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An orthogonal approach for the precise synthesis of phenylpropanoid sucrose esters†

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Phenylpropanoid sucrose esters (PSEs) are plant-derived metabolites that exist widely in medicinal plants and possess important bioactivities. Their precise synthesis is challenging due to the distinct and diverse substitution patterns at the sugar framework, and it is scarcely reported. Orthogonal protection/deprotection strategies for disaccharides are more complex and less developed than those for monosaccharides. We disclose a precise synthesis of PSEs starting from 2,1′:4,6-di-*O*-diisopropylidene sucrose **7** *via* an orthogonal protection/deprotection and selective cinnamoylation strategy. We demonstrate the strategy for the synthesis of several PSEs cinnamoylated at the *O*-3 and *O*-4′ positions of diisopropylidene sucrose **7**. The strategy is enabled by a carefully selected and synergistic set of protecting groups and deprotecting agents under the optimized conditions. It potentially gives access to the ~150 reported PSEs and opens the door for the custom synthesis of unnatural PSEs for industrial applications. The reported work also presents a viable strategy for the general orthogonal protection/deprotection of disaccharides for the precise synthesis of other classes of phenylpropanoid esters and related compounds.

Introduction

Phenylpropanoid sucrose esters (PSEs) are secondary metabolites widely distributed in various medicinal plants.[1] More than 150 PSEs have been isolated and characterized during the past decades.[1] They possess important biological activities[1] including antiproliferation,[2–7] antioxidation,[8–15] anti-inflammation,[16–18] and α-glucosidase inhibition activities.[12,19,20] The core sucrose unit of PSEs is selectively decorated with one or more (substituted) cinnamoyl moieties (*e.g.* cinnamoyl, coumaroyl, feruloyl, sinapoyl, *etc.*) *via* ester linkages, especially at *O*-3, *O*-3′, *O*-4′, and *O*-6′ (Fig. 1).[1] The variation in the type, number, and position of the cinnamoyl moieties causes structural (simple and mixed) and biological diversities among the PSEs. Examples of simple and mixed PSEs include sibiricose A_5 **1**,[26–29] sibiricose A_6 **2**,[28–30] reiniose A **3**,[29,30] heterosmilaside **4**[9] and glomeratose B **5**[31] (Fig. 1). The challenging synthesis of PSEs and their low natural abundance in the plant species hinder their exploitation as new lead drug candidates as well as food and cosmetic additives for industrial applications.[1]

Although their structures look simple (Fig. 1), only four reports dealing with their synthesis have appeared including two from our laboratory.[3,6,21,22] Direct cinnamoylation of unprotected sucrose **6** is inconceivable due to the poor chemoselection and regioselection between its eight free hydroxyl groups.[23–25] Therefore, we[3,6] and others[22] have used the partially protected 2,1′:4,6-di-*O*-diisopropylidene sucrose **7** as the starting material for direct acylation with cinnamoyl chlorides to synthesize niruriside **8**, helonioside A **9**, lapathoside C **10**, lapathoside D **11**, and several other analogues (Fig. 1). However, this approach suffers from several limitations including the following:[3,6,21,22] (i) direct acylation of diisopropylidene sucrose **7** gave mixtures of differently acylated products which compromised the yield and complicated the purification significantly; (ii) the products and yields of the direct acylation were unpredictable and significantly depended on the type of the acylating reagent (*e.g.* cinnamoyl chloride, coumaroyl chloride, feruloyl chloride, *etc.*) and the reaction conditions (moles of the acylating reagent, solvent, temperature, time and concentration); (iii) the preparation of mixed PSEs (Fig. 1) decorated with different types of cinnamoyl moieties using this approach was significantly challenging and practically tedious. Therefore, it is advantageous to develop a systematic and precise route for the efficient synthesis of natural and unnatural PSEs to

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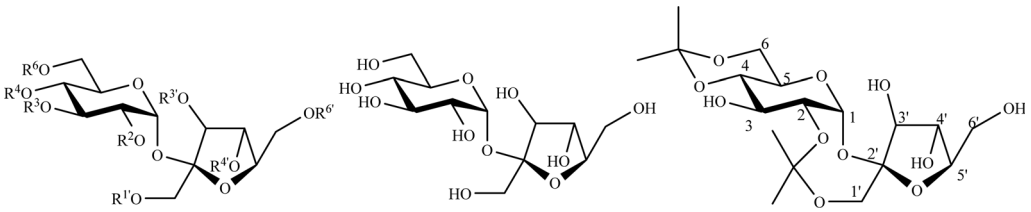


Simple PSEs have the same (substituted) cinnamoyl moieties while mixed PSEs have different (substituted) cinnamoyl moieties.

Sibiricose A5 **1**: $R^2 = R^3 = R^4 = R^6 = R^{1'} = H$, $R^{3'} =$ feru, $R^{4'} = R^{6'} = H$
Sibiricose A6 **2**: $R^2 = R^3 = R^4 = R^6 = R^{1'} = H$, $R^{3'} =$ sinap, $R^{4'} = R^{6'} = H$
Reiniose A **3**: $R^2 = R^3 = R^4 = H$, $R^6 =$ feru, $R^{1'} = H$, $R^{3'} =$ TMC, $R^{4'} = R^{6'} = H$
Heterosmilaside **4**: $R^2 = H$, $R^3 =$ feru, $R^4 = R^6 = R^{1'} = R^{3'} = R^{4'} = H$, $R^{6'} =$ feru
Glomeratose **5**: $R^2 = R^3 = R^4 = H$, $R^6 =$ coum, $R^{1'} = H$, $R^{3'} =$ sinap, $R^{4'} = R^{6'} = H$
Niuriside **8**: $R^2 =$ Ac, $R^3 = H$, $R^4 = R^6 = R^{1'} =$ Ac, $R^{3'} =$ cinn, $R^{4'} = H$, $R^{6'} =$ cinn
Helonioside A **9**: $R^2 = R^3 = R^4 = R^6 = R^{1'} = H$, $R^{3'} =$ feru, $R^{4'} = H$, $R^{6'} =$ feru
Lapathoside C **10**: $R^2 = R^3 = R^4 = H$, $R^6 =$ feru, $R^{1'} = H$, $R^{3'} =$ coum, $R^{4'} = H$, $R^{6'} =$ coum
Lapathoside D **11**: $R^2 = R^3 = R^4 = R^6 = R^{1'} = H$, $R^{3'} =$ coum, $R^{4'} = H$, $R^{6'} =$ coum

Cinnamoyl (cinn): $R^7 = R^8 = R^9 = H$
Coumaroyl (coum): $R^7 = R^9 = H$, $R^8 = OH$
Feruloyl (feru): $R^7 =$ OMe, $R^8 = OH$, $R^9 = H$
Sinapoyl (sinap): $R^7 = R^9 =$ OMe, $R^8 = OH$
Trimethoxycinnamoyl (TMC): $R^7 = R^8 = R^9 =$ OMe

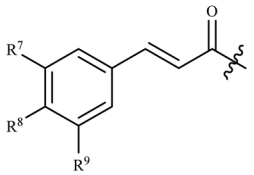

(Substituted) cinnamoly moiety

Fig. 1 Structures of PSEs **1–5** and **8–11**, sucrose **6**, and 2,1′:4,6-di-*O*-diisopropylidene sucrose **7**.

overcome the above challenges. This is specifically important to study the structure–activity relationships (SARs) of these compounds to develop lead drug candidates.[32]

Our earlier investigation of PSEs as potential antidiabetic lead candidates proved that the type, number, and position of the (substituted) cinnamoyl moieties greatly impact the α-glucosidase and α-amylase inhibition activities.[32] In particular, the moieties at *O*-3, *O*-3′, *O*-4′, and *O*-6′ play a critical role in the inhibition. To further broaden the SAR studies to identify efficient antidiabetic lead PSE candidates, we specifically needed to synthesize PSEs precisely decorated with diverse (substituted) cinnamoyl moieties at the *O*-3, *O*-3′, *O*-4′ and/or *O*-6′ positions of diisopropylidene sucrose **7**. Direct acylation methods failed to provide such compounds efficiently.[2,6]

Orthogonal protection/deprotection of monosaccharides and disaccharides is not unreported.[33–39] A few approaches exist for monosaccharides[34–36] and far less focus has been placed on disaccharides due to a higher complexity.[37–39] Therefore, further development is needed in the case of disaccharides to address their complex chemo- and regio-selection during the reactions. Existing approaches are not ideal for our purpose because of several incompatibilities of the protecting groups and deprotecting conditions with the vulnerable structure of the PSEs as they possess a sucrose core esterified with cinnamoyl moieties (see below).

Herein, we develop an orthogonal strategy for the precise synthesis of PSEs starting from sucrose **6**. The strategy is demonstrated by the synthesis of several complex PSEs selectively cinnamoylated at either C3-OH or C4′-OH. The strategy is applicable to the orthogonal protection of disaccharides in general for the preparation of complex disaccharide-based natural products.

Results and discussion

We envisioned that orthogonal protection of diisopropylidene sucrose **7** would give **12** which upon orthogonal deprotection would afford **13** (Fig. 2). Selective cinnamoylation of **13,** followed by removal of its protecting groups, would then give a wide range of simple and mixed PSEs **14.** This strategy should precisely give any natural or unnatural PSE with substituents at *O*-3, *O*-3′, *O*-4′, and *O*-6′.

To synthesize simple and mixed PSEs, the above strategy must (i) achieve orthogonal chemoselective and regioselective protection of C4-OH, C6-OH, C3′-OH, C4′-OH and C6′-OH (Fig. 1, **7** → **12**), (ii) achieve orthogonal chemoselective and regioselective deprotection of any desired protecting group in any order without affecting the integrity of the other groups (Fig. 1, **12** → **13**), (iii) preserve the integrity of the isopropylidene rings during protection, deprotection, and purification (Fig. 1, **7** → **14**), (iv) preserve the integrity of the cinnamoyl moieties and avoid transesterification (Fig. 1, **13** → **14**), and

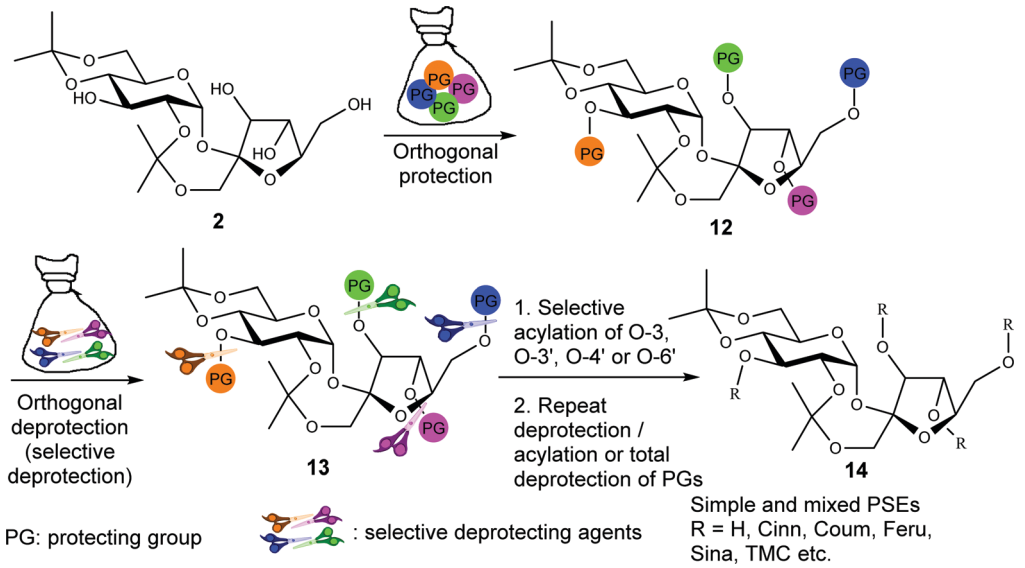
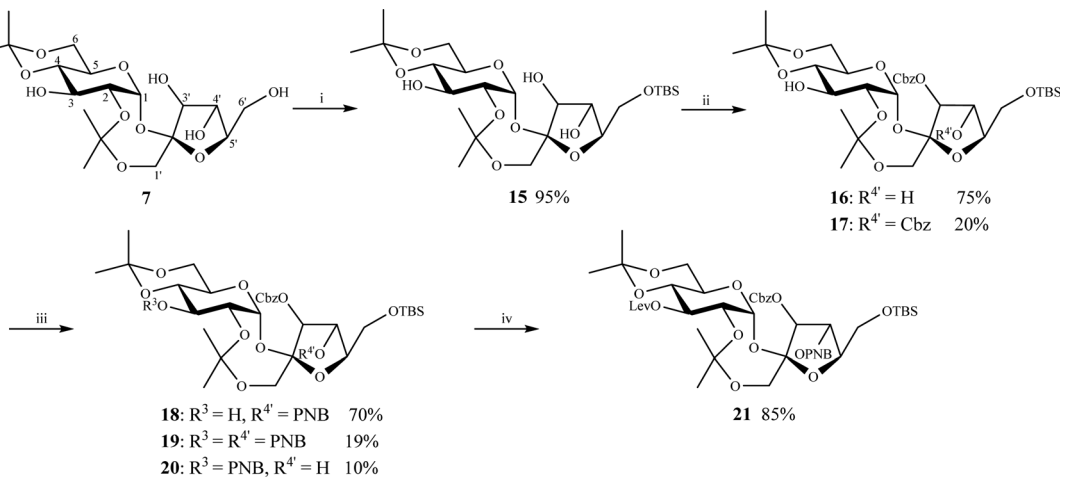


Fig. 2 Orthogonal protection/deprotection/cinnamoylation strategy for the synthesis of simple and mixed PSEs from diisopropylidene sucrose **7**.

(v) preserve the integrity of the core sucrose unit. The cinnamoyl and diisopropylidene moieties of **13** are incompatible with many common protecting/deprotecting conditions. The susceptibility of the cinnamoyl moieties to hydrogenation, acid/base hydrolysis, and transesterification prohibit employing common protecting groups such as benzoyl, pivaloyl, acetyl, or benzyl groups.[33] Additionally, the diisopropylidene moieties (Fig. 2) are cleaved under acidic conditions and such conditions must be avoided/controlled. Therefore, the choice of the protecting groups and their sequence of introduction and removal as well as the reagents and reaction conditions are critical in this strategy.

Our previous studies showed the reactivity order of the four hydroxyl groups towards acylation as C6′-OH > C3′-OH > C4′-OH > C3-OH.[3,6] C6′-OH is a primary OH and is most reactive. Secondary C3-OH is the least reactive due to the steric hindrance caused by the diisopropylidene rings of **7**. We envisioned that introducing a bulky protecting group at O-6′ should cause a steric hindrance to C4′-OH and reduce its reactivity in comparison to C3′-OH. Therefore, the ideal sequence of introducing the protecting groups should follow the above reactivity order employing a bulky protecting group at C6′-OH.[40–46] After numerous preliminary experiments using several protecting groups and conditions, we focused on *tert*-butyldimethylsilyl (TBS), carboxybenzyl (Cbz), *p*-nitrobenzoyl (PNB), and levulinoyl (Lev) as the ideal protecting groups.

At the start, selective silylation of the C6′-OH of diisopropylidene sucrose **7** using TBSCl efficiently gave 6′-*O*-TBS **15** in 95% yield (Scheme 1). The TBS was selected to provide enough

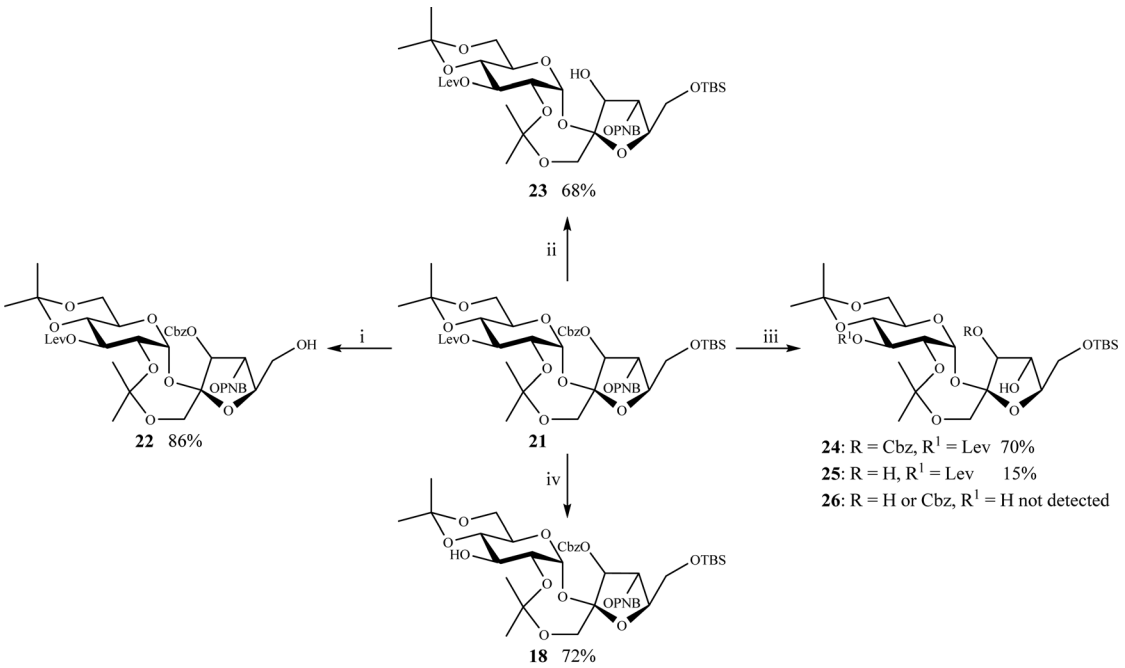


Reagents and conditions: i. TBSCl (1.2 equiv), NEt_3 (2.4 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h; ii. CbzCl (1.5 equiv), TMEDA (3 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h; iii. PNBCl, Et_3N, DMAP, CH_2Cl_2, 4 °C, 12 h; iv. LevOH (1.2 equiv), DCC (1.2 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h

Scheme 1 Synthesis of key compound **21** *via* orthogonal protection of diisopropylidene sucrose **7**.

bulkiness to favor the reactivity of C3′-OH over C4′-OH in subsequent steps. Next, optimized acylation of the C3′-OH of 6′-*O*-TBS **15** using CbzCl in the presence of tetramethylethylenediamine (TMEDA) efficiently gave 3′-*O*-Cbz **16** in 75% yield along with 3′,4′-*O*,*O*-diCbz **17** in 20% yield. The reaction was sluggish when using Et_3N, *N*,*N*-diisopropylethylamine (DIEA), and 1,4-diazabicyclo[2.2.2]octane (DABCO) bases. In comparison, acylation of the same C3′-OH with PNBCl or LevOH was less promising as it gave a mixture of products presumed to be 3-*O*-, 3′-*O*- and 3,3′-*O*,*O*-PNB/Lev substituted 6′-*O*-TBS **15** along with the starting material (TLC). The acylation of the C4′-OH of 3′-*O*-Cbz **16** using PNBCl in the presence of DMAP/Et_3N at room temperature gave three products: 4′-*O*-PNB **18** in 51% yield, 3-*O*-PNB **19** in 10% yield and 3,4′-*O*,*O*-diPNB **20** in 36% yield. However, at an optimum temperature of 4 °C, the same reaction gave a 70% yield of the desired 4′-*O*-PNB **18** along with a 10% yield of 3-*O*-PNB **19** and a 19% yield of 3,4′-*O*-PNB **20** (Scheme 1). Finally, Steglich esterification of the C3-OH of 4′-*O*-PNB **18** using LevOH in the presence of DCC/DMAP in CH_2Cl_2 gave the desired key compound **21** in 85% yield (Scheme 1). Based on these results, we concluded that the success of the orthogonal protection of diisopropylidene **7** depended on the choice of the protecting group and the reaction conditions employed. It is noted that any of these compounds **15–21** are intermediate structures that can be used to synthesize PSEs depending on the substitution pattern of the PSEs.

The orthogonal deprotection of the TBS, CBZ, PNB, and Lev groups of compound **21** was then attempted (Scheme 2). An important requirement is to achieve selective deprotection of these groups in any order to realize the planned cinnamoylation step at any desired position (Fig. 2). Extensive studies were performed before an ideal set of deprotection conditions were found. Initially, TBS removal using tetra-*n*-butylammonium fluoride (TBAF) in THF-buffer (K_2HPO_4, pH 7) gave product **22** in 60% yield along with side products, attributed to transesterification and/or removal of other protecting groups. The buffered medium was used to minimize/prevent possible migration of the secondary *O*-3′-Cbz or *O*-4′-PNB groups to the primary *O*-6′ position.[40] Fortunately, $Et_3N{\cdot}3HF$ cleanly removed TBS at room temperature to give product **22** in 86% yield (Scheme 2). Removal of the Cbz by classical hydrogenolysis is not possible in this protocol to avoid the potential reduction of the double bonds of the cinnamoyl moieties which will be introduced later (Fig. 2). Attempts to remove the Cbz of **21** *via* thermal treatment at 100 °C in water or 1,4-dioxane were unsuccessful since **21** was insoluble in water and it decomposed in 1,4-dioxane. However, $Pd(OAc)_2/Et_3SiH$ removed Cbz successfully to give **23** in 68% yield. Next, under optimized conditions, $Mg(OMe)_2$ in MeOH : THF (9 : 1) removed PNB from **21** at 4 °C within one hour and gave **24** in 70% yield. This reaction also gave **25** as a side product in 15% yield. However, under these conditions, compound **26** was not detected. The reaction was monitored closely using TLC and quenched with 1N HCl once the starting material was consumed completely to avoid further removal of Cbz. This kinetically controlled reaction using the weakly basic $Mg(OMe)_2$ selectively removed the PNB in the presence of Cbz and Lev groups.[39] The use of



Reagents and conditions: i)1.56 M 3HF·NEt_3 (3.0 equiv), NEt_3 (2.0 equiv), pyridine, rt, 12 h; ii) $Pd(OAc)_2$ (0.1 equiv), NEt_3 (0.16 equiv), Et_3SiH (1.6 equiv), CH_2Cl_2, rt, 12 h; iii) $Mg(OMe)_2$ (0.1 equiv), MeOH/THF (8:2), ice bath (4 °C), 1 h; iv) $NaBH_4$ (2.2 equiv), 1,4-dioxane, rt, 3 h.

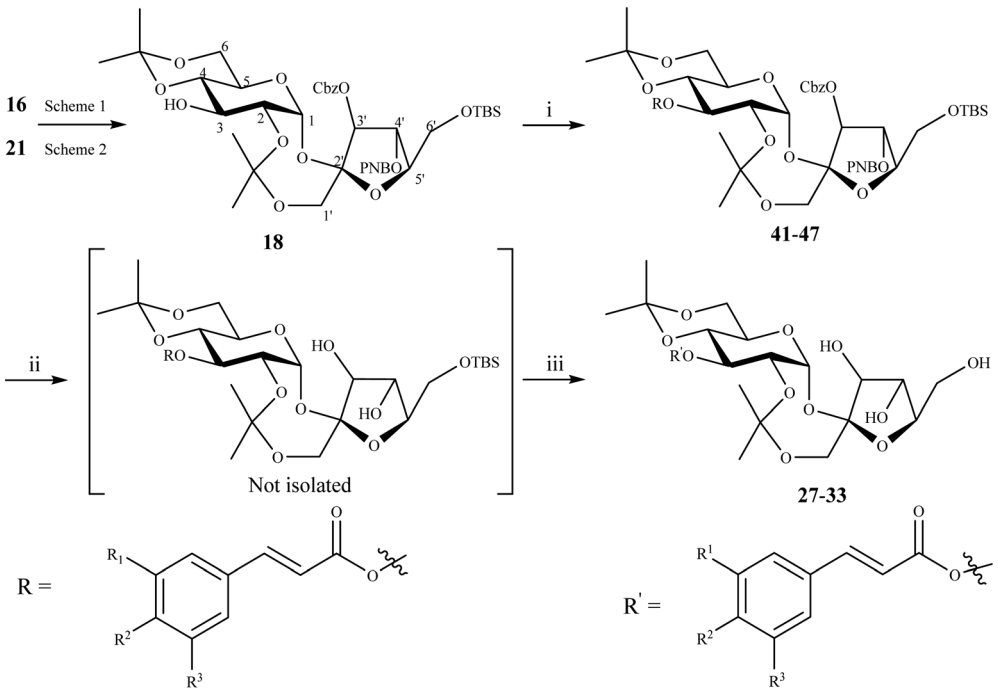
Scheme 2 Selective removal of the TBS, Cbz, PNB, and Lev protecting moieties from **21**.

$Mg(OMe)_2$ is advantageous since concurrent removal of both PNB and Cbz can also be achieved in one step by just extending the reaction time or increasing the moles of $Mg(OMe)_2$. Finally, treatment of **21** with $NaBH_4$ in 1,4-dioxane cleanly removed the Lev group to give **18** in 72% yield as a single product representing another approach to obtain compound **18** in a more selective fashion (see Scheme 1). The orthogonal deprotection protocol in Scheme 2 allows selective removal of any protecting group for subsequent introduction of the cinnamoyl moieties at any position to potentially obtain any desired simple and mixed PSEs.

To demonstrate the synthetic practicality of the above strategy, compound **18** was used to synthesize PSEs **27–33** cinnamoylated at the most challenging and least reactive C3-OH (Scheme 3). Many natural PSEs are substituted at this position and their synthesis poses major challenges.[1] Compound **18** can be obtained from compound **16** (Scheme 1) or compound **21** (Scheme 2) as discussed above. Steglich esterification between **18** and (substituted) cinnamic acids **34–40** gave the corresponding cinnamoylated products **41–47** in 76–89% yields. Concurrent removal of the Cbz and PNB groups using $Mg(OMe)_2$ over 12 h followed by TBS removal using $HF{\cdot}NEt_3$ in one-pot over a two-step process gave the desired 3-cinnamoylated PSEs **27–33** in 62–81% yields (Scheme 3).

To further demonstrate the robustness of the strategy, cinnamoylation of the C4′-OH of 3′-*O*-Cbz **16** was also attempted to synthesize PSEs **48–54** (Scheme 4). The esterification of **16** with cinnamic acids **34–40** proceeded selectively at C4′-OH due to its higher nucleophilicity in comparison with C3-OH and gave the corresponding compounds **55–61** in 81–87% yields. Step-wise removal of the Cbz using $Pd(OAc)_2/Et_3SiH$ and then TBS using $3HF{\cdot}NEt_3$ gave PSEs **48–54** in 82–88% yields.

In this work, the diisopropylidene rings of compounds **27–33** and **48–54** were not cleaved since our preliminary

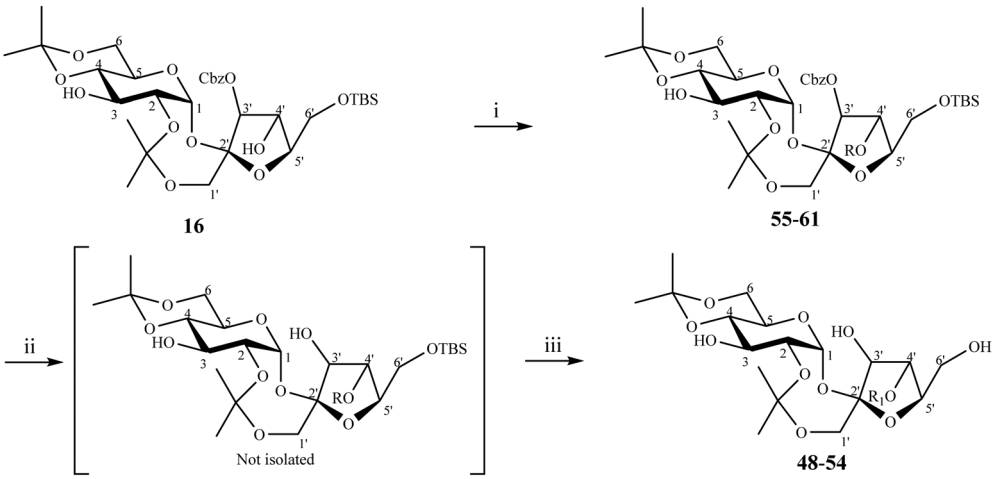


41 cinn: $R^1 = R^2 = R^3 = H$	76%	**27** cinn: $R^1 = R^2 = R^3 = H$	70%
42 diOMe-cinn: $R^1 = R^2 = OMe$, $R^3 = H$	80%	**28** diOMe: $R^1 = R^2 = OMe$, $R^3 = H$	76%
43 triOMe-cinn: $R^1 = R^2 = R^3 = OMe$	81%	**29** triOMe: $R^1 = R^2 = R^3 = OMe$	79%
44 OTBS-caff: $R^1 = R^2 = OTBS$, $R^3 = H$	80%	**30** caff: $R^1 = R^2 = OH$, $R^3 = H$	62%
45 OTBS-feru: $R^1 = H$, $R^2 = OTBS$, $R^3 = OMe$	89%	**31** feru: $R^1 = H$, $R^2 = OH$, $R^3 = OMe$	80%
46 OTBS-coum: $R^1 = R3 = H$, $R2 = OTBS$	80%	**32** coum: $R^1 = R^3 = H$, $R^2 = OH$	81%
47 OTBS-sinap: $R^1 = R^3 = OMe$, $R^2 = OTBS$	80%	**33** sinap: $R^1 = R^3 = OMe$, $R^2 = OH$	80%

Reagents and conditions: i. ROOH **34-40** (2 equiv), DCC (2 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 24 h; ii. $Mg(OMe)_2$ (0.5 equiv), 8:2 MeOH:THF, rt, 12 h; iii. 1.56 M $3HF{\cdot}NEt_3$ (3.0 equiv), NEt_3 (2.0 equiv), pyridine, rt, 12 h.

ROOH = cinnamic acid **34**
= diOMe cinnamic acid **35**
= triOMe cinnamic acid **36**
= diOTBS-caff acid **37**
= OTBS-feru acid **38**
= OTBS-coum acid **39**
= OTBS-sinap acid **40**

Scheme 3 Synthesis of PSEs **27–33** substituted with cinnamoyl moieties at C3-OH.



55 cinn: $R^1 = R^2 = R^3 = H$	82%	**48** cinn: $R^1 = R^2 = R^3 = H$	88%
56 diOMe-cinn: $R^1 = R^2 = OMe$, $R^3 = H$	81%	**49** diOMe: $R^1 = R^2 = OMe$, $R^3 = H$	85%
57 triOMe-cinn: $R^1 = R^2 = R^3 = OMe$	87%	**50** triOMe: $R^1 = R^2 = R^3 = OMe$	85%
58 OTBS-caff: $R^1 = R^2 = OTBS$, $R^3 = H$	86%	**51** caff: $R^1 = R^2 = OH$, $R^3 = H$	84%
59 OTBS-feru: $R^1 = H$, $R^2 = OTBS$, $R^3 = OMe$	83%	**52** feru: $R^1 = H$, $R^2 = OH$, $R^3 = OMe$	82%
60 OTBS-coum: $R^1 = R3 = H$, $R2 = OTBS$	87%	**53** coum: $R^1 = R^3 = H$, $R^2 = OH$	84%
61 OTBS-sinap: $R^1 = R^3 = OMe$, $R^2 = OTBS$	84%	**54** sinap: $R^1 = R^3 = OMe$, $R^2 = OH$	88%

See Scheme 3 for structures of ROOH, R, R' and R^1-R^3

Reagents and conditions: i. ROOH **34-40** (1.5 equiv), DCC (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h; ii. $Pd(OAc)_2$ (0.1 equiv), Et_3SiH (1.6 equiv), NEt_3 (0.16 equiv), CH_2Cl_2, rt, 12 h; iii. 1.56 M $3HF{\cdot}NEt_3$ in pyridine (3.0 equiv), NEt_3 (2.0 equiv), pyridine, rt, 12 h.

Scheme 4 Synthesis of PSEs **48–50** substituted with cinnamoyl moieties at C4′-OH.

structure–activity relationship (SAR) studies on several PSEs as alpha glucosidase inhibitors revealed their positive role in increasing the % inhibition of α-glucosidase and decreasing the % inhibition of α-amylase enzymes.[32] However, we previously established a convenient process to selectively remove the diisopropylidene rings easily without affecting the (substituted) cinnamoyl moieties using 60% aq. AcOH at 80 °C within 20–30 minutes.[3,6] In future work, compounds **27–33** and **48–50** will be tested as alpha glucosidase inhibitors for the treatment of diabetes as part of an extensive study in our lab.[32]

Conclusion

We developed an efficient strategy for the precise synthesis of PSEs starting from 2,1′:4,6-di-*O*-diisopropylidene **7**. With this strategy, synthesis of natural and unnatural PSEs is now achievable since cinnamoylation is attainable at any desired OH group of diisopropylidene sucrose **7**. In broader terms, this strategy solves a complex problem of orthogonal protection/deprotection of disaccharides which is far more complex than monosaccharides and opens the door for the synthesis of a wide range of not only PSEs but also phenylpropanoid esters and related compounds in general. We are currently using this strategy to prepare simple and mixed PSEs as alpha glucosidase inhibitor antidiabetic lead compounds.

Experimental section

Materials and methods

All commercial reagents and solvents used in this work were obtained from Sigma-Aldrich, Acros, and Merck and were used as received unless stated. Routine ^{1}H NMR spectra were recorded using a Bruker Avance DPX 300 spectrometer (300 MHz). ^{1}H NMR multiplicities were designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), and multiplet (m). ^{13}C NMR spectra were measured using a Bruker Avance DPX 300 spectrometer (75.47 MHz). HRMS spectra were recorded on a Finnigan MAT95XL-T spectrometer in the ESI positive mode. Flash chromatography and column chromatography were carried out using Merck silica gel 60 230–400 mesh. Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). The products on the TLC plates were visualized under UV light (254 nm) or by using a solution of 5% H_2SO_4 in EtOH (v/v).

General procedure for the acylation of compound 18: synthesis of compounds 41–47

To a stirred solution of compound **18** (500 mg, 0.610 mmol) and DMAP (7.5 mg, 0.0610 mmol) in CH_2Cl_2 (10 mL) was added the respective (substituted) cinnamic acid (0.610 mmol) and DCC (252 mg, 1.22 mmol) at room temperature. After 24 hours (TLC), CH_2Cl_2 was removed under vacuum and the residue was triturated with cold diethyl ether (20 mL) and filtered. Diethyl ether was then removed under vacuum, and the crude product was purified by column chromatography using 8 : 1 hexane/EtOAc as the eluent. This procedure was used to synthesize compounds **41–47**.

General procedure for acylation of 3′-*O*-Cbz 16: synthesis of compounds 55–61

The (substituted) cinnamic acid (1.12 mmol) and DCC (231 mg, 1.12 mmol) were added to a stirred solution of 3′-*O*-Cbz **16** (500, 0.746 mmol) and DMAP (9.2 mg, 0.0746 mmol) in CH_2Cl_2 (10 mL) at room temperature. After 12 hours (TLC), CH_2Cl_2 was removed under vacuum and the crude residue was triturated in cold diethyl ether (20 mL) and filtered. Diethyl ether was then removed under vacuum and the residue was purified by column chromatography using 4 : 1 hexane/EtOAc as the eluent. This procedure was used to synthesize compounds **55–61**.

Author contributions

Z. J. supervised the work and revised the manuscript; L. L., W. P. W. K., and S. D. R. synthesized the compounds and wrote the initial draft of the manuscript; D. D. K., P. P. and M. S. revised the manuscript and analysed the NMR data.

Conflicts of interest

The authors declare no conflict of interest.

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