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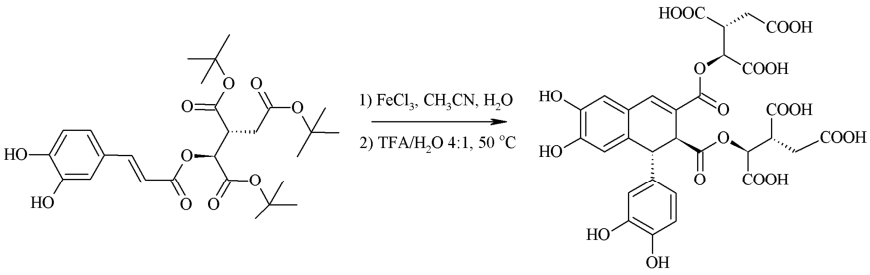

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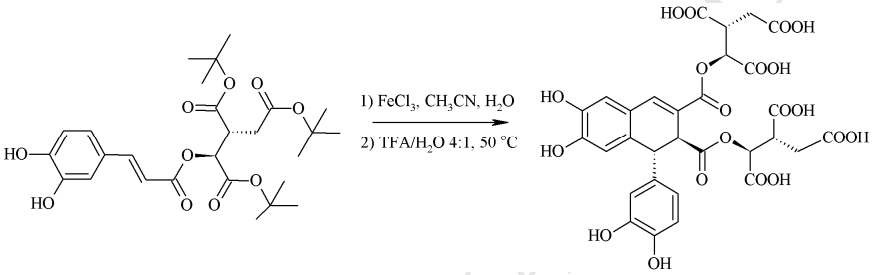

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ABSTRACT

Recently, a novel lignan sevanol was isolated from the thyme plant *Thymus armeniacus*. During structure-functional elucidation it showed significant biological activity on ASIC3 acid sensing channels. Herein we describe the first synthesis of sevanol with a 3% overall yield. The construction of a dihydronaphthalene ring by oxidative dimerization of a protected dihydroxycinnamic acid ester in the presence of ferric chloride (III) is a key step in this first total synthesis of sevanol.

1. Introduction

Many species of plant produce bioactive compounds, such as flavonoids, tannins, diterpenoids, alkaloids, peptides, furocoumarines and lignans. These exhibit pharmacological or toxicological effects in humans and in other animals.[1] One of the largest groups of these compounds, distributed widely within the plant kingdom, is the lignans.[2] This term was originally coined by Haworth[3] and relates to dimers generated by the β-β' (8-8') oxidative coupling of two cinnamic acid residues.[4] Lignans play an important protective role in the vascular systems of plants, which may explain their biological activity in living organisms.[5] Indeed, a wide variety of lignan derivatives are found in plants, covering a broad spectrum of chemical diversity and biological activities, including anti-tumor, anti-inflammatory, antiviral, cytotoxic, antimitotic, anti-fungal, anti-angiogenic and cardiovascular effects.[6,7,8] This family of polyphenols is attractive from the point of view of a pharmaceutical chemistry as promising targets for the development of potential drug candidates.

Previously, a novel lignan named sevanol (Fig. 1) was isolated from the acetic acid extract of *Thymus armeniacus*.[9] Based on NMR and LC-ESI-MS data the structure of sevanol was identified to be composed of esters of epiphyllic acid and two residues of isocitric acid.

This compound has six asymmetric centers and in nature is found in only one enantiomeric form.[9,10] We showed that sevanol **1** (Fig. 1) was the first low molecular weight natural molecule that has a reversible inhibitory effect on both the transient and the sustained current of human ASIC3 channels expressed in *Xenopus laevis* oocytes.[9] In the model of acid induced pain and thermal hypersensitivity in mice sevanol demonstrated a pronounced analgesic effect.[10] Thus, expecting a potential clinical application of sevanol we have developed a method for chemically synthesizing this molecule. This publication is dedicated to the development of the total synthesis of sevanol.

2. Results and Discussion

Considering that sevanol is formally a dimer of caffeic acid, it seemed possible to synthesize the target compound by oxidative coupling of two molecules of caffeic acid ester. Tri-*t*-butyl isocitrate **6** and suitably protected caffeic acid **2** were chosen as inputs for the retrosynthetic route to synthetic sevanol **1** (Scheme 1). The oxidative coupling of two molecules of a caffeic acid ester **3** in the presence of ferric chloride (III) was proposed as a key step. Synthesis of the key intermediate **4** included the step of removing the protective groups (PG) from the phenolic oxygen atoms of compound **3**.

According to data available in the literature, hydroxyl groups must be protected by either silyl or allyl groups in order for

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further dimerization of similar phenylpropanoid substrates to occur.[11,12] Thus, our initial choice of the protecting group for the phenolic oxygen atoms in cinnamic acid was based on the principle of orthogonality to *t*-butyl isocitric acid esters, which should be removed under acidic conditions in the next step after the preparation of dimeric product **5**.

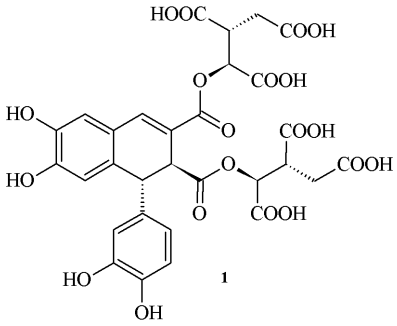
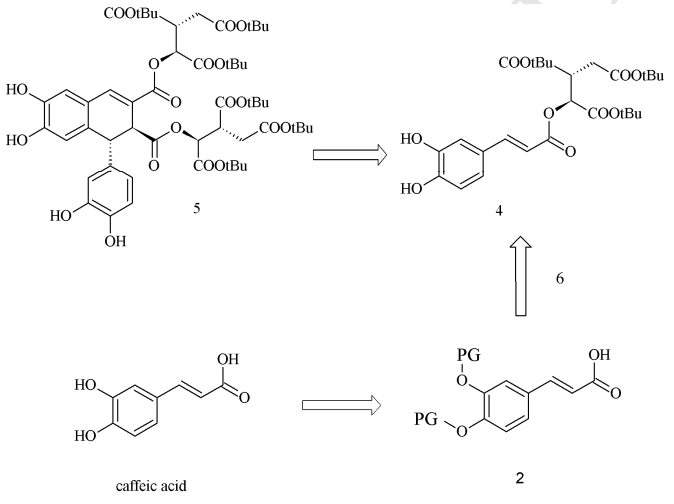


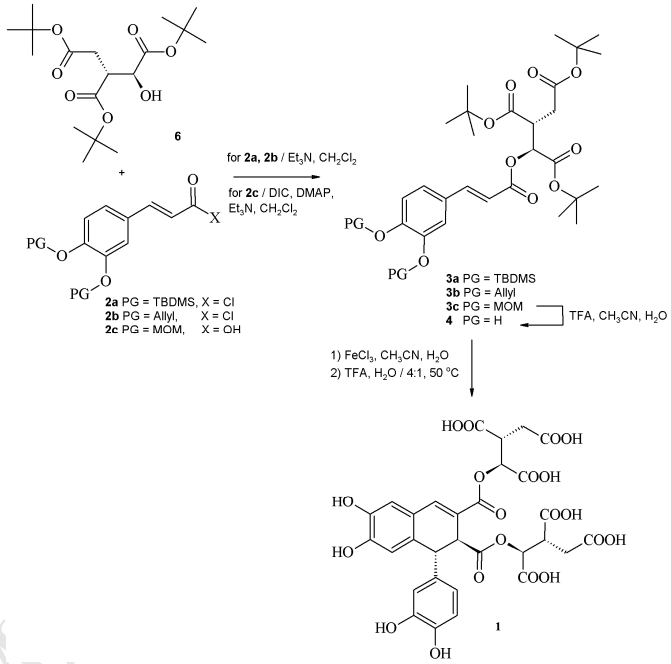
Figure 1. Structure of sevanol (**1**).

Therefore, initially we tried to use TBDMS-protection as described by Bogucki et al.[11] to synthesize (+)-rabdosiin, lignan which has a similar structure to sevanol. It seemed possible that TBDMS-protective groups would be removed using TBAF. Caffeic acid was treated with TBDMS triflate in the presence of Et_3N to give a product in 71% yield. The resulting substance was completely converted to the corresponding acid chloride **2a** followed by conversion into compound **3a** in 43% yield. Acid chloride **2a** was obtained using 1.5 equivalents of thionyl chloride and toluene as a solvent. The reaction was performed during four hours at 110 ^{o}C. Further acylation of TBDMS-protected compound **2a** was carried out in dichloromethane in the presence of triethylamine as a base. Unfortunately, all attempts to remove the silyl groups (TBAF/THF, KF alcohols, TBAF acetic acid) failed due to partial or total hydrolysis of the esters of cinnamic acid.



Scheme 1. Retrosynthetic path to synthetic sevanol.

Based on this precedent, it seemed at least possible to use allyl protection for the phenolic oxygen atoms. Caffeic acid was treated with allyl bromide in the presence of a base to provide the target product in 31% yield.[12] Allyl protected acid was transformed to the acid chloride **2b** with thionyl chloride and subsequently reacted with alcohol **6** to produce ester **3b** in 28% yield. Unfortunately, we could not remove the allyl groups efficiently due to high impurity formation and the extremely low yield of the reaction.



Scheme 2. Total synthesis of sevanol.

To overcome this problem we selected MOM-protecting groups as an alternative protection for the hydroxyl groups of cinnamic acid. Use of this approach required changing the initial route of the total synthesis. Commercially available 3,4-dihydroxybenzaldehyde was subjected to an alkylation in the presence of potassium carbonate[13] to provide 3,4-bis-MOM-protected benzaldehyde in 59% yield. Condensation of MOM-protected benzaldehyde with malonic acid afforded the MOM-protected caffeic acid derivative **2c**.[14] Caffeic isocitrate ester **3c** was synthesized in one step using acid **2c** with alcohol **1** in the presence of triethylamine, diisopropylcarbodiimide (DIC) and catalytic amounts of DMAP.[15,16] Treatment of **3c** with three equivalents of trifluoroacetic acid in acetonitrile-water (4:1) followed by purification on silica gel gave the target intermediate **4** in 53% yield. Finally, removal of protecting groups was achieved without TFA-mediated hydrolysis of *tert*-butyl esters.

The tri-*tert*-butyl ester of isocitric acid **6** was obtained in seven synthetic steps starting from (L)-malic acid with an overall yield of 36% using the method described by Calo et al.[17]

The stage was now set for the crucial coupling step.[18] In order to prepare the key intermediate **5,** oxidative dimerization of two molecules of caffeic isocitrate ester was used. It took several attempts to find the optimal reaction medium. Thus, we tried to perform an oxidative coupling using $Cu(OAc)_2$, $Fe(acac)_3$, $Pb(OAc)_4$ at room temperature. Despite the fact that the starting material was being consumed, the desired product could not be identified by HPLC/MS. $Cu(OAc)_2$ coupling afforded a dimerization product at the α – position without the desired cyclization.

Table 1. Solvent and oxidative reagent effects on the oxidative coupling of ester **4**[a].

Solvent	Oxidative reagent	Yield[b] %
Acetone-H_2O	$K_3[Fe(CN)_6]$ (2 equiv)	not found
Acetone-H_2O	MnO_2 (2 equiv)	not found
Acetone-H_2O	$Cu(OAc)_2$ (2 equiv)	1.5
Acetone-H_2O	$FeCl_3$ (2 equiv)	20
i-PrOH-H_2O	$FeCl_3$ (2 equiv)	not found
t-BuOH-H_2O	$FeCl_3$ (2 equiv)	not found
CH_2Cl_2-H_2O	$FeCl_3$ (2 equiv)	<1
THF-H_2O	$FeCl_3$ (2 equiv)	not found
MeCN-H_2O	$FeCl_3$ (1 equiv)	17
MeCN-H_2O	$FeCl_3$ (2 equiv)	32
MeCN-H_2O	$FeCl_3$ (2.5 equiv)	41
MeCN-H_2O	$FeCl_3$ (3 equiv)	10
MeCN-H_2O	$FeCl_3$ (4 equiv)	2

[a] The reaction was conducted in the absence of light at 5 °C for 2 h.

[b] Yield of product **5**.

Thus, the absence of the dihydronaphthalene molecule was determined by ^{1}H NMR spectra. Based on the literature data for the synthesis of analogues of natural lignans and neolignans[19,20,21] we chose the method of $FeCl_3$ oxidation in a mixture of acetone-water as a solvent at 25 °C over 18 hours using 2 equivalents of ferric chloride (III). The low yield (2%) of the cyclization product **5** showed that this is not an efficient set of reaction conditions for obtaining the target molecule. The unreacted starting material **4** could be recovered and recycled. Though this route gave an access to the desired compound **1**, the yield was too low for the following research to be conducted.

We made attempts to improve the yield by changing the reaction conditions. After careful consideration, we discovered that the main problem at this stage was the formation of chlorinated products. This problem was overcome by performing the dimerization process at 5 °C for two hours in the absence of light.[19d] As a result, the yield was improved to 20%.

A second attempt to optimize the synthesis of desired molecule **5** by the coupling of compound **4** involved searching for the most suitable solvent and amount of oxidant. The results of the study are displayed in Table 1. The general procedure for the study was to add an oxidant in water to ester **4** in organic solvent at 5 °C in the absence of light. The reaction mixture was stirred for two hours. The resulting products were isolated and analyzed with LC/MS spectroscopy. Contemporaneous observations in such synthetic projects confirmed that using $K_3[Fe(CN)_6]$[22] and MnO_2[4] could be useful. According to data in the literature, the yield of the dihydronaphthalene product would not be more than 20-25%. However, we did not identify the product **5** while performing dimerization of ester **4** in this reaction medium. The starting material was also not observed. $Cu(OAc)_2$ coupling in the absence of light afforded product **5** with 1.5% yield and 25% of dimerization product at the α–position described above. However, it seemed at least possible to isolate unreacted compound **4** from the crude mixture. Thus it appeared that using ferric chloride (III) was the best method to prepare a lignan with a skeleton similar to sevanol molecule **1**.

Although performing the reaction in aqueous acetone solvent provided a relatively good yield of 20% for compound **5**, further studies of optimal reaction conditions were required. Most of the solvents (*t*-BuOH, *i*-PrOH, CH_2Cl_2, THF) used resulted in the absence of the desired product **5** in the reaction mixture. Fortunately, the successful oxidative dimerization was carried out using aqueous acetonitrile as a solvent. The yield of compound **5** was 32% (Table 1). Moreover, experimental data showed that using of 1 equivalent of $FeCl_3$ provided a 17% yield of the target molecule while introducing more than 3 equivalents to the reaction led to tar formation and a product **5** (in 2-10% yield). After careful consideration of the research results we made an attempt to perform the key step of oxidative coupling with 2.5 equivalents of $FeCl_3$ in aqueous acetonitrile. Pleasingly we obtained intermediate **5** with 41% yield. We also studied temperature influence to complete our search for optimal conditions. The reaction was carried out over two hours using the general procedure described above (2.5 equiv. of $FeCl_3$ in MeCN-H_2O as a solvent). Performing oxidative dimerization at 25 °C led to the isolation of less than 2% of the target molecule **5** and full consumption of the starting ester **4**. Meanwhile, after cooling the reaction mixture to -10 °C we identified a large amount of unreacted starting material **4** and not more than 0.5% of the product **5**. Considering these results, it was recognized that oxidative coupling of *t*-butyl protected isocitate of caffeic acid **4** should be carried out at 5 °C as an optimal temperature.

After treating the resulting reaction mixture with diluted HCl, extraction in toluene and chromatographic purification on a silica gel column, product **5** as mixture of two diastereomers was finally obtained in 41% yield. It is important to note that *t*-butyl protected sevanol diastereomers **5** were not separable at the stage of oxidative dimerization. It was also impossible to separate the diastereomers **5** even using a semi-preparative HPLC system. Thus, the diastereomeric mixture of esters **5** was introduced into the next step without further purification. Treatment with 80% aqueous TFA for 1 hour at 50 °C gave a crude deprotected product **1** that appeared by ^{1}H NMR to be a mixture of two diastereomers of the desired lignan in a 1:3 ratio as determined by integration of corresponding signals. The crude product **1** was chromatographed on a semi-preparative HPLC reverse-phase column using MeCN-H_2O as the eluant. As a result, the separation of diastereomeric products was successfully

performed. Based on comparison of the NMR data and the value of the optical rotation ($[\alpha]_D^{25}$ = +65, *c* 1 H_2O), the major diastereomer was consistent with the structure of natural sevanol **1**. During our search for an optimum procedure for oxidative dimerization we came to the conclusion that changing either solvent or the amount of oxidant did not influence the diastereomeric ratio of 1:3. However, we did not study this aspect sufficiently to make any conclusion about other factors that control the predominant formation of one diastereomer over the other. Thus, the isomer identical to the natural lignan **1** isolated from thyme *Thymus armeniacus* was prepared in a 39% yield from the crude mixture after HPLC purification.

3. Conclusion

In conclusion we have developed a new method for the synthesis of novel lignan sevanol. The sevanol molecule was obtained in thirteen synthetic steps with a 3% overall yield from malic acid. The construction of a dihydronaphthalene ring by oxidative dimerization of a protected dihydroxycinnamic acid ester was carefully researched. As a result, we identified an optimal reaction conditions to perform the key step of the total synthesis of sevanol. Efforts to improve the synthetic route and to study biological activity of synthetic sevanol in detail are underway.

4. Experimental section

4.1 General Procedures:

All reactions utilizing moisture-sensitive reagents were performed under an inert atmosphere. Acetonitrile and dichloromethane were purchased from Merck and were used without further purification unless otherwise specified. Ethyl acetate, hexane, toluene and acetone were distilled from $CaCl_2$. 3,4-dihydroxybenzaldehyde, ferric chloride (III) were purchased from Acros. N-methylpiperazine was purchased from Fluorochem. DMAP, DIC were purchased from Merck. Other reagents were purchased from PanReac AppliChem. All commercially obtained reagents were used without further purification. TLC was carried out on pre-coated plates (silica gel 60, F_{254}, Fluka), and the spots were visualized with UV and fluorescent lights or by staining with phosphomolybdic acid stains. Column chromatography was performed on silica-gel (0.063-0.2 mm/70-230 mesh ASTM, MN Kieselgel). High-resolution mass spectra (HRMS) were measured on Agilent 6224 TOF LC/MS System. IR spectra were recorded with a Nicolet (Thermo scientific) iS50 ART using a KBr pellet. All NMR spectra obtained on Bruker AVANCE III spectrometers (Bruker BioSpin, Germany) with proton operating frequencies of 300 and 700 MHz. Chemical shifts are reported relative to residue peaks of $CDCl_3$ (7.27 ppm for ^1H and 77.0 ppm for ^{13}C), D_2O (4.79 ppm for ^1H).

*4.2 General Procedure for the preparation of substituted caffeic isocitrates **3a**, **3b**:*

The alcohol **6** (1.0 g, 2.8 mmol) was dissolved in CH_2Cl_2 (10 mL) followed by TEA (0.6 mL, 4.2 mmol) addition. The resulting reaction mixture was stirred for 30 minutes at 0-5 ^oC in an ice bath. A solution of the corresponding acid chloride (**2a**: 1.49 g, 3.5 mmol; **2b**: 0.97 g, 3.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the stirred mixture. The resulting yellow solution was stirred under a drying tube ($CaCl_2$) for 16 h, quenched with 1 M HCl (5 mL) and extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on silica gel (**3a**: EtOAc – hexane = 1:6; **3b**: EtOAc – hexane = 1:10) to give a colorless oil (**3a**: 0.51 g, 43%; **3b**: 0.23 g, 28%).

*2-{3-[3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-phenyl]-acryloyl oxy}-3-tert-butoxycarbonyl-pentanedioic acid di-tert-butyl ester **3a***:

R_f (10% EtOAc/hexane) 0.4; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.68 (1H, d, *J* = 15.9 Hz), 7.07 (1H, s), 7.07 (1H, s), 6.89 (1H, s), 6.33 (1H, d, *J* = 15.9 Hz), 5.34 (1H, d, *J* = 3.3 Hz), 3.50 - 3.52 (1H, m), 2.81 (1H, dd, *J* = 16.8, 9.8 Hz), 2.52 (1H, dd, *J* = 16.8, 4.8 Hz), 1.56 (9H, s), 1.56 (9H, s), 1.53 (9H, s), 1.07 (9H, s), 1.06 (9H, s), 0.29 (6H, s), 0.28 (6H, s); ^{13}C NMR (700 MHz, $CDCl_3$): 170.6, 169.3, 166.9, 166.1, 149.7, 147.2, 146.0, 127.9, 122.5, 121.1, 120.5, 114.5, 82.8, 81.9, 81.0, 72.1, 43.9, 33.9, 28.1, 25.9, 25.7, 0.0, 2.9, -4.0; IR (KBr): 1733, 2859, 2897, 2931, 2957; HRMS: MH+ calcld for $C_{39}H_{67}O_{10}Si_2$ 751.4267 $(MH)^+$: found 751.4273.

*2-[3-(3,4-Bis-allyloxy-phenyl)-acryloyloxy]-3-tert-butoxy carbonyl-pentanedioic acid di-tert-butyl ester **3b***:

R_f (15% EtOAc/hexane) 0.38; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.72 (1H, d, *J* = 15.9 Hz), 7.14 (1H, s), 7.14 (1H, s), 6.94 (1H, s), 6.35 (1H, d, *J* = 15.9 Hz), 6.16 (1H, ddd, *J* = 9.4, 7.4, 4.7 Hz), 6.13 (1H, ddd, *J* = 10.5, 7.4, 4.7 Hz), 5.51 (1H, dd, *J* = 3.4, 1.5 Hz), 5.49 (1H, dd, *J* = 3.4, 1.5 Hz), 5.37 (2H, dd, *J* = 3.4, 1.5 Hz), 5.35 (2H, dd, *J* = 3.4, 1.5 Hz). 5.35 (1H, d, *J* = 3.6 Hz), 4.71 (2H, d, *J* = 5.6 Hz), 4.70 (2H, d, *J* = 5.6 Hz), 3.50 - 3.52 (1H, m), 2.81 (1H, dd, *J* = 16.8, 9.8 Hz), 2.52 (1H, dd, *J* = 16.8, 9.8 Hz), 1.56 (9H, s), 1.55 (9H, s), 1.53 (9H, s); ^{13}C NMR (700 MHz, $CDCl_3$): 170.6, 169.4, 166.9, 166.0, 151.0, 148.6, 146.0, 133.1, 132.9, 127.5, 123.0, 118.0, 117.9, 114.7, 113.5, 112.8, 82.8, 81.9, 81.0, 72.0, 70.0, 69.8, 43.9, 33.9, 28.1; IR (KBr): 1732, 2933, 2979; HRMS: MH+ calcld for $C_{33}H_{47}O_{10}$ 603.3163 $(MH)^+$: found 603.3170.

*4.3 (1S,2S)-tri-tert-butyl-1-(((E)-3-(3,4-bis(methoxymethoxy) phenyl)acryloyl)oxy)propane-1,2,3-tricar¬boxylate (**3c**)*

The compound **2c** (2.4 g, 9.1 mmol) was dissolved in CH_2Cl_2 (20 mL). A solution of alcohol **6** (2.5 g, 7 mmol) in CH_2Cl_2 (10 mL) was added to the stirred mixture. The resulting reaction mixture was cooled to 0 ^oC in an ice bath under Ar gas followed by the addition of DMAP (85 mg, 0.7 mmol). A solution of DIC (1.4 mL, 9.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the stirred mixture. The resulting solution was stirred under a drying tube ($CaCl_2$) for 16 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was purified on silica gel (EtOAc – hexane = 1:3) to give a colorless oil **3c** (3.7 g, 87%): R_f (20% EtOAc/hexane) 0.25; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.64 (1H, d, *J* = 15.9 Hz), 7.35 (1H, s), 7.13 (1H, s), 7.13 (1H, s), 6.34 (1H, d, *J* = 15.9 Hz), 5.28 (1H, d, *J* = 3.6 Hz), 5.25 (2H, s), 5.22 (2H, s), 3.52 (3H, s), 3.50 (3H, s), 3.40 – 3.46 (1H, m), 2.73 (1H, dd, *J* = 16.8, 9.8 Hz), 2.44 (1H, dd, *J* = 16.8, 4.8 Hz), 1.48 (9H, s), 1.48 (9H, s), 1.42 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): 170.5, 169.3, 166.8, 165.8, 149.4, 147.4. 145.5, 128.4, 123.7, 116.1, 115.9, 115.4, 95.5, 95.1, 82.7, 81.8, 80.9, 72.0, 56.3, 56.3, 43.9, 33.7, 28.0; IR (KBr): 1731, 2933, 2978; HRMS: MH+ calcld for $C_{31}H_{47}O_{12}$ 611.3062 MH^+: found 611.3069.

*4.4 (1S,2S)-tri-tert-butyl-1-(((E)-3-(3,4-dihydroxyphenyl) acryloyl)oxy)propane-1,2,3-tricarboxylate (**4**)*

The compound **3c** (3.7 g, 6.1 mmol) was dissolved in 30 mL MeCN – H_2O (5:1). TFA (1.4 mL, 18.3 mmol) was added dropwise to the mixture at room temperature. The resulting solution was stirred for 10 h at 50 ^oC. The reaction mixture was quenched with saturated aqueous sodium hydrocarbonate ($NaHCO_3$), extracted with EtOAc (2x25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on silica gel (hexane – EtOAc = 2:1) to give the product **4** as a colorless oil (1.7 g, 53%): R_f (35% EtOAc/hexane) 0.3; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.54 (1H, d, *J* = 15.9 Hz), 6.99 (1H, s), 6.86 (1H, s), 6.85 (1H, s), 6.59 (1H, br s, OH), 6.17 (1H, d, *J* = 15.9 Hz), 6.03 (1H, br s, OH), 5.31 (1H, d, J 3.3 Hz), 3.45 – 3.51 (1H, m), 2.77 (1H, dd, *J* = 16.8, 9.7 Hz), 2.47 (1H, dd, *J* 16.8, 5.2 Hz), 1.52 (9H, s), 1.51 (9H, s), 1.48 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): 170.7, 169.5, 167.6, 166.3, 146.6, 146.3, 144.1, 127.1, 122.4, 115.5, 114.4, 113.9, 83.4, 82.3, 81.3, 71.9, 43.9, 34.0, 28.0; IR (KBr): 1721, 2936, 2980, 3391; HRMS: MH+ calcld for $C_{27}H_{39}O_{10}$ 523.2537 $(MH)^+$: found 523.2536.

*4.5 (1S,1'S,2S,2'S)-hexa-tert-butyl-1,1'-(((1R,2S)-1-(3,4-dihydroxyphenyl)-6,7-dihydroxy-1,2-dihydronaphthalene-2,3-dicarbonyl)bis(oxy))bis(propane-1,2,3-tricarboxylate) (**5**)*

Cinnamate **4** (1.7 g, 3.3 mmol) in acetonitrile (20 mL) was stirred at 5^oC while a solution of $FeCl_3$ (1.3 g, 8.1 mmol) in H_2O (13 mL) was added dropwise over 5 min. The dark green reaction mixture protected from light was stirred for 2 h at 5^oC. The resulting mixture was diluted with 1 M HCl (100 mL), extracted with toluene (3x10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* protected from light to give a brown amorphous solid. The residue was purified on silica gel in toluene – EtOAc = 4:1 (3% AcOH) to produce product **5** as a dark yellow oil (672 mg, 41%). The diastereomeric mixture of esters **5** was introduced into the next step without further purification.

*4.6 Sevanol (**1**)*

Product **5** (672 mg, 0.64 mmol) in a 50 mL round-bottom flask was stirred in the presence of 10 mL 20% solution TFA in water (TFA – H_2O = 4:1) during 1 hour at 50 ^oC. After slight cooling, most of the solvent was carefully evaporated *in vacuo* and the mixture was purified by a preparative HPLC reverse-phase column. The semi-preparative HPLC system Waters 2487 was used for this purpose on a tandem of two columns in size 20 x 250 mm reversed-phase sorbents 11AD2 11 microns and LPS-500 70 microns (LLC "Tehnosorbent", Russia) with a linear gradient of acetonitrile (mobile phase a: 0.1% TFA in water; mobile phase B: acetonitrile; gradient 2 – 30% B in 60 min at a flow rate of 10 mL/min; profile registration elution by UV absorbance at 220 and 280 nm). A light yellow powder was obtained after lyophilization (176 mg, 39%): ^1H NMR (700 MHz, D_2O): δ_H 7.75 (1H, s), 7.01 (1H, s), 6.72 (1H, s), 6.68 (1H, d, *J* = 8.3 Hz), 6.62, (1H, d, *J* = 1.7 Hz), 6.43 (1H, dd, *J* = 1.7 Hz, 8.3 Hz), 5.38 (1H, d, *J* = 4.0 Hz), 5.33 (1H, d, *J* = 3.4 Hz), 4.5 (1H, d, *J* = 1.9 Hz), 4.08 (1H, d, *J* = 1.9 Hz), 3.56 – 3.59 (1H, m), 3.45 - 3.47 (1H, m), 2.78 (1H, dd, *J* = 9.3 Hz, 17.2 Hz), 2.6 (1H, dd, *J* = 5.2 Hz, 17.2 Hz), 2.50 (1H, dd, *J* = 9.6 Hz, 17.3 Hz), 2.24 (1H, dd, *J* = 9.6 Hz, 17.3 Hz); ^{13}C NMR (300 MHz, D_2O): 175.4, 175.2, 174.2, 173.7, 172.8, 172.7, 171.8, 166.9, 147.5, 143.9, 143.3, 142.8, 141.4, 134.5, 130.7, 123.7, 119.8, 119.6, 117.4, 116.6, 116.1, 115.3, 73.2, 73.2, 46.4, 44.0, 43.2, 42.2, 32.3, 31.8; IR (KBr): 1709, 2648, 3253; HRMS: MH^- calcld for $C_{30}H_{25}O_{20}$ 705.0939 $(MH)^-$: found 705.0941.

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Supplementary Material

Detailed procedures and full characterization of all synthetic intermediates and products are provided. Supplementary data associated with this article can be found in the online version.