Tetrahedron xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A new class of flavonoids bearing macrocyclic polyethers by stereoselective photochemical cycloaddition reaction

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ARTICLE INFO

Article history:
Received 13 April 2019
Received in revised form
3 June 2019
Accepted 4 June 2019
Available online xxx

Keywords:
photochemical dimerization
Chromone
Cyclic polyether
Cyclobutane
C_2-symmetry

ABSTRACT

A new class of flavonoids bearing cyclic polyethers involving a phenyl ring was conveniently provided by the intramolecular photochemical dimerization of 2-chromonecarboxylic esters. Irradiation of 2-chromonecarboxylate with a polyether tethered at both ends promoted intramolecular [2 + 2] cyclobutane formation leading to 14- to 27-membered cyclic polyethers. The efficiency depended on the substituted position of the phenyl ring, with *ortho*- and *meta*-substituted derivatives giving cycloadducts in good chemical yields and quantum efficiencies, whereas the *para*-derivatives were inert toward photolysis. X-ray crystallographic analysis revealed that the stereochemistry of the macrocyclic cycloadducts exhibited C_2-symmetry.

1. Introduction

Chromone (benzo-γ-pyrone) **I** is the mother structure of naturally occurring flavonoids. Most of their derivatives, e.g., flavonol quercetin **II** [1–3], flavone luteolin **III** [4,5], and isoflavanone genistein **IV** [6,7], are widely used for drugs with antibacterial, anticancer, and antioxidant activities (Fig. 1) [8–10]. The hydroxyl groups of the phenol moieties play many important roles, one of which is the role of ionophore. We aimed to develop a new flavonoid analog having an ionophore by conversion of the hydroxy groups and to create a synthetic route to new derivatives possessing polyether ionophores because cyclic polyethers are well known to selectively incorporate alkali metals and organic cations depending on their ring size [11–18].

Many synthetic methods involving photochemical reactions have been developed to cyclize polyether chains; however, it is not easy to create desired polyether sizes [19–23]. Furthermore, the stereochemistry cannot be controlled except in rare cases [24–27]. If we can provide size-specific and stereo-controlled polyethers fused with flavonoids efficiently and selectively such as by click chemistry, this will provide a powerful tool for synthesizing macrocycles with functionality.

Recently, we reported the photochemical cyclization of covalently-linked chromonecarboxylic esters **1** leading to macrocyclic polyethers **2** (Scheme 1) [28]. The reaction selectively and predominantly gave C_2 symmetric products. Here, we introduce a benzene ring with the polyether chain at *o*-, *m*-, and *p*-positions to determine if the photochemical reactivity depends on the difference in the substituted positions and the stereochemistry of the products, and also to provide new functional macrocycles.

2. Results and discussion

Nine starting materials **5a-i** were prepared by esterification reactions as shown in Scheme 2. When two equimolar amounts of chromone-2-carbonyl acid chloride **3** were reacted with **4**, with three different lengths of polyethers and three positional *ortho*, *meta*, and *para* isomers, nine acyclic polyethers covalently-linked with two chromones were obtained in moderate yields. As the length of the polyether chain increased, the solubility of **5** decreased and the handling became troublesome.

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https://doi.org/10.1016/j.tet.2019.06.007

Please cite this article as: H. Ishikawa et al., A new class of flavonoids bearing macrocyclic polyethers by stereoselective photochemical cycloaddition reaction, Tetrahedron, https://doi.org/10.1016/j.tet.2019.06.007

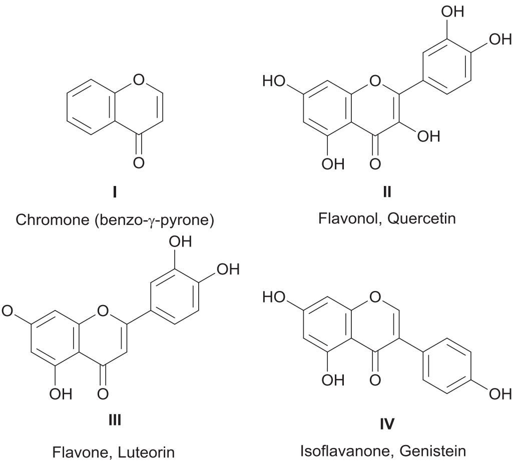
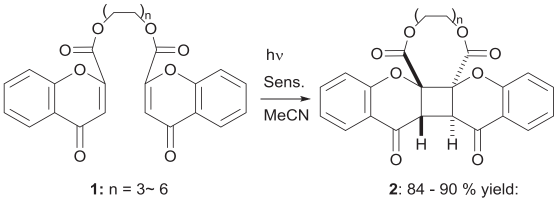
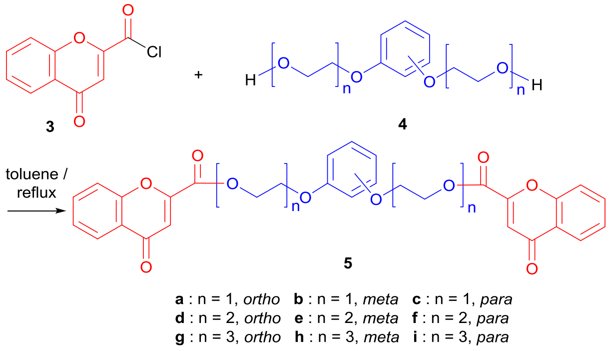


Fig. 1. Examples of naturally occurring flavonoids with high pharmaceutical activity.



Scheme 1. Photochemical reaction of bischromones tethered with a polyethylene chain.



Scheme 2. Synthesis of bischromones tethered with polyethers **5a-i**.

Whereas most of the polyethers **5** gave colorless powders, only **5d** gave a single crystal suitable for X-ray structural analysis. Its perspective views are shown in Fig. 2. The crystal structure shows that the molecule forms a spiral structure and the two chromones at both ends are aligned in an *anti*-parallel fashion. The distance between the two double bonds was about 7.07 Å, which is larger than 4.2 Å (Schmidt's rule) at which the photocycloaddition reaction proceeds in the solid-state [29,30], such that the reaction of **5d** in the solid-state did not proceed [31–34]. All other chromones **5** were also inert toward the solid-state photoreaction.

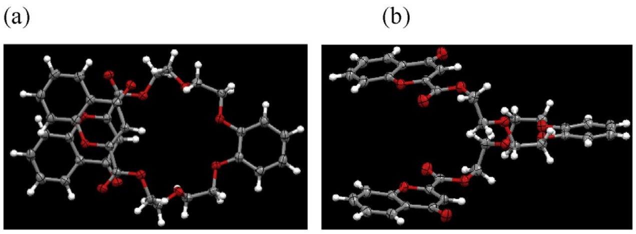


Fig. 2. Perspective views of **5d**: (a) top view and (b) side view.

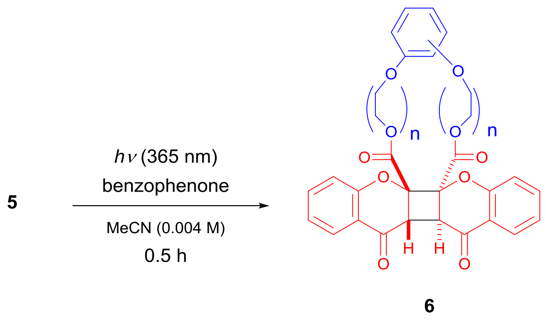
Next, we examined the direct irradiation of **5** in solution using the 365 nm line from a high pressure mercury lamp with uranium glass filter. It is known that the photodimerization of chromone-carboxylate proceeds from the triplet excited state. We also examined the sensitization reaction using benzophenone ($E_T = 69$ kcal mol^{-1}) [26–28].

When a MeCN solution of the *ortho*-isomer with diethyleneglycol unit **5a** was irradiated for 0.5 h, an effective cycloaddition reaction was promoted and cyclic polyether **6a** was obtained in 77% yield at 74% conversion (Scheme 3 and Table 1, entry 1, numbers in parentheses). The chemical yields were determined based on consumed starting materials. Prolonged irradiation did not give a better yield because **6a** also absorbs light. Fig. S1 shows the absorption spectra of **5a** and **6a**. The structure of **6a** includes two chromophore functions, thus the same concentration of spectra indicates the decrease of absorption co-efficiency for one chromone structure of **6a**; however, the absorption spectrum moved to the longer wavelength region due to the alkoxyphenone chromophore.

The triplet sensitization reaction using benzophenone as a sensitizer resulted in better conversion and chemical yield. In the case of **5a**, the conversion rose to 80% and a better chemical yield of 82% was obtained (Table 1, entry 1). Irradiation of *meta* derivative **5b** gave similar results; better yield and conversion were obtained than in the reaction by direct irradiation, and 74% of **6b** was isolated (entry 2). The *para* isomer **5c** was inert toward photolysis even in the sensitization reaction (entry 3), likely due to steric demands with the two chromones placed far away from each other.

When the chain length was expanded, diethyleneglycol and triethyleneglycol gave similar results, and the corresponding cyclic ethers (**6d**, **6e**, **6g**, and **6h**) were obtained. In these derivatives, the *para* isomers did not react and the starting materials were recovered. In all cases, sensitization experiments gave better results for conversion and chemical yield.

The stereo-structure was unequivocally established by single crystal X-ray analysis. The stereochemistry of the chromone dimer was *anti-head-to-head* as in the case of the photoreaction of aliphatic polyether-tethered materials **1** leading to **2** [28]. The dimeric structure exhibited C_2 symmetry and a C_2 structure for the hole crown ether with large molecules like **6** was formed (Fig. 3). Materials with C_2 symmetry are widely utilized as ligands in catalytic asymmetric synthesis and functional materials [35–38]. Thus, the development of a new reaction leading to C_2-symmetric materials would be extremely useful. Most C_2-symmetric polyethers are produced from C_2-symmetric units and polyethers. There are



Scheme 3. Intramolecular photocycloaddition of bischromones tethered with polyethers **5** leading to crown ethers **6**.

Please cite this article as: H. Ishikawa et al., A new class of flavonoids bearing macrocyclic polyethers by stereoselective photochemical cycloaddition reaction, Tetrahedron, https://doi.org/10.1016/j.tet.2019.06.007

Table 1
Photochemical reaction of chromonecarboxylate tethered with polyethers.

Entry	5	n	position	Conv. of 5[a]	Yield of 6 (%)[a]
1	**5a**	1	*ortho*	80 (74)	82 (77)
2	**5b**	1	*meta*	77 (52)	74 (70)
3	**5c**	1	*para*	0 (0)	0 (0)
4	**5d**	2	*ortho*	71 (58)	77 (79)
5	**5e**	2	*meta*	73 (45)	65 (49)
6	**5f**	2	*para*	0 (0)	0 (0)
7	**5g**	3	*ortho*	76 (58)	76 (48)
8	**5h**	3	*meta*	66 (40)	61 (49)
9	**5i**	3	*para*	0 (0)	0 (0)

[a] The values in parentheses show conversion and chemical yields by direct irradiation for 0.5 h. Direct irradiation: isolated yield, sensitization reaction: determined by ^{1}H NMR using triphenylmethane as an internal standard.

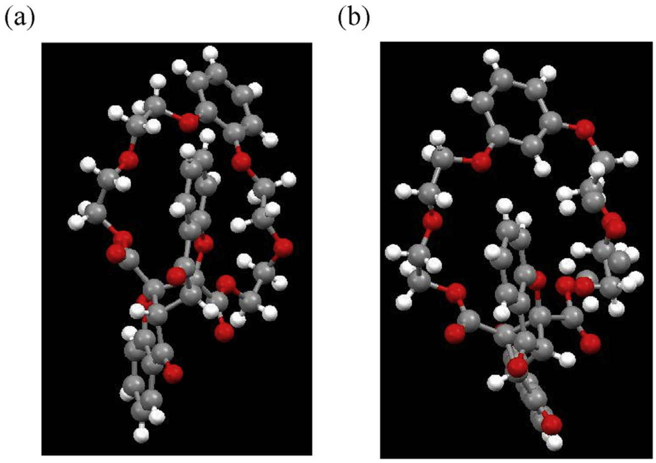


Fig. 3. Perspective view of (a) **6d** and (b) **6e**.

few examples of synthesizing C_2-symmetric units from linear materials with a polyethylene chain [24,25,28].

It is well documented that alkali cations are recognized by polyethers. Thus, there is the potential to influence the reactivity of the photoreaction. We examined the photoreaction of **5a**, **5d**, and **5g** in the presence of Li, Na, and K cations. The photocyclization of *ortho* and *meta* derivatives **5** leading to **6** proceeded effectively, with or without metal cations. The *para* derivatives did not give any photoproduct even in the presence of metal cations (Table S1). We are continuing to explore the asymmetric photocycloaddition by using chiral organic cations.

3. Conclusions

We developed a facile synthetic methodology for macrocyclic polyethers by the stereoselective dimerization of chromonecarboxylic esters connected by various polyether chains of differing lengths and positions on the benzene rings. The reaction proceeded effectively leading to 14- to 27-membered cyclic polyethers and the structures were determined to have C_2-symmetric stereochemistry. C_2-symmetric materials are very useful and widely found in synthetic materials, especially ligands for catalytic asymmetric synthesis and molecular recognition. Furthermore, the products contain flavonoid structures, which exist in many plants and pharmaceutical materials. This reaction provides a very efficient method for imparting C_2 symmetry to cyclic polyethers. The products also possess modifiable functional groups such as a ketone carbonyl group.

4. Experimental section

4.1. General information

NMR spectra were recorded in CDCl3 solution on Bruker 300 and JEOL ECA500 spectrometers for 1H- and 13C NMR. Chemical shifts are reported in parts per million (ppm) relative to TMS as an internal standard. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. UV absorption spectra were recorded on a JASCO V-570 spectrometer. High-resolution mass spectra (HRMS) were performed on an Orbitrap ThermoFisher Exactive ion trap mass spectrometer. X-ray single crystallographic analysis was conducted using a SMART APEX II (Bruker AXS) and APEX II ULTRA (Bruker AXS). Eikosya 500 W high pressure mercury lamp and SAN-EI super cure UVF-352S were used as irradiation sources. Commercially available reagents and solvents were used without further purification.

4.2. Synthesis of polyethers 4a-i

The polyethers were synthesized according to the reported procedure [39,40]. The corresponding benzenediol (0.5 g, 4.54 mmol) in acetonitrile (20 mL), the corresponding chloroethylene glycol (3.0 eq., 13.62 mmol), potassium carbonate (1.88 g, 13.62 mmol), and lithium bromide (0.039 g, 0.45 mmol) were mixed and the reaction was stirred at 90 °C for 3 days. After filtration of the precipitate, the solvent was removed under reduced pressure, and the obtained residue was separated by silica gel chromatography (hexane/ethyl acetate) to obtain the corresponding polyethers in 40–73% yields.

4.3. Synthesis of polyethers with chromone groups 5a-5i

Chromonecarbonyl chloride was prepared by the reaction of acid with thionyl chloride. After a toluene solution of 2-chromonic carboxylic acid (1.4 g, 7.6 mmol) and thionyl chloride (1.1 g, 9.1 mmol) was stirred at 90 °C for 2–3 h, thionyl chloride was removed under reduced pressure. The toluene solution of the corresponding polyethers **4a**-**4c** (0.5 g, 2.5 mmol) and chromonecarbonyl chloride was stirred at 120 °C overnight. After base extraction, the solvent was removed under reduced pressure, and the residue was separated by silica gel column chromatography (hexane/ethyl acetate) to obtain the corresponding chromone derivatives **5a-i** in 30–92% yields.

4.3.1. Photoreaction in solution

Chromone derivatives (0.004 M) were dissolved in a Pyrex test tube using acetonitrile as a solvent and bubbled with argon for 15 min. Thereafter, light irradiation was performed using a 500 W high pressure mercury lamp. After completion of the reaction, the solvent was removed under reduced pressure, and the obtained residue was separated by silica gel column chromatography (hexane/ethyl acetate or chloroform/ethyl acetate) to isolate the corresponding chromone derivatives.

4.3.2. Sensitization reaction

A chromone derivative (0.004 M) was dissolved in a Pyrex test tube using acetonitrile as a solvent. Benzophenone (5.0 eq.) was added as a triplet sensitizer, and the solution was bubbled with argon for 15 min then sealed. Thereafter, while rotating the test tube in a merry-go-round, the reaction was irradiated with light of 365 nm from a 500 W high pressure mercury lamp. After completion of the reaction, triphenylmethane was added as an internal standard, the solvent was removed under reduced pressure, and the conversion and product yield were calculated by ^{1}H NMR.

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4.3.3. Photoreaction of chromone derivatives 5 with alkali metal salts

Chromone derivatives **5a, 5d, 5g** (0.005 M) were dissolved in a Pyrex test tube with acetonitrile as a solvent. $LiClO_4$, $NaClO_4$, or $KClO_4$ as a metal cation (10.0 eq.) was added and the reaction was bubbled with argon for 15 min and sealed. Thereafter, the four samples were placed in a merry-go-round together with a sample to which no metal salt was added, and light irradiation was carried out using a 500 W high pressure mercury lamp while rotating the test tubes. After the reaction, triphenylmethane was added as an internal standard, the solvent was removed under reduced pressure, and the conversion and product yields were calculated by ^{1}H NMR.

4.3.4. (1,2-Phenylenebis(oxy))bis(ethane-2,1-diyl)bis(4-oxo-4H-chromene-2-carboxylate) (5a)

Colorless solid; m.p. 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 4.39 (t, $J = 4.7$ Hz, 4H), 4.76 (t, $J = 4.7$ Hz, 4H), 6.99 (s, 4H), 7.10 (m, 2H), 7.40–7.45 (m, 2H), 7.56–7.59 (m, 2H), 7.70–7.76 (m, 2H), 8.13–8.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 65.4, 67.5, 115.3, 116.3, 119.0, 122.9, 124.6, 125.9, 126.1, 135.0, 148.9, 151.9, 156.1, 160.6, 178.5; IR (cm^{-1}, neat) 1742, 1654; HRMS (ESI-MS) m/z calcd for $C_{30}H_{22}O_{10}+Na$ 565.1105, found 565.1099.

4.3.5. (1,3-Phenylenebis(oxy))bis(ethane-2,1-diyl)bis(4-oxo-4H-chromene-2-carboxylate) (5b)

Colorless solid; m.p. 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 4.32 (t, $J = 4.7$ Hz, 4H), 4.75 (t, $J = 4.7$ Hz, 4H), 6.56–6.60 (m, 3H), 7.13 (s, 2H), 7.20 (t, 1H), 7.42–7.47 (m, 2H), 7.59–7.62 (m, 2H), 7.71–7.77 (m, 2H), 8.17–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 65.2, 65.7, 102.3, 107.7, 115.4, 119.0, 124.6, 126.0, 126.2, 130.5, 135.0, 151.9, 156.2, 160.0, 160.7, 178.5; IR (cm^{-1}, neat) 1744, 1644; HRMS (ESI-MS) m/z calcd for $C_{30}H_{22}O_{10}+Na$ 565.1105, found 565.1090.

4.3.6. (1,4-Phenylenebis(oxy))bis(ethane-2,1-diyl)bis(4-oxo-4H-chromene-2-carboxylate) (5c)

Slightly yellow solid; m.p. 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 4.29 (t, $J = 4.7$ Hz, 4H), 4.73 (t, $J = 4.7$ Hz, 4H), 6.88–6.90 (m, 4H), 7.14 (s, 2H), 7.43–7.48 (m, 2H), 7.60–7.63 (m, 2H), 7.72–7.78 (m, 2H), 8.18–8.21 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 65.4, 66.4, 115.4, 116.1, 119.0, 124.6, 125.9, 126.2, 135.0, 151.9, 153.2, 156.2, 160.7, 178.6; IR (cm^{-1}, neat)1743, 1647; HRMS (ESI-MS) m/z calcd for $C_{30}H_{22}O_{10}+Na$ 565.1105, found 565.1093.

4.3.7. (((1,2-Phenylenebis(oxy))bis(ethane-2,1-diyl))bis(oxy)) bis(ethane-2,1-diyl)bis(4-oxo-4H-chromene-2-carboxylate) (5d)

Colorless crystal; m.p. 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 3.90–3.97 (m, 8H), 4.17–4.20 (m, 4H), 4.56–4.59 (m, 4H), 6.46–6.90 (m, 4H), 7.11 (s, 2H), 7.41–7.46 (m, 2H), 7.56–7.59 (m, 2H), 7.70–7.75 (m, 2H), 8.15–8.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 66.1, 69.0, 69.1, 70.1, 114.9, 115.2, 119.0, 121.9, 124.6, 125.9, 126.1, 134.9, 148.9, 152.1, 156.1, 160.7, 178.5; IR (cm^{-1}, neat) 1746, 1659; HRMS (ESI-MS) m/z calcd for $C_{34}H_{30}O_{12}+Na$ 653.1629, found 653.1619.

4.3.8. (((1,3-Phenylenebis(oxy))bis(ethane-2,1-diyl))bis(oxy)) bis(ethane-2,1-diyl)bis(4-oxo-4H-chromene-2-carboxylate) (5e)

Colorless solid; m.p. 79–81 °C; ^{1}H NMR ($CDCl_3$) δ 3.88–3.94 (m, 8H), 4.09–4.13 (m, 4H), 4.56–4.59 (m, 4H), 6.44–6.47 (m, 3H), 7.06–7.12 (m, 1H), 7.13 (s, 2H), 7.42–7.47 (m, 2H), 7.57–7.60 (m, 2H), 7.71–7.76 (m, 2H), 8.17–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 66.0, 67.6, 69.0, 70.0, 101.9, 107.3, 115.2, 119.0, 124.6, 125.9, 126.1, 130.1, 134.9, 152.0, 156.1, 160.0, 160.7, 178.5; IR (cm^{-1}, neat) 1748, 1659; HRMS (ESI-MS) m/z calcd for $C_{34}H_{31}O_{12}$ 631.1810, found 631.1794.

4.3.9. (((1,4-Phenylenebis(oxy))bis(ethane-2,1-diyl))bis(oxy)) bis(ethane-2,1-diyl)bis(4-oxo-4H-chromene-2-carboxylate) (5f)

Slightly yellow crystal; m.p. 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 3.82–3.94 (m, 8H), 4.05–4.08 (m, 4H), 4.57–4.60 (m, 4H), 6.75–6.81 (m, 4H), 7.14 (s, 2H), 7.43–7.48 (m, 2H), 7.57–7.60 (m, 2H), 7.70–7.77 (m, 2H), 8.17–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 66.0, 68.2, 69.0, 70.1, 115.2, 115.7, 119.0, 124.5, 125.9, 126.1, 134.9, 152.1, 153.1, 156.1, 160.7, 178.6; IR (cm^{-1}, neat) 1747, 1644; HRMS (ESI-MS) m/z calcd for $C_{34}H_{30}O_{12}+Na$ 653.1629, found 653.1630.

4.3.10. (((((1,2-Phenylenebis(oxy))bis(ethane-2,1-diyl))bis(oxy)) bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl) bis(4-oxo-4H-chromene-2-carboxylate) (5g)

Slightly yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.72–3.77 (m, 8H), 3.85–3.89 (m, 8H),4.14–4.17 (m, 4H), 4.53–4.56 (m, 4H), 6.84–6.91 (m, 4H), 7.13 (s, 2H), 7.41–7.47 (m, 2H), 7.58–7.60 (m, 2H), 7.70–7.76 (m, 2H), 8.16–8.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 65.8, 68.7, 68.8, 69.9, 70.8, 70.8, 114.8, 115.0, 118.8, 121.6, 124.4, 125.7, 125.9, 134.7, 148.9, 151.9, 155.9, 160.5, 178.3; IR (cm^{-1}, neat) 1745, 1653; HRMS (ESI-MS) m/z calcd for $C_{38}H_{38}O_{14}+Na$ 741.2154, found 741.2129.

4.3.11. (((((1,3-Phenylenebis(oxy))bis(ethane-2,1-diyl))bis(oxy)) bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl) bis(4-oxo-4H-chromene-2-carboxylate) (5h)

Slightly yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.75–3.88 (m, 16H), 4.07–4.11 (m, 4H), 4.54–4.57 (m, 4H), 6.44–6.48 (m, 3H), 7.10–7.14 (m, 3H), 7.42–7.45 (m, 2H), 7.58–7.61 (m, 2H), 7.71–7.73 (m, 2H), 8.17–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 66.0, 67.4, 68.8, 69.9, 70.9, 70.9, 101.7, 107.1, 115.1, 118.9, 124.5, 125.8, 126.0, 129.9, 134.9, 152.0, 156.1, 160.0, 160.1, 178.5; IR (cm^{-1}, neat) 1745, 1655; HRMS (ESI-MS) m/z calcd for $C_{38}H_{38}O_{14}+Na$ 741.2154, found 741.2140.

4.3.12. (((((1,4-Phenylenebis(oxy))bis(ethane-2,1-diyl))bis(oxy)) bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl)bis(4-oxo-4H-chromene-2-carboxylate) (5i)

Colorless crystal; m.p. 80–81 °C; ^{1}H NMR ($CDCl_3$) δ 3.75–3.89 (m, 16H), 4.04–4.07 (m, 4H), 4.54–4.57 (m, 4H), 6.79 (s, 4H), 7.13 (s, 2H), 7.42–7.47 (m, 2H), 7.58–7.60 (m, 2H), 7.70–7.76 (m, 2H), 8.16–8.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 65.9, 68.0, 68.7, 69.9, 70.8, 70.8, 115.0, 115.5, 118.8, 124.4, 125.7, 126.0, 134.8, 151.9, 153.0, 155.9, 160.5, 178.3; IR (cm^{-1}, neat) 1738, 1651; HRMS (ESI-MS) m/z calcd for $C_{38}H_{38}O_{14}+Na$ 741.2154, found 741.2118.

4.3.13. syn-6,7,15a,15b,24,25-Hexahydro-9H,22H-benzo[5′,6′][1,4,7,10]tetraoxacyclotetradecino[12′,13′:1,4]cyclobuta[1,2-b:4,3-b′]dichromene-9,15,16,22-tetraone (6a)

Colorless crystal; m.p. 219–221 °C; ^{1}H NMR ($CDCl_3$) δ 4.26–4.29 (m, 2H), 4.26 (s, 2H), 4.42–4.47 (m, 4H), 4.81 (m, 2H), 6.75 (m, 2H), 7.06–7.13 (m, 6H), 7.44–7.49 (m, 2H), 7.88–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 43.2, 64.9, 69.4, 83.9, 117.0, 118.5, 119.5, 123.0, 123.6, 127.7, 137.1, 150.0, 158.7, 165.3, 186.3; IR (cm^{-1}, neat) 1742, 1697; HRMS (ESI-MS) m/z calcd for $C_{30}H_{23}O_{10}$ 543.1286, found 543.1274.

4.3.14. syn-1^{5a},1^{5b},1^{11},1^{11a},1^{11b},1^{12}-Hexahydro-3,6,8,11-tetraoxa-1(5a,5b)-cyclobuta[1,2-b:4,3-b′]dichromene-7(1,3)-benzenacyclododecaphane-1^{11},1^{12},2,12-tetraone (6b)

Colorless crystal; m.p. 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 4.30 (s, 2H), 4.30–4.33 (m, 2H), 4.48 (m, 4H), 4.64 (m, 2H), 6.55–6.58 (m, 2H), 6.69–6.72 (m, 2H), 7.06–7.11 (m, 2H), 7.26–7.28 (m, 2H), 7.45 (m, 2H), 7.85–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 44.9, 67.3, 68.5, 84.8, 106.1, 112.0, 118.0, 119.4, 123.3, 127.4, 129.8, 136.9, 158.6, 161.3, 166.6, 187.6; IR (cm^{-1}, neat) 1741, 1697; HRMS (ESI-MS) m/z calcd for $C_{30}H_{23}O_{10}$ 543.1286, found 543.1286.

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4.3.15. *syn-6,7,9,10,18a,18b,27,28,30,31-Decahydro-12H,25H-benzo[8′,9′][1,4,7,10,13,16]hexaoxacycloicosino[18′,19':1,4]cyclobuta[1,2-b:4,3-b']dichromene-12,18,19,25-tetraone (6d)*

Colorless crystal; m.p. 182–183 °C; ^{1}H NMR (CDCl$_3$) δ 3.80 (m, 4H), 3.98–4.00 (m, 4H), 4.22–4.24 (m, 4H), 4.32 (s, 2H), 4.42 (m, 4H), 6.97–7.09 (m, 8H), 7.34–7.37 (m, 2H), 7.85–7.87 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 45.7, 67.1, 69.2, 69.2 70.4, 85.2, 102.0, 114.8, 118.2, 119.7, 122.0, 123.1, 127.2, 136.8, 149.1, 158.9, 167.3, 188.2; IR (cm^{-1}, neat) 1734, 1695; HRMS (ESI-MS) *m*/*z* calcd for $C_{34}H_{31}O_{12}$ 631.1810, found 631.1796.

4.3.16. *syn-1^{5a},1^{5b},1^{11},1^{11a},1^{11b},1^{12}-Hexahydro-3,6,9,11,14,17-hexaoxa-1(5a,5b)-cyclobuta[1,2-b:4,3-b']dichromene-10(1,3)-benzenacyclooctadecaphane-1^{11},1^{12},2,18-tetraone (6e)*

Colorless crystal; m.p. 169–171 °C; ^{1}H NMR (CDCl$_3$) δ 3.64–3.66 (m, 4H), 3.73–3.84 (m, 4H), 4.16–4.40 (m, 8H), 4.30 (s, 2H), 6.56–6.59 (m, 2H), 6.85–6.90 (m, 2H), 7.04–7.08 (m, 2H), 7.21–7.26 (m, 2H), 7.38–7.42 (m, 2H), 7.84–7.86 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 46.2, 66.1, 68.2, 68.7, 69.4, 85.2, 103.4, 108.0, 118.0, 119.6, 122.7, 126.8, 129.9, 136.4, 158.8, 160.1, 167.5, 188.4; IR (cm^{-1}, neat) 1735, 1691; HRMS (ESI-MS) *m*/*z* calcd for $C_{34}H_{30}O_{12}$+Na 653.1629, found 653.1611.

4.3.17. *syn-6,7,9,10,12,13,21a,21b,30,31,33,34,36,37-Tetradecahydro-15H,28H-benzo[11′,12′][1,4,7,10,13,16,19,22]octaoxacyclohexacosino[24′,25':1,4]cyclobuta[1,2-b:4,3-b']dichromene-15,21,22,28-tetraone (6g)*

Colorless crystal; m.p. 77–78 °C; ^{1}H NMR (CDCl$_3$) δ 3.647–3.75 (m, 8H), 3.80–3.83 (m, 4H), 3.92–3.94 (m, 4H), 4.18–4.21 (m, 4H), 4.26–4.38 (m, 2H), 4.32 (s, 2H), 4.39–4.41 (m, 2H), 6.93 (s, 4H), 7.04–7.26 (m, 4H), 7.45–7.50 (m, 2H), 7.87–7.89 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 45.4, 66.5, 68.8, 69.2, 70.0, 71.0, 71.0, 84.9, 114.3, 118.0, 119.5, 121.5, 122.9, 127.1, 136.6, 149.0, 158.7, 166.9, 187.8; IR (cm^{-1}, neat) 1737, 1699; HRMS (ESI-MS) *m*/*z* calcd for $C_{38}H_{38}O_{14}$+Na 741.2154, found 741.2130.

4.3.18. *syn-1^{5a},1^{5b},1^{11},1^{11a},1^{11b},1^{12}-hexahydro-3,6,9,12,14,17,20,23-octaoxa-1(5a,5b)-Cyclobuta[1,2-b:4,3-b']dichromene-13(1,3)-benzenacyclotetracosaphane-1^{11},1^{12},2,24-tetraone (6h)*

Colorless crystal; m.p. 148–150 °C; ^{1}H NMR (CDCl$_3$) δ 3.28 (m, 2H), 3.42 (m, 2H), 3.55 (m, 4H), 3.72 (m, 4H), 3.86–3.90 (m, 6H), 4.17–4.33 (m, 4H), 4.33 (s, 2H), 6.51 (m, 2H), 6.85 (m, 1H), 7.03–7.13 (m, 5H), 7.43–7.46 (m, 2H), 7.82–7.84 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 46.7, 66.0, 67.7, 68.1, 69.9, 70.7, 70.9, 85.1, 101.5, 107.7, 118.2, 119.7, 122.9, 127.0, 129.7, 136.8, 159.1, 160.3, 166.4, 188.6; IR (cm^{-1}, neat) 1748, 1698; HRMS (ESI-MS) *m*/*z* calcd for $C_{38}H_{38}O_{14}$+Na 741.2154, found 741.2137.

4.4. *Single crystal X-Ray structure analysis of 5d*

Colorless prism ($0.10 \times 0.10 \times 0.10$ mm^3), monoclinic space group *C*2/c, $a = 19.5670(9)$ Å, $b = 8.2178(4)$ Å, $c = 19.7851(10)$ Å, $\beta = 113.545(2)°$, $V = 2916.5(2)$ Å^3, $Z = 4$, λ (CuKα) = 1.54178 Å, $\rho = 1.436$ g/cm^3, μ (CuKα) = 0.922 cm, 9796 reflections measured (T = 173 K, $4.876° < \theta < 68.305°$), nb of independent data collected: 2592, nb of independent data used for refinement: 2453 in the final least-squares refinement cycles on F [2], the model converged at $R_1 = 0.0351$, w$R_2 = 0.0896$ [$I > 2\sigma(I)$], $R_1 = 0.0336$, w$R_2 = 0.0910$ (all data), and GOF = 1.066, H-atom parameters constrained. (CCDC1902864).

4.5. *Single crystal X-Ray structure analysis of 6d*

Colorless prism ($0.40 \times 0.20 \times 0.10$ mm^3), monoclinic space group *P*2$_1$/n, $a = 15.844(8)$ Å, $b = 11.487(6)$ Å, $c = 16.344(8)$ Å, $\beta = 102.106(7)$ °, $V = 2908.0(2)$ Å^3, $Z = 4$, λ (MoKα) = 0.71073 Å, $\rho = 1.440$ g/cm^3, μ (MoKα) = 0.110 cm, 16207 reflections measured (T = 173 K, $1.628° < \theta < 27.546°$), nb of independent data collected: 6591, nb of independent data used for refinement: 3991 in the final least-squares refinement cycles on F [2], the model converged at $R_1 = 0.0536$, w$R_2 = 0.1286$ [$I > 2\sigma(I)$], $R_1 = 0.0980$, w$R_2 = 0.1607$ (all data), and GOF = 0.975, H-atom parameters constrained. (CCDC1902865).

4.6. *Single crystal X-Ray structure analysis of 6e*

Colorless prism ($0.30 \times 0.30 \times 0.20$ mm^3), monoclinic space group *P*2$_1$/n, $a = 15.947(2)$ Å, $b = 11.4095(17)$ Å, $c = 16.328(3)$ Å, $\beta = 99.592(3)$ °, $V = 2929.3(8)$ Å^3, $Z = 4$, λ (MoKα) = 0.71073 Å, $\rho = 1.430$ g/cm^3, μ (MoKα) = 0.109 cm, 16430 reflections measured (T = 173 K, $1.653° < \theta < 27.455°$), nb of independent data collected: 6619, nb of independent data used for refinement: 2725 in the final least-squares refinement cycles on F [2], the model converged at $R_1 = 0.0626$, w$R_2 = 0.1430$ [$I > 2\sigma(I)$], $R_1 = 0.1688$, w$R_2 = 0.2032$ (all data), and GOF = 0.905, H-atom parameters constrained. (CCDC1902866).

4.7. *Single crystal X-Ray structure analysis of 6g*

Colorless prism ($0.50 \times 0.50 \times 0.30$ mm^3), orthorhombic space group *P*ca2$_1$, $a = 22.787(3)$ Å, $b = 9.2042(12)$ Å, $c = 18.492(2)$ Å, $V = 3878.4(9)$ Å^3, $Z = 4$, λ (MoKα) = 0.71073 Å, $\rho = 1.382$ g/cm^3, μ (MoKα) = 0.106 cm, 21372 reflections measured (T = 173 K, $2.099° < \theta < 27.587°$), nb of independent data collected: 6308, nb of independent data used for refinement: 5628 in the final least-squares refinement cycles on F [2], the model converged at $R_1 = 0.0332$, w$R_2 = 0.0773$ [$I > 2\sigma(I)$], $R_1 = 0.0396$, w$R_2 = 0.0809$ (all data), and GOF = 1.019, H-atom parameters constrained. (CCDC1902867).

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (Nos. 17K19114, 26410124 and 16H04144) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of the Japanese Government. Mr. Uemura acknowledges financial support from Frontier Science Program of Graduate School of Science and Engineering, Chiba University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.06.007.

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