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Synthesis and antitumor activity of lapathoside D and its analogs

Parthasarathi Panda [a], Manjuvani Appalashetti [a], Meenubharathi Natarajan [b], Mary B. Chan-Park [a], Subbu S. Venkatraman [b], Zaher M.A. Judeh [a,*]

[a] School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, N1.2-B1-14, Singapore 637459, Singapore
[b] School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, N4.1-02-06, Singapore 639798, Singapore

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ABSTRACT

Phenylpropanoid sucrose esters are important class of plant-derived natural products and have greater potential to be leads for new drugs because of their structural diversity and broad-array of pharmacological and biological activities. Regio- and chemo-selective acylation of 2,1′:4,6-*O*-di-isopropylidene sucrose **4** with cinnamoyl chloride **5** and *p*-acetoxycinnamoyl chloride **6** afforded mono-, di-, tri- and tetra- variant PSEs in moderate yields. The first total synthesis of di-substituted PSE, lapathoside D **1**′ has been achieved successfully in short and simple synthetic steps from sucrose **3** as an inexpensive starting material. Lapathoside D **1** and a set of selected synthesized PSEs were tested for *in vitro* cytotoxicity against human cervical epithelioid carcinoma (HeLa) cell lines. Most of the compounds exhibited significant antitumor activity with their IC_{50} values ranging from 0.05 to 7.63 μM. The primary screening results indicated that PSEs might be valuable source for new potent anticancer drug candidates.

1. Introduction

Cancer is a leading cause of death in the human population and is a huge health problem. Therefore, the search for efficient anticancer agents with minimum side effects is a significant research area. It is well established that natural products provide the most prolific source of new anticancer lead compounds/drugs [1–3]. During the past 3-4 decades, approximately 150 phenylpropanoid sucrose esters (PSEs) with the general structure shown in Fig. 1, have been isolated from various medicinal plant species of the families Arecaceae, Brassicaceae, Liliaceae, Polygonaceae, Polygalaceae, Rosaceae and Smilacaeae whose extracts have been used worldwide in various traditional and folk medicines [4]. The natural PSEs such as heloniosides, lapathosides, hydropiperoside, smilasides and vanicosides were reported to have antitumor activities against different human cancer cell lines [4]. The antitumor activities are said to be mediated by the free hydroxyl, phenol and acetate groups attached to the sucrose core of the PSEs [5–7].

Lapathoside D **1** (Fig. 1), a typical PSE, isolated from various Polygonaceous plant species such as *Polygonum lapathifolium*, *Polygonum sachalinensis* and *Polygonum Perfoliatum* [8–10] displayed inhibitory effects on the Epstein–Barr virus early antigen (EBV-EA) activation by tumor-promoters such as 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in Raji cells [6,8]. It also exhibited significant potent antioxidant and α-glucosidase inhibitory activities [10].

Interestingly, PSEs as lead compounds are completely unexplored in drug discovery and, with the exception of niruriside **2** [11,12] (Fig. 1), have not been chemically synthesized to date. In addition, very little work has been done concerning their mechanism of action and structure activity relationship (SAR). Intrigued by their remarkable therapeutic intervention in a wide range of diseases and motivated by the abundance of these compounds in nature, we became interested in developing a general synthetic strategy that can be utilized for the synthesis of natural and unnatural PSEs with the aim of studying their antitumor activity. Herein, we wish to present a general synthetic method for the synthesis of PSEs demonstrated by the first total synthesis of lapathoside D **1** and its analogs. In addition, we also report the *in vitro* antitumor activity of the synthesized compounds.

2. Results and discussion

2.1. Chemistry

Sucrose is the core structural moiety of all PSEs (Fig. 1). It has been well established that reactions of native sucrose are complex since regio- and chemo-selection between the eight hydroxyl groups is poor [13,14]. To reduce the complexity of the reaction products, protection/deprotection methodologies are usually

* Corresponding author. Tel.: +65 6790 6738; fax: +65 67947553.
E-mail address: zaher@ntu.edu.sg (Z.M.A. Judeh).

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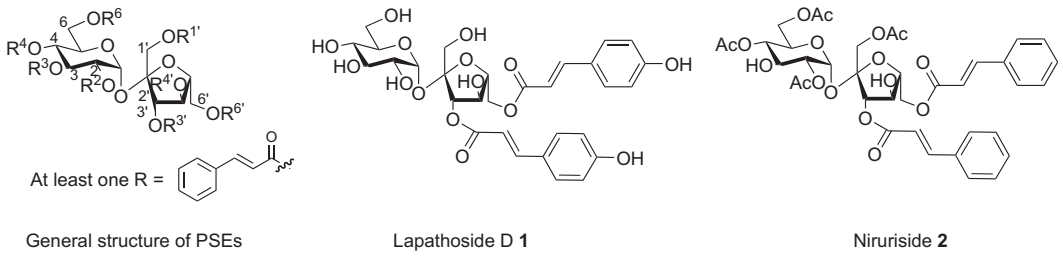


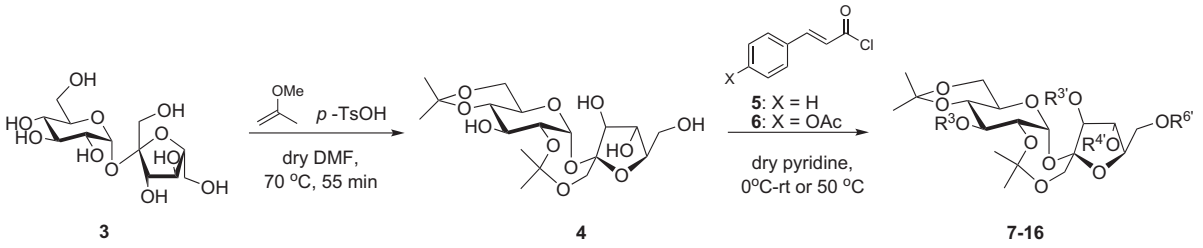
Fig. 1. General structure of PSEs, lapathoside D **1** and niruriside **2**.

followed. To this end, 2,1′:4,6-di-*O*-isopropylidene sucrose **4** (4 OH groups are protected, Scheme 1) has served as a viable substrate for the synthesis of various sucrose esters and, therefore, was chosen as the starting material for the synthesis of lapathoside D **1** and its analogs [15–19]. Moreover, the reactivity as well as selectivity of the remaining free OH groups of di-*O*-isopropylidene **4** in the acylation (e.g. benzoylation) and alkylation reactions were reported [14,20]. In our synthetic strategy, we anticipated that acylation of di-*O*-isopropylidene **4** with suitable acid chlorides should give access to the acylated sucrose derivatives that can be utilized for the synthesis of lapathoside D **1** and its analogs (Scheme 1). Initially, we decided to examine the feasibility of this strategy using simple acid chloride such as cinnamoyl chloride **5** to avoid complications due to substituents at the aromatic ring. It is worth noting that with the exception of niruriside **2**, all the reported natural PSEs have their phenyl rings substituted with either –OH, -OMe or combination of these substituents.

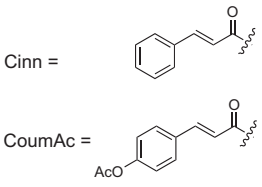
At the outset, acetonation of sucrose **3** to the required di-*O*-isopropylidene sucrose [15,17,21–27] **4** was successfully accomplished using 2-methoxypropene (4.5 equiv) according to the procedure reported by Poschalko et al. [28] (Scheme 1). However, in this method, purification of di-*O*-isopropylidene **4** relied on column chromatography followed by acetylation with excess Ac_2O, recrystallization and deacetylation [28]. This sequence proved to be tedious, time consuming, low yielding and problematic especially for large scale. We therefore looked for an alternative purification route that is simple and amenable for large scale. In our modified purification route, the crude syrupy product obtained from the reaction was initially subjected to flash column chromatography to remove the non-polar impurities. The more polar fractions were recrystallized using EtOAc to give di-*O*-isopropylidene **4** as white solid in 56% yield leaving behind various by-products in the solvent. This route was extremely suitable and convenient for large scale purification (*ca* 200–300 g).

2.1.1. *Regio- and chemo-selective acylation of di-O-isopropylidene **4** with cinnamoyl chloride **5***

Since di-*O*-isopropylidene **4** has four free OH groups, it is expected that a product distribution will be obtained when it is reacted with cinnamoyl chloride **5**. The free OH groups, like the parent sucrose **3**, were anticipated to have slight differences in their reactivities and selectivities. However, the most pronounced difference is expected to be between the primary 6′-OH and the rest of the secondary 3-OH, 3′-OH and 4′-OH. In order to explore these differences, regio- and chemo-selective acylation of di-*O*-isopropylidene **4** with cinnamoyl chloride **5** was studied under different reaction conditions (Table 1). When di-*O*-isopropylidene **4** was reacted with 1.1 equiv of acid chloride **5** (Table 1, entry 1),



Compound	R^3	$R^{3'}$	$R^{4'}$	$R^{6'}$
7	H	H	H	Cinn
8	H	Cinn	H	H
9	H	Cinn	H	Cinn
10	H	Cinn	Cinn	Cinn
11	Cinn	Cinn	Cinn	Cinn
12	H	H	H	CoumAc
13	H	CoumAc	H	H
14	H	CoumAc	H	CoumAc
15	H	CoumAc	CoumAc	CoumAc
16	CoumAc	CoumAc	CoumAc	CoumAc



Scheme 1. Regio- and chemo-selective acylation of di-*O*-isopropylidene **4** with cinnamoyl chloride **5** and *p*-acetoxycinnfamoyl chloride **6.**

Table 1
Regio- and chemo-selective acylation of di-*O*-isopropylidene sucrose **4** with cinnamoyl chloride **5**.

Entry	Equiv. of acid chloride 5	Time (d)	Product	Yield (%)	Total yield (%)
1	1.1	9	**7**	40	56
			8	16	
2	2.2	5	**9**	31	31
3	3.3	3	**9**	12	29
			10	17	
4	4.4	2	**10**	21	57
			11	36	

Table 2
Regio- and chemo-selective acylation of di-*O*-isopropylidene **4** with and *p*-acetoxycinnamoyl chloride **6**.

Entry	Equiv of acid chloride 6	Temp.	Time (d)	Product	Yield (%)	Total yield (%)
1[a]	1.1	rt	9	**12**	30	46
				13	10	
				14	6	
2[a]	1.1	50 °C	14	**12**	20	24
				14	4	
3[b]	2.2	rt	1	**12**	*ca* 5	56
				14	51	
4[c]	2.2	50 °C	14	**14**	20	20
5	3.3	rt	9	**14**	5	47
				15	33	
				16	9	
6	3.3	50 °C	2	**14**	5	49
				15	31	
				16	13	
7	4.4	rt	4	**15**	22	72
				16	50	
8	4.4	50 °C	2	**15**	24	91
				16	67	

[a] 40% of di-*O*-isopropylidene **4** was recovered.
[b] 20% of compound **4** was recovered.
[c] no improvement in the yield of product **14** was observed from day 2 to day 14 (TLC and ^{1}H NMR analysis).

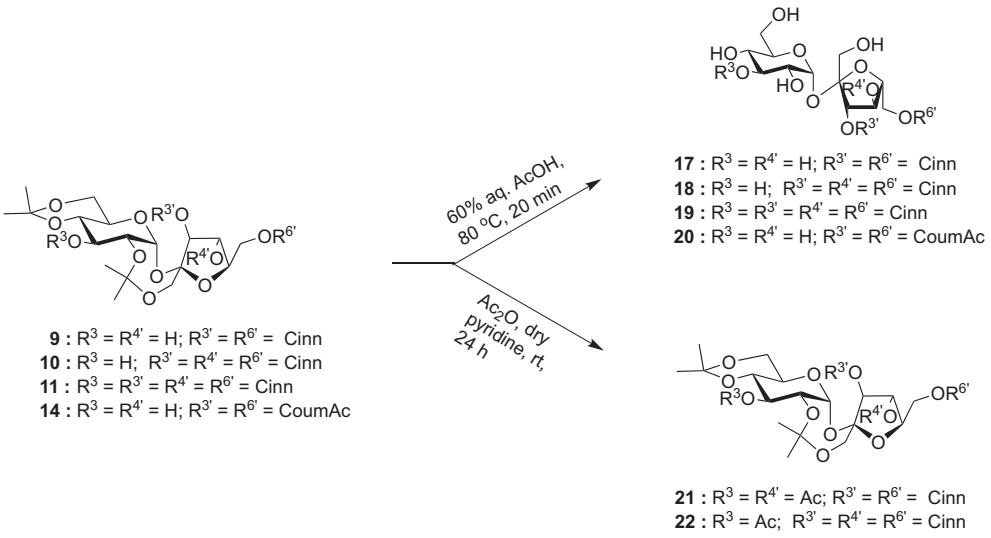
compound **7** was obtained as the major product in 40% yield along with compound **8** in 16% yield as white solids. Reaction of di-*O*-isopropylidene **4** with 2.2 mol equiv of acid chloride **5** (entry 2, Table 1) afforded compound **9** as the sole product (31% yield). Attempts to increase the yield of compound **9** according to the method reported by Duynstee et al. [12] where the reaction was conducted at −30 °C was not successful since majority of the starting material was recovered unchanged. When di-*O*-isopropylidene **4** was treated with 3.3 mol equiv of cinnamoyl chloride **5**, compound **10** was obtained as the major product in 17% yield along with compound **9** in 12% yield (Table 1, entry 3). Further increase in the amount of cinnamoyl chloride **5** to 4.4 mol equiv gave compound **11** in 36% yield along with compound **10** in 21% yield (Table 1, entry 4). The results above indicated that mono- (**7, 8**), di- (**9**), tri- (**10**) and tetra- (**11**) acylated PSEs can be obtained using appropriate number of equivalents of the acid chloride.

*2.1.2. Regio- and chemo-selective acylation of di-O-isopropylidene **4** with p-acetoxycinnamoyl chloride **6***

Following the conditions developed for acylation of di-*O*-isopropylidene **4** with cinnamoyl chloride **5**, we then focused our attention on the regio- and chemo-selective acylation using *p*-acetoxycinnamoyl chloride **6** [29] (Table 2, Scheme 1) in order to find out the optimal reaction conditions for the synthesis of lapathoside D **1**. When di-*O*-isopropylidene **4** was reacted at rt with 1.1 equiv of acid chloride **6**, compound **12** was obtained as the major product in 30% yield along with compounds **13** (10% yield), **14** (6% yield) and the starting material di-*O*-isopropylidene **4** (40%) (Table 2, entry 1). Attempts to drive the reaction to completion by raising the reaction temperature to 50 °C for extended time (up to 14 days) were not successful as compounds **12** and **14** were obtained only in 20% and 4% yields, respectively (Table 2, entry 2) along with the mixtures of intractable products. We observed that at higher reaction temperature, various decomposition products were obtained indicating the instability of the products at elevated temperature. When di-*O*-isopropylidene **4** was treated with 2.2 mol equiv of *p*-acetoxycinnamoyl chloride **6** at rt for 24 h (Table 2, entry 3), it afforded compound **14** as white solid in 51% yield along with compound **12** (*ca* 5%) and unreacted di-*O*-isopropylidene **4** (20%). Increasing the reaction temperature to 50 °C and reaction time (up to 14 days) has negative effect on the yield where compound **14** was obtained only in 20% yield (Table 2, entry 4). Here, it is important to note that as the reaction time increased, more intractable reaction mixtures were formed providing low yield of product **14** and making the purification very difficult. Subsequently, we attempted to increase the yield of compound **14**, the precursor for lapathoside D **1**, by reacting di-*O*-isopropylidene **4** with 3.3 equiv of *p*-acetoxycinnamoyl chloride **6** at rt. The reaction progress was followed by ^{1}H NMR and crude samples were taken every 12 h for 9 days to examine the distribution of the products and reactivity toward *p*-acetoxycinnamoyl chloride **6**. Analysis of the ^{1}H NMR spectra indicated that: (i) di-*O*-isopropylidene **4** was consumed within 12 h to give a product distribution of di-acylated **14**, tri-acylated **15** and tetra-acylated **16** products; (ii) at any instance, tri-acylated **15** dominated the reaction products while di-acylated **14** and tetra-acylated **16** were formed in much lower yields; (iii) After nine days, tri-acylated product **15** was obtained in 33% yield while di-acylated product **14** and tetra-acylated product **16** were obtained in 5% and 9% yields, respectively (Table 2, entry 5); (iv) the products distribution observed here is different to the one observed in Khan's [14] benzoylation where di-benzolylated product was a clear major product (36% yield) while tri-benzoylated product was obtained in 9% yield. This indicates that the selectivity and reactivity of the OH groups of di-*O*-isopropylidene **4** during the acylation with benzoyl chloride and *p*-acetoxycinnamoyl chloride **6** are different. When the same reaction was conducted at 50 °C for 2 days (Table 2, entry 6), again similar results were observed and di-acylated product **14** was formed in 5% yield, tri-acylated products **15** in 31% yield while tetra-acylated product **16** was obtained in 13% yield (Table 2, entry 6). Di-*O*-isopropylidene **4** on treatment with 4.4 equiv of *p*-acetoxycinnamoyl chloride **6** for 4 days (Scheme 1) provided compound **16** in 50% yield, together with compound **15** (22% yield) (Table 2, entry 7). When the same reaction was repeated at 50 °C, the yield of tetra-acylated product **16** improved to 67% while the yield of tri-esterified product **15** remained at 24% (Table 2, entry 8). We can conclude that the products distribution and yield depend upon the acid chloride used and the reaction conditions (time, temperature). Different acid chlorides give different product distributions, yields and products while higher reaction temperature and longer times reduce the product yield and lead to the formation of intractable products that complicate the purification process.

*2.1.3. Deprotection of the acetal groups: Preparation of compounds **17-20***

We then turned our attention to the deprotection of the acetal groups of precursors **9**–**11** and **14**. Several acetal deprotection conditions [12,16,30–34], have been reported with variable success depending upon the nature of the starting material. After several trials, deprotection using 60% aq. AcOH at 80 °C gave the best results (Scheme 2). Therefore, compounds **9**–**11** and **14** were subjected separately to acetal deprotection and the crude products were recrystallized from EtOAc or purified by column



Scheme 2. Preparation of compounds **17**–**22.**

chromatography using a gradient of CH_2Cl_2-EtOAc as eluent to afford compounds **17**–**20**, respectively, as white solids in yields ranging from 49% to 69% (Scheme 2).

In comparison to the NMR spectra of compounds **9**–**11** and **14**, compounds **17**–**20** indicated the absence of the characteristic signals for the two isopropylidene moieties usually observed in the ^{1}H NMR spectra at δ 1.20–1.53 ppm (4 × s, 12H, 2 (CH_3)$_2$C) and in the ^{13}C NMR spectra at δ 19.0–29.1 ppm (4 x 2 (CH_3)$_2$C) and 99.6–101.8 ppm (2 × (CH_3)$_2$*C*). Compounds **17**–**20** also showed a characteristic downfield shift of the anomeric (H-1) protons from a typical value of δ 6.15 ppm observed in the **9**–**11** and **14** to *ca* δ 5.0 ppm.

2.1.4. *Acetylation of the free OH groups using excess Ac_2O: synthesis of compounds **21** and **22***

Acetyl groups attached directly to the sucrose moiety were reported to influence the biological activity of some PSEs [5,35]. Consequently, compounds **9** and **10** were acetylated with excess Ac_2O to give compounds **21** and **22**, in 88% and 86% yield as white solids, respectively (Scheme 2). The antitumor activities of compounds **21** and **22** will be examined and compared with similar structures (See Section 2.2).

2.1.5. *Deacetylation of the acetylated phenyl rings: Preparation of lapathoside D **1** and compound **23***

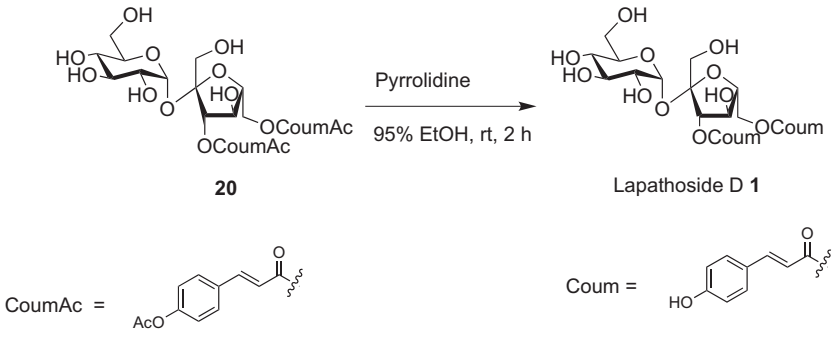
In order to complete the synthesis of lapathoside D **1**, deacetylation of the phenyl rings of compound **20** is required. Several deacetylation methods for sugar esters are known in literature [17,28,29,36–38]. For example, Helm et al. [29] successfully used 95% ethanolic solution of piperidine or pyrrolidine to remove the acetate protecting groups without affecting the cinnamate ester functionality in the fully protected *l*-arabinofuranoside. Gladly, when compound **20** was subjected to Helm et al. [29] deacetylation conditions, lapathoside D **1** was obtained as white solid in 70% yield (Scheme 3).

The ^{1}H (Fig. 2) and ^{13}C NMR spectra of lapathoside D **1** indicated the loss of the characteristic signals for the two acetyl moieties, represented by the proton signals at δ 2.28 (s, 6H, H-11″) and carbon signals at δ 21.0 (2 × C-11″) and 170.9 ppm (2 x C-10″). The success of the deprotection was further confirmed in the IR spectrum of the lapathoside D **1** where peaks corresponding to the acetyl ester carbonyl group at 1764 cm^{-1} in compound **20** have disappeared. Furthermore, the HR–ESI–MS spectrum of lapathoside D **1** showed *m*/*z* 657.1786 $[M + Na]^+$ (calcd 657.1790 for $C_{30}H_{34}O_{15}Na$). The structure of Lapathoside D **1** was further confirmed by comparison to the data reported for the isolated natural product (See supporting information) [8].

It was of interest to deacetylate compound **15** to further study the effect of the acetyl groups on the cytotoxicity. This was accomplished in a similar fashion to the deacetylation of compound **20**. Thus, compound **23** was obtained as white solid in 46% yield (Scheme 4).

2.2. *Biological activities*

Selected PSEs Lapathoside D **1**, **9**–**11** and **14**–**23** were subjected to *in vitro* cytotoxicity studies against human cervical epithelioid



Scheme 3. Preparation of lapathoside D **1.**

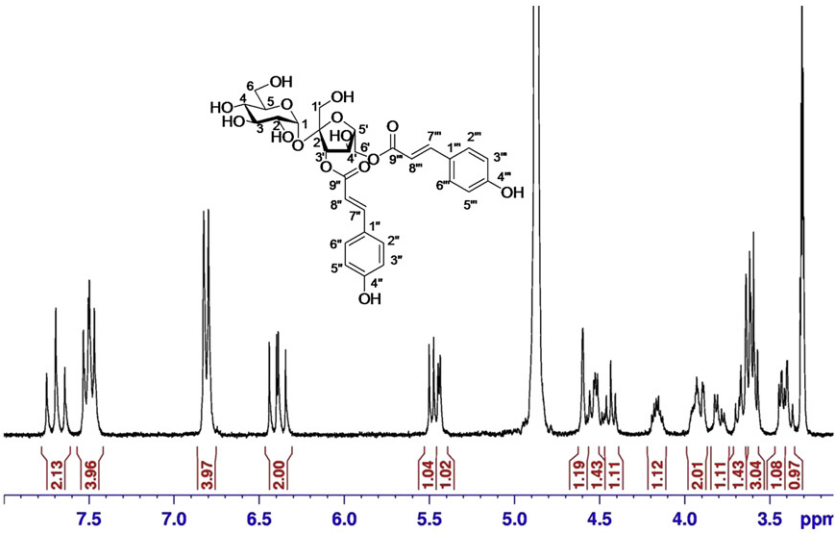


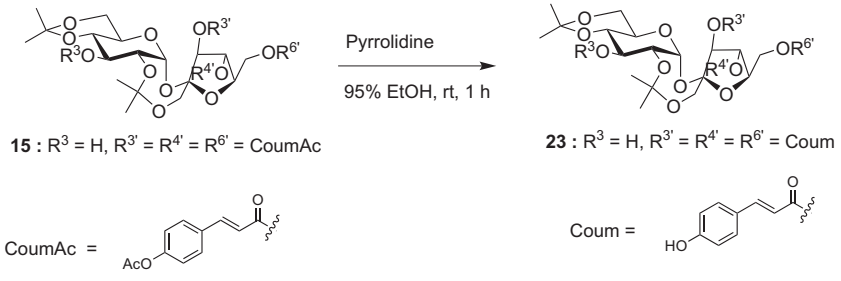
Fig. 2. ^{1}H NMR spectrum of lapathoside D **1** (300 MHz, CD_3OD).

carcinoma cells (HeLa) using MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay method at 48 h exposure and the results compared with camptothecin (CPT) as a positive control [5,39–42]. The IC_{50} values of these compounds are shown in Table 3. Lapathoside D **1** (Table 3, entry 1), its analog compounds **17** (Table 3, entry 8) and **20** (Table 4, entry 13) did not show any appreciable activity upto 100 μM concentration.

At this point, it seemed that the substitution on phenyl ring did not influence the antitumor activities. But the tri- **18** and tetra- **19** variant PSEs bearing cinnamoyl groups were found to have significant antitumor activity with the IC_{50} values of 4.10 and 0.47 μM, respectively (Table 3, entries 9 &10). With these encouraging results, it was of interest to find the antitumor activity of the corresponding di-*O*-isopropylidene compounds **9**–**11** and **14**–**16**. It was anticipated that the di-*O*-isopropylidene groups in compounds **9**–**11** and **14**–**16** would provide restricted conformation and may have an influence on the antitumor activity. Indeed, di-*O*-isopropylidene compounds **9** (0.97 μM), **10** (1.52 μM), **11** (0.25 μM) and **14** (2.46 μM) showed better IC_{50} values compared to their counterparts **17** (>100 μM), **18** (4.10 μM), **19** (0.47 μM) and **1** (>100 μM), respectively. Similarly, tri- and tetra- variants **15** and **16** were synthesized and found to have significant cytototoxicity with their IC_{50} values 5.26 and 0.56 μM, respectively. These results underscore the positive influence of the di-*O*-isopropylidene on the antitumor activity. Kawai et al.[23] and Kuo et al.[5] independently suggested that acetyl moieties on the sucrose core in PSEs might be responsible for mediating the observed activities. These reports encouraged us to synthesize compounds having acetyl groups attached to the sucrose moiety. Thus compounds **20** and **21** were prepared in the hope that these compounds would have better antitumor activities. To our delight, compounds **21** (0.58 μM) and **22** (0.05 μM) showed enhanced cytotoxicities in comparison to their corresponding parent compounds **9** (0.97 μM) and **10** (1.52 μM). The above results suggested that the acetyl and di-*O*-isopropylidene groups directly attached to the sucrose core play a positive role in mediating the cytotoxicities of PSEs.

From the results shown in Table 3, we can conclude:

(i) In general, cinnamoyl PSEs showed better IC_{50} values compared to coumaroyl and acetyl coumaroyl PSEs (Table 3).
(ii) The di-*O*-isopropylidene groups containing compounds exhibited significant cytotoxicities thus underscoring the positive effect of the di-*O*-isopropylidene groups in these compounds (Table 3).
(iii) Cinnamoyl di-*O*-isopropylidene sucrose esters: **11** (tetra-, IC_{50} = 0.25 μM) > **9** (di, IC_{50} = 0.97 μM) > **10** (tri-, IC_{50} = 1.52 μM).
(iv) Coumaryl di-*O*-isopropylidene sucrose esters: **16** (tetra-, IC_{50} = 0.56 μM) > **14** (di-, IC_{50} = 2.46 μM) > **15** (tri-, IC_{50} = 5.26 μM).
(v) The activity data for the compounds containing phenolic and acetyl groups on the phenyl ring seems to vary with the structure of the PSE. It appears that both phenolic and acetyl groups on the phenyl ring don't play a major role in mediating the cytotoxic activities of the PSEs shown in Table 3.
(vi) Compound **21** bearing two acetyl groups on sucrose moiety showed 2 times improved activity compared to its parent compound **9** without acetyl groups. Similarly, compound **22** bearing one acetyl group on sucrose moiety showed 5 times



Scheme 4. Preparation of compound **23.**

Table 3
In Vitro cytotoxicity (IC_{50} (μM)) of selected PSEs against human cervical epithelioid carcinoma (HeLa) cells at 48 h of exposure.

Entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Comp	**1**	**9**	**10**	**11**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**CPT**
IC_{50} [a]	>100	0.97	1.52	0.25	2.46	5.26	0.56	>100	4.10	0.47	>100	0.58	0.05	7.63	0.40

[a] IC_{50} (μM): the concentration that induces 50% growth inhibition compared with untreated control cells and were calculated from three independent experiments.

Table 4
IC_{50} values of selected synthesized PSEs **14**, **15** and **18** along with CPT at 24 h and 48 h of exposure.

No	Compound	IC_{50} (μM)	
		24 H	48 H
1	**14**	19.44	2.46
2	**15**	12.22	5.26
3	**18**	7.64	4.10
4	CPT	1.57	0.40

improved activity compared to its parent compound **11** which did not bear acetyl group. These results support the literature precedents which indicated the positive influence of the acetyl groups on sucrose moiety.

To examine if the cytotoxicity is time dependent, a few compounds were selected for evaluation of cytotoxicity at two different time intervals of drug exposure by MTS assay (Table 4).

In the MTS time course of study, the selected PSEs shown in Table 4 exhibited time-dependent antitumor activities with the IC_{50} values as shown. In all cases, using compounds **14**, **15** and **18**, the IC_{50} values improved as the time increased from 24 to 48 h exposure especially with compound **14** (Table 4, entry 1).

3. Conclusions

Regio- and chemo-selective acylation of the free hydroxyl groups of di-*O*-isopropylidene sucrose **4** with acid chlorides **5** and **6** was achieved in moderate yields and their reactivities were found to be in the order of 6′-OH > 3′-OH > 4′-OH > 3-OH. The selectivity is affected by the reaction temperature, time and the nature of the acylating agent. To our knowledge this is the first successful report for the total synthesis of lapathoside D **1** together with 16 unnatural PSEs in simple and short synthetic routes from sucrose **3** as inexpensive starting material. The preliminary MTS screening results indicated that 11 out of the 14 synthesized PSEs showed significant antitumor activities against HeLa cells at 48 h drug exposure with their IC_{50} values ranging from 0.05 to 7.63 μM compared with standard anticancer drug CPT. Time-dependent antitumor activities were also evaluated. The preliminary SAR correlation studies revealed that the type, number and positionof the phenylpropanoid units on the sucrose core influence the activity against HeLa cells. We envision that the present approach will not only form a model synthesis for such useful PSEs but also helps to provide sufficient materials for carrying out proper mechanism of action and structure activity relationship studies. The MTS primary screening results also indicated that PSEs might be potentially valuable source for new potent anticancer drug candidates.

4. Experimental section

4.1. Chemistry

For the synthesis of 2,1′:4,6-di-*O*-isopropylidene sucrose **4** and *p*-acetoxycinnamoyl chloride **6** see Supporting Information.

4.1.1. General procedure 1: Regioselective acylation of di-*O*-isopropylidene ***4*** with cinnamoyl chloride ***5*** and *p*-acetoxycinnamoyl chloride ***6***

Di-*O*-isopropylidene **4** (1.0 g, 2.4 mmol) was dissolved in dry pyridine (*ca* 10 mL) by stirring under nitrogen atmosphere. The resulting solution was then cooled to 0 °C in an ice bath. Cinnamoyl chloride **5** or *p*-acetoxycinnamoyl chloride **6** was added slowly at 0 °C and the reaction was left to stir while warming to rt. Stirring was continued until the reaction was complete (TLC, 3:1 EtOAc-hexanes). The resulting mixture was poured into vigorously stirred ice-water (100 mL) and the white solid precipitated was filtered using a Buchner funnel. The precipitate was redissolved in EtOAc (25 mL) and washed once with 1N HCl (50 mL). The aqueous layer was back extracted with EtOAc (2 × 50 mL) and combined with the original organic layer. The organic solution was then successively washed with 5% $NaHCO_3$ (50 mL) and brine (25 mL) and then dried over anhydrous $MgSO_4$ before being filtered. The EtOAc filtrates were concentrated and the gummy residue obtained was subjected to column chromatography using a gradient of CH_2Cl_2-EtOAc as eluent. The product(s) were collected as separate fractions.

4.1.1.1. 6′-Mono-O-cinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose ***7*** *and 3′-mono-O-cinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose* ***8***. Following general procedure 1, reaction between di-*O*-isopropylidene **4** (0.5 g, 1.2 mmol) and cinnamoyl chloride **5** (0.2 g, 1.3 mmol) in dry pyridine (5 mL) for 9 days gave compounds **7** (0.25 g, 40% yield) and **8** (0.10 g, 16% yield) as white solids. Analytical data for **7**: R_f = 0.09 (3:1 EtOAc-hexanes); mp 126–129 °C; FT–IR (KBr) ν_{max}: 3445, 2994, 2939, 1712, 1638, 1451, 1384, 1312, 1270, 1204, 1173, 1135, 1069, 943, 859, 770, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.43, 1.45, 1.46, 1.51 (4 × s, 12H, $(CH_3)_2C$), 3.52 (d, 1H, J = 12.6 Hz, H-1′a), 3.60 (dd, 1H, J = 9.3 Hz, 9.5 Hz, H-4), 3.70 (m, 1H, H-6a), 3.77 (dd, 1H, J = 3.3 Hz, 8.7 Hz, H-2), 3.89–3.98 (m, 3H, H-3′, H-5, H-6b), 4.10 (dd, 1H, J = 9.3 Hz, 9 Hz, H-3), 4.21 (m, 2H, H-4′, H-5′), 4.28 (m, 1H, H-1′b), 4.34 (m, 1H, H-6′a), 4.54 (dd, 1H, J = 4.2 Hz, 11.4 Hz, H-6′b), 6.21 (d, 1H, J = 3.3 Hz, H-1); *trans*-cinnamoyl units: 6.46 (d, 1H, J = 16.2 Hz, H-8″), 7.27–7.37 (m, 3H, H-3″, H-4″, H-5″), 7.48–7.55 (m, 2H, H-2″, H-6″), 7.69 (d, 1H, J = 16.2 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.2, 24.2, 25.2, 29.0 (4 × $(CH_3)_2C$), 62.3 (C-6), 63.7 (C-5), 65.9 (C-6′), 66.5 (C-1′), 69.2 (C-3), 73.4 (C-4), 73.9 (C-2), 77.3 (C-4′), 78.9 (C-3′), 79.6 (C-5′), 91.0 (C-1), 100.1, 102.3 (2 × $(CH_3)_2C$), 103.6 (C-2′), *trans*-cinnamoyl units: 117.6 (C-8″), 128.2 (C-2″, C-6″), 128.9 (C-3″, C-5″), 130.4 (C-4″), 134.3 (C-1″), 145.5 (C-7″), 167.2 (C-9″); ESI-Mass (positive mode): m/z 575.20 $[M + Na]^+$, calcd 575.22 for $C_{27}H_{36}O_{12}Na$; HR–ESI–MS (positive mode): found m/z 575.2092 $[M + Na]^+$, calcd 575.2099 for $C_{27}H_{36}O_{12}Na$. Analytical data for **8**: R_f = 0.24 (3:1 EtOAc-hexanes); FT–IR (KBr) ν_{max}: 3468, 2993, 2927, 1718, 1636, 1576, 1507, 1496, 1452, 1384, 1331, 1269, 1205, 1171, 1093, 1069, 1012, 944, 860, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39, 1.45, 1.52, 1.53 (4 × s, 12H, $(CH_3)_2C$), 3.60 (m, 2H, H-1′a, H-2), 3.70 (m, 2H, H-6a, H-6′a), 3.77 (m, 1H, H-4), 3.85 (m, 2H, H-5, H-6b), 3.93 (m, 2H, H-3, H-6′b), 4.07 (d, 1H, J = 12.3 Hz, H-1′b), 4.13 (m, 1H, H-5′), 4.84–4.95 (m, 1H, H-4′), 5.03 (d, 1H, J = 7.5 Hz, H-3′), 6.21 (d, 1H, J = 3.6 Hz, H-1); *trans*-cinnamoyl units: 6.55 (d, 1H, J = 16.2 Hz, H-8″), 7.39–7.45 (m, 3H, H-3″, H-4″, H-5″), 7.60–7.63 (m, 2H, H-2″, H-6″), 7.82 (d, 1H, J = 16.2 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$):

δ 19.1, 24.2, 25.4, 29.0 (4 × (CH_3)$_2$C), 61.2 (C-6), 61.9 (C-5), 64.0 (C-6′), 66.5 (C-1′), 70.1 (C-3); 71.7 (C-4′); 72.7 (C-2), 73.5 (C-4), 80.4 (C-3′), 84.3 (C-5′), 91.0 (C-1), 100.0, 102.0 (2 × (CH_3)$_2$C), 103.5 (C-2′); *trans*-cinnamoyl units: 116.6 (C-8″), 128.5 (C-2″, C-6″), 129.0 (C-3″, C-5″), 130.9 (C-4″), 133.9 (C-1″), 147.1 (C-7″), 167.6 (C-9″); ESI-Mass (positive mode): *m/z* 575.26 [M + Na] $^+$, calcd 575.22 for $C_{27}H_{36}O_{12}Na$.

4.1.1.2. 3′,6′-Di-O-cinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose ***9***. Following general procedure 1, reaction between the di-*O*-isopropylidene **4** (2.2 g, 5.2 mmol) and cinnamoyl chloride **5** (1.9 g, 11.5 mmol) in dry pyridine (20 mL) for 5 days gave compound **9** [12] (1.1 g, 31% yield) as white solid. Analytical data for **9**: R_f = 0.73 (3:1 EtOAc-hexanes); mp 118–120 °C; FT–IR (KBr) ν_{max}: 3479, 3418, 2992, 2941, 1715, 1637, 1578, 1497, 1451, 1384, 1312, 1270, 1204, 1169, 1070, 1011, 944, 860, 768, 712, 684, 658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39, 1.42, 1.52, 1.53 (4 × s, 12H, (CH_3)$_2$C), 3.60 (m, 1H, H-1′a), 3.67 (m, 1H, H-4), 3.75 (m, 2H, H-2, H-6a), 3.83 (dd, 1H, *J* = 9.9 Hz, 4.5 Hz, H-5), 3.90 (m, 1H, H-3), 3.97 (dd, 1H, *J* = 4.8 Hz, 9.9 Hz, H-6b), 4.08 (m, 1H, H-1′b), 4.39 (m, 2H, H-5′, H-6′a), 4.50 (m, 2H, H-4′, H-6′b), 4.95 (d, 1H, *J* = 6.3 Hz, H-3′), 6.13 (d, 1H, *J* = 3.6 Hz, H-1); *trans*-cinnamoyl units: R_1: 6.48 (d, 1H, *J* = 16.2 Hz, H-8″), 7.37–7.43 (m, 3H, H-3″, H-4″, H-5″), 7.51–7.54 (m, 2H, H-2″, H-6″), 7.71 (d, 1H, *J* = 16.2 Hz, H-7″); R_2: 6.54 (d, 1H, *J* = 16.2 Hz, H-8″), 7.37–7.43 (m, 3H, H-3″, H-4″, H-5″), 7.59–7.62 (m, 2H, H-2″, H-6″), 7.82 (d, 1H, *J* = 16.2 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.1, 24.1, 25.5, 29.1 (4 × (CH_3)$_2$C), 62.1 (C-6), 63.8 (C-5), 65.7 (C-6′), 65.9 (C-1′), 70.3 (C-3), 72.9 (C-4), 73.8 (C-2), 76.6 (C-4′), 81.2 (C-3′), 81.4 (C-5′), 90.9 (C-1), 99.9, 101.8 (2 × (CH_3)$_2$C), 104.5 (C-2′), *trans*-cinnamoyl units: R_1: 116.5 (C-8″), 128.2 (C-2″, C-6″), 128.9 (C-3″, C-5″), 130.4 (C-4″), 133.8 (C-1″), 145.4 (C-7″), 166.8 (C-9″); R_2: 117.6 (C-8″), 128.5 (C-2″, C-6″), 129.0 (C-3″, C-5″), 131.0 (C-4″), 134.3 (C-1″), 147.3 (C-7″), 167.7 (C-9″); ESI-Mass (positive mode): *m/z* 705.32 [M + Na]$^+$, calcd 705.26 for $C_{36}H_{42}O_{13}Na$; HR–ESI–MS (positive mode): found *m/z* 705.2502 [M + Na]$^+$, calcd 705.2518 for $C_{36}H_{42}O_{13}Na$; Anal. Calcd for $C_{36}H_{42}O_{13}$: C, 63.33; H, 6.20; found: C, 62.51; H, 6.12.

4.1.1.3. 3′,4′,6′-Tri-O-cinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose ***10***. Following general procedure 1, reaction between the di-*O*-isopropylidene **4** (0.5 g, 1.2 mmol) and cinnamoyl chloride **5** (0.7 g, 3.9 mmol) in dry pyridine (5 mL) for 3 days afforded compounds **9** (0.10 g, 12% yield) and **10** (0.16 g, 17% yield) as white solids. Analytical data for **10**: R_f = 0.80 (3:1 EtOAc-hexanes); mp 116–120 °C; FT–IR (KBr) ν_{max}: 3475, 2992, 2943, 1723, 1635, 1539, 1507, 1330, 1312, 1255, 1204, 1158, 1093, 1066, 1010, 943, 860, 767, 710, 684, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29, 1.38, 1.47, 1.50 (4 × s, 12H, (CH_3)$_2$C), 3.58 (app t, 1H, *J* = 9.3 Hz, H-4); 3.68 (m, 2H, H-6a, H-1′a), 3.73 (dd, 1H, *J* = 3.3 Hz, 5.4 Hz, H-2), 3.80–3.86 (m, 2H, H-3, H-5), 4.02 (dd, 1H, *J* = 5.1 Hz, 10.2 Hz, H-6b), 4.19 (d, 1H, *J* = 12.3 Hz, H-1′b), 4.54 (m, 2H, H-5′, H-6′a), 4.61 (m, 1H, H-6′b), 5.37 (d, 1H, *J* = 5.4 Hz, H-4′), 5.61 (dd, 1H, *J* = 3.6 Hz, 4.8 Hz, H-3′), 6.14 (d, 1H, *J* = 3.3 Hz, H-1); *trans*-cinnamoyl units: R_1: 6.55 (d, 1H, *J* = 16.2 Hz, H-8″), 7.26–7.38 (m, 3H, H-3″, H-4″, H-5″), 7.47–7.49 (m, 2H, H-2″, H-6″), 7.82 (d, 1H, *J* = 16.2 Hz, H-7″); R_2 : 6.45 (d, 1H, *J* = 16.2 Hz, H-8″), 7.26–7.38 (m, 3H, H-3″, H-4″, H-5″), 7.47–7.49 (m, 2H, H-2″, H-6″), 7.71 (d, 1H, *J* = 16.2 Hz, H-7″); R_3 : 6.43 (d, 1H, *J* = 16.2 Hz, H-8″), 7.26–7.38 (m, 3H, H-3″, H-4″, H-5″), 7.57–7.60 (m, 2H, H-2″, H-6″), 7.69 (d, 1H, *J* = 16.2 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.0, 24.0, 25.4, 28.8 (4 × (CH_3)$_2$C), 62.0 (C-6), 63.8 (C-5), 64.8 (C-6′), 66.2 (C-1′), 70.1 (C-3), 72.8 (C-4), 73.8 (C-2), 77.3 (C-4′), 77.7 (C-3′), 80.1 (C-5′), 91.3 (C-1), 99.6, 101.7 (2 × (CH_3)$_2$C), 104.8 (C-2′); *trans*-cinnamoyl units: R_1: 116.4 (C-8″), 128.0 (C-2″, C-6″), 128.8 (C-3″, C-5″), 130.2 (C-4″), 133.9 (C-1″), 145.1 (C-7″), 165.7 (C-9″); R_2: 116.6 (C-8″), 128.2 (C-2″, C-6″), 128.8 (C-3″, C-5″), 130.6 (C-4″), 134.0 (C-1″), 146.4 (C-7″), 165.8 (C-9″); R_3: 117.6 (C-8″), 128.4 (C-2″, C-6″), 128.8 (C-3″, C-5″), 130.7 (C-4″), 134.3 (C-1″), 147.0 (C-7″), 166.3 (C-9″); ESI-Mass (positive mode): *m/z* 835.34 [M + Na] $^+$, calcd 835.30 for $C_{45}H_{48}O_{14}Na$; HR–ESI–MS (positive mode): found *m/z* 835.2954 [M + Na]$^+$, calcd 835.2936 for $C_{45}H_{48}O_{14}Na$; Anal. Calcd for $C_{45}H_{48}O_{14}$: C, 66.49; H, 5.95; found: C, 67.12; H, 6.37.

4.1.1.4. 3,3′,4′,6′-Tetra-O-cinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose ***11***. Following general procedure 1, reaction between the di-*O*-isopropylidene **4** (0.5 g, 1.2 mmol) and cinnamoyl chloride **5** (0.9 g, 5.2 mmol) in dry pyridine (5 mL) for 2 days furnished compounds **11** (0.40 g, 36% yield) and **10** (0.20 g, 21% yield) as white solids. Analytical data for **11**: R_f = 0.92 (3:1 EtOAc-hexanes); mp 88–93 °C; FT–IR (KBr) ν_{max}: 2992, 2941, 1719, 1636, 1578, 1497, 1450, 1384, 1310, 1270, 1203, 1155, 1072, 1008, 944, 861, 767, 708, 683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20, 1.28, 1.44, 1.47 (4 × s, 12H, (CH_3)$_2$C), 3.64 (d, 1H, *J* = 12.3 Hz, H-1′a); 3.68–3.78 (m, 2H, H-4, H-6a), 3.92–4.00 (m, 2H, H-2, H-5), 4.05 (dd, 1H, *J* = 5.1 Hz, 10.2 Hz, H-6b), 4.24 (d, 1H, *J* = 12.6 Hz, H-1′b), 4.53–4.61 (m, 3H, H-5′, H-6′a, H-6′b), 5.37–5.43 (m, 2H, H-3, H-4′), 5.62 (dd, 1H, *J* = 3.3 Hz, 5.1 Hz, H-3′), 6.20 (d, 1H, *J* = 3.6 Hz, H-1); *trans*-cinnamoyl units: R_1: 6.43 (d, 1H, *J* = 15.9 Hz, H-8″), 7.35–7.40 (m, 3H, H-3″, H-4″, H-5″), 7.49–7.52 (m, 2H, H-2″, H-6″), 7.63–7.75 (d, 1H, *J* = 15.9 Hz, H-7″); R_2 : 6.45 (d, 1H, *J* = 15.9 Hz, H-8″), 7.35–7.40 (m, 3H, H-3″, H-4″, H-5″), 7.49–7.52 (m, 2H, H-2″, H-6″), 7.63–7.75 (m, 1H, H-7″); R_3 : 6.46 (d, 1H, *J* = 15.9 Hz, H-8″), 7.35–7.40 (m, 3H, H-3″, H-4″, H-5″), 7.49–7.52 (m, 2H, H-2″, H-6″), 7.63–7.75 (m, 1H, H-7″); R_4 : 6.63 (d, 1H, *J* = 15.9 Hz, H-8″), 7.35–7.40 (m, 3H, H-3″, H-4″, H-5″), 7.63–7.75 (m, 2H, H-2″, H-6″), 7.96 (d, 1H, *J* = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.0, 23.9, 25.5, 28.8 (4 × (CH_3)$_2$C), 62.1 (C-6), 64.3 (C-5), 65.0 (C-6′), 66.2 (C-1′), 71.0 (C-3), 71.6 (C-4), 71.9 (C-2), 77.4 (C-4′), 77.8 (C-3′), 80.2 (C-5′), 91.7 (C-1), 99.6, 101.5 (2 × (CH_3)$_2$C), 105.0 (C-2′); *trans*-cinnamoyl units: R_1: 116.5 (C-8″), 128.1 (C-2″, C-6″), 128.7 (C-3″, C-5″), 130.2 (C-4″), 134.0 (C-1″), 144.7 (C-7″), 165.8 (C-9″); R_2: 116.8 (C-8″), 128.2 (C-2″, C-6″), 128.8 (C-3″, C-5″), 130.3 (C-4″), 134.3 (C-1″), 145.2 (C-7″), 165.9 (C-9″); R_3: 117.7 (C-8″), 128.3 (C-2″, C-6″), 128.9 (C-3″, C-5″), 130.5 (C-4″), 134.4 (C-1″), 146.4 (C-7″), 166.2 (C-9″); R_4: 118.2 (C-8″), 128.3 (C-2″, C-6″), 128.9 (C-3″, C-5″), 130.7 (C-4″), 134.5 (C-1″), 147.4 (C-7″), 166.5 (C-9″); ESI-Mass (positive mode): *m/z* 965.36 [M + Na] $^+$, calcd 965.35 for $C_{54}H_{54}O_{15}Na$; HR–ESI–MS (positive mode): found *m/z* 965.3326 [M + Na]$^+$, calcd 965.3355 for $C_{54}H_{54}O_{15}Na$; Anal. Calcd for $C_{54}H_{54}O_{15}$: C, 68.78; H, 5.77; found: C, 68.80; H, 6.09.

4.1.1.5. 6′-Mono-O-acetoxycinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose ***12*** *and 3′-mono-O-acetoxycinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose* ***13***. Following general procedure 1, the reaction between di-*O*-isopropylidene **4** (1.0 g, 2.4 mmol) and *p*-acetoxycinnamoyl chloride **6** (0.6 g, 2.7 mmol) in dry pyridine (10 mL) for 9 days at rt afforded compounds **12** (0.44 g, 30% yield), **13** (0.15 g, 10% yield) and **14** (0.11 g, 6% yield) as white solids. Analytical data for **12**: R_f = 0.10 (3:1 EtOAc-hexanes); mp 127–129 °C; FT–IR (KBr) ν_{max}: 2994, 2934, 1702, 1636, 1558, 1507, 1374, 1319, 1206, 1167, 1134, 1069, 1014, 942, 857, 836, 700, 649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45, 1.52 (2s, 12H, (CH_3)$_2$C), 3.50 (m, 1H, H-1′a), 3.61 (dd, 1H, *J* = 9.3 Hz, 9.0 Hz, H-4), 3.73 (m, 2H, H-2, H-6a), 3.92 (m, 3H, H-3′, H-5, H-6b), 4.07 (m, 1H, H-3), 4.19 (m, 2H, H-4′, H-5′), 4.30 (m, 2H, H-1′b, H-6′a), 4.52 (m, 1H, H-6′b), 6.19 (d, 1H, *J* = 3.0 Hz, H-1); *trans*-*p*-coumaroyl units: δ 2.31 (1s, 3H, H-11″), 6.41 (d, 1H, *J* = 15.9 Hz, H-8″), 7.11 (d, 2H, J = 8.7 Hz, H-3″, H-5″), 7.52 (d, 2H, *J* = 8.4 Hz, H-2″, H-6″), 7.66 (d, 1H, *J* = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.2, 24.3, 25.3, 29.1 (4 × (CH_3)$_2$C), 62.3 (C-6), 63.8 (C-5), 65.9 (C-6′), 66.5 (C-1′), 69.4 (C-3), 73.4 (C-4), 73.9 (C-2), 77.5 (C-4′), 79.0 (C-3′),

79.6 (C-5′), 91.0 (C-1), 100.1, 102.3 (2 × $(CH_3)_2C$), 103.6 (C-2′); *trans-p*-coumaroyl units: 21.1 (C-11″), 117.8 (C-8″), 122.2 (C-3″, C-5″), 129.4 (C-2″, C-6″), 132.0 (C-1″), 144.4 (C-7″), 152.2 (C-4″), 167.1 (C-9″), 169.2 (C-10″); ESI-Mass (positive mode): *m/z* 633.26 $[M + Na]^+$, calcd 633.23 for $C_{29}H_{38}O_{14}Na$; HR–ESI–MS (positive mode): found *m/z* 633.2144 $[M + Na]^+$, calcd 633.2154 for $C_{29}H_{38}O_{14}Na$; Anal. Calcd for $C_{29}H_{38}O_{14}$: C, 57.04; H, 6.27; found: C, 54.78; H, 6.07. Analytical data for **13**: R_f = 0.16 (3:1 EtOAc-hexanes); mp 120–124 °C; FT–IR (KBr) ν_{max}: 3485, 2994, 2925, 1768, 1718, 1636, 1602, 1508, 1419, 1373, 1322, 1269, 1206, 1167, 1091, 1069, 1016, 946, 856, 754, 729, 655; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39, 1.45, 1.52, 1.53 (4 × s, 12H, $(CH_3)_2C$), 3.54 (m, 1H, H-1′a), 3.64 (m, 1H, H-4), 3.68 (m, 2H, H-6a, H-6′a), 3.77 (dd, 1H, J = 3.6 Hz, 9.0 Hz, H-2), 3.90 (m, 4H, H-3, H-5, H-6b, H-6′b), 4.07 (m, 1H, H-1′b), 4.13 (m, 1H, H-5′), 4.86 (dd, 1H, J = 7.5 Hz, 7.2 Hz, H-4′), 5.04 (d, 1H, J = 7.8 Hz, H-3′), 6.21 (d, 1H, J = 3.6 Hz, H-1); *trans-p*-coumaroyl units: δ 2.32 (1s, 3H, H-11″), 6.51 (d, 1H, J = 15.9 Hz, H-8″), 7.16 (d, 2H, J = 8.7 Hz, H-3″, H-5″), 7.63 (d, 2H, J = 8.4 Hz, H-2″, H-6″), 7.79 (d, 1H, J = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.1, 24.2, 25.4, 29.0 (4 × $(CH_3)_2C$), 61.2 (C-6), 61.9 (C-6′), 64.0 (C-5), 66.5 (C-1′), 70.1 (C-3), 71.6 (C-4′), 72.7 (C-4), 73.5 (C-2), 80.45 (C-3′), 84.3 (C-5′), 90.8 (C-1), 99.9, 102.0 (2 × $(CH_3)_2C$), 103.1 (C-2′), *trans-p*-coumaroyl units: δ 21.2 (C-11″), 116.8 (C-8″), 122.3 (C-3″, C-5″), 129.7 (C-2″, C-6″), 131.6 (C-1″), 145.9 (C-7″), 152.6 (C-4″), 167.4 (C-9″), 169.1 (C-10″); ESI-Mass (positive mode): *m/z* 633.18 $[M + Na]^+$, calcd 633.23 for $C_{29}H_{38}O_{14}Na$; HR–ESI–MS (positive mode): found *m/z* 633.2151 $[M + Na]^+$, calcd 633.2154 for $C_{29}H_{38}O_{14}Na$.

*4.1.1.6. 3′,6′-Di-O-acetoxycinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose **14**.* Following general procedure 1, the reaction between di-*O*-isopropylidene **4** (1.0 g, 2.4 mmol) and *p*-acetoxycinnamoyl chloride **6** (1.2 g, 5.2 mmol) in dry pyridine (10 mL) for 1 day at rt gave compounds **14** (0.96 g, 51% yield) and **12** (0.07 g, 5% yield) as white solids. Analytical data for **14**: R_f = 0.62 (3:1 EtOAc-hexanes); mp 109–111 °C; FT–IR (KBr) ν_{max}: 3486, 2993, 2942, 1768, 1715, 1637, 1602, 1508, 1418, 1372, 1322, 1270, 1166, 1068, 1013, 945, 912, 858, 837, 792, 724, 652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39, 1.43, 1.49, 1.52 (4 × s, 12H, $(CH_3)_2C$), 3.67 (m, 2H, H-1′a, H-4), 3.74 (m, 2H, H-2, H-6a), 3.84 (m, 2H, H-3, H-5), 3.96 (m, 1H, H-6b), 4.07 (m, 1H, H-1′b), 4.38 (m, 2H, H-5′, H-6′a), 4.45 (m, 1H, H-4′), 4.52 (m, 1H, H-6′b), 4.91 (d, 1H, J = 6.3 Hz, H-3′), 6.13 (d, 1H, J = 3.3 Hz, H-1); *trans-p*-coumaroyl units: R_1: 2.32 (s, 3H, H-11″), 6.43 (d, 1H, J = 15.9 Hz, H-8″), 7.12 (d, 2H, J = 8.7 Hz, H-3″, H-5″), 7.54 (d, 2H, J = 8.4 Hz, H-2″, H-6″), 7.73 (d, 1H, J = 15.9 Hz, H-7″), R_2: 2.32 (s, 3H, H-11″), 6.49 (d, 1H, J = 15.9 Hz, H-8″), 7.17 (d, 2H, J = 8.7 Hz, H-3″, H-5″), 7.62–7.66 (m, 2H, H-2″, H-6″), 7.79 (d, 1H, J = 16.2 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.1, 24.1, 25.4, 29.1 (4 × $(CH_3)_2C$), 62.1 (C-6), 63.8 (C-5), 65.8 (C-6′), 66.0 (C-1′), 70.3 (C-3), 73.0 (C-4), 73.8 (C-2), 76.3 (C-4′), 80.8 (C-3′), 81.3 (C-5′), 91.0 (C-1), 99.8, 101.7 (2 × $(CH_3)_2C$), 104.4 (C-2′); *trans-p*-coumaroyl units: R_1: 21.1 (C-11″), 116.7 (C-8″), 122.1 (C-3″, C-5″), 129.3 (C-2″, C-6″), 131.6 (C-1″), 144.2, 145.9 (C-7″), 152.1 (C-4″), 166.7 (C-9″), 169.0 (C-10″); R_2: 21.1 (C-11″), 117.8 (C-8″), 122.2 (C-3″, C-5″), 129.7 (C-2″, C-6″), 132.0 (C-1″), 145.9 (C-7″), 152.6 (C-4″), 167.2 (C-9″), 169.1 (C-10″); ESI-Mass (positive mode): *m/z* 821.31 $[M + Na]^+$, calcd 821.27 for $C_{40}H_{46}O_{17}Na$. HR–ESI–MS (positive mode): found *m/z* 821.2618 $[M + Na]^+$, calcd 821.2627 for $C_{40}H_{46}O_{17}Na$. Anal. Calcd for $C_{40}H_{46}O_{17}$: C, 60.14; H, 5.80; found: C, 59.24; H, 6.04.

*4.1.1.7. 3′,4′,6′-Tri-O-acetoxycinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose **15**.* Following general procedure 1, the reaction between di-*O*-isopropylidene **4** (1.0 g, 2.5 mmol) and *p*-acetoxycinnamoyl chloride **6** (1.9 g, 8.2 mmol) in dry pyridine (10 mL) for 9 days at rt afforded compounds **15** (0.80 g, 33% yield), **14** (0.10 g, 5% yield) and **16** (0.25 g, 9% yield) as white solids. Analytical data for **15**: R_f = 0.67 (3:1 EtOAc-hexanes); mp 135–138 °C; FT–IR (KBr) ν_{max}: 2993, 2942, 1768, 1718, 1636, 1602 1559, 1507, 1419, 1372, 1322, 1205, 1165, 1065, 1012, 945, 912, 858, 837, 726, 653 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$): δ 1.29, 1.37, 1.47, 1.49 (4 × s, 12H, $(CH_3)_2C$), 3.56 (m, 2H, H-1′a, H-4), 3.62 (m, 1H, H-6a), 3.77 (m, 1H, H-2), 3.85 (m, 2H, H-3, H-5), 4.00 (dd, 1H, J = 4.8 Hz, 10.2 Hz, H-6b), 4.17 (d, 1H, J = 12.6 Hz, H-1′b), 4.50 (m, 2H, H-5′, H-6′a), 4.60 (m, 1H, H-6′b), 5.33 (d, 1H, J = 5.1 Hz, H-4′), 5.57 (m, 1H, H-3′), 6.11 (d, 1H, J = 3.3 Hz, H-1); *trans-p*-coumaroyl units: R_1: 2.29 (s, 3H, H-11″), 6.38 (d, 1H, J = 15.9 Hz, H-8″), 7.06–7.14 (m, 2H, H-3″, H-5″), 7.48–7.51 (m, 2H, H-2″, H-6″), 7.60–7.69 (m, 1H, H-7″), R_2: 2.29 (s, 3H, H-11″), 6.39 (d, 1H, J = 15.9 Hz, H-8″), 7.06–7.14 (m, 2H, H-3″, H-5″), 7.48–7.51 (m, 2H, H-2″, H-6″), 7.60–7.69 (m, 1H, H-7″), R_3: 2.29 (s, 3H, H-11″), 6.49 (d, 1H, J = 15.9 Hz, H-8″), 7.06–7.14 (m, 2H, H-3″, H-5″), 7.60–7.69 (m, 2H, H-2″, H-6″), 7.78 (d, 1H, J = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.1, 24.1, 25.5, 29.0 (4 × $(CH_3)_2C$), 62.0 (C-6), 63.9 (C-5), 64.9 (C-6′), 66.3 (C-1′), 70.2 (C-3), 72.9 (C-4), 73.8 (C-2), 77.4 (C-4′), 77.8 (C-3′), 80.1 (C-5′), 91.4 (C-1), 99.7, 101.8 (2 × $(CH_3)_2C$), 104.8 (C-2′); *trans-p*-coumaroyl units: R_1: 21.1 (C-11″), 116.6 (C-8″), 122.1 (C-3″,C-5″), 129.3 (C-2″, C-6″), 131.6 (C-1″), 144.1 (C-7″), 152.1 (C-4″), 165.7 (C-9″), 169.0 (C-10″), R_2: 21.1 (C-11″), 116.8 (C-8″), 122.1 (C-3″, C-5″), 129.4 (C-2″, C-6″), 131.7 (C-1″), 145.4 (C-7″), 152.4 (C-4″), 165.8 (C-9″), 169.0 (C-10″), R_3: 21.1 (C-11″), 117.8 (C-8″), 122.2 (C-3″, C-5″), 129.7 (C-2″, C-6″), 132.1 (C-1″), 145.9 (C-7″), 152.5 (C-4″), 166.3 (C-9″), 169.1 (C-10″); ESI-Mass (positive mode): *m/z* 1009.31 $[M + Na]^+$, calcd 1009.32 for $C_{51}H_{54}O_{20}Na$; HR–ESI–MS (positive mode): found *m/z* 1009.3087 $[M + Na]^+$, calcd 1009.3101 for $C_{51}H_{54}O_{20}Na$; Anal. Calcd for $C_{51}H_{54}O_{20}$: C, 62.06; H, 5.51; found: C, 61.68; H, 5.91.

*4.1.1.8. 3,3′,4′,6′-Tetra-O-acetoxycinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose **16**.* Following general procedure 1, the reaction between di-*O*-isopropylidene **4** (1.0 g, 2.4 mmol) and *p*-acetoxycinnamoyl chloride **6** (2.4 g, 10.7 mmol) in dry pyridine (10 mL) for 4 days at rt furnished compounds **16** (1.40 g, 50% yield) and **15** (0.51 g, 22% yield) as white solids. Analytical data for **16**: R_f = 0.89 (3:1 EtOAc-hexanes); mp 138–140 °C; FT–IR (KBr) ν_{max}: 2992, 2943, 1764, 1718, 1635, 1601, 1559, 1507, 1419, 1374, 1319, 1204, 1165, 1047, 1011, 946, 911, 860, 836, 669, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19, 1.27, 1.43, 1.47 (4 × s, 12H, $(CH_3)_2C$), 3.65 (m, 2H, H-1′a, H-6a), 3.74 (d, 1H, J = 9.9 Hz, H-4), 3.89–3.97 (m, 2H, H-2, H-5), 4.00–4.06 (m, 1H, H-6b), 4.24 (d, 1H, J = 12.3 Hz, H-1′b), 4.48–4.59 (m, 3H, H-5′, H-6′a, H-6′b), 5.33–5.40 (m, 2H, H-3, H-4′), 5.59 (br dd, 1H, J = 3.0 Hz, 5.4 Hz, H-3′), 6.18 (d, 1H, J = 3.6 Hz, H-1); *trans-p*-coumaroyl units: R_1: 2.31 (s, 3H, H-11″), 6.38 (d, 1H, J = 15.9 Hz, H-8″), 7.04–7.14 (m, 2H, H-3″, H-5″), 7.45–7.55 (m, 2H, H-2″, H-6″), 7.60–7.75 (m, 1H, H-7″), R_2: 2.31 (s, 3H, H-11″), 6.40 (d, 1H, J = 15.9 Hz, H-8″), 7.04–7.14 (m, 2H, H-3″, H-5″), 7.45–7.55 (m, 2H, H-2″, H-6″), 7.60–7.75 (m, 1H, H-7″), R_3: 2.31 (s, 3H, H-11″), 6.41 (d, 1H, J = 15.9 Hz, H-8″), 7.04–7.14 (m, 2H, H-3″, H-5″), 7.45–7.55 (m, 2H, H-2″, H-6″), 7.60–7.75 (m, 1H, H-7″), R_4: 2.31 (s, 3H, H-11″), 6.58 (d, 1H, J = 15.9 Hz, H-8″), 7.04–7.14 (m, 2H, H-3″, H-5″), 7.60–7.75 (m, 2H, H-2″, H-6″), 7.93 (d, 1H, J = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.0, 23.9, 25.5, 28.8 (4 × $(CH_3)_2C$), 62.1 (C-6), 64.3 (C-5), 65.0 (C-6′), 66.2 (C-1′), 70.9 (C-3), 71.5 (C-4), 71.9 (C-2), 77.5 (C-4′), 77.8 (C-3′), 80.2 (C-5′), 91.7 (C-1), 99.6, 101.5 (2 × $(CH_3)_2C$), 105.0 (C-2′), *trans-p*-coumaroyl units: R_1: 21.1 (C-11″), 116.6 (C-8″), 122.0 (C-3″, C-5″), 129.2 (C-2″, C-6″), 131.7 (C-1″), 143.6 (C-7″), 152.0 (C-4″), 165.7 (C-9″), 169.0 (C-10″), R_2: 21.1 (C-11″), 116.9 (C-8″), 122.1 (C-3″, C-5″), 129.3 (C-2″, C-6″), 132.0 (C-1″), 144.0 (C-7″), 152.1 (C-4″), 165.7 (C-9″), 169.1 (C-10″), R_3: 21.1 (C-11″), 117.8 (C-8″), 122.1 (C-3″, C-5″), 129.4 (C-2″, C-6″), 132.1 (C-1″), 145.3 (C-7″), 152.3 (C-4″), 166.0 (C-9″), 169.1 (C-10″), R_4: 21.1 (C-11″), 118.3 (C-8″), 122.2 (C-3″, C-5″), 130.0 (C-2″, C-6″), 132.2 (C-1″), 146.2 (C-7″), 152.4 (C-4″), 166.3 (C-9″), 169.2 (C-10″);

ESI-Mass (positive mode): *m/z* 1197.36 $[M + Na]^+$, calcd 1197.37 for $C_{62}H_{62}O_{23}Na$; HR–ESI–MS (positive mode): found *m/z* 1197.3598 $[M + Na]^+$, calcd 1197.3574 for $C_{62}H_{62}O_{23}Na$; Anal. Calcd for $C_{62}H_{62}O_{23}$: C, 63.37; H, 5.32; found: C, 63.29; H, 5.60.

*4.1.2. General procedure 3: Cleavage of the isopropylidene groups of compounds **9-11** and **14***

A solution of the diacetonide compound (1 mmol) in 60% aq. AcOH (64 mL) was heated at 80 °C until the reaction was completed (TLC, 3:1 EtOAc-hexanes). The reaction mixture was then evaporated to dryness under reduced pressure by co-distillation with toluene (3 × 100 mL). The product was obtained as a white solid by recrystallization in EtOAc (in case of **9** and **14**) or purified by column chromatography using a gradient of CH_2Cl_2-EtOAc as eluent (in case of **10** and **11**). The general procedure was used to prepare compounds **17**-**20**.

*4.1.2.1. 3′,6′-Di-O-cinnamoylsucrose **17**.* Following general procedure 3, a solution of compound **9** (0.4 g, 0.6 mmol) was stirred with 60% aq. AcOH (26 mL) at 80 °C for 20 min. The reaction afforded compound **17** (0.2 g, 54% yield) as white solid. Analytical data for **17**: R_f = 0.06 (3:1 EtOAc-hexanes); mp 159–161 °C; FT–IR (KBr) ν_{max}: 3453, 2925, 1712, 1693, 1640, 1496, 1451, 1353, 1313, 1283, 1206, 1156, 1066, 1032, 997, 924, 865, 766, 709, 681 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 3.41 (m, 1H, H-4), 3.45 (m, 1H, H-2), 3.62 (m, 2H, H-1′b, H-1′a), 3.70 (m, 1H, H-3), 3.81 (dd, 1H, *J* = 4.8 Hz, 12 Hz, H-6a), 3.91–3.95 (m, 2H, H-6b, H-5), 4.17–4.23 (m, 1H, H-5′), 4.47 (app t, 1H, *J* = 8.1 Hz, H-4′), 4.57 (m, 2H, H-6′a, H-6′b), 5.45 (d, 1H, *J* = 3.6 Hz, H-1), 5.53 (d, 1H, *J* = 7.8 Hz, H-3′); *trans*-cinnamoyl units: R_1: 6.57 (d, 1H, *J* = 15.9 Hz, H-8″), 7.40–7.42 (m, 3H, H-3″, H-4″, H-5″), 7.60–7.67 (m, 2H, H-2″, H-6″), 7.74 (d, 1H, *J* = 15.9 Hz, H-7″); R_2: 6.62 (d, 1H, *J* = 15.9 Hz, H-8″), 7.40–7.42 (m, 3H, H-3″, H-4″, H-5″), 7.60–7.67 (m, 2H, H-2″, H-6″), 7.80 (d, 1H, *J* = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, CD_3OD): δ 62.7 (C-6), 65.1 (C-1′), 66.6 (C-6′), 71.5 (C-4), 73.2 (C-2), 74.5 (C-5), 75.0 (C-4′, C-3), 79.5 (C-3′), 81.2 (C-5′), 93.2 (C-1), 105.1 (C-2′), *trans*-cinnamoyl units: R_1: 118.5 (C-8″), 129.4 (C-3″, C-5″), 130.1 (C-2″, C-6″), 131.7 (C-4″), 135.7 (C-1″), 146.8 (C-7″), 167.8 (C-9″); R_2: 118.6 (C-8″), 129.6 (C-3″, C-5″), 130.1 (C-2″, C-6″), 131.7 (C-4″), 135.8 (C-1″), 147.3 (C-7″), 168.5 (C-9″); ESI-Mass (positive mode): *m/z* 625.23 $[M + Na]^+$, calcd 625.20 for $C_{30}H_{34}O_{13}Na$; HR–ESI–MS (positive mode): found *m/z* 625.1879 $[M + Na]^+$, calcd 625.1892 for $C_{30}H_{34}O_{13}Na$; Anal. Calcd for $C_{30}H_{34}O_{13}$: C, 59.80; H, 5.69; found: C, 59.73; H, 5.82.

*4.1.2.2. 3′,4′,6′-Tri-O-cinnamoylsucrose **18**.* Following general procedure 3, a solution of compound **10** (0.3 g, 0.4 mmol) was stirred with 60% aq. AcOH (21 mL) at 80 °C for 20 min. The reaction afforded compound **18** (0.2 g, 69% yield) as white solid. Analytical data for **18**: R_f = 0.11 (3:1 EtOAc-hexanes); mp 127–129 °C; FT–IR (KBr) ν_{max} cm^{-1}: 3061, 3028, 2927, 1716, 1636, 1578, 1497, 1450, 1313, 1283, 1255, 1204, 1170, 1002, 864, 710, 683; ^1H NMR (300 MHz, CD_3OD): δ 3.52 (m, 2H, H-1′a, H-4), 3.61 (m, 2H, H-2, H-6a), 3.72 (m, 2H, H-1′b, H-3), 3.84 (m, 2H, H-6b, H-5), 4.27 (m, 2H, H-5′, H-6′a), 4.44 (m, 1H, H-6′b), 5.40 (br s, 1H, H-1), 5.55 (br s, 2H, H-3′, H-4′); *trans*-cinnamoyl units: 6.22–6.40 (m, 1H, H-8″), 7.17–7.30 (m, 3H, H-3″, H-4″, H-5″), 7.32–7.39 (m, 2H, H-2″, H-6″), 7.56–7.65 (m, 1H, H-7″), R_2: 6.22–6.40 (m, 1H, H-8″), 7.17–7.30 (m, 3H, H-3″, H-4″, H-5″), 7.32–7.39 (m, 2H, H-2″, H-6″), 7.56–7.65 (m, 1H, H-7″), R_3: 6.22–6.40 (m, 1H, H-8″), 7.17–7.30 (m, 3H, H-3″, H-4″, H-5″), 7.32–7.39 (m, 2H, H-2″, H-6″), 7.56–7.65 (m, 1H, H-7″); ^{13}C NMR (75.48 MHz, CD_3OD): δ 61.3 (C-6), 64.3 (C-1′, C-6′), 69.4 (C-4), 71.7 (C-2), 73.1 (C-5), 73.9 (C-3), 76.7 (C-4′), 77.2 (C-3′), 79.4 (C-5′), 92.4 (C-1); 105.5 (C-2′); *trans*-cinnamoyl units: R_1: 116.6 (C-8″), 128.3 (C-3″, C-5″), 128.8 (C-2″, C-6″), 130.4 (C-4″), 134.0 (C-1″), 145.9 (C-7″), 165.8 (C-9″), R_2: 116.6 (C-8″), 128.4 (C-3″, C-5″), 128.9 (C-2″, C-6″), 130.7 (C-4″), 134.1 (C-1″), 146.7 (C-7″), 166.1 (C-9″), R_3: 117.2 (C-8″), 128.6 (C-3″, C-5″), 128.9 (C-2″, C-6″), 130.7 (C-4″), 134.2 (C-1″), 147.1 (C-7″), 166.8 (C-9″); ESI-Mass (positive mode): *m/z* 755.23 $[M + Na]^+$, calcd 755.24 for $C_{39}H_{40}O_{14}Na$; HR-ESI-MS (positive mode): found *m/z* 755.2310 $[M + Na]^+$, calcd 755.2310 for $C_{39}H_{40}O_{14}Na$.

*4.1.2.3. 3,3′,4′,6′-Tetra-O-cinnamoylsucrose **19**.* Following general procedure 3, a solution of compound **11** (0.5 g, 0.5 mmol) was stirred with 60% aq. AcOH (32 mL) at 80 °C for 20 min. The reaction afforded compound **19** (0.25 g, 54% yield) as white solid. Analytical data for **19**: R_f = 0.72 (3:1 EtOAc-hexanes); mp 91–94 °C; FT–IR (KBr) ν_{max} cm^{-1}: 3061, 3028, 2992, 1716, 1636, 1578, 1497, 1450, 1384, 1313, 1270, 1255, 1204, 1170, 1002, 943, 861, 708, 683; ^1H NMR (300 MHz, CD_3OD): δ 3.64–3.68 (m, 1H, H-4), 3.84 (m, 4H, H-1′b, H-1′a, H-2, H-6a), 4.06 (m, 2H, H-6b, H-5), 4.49–4.59 (m, 2H, H-5′, H-6′a), 4.69 (dd, 1H, *J* = 7.2 Hz, 11.1 Hz, H-6′b), 5.16 (app t, 1H, *J* = 9.6 Hz, H-3), 5.54–5.61 (m, 2H, H-1, H-3′), 5.77 (app t, 1H, *J* = 5.1 Hz, H- 4′); *trans*-cinnamoyl units: R_1: 6.44 (d, 1H, *J* = 15.9 Hz, H-8″), 7.35–7.38 (m, 3H, H-3″, H-4″, H-5″), 7.45–7.51 (m, 2H, H-2″, H-6″), 7.72 (d, 1H, *J* = 15.9 Hz, H-7″), R_2: 6.45 (d, 1H, *J* = 15.9 Hz, H-8″), 7.35–7.38 (m, 3H, H-3″, H-4″, H-5″), 7.45–7.51 (m, 2H, H-2″, H-6″), 7.73 (d, 1H, *J* = 15.9 Hz, H-7″), R_3: 6.47 (d, 1H, *J* = 16.2 Hz, H-8″), 7.35–7.38 (m, 3H, H-3″, H-4″, H-5″), 7.45–7.51 (m, 2H, H-2″, H-6″), 7.74 (d, 1H, *J* = 16.2 Hz, H-7″), R_4: 6.62 (d, 1H, *J* = 15.9 Hz, H-8″), 7.35–7.38 (m, 3H, H-3″, H-4″, H-5″), 7.60–7.64 (m, 2H, H-2″, H-6″), 7.89 (d, 1H, *J* = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, CD_3OD): δ 62.4 (C-6), 64.3 (C-6′), 64.6 (C-1′), 69.6 (C-4), 70.6 (C-2), 73.6 (C-5), 76.4 (C-4′), 77.1 (C-3), 78.0 (C-3′), 79.6 (C-5′), 92.5 (C-1), 105.5 (C-2′); *trans*-cinnamoyl units: R_1: 116.2 (C-8″), 128.3 (C-3″, C-5″), 128.7 (C-2″, C-6″), 130.6 (C-4″), 133.9 (C-1″), 146.1 (C-7″), 165.9 (C-9″), R_2: 116.4 (C-8″), 128.3 (C-3″, C-5″), 128.9 (C-2″, C-6″), 130.6 (C-4″), 134.0 (C-1″), 146.3 (C-7″), 166.9 (C-9″), R_3: 117.1 (C-8″), 128.4 (C-3″, C-5″), 128.9 (C-2″, C-6″), 130.8 (C-4″), 134.1 (C-1″), 146.9 (C-7″), 167.0 (C-9″), R_4: 117.2 (C-8″), 128.4 (C-3″, C-5″), 129.0 (C-2″, C-6″), 130.8 (C-4″), 134.1 (C-1″), 148.0 (C-7″), 168.6 (C-9″); ESI-Mass (positive mode): *m/z* 885.27 $[M + Na]^+$, calcd 885.28 for $C_{48}H_{46}O_{15}Na$; HR–ESI–MS (positive mode): found *m/z* 885.2725 $[M + Na]^+$, calcd 885.2729 for $C_{48}H_{46}O_{15}Na$.

*4.1.2.4. 3′,6′-Di-O-acetoxycinnamoylsucrose **20**.* Following general procedure 3, a solution of compound **14** (1.6 g, 2.2 mmol) was stirred in 60% aq. AcOH (103 mL) at 80 °C for 20 min. The reaction mixture afforded compound **20** (0.70 g, 49% yield) as a white solid. Analytical data for **20**: R_f = 0.61 (15:1 EtOAc-MeOH); mp 108–110 °C; FT–IR (KBr) ν_{max}: 3326, 2969, 2930, 1764, 1699, 1635, 1601, 1558, 1539, 1507, 1419, 1371, 1323, 1208, 1166, 1062, 995, 917, 862, 833, 700, 650 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 3.39–3.48 (m, 2H, H-2, H-4), 3.66 (m, 3H, H-1′a, H-1′b, H-3), 3.80 (m, 1H, H-6a), 3.95 (m, 2H, H-6b, H-5), 4.16–4.24 (m, 1H, H-5′), 4.47 (dd, 1H, *J* = 8.1 Hz, 8.4 Hz, H-4′), 4.58 (m, 2H, H-6′b, H-6′a), 5.45 (br s, 1H, H-1), 5.53 (d, 1H, *J* = 7.8 Hz, H-3′); *trans*-*p*-coumaroyl units: R_1: 2.28 (s, 3H, H-11″), 6.55 (d, 1H, *J* = 15.9 Hz, H-8″), 7.16 (m, 2H, H-3″, H-5″), 7.63–7.73 (m, 2H, H-2″, H-6″), 7.79 (d, 1H, *J* = 15.9 Hz, H-7″), R_2: 2.28 (s, 3H, H-11″), 6.60 (d, 1H, *J* = 15.9 Hz, H-8″), 7.16 (m, 2H, H-3″, H-5″), 7.63–7.73 (m, 2H, H-2″, H-6″), 7.79 (d, 1H, *J* = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, CD_3OD): δ 62.7 (C-6), 65.2 (C-1′), 66.6 (C-6′), 71.5 (C-4), 73.2 (C-2), 74.6 (C-5), 75.1 (C-4′, C-3), 79.5 (C-3′), 81.3 (C-5′), 93.2 (C-1), 105.1 (C-2′); *trans*-*p*-coumaroyl units: R_1: 21.0 (C-11″), 118.7 (C-8″), 123.5 (C-3″, C-5″), 130.6 (C-2″, C-6″), 133.5 (C-1″), 145.7 (C-7″), 154.0 (C-4″), 167.7 (C-9″), 170.9 (C-10″), R_2: 21.0 (C-11″), 118.8 (C-8″), 123.5 (C-3″, C-5″), 130.8 (C-2″, C-6″), 133.5 (C-1″), 146.2 (C-7″), 154.0 (C-4″), 168.4 (C-9″), 170.9 (C-10″);

ESI-Mass (positive mode): *m/z* 741.22 $[M + Na]^+$, calcd 741.21 for $C_{34}H_{38}O_{17}Na$; HR–ESI–MS (positive mode): found *m/z* 741.2001 $[M + Na]^+$, calcd 741.2001 for $C_{34}H_{38}O_{17}Na$. Anal. Calcd for $C_{34}H_{38}O_{17}$: C, 56.28; H, 5.33; found: C, 56.23; H, 5.49.

*4.1.3. General procedure 2: acetylation of compounds **9** and **10***

To a stirred solution of the cinnamoylated compound (1.0 g) in dry pyridine (10 mL per mmol) was added excess Ac_2O (0.6 mL per mmol) dropwise. The mixture was stirred at rt for 24 h (TLC, 1:2 EtOAc-hexanes). The resulting mixture was then poured into vigorously stirred ice-water (200 mL) and the white solid precipitated was filtered using a Buchner funnel. The precipitate was redissolved in EtOAc (50 mL). The aqueous layer was back extracted with EtOAc (2 × 50 mL) and combined with the original organic layer. The organic solution was washed with 1N HCl (100 mL), 5% $NaHCO_3$ (2 × 100 mL), brine (100 mL) and then dried over anhydrous $MgSO_4$ before being filtered. The EtOAc filtrates were concentrated under vacuum and acetylated compounds were obtained as an off-white solid.

*4.1.3.1. 3,4′-Di-O-acetyl-3′,6′-di-O-cinnamoyl-2,1′:4,6–2,1′:4,6-di-O-isopropylidene sucrose **21**.* Following general procedure 2, reaction between compound **9** (0.6 g, 0.9 mmol) and Ac_2O (0.6 mL, 0.7 g, 6.5 mmol) in pyridine (5.0 mL) for 24 h gave compound **21** (0.6 g, 88% yield) as white solid. Analytical data for **21**: R_f = 0.91 (3:1 EtOAc-hexanes); mp 88–90 °C; FT–IR (KBr) ν_{max} cm^{-1}: 3471, 3418, 2993, 2942, 1753, 1720, 1637, 1579, 1497, 1451, 1371, 1312, 1233, 1203, 1159, 1072, 1049, 990, 946, 893, 860, 769, 712, 685; ^1H NMR (300 MHz, $CDCl_3$): δ 1.20, 1.29, 1.42, 1.46 (4 × s, 12H, $(CH_3)_2C$), 2.02, 2.11 (2 × s, 6H, -$COCH_3$), 3.60 (m, 2H, H-1′a, H-4), 3.68 (d, 1H, *J* = 10.5 Hz, H-6a), 3.80–3.92 (m, 2H, H-2, H-5), 4.00 (dd, 1H, *J* = 5.1 Hz, 10.2 Hz, H-6b), 4.18 (d, 1H, *J* = 12.3 Hz, H-1′b), 4.42 (m, 1H, H-6′a), 4.51 (m, 2H, H-5′, H-6′b), 5.20–5.28 (m, 2H, H-3′, H-3), 5.45 (dd, 1H, *J* = 3.6 Hz, 5.1 Hz, H-4′), 6.14 (d, 1 H, *J* = 3.3 Hz, H-1); *trans*-cinnamoyl units: R_1: 6.46 (d, 1H, *J* = 16.2 Hz, H-8″), 7.36–7.40 (m, 3H, H-3″, H-4″, H-5″), 7.51–7.54 (m, 2H, H-2″, H-6″), 7.71 (d, 1H, *J* = 16.2 Hz, H-7″); R_2: 6.58 (d, 1H, *J* = 16.2 Hz, H-8″), 7.36–7.40 (m, 3H, H-3″, H-4″, H-5″), 7.63–7.66 (m, 2H, H-2″, H-6″), 7.90 (d, 1H, *J* = 16.2 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.0, 23.9, 25.5, 28.8 (4 × $(CH_3)_2C$), 20.8, 21.0 (2 × C-11″), 62.1 (C-6), 64.2 (C-5), 64.9 (C-6′), 66.1 (C-1′), 70.7 (C-3), 71.5 (C-4), 71.8 (C-2), 77.29 (C-4′), 77.5 (C-3′), 80.2 (C-5′), 91.6 (C-1), 99.5, 101.4 (2 × $(CH_3)_2C$), 104.9 (C-2′); *trans*-cinnamoyl units: R_1: 116.4 (C-8″), 128.1 (C-2″, C-6″), 128.8 (C-3″, C-5″), 130.3 (C-4″), 134.2 (C-1″); 145.2 (C-7″); 166.1 (C-9″); R_2: 117.7 (C-8″), 128.7 (C-2″, C-6″), 128.9 (C-3″, C-5″), 130.5 (C-4″), 134.4 (C-1″); 147.4 (C-7″); 166.5 (C-9″), 169.7, 170.1 (2 × C-10″); ESI-Mass (positive mode): *m/z* 789.34 $[M + Na]^+$, calcd 789.28 for $C_{40}H_{46}O_{15}Na$; HR–ESI–MS (positive mode): found *m/z* 789.2727 $[M + Na]^+$, calcd 789.2729 for $C_{54}H_{54}O_{15}Na$; Anal. Calcd for $C_{40}H_{46}O_{15}$: C, 62.65; H, 6.05; found: C, 62.22; H, 6.33.

*4.1.3.2. 3-O-Acetyl-3′,4′,6′-tri-O-cinnamoyl-2,1′:4,6-di-O-isopropylidene sucrose **22**.* Following general procedure 2, reaction between **10** (1.1 g, 1.4 mmol) and acetic anhydride (0.8 mL, 0.9 g, 8.9 mmol) in pyridine (10 mL) for 24 h gave compound **22** (1.0 g, 86% yield) as white solid. Analytical data for **22**: R_f = 0.94 (3:1 EtOAc-hexanes); mp 132–134 °C; FT–IR (KBr) ν_{max}: 3336, 2927, 1765, 1701, 1636, 1601, 1507, 1374, 1323, 1284, 1209, 1167, 1063, 994, 915, 860, 838, 794, 694, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.19, 1.31, 1.42, 1.47 (4 × s, 12H, $(CH_3)_2C$), 2.02 (1s, 3H, -$COCH_3$), 3.57 (m, 1H, H-4), 3.64 (m, 1H, H-1′a), 3.70 (d, 1H, *J* = 10.5 Hz, H-6a), 3.85 (dd, 1H, *J* = 3.3 Hz, 9.3 Hz, H-2), 3.92 (m, 1H, H-5), 4.04 (dd, 1H, *J* = 5.1 Hz, 10.5 Hz, H-6b), 4.23 (d, 1H, *J* = 12.3 Hz, H-1′b), 4.54 (m, 2H, H-5′, H-6′a), 4.61 (m, 1H, H-6′b), 5.25 (dd, 1H, *J* = 9.6 Hz, 9.3 Hz, H-3), 5.38 (d, 1H, *J* = 5.4 Hz, H-4′), 5.61 (br dd, 1H, *J* = 4.8 Hz, 3.3 Hz, H-3′), 6.18 (d, 1H, *J* = 3.3 Hz, H-1); *trans*-cinnamoyl units: R_1: 6.45 (d, 1H, *J* = 16.2 Hz, H-8″), 7.30–7.39 (m, 3H, H-3″, H-4″, H-5″), 7.48–7.52 (m, 2H, H-2″, H-6″), 7.70 (d, 1H, *J* = 16.2 Hz, H-7″); R_2: 6.45 (d, 1H, *J* = 16.2 Hz, H-8″), 7.30–7.39 (m, 3H, H-3″, H-4″, H-5″), 7.48–7.52 (m, 2H, H-2″, H-6″), 7.72 (d, 1H, *J* = 16.2 Hz, H-7″); R_3: 6.60 (d, 1H, *J* = 15.9 Hz, H-8″), 7.30–7.39 (m, 3H, H-3″, H-4″, H-5″), 7.62–7.67 (m, 2H, H-2″, H-6″), 7.92 (d, 1H, *J* = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 19.0, 23.9, 25.4, 29.1 (4 × $(CH_3)_2C$), 21.0 (C-11″), 62.1 (C-6), 64.3 (C-5), 65.0 (C-6′), 66.2 (C-1′), 70.7 (C-3), 71.5 (C-4), 71.8 (C-2), 77.4 (C-4′), 77.7 (C-3′), 80.2 (C-5′), 91.6 (C-1), 99.5, (101.4 (2 × $CH_3)_2C$), 105.0 (C-2′); *trans*-cinnamoyl units: R_1: 116.4 (C-8″), 128.1 (C-2″, C-6″), 128.7 (C-3″, C-5″), 130.3 (C-4″), 134.0 (C-1″), 145.2 (C-7″), 165. 9 (C-9″), R_2: 116.7 (C-8″), 128.1 (C-2″, C-6″), 128.8 (C-3″, C-5″), 130.5 (C-4″), 134.3 (C-1″), 146.4 (C-7″), 166.1 (C-9″), R_3: 117.7 (C-8″), 128.3 (C-2″, C-6″), 128.9 (C-3″, C-5″), 130.7 (C-4″), 134.4 (C-1″), 147.4 (C-7″), 166.4 (C-9″), 169.7 (C-10″); ESI-Mass (positive mode): *m/z* 877.36 $[M + Na]^+$, calcd 877.31 for $C_{47}H_{50}O_{15}Na$; HR–ESI–MS (positive mode): found *m/z* 877.3051 $[M + Na]^+$, calcd 877.3042 for $C_{47}H_{50}O_{15}Na$; Anal. Calcd for $C_{47}H_{50}O_{15}$: C, 66.03; H, 5.90; found: C, 66.45; H, 6.27.

*4.1.4. General procedure 4: preparation of compounds **1** and **23***

Pyrrolidine (3 mol equiv per acetyl group) was added dropwise to a stirred suspension of acetylated compound **20** or compound **15** (1 mmol) in 95% EtOH (40.0 mL) causing the mixture to turn yellow. The acetylated compound typically dissolved within 15 min and the reaction was allowed to continue at rt for a total of 1–2 h (TLC, 3:1 EtOAC-hexanes). The crude reaction mixture was then poured directly to a column of strongly acidic ion-exchange resin [Amberlite IRA-120 (H^+), washed and packed in 95% EtOH]. The appropriate fraction was then collected and concentrated to a residue under reduced pressure. The residue was subjected to silica gel column chromatography using a gradient of CH_2Cl_2-EtOAc-MeOH as eluent. The appropriate fraction was evaporated under reduced pressure to furnish the product as a white solid. The general procedure was used to prepare compounds **1** and **23**.

*4.1.4.1. Preparation of lapathoside D **1**.* Following general procedure 4, a suspension of compound **20** (0.5 g, 0.7 mmol) in 95% EtOH (21 mL) was treated with pyrrolidine (325.0 μL, 281.4 mg, 4.0 mmol) for a total of 2 h. The reaction mixture afforded compound **1** (0.31 g, 70% yield) as white solid. Analytical data for **1**: R_f = 0.55 (15:1 EtOAc-MeOH); mp 98–100 °C; FT–IR (KBr) ν_{max}: 3304, 2938, 1706, 1636, 1606, 1516, 1438, 1330, 1264, 1204, 1171, 1062, 1002, 863, 831 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 3.41 (m, 1H, H-4), 3.44 (m, 1H, H-2), 3.61 (m, 2H, H-1′b, H-1′a), 3.63 (m, 1H, H-3), 3.80 (m, 1H, H-6a), 3.91 (m, 2H, H-6b, H-5), 4.15 (m, 1H, H-5′), 4.43 (dd, 1H, *J* = 7.8 Hz, 8.1 Hz, H-4′), 4.54 (m, 2H, H-6′b, H-6′a), 5.44 (d, 1H, *J* = 3.6 Hz, H-1), 5.49 (d, 1H, *J* = 8.1 Hz, H-3′); *trans-p*-coumaroyl units: R_1: 6.41 (d, 1H, *J* = 15.9 Hz, H-8″), 6.81 (d, 2H, *J* = 8.4 Hz, H-3″, H-5″), 7.52 (d, 2H, *J* = 9.0 Hz, H-2″, H-6″), 7.72 (d, 1H, *J* = 15.9 Hz, H-7″); R_2: 6.37 (d, 1H, *J* = 15.9 Hz, H-8″), 6.81 (d, 2H, *J* = 8.4 Hz, H-3″, H-5″), 7.48 (d, 2H, *J* = 9 Hz, H-2″, H-6″), 7.67 (d, 1H, *J* = 15.9 Hz, H-7″); ^{13}C NMR (75.48 MHz, CD_3OD): δ 62.6 (C-6), 65.1 (C-1′), 66.4 (C-6′), 71.4 (C-4), 73.2 (C-2), 74.4 (C-5), 75.0 (C-4′, C-3), 79.3 (C-3′), 81.2 (C-5′), 93.2 (C-1), 105.1 (C-2′); *trans-p*-coumaroyl units: R_1: 114.6 (C-8″), 116.9 (C-3″, C-5″), 127.2 (C-1″), 131.5 (C-2″, C-6″); 147.6 (C-7″), 161.3 (C-4″), 168.4 (C-9″), R_2: 114.8 (C-8″), 116.9 (C-3″, C-5″), 127.2 (C-1″), 131.3 (C-2″, C-6″); 147.0 (C-7″), 161.3 (C-4″), 169.2 (C-9″); ESI-Mass (positive mode): *m/z* 657.1 $[M + Na]^+$, calcd 657.1 for $C_{30}H_{34}O_{15}Na$; HR–ESI–MS (positive mode): found *m/z* 657.1786 $[M + Na]^+$, calcd 657.1790 for $C_{30}H_{34}O_{15}Na$; Anal. Calcd for

$C_{30}H_{34}O_{15}$: C, 56.78; H, 5.40; found: C, 55.31; H, 6.12. Spectral data of compound **1** was the same as reported previously [8].

4.1.4.2. 3′,4′,6′-Tri-O-coumaroyl-2,1′:4,6-di-O-isopropylidene sucrose ***23***. Following general procedure 4, a suspension of compound **15** (0.1 g, 0.1 mmol) in 95% EtOH (4.0 mL) was stirred with pyrrolidine (97.5 μL, 84.4 mg, 1.2 mmol) for a total of 1 h. The reaction mixture afforded compound **23** (0.04 g, 46% yield) as white solid. Analytical data for **23**: R_f = 0.57 (9:1 EtOAc-MeOH); mp 115–118 °C; FT–IR (KBr) ν_{max}: 3290, 1700, 1632, 1605 1515, 1443, 1374, 1330, 1263, 1204, 1170, 1106, 1057, 995, 864, 830 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 1.24, 1.33, 1.44 (3 × s, 12H, $(CH_3)_2C$), 3.52 (m, 1H, H-4); 3.68 (m, 4H, H-2, H-3, H-1′a, H-6a), 3.78 (m, 1H, H-5), 3.96 (m, 1H, H-6b), 4.20 (m, 1H, H-1′b), 4.46 (m, 2H, H-5′, H-6′a), 4.59 (m, 1H, H-6′b), 5.33 (br s, 1H, H-4′), 5.60 (br s, 1H, H-3′), 6.09 (br s, 1H, H-1); *trans-p*-coumaroyl units: R_1: 6.26–6.42 (m, 1H, H-8″), 6.72–6.80 (m, 2H, H-3″, H-5″), 7.39 (m, 2H, H-2″, H-6″), 7.63 (m, 1H, H-7″), R_2: 6.26–6.42 (m, 1H, H-8″), 6.72–6.80 (m, 2H, H-3″, H-5″), 7.39 (m, 2H, H-2″, H-6″), 7.63 (m, 1H, H-7″), R_3: 6.26–6.42 (m, 1H, H-8″), 6.72–6.80 (m, 2H, H-3″, H-5″), 7.52 (m, 2H, H-2″, H-6″), 7.75 (m, 1H, H-7″); ^{13}C NMR (75.48 MHz, CD_3OD): δ 19.5, 24.4, 25.8, 29.5 (4 × $(CH_3)_2C$), 63.3 (C-6), 65.4 (C-5), 66.1 (C-6′), 67.6 (C-1′), 71.3 (C-3), 74.6 (C-4), 75.1 (C-2), 79.0 (C-4′), 79.3 (C-3′), 81.2 (C-5′), 93.1 (C-1), 101.0, 103.0 (2 × $(CH_3)_2C$), 106.5 (C-2′); *trans-p*-coumaroyl units: R_1: 114.0 (C-8″), 116.9 (C-3″,C-5″), 127.1 (C-1″), 131.4 (C-2″, C-6″), 147.0 (C-7″), 161.3 (C-4″), 168.0 (C-9″), R_2: 114.2 (C-8″), 117.0 (C-3″, C-5″), 127.1 (C-1″), 131.7 (C-2″, C-6″), 148.1 (C-7″), 161.6 (C-4″), 168.3 (C-9″), R_3: 115.0 (C-8″), 117.0 (C-3″, C-5″), 127.2 (C-1″), 131.9 (C-2″, C-6″), 148.5 (C-7″), 161.6 (C-4″), 168.8 (C-9″); HR–ESI–MS (positive mode): found *m/z* 883.2793 $[M + Na]^+$, calcd 883.2784 for $C_{45}H_{48}O_{17}Na$.

4.2. In vitro cytotoxicity of selected PSEs against HeLa cells

In Vitro cytotoxicity activities of the selected PSEs against HeLa cell lines were evaluated by measuring the metabolism of a standard tetrazolium substrate, MTS at 24 and 48 h of drug exposure. Human cervical epithelioid carcinoma cells (HeLa) was cultured in MEM media supplemented with 10% *v/v* fetal bovine serum (FBS) and 1% *v/v* penicillin-streptomycin in a CO_2 incubator in a humidified condition with 5% CO_2 and 95% air at 37 °C.

Stock solutions (50 mM) of the test compounds (i.e. selected synthesized PSEs and camptothecin (as positive control)) were first prepared in DMSO and then diluted with MEM (1% *v/v* penicillin-streptomycin was added; no FBS was added) to the desired final concentrations prior to the experiment. The final DMSO concentration was 0.2% in each well. This DMSO concentration exhibited no interference with the biological activities tested. The cells (1×10^4 cells per well) were incubated in 96-well plates in which each cell well contained 100 μl of the MEM media. After 24 h of incubation, the medium was removed and replaced with 100 μl of test solution of varying concentration (0.001–100 μM). The samples were again incubated for 24 h and 48 h at 37 °C. After incubation, the samples were removed and 100 μl of the medium containing MTS at conc. of 5:1 without serum was added into the wells and then incubated at 37 °C for 4 h. After 4 h of incubation, the absorbencies of the samples were measured at 490 nm using Infinite M200 micro plate reader controlled by Magellan and i-control softwares (Tecan Group Ltd, Mannedorf, Switzerland). The samples containing media with and without cells were also analyzed and labeled as 'control' and 'blank', respectively. Subtracting the average 490 nm absorbance from the "no-cell" control from all other absorbance values yielded the correct absorbance. All experiments were performed in triplicate. The percentage of cytotoxicity (or growth inhibition) was calculated as (1-(Net A_{490} (testing drug)/Net A_{490} (control)) x 100%. Hence, the negative control was set to 100% survival or 0% toxicity. IC_{50} is the concentration that induces 50% growth inhibition compared with untreated control cells. The IC_{50} values of the screened PSEs were calculated from the dose–response curve by non-linear regression analysis using the data analysis software (Graph Pad Prism) from three independent experiments. Comparisons between multiple groups were carried out using one-way analysis of variance (one-way ANOVA) with Bonferroni's correction. Differences were considered statistically significant when $P < 0.05$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2012.02.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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