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SYNTHETIC STUDIES OF FISETIN, MYRICETIN AND NOBILETIN ANALOGS AND RELATED PROBE MOLECULES

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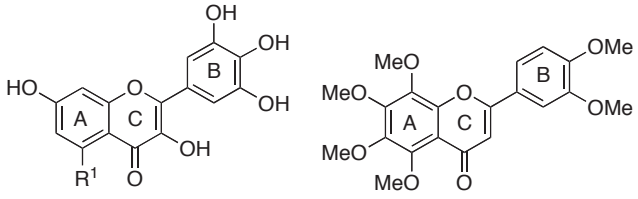
Abstract – We synthesized a series of analogs of fisetin, myricetin and nobiletin, as well as related fluorescein- and biotin-based flavone-probe molecules, on a suitable scale for biological and structure-activity relationship studies.

INTRODUCTION

Flavones, as represented by fisetin (**1**),[1] myricetin (**2**)[2] and nobiletin (**3**),[3] are widely distributed in the plant kingdom, and have been reported to show beneficial effects on health.[4] In particular, fisetin (**1**) and nobiletin (**3**) enhance PKA/ERK/CREB signaling in cell culture systems and prevent fibril formation of amyloid β protein (Aβ), so they are considered to be promising lead compounds for developing drugs to treat Alzheimer's disease.[5] However, it is often difficult to obtain sufficient amounts of natural products for clinical and epidemiological studies, or for investigating structure-activity relationships (SAR). Further, for imaging studies and/or analysis of the dynamics of flavones we require tools such as fluorescence probes and biotin-labeled probes. We have recently developed an efficient synthetic route to the flavone skeleton through a β-diketone intermediate.[6] Herein, we described the application of this method to synthesize a series of fisetin, myricetin and nobiletin analogs for SAR studies, as well as several fluorescein- and biotin-based flavone probes.



fisetin (**1**): R^1 = H
myricetin (**2**): R^1 = OH

nobiletin (**3**)

Figure 1. Natural flavonoids: Attracting seeds of the drug

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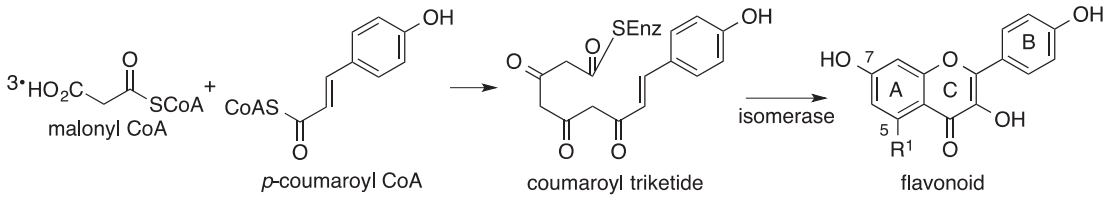
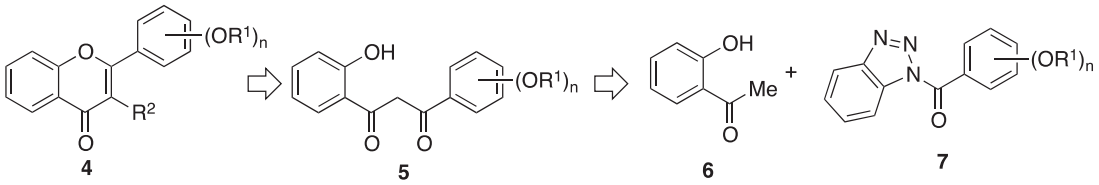
RESULTS AND DISCUSSION

Natural flavones have oxygen-containing functional groups at the 5- and/or 7-positions as a consequence of their biosynthesis via the polyketide pathway[7] (Scheme 1). Although flavonoids have been investigated for decades, no detailed SAR studies of deoxy derivatives have been reported, to our knowledge. During the course of our investigation of epigallocatechin gallate (EGCg), we found that synthetic deoxyepigallocatechin gallate (DOEGCg) possessed more potent anti-influenza infection activity than natural EGCg.[8] Inspired this finding, we aimed to synthesize a series of flavones and flavonols lacking hydroxyl groups at the 5- and/or 7-positions on the A-ring as candidate bioactive agents.



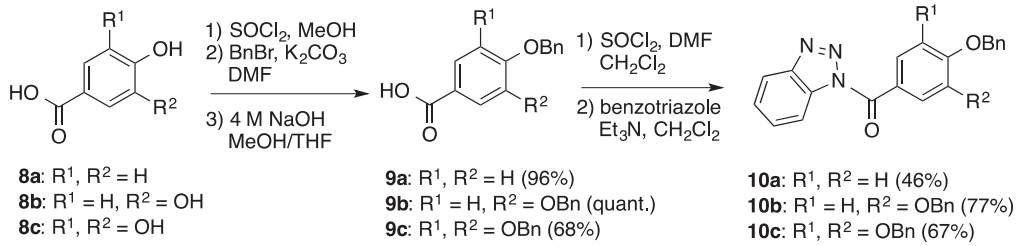
Scheme 1. Biosynthetic pathway to flavonoids

Our synthetic plan is illustrated in Scheme 2. The flavone ring of **4** is constructed by condensation of acetophenone (**6**) and acyl benzotriazoles[9] **7**, followed by cyclization of the β-diketone intermediate **5**.



Scheme 2. Strategy for flavonoid synthesis via β-diketone

For this synthesis, benzotriazoles **10a-c** were considered to be suitable acyl donors that could be readily obtained from the corresponding benzoic acid derivatives **8a-c**. The Bn-protected benzoic acids **9a-c** were obtained by esterification, incorporation of benzyl ether and hydrolysis of methyl ester. After treatment with $SOCl_2$, condensation with benzotriazole afforded the *C*-acylation donors **10a-c**. Although **10a-c** are activated acylating reagents, they are very stable crystalline solids that can be stored in refrigerator for several years without decomposition.



Scheme 3. Synthesis of acyl benzotriazoles **10a-c** as *C*-acylation reagents

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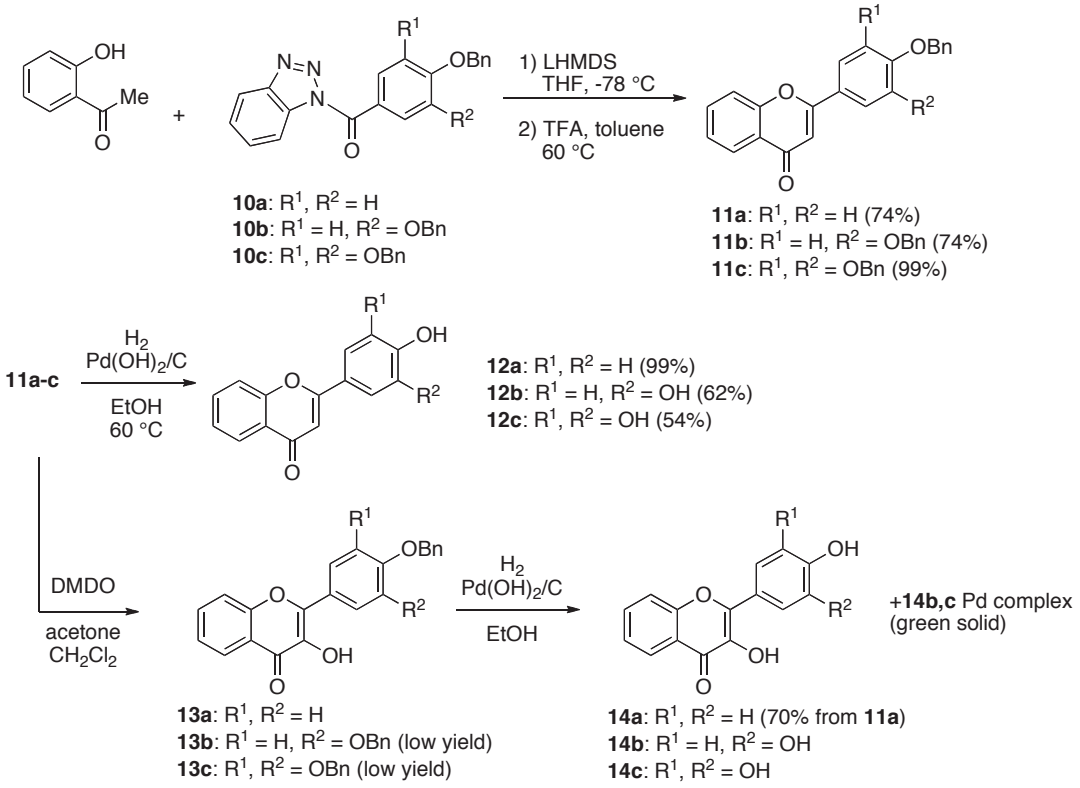
Upon treatment of acetophenone and **10a-c** with LHMDS at -78 °C, the *C*-acylation reaction proceeded smoothly to give the desired β-diketones. Subsequent acidic cyclization afforded the corresponding protected flavones. Deprotection of the Bn groups gave the desired flavones **12a-c**. Flavonols **14a-c** were obtained by oxidation of **11a-c** with DMDO followed by deprotection. However, **11b** and **11c** were poorly soluble in the reaction solvents, and the reproducibility of the oxidation steps was poor. Furthermore, polyphenol derivatives **14b** and **14c** readily formed complexes with Pd derivatives under hydrogenolysis conditions, and it was difficult to remove palladium metal from the complexes.



Scheme 4. Synthesis of flavone and flavonol analogs

Therefore, we decided to change the protecting groups of **12b**,**c** from Bn ether to TBS. The flavone derivatives **15b**,**c** were prepared by replacing Bn with TBS. The DMDO-mediated oxidation of **15b**,**c** proceeded smoothly to give the corresponding flavonols **16b**,**c** in moderate yields with good reproducibility, since the TBS flavones **15b**,**c** were readily soluble in CH_2Cl_2, as expected. Deprotection of TBS with TBAF in the presence of AcOH proceeded smoothly to give the desired flavonols **14b**,**c** in good yield.

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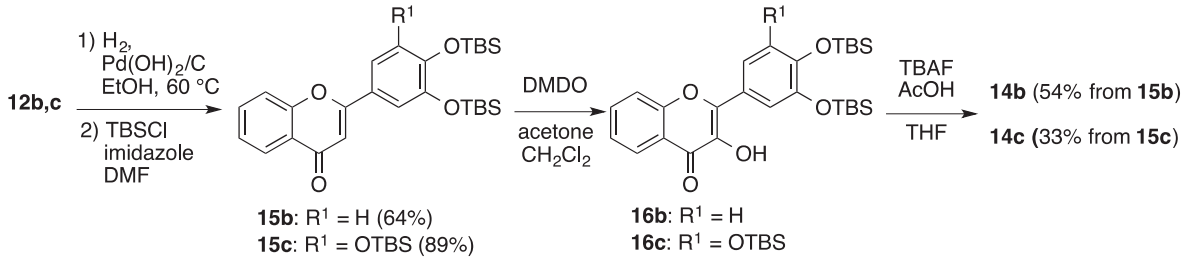
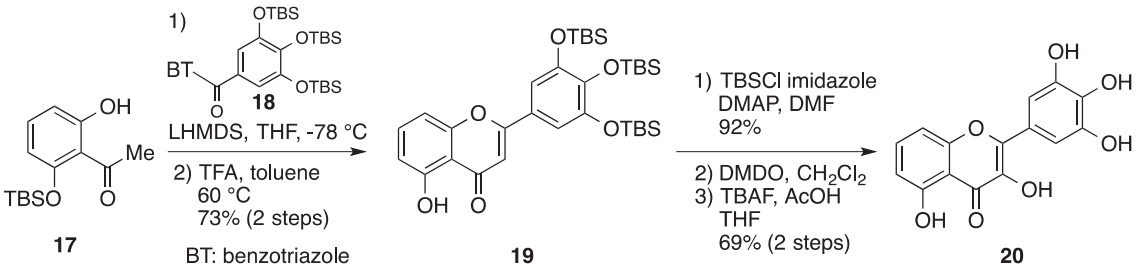


Scheme 5. Modified synthesis of flavonols **14b,c**

On the other hand, 7-deoxymyricetin (**20**) was synthesized from acetophenone **17** and acyl benzotriazole **18** in the same manner as described for the preparation of **14c**.



Scheme 6. Synthesis of 7-deoxymyricetin (**20**)

A SAR study of **14a**-**c** and **20** for inhibition of Aβ fibril formation has already been reported by our group.[10] 7-Deoxymyricetin (**20**) was a more potent inhibitor of Aβ fibril aggregation than myricetin.

Nobiletin (**3**) is considered an attractive candidate for treatment of Alzheimer's disease. Recently we accomplished a practical total synthesis of **3**,[6b] and applied it to obtain ^{11}C-labeled nobiletin, which is suitable for positron emission tomography (PET) analysis. However, for detailed biodistribution and metabolism studies of **3**, authentic samples of candidate metabolites of nobiletin are required.[11] As shown in Scheme 7, nobiletin (**3**), 3'-demethylnobiletin (**23b**) and 4'-demethylnobiletin (**23c**) were synthesized by our reported method. The two metabolites were obtained by using Bn-protected **22b**,**c** instead of **22a**, followed by deprotection. Upon treatment of **21** and **22b**,**c** with LHMDS at 0 °C, the *C*-acylation reaction proceeded smoothly to give the desired β-diketone intermediates. Subsequent acidic cyclization and deprotection afforded **23b**,**c**. Compounds **23b**,**c** have been used in a detailed investigation of the metabolism of **3** in a collaborative study involving our group[12] (Onoue *et al*.).

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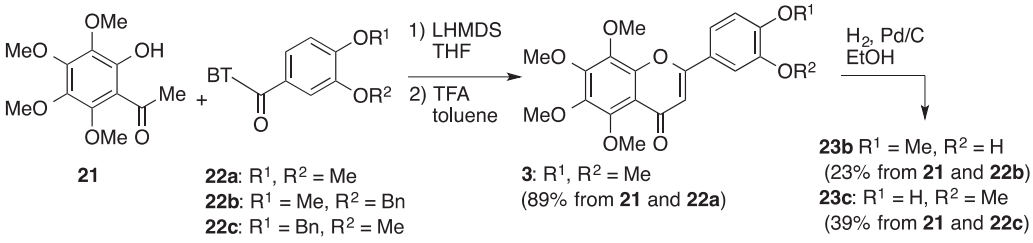
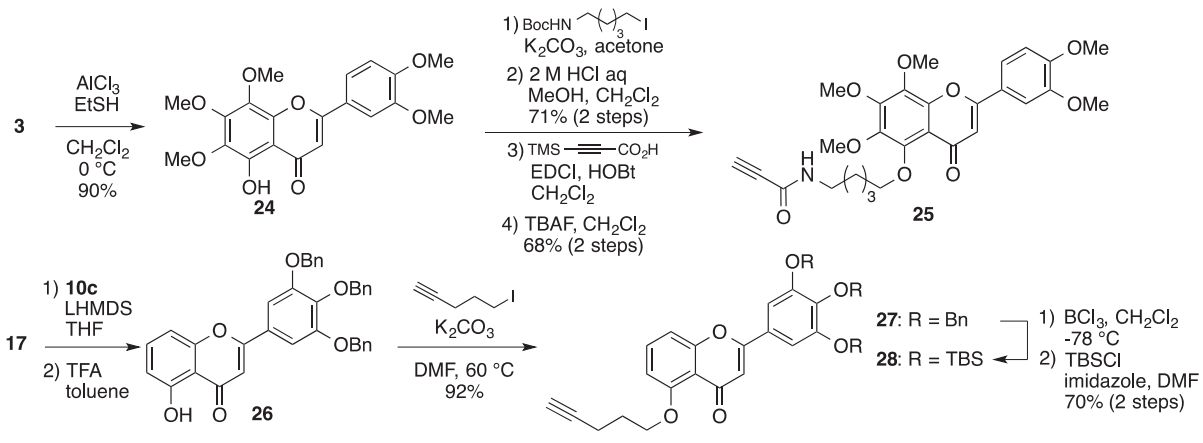


Scheme 7. Synthesis of nobiletin and its metabolites

Next, we turned our attention to the preparation of probe molecules for chemical-biological studies of flavone **20** and nobiletin (**3**). For this purpose, compounds labeled with fluorescein and biotin moieties are expected to be particularly useful. During the course of our work on tea catechins, we found that a precursor having a side chain on A-ring and a reactive amine unit was readily convertible into probe molecules.[13] We envisioned that a similar approach would be also applicable for the preparing flavonoid probes. Furthermore, a terminal alkyne group is useful for incorporation of a probe moiety via Hüisgen reaction.[14] Thus, introduction of two different types of alkyne linker moiety was performed by alkylation of the phenolic hydroxyl group at the 5-position of each flavone. Since regioselective removal of the 5-methyl group of nobiletin (**3**) proceeded smoothly, a terminal alkyne group was introduced by alkylation reaction of Boc-5-aminopentyl-1-iodide with 5-demethylnobiletin **24**. After removal of the Boc group, incorporation of a propiolic acid derivative provided the desired nobiletin probe precursor **25**. For the preparation of the flavone probe precursor, we first examined alkylation of flavone **19**. However, incorporation reaction did not proceeded and decomposition of the TBS ether of **19** was observed. Thus, alkylation reaction was performed using Bn ether derivative **26** to afford **27**. After deprotection of Bn ether by treatment with BCl_3 at -78 °C, protection with TBS groups afforded the flavone-probe precursor **28**. Since the Hüisgen reaction proceeded smoothly under extra-mild conditions and is compatible with many functional groups, terminal alkyne probe precursors are convenient for easy incorporation of several lengths of side chain and hydrophobic as well as hydrophilic linkers. This flexible synthetic strategy should be useful for optimization of probe molecules.



Scheme 8. Introduction of alkyne linker moiety on the flavone A-ring

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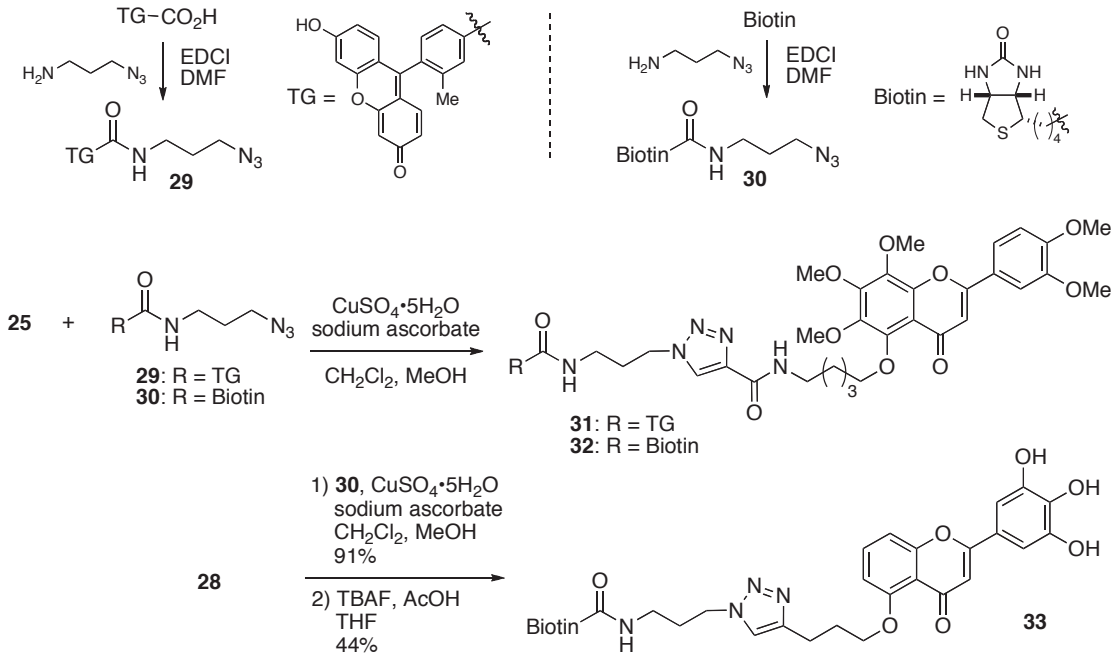
Using this approach, we prepared the fluorescein- and biotin-based probes **31**, **32** and **33**. Fluorescein is well-known to be suitable for in vivo imaging under physiological conditions. Among several fluorescein variants, we selected TokyoGreen[15] (TG) as a reliable photophore. As shown in Scheme 9, TG-conjugated alkyl azide **29** was prepared by condensation of a TG derivative with 3-aminopropyl-1-azide. Hüisgen reaction of nobiletin probe precursor **25** and TG derivative **29** proceeded smoothly to provide the fluorescent probe **31**. Incorporation of biotin moiety **30** instead of **29** into nobiletin precursor **25** was also carried out. The biotin-alkyl azide **30** was prepared by condensation of a biotin derivative with 3-aminopropyl-1-azide, and condensation reaction of probe precursor **25** and biotin-alkyl azide **30** provided the nobiletin-biotin probe **32**. Flavonol probe **33** was also synthesized by TBAF-mediated deprotection of TBS after click coupling of **28** with **30**. Our group is currently undertaking fluorescence imaging studies with **31** and target-protein detection with **32** and **33.** The results will be reported in due course.



Scheme 9. Synthesis of fluorescein- and biotin-based flavonoid probes

In summary, we have synthesized a series of flavonoid analogs for SAR studies, including 7-deoxymyricetin (**20**), which is a more potent inhibitor of Aβ fibril aggregation than myricetin. We found that a terminal alkyne group was useful for development of various fluorescein- and biotin-based flavonoid probe molecules that are expected to be useful for imaging studies of flavones at the cellular and organ level, respectively, as well as for investigations into the localization and target sites of flavones.

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EXPERIMENTAL

General. Nuclear magnetic resonance [^{13}C NMR (68 MHz)] spectra were determined on a JEOL EX-270 instrument, [^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz)] spectra were determined on a JEOL-LA400 instrument, and [^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz)] spectra were determined on a JEOL ECA 500 instrument and JEOL α–500 instrument. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane (δ) in deuterochloroform ($CDCl_3$) or deuteromethanol (CD_3OD) as an internal standard or relative to the signal at 7.26 (3.31) ppm for deuterochloroform (deuteromethanol), while coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm relative to the centerline of the triplet at 77.0 ppm for deuterochloroform or the centerline of a septet at 118.2 (49.0) ppm for deuteroacetonitrile (CD_3CN) [deuteromethanol (CD_3OD)]. Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Infrared spectra (IR), which are reported in wavenumbers (cm^{-1}), were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-GCmate MS-DIP20 with polyethylene glycol as the internal standard or a JEOL MStation 700 using the Fast Atom Bombardment (FAB) method and 3-nitrobenzylalcohol as the matrix. Analytical thin layer chromatography (TLC) was performed on 0.25-mm thick Merck precoated analytical plates of silica gel 60 F254. Preparative TLC separations were conducted on 0.50-mm thick Merck precoated of silica gel 60 F254. Compounds were eluted from the adsorbent with 10% methanol (MeOH) in chloroform ($CHCl_3$). Flash column chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40-100 mesh). All non-aqueous reactions were carried out in oven-dried glass apparatuses under a slight positive pressure of argon. Prior to use, all solvents were dried over molecular sieves 3A or 4A. All other reagents were commercially available, and unless otherwise specified, were used without further purification.

4-Benzyloxybenzoic acid (9a)

To a solution of **8a** (15.0 g, 0.109 mol) in MeOH (360 mL) was added $SOCl_2$ (7.90 mL, 0.109 mol) for dropwise at 60 °C. After stirring at 60 °C for 5 h, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a mixture of crude residue and K_2CO_3 (45.2 g, 0.329 mol) in DMF (182 mL) was added benzyl bromide (19.4 mL, 0.163 mol) at 100 °C. The reaction mixture was stirred at 100 °C for 16 h. Then, the reaction mixture was filtered through a pad of Celite, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with water followed by brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude residue was applied to following reaction without further purification.

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To a stirred solution of crude residue in MeOH/THF (1/1, 360 mL) was added 4 M NaOH aq. (90 mL, 0.36 mol) at 80 °C. The reaction mixture was stirred at 80 °C for 1 h. Then, the reaction mixture was quenched with 6 M HCl aq., and filtered. The filtrate was washed with H_2O to give **9a** (23.9 g, 0.104 mol, 96%) as a white solid.

Spectral data for **9a** were in good agreement with those reported in reference.[16]

3,4-Dibenzyloxybenzoic acid (9b)

To a solution of **8b** (15.0 g, 97.4 mmol) in MeOH (360 mL) was added $SOCl_2$ (7.9 mL, 48.7 mmol) for dropwise at 60 °C. The reaction mixture was stirred at 60 °C for 10 h. Then, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a mixture of crude residue and K_2CO_3 (40.4 g, 0.292 mol) in DMF (162 mL) was added benzyl bromide (29.0 mL, 0.244 mol) at 100 °C. The reaction mixture was stirred at 100 °C for 16 h. Then, the reaction mixture was filtered through a pad of Celite, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a stirred solution of crude residue in MeOH/THF (1/1, 324 mL) were added 4 M NaOH aq. (85 mL, 0.34 mol) at 80 °C. The reaction mixture was stirred at same temperature for 1 h. Then, the reaction mixture was quenched with 6 M HCl aq., filtered and washed with H_2O to give **9b** (32.2 g, 96.3 mmol, 99%) as a white solid.

Spectral data for **9b** were in good agreement with those reported in reference.[16]

3,4,5-Tribenzyloxybenzoic acid (9c)

To a solution of **8c** (60.0 g, 0.318 mol) in MeOH (638 mL) was added $SOCl_2$ (23.2 mL, 0.319 mol) for dropwise at 60 °C. The reaction mixture was stirred at 60 °C for 8 h. Then, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a mixture of crude material (2.00 g, 10.9 mmol) and K_2CO_3 (6.78 g, 49.0 mmol) in DMF (36.0 mL) were added benzyl bromide (4.10 mL, 35.9 mmol) and TBAI (1.60 g, 4.33 mmol) at room temperature. The reaction mixture was stirred at room temperature for 11 h. Then, the reaction mixture was filtered through a pad of Celite, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a stirred solution of crude residue in MeOH/THF (1/1, 36.3 mL) was added 4 M NaOH aq. (9.50 mL, 38.0 mmol) at 80 °C. The reaction mixture was stirred at 80 °C for 1 h. Then, the reaction mixture was quenched with 6 M HCl aq., and filtered. The filtrate was washed with H_2O to give **9c** (3.30 g, 7.49 mmol,

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68%) as a white solid.

Spectral data for **9c** were in good agreement with those reported in reference.[16]

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)[4-(benzyloxy)phenyl]methanone (10a)

To a solution of **9a** (10.0 g, 43.8 mmol) in CH_2Cl_2 (100 mL) were added $SOCl_2$ (4.8 mL, 66.0 mmol) and DMF (1.4 mL, 18.0 mmol) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at 0 °C for 2 h. Then, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH_2Cl_2 (150 mL) were added Et_3N (6.1 mL, 43.8 mmol) and benzotriazole (5.2 g, 43.8 mmol) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at room temperature for 1 h. Then, the reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a residue including **10a**. The residue was recrystallized from *n*-hexane/CH_2Cl_2 to afford **10a** (9.1 g, 62%) as a white powder.

IR (film) 3072, 3034, 2916, 2857, 1694, 1605, 1361, 1267, 1177, 1047, 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 9.2 Hz, 2H), 8.16 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.50-7.30 (m, 5H), 7.14 (d, J = 9.2 Hz, 2H), 5.21 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 165.5, 163.3, 145.6, 135.9, 134.4, 132.5, 130.1, 128.7, 128.3, 127.4, 126.1, 123.6, 120.0, 114.8, 114.7, 70.2; MS (FAB): *m/z* 330 $(M+H)^+$; HRMS (FAB) calcd for $C_{20}H_{16}N_3O_2^+$, $(M+H)^+$ 330.1243, found 330.1231.

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)[3,4-bis(benzyloxy)phenyl]methanone (10b)

To a solution of **9b** (11.0 g, 33.0 mmol) in CH_2Cl_2 (100 mL) were added $SOCl_2$ (7.2 mL, 99.0 mmol) and DMF (1.0 mL, 13.2 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. Then, the reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH_2Cl_2 (110 mL) were added Et_3N (4.6 mL, 33.0 mmol) and benzotriazole (3.9 g, 33.0 mmol) at 0 °C under an Ar atmosphere, the reaction mixture was stirred for 12 h at room temperature. Then, the reaction mixture was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with 3 M NaOH aq., dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from *n*-hexane/CH_2Cl_2 to afford **10b** (11.4 g, 77%) as a white powder.

IR (film) 3062, 3032, 2916, 2870, 1692, 1597, 1514, 1360, 1271, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.35 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.97 (dd, J_1 = 8.6, J_2 = 1.8 Hz, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.69 (td, J_1 = 8.6, J_2 = 0.95 Hz, 1H), 7.54 (td, J_1 = 8.6, J_2 = 0.95 Hz, 1H), 7.53-7.45 (m, 4H), 7.43-7.30 (m, 6H), 7.07 (d, J = 8.6 Hz, 1H), 5.22 (s, 2H), 5.19 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ

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165.5, 153.9, 148.3, 145.7, 136.5, 136.2, 132.6, 130.2, 128.6, 128.5, 128.1, 128.0, 127.4, 127.1, 126.1, 123.6, 120.0, 117.5, 114.8, 112.9, 71.3, 70.8; MS (FAB): *m/z* 435 $(M+H)^+$; HRMS (FAB) calcd for $C_{27}H_{21}N_3O_3^+$, $(M+H)^+$ 435.1583, found 435.1555.

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)[3,4,5-tris(benzyloxy)phenyl]methanone (10c)

To a solution of **9c** (10.0 g, 23.0 mmol) in CH_2Cl_2 (52 mL) were added $SOCl_2$ (2.5 mL, 35.0 mmol) and DMF (0.70 mL, 9.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Then, the reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH_2Cl_2 (80 mL) were added Et_3N (3.2 mL, 23.0 mmol) and benzotriazole (2.7 g, 23.0 mmol) at 0 °C under an Ar atmosphere. After stirring at 0 °C for 24 h, the reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc. The organic layer was washed with 3 M NaOH aq., dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from *n*-hexane/EtOAc to afford **10c** (11 g, 88%) as a white powder.

IR (film) 3090, 3028, 2981, 2851, 1686, 1582, 1423, 1361, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.36 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.71 (td, J_1 = 7.3, J_2 = 1.0 Hz, 1H), 7.68 (s, 2H), 7.56 (td, J_1 = 7.3, J_2 = 1.0 Hz, 1H), 7.50-7.20 (m, 15H), 5.20 (s, 2H), 5.19 (s, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 165.6, 152.5, 145.6, 143.5, 137.3, 136.6, 132.6, 130.4, 128.6, 128.5, 128.2, 128.1, 128.0, 127.6, 126.3, 125.9, 120.2, 114.9, 111.8, 75.3, 71.4; MS (FAB): *m/z* 542 $(M+H)^+$; HRMS (FAB) calcd for $C_{34}H_{28}N_3O_4^+$, $(M+H)^+$ 542.2080, found 542.2032.

2-[4-(Benzyloxy)phenyl]-4*H*-chromen-4-one (11a)

To a mixture of 2'-hydroxyacetophenone (1.0 g, 7.48 mmol) and **10a** (2.6 g, 7.85 mmol) in THF (24.9 mL) was added LHMDS (29.9 mL, 29.9 mmol, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 2 h. Then, the reaction mixture was quenched with sat. NH_4Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue in toluene (25 mL) was added TFA (5.56 mL, 74.8 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 3 h. Then, the resulting solution was evaporated under reduced pressure to give a residue including **11a**. The residue was washed with Et_2O to afford **11a** (1.30 g, 5.5 mmol, 74%) as a white solid.

Spectral data for **11a** were in good agreement with those reported in reference.[17]

2-[3,4-(Dibenzyloxy)phenyl]-4*H*-chromen-4-one (11b)

To a mixture of 2'-hydroxyacetophenone (1.0 g, 7.37 mmol) and **10b** (3.4 g, 7.74 mmol) in THF (24.6 mL) was added LHMDS (29.5 mL, 29.5 mmol, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The

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reaction mixture was stirred at -78 °C for 3 h. Then, the reaction mixture was quenched with sat. NH_4Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue in toluene (25 mL) was added TFA (5.48 mL, 7.37 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 1 h. Then, the resulting solution was evaporated under reduced pressure to give a residue including **11b**. The residue was washed with Et_2O to afford **11b** (2.64 g, 6.1 mmol, 82%) as a white solid.

IR (film) 3051, 3034, 2864, 1645, 1599, 1518, 1433, 1329, 1271, 1142, 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (dd, J_1 = 7.9, J_2 = 1.6 Hz, 1H), 7.68 (td, J_1 = 7.9, J_2 = 1.6 Hz, 1H), 7.55-7.30 (m, 14H), 7.03 (d, J = 8.5 Hz, 1H), 6.68 (s, 1H), 5.27 (s, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 178.3, 163.1, 156.1, 152.0, 148.9, 136.7, 136.4, 133.5, 128.6, 128.1, 127.3, 127.1, 125.6, 124.6, 123.9, 120.5, 117.9, 114.1, 112.8, 106.4, 71.5, 70.9; MS (FAB): *m/z* 434 $(M+H)^+$; HRMS (FAB) calcd for $C_{29}H_{22}O_4^+$, $(M+H)^+$ 434.1518, found 434.1548.

2-[3,4,5-(Tribenzyloxy)phenyl]-4*H*-chromen-4-one (11c)

To a mixture of 2'-hydroxyacetophenone (0.5 g, 3.63 mmol) and **10c** (2.06 g, 3.81 mmol) in THF (12.7 mL) was added LHMDS (14.5 mL, 14.5 mmol, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 2.5 h. Then, the reaction mixture was quenched with H_2O and sat. NH_4Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue (3.0 g) in toluene (17.8 mL) was added TFA (3.96 mL, 53.3 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 0.5 h. Then, the resulting solution was evaporated under reduced pressure to give a residue including **11c**. The residue was washed with Et_2O to afford **11c** (2.9 g, 5.36 mmol, 99%) as a white solid.

IR (film) 3048, 2834, 1632, 1585, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (dd, J_1 = 7.9, J_2 = 1.6 Hz, 1H), 7.70 (td, J_1 = 7.9, J_2 = 1.6 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.50-7.25 (m, 16H), 7.21 (s, 2H), 6.68 (s, 1H), 5.20 (s, 4H), 5.16 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 180.8, 163.0, 153.2, 136.5, 133.7, 130.6, 128.7, 128.6, 128.3, 128.2, 128.1, 127.5, 127.0, 125.7, 125.3, 118.0, 116.1, 111.3, 107.3, 106.3, 75.3, 71.5; MS (FAB): *m/z* 541 $(M+H)^+$; HRMS (FAB) calcd for $C_{36}H_{29}O_5^+$, $(M+H)^+$ 541.2015, found 541.2020.

3-Hydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one (12a)

To a solution of **11a** (100 mg, 0.30 mmol) in EtOH (12 mL) was added 10% $Pd(OH)_2$ on charcoal (5 mg) at room temperature, and the reaction mixture was stirred at 60 °C for 1 h under H_2 atmosphere. Then, the

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reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **12a**. The residue was washed with Et_2O to afford **12a** (71 mg, 99%) as a white powder.

IR (film) 2918, 1636, 1601, 1564, 1481, 1389, 1267 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ 8.02 (dd, J_1 = 8.6, J_2 = 1.4 Hz, 1H), 7.95 (d, J = 8,6 Hz, 2H), 7.83-7.70 (m, 2H), 7.47 (td, J_1 = 8.6, J_2 = 1.4 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.85 (s, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6): δ 177.1, 163.3, 161.1, 155.7, 134.2, 125.5, 124.8, 123.4, 121.7, 118.5, 104.9; MS (FAB): *m/z* 239 $(M+H)^+$; HRMS (FAB) calcd for $C_{15}H_{11}O_3^+$, $(M+H)^+$ 239.0708, found 239.0734.

3-Hydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one (12b)

To a solution of **11b** (100 mg, 0.30 mmol) in EtOH (14 mL) was added 10% $Pd(OH)_2$ in charcoal (5 mg) at room temperature, and the reaction mixture was stirred at 60 °C for 1 h under H_2 atmosphere. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **12b**. The residue was washed with Et_2O to give **12b** (36 mg, 62%) as a white powder.

IR (film) 3107, 2747, 1607, 1557, 1385, 1281, 1134,1121 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ 8.08 (d, J = 7.9 Hz, 1H), 8.85-7.65 (m, 4H), 7.59 (d, J = 7.3 Hz, 1H), 7.44 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6): δ 176.9, 163.4, 155.6, 149.6, 145.8, 134.2, 125.4, 124.8, 121.9, 118.9, 118.4, 116.1, 113.4, 104.9; MS (FAB): *m/z* 255 $(M+H)^+$; HRMS (FAB) calcd for $C_{15}H_{11}O_4^+$, $(M+H)^+$ 255.0657, found 255.0629.

2-(3,4,5-Trihydroxyphenyl)-4*H*-chromen-4-one (12c)

To a solution of **11c** (100 mg, 0.18 mmol) in EtOH (4 mL) was added 10% $Pd(OH)_2$ on charcoal (9 mg) at room temperature, and the mixture was stirred at 60 °C for 2.5 h under a H_2 atmosphere. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **12c**. The residue was washed with Et_2O to give **12c** (26 mg, 54%) as a green solid.

IR (film) 3087, 2849, 1605, 1553, 1121 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ 8.08 (dd, J_1 = 7.9, J_2 = 1.3 Hz, 1H), 7.77 (td, J_1 = 7.9, J_2 = 1.3 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.29 (s, 2H), 6.89 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 177.0, 163.6, 155.7, 146.4, 137.7, 134.2, 125.5, 124.9, 123.4, 120.9, 118.3, 105.7, 104.9; MS (FAB): *m/z* 271 $(M+H)^+$; HRMS (FAB) calcd for $C_{15}H_{11}O_5^+$, $(M+H)^+$ 271.0606, found 271.0611.

3-Hydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one (14a)

To a solution of **11a** (100 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) was added DMDO (9.00 mL, 0.09-0.11 M in acetone) at room temperature under an Ar atmosphere, and the reaction mixture was stirred at 30 °C for 1.8 h. Then, the reaction mixture was concentrated under reduced pressure to give a residue including **13a**.

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The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **13a** (93.6 mg, 89%) as a light brown powder.

Spectral data for **13a** were in good agreement with those reported in reference.[18]

To a solution of **13a** (100 mg, 0.29 mmol) in EtOH (16 mL) was added 10% $Pd(OH)_2$ on charcoal (5 mg) at room temperature, and the reaction mixture was stirred at 60 °C for 1 h under H_2 atmosphere. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **14a**. The residue was washed with Et_2O to give **14a** (44 mg, 67%) as a white powder.

^{1}H NMR (270 MHz, DMSO-d_6): δ 10.13 (brs, 1H), 9.32 (brs, 1H), 8.10 (d, J = 9.2 Hz, 2H), 8.09 (d, J = 7.9 Hz, 1H), 7.65-7.85 (m, 2H), 7.44 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 9.2 Hz, 2H); ^{13}C NMR (67.8 MHz, DMSO-d_6): δ 172.6, 159.2, 154.4, 146.2, 137.8, 133.5, 124.7, 124.5, 122.0, 121.4, 118.3; IR (film, cm^{-1}) 2980, 2868, 1604, 1557, 1420, 1207, 1107, 1015; MS (FAB): *m/z* 255 $(M+H)^+$; HRMS (FAB) calcd for $C_{15}H_{11}O_4^+$, $(M+H)^+$ 255.0657, found 255.0671.

3-Hydroxy-2-(3,4-dihydroxyphenyl)-4*H*-chromen-4-one (14b)

To a solution of **11b** (100 mg, 0.231 mmol) in CH_2Cl_2 (10.0 mL) was added DMDO (6.90 mL, 0.1 M in acetone) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 3 h. Then, the reaction mixture was concentrated under reduced pressure to give a residue including **13b**. The crude material was applied to following reaction without further purification.

To a solution of crude residue including **13b** in EtOH (25.0 mL) was added 20% $Pd(OH)_2$/C (3.41 mg) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at 60 °C under H_2 atmosphere for 3 h. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **14b**. The residue was washed with CH_2Cl_2 / MeOH (30 / 1) to give **14b** (38.4 mg, 59%) as a green solid.

^{1}H NMR (270 MHz, DMSO-d_6): δ 8.07 (d, J = 7.9 Hz, 1H), 8.85-7.65 (m, 3H), 7.59 (dd, J_1 = 7.9, J_2 = 2.0 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6): δ 172.5, 154.4, 147.7, 146.2, 145.2, 137.9, 133.5, 124.8, 124.5, 122.3, 121.3, 120.1, 118.2, 115.6, 115.3; MS (FAB): *m/z* 271 $(M+H)^+$; HRMS (FAB) calcd for $C_{15}H_{11}O_5^+$, $(M+H)^+$ 271.0606, found 271.0566.

2-(3,4,5-Tris((*tert*-butyldimethylsilyl)oxy)phenyl)-4*H*-chromen-4-one (15c)

To a solution of **12c** (300 mg, 1.11 mmol) in DMF (1.5 mL) were added TBSCl (1.00g, 6.67 mmol, 6.0 equiv) and imidazole (0.53 g, 7.78 mmol, 7.0 equiv) and DMAP (68 mg, 0.556 mmol, 0.5 equiv) under an Ar atmosphere. The reaction mixture was stirred at 100 °C for 24 h. The reaction mixture were added TBSCl (0.50 g, 3.34 mmol, 3.0 equiv) and imidazole (0.26 g, 3.89 mmol, 3.5 equiv) at 100 °C. The reaction mixture was stirred at 100 °C for 30 h. The resulting mixture was quenched with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with water followed by brine, dried over anhydrous

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$MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 20/1) to afford **15c** (607 mg, 0.989 mmol, 89%) as a white solid.

IR (film): 2953, 2959, 2856, 1645, 1564, 1492, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H, Ar), 7.67 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H, Ar), 7.48 (d, J = 8.0 Hz, 1H, Ar), 7.40 (t, J = 7.4 Hz, 1H, Ar), 7.11 (s, 2H, Ar), 6.65 (s, 1H), 1.00 (s, 9H), 0.98 (s, 18H), 0.27 (s, 12H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 178.5, 163.3, 156.2, 149.3, 142.2, 133.7, 125.8, 125.2, 124.0, 123.6, 118.0, 112.4, 106.4, 26.3, 26.2, 19.0, 18.6, -3.5, -3.8; MS (ESI): *m/z* 652 $(M+Na)^+$; HRMS (ESI): calcd for $C_{33}H_{53}NaO_6Si^+$, $(M+Na)^+$ 652.3042, found 652.3038.

3-Hydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-4-one (14c)

To a solution of **15c** (115 mg, 0.155 mmol) in CH_2Cl_2 (0.52 mL) was added DMDO (3.1 mL, 0.1 M in acetone) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 2 h. The resulting solution was diluted with acetone and concentrated under reduced pressure to give a residue including **16c**. The crude residue was applied to following reaction without further purification.

To a solution of crude residue including **16c** in THF (2.3 mL) were added TBAF (0.69 mL, 0.69 mmol, 5.0 equiv) and AcOH (40 μL) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 0.5 h. The resulting mixture was quenched with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was washed with Et_2O and hexane to afford **14c** (29 mg, 0.096 mmol, 69%) as a yellow solid.

IR (film): 3265, 1585, 1537, 1506, 1489, 0346, 1398, 1209, 1035 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ 9.27 (s, 1H, OH), 9.25 (s, 2H, OH), 8.81 (s, 1H, OH), 8.50 (dd, J_1 = 7.4, J_2 = 1.7 Hz, 1H, Ar), 7.74 (td, J_1 = 8.5, J_2 = 1.7 Hz, 1H, Ar), 7.64 (d, J = 8.5 Hz, 1H, Ar), 7.42 (t, J = 7.4 Hz, 1H, Ar), 7.27 (s, 2H, Ar); ^{13}C NMR (125 MHz, DMSO-d_6); δ 172.9, 154.8, 146.7, 146.3, 138.5, 136.3, 133.9, 125.3, 124.9, 121.8, 121.7, 118.6, 107.8; MS (FAB): *m/z* 287 $(M+H)^+$; HRMS (FAB) calcd for $C_{15}H_{11}O_6^+$, $(M+H)^+$ 287.1556, found 287.1574.

1-(2-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxyphenyl)ethanone (17)

To a solution of 2',6'-dihydroxyacetophenone (500 mg, 3.30 mmol) in DMF (11 mL) were added TBSCl (497 mg, 3.30 mmol, 1.0 equiv) and imidazole (247 mg, 3.63 mmol, 1.2 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 13 h. The resulting mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc. The organic layer was washed with H_2O followed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30/1) to afford **17** (806 mg, 92%) as a yellow solid.

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IR (film): 2956, 2927, 2856, 1614, 1591, 1452, 1255, 1222, 831, 786 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.91 (s, 1H, OH), 7.23 (dd, J_1 = 8.6 Hz, J_2 = 8.0 Hz, 1H), 6.54 (dd, J_1 = 8.6 Hz, J_2 = 1.2 Hz, 1H), 6.34 (dd, J_1 = 8.6 Hz, J_2 = 1.2 Hz, 1H), 2.68 (s, 3H), 1.00 (s, 9H), 0.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 164.2, 157.9, 135.5, 113.8, 110.6, 109.6, 33.3, 26.1, 18.8, -3.6; MS (ESI): *m/z* 289 $(M+Na)^+$; HRMS (ESI) calcd for $C_{14}H_{22}NaO_3Si^+$, $(M+Na)^+$ 289.1230, found 289.1240.

5-Hydroxy-2-(3,4,5-tris((*tert*-butyldimethylsilyl)oxy)phenyl)-4*H*-chromen-4-one (19)

To a mixture of **17** (553 mg, 2.08 mmol) and crude material **18** (1.66 g, 2.70 mmol, 1.3 equiv) in THF (7 mL) was added LHMDS (8.3 mL, 8.31 mmol, 1M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 3.5 h. Then, the reaction mixture was quenched with sat. NH_4Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue in toluene (10 mL) was added TFA (1 mL) at 60 °C. The reaction mixture was stirred at 60 °C for 5 min. Then, the resulting solution was evaporated under reduced pressure to give a residue including **19**. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 50/1) to give **19** (955 mg, 1.52 mmol, 73%) as a yellow powder.

IR (film): 2929, 2856, 1658, 1616, 1359, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.65 (s, 1H, OH), 7.53 (t, *J* = 8.3 Hz, 1H), 7.09 (s, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.55 (s, 1H), 1.01 (s, 9H), 0.98 (s, 18H), 0.28 (s, 12H), 0.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.6, 164.6, 160.9, 156.4, 149.4, 142.7, 135.3, 123.0, 112.5, 111.4, 110.8, 106.9, 104.8, 26.3, 26.2, 19.0, 18.6, -3.5, -3.8; MS (ESI): *m/z* 651 $(M+Na)^+$; HRMS (ESI): calcd for $C_{33}H_{52}NaO_6Si_3^+$, $(M+Na)^+$ 651.2949, found. 651.2963.

3,5-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-4-one (20)

To a solution of **19** (364 mg, 0.579 mmol) in DMF (0.58 mL) were added imidazole (394 mg, 5.79 mmol) and TBSCl (872 mg, 5.79 mmol) and DMAP (2.0 mg) at room temperature and the mixture was stirred at 100 °C for 9 h and allowed to cool to room temperature. Then, the reaction mixture was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine. The extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a residue including **19'**. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30/1) to afford **19'** (397 mg, 92%) as a yellow solid.

IR (film): 2954, 2858, 1710, 1654, 1490, 1355, 1253, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (dd, J_1 = 8.5 Hz, J_2 = 7.9 Hz, 1H), 7.07 (s, 2H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.48 (s, 1H), 1.07 (s, 9H, *t*-Bu), 1.00 (s, 9H, *t*-Bu), 0.97 (s, 18H, *t*-Bu), 0.27 (s, 6H, Me), 0.27 (s, 12H, Me), 0.16 (s, 6H, Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 161.0, 157.9, 155.6, 149.1, 141.7, 132.9, 116.9, 112.0, 111.9, 110.5, 107.3, 26.2, 26.1, 25.9, 18.8, 18.7, 18.5, -3.6, -3.9, -4.4; MS (ESI): *m/z* 743 $(M+H)^+$; HRMS (ESI):

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calcd for $C_{39}H_{67}O_6Si_4^+$, $(M+H)^+$ 743.4009, found 743.4015.

To a solution of **19'** (105 mg, 0.155 mmol) in CH_2Cl_2 (0.52 mL) was added DMDO (3.1 mL, 0.09 - 0.11 M in acetone) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was concentrated under reduced pressure to give a pale yellow amorphous.

To a solution of the crude material in THF (2.3 mL) were added AcOH (100 μL) and TBAF (0.69 mL, 5.0 equiv) at 0 °C under an Ar atmosphere, and the mixture was stirred at room temperature for 0.5 h. Then, the reaction mixture was diluted with CH_2Cl_2. The resulting solution was washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue including **20**. The residue was washed with Et_2O to give **20** (28.8 mg, 69%) as an orange solid.

IR (film): 3338, 1597, 1525, 1463, 1192, 1012, 800 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.43 (s, 1H, OH), 9.56 (brs, 1H, OH), 9.23 (brs, 2H, OH), 7.61 (dd, J_1 = 8.6 Hz, J_2 = 8.0 Hz, 1H), 7.32 (s, 2H), 7.08 (d, J = 8.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 177.2, 159.8, 155.0, 148.7, 146.3, 137.2, 136.9, 135.6, 121.1, 109.7, 109.4, 108.1, 107.8, 103.3; MS (ESI): *m/z* 325 $(M+Na)^+$; HRMS (ESI): calcd for $C_{15}H_{10}NaO_7^+$, $(M+Na)^+$ 325.0318, found 325.0306.

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)(3-(benzyloxy)-4-methoxyphenyl)methanone (22b)

To a solution of 3-(benzyloxy)-4-methoxybenzoic acid (1.27 g, 4.91 mmol) in CH_2Cl_2 (16.4 mL) were added $SOCl_2$ (3.08 mL, 44.2 mmol, 9.0 equiv) and DMF (0.15 mL, 1.97 mmol, 0.4 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH_2Cl_2 (16.4 mL) were added Et_3N (1.03 mL, 7.37 mmol, 2.5 equiv) and benzotriazole (1.17 g, 9.83 mmol, 2.0 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 30 min. After stirring, the reaction mixture was quenched with sat. NH_4Cl solution at 0 °C and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **22b**. The crude residue was purified by recrystallization from *n*-hexane/CH_2Cl_2 to afford **22b** (1.10 g, 3.06 mmol, 82%) as a white solid.

IR (film): 3086, 3012, 2939, 2837, 1699, 1595, 1516, 1357, 1267, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, J = 8.3 Hz, 1H, Ar), 8.17(d, J = 8.3 Hz, 1H, Ar), 8.03 (t, J = 8.3 Hz, 1H, Ar), 7.90 (t, J = 8.3 Hz, 1H, Ar), 7.89 (t, J = 8.3 Hz, 1H, Ar), 7.56-7.26 (m, 6H, Ar), 7.01 (d, J = 8.3 Hz, 1H, Ar), 5.26 (s, 2H, CH_2), 4.00 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 154.7, 147.9, 145.6, 136.4, 132.0, 130.2, 128.7, 128.2, 127.0, 126.2, 123.3, 120.1, 116.6, 114.9, 110.7, 77.4, 76.9, 71.2, 56.2; MS (ESI): *m/z* 382 $(M+Na)^+$; HRMS (ESI): calcd for $C_{21}H_{17}N_3NaO_3^+$, $(M+Na)^+$ 382.1162, found 382.1174.

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)(4-(benzyloxy)-3-methoxyphenyl)methanone (22c)

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To a solution of 4-(benzyloxy)-3-methoxybenzoic acid (1.0 g, 3.87 mmol) in CH_2Cl_2 (13.0 mL) were added $SOCl_2$ (0.84 mL, 11.6 mmol, 3.0 equiv) and DMF (0.12 mL, 1.55 mmol, 0.4 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH_2Cl_2 (13.0 mL) were added Et_3N (0.81 mL, 5.81 mmol, 1.5 equiv) and benzotriazole (0.51 g, 5.81 mmol, 1.1 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 30 min. After stirring, the reaction mixture was quenched with sat. NH_4Cl solution at 0 °C, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **22c**. The crude residue was purified by recrystallization from *n*-hexane/CH_2Cl_2 to afford **22c** (1.10 g, 3.06 mmol, 79%) as a white solid.

IR (film): 3111, 3030, 2958, 2875, 1701, 1597, 1512, 1359, 1215, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, J = 8.3 Hz, 1H, Ar), 8.15 (d, J = 8.3 Hz, 1H, Ar), 7.95 (dd, J_1 =8.3 Hz, J_2 = 2.6 Hz 1H, Ar), 7.82 (s, 1H, Ar), 7.65 (d, J = 8.3 Hz, 1H, Ar), 7.56-7.26 (m, 6H, Ar), 7.04 (d, J = 8.3 Hz, 1H, Ar), 5.28 (s, 2H, CH_2), 4.00 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 153.2, 149.3, 147.8, 136.1, 130.2, 128.8, 128.3, 127.3, 127.0, 126.2, 123.6, 120.1, 114.9, 112.3, 77.4, 77.2, 76.9, 70.9, 56.2; MS (ESI): *m/z* 382 $(M+Na)^+$; HRMS (ESI): calcd for $C_{21}H_{17}N_3NaO_3^+$, $(M+Na)^+$ 382.1162, found 382.1100.

3'-Demethylnobiletin (23b)

To a mixture of **21** (110 mg, 0.43 mmol) and **22b** (169.1 mg, 0.470 mmol, 1.1 equiv) in THF (1.43 mL) was added LHMDS (1.72 mL, 1.72 mmol, 4.0 equiv, 1 M sol. in THF) under an Ar atmosphere at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. The resulting mixture was quenched with sat. NH_4Cl solution at 0 °C, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **22b'** as a yellow solid. The crude solid was applied to following reaction without further purification.

To a solution of crude solid including **22b'** (283.1 mg) in toluene (1.96 mL) was added TFA (0.44 mL) at room temperature. The reaction mixture was stirred at 60 °C for 30 min. After stirring, the reaction mixture was concentrated under reduced pressure to give a residue including **22b''** as a pale yellow solid. The crude solid was applied to following reaction without further purification.

To a mixture of **22b''** (50.0 mg) in EtOH (10 mL) added $Pd(OH)_2$ (1.46 mg, 2.09 μmol) under an Ar atmosphere, then purged with H_2 gas. The reaction mixture was stirred at 60 °C for 2 h. The resulting mixture was filtered with a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **23b**. The crude residue was purified by recrystallization from *n*-hexane/CH_2Cl_2 to afford **23b** (23.6 mg, 23%, 3 steps from **21**) as a yellow solid.

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IR (film): 2939, 2841, 1629, 1589, 1509, 1438, 1359, 1280, 1016, 842, 808 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, Ar), 7.46 (d, J = 8.4 Hz, 1H, Ar), 6.97 (d, J = 8.4 Hz, 1H, Ar), 6.58 (s, 1H, CH), 4.09 (s, 3H, OCH_3), 4.01-3.95 (m, 12H, OCH_3).^{13}C NMR (125 MHz, $CDCl_3$): δ 179.6, 163.9, 153.3, 152.6, 149.3, 149.1, 148.3, 145.6, 139.6, 124.9, 119.8, 115.3, 113.8, 112.7, 106.8, 110.7, 62.6, 62.6, 62.2, 62.1; MS (ESI): *m/z* 411 $(M+Na)^+$; HRMS (ESI): calcd for $C_{20}H_{20}NaO_8^+$, $(M+Na)^+$ 411.1050, found 411.1067.

4'-Demethylnobiletin (23c)

To a mixture of **21** (100 mg, 0.39 mmol) and **22c** (154 mg, 0.429 mmol, 1.1 equiv) in THF (1.3 mL) was added LHMDS (1.56 mL, 1.56 mmol, 4.0 equiv, 1 M sol. in THF) under an Ar atmosphere at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. The resulting mixture was quenched with sat. NH_4Cl solution at 0 °C, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **22c'** as a yellow solid. The crude solid was applied to following reaction without further purification.

To a solution of crude solid including **22c'** (280.4 mg) in toluene (1.95 mL) was added TFA (0.43 mL) at room temperature. The reaction mixture was stirred at 60 °C for 30 min. After stirring, the reaction mixture was concentrated under reduced pressure to give a residue including **22c''** as a pale yellow solid. The crude solid was applied to following reaction without further purification.

To a mixture of **22c''** (51.0 mg, 0.107 mmol) in EtOH (10 mL) was added $Pd(OH)_2$ (1.5 mg, 2.14 μmol) under an Ar atmosphere, then purged with H_2 gas. The reaction mixture was stirred at 60 °C for 2 h. The resulting mixture was filtered with a pad of Cellite. The filtrate was concentrated under reduced pressure to give a residue including **23c**. The crude residue was purified by silica gel column chromatography with (*n*-hexane/AcOEt = 2 : 3) to afford **23c** (39.7 mg, 39%, 3 steps from **21**) as a white solid.

IR (film): 2937, 2851, 1629, 1589, 1517, 1429, 1367, 1273, 1022, 842, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 8.4 Hz, 1H, Ar), 7.00 (s, 1H, Ar), 6.76 (d, J = 8.4 Hz, 1H, Ar), 6.60 (s, 1H, CH), 4.08 (s, 3H, OCH_3), 4.03-3.95 (m, 12H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.5, 163.2, 153.5, 153.1, 149.2, 149.1, 148.6, 145.5, 139.3, 125.0, 121.3, 115.9, 112.7, 110.1 107.5, 63.2, 63.0, 62.0, 61.5; MS (ESI): *m/z* 411 $(M+Na)^+$; HRMS (ESI): calcd for $C_{20}H_{20}NaO_8^+$, $(M+Na)^+$ 411.1050, found 411.1061.

5-Demethylnobiletin (24)

To a solution of **3** (50 mg, 0.13 mmol) in CH_2Cl_2 (40 mL) was added $AlCl_3$ (33 mg, 0.26 mmol, 2.0 equiv) in EtSH (0.66 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was quenched with 6 M HCl aq. at 0 °C, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1, 1/1) to afford **24** (36 mg, 76%) as a yellow powder.

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Spectral data for **24** were in good agreement with those reported in reference.[19]

***N*-(5-((2-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxy-4-oxo-4*H*-chromen-5-yl)oxy)pentyl)propiolyl-amide (25)**

To a mixture of **24** (0.28 g, 0.73 mmol) and *tert*-butyl (5-iodopentyl)carbamate (0.68 g, 2.2 mmol, 3.0 equiv) in acetone (2.4 mL) was added K_2CO_3 (0.30 g, 2.2 mmol, 3.0 equiv) at 50 °C. The reaction mixture was stirred at 50 °C for 48 h, and allowed to cool to room temperature. The resulting mixture was poured into Et_2O, and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **24a**. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1, 1/1) to give a crude material including **24a**. The crude material including **24a** was applied to following reaction without further purification.

To a solution of crude **24a** in CH_2Cl_2 (2.0 mL) and MeOH (10 mL) was added 2 M HCl aq. (5.0 mL). The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was quenched with 2 M NaOH aq. at 0 °C, concentrated under reduced pressure to remove MeOH, extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **24b**. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH/*i*-$PrNH_2$ = 10/10/0.1) to afford **24b** (0.25 g, 71%) as a yellow oil.

IR (film): 3404, 2939, 1629, 1517, 1429, 1367, 1273, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, J_1 = 8.5 Hz, J_2 = 2.7 Hz, 1H, Ar), 7.41 (s, 1H, Ar), 6.98 (d, J = 8.5 Hz, 1H, Ar), 6.60 (s, 1H, CH), 4.10 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.02 (t, J = 6.8 Hz, 2H, CH_2), 3.98 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.80 (t, J = 6.8 Hz, 2H, CH_2), 1.91 (m, 2H, CH_2), 1.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 161.5, 152.0, 151.7, 149.3, 147.8, 147.4, 144.3, 137.9, 123.8, 119.9, 114.7, 111.2, 108.6, 106.7, 74.7, 62.0, 61.9, 61.7, 56.1, 39.7, 29.3, 27.2, 22.7; MS (ESI): *m/z* 474 $(M+H)^+$; HRMS (ESI): calcd for $C_{25}H_{32}N_1O_8^+$, $(M+H)^+$ 474.2121, found 474.2122.

To a mixture of **24b** (66 mg, 0.14 mmol) and 3-(trimethylsilyl)propiolic acid (40 mg, 0.28 mmol, 2.0 equiv) in CH_2Cl_2 (0.50 mL) were added EDCI (0.16 g, 0.83 mmol, 4.0 equiv) and HOBt (2.0 mg) at room temperature. The reaction mixture was stirred at room temperature for 24 h. The resulting mixture was poured into H_2O. The organic layer was separated, and aqueous phase was extracted with CH_2Cl_2.The organic layer was combined, washed with H_2O followed by brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **24c**. The residue was purified by silica gel column chromatography (EtOAc 100%) to give a crude material including **24c**. The crude material including **24c** was applied to following reaction without further purification.

To a solution of crude **24c** in CH_2Cl_2 (2.0 mL) was added TBAF (0.30 mL, 1.0 M sol. in THF). The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was poured into H_2O. The organic layer was separated, and aqueous phase was extracted with CH_2Cl_2. The organic layer was

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combined, washed with H_2O followed by brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **25**. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to afford **25** (50 mg, 68%) as a colorless oil.

IR (film): 3232, 2939, 2104, 1637, 1629, 1518, 1365, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (dd, J_1 = 8.5 Hz, J_2 = 2.3 Hz, 1H, Ar), 7.42 (s, 1H, Ar), 7.00 (d, J = 8.5 Hz, 1H, Ar), 6.61 (s, 1H, CH), 4.11 (s, 3H, OCH_3), 4.07 (t, J = 5.9 Hz, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.39 (q, J = 5.9 Hz, 2H, CH_2), 2.74 (s, 1H, CH) 1.89 (m, 2H, CH_2), 1.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 161.2, 152.4, 152.0, 151.6, 149.3, 147.9, 147.6, 144.3, 137.9, 123.9, 119.7, 114.9, 111.3, 108.5, 106.9, 74.4, 72.5, 62.0, 61.9, 61.7, 56.1, 56.0, 39.9, 29.6, 28.2, 23.0, 22.9; MS (ESI): *m/z* 548 $(M+H)^+$; HRMS (ESI): calcd for $C_{28}H_{31}N_1O_9^+$, $(M+H)^+$ 548.1891, found 548.1893.

5-Hydroxy-2-(3,4,5-tris(benzyloxy)phenyl)-4*H*-chromen-4-one (26)

To a mixture of **17** (1.0 g, 3.75 mmol) and **10c** (2.04 g, 4.96 mmol, 1.3 equiv) in THF (12.7 mL) was added LHMDS (15.0 mL, 15.0 mmol, 4.0 equiv, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 2.5 h. Then, the reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **10c'** as a yellow solid. The crude mixture was applied to the following reaction without further purification.

To a solution of the crude residue including **10c'** (3.14 g) in toluene (12.5 mL) was added TsOH (1.43 g, 7.5 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 3 h. The crude mixture was diluted with EtOAc and washed with water. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **26**. The residue was purified by silica gel column chromatography (CH_2Cl_2/*n*-hexane = 15/1) to afford **26** (2.00 g, 95%, 2 steps) as a white solid.

IR (film): 3032, 1649, 1633, 1159, 1433, 1340, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.57 (s, OH), 7.54 (dd, J_1 = 8.6 Hz, J_2 = 8.0 Hz 1H, Ar), 7.46-7.34 (m, 15H, Ar), 7.17 (s, 2H, Ar), 6.95 (d, J = 8.6 Hz, 1H, Ar), 6.81 (d, J = 8.6 Hz, 1H, Ar), 6.57 (s, 1H, Ar), 5.19 (s, 4H), 5.17 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.5, 164.3, 160.9, 156.4, 153.3, 142.0, 137.4, 136.6, 135.4, 128.8, 128.7, 128.4, 128.3, 128.2, 127.6, 126.4, 111.6, 110.9, 107.1, 106.5, 105.8, 75.4, 71.6; MS (ESI): *m/z* 579 $(M+Na)^+$; HRMS (ESI): calcd for $C_{36}H_{28}NaO_6^+$, $(M+Na)^+$ 579.1778, found 579.1769.

5-(Pent-4-yn-1-yloxy)-2-(3,4,5-tris(benzyloxy)phenyl)-4*H*-chromen-4-one (27)

To a mixture of **6** (300 mg, 0.54 mmol) and 1-iodo-4-pentyn (420 mg, 2.2 mmol, 4.0 equiv) in DMF (4.0 mL) was added K_2CO_3 (300 mg, 2.2 mmol, 4.0 equiv) at room temperature. The reaction mixture was stirred at 100 °C for 8 h, and allowed to cool to room temperature. The resulting mixture was diluted with Et_2O, and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and

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extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give a residue including **27**. The residue was recrystallized from CH_2Cl_2/Et_2O to afford **27** (297 mg, 92%) as a white solid.

IR (film): 3213, 2332, 1637, 1126, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (dd, J_1 = 8.6 Hz, J_2 = 8.0 Hz, 1H, Ar), 7.47-7.34 (m, 15H, Ar), 7.17 (s, 2H, Ar), 7.06 (d, J = 8.6 Hz, 1H, Ar), 6.82 (d, J = 8.0 Hz, 1H, Ar), 6.53 (s, 1H, Ar), 5.18 (s, 4H), 5.15 (s, 2H), 4.21 (dd, J_1 = 6.3 Hz, J_2 = 5.7 Hz, 2H), 2.60 (dt, J_1 = 6.9 Hz, J_2 = 2.9 Hz, 2H), 2.14 (quint, J = 6.3 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 160.7, 159.2, 158.2, 153.2, 141.3, 137.5, 136.7, 133.7, 128.7, 128.7, 128.4, 128.2, 128.1, 127.6, 126.8, 114.9, 110.1, 108.9, 107.8, 106.2, 83.9, 75.4, 69.0, 67.7, 28.1, 15.2; MS (ESI): *m/z* 645 $(M+Na)^+$; HRMS (ESI): calcd for $C_{41}H_{34}NaO_6^+$, $(M+Na)^+$ 645.2247, found 645.2245.

5-(Pent-4-yn-1-yloxy)-2-(3,4,5-tris((*tert*-butyldimethylsilyl)oxy)phenyl)-4*H*-chromen-4-one (28)

To a mixture of **27** (200 mg, 0.32 mmol) in CH_2Cl_2 (6.40 mL) was added BCl_3 (1.0 mL, 1.0 mmol, 3.1 equiv, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 1.5 h. Then, the reaction mixture was quenched with MeOH at -78 °C and concentrated under reduced pressure to give a residue the reaction mixture as an orange solid. The crude mixture was applied to following reaction without further purification.

To a solution of the reaction mixture (190 mg) in DMF (0.65 mL) were added imidazole (220 mg, 3.21 mmol, 10 equiv) and TBSCl (480 mg, 3.21 mmol, 10 equiv) at room temperature under an Ar atmosphere. The reaction mixture was stirred at 100 °C for 5 h. Then, the reaction mixture was quenched with H_2O and sat. NH_4Cl solution, and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **28** as a brown oil. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 6/1) to afford **28** (154 mg, 70%, 2 steps) as a white solid.

IR (film): 3236, 2928, 2856, 2324, 1645, 1602, 1481, 1084 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, J_1 = 8.6 Hz, J_2 = 8.0 Hz, 1H, Ar), 7.06 (s, 2H, Ar), 7.03 (d, J = 8.6 Hz, 1H, Ar), 6.80 (d, J = 8.0 Hz, 1H, Ar), 6.49 (s, 1H, Ar), 4.21 (dd, J_1 = 6.3 Hz, J_2 = 5.7 Hz, 2H), 2.59 (dt, J_1 = 6.9 Hz, J_2 = 2.3 Hz, 2H), 2.13 (quint, J = 6.9 Hz, 2H), 1.93 (t, J = 2.3 Hz, 1H), 1.00 (s, 9H), 0.97 (s, 18H), 0.26 (s, 12H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.2, 161.0, 159.2, 158.2, 149.2, 141.9, 133.5, 123.3, 114.9, 112.1, 110.1, 108.0, 107.8, 83.9, 68.8, 67.7, 28.1, 26.3, 26.2, 19.0, 18.6, 15.1, -3.5, -3.8; MS (ESI): *m/z* 717 $(M+Na)^+$; HRMS (ESI): calcd for $C_{38}H_{58}NaO_6Si_3^+$, $(M+Na)^+$ 717.3433, found 717.3432.

***N*-(3-Azidopropyl)-4-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)-3-methylbenzamide (29)**

To a mixture of TokyoGreen (0.10 g, 0.30 mmol) and 3-azidopropan-1-amine (60 mg, 0.60 mmol, 2.0 equiv) in DMF (1.0 mL) was added EDCI (0.23 g, 1.2 mmol, 4.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 12 h. After stirring, the reaction mixture was

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concentrated under reduced pressure to give a residue including **29**. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to afford **29** (97 mg, 76%) as an orange solid.

IR (film): 3251, 2094, 1633, 1600, 1099, 913, 836 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.63 (t, J = 5.4 Hz, 1H, NH), 7.91 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 6.80 (d, J = 9.2 Hz, 2H), 6.55 (d, J = 8.0 Hz, 4H) 3.47-3.39 (m, 4H), 2.04 (s, 3H), 1.78 (quint, J = 5.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ166.4, 149.1, 136.5, 136.0, 135.6, 125.5, 104.1, 79.8, 79.5, 79.2, 49.1, 28.9, 19.6; MS (ESI): m/z 429 $(M+H)^+$; HRMS (ESI): calcd for $C_{24}H_{21}N_4O_4^+$, $(M+H)^+$ 429.1559, found 429.1557.

***N*-(3-Azidopropyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (30)**

To a mixture of biotin (0.30 g, 1.2 mmol) and 3-azidopropan-1-amine (0.25 g, 2.5 mmol, 2.0 equiv) in DMF (4.0 mL) was added EDCI (0.47 g, 2.5 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 10 h. After stirring, the reaction mixture was concentrated under reduced pressure to give a residue including **30**. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to afford **30** (0.30 g, 74%) as a white solid.

IR (film): 3278, 2098, 1690, 1672, 1642, 1544, 1262 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.83 (t, J = 5.7 Hz, 1H, NH), 6.43 (s, 1H, NH), 6.36 (s, 1H, NH), 4.29 (t, J = 5.7 Hz, 1H, CH), 4.12 (t, J = 5.7 Hz, 1H, CH), 3.33 (t, J = 7.1 Hz, 2H, CH_2), 3.10-3.05 (m, 3H), 2.81 (dd, J_1 = 17.6 Hz, J_2 = 7.1 Hz, 1H, CH), 2.56 (d, J = 17.6 Hz, 1H, CH), 2.49 (s, 1H, CH), 2.04 (t, J = 7.1 Hz, 2H, CH_2) 1.65-1.41 (m, 6H, CH_2), 1.35-1.23 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.6, 163.2, 61.5, 59.7, 55.9, 48.9, 36.2, 35.7, 28.9, 28.7, 28.5, 25.8; MS (ESI): m/z 349 $(M+Na)^+$; HRMS (ESI): calcd for $C_{13}H_{22}N_6NaO_2S^+$, $(M+Na)^+$ 349.1419, found 349.1417.

***N*-(5-((2-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxy-4-oxo-4*H*-chromen-5-yl)oxy)pentyl)-1-(3-(4-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)-3-methylbenzamido)propyl)-1*H*-1,2,3-triazole-4-carboxamide (31)**

To a mixture of **25** (25 mg, 48 μmol, 1.2 equiv) and **29** (17 mg, 40 μmol, 1.0 equiv) in CH_2Cl_2 (0.10 mL) and MeOH (0.10 mL) were added $CuSO_4$ (0.63 mg, 4.0 μmol, 0.10 equiv) and sodium *L*-ascorbate (1.2 mg, 5.9 μmol, 0.15 equiv) at room temperature. The reaction mixture was stirred at room temperature for 24 h. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **31**. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 30/1, 20/1, 10/1) to afford **31** (27 mg, 2.8 μmol, 71%) as an orange solid.

IR (film): 1636, 1588, 1262, 1202, 849 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.68 (t, J = 5.7 Hz, 1H), 8.61 (s, 1H), 8.54 (t, J = 5.7 Hz, 1H), 7.91 (s, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.52 (s, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 4.0 Hz, 2H), 6.80 (s, 1H), 6.58 (brs, 2H) 4.49 (t, J = 6.2 Hz, 2H), 4.00 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.89 (t, J = 6.2 Hz, 2H, CH_2), 3.86

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(s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.26 (t, *J* = 6.8 Hz, 2H, CH_2), 2.14 (quint, *J* = 6.8 Hz, 2H, CH_2), 2.05 (s, 3H, CH_3), 1.77 (quint, *J* = 6.8 Hz, 2H, CH_2), 1.59 (quint, *J* = 6.8 Hz, 2H, CH_2), 1.48 (quint, *J* = 6.8 Hz, 2H, CH_2), 1.22 (m, 2H, CH_2), 0.83 (t, *J* = 6.8 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.4, 166.4, 160.7, 160.2, 152.3, 151.5, 149.6, 149.2, 147.7, 147.3, 144.1, 143.4, 138.0, 136.4, 135.8, 135.6, 130.4, 129.7, 127.0, 125.4, 123.6, 119.8, 114.9, 112.3, 109.3, 106.8, 75.0, 62.3, 62.0, 61.9, 56.2, 56.1, 48.2, 38.9, 37.0, 30.1, 29.8, 29.5, 23.4, 19.6; MS (ESI): *m/z* 954 $(M+H)^+$; HRMS (ESI): calcd for $C_{52}H_{52}N_5O_{13}^+$, $(M+H)^+$ 954.3556, found 954.3556.

***N*-(5-((2-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxy-4-oxo-4*H*-chromen-5-yl)oxy)pentyl)-1-(3-(5-((3a*S*,-4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)propyl)-1*H*-1,2,3-triazole-4-arboxamide (32)**

To a mixture of **25** (7.0 mg, 13 μmol) and **30** (4.4 mg, 13 μmol) in CH_2Cl_2 (0.10 mL) and MeOH (0.10 mL) were added $CuSO_4$ (0.42 mg, 2.7 μmol, 0.2 equiv) and sodium *L*-ascorbate (0.80 mg, 4.0 μmol, 0.30 equiv) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **32**. The residue was purified by preparative TLC (CH_2Cl_2/MeOH = 20/1, 15/1) to afford **32** (5.5 mg, 48%) as a white solid.

IR (film): 2937, 1701, 1647, 1637, 1629, 1273 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.52 (dd, J_1 = 6.3 Hz, J_2 = 5.7 Hz, 1H, Ar), 7.89 (t, *J* = 5.7 Hz, 1H, Ar), 7.64 (dd, J_1 = 8.6 Hz, J_2 = 2.3 Hz, 1H, Ar), 7.53 (d, *J* = 2.3 Hz, 1H, Ar) 7.16 (d, *J* = 8.6 Hz, 1H, Ar), 6.83 (s, 1H), 6.42 (s, 1H), 6.36 (s, 1H), 4.39 (t, *J* = 6.9 Hz, 2H), 4.29 (t, *J* = 6.3 Hz, 1H), 4.12 (t, *J* = 5.2 Hz, 1H), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.91 (t, *J* = 6.3 Hz, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.29 (q, *J* = 6.3 Hz, 2H), 3.09 (q, *J* = 5.7 Hz, 2H), 3.03 (q, *J* = 6.3 Hz, 2H), 2.81 (dd, J_1 = 12.3 Hz, J_2 = 5.2 Hz, 1H), 2.57 (d, *J* = 12.6 Hz, 1H), 2.06 (t, *J* = 7.5 Hz, 2H) 1.96 (quint, *J* = 6.9 Hz, 2H), 1.78 (quint, *J* = 6.87 Hz, 1H), 1.65-1.56 (m, 4H), 1.56-1.42 (m, 8H), 1.36-1.23 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.4, 172.7, 172.6, 163.2, 160.7, 160.2, 152.3, 151.5, 149.5, 147.7, 147.3, 144.2, 143.5, 138.0, 126.9, 123.7, 119.9, 115.0, 112.4, 109.4, 106.9, 75.0, 62.3, 62.0, 61.6, 59.7, 56.3, 56.2, 55.9, 48.9, 48.1, 39.0, 36.3, 36.0, 35.7, 30.3, 29.9, 29.5, 28.7, 28.6, 25.8, 23.4; MS (ESI): *m/z* 875 $(M+Na)^+$; HRMS (ESI): calcd for $C_{41}H_{54}N_7NaO_{11}S^+$, $(M+Na)^+$ 875.3492, found 875.3494.

***N*-(3-(4-(3-((4-Oxo-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-5-yl)oxy)propyl)-1*H*-1,2,3-triazol-1-yl)-propyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (33)**

To a mixture of **28** (100 mg, 0.14 mmol, 1.1 equiv) and **30** (43 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (1.00 mL) and MeOH (1.00 mL) were added $CuSO_4$•$5H_2O$ (10 mg, 0.065 mmol, 0.5 equiv) and sodium *L* -ascorbate (13 mg, 0.065 mmol, 0.5 eq) at room temperature. The reaction mixture was stirred at room temperature for 5 h. The resulting mixture was filtered through a pad of Celite. The filtrate was

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concentrated under reduced pressure to give a residue including **28'**. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to afford **28'** (124 mg, 0.12 mmol, 91%) as a white solid.

IR (film): 3284, 2958, 2858, 1701, 1647, 1460, 1427, 1357, 1261, 1095, 1051, 896, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.51 (t, J = 5.8 Hz, 1H), 7.05 (s, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.68 (dd, J_1 = 6.2 Hz, J_2 = 5.7 Hz, 1H), 6.50 (s, 1H), 4.49 (dd, J_1 = 6.8 Hz, J_2 = 5.7 Hz, 2H), 4.37 (t, J = 6.8 Hz, 1H), 4.30 (dd, J_1 = 6.2 Hz, J_2 = 5.7 Hz, 1H), 4.13 (dd, J_1 = 6.2 Hz, J_2 = 5.8 Hz, 1H), 3.27-3.11 (m, 2H), 3.04, (dd, J_1 = 7.4 Hz, J_2 = 6.8 Hz, 2H), 2.89 (dd, J_1 = 13.0 Hz, J_2 = 5.1 Hz, 1H), 2.73 (d, J = 13.0 Hz, 1H), 2.29 (quint, J = 6.8 Hz, 2H), 2.18 (quint, J = 6.8 Hz, 2H), 2.08 (quint, J = 6.8 Hz, 2H), 1.76-1.60 (m, 4H), 1.41 (quint, J = 6.8 Hz, 2H), 1.23 (t, J = 6.8 Hz 1H), 0.99 (s, 9H), 0.96 (s, 18H), 0.25 (s, 12H), 0.15 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 178.5, 174.0, 164.4, 164.4, 161.3, 158.9, 158.3, 158.2, 149.3, 149.2, 147.3, 142.0, 133.8, 123.1, 114.6, 112.5, 112.1, 110.0, 107.8, 107.7, 77.3, 76.8, 70.5, 68.2, 61.8, 60.3, 55.9, 47.9, 40.8, 40.7, 36.3, 35.8, 30.1, 28.5, 28.2, 27.9, 26.3, 26.2, 26.1, 22.0, 19.0, 18.9, 18.5, -3.41, -3.50, -3.80; MS (ESI): m/z 1043 $(M+Na)^+$; HRMS (ESI): calcd for $C_{51}H_{80}N_6NaO_8SSi_3^+$, $(M+Na)^+$ 1043.4958, found 1043.4951.

To a mixture of **28'** (25 mg, 48 μmol, 1.0 equiv) in THF (0.10 mL) were added AcOH (6.3 μL, 4.0 μmol, 3.5 equiv) and TBAF (1.2 μL, 5.9 μmol, 3.0 equiv, 1 M sol. in THF) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue including **33**. The residue was washed with EtOAc and 2 M HCl aq. to give **33** (13.3 mg, 44%) as an orange solid.

IR (film): 3246, 2962, 2875, 1629, 1438, 1269, 1095, 1054, 881, 848 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.97 (s, 1H, NH), 7.92 (s, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.93 (s, 2H), 6.37 (s, 1H), 4.29 (m, 3H), 4.07 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 2H), 3.98 (q, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 3.08-3.01 (m, 1H), 2.98, (dd, J_1 = 12.0 Hz, J_2 = 6.3 Hz, 2H), 2.89 (t, J = 7.45 Hz, 2H), 2.77 (dd, J_1 = 12.0 Hz, J_2 = 6.3 Hz, 1H), 2.53 (d, J = 8.0 Hz, 1H), 2.08 (t, J = 6.8 Hz, 1H), 2.03 (t, J = 7.5 Hz, 1H), 1.88 (t, J = 6.8 Hz, 2H), 1.49 (m, 4H), 1.25 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD): δ 178.6, 178.5, 174.0, 164.4, 164.4, 161.3, 158.9, 158.3, 158.2, 149.3, 149.2, 147.3, 142.0, 133.8, 123.1, 114.6, 112.5, 112.1, 110.0, 107.8, 107.7, 77.3, 76.8, 70.5, 68.2, 61.8, 60.3, 55.9, 47.9, 40.8, 40.7, 36.3, 35.8, 30.1, 28.5, 28.2, 27.9, 26.3, 26.2, 26.1, 22.0, 19.0, 18.9, 18.5,-3.41, -3.41, -3.50, -3.50, -3.80, -3.80; MS (ESI): m/z 701 $(M+Na)^+$; HRMS (ESI): calcd for $C_{33}H_{38}N_6NaO_8S^+$, $(M+Na)^+$ 701.2588, found 701.2579.

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