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Total synthesis of Daphnodorin A

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ABSTRACT

A total synthesis of Daphnodorin A, a member of the Daphnodorins, was accomplished. Key features of the synthetic strategy include construction of 2-substituted-3-functionalized benzofuran via intramolecular Heck reaction and a mild Barton–McCombie deoxygenation process mediated by triethylborane. The total synthesis provided Daphnodorin A in 19.7% or 5.6% overall yield over 7 or 15 steps.

1. Introduction

The biflavonoid Daphnodorin A was originally isolated from the root of *Daphne odora Thunb*[1] and shown to exhibit notable biological properties, including α-glucosidase inhibitory activity (3 μM),[2] gastric H^+, K^+-ATPase inhibitory activity (4.5 μM),[3] anti-HIV-1 activity,[4] antifungal and insecticidal activities,[5] 12-lipoxygenase and cyclooxygenase inhibitory activities,[6] human chymase-dependent angiotensin II inhibitory activity[7] and antitumour properties.[8] The Daphnodorins, and the related biflavonoids known as the Genkwanols[9] and Daphnogirins,[10] constitute the characteristic constituents from *Thymelaeaceae*, which contain a 2,3-functionalized benzofuran[11] moiety (Fig. 1). Very recently, We reported an efficient synthetic approach to 2-substituted-3-functionalized benzofurans that we have applied in the enantioselective total synthesis of Daphnodorin B,[12] an analogue of Daphnodorin A bearing a hydroxyl group at C-3 position. We reasoned that an enantioenriched flavan-3-ol could be used as a starting point for a distinct approach toward the synthesis of Daphnodorin A.

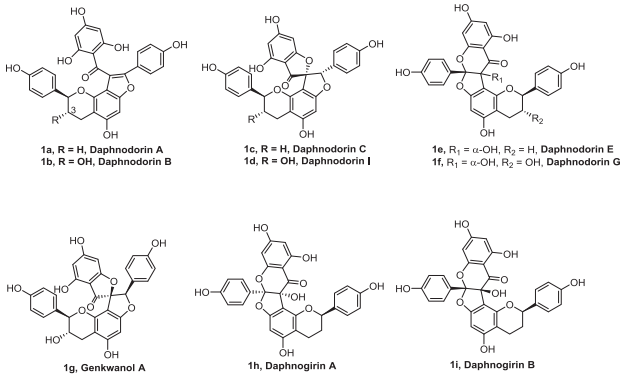

Fig. 1. Selected Daphnodorins and their analogues.

2. Results and discussion

2.1. Synthesis of Daphnodorin A from a known flavan-3-ol (approach I)

We began our synthetic efforts with flavan-3-ol **2** (Scheme 1), which was accessed in 47% total yield from 2,4,6-trihydroxyacetophenone.[12] Deoxygenation of **2** was effected by means of the Barton protocol,[13] yielding the deoxygenated product **3** in the 80% yield. 8-Iodo derivative **4** was readily prepared in 99% yield by

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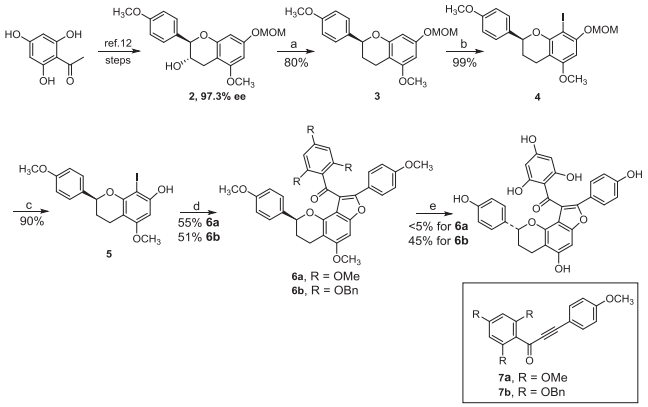


Reagents and Conditions: a) i. NaH, CS_2, MeI, DMF, 0 ºC to rt; ii. *n*-Bu_3SnH, AIBN, toluene, 105 ºC/Ar. b) NIS, DMF, 0 ºC to rt. c) 3 M HCl, MeOH, 50 ºC. d) K_3PO_4, CH_3CN, 75 ºC, then $Pd(AcO)_2$, PPh_3, Ag_2CO_3, CH_3CN, 115 ºC/Ar. e) BBr_3/DCM, −78 to −10 ºC, overnight

Scheme 1. Synthesis of Daphnodorin A (approach I).

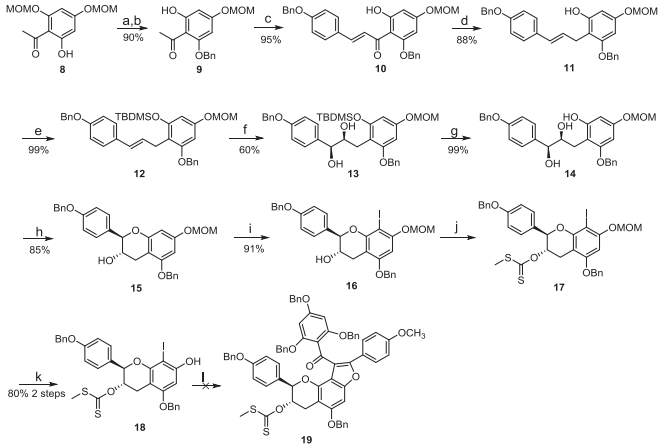
reacting **3** with 1 equiv of recrystallized NIS[14] in DMF. Deprotection of methoxymethyl (MOM) ether with 3 M HCl afforded *o*-iodophenol **5**, which underwent conjugate addition and subsequent intramolecular Heck reaction with ynones (**7a** and **7b**) to generate the fully protected Daphnodorin A (**6a** and **6b**). Deprotection of **6b** with 1 M BBr_3 furnished Daphnodorin A whose spectral data were in complete agreement with those reported in literature[2,15] except optical rotation data ($[\alpha]_D^{20}$ −6.6 (*c* 0.6, MeOH); lit.[16] value $[\alpha]_D^{20}$ −59.2 (*c* 1.14, MeOH)), which indicated that a racemization occurred under the reaction conditions. We speculate that flavan with a single chiral centre may be prone to epimerization under harsh conditions.

Actually, **4**, which exhibited an $[\alpha]_D^{20}$ of −59.6 (*c* 0.37, CH_3CN) was heated to 75 °C in MeOH for 4 h gave an $[\alpha]_D^{20}$ of only −39.6 (*c* 0.3, CH_3CN). The ee value was 83% for compound **5**, 9% for compound **6a**, and 6.5% for compound **6b**, respectively. These finding disqualified **3** as an intermediate in a controlled Daphnodorin A synthesis and prompted us to turn to the route eliminating the 3-OH in a late stage and employing benzyl as the protecting group for phenolic hydroxyls.

2.2. Synthesis of Daphnodorin A (approach II)

As illustrated in Scheme 2, the route started by a benzylation of 2,4-dimethoxymethyl 6-hydroxy phenylacetone **8**, followed by deprotection of the MOM group at the *ortho* position and condensation with 4-(benzyloxy) benzaldehyde to give the chalcone **10** in 95% yield. Decarbonylation of **10** using an improved methodology of Minami's method we reported[17] provided the excellent 1,2-reduction selectivity and yield of **11**. The phenol was protected as the TBDMS ether and then subjected to asymmetric dihydroxylation with AD-mix-α, affording the TBS protected diol **13** in 60% yield (35% starting material was recovered) and 90.8% ee. De-silylation of and subsequent cyclization under the orthoformate/acidic conditions[18] followed by base hydrolysis of the formate ester gave the protected flavan-3-ol **15**. 8-Iodo derivative **16** was readily prepared by reacting **15** with NIS, and its free hydroxyl group was protected as Barton–McCombie precursor xanthate by a NaH/CS_2/MeI system. Deprotection of MOM ether with 2 M HCl afforded *o*-iodophenol **18**. Unfortunately, subsequent conjugate addition and intramolecular Heck cyclization failed to yield **19**, a complex mixture was obtained, which might be attributed to the catalyst deactivation from sulfur poisoning.

Thus, the free hydroxyl group of **16** was protected by *p*-methoxybenzyl (PMB) ether. Several conditions were examined for selective

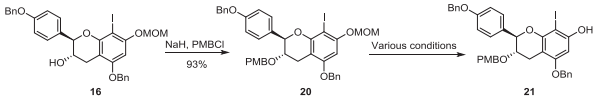


Reagents and Conditions: a) BnBr, K_2CO_3, TBAB, acetone, rt. b) 1 M HCl, MeOH, rt. c) NaH, DMF, 0 ºC, then 4-(benzyloxy)benzaldehyde, rt. d) ClCOOEt, TEA, THF, 0 ºC, then $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, −5 ºC. e) TBDMSCl, imidazole, dry DMF. f) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH:H_2O 1:1, 0 ºC. g) TBAF, THF, rt. h) $CH(OEt)_3$, PPTS, $ClCH_2CH_2Cl$, rt to 55 ºC, then K_2CO_3, MeOH, rt. i) NIS, DMF, 0 ºC to rt. j) NaH, CS_2, MeI, DMF. k) 2 M HCl, MeOH, THF, 50 ºC. l) **7b**, K_3PO_4, CH_3CN, 75 ºC, then $Pd(AcO)_2$, PPh_3, Ag_2CO_3, CH_3CN, 115 ºC/Ar.

Scheme 2. Synthesis of iodophenol **18**.

deprotection of MOM ether. Exposure of **20** to HOAc, TFA, $NbCl_5$,[19] or $ZnBr_2$[20] resulted in deprotection of PMB ether and benzyl ether (Table 1, entry 1–4). The MOM ether was successfully cleaved by HCl, along with iodide eliminated byproduct (Table 1, entry 5–7). After varying other parameters, we were delighted to find that treatment of **20** with 3 M HCl in MeOH and THF at 40 °C under Ar (in dark) furnished the desired *o*-iodophenol **21** in 85% yield (Table 1, entry 8).

Table 1
Deprotection of intermediate **20**

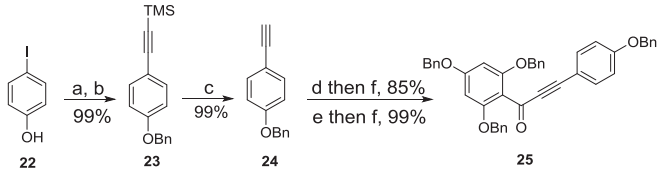


Entry	Deprotection conditions	Yield/%[a]
1	HOAc/THF/*i*-PrOH, 50 °C	0
2	TFA/DCM, 0–20 °C	0[b]
3	$NbCl_5/CH_3CN$, 20 °C	0[b]
4	$ZnBr_2$, EtSH/DCM, 0–20 °C	0[c]
5	1 M HCl/MeOH/THF=1:1:1, 60 °C	20(35[d])
6	1 M HCl/*i*-PrOH/THF=1:1:1, 50 °C	33(30[d])
7	3 M HCl/MeOH/THF=1:1:1, 40 °C	43(12[d])
8	3 M HCl/MeOH/THF=1:1:2, 40 °C/Ar, dark	85

[a] Isolated yield.
[b] PMB was removed.
[c] PMB and Bn were removed.
[d] PMB and iodide were removed.

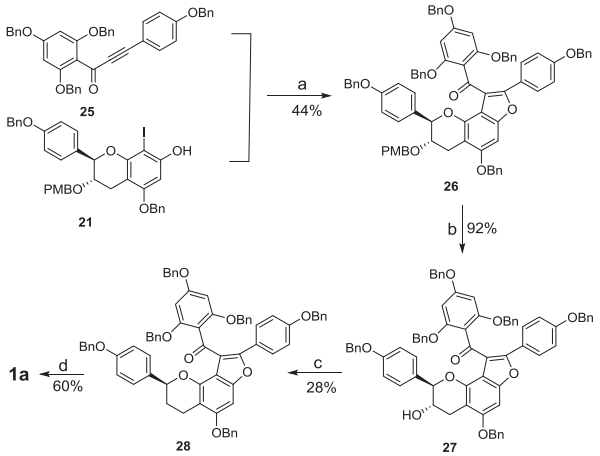
Synthesis of the ynone fragment **25** commenced with preparation of 4-(benzyloxy) phenylacetylene **24**,[21] prepared in three steps from the known iodophenol **22** (Scheme 3). **24** was transformed to alkynyl-metal reagents and underwent nucleophilic addition to aldehyde, followed by quantitative oxidization to ynone **25** by MnO_2.

Compound **21** underwent conjugate addition and subsequent intramolecular Heck reaction with ynone **25** to generate a fully protected Daphnodorin B **26**, which was treated with DDQ to remove the PMB group. Subsequent cleavage of the OH group via Barton-McCombie process[22] followed by debenzylation with BCl_3 furnished Daphnodorin A with an $[\alpha]_D^{20}$ of −6.9 (*c* 0.5, MeOH). We attributed that to the partial racemization of **28** under the Barton–McCombie reaction conditions since **27** was found to be optically stable under heating (Scheme 4).



Reagents and Conditions: a) BnBr, K_2CO_3, acetone, reflux. b) ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$, CuI, DIEA, THF, rt. c) K_2CO_3, MeOH, THF, rt. d) *n*-BuLi, THF, −78 °C, then 2,4,6-tri(benzyloxy) benzaldehyde. e) CH_2=CH_2MgBr, THF, rt–40 °C, then 2,4,6-tri(benzyloxy) benzaldehyde, rt. f) MnO_2, DCM, rt.

Scheme 3. Synthesis of ynone **25**.

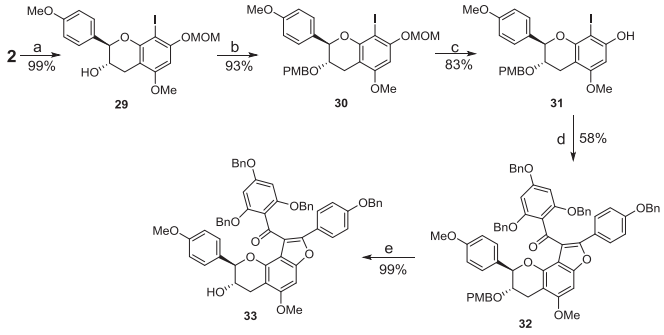


Reagents and Conditions: a) K_3PO_4, CH_3CN, 75 °C, then $Pd(AcO)_2$, PPh_3, Ag_2CO_3, CH_3CN, 115 °C, Ar. b) DDQ, DCM:H_2O 10:1, rt. c) i. PhOC(S)OCl, pyridine, DCM, 0 to 30 °C or NaH, CS_2, MeI, DMF. ii. *n*-Bu_3SnH, AIBN, toluene, 100 °C. d) BCl_3, DCM, −5 °C.

Scheme 4. Synthesis of Daphnodorin A (approach II).

2.3. Deoxygenated of xanthates under mild conditions (optimized approach II)

Then we tried to explore a mild and efficient deoxygenation condition. The enantioenriched **29** was employed to construct a protected Daphnodorin B **33** (Scheme 5), whose free hydroxyl group at C-3 was transformed into xanthate. Reduction of the xanthate by conventional *n*-Bu_3SnH/AIBN system gave the deoxygenated product **28** or **34** in less than 30% yield.

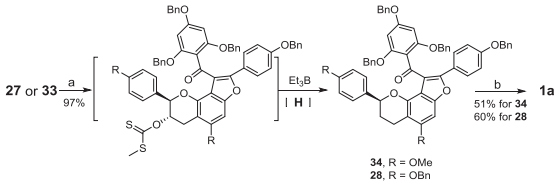


Reagents and Conditions: a) NIS, DMF, 0 °C to rt. b) NaH, PMBCl, DMF, 0 °C to rt. c) 3 M HCl/MeOH/THF = 1:1:2, 40 °C/Ar, dark. d) **25**, K_3PO_4, CH_3CN, 75 °C, then $Pd(AcO)_2$, PPh_3, Ag_2CO_3, CH_3CN, 115 °C/Ar. e) DDQ, DCM:H_2O 10:1, rt.

Scheme 5. Preparation of **33**.

John L. Wood[23] and Doo Ok Jang[24] discovered that water and MeOH could replace toxic metal hydrides as the source of hydrogen in trialkylborane-mediated variants of the Barton–McCombie process. In the event, a triethylborane (Et_3B)/air or O_2/MeOH or water system using toluene as the solvent was effective (Table 2, entry 1–4), while a higher yield was obtained using THF as the solvent (Table 2, entry 5–7). To our surprise, the transformation proved fruitful when it was conducted under Ar (Table 2, entry 6–7), which suggests that the liberation of the alkyl radical may also be resulted from a triethylborane-water complex.

Table 2
Reduction of xanthate intermediate



Entry	Deoxygenation conditions	Yield/(34/28, %)[c]
1	H_2O–Et_3B–air, toluene, 0 °C, 12 h	45/34
2	H_2O–Et_3B–O_2, toluene, rt, 12 h	53/47
3	MeOH–Et_3B–O_2, toluene, rt, 12 h	43/45
4	H_2O–MeOH–Et_3B–O_2, toluene, 0 °C, 12 h	46/41
5	H_2O–MeOH–Et_3B–O_2, THF, 0 °C, 12 h	59/55
6	MeOH–Et_3B, THF, rt/Ar, 4 h	71/63
7	H_2O–MeOH–Et_3B, THF, 0 °C/Ar, 2 h	88/85

[a] NaH, CS_2, MeI, DMF, 0 °C to rt.
[b] BBr_3, DCM, −70 °C to −5 °C or BCl_3, DCM, −10 °C.
[c] Isolated yield.

To prevent the partial racemization, freshly prepared **34** or **35** was immediately deprotected by BBr_3 or BCl_3 to produce **1a** ($[\alpha]_D^{20}$ −26.9 (*c* 0.13, MeOH)), whose enantioselectivity was improved from *er* 1:1 to *er* 2:1. The result showed that the single chiral centre of the fully protected Daphnodorin A may be prone to racemization under the mild conditions. In the future, a higher enantioselectivity may be obtained in a protecting-group-free synthesis manner.

In conclusion, we have achieved the total synthesis of Daphnodorin A in 15 linear steps and 5.6% overall yield (2:1 *er*) starting from 2,4-dimethoxymethyl 6-hydroxy phenylacetone or seven linear steps and 19.7% overall yield (2:1 *er*) starting from a known flavan-3-ol **2**. Key features of this synthesis include a construction of 2-substituted-3-functionalized benzofuran via intramolecular Heck reaction and a mild Barton–McCombie deoxygenation process mediated by triethylborane. Efforts are now focused on the synthesis and extended biological evaluation of other Daphnodorins. Results will be reported in due course.

3. Experimental section

3.1. General

All reactions were performed in dried tube and monitored by TLC to ensure the completion of the reaction. Nuclear magnetic resonance (NMR) spectra were recorded using TMS as the internal standard in DMSO-d_6, CD_3OD or $CDCl_3$ with a Bruker BioSpin GmbH spectrometer at 500 or 600 MHz. When peak multiplicities are reported, the following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets; ESI-MS was recorded on Agilent 1100 LC/MSD (70 eV) spectrometers. HRMS was recorded on a Waters Q-Tof micro. Melting points (mp) were determined by microscope melting point apparatus with aromatic temperature control system (XT4A). Flash column chromatography was performed by using silica gel (200–300 mesh). All

commercially available reagents were used without purification unless otherwise indicated and were purchased from standard chemical suppliers.

3.2. Experimental procedures and data of synthetic intermediates

*3.2.1. (S)-5-Methoxy-7-(methoxymethoxy)-2-(4-methoxyphenyl) chroman (**3**).* To 1.73 g (5.0 mmol) of **2** in 15 mL of DMF was added all at once 0.25 g (6.4 mmol) of NaH (60% in oil). The mixture was stirred with a powerful magnetic stirrer at rt (mild exotherm) for 10 min, and then it was immersed in a 10 °C water bath, 0.31 mL (5.0 mmol) of CS_2 was added in 5 min, and stirring at 10 °C was continued for 10 min. To the resulting yellow to amber suspension was added 0.32 mL (5.0 mmol) of MeI in 5 min. The reaction mixture was left at rt for 20 min and then dissolved in 40 mL of H_2O and 60 mL of EtOAc. The phases were separated, and the aqueous phase was extracted with 20 mL of EtOAc. The combined organic phases were washed with H_2O (3×40 mL), dried ($MgSO_4$) and concentrated to give the crude product. A stirred solution of the crude product in 80 mL of anhydrous toluene was heated to 105 °C under Ar, and a solution of 1.4 mL (5.1 mmol) of *n*-Bu_3SnH and 0.82 g (5.1 mmol) of AIBN in 40 mL of anhydrous toluene was slowly added over a period of 4 h. After stirring at 105 °C for 10 h, the reaction mixture was cooled and directly chromatographed on SiO_2 (1:15 EtOAc/petroleum ether(PE)) to yield 1.32 g (80% over two steps) of **3**.

Colourless glass, mp 101–103 °C; $[\alpha]_D^{20}$ +5.9 (*c* 0.31, CH_3CN); IR (KBr) ν_{max} 3349, 2996, 2953, 1599, 1556, 1441, 1020, 794 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.5 Hz, 2H), 6.89 (dd, *J*=2.0, 8.5 Hz, 2H), 6.27 (d, *J*=2.0 Hz, 1H), 6.16 (d, *J*=2.0 Hz, 1H), 5.11 (s, 2H), 4.90 (dd, *J*=2.0, 10.5 Hz, 1H), 3.79 (br s, 3H), 3.78 (br s, 3H), 3.45 (br s, 3H), 2.77–2.72 (m, 1H), 2.65–2.58 (m, 1H), 2.17–2.12 (m, 1H), 2.02–1.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 158.7, 157.0, 156.6, 134.0, 127.6 (2×C), 114.1 (2×C), 104.8, 96.9, 94.8, 92.7, 77.7, 56.2, 55.7, 55.5, 29.5, 19.7; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{23}O_5[M+H]^+$: 331.1540, found 331.1559.

*3.2.2. (S)-8-Iodo-5-methoxy-7-(methoxymethoxy)-2-(4-methoxyphenyl)chroman (**4**).* To a solution of **3** (0.66 g, 2 mmol) in 10 mL of anhydrous DMF was added 0.45 g (2 mmol) of recrystallized NIS at 0 °C. The mixture was stirred overnight, and a solution of 3 M $Na_2S_2O_3$ (20 mL) was added. The mixture was extracted with EtOAc (3×20 mL). The combined organic layer was washed with brine (25 mL) and H_2O (25 mL). The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure. This material was readily recrystallized from DCM/PE to afford the desired product (0.91 g, 99%).

White solid, mp 143–145 °C; $[\alpha]_D^{20}$ −59.6 (*c* 0.37, CH_3CN); IR (KBr) ν_{max} 3056, 2936, 1598, 1556, 1436, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J*=8.5 Hz, 2H), 6.90 (d, *J*=9.0 Hz, 2H), 6.35 (s, 1H), 5.21 (s, 2H), 5.07 (dd, *J*=2.0, 10.0 Hz, 1H), 3.79 (br s, 6H), 3.52 (br s, 3H), 2.72–2.59 (m, 2H), 2.25–2.19 (m, 1H), 1.96–1.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.9, 156.0, 154.8, 133.5, 127.1 (2×C), 121.6, 114.0 (2×C), 106.2, 95.6, 91.9, 78.0, 68.7, 56.6, 55.8, 55.4, 29.4, 19.5; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{22}IO_5[M+H]^+$: 457.0506, found 457.0515.

*3.2.3. (S)-8-Iodo-5-methoxy-2-(4-methoxyphenyl)chroman-7-ol (**5**).* A solution of **4** (456 mg, 1 mmol) in 20 mL MeOH was added 3 M HCl (3 mL) and stirred at 55 °C for 3 h. The reaction was quenched by the addition of water and extracted with EtOAc (3×120 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on a silica gel column chromatography (5:1 PE/EtOAc) to afford **5** (371 mg, 90%).

Colourless solid, mp 123–124 °C; 83% ee (determined by HPLC on a CHIRALPAK® IA column using *n*-hexane/isopropanol=85/15 as eluent); IR (KBr) ν_{max} 3004, 2959, 1714, 1599, 1556, 1423, 1363, 1222, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J*=8.5 Hz, 2H), 6.91 (d, *J*=8.5 Hz, 2H), 6.26 (s, 1H), 5.39 (s, 1H), 5.05 (dd, *J*=2.5, 10.0 Hz, 1H), 3.80 (br s, 3H), 3.78 (br s, 3H), 2.72–2.58 (m, 2H), 2.24–2.19 (m, 1H), 1.96–1.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 159.3, 154.6, 154.0, 133.5, 127.2 (2×C), 114.0 (2×C), 104.4, 90.9, 78.3, 67.1, 55.8, 55.5, 29.5, 19.4; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}O_4I[M+H]^+$: 413.0244, found 413.0254.

3.2.4. General procedure for the cyclization reactions. To a solution of *o*-iodophenol (0.25 mmol) and ynone (0.38 mmol) in CH_3CN (2.0 mL) was added K_3PO_4 (0.25 mmol), and then the reaction mixture was heated until the reaction reached to completion. After cooling, the reaction mixture was diluted with water (15 mL), and extracted with EtOAc (2×15 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash silica gel column chromatography (5:1 PE/EtOAc). A mixture of the conjugate addition intermediate (0.25 mmol), $Pd(OAc)_2$ (5.7 mg, 0.025 mmol), PPh_3 (13 mg, 0.05 mmol), Ag_2CO_3 (55 mg, 0.25 mmol), and dry CH_3CN (8.0 mL) was stirred at 115 °C for 15 h under Ar atmosphere. The reaction mixture was cooled to rt, diluted with water (15 mL), and extracted with EtOAc (2×15 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under vacuo. The crude product was chromatographed on silica gel (1:8 EtOAc/PE) to give the title compound compound as characterization.

*3.2.4.1. (S)-(5-Methoxy-2,8-bis(4-methoxyphenyl)-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl)(2,4,6-trimethoxyphenyl)methanone (**6a**).* 55% yield, yellow viscous solid, $[\alpha]_D^{20}$ −38.8 (*c* 0.25, CH_3CN); 9% ee (determined by HPLC on a CHIRALPAK® IA column using *n*-hexane/isopropanol=75/25 as eluent); IR (KBr) ν_{max} 3250, 1618, 1516, 1433, 1066 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J*=9.0 Hz, 2H), 7.21 (d, *J*=8.5 Hz, 2H), 6.90 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=9.0 Hz, 2H), 6.73 (s, 1H), 5.97 (s, 2H), 4.99 (dd, *J*=2.8, 8.8 Hz, 1H), 3.86 (br s, 3H), 3.80 (br s, 3H), 3.77 (br s, 3H), 3.73 (br s, 3H), 3.49 (br s, 6H), 2.72–2.66 (m, 1H), 2.60–2.54 (m, 1H), 2.16–2.11 (m, 1H), 2.00–1.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 164.2, 161.6, 161.0, 159.9, 157.4, 154.6, 153.5, 149.8, 134.8, 129.9, 127.8, 124.3, 121.4, 115.0, 114.5, 114.4, 111.8, 106.7, 91.9, 87.0, 77.3, 56.3, 56.2, 55.8, 55.7, 55.9, 30.7, 19.5; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{35}O_9[M+H]^+$: 611.2276, found 611.2270.

*3.2.4.2. (S)-(5-Methoxy-2,8-bis(4-methoxyphenyl)-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl)(2,4,6-tris(benzyloxy)phenyl)methanone (**6b**).* 51% yield, yellow viscous solid, $[\alpha]_D^{20}$ −45.3 (*c* 0.36, CH_3CN); 6.5% ee (determined by HPLC on a CHIRALPAK® IA column using *n*-hexane/isopropanol=75/25 as eluent); IR (KBr) ν_{max} 3268, 1615, 1528, 1399, 1078, 989 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J*=9.0 Hz, 2H), 7.39–7.31 (m, 5H), 7.22–7.16 (m, 5H), 7.06–7.05 (m, 5H), 7.00 (d, *J*=8.5 Hz, 2H), 6.73 (d, *J*=8.5 Hz, 2H), 6.64 (d, *J*=9.0 Hz, 2H), 6.55 (s, 1H), 5.92 (s, 2H), 4.87 (d, *J*=3.0 Hz, 2H), 4.65 (br s, 5H, overlapped), 3.85 (br s, 3H), 3.76 (br s, 3H), 3.61 (br s, 3H), 2.62–2.58 (m, 2H), 1.98–1.93 (m, 1H), 1.88–1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 161.9, 160.0, 159.8, 158.8, 156.4, 154.2, 153.8, 149.1, 136.8, 136.6, 134.3, 129.7, 128.8, 128.4, 127.7, 127.6, 127.1, 127.0, 123.5, 120.7, 115.1, 113.7, 113.5, 110.9, 105.9, 93.1, 86.4, 76.7, 70.4, 70.1, 55.9, 55.5, 55.4, 29.5, 18.9; HRMS (ESI): *m*/*z* calcd for $C_{54}H_{47}O_9[M+H]^+$: 839.3215, found 839.3219.

*3.2.5. 1-(2-(Benzyloxy)-6-hydroxy-4-(methoxymethoxy)phenyl) ethan-1-one (**9**).*[25] To a mixture of 2,4-bis(methoxymethoxy)-6-hydroxy phenylacetone (5.12 g, 20 mmol) and anhydrous potassium carbonate (2.8 g, 21 mmol) in dry acetone (100 mL) was added BnBr (3.4 g, 20 mmol) at rt. After stirring at rt for 10 min, TBAB

(2.3 g, 7 mmol) was added, and the resulting mixture was stirred at rt for 20 h. The resulting mixture was quenched by addition of water (200 mL) at 0 °C and the aqueous layer was extracted with EtOAc (3×250 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to furnish a white residue, which was added to a solution of MeOH (100 mL) and 1 M HCl (5.0 mL) at rt. After stirring at 30 °C for 12 h, the resulting mixture was cooled to room temperature, filtered and washed with MeOH (100 mL) to afford **9** (5.4 g, 90%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.36 (m, 5H), 6.23 (d, J=2.0 Hz, 1H), 6.13 (d, J=2.0 Hz, 1H), 5.17 (s, 2H), 5.08 (s, 2H), 3.47 (br s, 3H), 2.55 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 168.1, 164.5, 163.1, 136.6, 129.7, 129.5, 129.0, 107.8, 97.6, 95.0, 93.4, 72.1, 57.4, 34.4; ESI-MS: m/z 325.1 $[M+Na]^+$.

*3.2.6. (E)-1-(2-(Benzyloxy)-6-hydroxy-4-(methoxymethoxy)phenyl)-3-(4-(benzyloxy)phenyl)prop-2-en-1-one (**10**).* To a suspension of NaH (1.05 g, 25 mmol, 60% dispersion in oil) in dry DMF (30 mL) was slowly added **9** (3.02 g, 10 mmol). The resulting mixture was stirred at this temperature for 15 min. A solution of 4-(benzyloxy) benzaldehyde (2.12 g, 10 mmol) in DMF (20 mL) was added over a period of 10 min to the reaction mixture via an addition funnel. The resulting red-brown solution was stirred at this temperature for an additional 30 min before stirring at rt for 10 h. The reaction mixture was quenched with H_2O (50 mL) and diluted with EtOAc (500 mL). The organic layer was separated, washed with H_2O (50 mL), satd $NaHCO_3$ (2×50 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford a yellow solid. The solid was triturated with heptane (80 mL) at rt for 1 h and filtered to produce **10** (4.71 g, 95%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, J=16.5, 41.5 Hz, 2H), 7.50–7.33 (m, 10H), 7.00 (d, J=8.0 Hz, 2H), 6.77 (d, J=8.0 Hz, 1H), 6.29 (s, 1H), 6.20 (s, 1H), 5.21 (s, 2H), 5.08 (s, 4H), 3.50 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 169.3, 164.5, 162.8, 161.3, 143.8, 137.6, 136.5, 131.2, 129.9, 129.8, 129.7, 129.6, 129.3, 129.2, 128.47, 126.3, 116.0, 107.869, 98.0, 95.1, 93.465, 72.4, 71.1, 57.5; ESI-MS: m/z 519.1 $[M+Na]^+$.

*3.2.7. (E)-3-(Benzyloxy)-2-(3-(4-(benzyloxy)phenyl)allyl)-5-(methoxymethoxy)phenol (**11**).* Ethyl chloroformate (1.2 g, 11.0 mmol) in THF (10 mL) was slowly added at 0 °C to a solution of TEA (1.1 g, 11.0 mmol) and the chalcone **10** (4.96 g, 10 mmol) in THF (20 mL) over 3 min. The resulting mixture was then stirred at the same temperature for 30 min. The insoluble amine salt was filtered, the filter cake washed with an additional volume of THF (20 mL). The filtrate was added to a vigorously stirred solution of $CeCl_3\cdot 7H_2O$ (4.1 g, 11.0 mmol) in EtOH (50 mL) and stirred at rt for 30 min. $NaBH_4$ (910 mg, 24.0 mmol) in EtOH (30 mL) was slowly added to the mixture (30 min) at −10 °C. The mixture was allowed to react for another 45 min, diluted with H_2O, cooled, acidified/neutralized (to pH 3.0–4.0) with dilute HCl, and extracted with DCM (3 portions). The combined DCM extracts were washed in turn with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum, which was further purified by column chromatography (1:6 EtOAc/PE) to give the product **11** as a white solid (4.2 g, 88%).

Mp 81–83 °C; IR (KBr) ν_{max} 3310, 3000, 2961, 2883, 2831, 1628, 1508, 1466, 1401 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 12H), 7.24 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 6.42 (d, J=16.0 Hz, 1H), 6.32 (d, J=2.0 Hz, 1H), 6.26 (d, J=2.0 Hz, 1H), 6.20–6.14 (m, 1H), 5.12 (s, 2H), 5.05 (s, 4H), 3.56 (dd, J=1.5, 6.5 Hz, 2H), 3.47 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 157.8, 157.1, 155.7, 137.1, 137.0, 130.4, 130.0, 128.7, 128.6, 128.5, 127.9, 127.8, 127.4, 127.3, 127.3, 126.2, 115.0, 114.9, 108.2, 96.9, 94.6, 94.5, 70.4, 70.0, 56.0, 26.4; ESI-MS: m/z 505.2 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{31}H_{31}O_5[M+H]^+$: 483.2166, found 483.2157.

*3.2.8. (E)-(3-(Benzyloxy)-2-(3-(4-(benzyloxy)phenyl)allyl)-5-(methoxymethoxy)phenoxy)(tert-butyl)dimethylsilane (**12**).* The propene **11** (2.41 g, 5.0 mmol) was dissolved in dry DMF (20 mL), and to this solution were added imidazole (0.38 g, 6.0 mmol) and TBSCl (0.9 g, 6 mmol) successively at 0 °C. The resulting mixture was stirred at rt overnight, and then saturated Na_2CO_3 solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatograph on silica gel (10/1 PE/EtOAc) to afford **12** (2.95 g, 99%) as an oil.

IR (KBr) ν_{max} 3000, 2900, 2840, 1633, 1515, 1456, 1397 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 12H), 7.24 (d, J=9.0 Hz, 2H), 6.89 (d, J=8.5 Hz, 2H), 6.36 (d, J=2.0 Hz, 1H), 6.29 (d, J=16.0 Hz, 1H), 6.28 (d, J=2.0 Hz, 1H), 6.21–6.15 (m, 1H), 5.12 (s, 2H), 5.05 (s, 4H), 3.51 (d, J=6.0 Hz, 2H), 3.48 (br s, 3H), 1.04 (br s, 9H), 0.28 (br s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 157.7, 156.6, 154.7, 137.3, 137.1, 131.3, 128.9, 128.5, 128.5, 127.9, 127.7, 127.5, 127.4, 127.3, 127.0, 114.8, 113.3, 100.1, 94.8, 94.7, 70.1, 70.0, 55.9, 26.9, 25.9, 18.3, −4.1; ESI-MS: m/z 619.1 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{37}H_{45}O_5Si[M+H]^+$: 597.3031, found 597.3035.

*3.2.9. (1S,2S)-3-(2-(Benzyloxy)-6-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)phenyl)-1-(4-(benzyloxy)phenyl)propane-1,2-diol (**13**).* To a solution containing the TBS ether **12** (1.2 g, 2.0 mmol) in t-BuOH/H_2O (1:1, 40 mL) was added AD-mix-α (2.0 g) in portions. The heterogeneous mixture was cooled to 0 °C in an ice bath and methanesulfonamide (0.19 g, 2 mmol) was also added in portions. The reaction was stirred at 0 °C for 3 days, quenched by addition of Na_2SO_3 (1 M, 10 mL) and diluted with EtOAc (60 mL) and H_2O (60 mL). The organic layer was separated and washed with KOH (2 M, 2×40 mL), followed by H_2O (60 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography on a silica gel column (1/3 EtOAc/PE) to afford TBS-protected diol **13** (1.14 g, 90%) as an oil.

$[\alpha]_D^{20}$ +7.5 (c 0.8, CH_3CN); IR (KBr) ν_{max} 3508, 2926, 2850, 1586, 1028, 827, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.31 (m, 10H), 7.25 (d, J=8.5 Hz, 2H, overlapped with the peak of $CDCl_3$), 6.89 (d, J=9.0 Hz, 2H), 6.36 (d, J=2.0 Hz, 1H), 6.29 (d, J=2.0 Hz, 1H), 5.10 (s, 2H), 5.04 (s, 2H), 4.99 (s, 2H), 4.42 (d, J=5.5 Hz, 1H), 3.88–3.85 (m, 1H), 3.46 (br s, 3H), 2.85–2.76 (m, 2H), 0.97 (br s, 9H), 0.22 (br s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 157.0, 155.2, 137.1, 136.5, 133.5, 128.7, 128.6, 128.1, 128.0, 127.9, 127.4, 114.7, 110.7, 100.5, 94.9, 94.7, 76.9, 75.6, 70.5, 70.0, 55.9, 27.6, 25.8, 18.3, −4.0, −4.2; ESI-MS: m/z 653.3 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{37}H_{47}O_7Si[M+H]^+$: 631.3086, found 631.3079.

*3.2.10. (1S,2S)-3-(2-(Benzyloxy)-6-hydroxy-4-(methoxymethoxy)phenyl)-1-(4-(benzyloxy)phenyl)propane-1,2-diol (**14**).* To a solution of TBS-protected diol **13** (0.63 g, 1 mmol) in anhydrous THF (20 mL) was added TBAF (0.32 g, 1.0 mmol). The reaction mixture was stirred at rt for 1.5 h. After complete conversion (monitored by TLC), the reaction mixture was quenched by addition of satd aq $NaHCO_3$ (20 mL). The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3×30 mL). The combined organic layer was washed with brine (25 mL) and H_2O (25 mL). The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure to obtain a brown residue, which was purified by flash chromatography on a silica gel column (1/2 EtOAc/PE) to obtain the triol **14** (0.51 g, 99%) as a colourless oil.

$[\alpha]_D^{20}$ +7.2 (c 0.4, CH_3CN); IR (KBr) ν_{max} 3497, 3266, 2933, 2841, 1576, 1443, 1108, 835, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.25 (m, 8H), 7.19 (d, J=9.0 Hz, 2H), 7.13 (d, J=9.0 Hz, 2H), 6.83 (d, J=8.5 Hz, 2H), 6.33 (d, J=2.0 Hz, 1H), 6.24 (d, J=2.5 Hz, 1H), 5.11 (s, 2H), 4.95 (s, 2H), 4.86 (dd, J=12.0, 23.0 Hz, 2H), 4.45 (d,

J=7.0 Hz, 1H), 4.00–3.96 (m, 1H), 3.46 (br s, 3H), 2.89 (dd, J=3.5, 14.5 Hz, 1H), 2.70 (dd, J=3.8, 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 157.8, 157.4, 157.4, 136.9, 136.8, 132.7, 130.9, 128.8, 128.6, 128.4, 128.2, 128.0, 127.6, 127.5, 127.08, 114.8, 107.3, 98.0, 94.5, 94.0, 70.1, 69.9, 56.0, 26.5; ESI-MS: m/z 539.1 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{31}H_{33}O_7[M+H]^+$: 517.2221, found 517.2212.

*3.2.11. (2R,3S)-5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-7-(methoxymethoxy)chroman-3-ol (**15**).* To a suspension of **14** (0.52 g, 1 mmol) in 1,2-dichloroethane (20 mL) was added triethyl orthoformate (1 mL), followed by PPTS (176 mg, 0.7 mmol). The mixture was stirred at rt for 20 min and then heated to 50 °C for 5 h until TLC showed the reaction had been completed. After evaporation of the solvent, the residue was redissolved in 1,2-dichloroethane (10 mL) and MeOH (10 mL), K_2CO_3 (200 mg) was added, and the mixture was stirred at rt overnight. The K_2CO_3 was filtered and the filtrate was concentrated under reduced pressure. The residue was then recrystallized from DCM/PE to afford the desired product **15** as a white solid (0.41 g, 85% for two steps).

Mp 144–145 °C; $[\alpha]_D^{20}$ +6.7 (c 0.35, CH_3CN); IR (KBr) ν_{max} 3318, 2977, 1699, 1578, 1131, 1059 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.31 (m, 12H), 7.01 (d, J=8.5 Hz, 2H), 6.31 (dd, J=2.5, 9.0 Hz, 2H), 5.11 (s, 2H), 5.08 (s, 2H), 5.04 (dd, J=11.5, 15.0 Hz, 2H), 4.69 (d, J=8.0 Hz, 1H), 4.09–4.05 (m, 1H), 3.46 (br s, 3H), 3.14 (dd, J=5.5, 11.2 Hz, 1H), 2.68 (dd, J=4.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 157.7, 157.2, 155.4, 136.9, 136.8, 130.1, 128.6, 128.6, 128.5, 128.0, 127.9, 127.4, 127.2, 115.2, 103.3, 96.7, 94.6, 94.3, 81.5, 70.1, 70.0, 68.2, 56.0, 27.8; ESI-MS: m/z 521.1 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{31}H_{31}O_6[M+H]^+$: 499.2115, found 499.2119.

*3.2.12. (2R,3S)-5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-8-iodo-7-(methoxymethoxy)chroman-3-ol (**16**).* Compound **16** was prepared by the same procedure as **4**. 91% yield, white solid, mp 171–172 °C; $[\alpha]_D^{20}$ +11.7 (c 0.22, CH_3CN); IR (KBr) ν_{max} 3323, 2991, 1718, 1587, 1547, 1122, 1066, 988 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.32 (m, 12H), 7.01 (d, J=9.0 Hz, 2H), 6.49 (s, 1H), 5.21 (s, 2H), 5.08 (s, 2H), 5.05 (d, J=12.0, 16.5 Hz, 2H), 4.87 (d, J=7.5 Hz, 1H), 4.07–4.03 (m, 1H), 3.52 (br s, 3H), 3.04 (dd, J=5.5, 16.5 Hz, 1H), 2.72 (dd, J=8.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 158.0, 156.2, 153.8, 136.89, 136.6, 129.9, 128.6, 128.5, 128.1, 128.0, 127.5, 127.3, 115.1, 104.2, 95.4, 93.5, 81.9, 70.2, 70.1, 68.2, 60.4, 56.4, 27.4; ESI-MS: m/z 647.1 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{31}H_{30}O_6I$ $[M+H]^+$: 625.1082, found 625.1080.

*3.2.13. O-((2R,3S)-5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-7-hydroxy-8-iodochroman-3-yl) S-methyl carbonodithioate (**18**).* To 62 mg (0.1 mmol) of **16** in 3 mL of dry DMF was added 4.5 mg (0.11 mmol) of NaH (60% in oil). The mixture was stirred with a powerful magnetic stirrer at rt for 10 min, and then it was immersed in a 10 °C water bath, 13 μL (0.2 mmol) of CS_2 was slowly added in 5 min, and stirring at 10 °C was continued for 30 min. To the resulting yellow to amber suspension was added 13 μL (0.2 mmol) of MeI. The reaction mixture was left at rt for 20 min and then dissolved in 5 mL of H_2O and 6 mL of EtOAc. The phases were separated, and the aqueous phase was extracted with 10 mL of EtOAc. The combined organic phases were washed with H_2O (3×10 mL), dried ($MgSO_4$) and concentrated to give the crude product. A solution of the crude product in 5 mL MeOH and 5 mL THF was added 3 M HCl (2 mL) and stirred at 55 °C for 3 h. The reaction was quenched by the addition of water and extracted with EtOAc (3×120 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on a silica gel column chromatography (5:1 PE/EtOAc) to afford **18** (54 mg, 80% for two steps) a viscous solid.

IR (KBr) ν_{max} 2922, 1708, 1566, 1421, 1267, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.30 (m, 10H), 7.24 (d, J=9.0 Hz, 2H), 6.94 (d, J=9.0 Hz, 2H), 6.38 (s, 1H), 6.20 (dd, J=5.0, 8.7 Hz, 1H), 5.57 (d, J=4.5 Hz, 1H), 5.45 (s, 1H), 5.04 (s, 2H), 5.00 (s, 2H), 2.95 (dd, J=4.5, 16.5 Hz, 1H), 2.85 (dd, J=5.0, 16.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 159.7, 159.3, 155.9, 153.3, 137.8, 137.4, 130.6, 129.6, 129.6, 129.0, 129.0, 128.5, 128.2, 128.0, 116.0, 102.2, 93.5, 78.8, 78.4, 67.5, 71.2, 71.0, 23.2, 19.9; ESI-MS: m/z 693.1 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{31}H_{28}O_5IS_2[M+H]^+$: 671.0417, found 671.0427.

*3.2.14. (2R,3S)-5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-8-iodo-3-((4-methoxybenzyl)oxy)-7-(methoxymethoxy)chromane (**20**).* 90 mg of NaH (2.1 mmol, 60% in oil) was added in one portion to a stirred solution of **16** (0.62 g, 1 mmol) in dry DMF (10 mL) at 0 °C. After gas evolution had subsided, PMBCl (0.16 g, 1.1 mmol) was added, and the cooling bath was removed and stirring was continued for 5 h. The mixture was recooled to 0 °C, whereupon saturated NH_4Cl (10 mL) and H_2O (10 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organics were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (6:1) to afford 0.67 g (90%) of the target compound as a viscous solid.

$[\alpha]_D^{20}$ −14.3 (c 0.28, CH_3CN); IR (KBr) ν_{max} 3010, 2945, 1719, 1601, 1543, 1421, 1178, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.31 (m, 12H), 7.07 (d, J=8.5 Hz, 2H), 6.99 (d, J=8.5 Hz, 2H), 6.80 (d, J=8.5 Hz, 2H), 6.47 (s, 1H), 5.21 (s, 2H), 5.09 (s, 2H), 5.05–5.02 (m, 3H, overlapped), 4.29 (dd, J=11.5, 44.5 Hz, 2H), 3.81–3.75 (m, 1H, overlapped), 3.78 (br s, 3H), 3.52 (br s, 3H), 2.92 (dd, J=5.0, 16.5 Hz, 1H), 2.72 (dd, J=7.8, 16.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.6, 157.9, 156.1, 153.9, 137.0, 136.7, 131.2, 130.0, 129.4, 128.6, 128.6, 128.0, 128.0, 127.5, 127.4, 114.7, 113.7, 104.4, 95.4, 93.5, 80.1, 74.1, 71.2, 70.2, 70.0, 68.1, 56.4, 55.3, 25.5. ESI-MS: m/z 767.2 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{39}H_{38}O_7I$ $[M+H]^+$: 745.1657, found 745.1666.

*3.2.15. (2R,3S)-5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-8-iodo-3-((4-methoxybenzyl)oxy)chroman-7-ol (**21**).* A solution of **20** (74 mg, 0.1 mmol) in 5 mL MeOH and 10 mL THF was added 3 M HCl (5 mL) and stirred at 40 °C for 10 h under Ar (in dark). The reaction was cooled to rt, quenched by the addition of water and extracted with EtOAc (3×20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on a silica gel column chromatography (5/1 PE/EtOAc) to afford **21** (60 mg, 85%) as a viscous solid.

$[\alpha]_D^{20}$ −21.2 (c 0.58, CH_3CN); IR (KBr) ν_{max} 3354, 2921, 1708, 1578, 1509, 1255, 1119 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.28 (m, 13H), 7.05 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 6.79 (d, J=8.5 Hz, 2H), 6.35 (s, 1H), 5.40 (s, 1H), 5.09 (s, 2H), 5.04–5.00 (m, 3H, overlapped), 4.29 (dd, J=11.5, 49.0 Hz, 2H), 3.78 (br s, 3H), 3.78–3.74 (m, 1H, overlapped), 3.77 (br s, 3H), 2.92 (dd, J=5.0, 16.3 Hz, 1H), 2.74 (dd, J=8.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.6, 158.4, 154.6, 153.1, 136.9, 136.7, 131.1, 130.0, 129.4, 128.6, 128.6, 128.0, 128.0, 127.5, 127.2, 114.8, 114.7, 113.7, 102.5, 92.2, 74.1, 71.2, 70.1, 70.0, 66.6, 55.3, 25.3; ESI-MS: m/z 723.2 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{37}H_{34}O_6I[M+H]^+$: 701.1395, found 701.1399.

*3.2.16. ((4-(Benzyloxy)phenyl)ethynyl)trimethylsilane (**23**).* A solution of 4-iodophenol (6 g, 27.3 mmol), K_2CO_3 (11.3 g, 81.9 mmol) and BnBr (4.7 g, 27.5 mmol) in acetone (30 mL) was stirred under reflux for 24 h. Then the reaction mixture was diluted with EtOAc and washed with 3 M NaOH, dried over Na_2SO_4, evaporated in low pressure to give a white solid (8.4 g, 99%). To a solution of this white solid (7 g, 22.6 mmol), CuI (43 mg, 0.23 mmol), $PdCl_2(PPh_3)_2$ (159 mg, 0.23 mmol) and trimethylsilylacetylene (4.44 g, 45.2 mmol) in dry THF (50 mL) was added diisoproplamine (6 g, 60 mmol) and

the reaction mixture was stirred at rt for 12 h. Then the solution was filtered off and concentrated under reduced pressure. The crude product was purified by flash master chromatography (100/1 PE/EtOAc). A yellow solid product was obtained (6 g, 99%).

Mp 76–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.35 (m, 7H), 6.85 (d, J=8.5 Hz, 2H), 5.02 (s, 2H), 0.3 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 138.2 (2×C), 133.4, 128.6 (2×C), 128.0, 127.9(2×C), 117.2 (2×C), 114.6, 105.1, 83.0, 70.0, 0.0.

*3.2.17. 1-(Benzyloxy)-4-ethynylbenzene (**24**).* A solution of **23** (5.9 g, 21 mmol) and K_2CO_3 (10.2 g, 73.4 mmol) in dry methanol (30 mL) and THF (30 mL) was stirred at rt for 12 h. The reaction mixture was filtered off and the filtrate was evaporated under reduced pressure. The crude product was dissolved in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and evaporated in vacuum to get a white crystal (4.43 g, 99%).

Mp 65–66 °C[21]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.42 (m, 7H), 6.95 (d, J=8.5 Hz, 2H), 5.10 (s, 2H), 3.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 138.7 (2×C), 134.1, 129.1 (2×C), 128.6, 127.9 (2×C), 117.7 (2×C), 115.3, 83.5, 76.3.

*3.2.18. 3-(4-(Benzyloxy)phenyl)-1-(2,4,6-tris(benzyloxy)phenyl) prop-2-yn-1-one (**25**).* To a solution of **24** (1.27 g, 6 mmol) in dry THF was added vinylmagnesium bromide (3 mL, 2 M in THF solution) dropwisely at 0 °C under Ar. After being stirred at 40 °C for 1 h, a solution of 2,4,6-tris(benzyloxy)benzaldehyde (1.31 g, 3 mmol) in dry THF (1 mL/mmol) was added at 0 °C and stirred continuously at the same temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. The residue was purified by flash column chromatography, eluting with PE/EtOAc/acetone (8:1:1) to afford a crude alcohol. To a solution of the crude alcohol in dry DCM (1 mL/mmol) was added MnO_2 (5.00 equiv) at rt under Ar. After being stirred at the same temperature for 12 h, the reaction mixture was filtered thorough a pad of Celite* and the filtrate was concentrated in vacuo. The target compound was recrystallized from DCM/PE to afford the desired product **25** as a yellow solid (0.92 g, 99% for two steps).

Mp 101–102 °C; IR (KBr) ν_{max} 1632, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.23 (m, 22H), 6.89 (d, J=9.0 Hz, 2H), 6.26 (s, 2H), 5.11 (s, 4H), 5.07 (s, 2H), 5.02 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 162.3, 160.3, 158.9, 136.4, 136.3, 136.2, 134.8, 128.7, 128.7, 128.5, 128.3, 128.2, 127.8, 127.6, 127.5, 127.0, 115.0, 113.7, 113.0, 93.5, 90.8, 90.7, 70.6, 70.3, 70.1; ESI-MS: m/z 631.2 $[M+H]^+$, 653.2 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{43}H_{35}O_5[M+H]^+$: 631.2479, found 631.2476.

*3.2.19. ((2R,3S)-5-(Benzyloxy)-2,8-bis(4-(benzyloxy)phenyl)-3-((4-methoxybenzyl)oxy)-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl)(2,4,6-tris(benzyloxy)phenyl)methanone (**26**).* Compound **26** was prepared by the same procedure as **6a** and **6b**.

Yellow viscous solid, $[\alpha]_D^{20}$ −13.5 (c 0.3, CH_3CN); IR (KBr) ν_{max} 2931, 1621, 1596, 1423 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J=8.5 Hz, 2H), 7.46 (d, J=7.0 Hz, 2H), 7.43–7.29 (m, 18H), 7.19–7.12 (m, 6H), 7.03–7.01 (m, 4H), 6.98 (d, J=8.5 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 6.84 (d, J=9.0 Hz, 2H), 6.75 (d, J=8.5 Hz, 2H), 6.72 (d, J=8.5 Hz, 2H), 6.64 (s, 1H), 5.91 (s, 2H), 5.11 (s, 2H), 5.04 (s, 2H), 4.92 (s, 2H), 4.84 (dd, J=11.5, 17.0 Hz, 2H), 4.66–4.59 (m, 5H, overlapped), 4.16 (dd, J=11.5, 33.5 Hz, 2H), 3.75 (br s, 3H), 3.65 (dd, J=6.5, 12.0 Hz, 1H), 2.85 (dd, J=5.0, 16.5 Hz, 1H), 2.78 (dd, J=6.5, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 161.8, 159.7, 159.1, 158.1, 155.1, 154.4, 153.5, 147.9, 137.1, 137.0, 136.9, 136.5, 136.4, 131.8, 130.2, 129.6, 129.2, 128.6, 128.6, 128.2, 127.9, 127.889, 127.7, 127.6, 127.5, 127.4, 127.2, 126.9, 123.4, 120.4, 115.0, 114.4, 114.3, 113.6, 110.5, 104.2, 92.8, 88.0, 78.4, 73.8, 70.6, 70.2, 69.9, 69.9, 69.8, 55.2, 24.9; ESI-MS: m/z 1225.4 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{80}H_{67}O_{11}[M+H]^+$: 1203.4678, found 1203.4671.

*3.2.20. ((2R,3S)-5-(Benzyloxy)-2,8-bis(4-(benzyloxy)phenyl)-3-hydroxy-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl)(2,4,6-tris(benzyloxy)phenyl)methanone (**27**).* A solution of **26** (12 mg, 0.01 mmol) in 3 mL DCM and 0.3 mL H_2O was added DDQ (3 mg, 0.012 mmol) and stirred at rt for 1.5 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with DCM (2×10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC (3/1 PE/EtOAc) to afford **27** (10 mg, 92%).

Yellow amorphous solid, $[\alpha]_D^{20}$ −19.8 (c 0.45, CH_3CN); IR (KBr) ν_{max} 3318, 2952, 1627, 1605 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J=8.5 Hz, 2H), 7.48 (d, J=7.0 Hz, 2H), 7.43–7.31 (m, 18H), 7.21–7.15 (m, 6H), 7.05–7.01 (m, 4H), 6.99 (d, J=8.5 Hz, 2H), 6.84 (d, J=9.0 Hz, 2H), 6.74 (d, J=8.5 Hz, 2H), 6.69 (s, 1H), 5.91 (s, 2H), 5.12 (s, 2H), 5.04 (s, 2H), 4.92 (s, 2H), 4.88 (s, 2H), 4.63 (br s, 4H), 4.45 (d, J=6.0 Hz, 1H), 3.93 (dd, J=1.8, 12.3 Hz, 1H), 2.96 (dd, J=5.0, 16.5 Hz, 1H), 2.74 (dd, J=7.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 161.9, 159.6, 159.2, 158.4, 155.3, 154.5, 153.7, 147.7, 136.9, 136.9, 136.8, 136.4, 136.3, 130.5, 129.6, 128.7, 128.6, 128.6, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 127.59, 127.4, 127.2, 126.9, 123.2, 120.3, 114.7, 114.6, 114.3, 110.5, 104.0, 92.8, 88.3, 80.8, 70.2, 69.9, 69.8, 67.8, 26.8; ESI-MS: m/z 1105.4 $[M+Na]^+$. HRMS (ESI): m/z calcd for $C_{72}H_{59}O_{10}$ $[M+H]^+$: 1083.4103, found 1083.4111.

*3.2.21. (S)-(5-(Benzyloxy)-2,8-bis(4-(benzyloxy)phenyl)-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl)(2,4,6-tris(benzyloxy)phenyl) methanone (**28**).* Phenyl chlorothionocarbonate (4 mg, 0.012 mmol) was added to a solution of **27** (22 mg, 0.02 mmol) and pyridine (5 μL) in DCM (5 mL). After stirring for 6 h at 30 °C, the reaction was quenched by water and extracted with EtOAc (3×5 mL). The organic layers were washed with 1 M HCl, water and saturated Na_2CO_3 solution, dried over $MgSO_4$, and concentrated to get the crude product, which was dissolved in 3 mL of anhydrous toluene and heated to 100 °C under Ar. A solution of n-Bu_3SnH (7.8 mg, 0.03 mmol) and AIBN (1.6 mg, 0.01 mmol) in 1 mL of anhydrous toluene was added over a period of 30 min. After stirring at 100 °C for 1.5 h, the cooled reaction mixture was directly purified by preparative TLC (1/1/8 DCM/EtOAc/PE) to afford **28** (6 mg, 28%) as a yellow amorphous solid.

IR (KBr) ν_{max} 2959, 1621, 1592 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J=8.5 Hz, 2H), 7.48 (d, J=7.5 Hz, 2H), 7.42–7.31 (m, 18H), 7.19–7.14 (m, 6H), 7.06–7.04 (m, 4H), 7.00 (d, J=8.5 Hz, 2H), 6.81 (d, J=9.0 Hz, 2H), 6.74 (d, J=9.0 Hz, 2H), 6.63 (s, 1H), 5.91 (s, 2H), 5.11 (s, 2H), 5.03 (s, 2H), 4.92 (s, 2H), 4.88 (s, 2H), 4.67 (dd, J=2.0, 8.0 Hz, 1H), 4.62 (dd, J=12.3, 14.7 Hz, 4H), 2.72–2.69 (m, 2H), 2.01–1.96 (m, 1H), 1.89–1.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 161.7, 159.6, 159.0, 157.8, 155.1, 154.1, 153.4, 149.0, 137.2, 137.1, 136.9, 136.5, 136.4, 134.3, 129.5, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.5, 127.4, 127.3, 127.1, 127.0, 126.9, 123.5, 120.0, 114.4, 114.2, 110.9, 106.1, 92.9, 87.5, 77.2, 76.6, 70.2, 69.9, 69.8, 29.3, 19.0; ESI-MS: m/z 1089.5 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{72}H_{59}O_9[M+H]^+$: 1067.4154, found 1067.4157.

*3.2.22. (2R,3S)-8-Iodo-5-methoxy-3-((4-methoxybenzyl)oxy)-7-(methoxymethoxy)-2-(4-methoxyphenyl)chromane (**30**).* Compound **30** was prepared by the same procedure as **20**.

93% yield, white viscous solid; $[\alpha]_D^{20}$ −35.1 (c 0.25, CH_3CN); IR (KBr) ν_{max} 2941, 1700, 1589, 1549, 1431, 1232, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J=8.5 Hz, 2H), 7.06 (d, J=9.0 Hz, 2H), 6.91 (d, J=8.5 Hz, 2H), 6.81 (d, J=9.0 Hz, 2H), 6.37 (s, 1H), 5.23 (s, 2H), 5.01 (d, J=7.0 Hz, 1H), 4.30 (dd, J=11.5, 41.0 Hz, 2H), 3.83 (br s, 3H), 3.81 (br s, 3H), 3.79 (br s, 3H), 3.77–3.73 (m, 1H), 3.54 (br s, 3H), 2.88 (dd, J=5.0, 16.5 Hz, 1H), 2.69 (dd, J=7.5, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 159.2, 158.8, 156.1, 153.8, 130.9, 130.0, 129.3, 128.0, 113.7, 113.7, 103.9, 95.4, 92.0, 80.1, 74.0, 71.0, 67.7, 56.4, 55.6, 55.3, 55.2, 25.3; ESI-MS: m/z 615.1 $[M+Na]^+$;

HRMS (ESI): *m/z* calcd for $C_{27}H_{30}O_7I[M+H]^+$: 593.1031, found 593.1018.

*3.2.23. (2R,3S)-8-Iodo-5-methoxy-3-((4-methoxybenzyl)oxy)-2-(4-methoxyphenyl)chroman-7-ol (**31**).* Compound **31** was prepared by the same procedure as **21**.

83% yield, white viscous solid; $[\alpha]_D^{20}$ −51.6 (*c* 0.29, CH_3CN); IR (KBr) ν_{max} 3347, 2941, 1721, 1602, 1522, 1255, 1141, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.5 Hz, 2H), 7.06 (d, *J*=8.5 Hz, 2H), 6.92 (d, *J*=8.5 Hz, 2H), 6.81 (d, *J*=8.5 Hz, 2H), 6.27 (s, 1H), 4.99 (d, *J*=7.5 Hz, 1H), 4.30 (dd, *J*=11.5, 44.5 Hz, 2H), 3.83 (br s, 3H), 3.78 (br s, 3H), 3.77 (br s, 3H), 3.80–3.73 (m, 1H, overlapped), 2.89 (dd, *J*=5.5, 16.5 Hz, 1H), 2.69 (dd, *J*=8.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 159.2, 159.1, 154.7, 153.0, 130.8, 130.0, 129.3, 128.0, 113.7, 102.0, 91.1, 80.3, 74.0, 71.0, 66.1, 55.6, 55.3, 55.2, 25.2; ESI-MS: *m/z* 571.0 $[M+Na]^+$; HRMS (ESI): *m/z* calcd for $C_{25}H_{26}O_6I[M+H]^+$: 549.0769, found 549.0766.

*3.2.24. ((2R,3S)-8-(4-(Benzyloxy)phenyl)-5-methoxy-3-((4-methoxybenzyl)oxy)-2-(4-methoxyphenyl)-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl)(2,4,6-tris(benzyloxy)phenyl)methanone (**32**).* Compound **32** was prepared by the same procedure as **6a** and **6b**.

58% yield, yellow amorphous solid; $[\alpha]_D^{20}$ −29.6 (*c* 0.34, CH_3CN); IR (KBr) ν_{max} 2940, 1625, 1596, 1450, 1409 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*=9.0 Hz, 2H), 7.43–7.32 (m, 10H), 7.19–7.16 (m, 6H), 7.04–7.02 (m, 4H), 6.98 (d, *J*=8.5 Hz, 2H), 6.94 (d, *J*=9.0 Hz, 2H), 6.85 (d, *J*=9.0 Hz, 2H), 6.75 (d, *J*=8.5 Hz, 2H), 6.63 (d, *J*=8.5 Hz, 2H), 6.57 (s, 1H), 5.92 (s, 2H), 5.05 (s, 2H), 4.85 (dd, *J*=11.5, 20.5 Hz, 2H), 4.62 (br s, 4H), 4.58 (dd, *J*=5.5, 11.5 Hz, 1H, overlapped), 4.17 (dd, *J*=11.5, 32.0 Hz, 2H), 3.86 (br s, 3H), 3.75 (br s, 3H), 3.68 (br s, 3H), 3.63–3.60 (m, 1H), 2.78 (dd, *J*=5.0, 16.5 Hz, 1H), 2.70 (dd, *J*=7.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.9, 161.7, 159.6, 159.0, 158.8, 156.1, 154.2, 153.6, 147.8, 136.8, 136.5, 136.4, 131.5, 130.2, 129.5, 129.1, 128.6, 128.5, 128.2, 127.9, 127.6, 127.5, 127.4, 127.3, 126.8, 123.4, 120.4, 115.0, 114.3, 113.6, 113.3, 110.2, 103.6, 92.8, 86.5, 78.3, 73.7, 70.4, 70.2, 69.9, 69.9, 55.7, 55.2, 55.1, 30.9, 24.6; ESI-MS: *m/z* 1073.5 $[M+Na]^+$; HRMS (ESI): *m/z* calcd for $C_{68}H_{59}O_{11}[M+H]^+$: 1051.4052, found 1051.4044.

*3.2.25. ((2R,3S)-8-(4-(Benzyloxy)phenyl)-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl) (2,4,6-tris(benzyloxy)phenyl)methanone (**33**).* Compound **33** was prepared by the same procedure as **27**.

99% yield, yellow amorphous solid, $[\alpha]_D^{20}$ −34.5 (*c* 0.24, CH_3CN); IR (KBr) ν_{max} 3333, 2928, 1621, 1425 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*=9.0 Hz, 2H), 7.43–7.32 (m, 10H), 7.22–7.16 (m, 6H), 7.06–7.03 (m, 4H), 6.98 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=9.0 Hz, 2H), 6.65 (d, *J*=9.0 Hz, 2H), 6.61 (s, 1H), 5.93 (s, 2H), 5.05 (s, 2H), 4.88 (dd, *J*=11.5, 15.0 Hz, 2H), 4.65 (br s, 4H), 4.45 (d, *J*=6.5 Hz, 1H), 3.94–3.90 (m, 1H), 3.86 (br s, 3H), 3.68 (br s, 3H), 2.82 (dd, *J*=5.5, 16.5 Hz, 1H), 2.70 (dd, *J*=6.7, 16.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 161.8, 159.5, 159.1, 156.4, 154.3, 153.8, 147.5, 136.8, 136.4, 136.4, 130.3, 129.5, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.6, 127.5, 126.9, 123.3, 120.3, 114.8, 114.3, 113.7, 110.3, 103.5, 92.8, 86.9, 80.7, 70.2, 69.9, 67.7, 55.7, 55.1, 30.9, 26.3; ESI-MS: *m/z* 953.4 $[M+Na]^+$; HRMS (ESI): *m/z* calcd for $C_{60}H_{51}O_{10}[M+H]^+$: 931.3477, found 931.3482.

*3.2.26. (S)-(8-(4-(Benzyloxy)phenyl)-5-methoxy-2-(4-methoxyphenyl)-3,4-dihydro-2H-furo[2,3-h]chromen-9-yl)(2,4,6-tris(benzyloxy)phenyl)methanone (**34**).* The xanthate was prepared by the same procedure described in Section 3.2.1. To a solution of the xanthate (102 mg, 0.1 mmol, 1.0 equiv) dissolved in dry THF (4 mL) was added MeOH and H_2O (100 μL, 1:1) and the mixture was allowed to stir for 5 min. Ar was then bubbled through the solution for a period of 1 h, at which time, a solution of Et_3B (1 mL, 1 M in THF) in THF was added via a syringe pump over 90 min. After complete conversion (monitored by TLC), the reaction mixture was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by preparative TLC (7/1/0.03 PE/DCM/MeOH) to afford **34** (80 mg, 88%).

Yellow amorphous solid, $[\alpha]_D^{20}$ −54.1 (*c* 0.50, CH_3CN); IR (KBr) ν_{max} 2922, 1626, 1427 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J*=8.5 Hz, 2H), 7.41–7.31 (m, 10H), 7.19–7.16 (m, 6H), 7.06–7.04 (m, 4H), 7.01 (d, *J*=8.5 Hz, 2H), 6.81 (d, *J*=9.0 Hz, 2H), 6.65 (d, *J*=9.0 Hz, 2H), 6.56 (s, 1H), 5.92 (s, 2H), 5.03 (s, 2H), 4.88 (dd, *J*=11.5, 13.5 Hz, 2H), 4.67 (d, *J*=2.5 Hz, 1H), 4.65 (br s, 4H), 3.86 (br s, 3H), 3.68 (br s, 3H), 2.63–2.59 (m, 2H), 2.01–1.99 (m, 1H), 1.88–1.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 161.7, 159.6, 159.0, 158.6, 156.2, 153.6, 148.9, 136.9, 136.5, 136.4, 134.1, 129.5, 128.6, 128.6, 128.2, 128.2, 127.9, 127.5, 127.4, 127.4, 126.9, 126.8, 123.5, 114.9, 114.2, 113.4, 110.7, 105.7, 92.9, 86.1, 76.5, 70.2, 69.9, 55.67, 55.1, 29.2, 18.7; ESI-MS: *m/z* 937.4 $[M+Na]^+$; HRMS (ESI): *m/z* calcd for $C_{60}H_{51}O_9[M+H]^+$: 915.3528, found 915.3518.

*3.2.27. Daphnodorin A (**1a**).* Freshly prepared **34** or **28** (0.05 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (2 mL), and BBr_3 or BCl_3 (0.9 mL, 0.9 mmol, 1.0 M in CH_2Cl_2) was added at −78 °C. The resultant red-brown solution was warmed to −10 °C and stirred for 10 h under Ar. Upon completion, the reaction contents were quenched by the addition of water (2 mL), stirred vigorously for 3 min at 0 °C, and extracted with EtOAc (3×5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by preparative TLC (100:10:1 CH_2Cl_2/MeOH/AcOH) to give Daphnodorin A as a yellow amorphous powder (13.4 mg, 51% from **28**; 15.8 mg, 60% from **34**).

2:1 *er* (determined by HPLC on a CHIRALPAK® IE column using *n*-Hexane/EtOH/MeOH/TFA=84/12/4/0.1 as eluent); IR (KBr) ν_{max} 3245, 1623, 1516, 1047 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.45 (d, *J*=9.0 Hz, 2H), 6.88 (d, *J*=8.5 Hz, 2H), 6.73 (d, *J*=8.5 Hz, 2H), 6.62 (d, *J*=8.5 Hz, 2H), 6.50 (s, 1H), 5.71 (s, 2H), 4.78 (d, *J*=10.0 Hz, 1H), 2.79–2.64 (m, 2H), 2.20–2.16 (m, 1H), 1.83–1.75 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 197.3, 167.8, 158.8, 157.5, 155.1, 154.7, 150.4, 149.5, 134.1, 128.4, 127.7, 123.8, 118.9, 116.6, 116.0, 112.2, 108.1, 106.1, 96.0, 90.5, 78.6, 31.3, 21.4; HRMS (ESI): *m/z* calcd for $C_{30}H_{23}O_9[M+H]^+$: 527.1337, found 527.1345.

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Supplementary data

^1H and ^{13}C NMR spectra of all the new compounds is available free of charge. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.10.010.

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