brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.50—4.62 (4H, m), 5.23 (2H, br d, J=10 Hz), 5.34 (2H, dq, J=17, 1 Hz), 5.64 (2H, dd, J=7, 2 Hz), 5.91 (2H, ddt, J=17, 10, 6 Hz), 7.39 (1H, t, J=8 Hz), 7.57 (1H, d, J=8 Hz), 7.81 (1H, d, J=8 Hz). IR ($CHCl_3$) cm^{-1}: 2951, 1727, 1267, 1025. MS *m*/*z* (FAB): 347 (M^++1).

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-chlorobenzoate (31e) In a similar manner to **9**, **31e** was obtained from CS-758 and crude **31e** in 72% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (3H, dd, J=7, 2 Hz), 3.02 (1H, tt, J=11, 5 Hz), 3.45 (1H, t, J=11 Hz), 3.51 (1H, t, J=11 Hz), 4.00 (1H, q, J=7 Hz), 4.07 (1H, ddd, J=11, 5, 2 Hz), 4.18 (1H, ddd, J=11, 5, 2 Hz), 4.45—4.58 (4H, m), 4.96 (1H, d, J=4 Hz), 5.20 (2H, br d, J=10 Hz), 5.31 (2H, br d, J=17 Hz), 5.45 (1H, dd, J=15, 3 Hz), 5.51 (1H, d, J=15 Hz), 5.56 (1H, dd, J=10, 6 Hz), 5.59 (1H, dd, J=10, 6 Hz), 5.82 (1H, dd, J=15, 4 Hz), 5.85—5.94 (2H, m), 6.55 (1H, dd, J=15, 11 Hz), 6.73 (1H, d, J=16 Hz), 6.95 (1H, dd, J=16, 11 Hz), 6.87—7.03 (2H, m), 7.32—7.50 (5H, m), 7.57 (1H, t, J=8 Hz), 7.63 (1H, dd, J=8, 1 Hz), 7.94 (1H, s), 8.00 (1H, s). IR ($CHCl_3$) cm^{-1}: 2233, 1732, 1504, 1276, 1140, 1019, 991. MS *m*/*z* (FAB): 871 (M^++1).

Disodium 2-Chloro-6-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)benzyl Phosphate (17e) In a similar manner to **17a**, **17e** was obtained from **31e** in 30% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.42 (3H, dd, J=7, 2 Hz), 2.98 (1H, tt, J=11, 5 Hz), 3.46 (1H, t, J=11 Hz), 3.52 (1H, t, J=11 Hz), 4.00—4.06 (2H, m), 4.14 (1H, ddd, J=11, 5, 2 Hz), 5.00 (1H, d, J=4 Hz), 5.35 (1H, dd, J=11, 4 Hz), 5.42 (1H, dd, J=11, 4 Hz), 5.53 (1H, dd, J=15, 3 Hz), 5.67 (1H, d, J=15 Hz), 5.83 (1H, dd, J=15, 4 Hz), 6.55 (1H, dd, J=15, 11 Hz), 6.78 (1H, d, J=15 Hz), 7.00—7.16 (3H, m), 7.38 (1H, t, J=8 Hz), 7.49—.54 (2H, m), 7.62—7.71 (3H, m), 7.78 (1H, t, J=8 Hz), 7.98 (1H, s), 8.63 (1H, s). IR (KBr) cm^{-1}: 2231, 1732, 1615, 1503, 1275, 1257, 1142, 1105, 1048, 974. MS *m*/*z* (FAB): 835 (M^++1). $[\alpha]_D^{25}$ +7.7° (c=1.20, MeOH).

[2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-methylphenyl]methanol (26f) In a similar manner to **26e**, **26f** was obtained from **25f** in 68% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.13 (6H, s), 0.92 (9H, s), 2.46 (3H, s), 3.04 (1H, t, J=6 Hz), 4.72 (2H, d, J=6 Hz), 4.80 (2H, s), 7.11 (1H, dd, J=6, 2 Hz), 7.15—7.19 (2H, m). IR ($CHCl_3$) cm^{-1}: 3459, 1732, 1599, 1471, 1257, 1061, 1038, 1005, 840. MS *m*/*z* (FAB): 267 (M^++1).

Diallyl 2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-methylbenzyl Phosphate (27f) In a similar manner to **27e**, **27f** was obtained from **26f** in 74% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.09 (6H, s), 0.93 (9H, s), 2.44 (3H, s), 4.45—4.51 (4H, m), 4.86 (2H, s), 5.20—5.25 (4H, m), 5.32 (2H, dq, J=17, 1 Hz), 5.89 (2H, ddt, J=17, 10, 6 Hz), 7.13 (1H, d, J=7 Hz), 7.25 (1H, t, J=7 Hz), 7.32 (1H, d, J=7 Hz). IR ($CHCl_3$) cm^{-1}: 1598, 1732, 1471, 1464, 1258, 1005. MS *m*/*z* (FAB): 427 (M^++1).

Diallyl 2-(Hydroxymethyl)-6-methylbenzyl Phosphate (28f) In a similar manner to **28e**, **28f** was obtained from **27f** in 87% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.46 (3H, s), 3.33 (1H, t, J=6 Hz), 4.36—4.49 (4H, m), 4.75 (2H, d, J=6 Hz), 5.22 (2H, br d, J=11 Hz), 5.30 (2H, dq, J=17, 1 Hz), 5.32 (2H, d, J=10 Hz), 5.86 (2H, ddt, J=17, 11, 5 Hz), 7.18 (1H, t, J=4 Hz), 7.26—7.28 (2H, m). IR ($CHCl_3$) cm^{-1}: 3607, 1732, 1598, 1466, 1266, 1006. MS *m*/*z* (FAB): 313 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-methylbenzoic Acid (29f) In a similar manner to **29e**, **29f** was obtained from **28f** in 71% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.49 (3H, s), 4.43—4.55 (4H, m), 5.22 (2H, dd, J=10, 1 Hz), 5.32 (2H, dq, J=17, 1 Hz), 5.53 (2H, d, J=8 Hz), 5.88 (2H, ddt, J=17, 10, 6 Hz), 7.34 (1H, t, J=7 Hz), 7.38 (1H, dd, J=8, 1 Hz), 7.72 (1H, d, J=8 Hz). IR ($CHCl_3$) cm^{-1}: 2960, 1725, 1271, 1012. MS *m*/*z* (FAB): 327 (M^++1).

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-methylbenzoate (31f) In a similar manner to **9**, **31f** was obtained from CS-758 and **29f** in 69% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (3H, dd, J=7, 2 Hz), 2.51 (3H, s), 3'.04 (1H, tt, J=11, 5 Hz), 3.45 (1H, t, J=11 Hz), 3.51 (1H, t, J=11 Hz), 4.00 (1H, q, J=7 Hz), 4.09

(1H, ddd, *J*=11, 5, 2 Hz), 4.19 (1H, ddd, *J*=11, 5, 2 Hz), 4.42—4.55 (4H, m), 4.96 (1H, d, *J*=5 Hz), 5.19 (2H, br d, *J*=10 Hz), 5.30 (2H, br d, *J*=18 Hz), 5.43—5.56 (4H, m), 5.83 (1H, dd, *J*=16, 5 Hz), 5.82—5.92 (2H, m), 6.55 (1H, dd, *J*=16, 11 Hz), 6.73 (1H, d, *J*=16 Hz), 6.86—6.99 (3H, m), 7.30—7.35 (2H, m), 7.39—7.43 (3H, m), 7.48 (1H, td, *J*=9, 6 Hz), 7.57 (1H, t, *J*=8 Hz), 7.94 (1H, s), 8.00 (1H, s). IR ($CHCl_3$) cm^{-1}: 2233, 1727, 1616, 1504, 1419, 1387, 1276, 1141, 1211. MS *m*/*z* (FAB): 851 (M^++1).

Disodium 2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl) buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-6-methylbenzyl Phosphate (17f) In a similar manner to **17a**, **17f** was obtained from **31f** in 57% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.41 (3H, dd, *J*=7, 2 Hz), 2.58 (3H, s), 2.99 (1H, tt, *J*=11, 5 Hz), 3.45 (1H, t, *J*=11 Hz), 3.52 (1H, t, *J*=11 Hz), 4.03 (1H, ddd, *J*=11, 5, 2 Hz), 4.08 (1H, q, *J*=7 Hz), 4.14 (1H, ddd, *J*=11, 5, 2 Hz), 4.99 (1H, d, *J*=5 Hz), 5.15 (1H, dd, *J*=11, 4 Hz), 5.30 (1H, dd, *J*=11, 4 Hz), 5.51 (1H, dd, *J*=15, 4 Hz), 5.69 (1H, d, *J*=15 Hz), 5.83 (1H, dd, *J*=16, 5 Hz), 6.55 (1H, dd, *J*=15, 11 Hz), 6.77 (1H, d, *J*=15 Hz), 7.01—7.11 (3H, m), 7.27 (1H, t, *J*=8 Hz), 7.41 (1H, d, *J*=7 Hz), 7.49—7.54 (3H, m), 7.64 (1H, td, *J*=9, 6 Hz), 7.77 (1H, t, *J*=8 Hz), 7.98 (1H, s), 8.60 (1H, s). IR (KBr) cm^{-1}: 2231, 1725, 1615, 1503, 1276, 1141, 1048, 974. MS *m*/*z* (FAB): 815 (M^++1). $[\alpha]_D^{25}$ +16.3° (*c*=1.01, MeOH)

[2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-methoxyphenyl]methanol (26g) In a similar manner to **26e**, **26g** was obtained from **25g** in 53% yield as a colorless oil. H-3 and ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.11 (6H, s), 0.91 (9H, s), 3.03 (1H, br), 3.86 (3H, s), 4.77 (2H, s), 4.79 (2H, s), 6.88 (1H, d, *J*=8 Hz), 6.94 (1H, d, *J*=8 Hz), 7.24 (1H, t, *J*=8 Hz). IR ($CHCl_3$) cm^{-1}: 2957, 2931, 1588, 1472, 1463, 1264. MS *m*/*z* (FAB): 283 (M^++1). The structure of **26g** was assigned by means of NOE when positive NOE was found between signals of the methylene protons of the CH_2OTBS group and the proton in position 3 of the benzene ring.

Diallyl 2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-methoxybenzyl Phosphate (27g) In a similar manner to **27e**, **27g** was obtained from **26g** in 60% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.10 (6H, s), 0.93 (9H, s), 3.84 (3H, s), 4.49—4.52 (4H, m), 4.86 (2H, s), 5.22 (2H, dd, *J*=10, 1 Hz), 5.25 (2H, d, *J*=6 Hz), 5.33 (2H, dd, *J*=17, 1 Hz), 5.91 (2H, ddt, *J*=17, 10, 5 Hz), 6.83 (1H, d, *J*=8 Hz), 7.12 (1H, d, *J*=8 Hz), 7.33 (1H, t, *J*=8 Hz). IR ($CHCl_3$) cm^{-1}: 2956, 2931, 1591, 1472, 1270, 1015. MS *m*/*z* (FAB): 443 (M^++1).

Diallyl 2-(Hydroxymethyl)-6-methoxybenzyl Phosphate (28g) In a similar manner to **28e**, **28g** was obtained from **27g** in 93% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.3 (1H, br), 3.86 (3H, s), 4.42—4.50 (4H, m), 4.75 (2H, s), 5.22 (2H, d-like, *J*=10 Hz), 5.32 (2H, d-like, *J*=17 Hz), 5.34 (2H, d, *J*=10 Hz), 5.89 (2H, ddt, *J*=17, 10, 6 Hz), 6.88 (1H, d, *J*=8 Hz), 7.06 (1H, d, *J*=8 Hz), 7.35 (1H, t, *J*=8 Hz). IR ($CHCl_3$) cm^{-1}: 3385, 1473, 1463, 1271, 1021, 989. MS *m*/*z* (FAB): 329 (M^++1).

2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-methoxybenzoic Acid (29g) In a similar manner to **29e**, **29g** was obtained from **28g** in 60% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.89 (3H, s), 4.47—4.57 (4H, m), 5.21 (2H, d-like, *J*=10 Hz), 5.32 (2H, d-like, *J*=17 Hz), 5.53 (2H, d, *J*=8 Hz), 5.90 (2H, ddt, *J*=17, 10, 6 Hz), 7.07 (1H, dd, *J*=8, 1 Hz), 7.41 (1H, t, *J*=8 Hz), 7.48 (1H, d, *J*=8 Hz). IR ($CHCl_3$) cm^{-1}: 1725, 1587, 1461, 1272, 1021, 989. MS *m*/*z* (FAB): 343 (M^++1).

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 2-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-methoxybenzoate (31g) In a similar manner to **9**, **31g** was obtained from CS-758 and **29g** in 49% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (3H, dd, *J*=7, 2 Hz), 3.04 (1H, tt, *J*=12, 5 Hz), 3.45 (1H, t, *J*=12 Hz), 3.51 (1H, t, *J*=12 Hz), 3.89 (3H, s), 3.98 (1H, q, *J*=7 Hz), 4.09 (1H, ddd, *J*=12, 5, 2 Hz), 4.18 (1H, ddd, *J*=12, 5, 2 Hz), 4.43—4.55 (4H, m), 4.96 (1H, d, *J*=4 Hz), 5.19 (2H, dd, *J*=10, 1 Hz), 5.31 (2H, dq, *J*=17, 1 Hz), 5.43—5.55 (4H, m), 5.83 (1H, dd, *J*=15, 4 Hz), 5.84—5.94 (2H, m), 6.56 (1H, dd, *J*=15, 10 Hz), 6.73 (1H, d, *J*=16 Hz), 6.93 (1H, dd, *J*=16, 10 Hz), 6.86—7.00 (2H, m), 7.12 (1H, d, *J*=8 Hz), 7.16 (1H, d, *J*=8 Hz), 7.34 (1H, dd, *J*=9, 1 Hz), 7.39 (2H, t, *J*=8 Hz), 7.48 (1H, td, *J*=9, 6 Hz), 7.57 (1H, t, *J*=8 Hz), 7.93 (1H, s), 8.00 (1H, s). IR ($CHCl_3$) cm^{-1}: 2233, 1731, 1504, 1462, 1277, 1141, 1059, 1018, 991. MS *m*/*z* (FAB): 867 (M^++1).

Disodium 2-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl) buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-6-methoxybenzyl Phosphate (17g) In a similar manner to **17a**, **17g** was obtained from **31g** in 24% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.42 (3H, dd, *J*=7, 2 Hz), 3.00 (1H, tt, *J*=11, 5 Hz), 3.46 (1H, t, *J*=11 Hz), 3.52 (1H, t, *J*=11 Hz), 3.88 (3H, s), 4.01—4.77 (2H, m), 4.15 (1H, ddd, *J*=11, 5, 2 Hz), 5.00 (1H, d, *J*=4 Hz), 5.28 (1H, dd, *J*=10, 4 Hz), 5.32 (1H, dd, *J*=10, 4 Hz), 5.58 (1H, dd, *J*=15, 3 Hz), 5.68 (1H, d, *J*=15 Hz), 5.84 (1H, dd, *J*=15, 4 Hz), 6.56 (1H, dd, *J*=11, 15 Hz), 6.78 (1H, d, *J*=15 Hz), 6.99—7.13 (2H, m), 7.08 (1H, dd, *J*=15, 11 Hz), 7.21 (1H, d, *J*=7 Hz), 7.30 (1H, d, *J*=7 Hz), 7.36 (1H, t, *J*=8 Hz), 7.51 (1H, t, *J*=8 Hz), 7.52 (1H, t, *J*=8 Hz), 7.62—7.70 (1H, m), 7.78 (1H, t, *J*=8 Hz), 7.97 (1H, s), 8.62 (1H, s). IR (KBr) cm^{-1}: 2231, 1730, 1615, 1503, 1278, 1142, 1054. MS *m*/*z* (FAB): 831 (M^++1). $[\alpha]_D^{25}$ +15.4° (*c*=0.84, MeOH).

Diallyl [8-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-1-naphthyl]methyl Phosphate (33) In a similar manner to **27e**, **33** was obtained from **32** in 81% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.87 (9H, s), 4.37—4.45 (4H, m), 5.16 (2H, br d, *J*=10 Hz), 5.24 (2H, dq, *J*=18, 1 Hz), 5.25 (2H, s), 5.80 (2H, d, *J*=10 Hz), 5.77—5.86 (2H, m), 7.44—7.48 (2H, m), 7.61 (1H, dd, *J*=7, 1 Hz), 7.69 (1H, dd, *J*=7, 1 Hz), 7.84 (1H, dd, *J*=8, 1 Hz), 7.89 (1H, dd, *J*=7, 1 Hz). IR ($CHCl_3$) cm^{-1}: 1732, 1471, 1464, 1259, 1027, 999. MS *m*/*z* (FAB): 463 (M^++1).

Diallyl [8-(Hydroxymethyl)-1-naphthyl]methyl Phosphate (34) In a similar manner to **28e**, **34** was obtained from **33** in 59% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.41—4.46 (4H, m), 5.18 (2H, br d, *J*=10 Hz), 5.19 (2H, s), 5.26 (2H, br d, *J*=17 Hz), 5.82 (2H, d, *J*=9 Hz), 5.84 (2H, ddt, *J*=17, 10, 6 Hz), 7.47 (1H, t, *J*=7 Hz), 7.49 (1H, t, *J*=7 Hz), 7.61 (1H, dd, *J*=7, 1 Hz), 7.71 (1H, dd, *J*=7, 1 Hz), 7.88 (1H, d, *J*=7 Hz), 7.92 (1H, d, *J*=7 Hz). IR ($CHCl_3$) cm^{-1}: 3603, 1732, 1270, 1028, 990. MS *m*/*z* (FAB): 349 (M^++1).

8-({[Bis(allyloxy)phosphoryl]oxy}methyl)-1-naphthoic Acid (35) In a similar manner to **29e**, **35** was obtained from **34** in quantitative yield as a colorless oil. This compound was used for the next step without further purification.

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 8-({[Bis(allyloxy)phosphoryl]oxy}methyl)-1-naphthoate (37) In a similar manner to **9**, **37** was obtained from CS-758 and **35** in 52% yield as a pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.47 (3H, dd, *J*=7, 2 Hz), 3.18 (1H, tt, *J*=11, 5 Hz), 3.46 (1H, t, *J*=11 Hz), 3.55 (1H, t, *J*=11 Hz), 4.20 (1H, ddd, *J*=11, 5, 2 Hz), 4.22—4.42 (6H, m), 4.94 (1H, d, *J*=4 Hz), 5.13 (2H, br d, *J*=11 Hz), 5.20 (2H, br d, *J*=18 Hz), 5.34 (1H, dd, *J*=14, 10 Hz), 5.43—5.56 (3H, m), 5.70—5.82 (3H, m), 6.50 (1H, dd, *J*=15, 11 Hz), 6.70 (1H, d, *J*=15 Hz), 6.90 (1H, dd, *J*=15, 11 Hz), 6.90—6.95 (1H, m), 7.14 (1H, td, *J*=8, 3 Hz), 7.33 (1H, dd, *J*=10, 1 Hz), 7.38—7.44 (3H, m), 7.56 (1H, t, *J*=8 Hz), 7.58 (1H, t, *J*=8 Hz), 7.79 (1H, s), 7.83—7.89 (3H, m), 8.01 (1H, s), 8.05 (1H, dd, *J*=6, 3 Hz). IR (KBr) cm^{-1}: 3431, 2230, 1718, 1615, 1503, 1274, 1143, 1039, 1011. MS *m*/*z* (FAB): 887 (M^++1).

Disodium [8-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl) buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-1-naphthyl]methyl Phosphate (17j) In a similar manner to **17a**, **17j** was obtained from **37** in 27% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.48 (3H, dd, *J*=7, 2 Hz), 3.15 (1H, tt, *J*=11, 5 Hz), 3.49 (1H, t, *J*=11 Hz), 3.58 (1H, t, *J*=11 Hz), 4.17 (1H, ddd, *J*=11, 5, 2 Hz), 4.24 (1H, ddd, *J*=11, 5, 2 Hz), 4.34 (1H, q, *J*=7 Hz), 5.00 (1H, d, *J*=4 Hz), 5.21 (1H, dd, *J*=15, 8 Hz), 5.26 (1H, dd, *J*=15, 8 Hz), 5.59 (1H, dd, *J*=15, 3 Hz), 5.69 (1H, d, *J*=15 Hz), 5.82 (1H, dd, *J*=16, 4 Hz), 6.54 (1H, dd, *J*=16, 11 Hz), 6.77 (1H, d, *J*=16 Hz), 7.02 (1H, ddd, *J*=13, 9, 3 Hz), 7.07 (1H, dd, *J*=16, 11 Hz), 7.30 (1H, td, *J*=8, 3 Hz), 7.42 (1H, t, *J*=8 Hz), 7.49—7.54 (2H, m), 7.58 (1H, t, *J*=8 Hz), 7.70 (1H, d, *J*=7 Hz), 7.77 (1H, t, *J*=7 Hz), 7.84 (1H, d, *J*=8 Hz), 7.96 (1H, td, *J*=9, 6 Hz), 8.05 (1H, s), 8.09 (1H, dd, *J*=8, 1 Hz), 8.19 (1H, d, *J*=7 Hz), 8.39 (1H, s). MS *m*/*z* (FAB): 851 (M^++1). $[\alpha]_D^{25}$ +63.0° (*c*=0.61, MeOH).

[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-furyl]methanol (39) In a similar manner to **26e**, **39** was obtained from **38** in 50% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.125 (6H, s), 0.916 (9H, s), 3.177 (1H, t, *J*=6 Hz), 4.522 (2H, d, *J*=6 Hz), 4.640 (2H, s), 7.317 (1H, s), 7.371 (1H, s). IR ($CHCl_3$) cm^{-1}: 3449, 2956, 2931, 2859, 1471, 1258, 1040. MS *m*/*z* (FAB): 243 (M^++1).

Diallyl [4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-furyl]methyl Phosphate (40) In a similar manner to **27e**, **40** was obtained from **39** in 93% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.083 (6H, s), 0.908 (9H, s), 4.55—4.55 (4H, m), 4.627 (2H, s), 5.003 (2H, d, *J*=8, 2 Hz), 5.328 (2H, dd, *J*=10.4, 1.2 Hz), 5.340 (1H, dddd, *J*=17, 1.5, 1.5, 1.2 Hz), 5.912 (2H, ddt, *J*=17, 10, 5 Hz), 7.328 (1H, s), 7.447 (1H, s). IR ($CHCl_3$) cm^{-1}: 2956, 2931, 1258, 1010. MS *m*/*z* (FAB): 403 (M^++1).

Diallyl [4-(Hydroxymethyl)-3-furyl]methyl Phosphate (41) In a simi-

lar manner to **28e**, **41** was obtained from **40** in 76% yield as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.168 (1H, t-like, J=*ca.* 6 Hz), 4.523 (4H, td, J=7, 1.2 Hz), 4.580 (2H, d, J=6 Hz), 5.050 (2H, d, J=9.5 Hz), 5.255 (2H, dd-like, J=10, *ca.* 1.2 Hz), 5.350 (2H, dt-like, J=17, *ca*. 1.2 Hz), 5.917 (2H, ddt, J= 17, 10, 6 Hz), 7.414 (1H, s), 7.483 (1H, s). IR (CHCl3) cm^{-1}: 3401, 1602, 1554, 1462, 1424, 1267, 1022. MS *m*/*z* (FAB): 289 (M^++1).

Diallyl (4-Formyl-3-furyl)methyl Phosphate (42) To a solution of **41** (113 mg, 0.39 mmol) in CH_2Cl_2 (2 ml), activated manganese dioxide (0.52 g, 6.0 mmol) was added, then the reaction mixture was stirred at room temperature for 8 h. Then activated manganese dioxide (40 mg, 0.46 mmol) was further added to the solution and the mixture was stirred at room temperature for 1.5 h. EtOAc was added to the solution and filtered. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by flash chromatography to afford **42** (101 mg, 90% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.569 (4H, dd-like, J=7, 6 Hz), 5.245 (2H, dd-like, J=6, 1 Hz), 5.259 (2H, dd-like, J=11, 1 Hz), 5.369 (2H, dd-like, J= 17, 1 Hz), 5.943 (2H, d, J=17, 11, 6 Hz), 7.569 (1H, br s), 8.046 (1H, d, J= 1.6 Hz), 9.971 (1H, s). IR ($CHCl_3$) cm^{-1}: 1689, 1544, 1273, 1147, 1027. MS *m*/*z* (EI): 287 (M^++1).

4-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-furoic Acid (43) A solution of sodium chlorite (122 mg, 1.35 mmol) and sodium dihydrogen phosphate dihydrate (1.034 g, 6.76 mmol) in water (1.2 ml) was added to a solution of diallyl (4-formyl-3-furyl)methyl phosphate **42** (97 mg, 0.34 mmol) and 2-methyl-2-butene (1.18 g, 19.9 mmol) in *tert*-butyl alcohol (2.70 ml) at 0 °C. The mixture was stirred for 2 h at room temperature, and partitioned between EtOAc and an aqueous solution of sodium chloride, then the organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was subjected to chromatography on a silica gel (2 g) column (EtOAc) to afford **43** (74 mg, 72% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.572 (4H, dd-like, J=7, 6 Hz), 5.25 (4H, d-like, J=9 Hz), 5.367 (2H, dd-like,J=17, 1.4 Hz), 5.940 (2H, ddt, J=17, 10, 6 Hz), 7.533 (1H, d, J=*ca.* 1.4 Hz), 8.059 (1H, d, J=*ca.* 1.7 Hz). IR (CHCl3) cm^{-1}: 1736, 1697, 1549, 1269, 1149, 1029. MS *m*/*z* (EI): 303 (M^++1).

(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl)buta-1, 3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl 4-({[Bis(allyloxy)phosphoryl]oxy}methyl)-3-furoate (45) In a similar manner to **9**, **45** was obtained from CS-758 and **43** in 70% yield as a colorless amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43 (3H, dd, J=7, 2 Hz), 3.05 (1H, tt, J=11, 5 Hz), 3.53 (2H, t, J=11 Hz), 3.96 (1H, q, J=7 Hz), 4.14—4.22 (2H, m), 4.53 (4H, br t, J=7 Hz), 5.01 (1H, d, J=5 Hz), 5.10—5.18 (2H, m), 5.25 (2H, d, J=10 Hz), 5.35 (2H, dd, J=17, 1 Hz), 5.40 (1H, dd, J=15, 3 Hz), 5.47 (1H, d, J=15 Hz), 5.85 (1H, dd, J=15, 5 Hz), 5.92 (2H, ddt, J=17, 10, 5 Hz), 6.58 (1H, dd, J=15, 11 Hz), 6.74 (1H, d, J=16 Hz), 6.88—6.93 (2H, m), 6.93 (1H, dd, J=16, 11 Hz), 7.32—7.37 (2H, m), 7.40 (1H, dd, J= 8, 1 Hz), 7.56—7.59 (2H, m), 7.89 (1H, s), 7.92 (2H, s). IR (KBr) cm^{-1}: 2230, 1727, 1615, 1504, 1276, 1258, 1143, 1051, 1021, 973. MS *m*/*z* (FAB): 827 (M^++1).

Disodium [4-({[(2*R*,3*R*)-3-({*trans*-2-[(1*E*,3*E*)-4-(4-Cyano-2-fluorophenyl) buta-1,3-dien-1-yl]-1,3-dioxan-5-yl}sulfanyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]oxy}carbonyl)-3-furyl]methyl Phosphate (17k) In a similar manner to **2**, **17k** was obtained from **45** in 87% yield as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.38 (3H, dd, J=7, 2 Hz), 3.07 (1H, tt, J=11, 5 Hz), 3.54 (1H, t, J=11 Hz), 3.55 (1H, t, J=11 Hz), 4.00 (1H, q, J=7 Hz), 4.16 (2H, dd, J=11, 5 Hz), 4.98 (1H, ddd, J=15, 6, 1 Hz), 5.03 (1H, ddd, J=15, 6, 1 Hz), 5.05 (1H, d, J=4 Hz), 5.51 (2H, s), 5.88 (1H, dd, J=15, 4 Hz), 6.59 (1H, dd, J=15, 11 Hz), 6.79 (1H, d, J=15 Hz), 6.97—7.06 (2H, m), 7.01 (1H, dd, J=15, 11 Hz), 7.48—7.54 (3H, m), 7.69 (1H, q, J=2 Hz), 7.78 (1H, t, J=8 Hz), 7.92 (1H, s), 7.99 (1H, d, J=1 Hz), 8.27 (1H, s). IR (KBr) cm^{-1}: 2231, 1726, 1615, 1503, 1143, 1101, 1052, 975. MS *m*/*z* (ESI): 745 [M (non sodium part)+1]$^-$.

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References and Notes

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