Synthetic Study on Telomerase Inhibitor, D8646-2-6: Synthesis of the Key Intermediate Using $Sn(OTf)_2$ or $Sc(OTf)_3$ Mediated Aldol-Type Reaction and Stille Coupling

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The synthesis of the key intermediate (4) in the proposed route to D8646-2-6 is described. The aldol reaction of the carbohydrate-containing pyrone 7 with the aldehyde 6 was accomplished by using LiHMDS and $Sc(OTf)_3$ or $Sn(OTf)_2$. The stepwise dehydration reaction of the aldol adduct 14, followed by Stille coupling with vinyl stannane 5 which contained phosphonate gave the desired 4.

Key words aldol-type reaction; carbohydrate-containing pyrone; stille coupling; scandium triflate; tin triflate; vinyl stannane which contains phosphonate

In 2002, the Mitsubishi Pharma group reported the isolation of a telomerse inhibitor, D8646-2-6 (**1**) from the culture broth of fungus *Epicoccum purpurascens*.[1] The compound has a unique C^3-pyranosyl 4-hydroxypyrone moiety[2] and conjugated polyene unit.[3—7] However the structure of **1** including the relative and absolute stereochemistry has not been fully elucidated yet. The potent biological activity and structural complexity of this compound prompted us to initiate synthetic studies toward **1**. In our preceding paper, we have reported the construction of the *C*-glycosyl 4-hydroxy pyrone moiety of **1**. Comparison of the NMR spectra of the C^3-galactopyranosyl 4-hydroxy-2-pyrone moiety **2** with those of natural **1**, demonstrated that the carbohydrate moiety of the latter compound to be C^3-galactopyranoside (Fig. 1).[8]

Our synthetic strategy toward the total synthesis of **1** is shown in Chart 1. Due to the labile nature of the polyeninc side chain, our synthestic strategy involved an initial aldol condensation of the pyrone moiety with the side chain unit (C8—C12), followed by the elongation of the remaining side chain unit. Since the stereochemistry at C21 and C23 was not determined, we envisaged that phosphonate **4** would serve as a versatile key intermediate for the synthesis of D8646-2-6 and its stereoisomeres. Horner–Wadsworth–Emmons reaction was successfully utilized by Cha and co-workers in the total synthesis of citreoviridin[9] which contains polyene conjugated with pyrone ring. Phosphonate **4** could be synthesized by Stille coupling[10] of triene **15** with vinyl stannane which contains phosphonate.[11] Although there have been some reports concerning the aldol-type reaction and alkylation of pyrones,[12—24] the application of this approach to a carbohydrate-containing compound is unprecedented. Since oxygenated functionalities of substrates might influence on the reactivity of carbanion, the reactivity of such carbohyrare-bearing pyrones as well as its synthetic utilities is quite interesting. Herein, we report the synthesis of the key intermediate **4** using aldol-type reaction of carbohydrate containing pyrone **7** followed by stepwise dehydration and Stille coupling with vinyl stannane **5** which contains phosphonate group.

The feasibility of the key aldol-type reaction was evaluated through model systems. The aldol-type reaction of **7**[25—27] with (2*E*,4*E*)-hexa-2,4-dienal by the simple treatment with LiHMDS to give **8** in only 6% yield and 62% of **7** was recovered (Chart 2).

However, the aldol-type reaction of 4-methoxy-6-methyl-2-pyrone **9** with (2*E*,4*E*)-hexa-2,4-dienal proceeded smoothly under the same conditions to afford the aldol product **10** in 87% yield. These results indicated that the carbohydrate moiety greatly influenced the aldol-type reaction. We reasoned that the highly oxygenated functional group of **7** might decrease the reactivity of the pyrone-stabilized carbanion through the coordination to the lithium ion or by steric

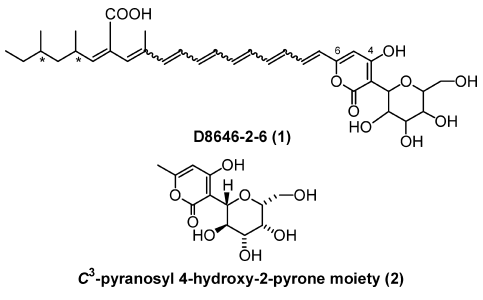

Fig. 1. Structure of D8646-2-6 and C^3-Pyranosyl 4-Hydroxy-2-pyrone Moiety

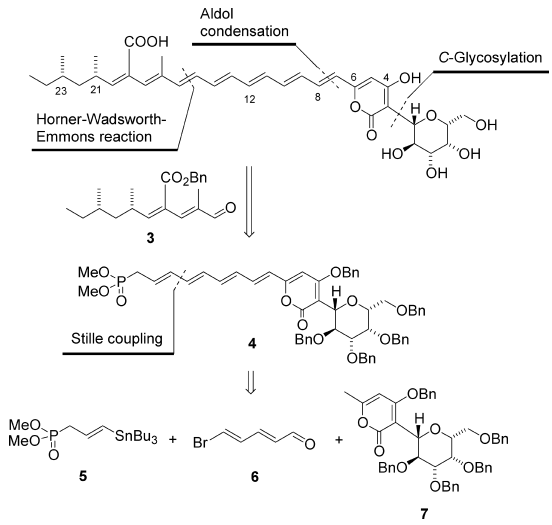

Chart 1. Synthetic Strategy of D8646-2-6

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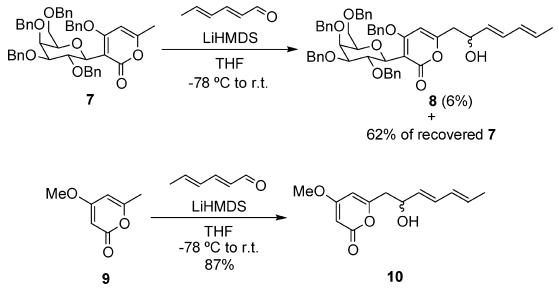
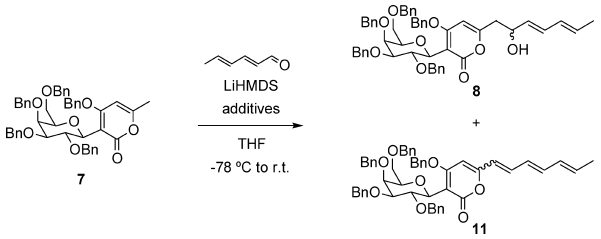


Chart 2. The Aldol Reaction of Pyrone **7** and Pyrone **9** with (2*E*,4*E*)-Hexa-2,4-dienal

Table 1. Aldol-Type Reaction of Pyrone Moiety **7** with (2*E*,4*E*)-Hexa-2,4-dienal



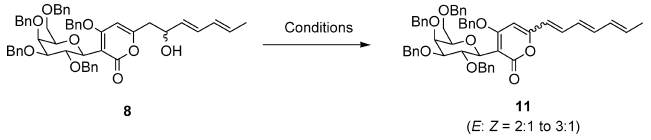
Entry	LiHMDS (eq)	Additive (1.0 eq)	Yield (%)	
			8	**11**
1	1	LiCl	0	9
2	1	Me_2AlCl	35	Trace
3	3	Me_2AlCl	26	15
4	1	$TiCl(Oi\text{-}Pr)_3$	45	0
5	3	$TiCl(Oi\text{-}Pr)_3$	0	22
6	1	$Sc(OTf)_3$	6	29
7	3	$Sc(OTf)_3$	54	20
8	1	$SnCl_4$	9	7
9	1	$Sn(OTf)_2$	4	37
10	3	$Sn(OTf)_2$	69	3

hidrance.

We next examined a variety of additives in the above aldol-type reaction (Table 1). The addition of LiCl did not affect the yield of the aldol products **8** and **11** (entry 1). However, the addition of Me_2AlCl, $TiCl(Oi\text{Pr})_3$, $Sc(OTf)_3$, $SnCl_4$ or $Sn(OTf)_2$, improved the yield of the products (entries 2, 4, 6, 8, 9). When Me_2AlCl or $TiCl(Oi\text{Pr})_3$ was used, the major product was **8** (entries 2, 4). On the other hand, the dehydrated product **11** was obtained as a major product using $Sc(OTf)_3$ or $Sn(OTf)_2$ as an additive (entries 6, 9). The addition of $SnCl_4$ slightly improved the yield of the aldol products with almost 1:1 ratio of **8** and **11** (entry 8). Using 3 eq of LiHMDS, no significant improvement was achieved with Me_2AlCl or $TiCl(Oi\text{-Pr})_3$ as an additive (entries 3, 5). However, we found that the aldol-type reaction proceeded smoothly when LiHMDS (3 eq) and $Sc(OTf)_3$ or $Sn(OTf)_2$ (1 eq) were used in the reaction (entries 7, 10).

We tentatively speculate that scandium(III) and tin(II) might coordinate to both carbonyl oxygen of the aldehyde (activation of an electrophile) and ether oxygen of galactose moiety (proximity effect). We also believe that $Sc(OTf)_3$ or $Sn(OTf)_2$ stabilize the alkoxide derivative of the aldol-type product by the formation of the stable scandium(III) or tin(II) alkoxide.

Table 2. Dehydration of Aldol Adduct **8**



Entry	Conditions	Yield (%)
1	CCl_3COCl, Et_3N/CH_2Cl_2, 0 °C, 0.5 h	57
2	TFAA, Et_3N/CH_2Cl_2, 0 °C, 0.5 h	29
3	Tf_2O/CH_2Cl_2, 0 °C, 10 min	55
4	$HfCl_4(THF)_2$/THF, 0 °C, 3 h	21
5	Ac_2O, Py, DMAP/CH_2Cl_2, 2 h then DBU/CH_2Cl_2, 0 °C, 3 h	74

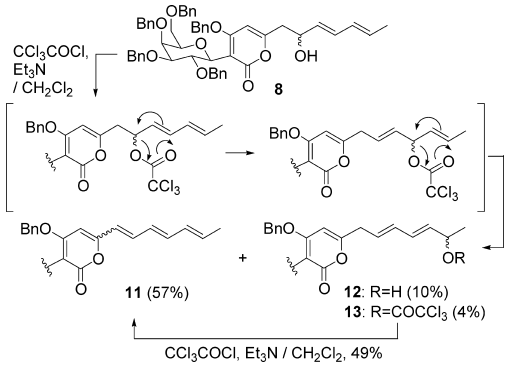


Chart 3. Dehydration of Aldol Adduct **8** with Trichloroacetylchloride, and Plausible Mechanism of the Rearrangement

With the aldol adduct **8** in hand, direct dehydration was next investigated. When the aldol adduct **8** was subjected to a conventional dehydration conditions using CCl_3COCl and Et_3N,[28] the desired triene **11** was obtained in 57% yield as a 2 : 1 mixture of *E* and *Z* isomers, in addition to alcohol **12** (10%) and trichloroacetate **13** (4%) (Table 2, entry 1 and Chart 3).[29]

The formation of alcohol **12** and trichloroacetate **13** might be explained by the rearrangement shown in Chart 3. Similar sigmatropic rearrangement of allylic trichloroacetimidate was also reported by Overman.[30,31] We also examined other direct dehydration methods such as TFAA–Et_3N, Tf_2O and $HfCl_4(thf)_2$[32] to afford the triene **11** in low to moderate yield (Table 2, entries 2—4). Finally we found that the stepwise method involving an initial acetylation (Ac_2O–pyridine, DMAP) followed by elimination with DBU afforded the best result (74%) (entry 5).

The present $Sc(OTf)_3$ or $Sn(OTf)_2$ mediated aldol-type reaction was successfully applied to the synthesis of the key intermediate of D8646-2-6. Pyrone **7** was reacted with (2*E*,4*E*)-5-bromopenta-2,4-dienal **6**[33,34] using LiHMDS and $Sc(OTf)_3$ or $Sn(OTf)_2$ to give the aldol product **14** in 85% or 83% yield, respectively (Chart 4). It should be emphasized that no reaction occurred without $Sn(OTf)_2$ or $Sc(OTf)_3$. Aldol adduct **14** was then subjected to a stepwise elimination described above (Ac_2O, pyridine and DMAP, then DBU; 78%[35]) to obtain the triene **15** with complete stereoselectivity.

With the triene **15** in hand, we next examined Stille coupling of **15** with vinyl stannane **5** which is bearing phospho-

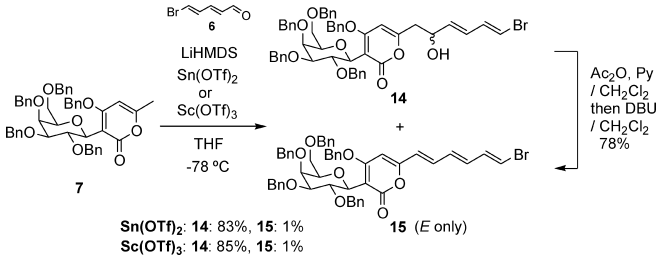


Chart 4. Application of the Methodology for the Preparation of the Triene **15**

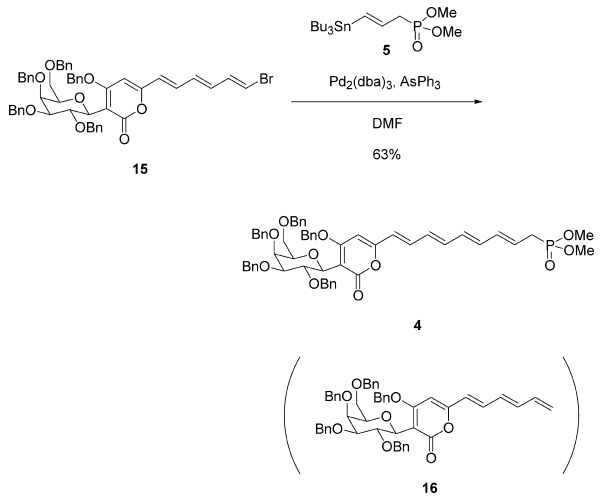


Chart 5. Stille Coupling of Triene **15** with Vinyl Stannane **5** which Contains Phosphonate

nate (Chart 5). Although the Stille coupling of **15** with vinyl stannane **5** did not proceed in the presence of $Pd(PPh_3)_4$ as catalyst precursor, desired coupling product **4** was obtained in 42% yield and reductive product **16** in 12% yield in the presence of $Pd_2(dba)_3$. When $AsPh_3$ was added in the reaction mixture, the coupling product was obtained in 63% yield without accompanying an undesired **16**.

In conclusion, we found that the aldol-type reaction of carbohydrate-bearing pyrone with aldehyde proceeded by the addition of $Sn(OTf)_2$ or $Sc(OTf)_3$. Using a combination of this methodology, followed by stepwise dehydration reaction and stille coupling, we were able to achieve the synthesis of a key intermediate **4**. Further investigation toward the total synthesis of D8646-2-6 (**1**) is currently in progress.

Experimental

All moisture-sensitive reactions were carried out under an atmosphere of argon in oven-dried glassware and the solvents were freshly distilled. All reactions were monitored by TLC, which was carried out on 0.25 mm Silica Gel 60 F_{254} plates (E. Merck) and spots were visualized with UV light. Column chromatography utilized PSQ 100B (Fuji Silysia Co., Ltd., Japan). The NMR spectra (^{1}H, ^{13}C, two-dimensional ^{1}H–^{1}H COSY, HMQC, HMBC and NOESY) were obtained on a Bruker 600 MHz spectrometer (Avance DRX-600) or Bruker 400 MHz spectrometer (Avance DRX-400), using $CDCl_3$ solutions, unless otherwise noted. Chemical shifts for ^{1}H-NMR were expressed in parts per million (ppm) downfield from tetramethylsilane (δ) in deuteriochloroform as internal standard or in ppm relative to the centerline of a quintet at 2.54 ppm for dimethylsulfoxide in duteriodimethylsulfoxide and coupling constants (J) are in hertz (Hz). Optical rotations were recorded using $CHCl_3$ or MeOH as solvents on a JASCO P-1030 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-410 spectrometer using NaCl plate (neat). Mass spectra were recorded on an Applied Biosystems mass spectrometer (API QSTAR pulsar i) under conditions as High resolution, using poly(ethylene glycol) as internal standard.

4-Benzyloxy-6-methyl-3-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)-2-pyrone (7) To a stirred solution of C^3-galactopyranosyl 4-hydroxy-2-pyrone (10.13 g, 15.6 mmol), BnOH (2.5 ml, 24.1 mmol), and PPh_3 (5.3 g, 20.1 mmol) in dry THF (50 ml) under argon was added DIAD (11.0 ml, 40% solution in toluene, 24.1 mmol) at room temperature. After stirred for 2 h, the reaction mixture was evaporated *in vacuo.* The residue was purified by flash chromatography (silica gel, 2 : 1 hexane/EtOAc) to afford corresponding benzyl ether (**7**) (9.9 g, 86%) as colorless foam.

Rf 0.38 (1 : 1 hexane–EtOAc). $[\alpha]_D^{24}$ −48.2° (c=0.38, $CHCl_3$). IR (neat) cm^{-1}: 2873, 1702, 1645, 1561, 1453, 1215, 1090, 756. ^{1}H-NMR (600 MHz, DMSO-d_6, mixture of rotamers): δ 2.19 (1.5H, s), 2.20 (1.5H, s), 3.45—3.56 (2H, m), 3.67—3.75 (2H, m), 4.06 (1H, dd, J=2.4, 9.5 Hz), 4.24 (0.5H, d, J=9.9 Hz), 4.38—4.41 (1.5H, m), 4.44—4.49 (2H, m), 4.54—4.57 (1.5H, m), 4.59 (0.5H, d, J=12.1 Hz), 4.65 (0.5H, d, J=11.9 Hz), 4.65 (0.5H, d, J=12.1 Hz), 4.74 (0.5H, d, J=10.9 Hz), 4.76 (0.5H, d, J=11.0 Hz), 4.78 (0.5H, d, J=12.1 Hz), 4.78 (0.5H, d, J=11.9 Hz), 4.84 (0.5H, d, J=12.1 Hz), 4.85 (0.5H, d, J=11.8 Hz), 5.07 (0.5H, d, J=13.1 Hz), 5.22 (0.5H, d, J=13.1 Hz), 5.27 (0.5H, d, J=12.8 Hz), 5.32 (0.5H, d, J=12.8 Hz), 6.51 (0.5H, S), 6.53 (0.5H, S), 7.00—7.43 (25H, m). ^{13}C-NMR (100 MHz, DMSO-d_6, mixture of rotamers): δ 19.9, 20.0, 69.3, 70.1, 70.6, 71.3, 72.1, 72.5, 72.6, 73.7, 73.9, 74.0, 74.0, 74.5, 74.6, 75.0, 75.7, 76.9, 77.1, 84.4, 84.5, 96.1, 96.5, 100.9, 101.2, 127.1, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8, 127.9, 128.1, 128.1, 128.1, 128.2, 128.3, 128.3, 128.4, 128.7, 135.9, 136.0, 138.3, 138.9, 139.0, 139.0, 139.3, 139.3, 139.4, 161.7, 163.3, 164.2, 164.5, 168.2, 168.8. HR-ESI-MS m/z: Calcd for $C_{47}H_{46}O_8Na$ ([M+Na]$^+$) 761.3084, Found 761.3089.

Aldol Condensation of Pyrone Moiety 7 with 2*E*,4*E*-Hexa-2,4-dienal. $Sn(OTf)_2$ Mediated Aldol Reaction To a stirred solution of pyrone moiety **7** (2.0 g, 3.00 mmol) in dry THF (30 ml) at −78 °C under argon was dropwise added LiHMDS (9.0 ml, 1.0 M solution in THF, 9.00 mmol). After being stirred for 30 min, 2*E*,4*E*-hexa-2,4-dienal (0.7 ml, 6.0 mmol) and $Sn(OTf)_2$ (1.2 g, 2.8 mmol) was added successively at −78 °C. After the reaction mixture was stirred for additional 2.5 h, it was allowed to warm up to the room temperature. Then it was poured into saturated aqueous NH_4Cl. After the mixture was filtered through Celite®, the product was extracted with EtOAc. The organic phase was washed with 1 N HCl, and it was neutralized with saturated aqueous $NaHCO_3$. The organic extract was washed with Brine, dried with Na_2SO_4, then filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 2 : 1 benzene/Et_2O) to afford aldol adduct **8** (1.48 g, 69%) as a pearl yellow foam and triene **11** (0.09 g, 3%) as a yellow foam.

$Sc(OTf)_3$ mediated aldol reaction was carried out with the same procedure described above to afford aldol adduct **8** (54%) and triene **11** (20%).

(1*E*,3*E*,5*E*)-1-{4-Benzyloxy-3-(2,3,4,6,-tetra-*O*-benzyl-β-D-galactopyranosyl)-2-pyrone}-1,3,5-heptatriene (11) To a stirred solution of aldol adduct **8** (0.46 g, 0.55 mmol) in dry CH_2Cl_2 (6 ml) at room temperature under argon was added acetic anhydride (0.26 ml, 2.75 mmol), pyridine (0.23 ml, 2.75 mmol), and 4-dimethylamino pyridine (0.007 g, 0.05 mmol). After being stirred for 2 h, the reaction medium was poured into saturated aqueous NH_4Cl and the product was extracted with CH_2Cl_2 (100 ml). The organic extract was washed with Brine, dried with Na_2SO_4, then filtered, and evaporated *in vacuo*. The residue was through short plug of silica gel to remove pyridine and evaporated *in vacuo*. The crude product was used in the next step without further purification.

To a cold (0 °C) solution of crude product in 50 ml of CH_2Cl_2 was added DBU (0.12 ml, 0.83 mmol). After being stirred for 3 h, the reaction medium was poured into saturated aqueous NH_4Cl and the product was extracted with CH_2Cl_2 (150 ml). The organic extract was washed with Brine, dried with Na_2SO_4, then filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 4 : 1 hexane/EtOAc) to afford triene **11** (0.33 g, 74% over 2 steps) as a yellow foam.

The stereochemistry of compound **11** was determined by ^{1}H-NMR analysis in DMSO-d_6 at 100 °C.

Rf 0.46 (2 : 1 hexane–EtOAc). $[\alpha]_D^{24}$ −10.8°(c=0.35, $CHCl_3$). IR (neat) cm^{-1}: 2927, 1701, 1636, 1540, 1097. ^{1}H-NMR (600 MHz, DMSO-d_6, mixture of rotamers): δ 1.79—1.83 (3H, m), 3.48—3.58 (2H, m), 3.69—3.76 (2H, m), 4.07—4.08 (1H, m), 4.26 (0.5H, d, J=11.6 Hz), 4.40 (0.5H, d, J=11.9 Hz), 4.41 (0.5H, d, J=11.9 Hz), 4.43 (0.5H, d, J=11.7 Hz), 4.47—4.51 (2H, m), 4.57—4.60 (1.5H, m), 4.60 (0.5H, d, J=12.1 Hz), 4.66 (0.5H, d, J=11.9 Hz), 4.67 (0.5H, d, J=12.1 Hz), 4.75—4.80 (1.5H, m), 4.80 (0.5H, d, J=12.0 Hz), 4.85 (0.5H, d, J=12.1 Hz), 4.87 (0.5H, d, J=12.1 Hz), 5.10 (0.5H, d, J=13.1 Hz), 5.24 (0.5H, d, J=13.1 Hz), 5.30 (0.5H, d, J=12.7 Hz),

5.35 (0.5H, d, J=12.7 Hz), 5.92—5.97 (1H, m), 6.20—6.26 (1H, m), 6.27 (0.5H, d, J=15.2 Hz), 6.28 (0.5H, d, J=15.4 Hz), 6.32—6.37 (1H, m), 6.63—6.67 (1H, m), 6.64 (0.5H, s), 6.66 (0.5H, s), 7.01—7.45 (26H, m). ^{13}C-NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 18.6, 68.7, 69.1, 70.3, 70.8, 72.3, 72.5, 72.8, 73.4, 73.8, 74.0, 74.2, 74.4, 74.6, 75.0, 75.5, 75.7, 77.2, 77.6, 85.3, 85.5, 95.7, 96.4, 102.9, 103.6, 120.9, 126.6, 127.1, 127.4, 127.4, 127.5, 127.5, 127.6, 127.7, 127.9, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.8, 131.4, 134.4, 135.3, 135.3, 137.1, 137.3, 138.0, 138.0, 138.7, 139.0, 139.2, 139.3, 139.5, 139.5, 139.6, 159.3, 160.3, 161.5, 164.3, 167.6, 168.3. HR-ESI-MS m/z: Calcd for $C_{53}H_{52}O_8Na$ ([M+Na]$^+$) 839.3554, Found 839.3524.

(1*E*,3*E*,5*E*)-6-Bromo-1-{4-benzyloxy-3-(2,3,4,6,-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-pyrone}-1,3,5-hexatriene (15) The aldol reaction of pyrone moiety **7** with aldehyde **6** was carried out with the same procedure described above.

The stereochemistry of compound **15** was determined by ^{1}H-NMR analysis in DMSO-d_6 at 100 °C.

Rf 0.4 (15 : 1 benzene–CH_3CN). $[\alpha]_D^{24}$ −5.1° (c=1.38, $CHCl_3$); IR (neat) cm^{-1}: 3060, 3029, 2869, 1701, 1536, 1357, 1098, 997, 744, 699. ^{1}H-NMR (600 MHz, DMSO-d_6, mixture of rotamers): δ 3.45—3.56 (2H, m), 3.68—3.74 (2H, m), 4.06 (1H, m), 4.25 (0.5H, d, J=11.6 Hz), 4.37—4.50 (4H, m), 4.55—4.60 (2H, m), 4.65 (0.5H, d, J=12.2 Hz), 4.65 (0.5H, d, J=12.2 Hz), 4.73—4.79 (2H, m), 4.84 (0.5H, d, J=12.9 Hz), 4.87 (0.5H, d, J=12.7 Hz), 5.09 (0.5H, d, J=13.1 Hz), 5.22 (0.5H, d, J=13.1 Hz), 5.28(0.5H, d, J=12.7 Hz), 5.33 (0.5H, d, J=12.7 Hz), 6.37 (0.5H, d, J=15.3 Hz), 6.38 (0.5H, d, J=15.3 Hz), 6.53 (0.5H, dd, J=11.0, 14.9 Hz), 6.54 (0.5H, dd, J=10.9, 14.8 Hz), 6.62 (1H, dd, J=10.8, 14.8 Hz), 6.70 (0.5H, s), 6.71 (0.5H, s), 6.85 (0.5H, d, J=13.4 Hz), 6.86 (0.5H, d, J=13.4 Hz), 6.95 (0.5H, dd, J=10.8, 13.4 Hz), 6.96 (0.5H, dd, J=10.6, 13.3 Hz), 6.99—7.43 (26H, m). ^{13}C-NMR (100 MHz, DMSO-d_6, mixture of rotamers): δ 69.3, 70.2, 70.7, 71.3, 72.1, 72.5, 72.6, 73.1, 73.9, 74.0, 74.1, 74.5, 74.6, 75.0, 75.7, 76.9, 77.1, 84.3, 84.5, 97.7, 98.2, 102.9, 103.2, 113.3, 113.4, 124.0, 127.2, 127.2, 127.3, 127.3, 127.4, 127.4, 127.5, 127.5, 127.6, 127.6, 127.7, 127.9, 127.9, 128.1, 128.1, 128.1, 128.2, 128.3, 128.4, 128.4, 128.7, 132.2, 132.3, 135.0, 135.2, 135.5, 135.6, 135.8, 136.0, 137.5, 138.3, 138.9, 139.0, 139.0, 139.2, 139.3, 139.4, 158.5, 159.3, 160.6, 163.4, 167.8, 168.3. HR-ESI-MS m/z: Calcd for $C_{52}H_{49}O_8NaBr$ ([M+Na]$^+$) 903.2508, Found 903.2509.

(1*E*,3*E*,5*E*,7*E*)-9-(Dimethoxyphosphinyl)-1-{4-benzyloxy-3-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-pyrone}-1,3,5,7-nonatetraene (4) To a stirred solution of vinyl stannane **5** (0.064 g, 0.145 mmol) and vinyl bromide **15** (0.064 g, 0.073 mmol) in DMF (1.0 ml) was added $Pd_2(dba)_3$ (0.001 g, 0.001 mmol) and $AsPh_3$ (0.022 g, 0.073 mmol) successively. The resultant mixture was stirred for 30 min at 70 °C. Water was added to the reaction mixture and extracted with AcOEt. The organic extract was washed with Brine, dried with Na_2SO_4, then filtered, and evaporated *in vacuo.* After the residue was purified by short plug of silica gel, the resultant oil was purified by chromatography (preparative TLC; silica gel, AcOEt) in the dark room with a red light to afford coupling product **4** (0.043 g, 63%) as yellow oil.

Rf 0.2 (AcOEt). $[\alpha]_D^{21}$ −6.37° (c=0.472, MeOH). IR (neat) cm^{-1}: 2254, 2128, 1661, 1448, 1410, 1025. ^{1}H-NMR (600 MHz, DMSO-d_6, mixture of rotamers): δ 2.79 (1H, d, J=22.9 Hz), 2.80 (1H, d, J=22.9 Hz), 3.45—3.56 (2H, m), 3.61 (1.5H, s), 3.61 (1.5H, s), 3.63 (1.5H, s), 3.63 (1.5H, s), 3.66—3.74 (2H, m), 4.05—4.06 (1H, m), 4.24 (0.5H, d, J=11.6 Hz), 4.38 (0.5H, d, J=12.0 Hz), 4.39 (0.5H, d, J=12.0 Hz), 4.41 (0.5H, d, J=11.9 Hz), 4.45 (0.5H, d, J=11.9 Hz), 4.46—4.49 (1H, m), 4.47 (0.5H, d, J=12.3 Hz), 4.55—4.60 (2H, m), 4.64 (0.5H, d, J=11.9 Hz), 4.65 (0.5H, d, J=12.1 Hz), 4.73—4.79 (2H, m), 4.83 (0.5H, d, J=13.0 Hz), 4.85 (0.5H, d, J=13.0 Hz), 5.09 (0.5H, d, J=13.1 Hz), 5.22 (0.5H, d, J=13.1 Hz), 5.28 (0.5H, d, J=12.7 Hz), 5.33 (0.5H, d, J=12.7 Hz), 5.69—5.76 (1H, m), 6.29 (0.5H, d, J=15.2 Hz), 6.30 (0.5H, d, J=15.1 Hz), 6.32—6.39 (2H, m), 6.43—6.51 (2H, m), 6.65 (0.5H, s), 6.66 (0.5H, s), 6.71 (1H, dd, J=11.1, 14.5 Hz), 6.99—7.43 (26H, m). ^{13}C-NMR (100 MHz, DMSO-d_6, mixture of rotamers): δ 28.9 (d, J=135 Hz), 52.5, 52.6, 69.3, 70.2, 70.6, 71.3, 72.1, 72.5, 72.6, 73.8, 74.0, 74.1, 74.5, 74.6, 75.0, 75.7, 76.9, 77.1, 84.4, 84.5, 97.2, 97.7, 102.5, 102.8, 122.4, 125.7, 125.8, 127.2, 127.3, 127.4, 127.5, 127.5, 127.5, 127.6, 127.7, 127.7, 127.9, 128.0, 128.1, 128.1, 128.2, 128.3, 128.4, 128.4, 128.4, 128.7, 131.6, 131.6, 132.0, 132.1, 134.7, 134.8, 135.8, 135.8, 135.9, 136.0, 138.3, 138.3, 138.9, 139.0, 139.0, 139.1, 139.2, 139.2, 139.3, 139.4, 158.9, 159.7, 160.8, 163.6, 167.9, 168.4. HR-ESI-MS m/z: Calcd for $C_{57}H_{59}O_{11}NaP$ ([M+Na]$^+$) 973.3687, Found 973.668.

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25) Since all protective groups are desirable to be deprotected in one operation at the final step, benzyl group was chosen as the protective group.
26) Direct *C*-glycosylation of 4-benzyloxy-6-methyl pyrone gave only α-*C*-glycoside in low yield.
27) Protection of the hydroxyl group of pyrone moiety proceeded smoothly to afford the corresponding benzyl ether **7** in 86% yield as a mixture of rotamers under Mitsunobu conditions (DEAD, PPh_3 and BnOH).The ^{1}H-NMR ($CDCl_3$ at 25 °C) of benzyl protected pyrone **7** was rather complex, and it seemed to be a mixture of two isomers. However, the ^{1}H-NMR of **7** in DMSO-d_6 at 80 °C was gathered and bundled to single isomer. That means that C^3-β-galactopyranosyl-4-benzyloxy-6-methylpyrone might exist as a mixture of rotamer at 25 °C. In contrast, a rotamer was not observed in the case of the corresponding α-isomer.

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