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Diversity-Oriented Synthesis of Steviol Glycosides

Zhi Qiao,[a] Hui Liu,[a] Jing-Jing Sui,[a] Jin-Xi Liao,[a] Yuan-Hong Tu,[a] Richard R. Schmidt,[a,b,*] and Jian-Song Sun[a,*]

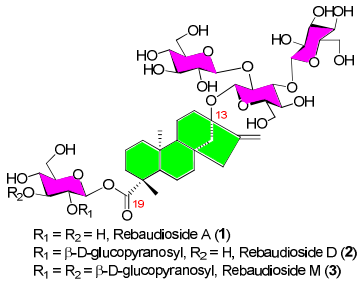
[a]*The National Research Centre for Carbohydrate Synthesis, Jiangxi Normal University 99 Ziyang Avenue, Nanchang 330022 (China)*

jssun@jxnu.edu.cn

[b]*Department of Chemistry, University of Konstanz, D-78457, Konstanz, Germany*

richard.schmidt@uni-konstanz.de

Table of content:



Abstract: With cheap and easily available mixtures of steviol glycosides as starting material, a practical method for steviol acquisition has been developed, based on which a facile, diversity-oriented and economic protocol for the synthesis of structurally defined steviol glycosides was established. The novel approach is featured by the highly efficient glycosylation of sterically hindered and acid-sensitive steviol via orchestrated application of Yu glycosylation, Schmidt glycosylation and PTC glycosylation. Hence, the high-intensity sweeteners and potential lead compounds for drug development are now readily accessible.

Introduction

FDA accepted in 2010 the statement that steviol glycosides (rebaudienosides, Figure 1) are "Generally Recognized As Safe" (GRAS).[1] Thus, the rapid development of stevioside industry and health benefit studies were promoted,[2] as steviosides are regarded as zero-caloric, powerful sweeteners of natural origin. In addition, they possess also a long application history.[3] The unpleasant sensory property of the widely applied stevioside sweetener as well as the unclear function mechanisms of bioactive steviosides call on an efficient approach to obtain pure and ample amounts of individual steviosides. Furthermore, for stevioside feedstock manufacturers, the establishment of accurate quality control system also requires an easy access to various pure steviosides as reference compounds.

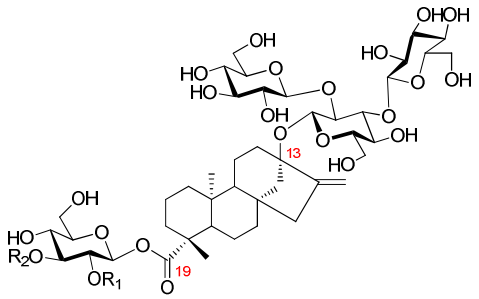


Figure 1. The chemical structures of rebaudioside A, D, and M.

Existing methods for pure stevioside acquisition, including phytochemical isolation[4] and enzymatic synthesis,[5] suffer from tedious processes and low efficiency, due to the heterogeneity either of naturally occurring steviosides[6] or of the products obtained via enzymatic synthesis. Chemical synthesis holds the promise to solve the sample access problem. However, the chemical structure of steviosides, containing the acid-sensitive *ent*-kaurene skeleton as aglycon and branched sugar chains at the

tertiary C-13 hydroxy group and at the C-19 carboxylic group, poses a considerable synthetic challenge. As shown in Figure 2, under acidic conditions steviol derivatives are prone to undergo Wagner-Meerwein rearrangement or double bond migration reaction to afford isosteviol and double bond-shifted byproducts.[7] As a result, despite of a long investigation history, the chemical synthesis of steviosides has only been reported sporadically with structurally simple steviosides as target molecules; in addition, the reaction protocol was based on the use of stoichiometric amounts of toxic heavy metals and low to moderate overall yields were recorded.[8] The urgent need of pure steviosides coupled with our continuous efforts to synthesize naturally occurring glycosides[9] promoted us to develop an efficient, diversity-oriented as well as economic synthetic strategy to produce steviosides, culminating in the first total synthesis of rebaudiosides A, D and M. Among these target compounds reb-D (**2**) has been regarded as 'the gold of the steviosides', due to the improved flavor and low natural content (0.3-0.8%);[6] moreover, reb-M (**3**) has been proven to possess even better taste than reb-D, although an extremely low natural content (0.06%) was detected.[10]

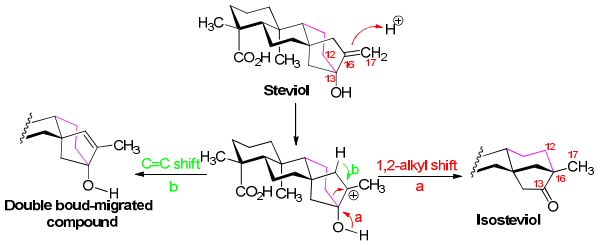


Figure 2. Acid-elicited rearrangements of steviol aglycon.

Results and Discussion

For high efficiency of the designed synthesis, a modular strategy is required that

takes diversity and flexibility into account. To this end, the target molecules **1**-**3** were projected to be assembled by building blocks **4**-**7** with **4** as building block for all target molecules (Figure 3). Due to the acidity of the C-19 carboxylic group, the installation of the sugar chain was envisioned to be achievable with glycosyl bromides **5**, **6** and **7** as glycosyl donors in the presence of base under phase-transfer conditions (PTC).[11] The PTC glycosylation protocol could on one hand ensure the structural integrity of the acid sensitive steviol aglycone; on the other hand, the diversity as well as the convergency of the whole synthetic strategy could also be expected simply by employing different glycosyl bromide donors. In turn, to generate the common building block **4**, the mild Yu glycosylation protocol[12] and, more ideally from the synthetic cost perspective, the Schmidt glycosylation method[13] could be conceived.

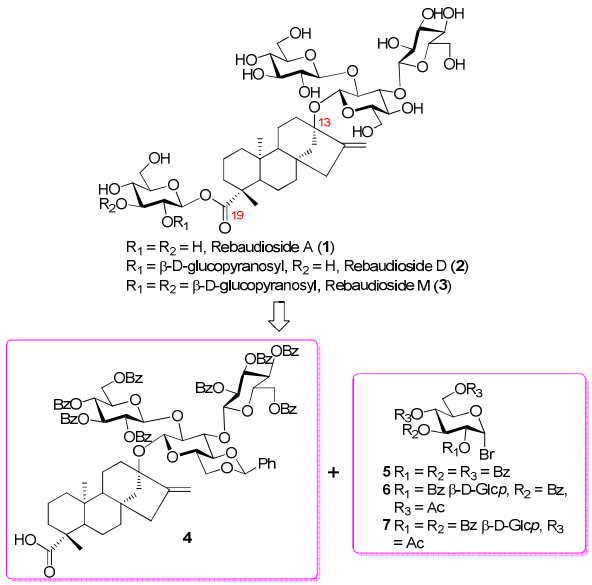
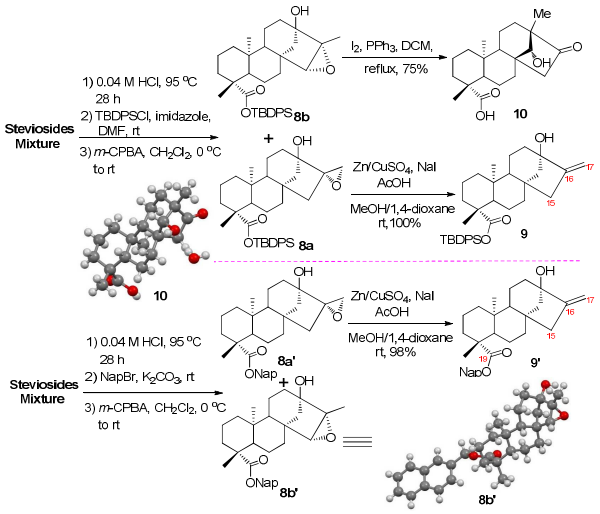


Figure 3. Retrosynthetic analysis of rebaudioside A, D, and M.

First of all, a practical process for steviol acqusition had to be installed. To this goal, the acidic hydrolysis of *S. rebaudiana* leaves was investigated (Scheme 1).[14] To suppress the acid-catalyzed steviol rearrangement to a practical extent, a panel of

acids were screened at different concentrations and temperatures, finally leading to optimal conditions of 0.04 M HCl at 95 °C for 28 h. Under these conditions, the desired steviol was obtained accompanied by isosteviol and the double-bond migrated product (from C16,17 to C15,16) in a 1:1:1 ratio. The crude products containing steviol precipitated from the reaction mixture, and after filtration and recrystallization from methanol, the mixture was directly silylated (or naphthylmethylated) at the carboxylic group and then epoxidized to generate **8a**, **8b** and **8a'**, **8b'**, respectively. These compounds can be easily purified by silica gel chromatography (> 5g of **8a** or **8a'**/100 g stevioside mixture). The epoxidation step was introduced to facilitate the elimination of the double-bond-migrated side-products **8b** and **8b'** from **8a** and **8a'**, respectively.[15,16] Restoration of the C16,17 double-bond was achieved quantitatively by reduction with $Zn/CuSO_4/NaI$ in the presence of acetic acid to produce **9** or **9'**.[17] Interestingly, the epoxide reduction occurred selectively at the disubstituted epoxides (in **8a** or **8a'**) while keeping the trisubstituted epoxides (in **8b** and **8b'**) untouched. Based on this observation, access to **9** or **9'** was finally realized via four sequential steps with only one silica-gel purification. Also appealing is that this process can be easily scaled up and ten grams of **9** or **9'** can be conveniently obtained in one batch. Though resistant to the epoxide reduction conditions, **8b** could undergo with I_2/PPh_3 Wagner-Meerwein rearrangement to afford **10**; the structure of **10** was confirmed by X-ray analysis.[16,18] Because of the problems encountered in Nap cleavage in **9'** in model reactions, the silyl ester **9** was chosen for the following studies.



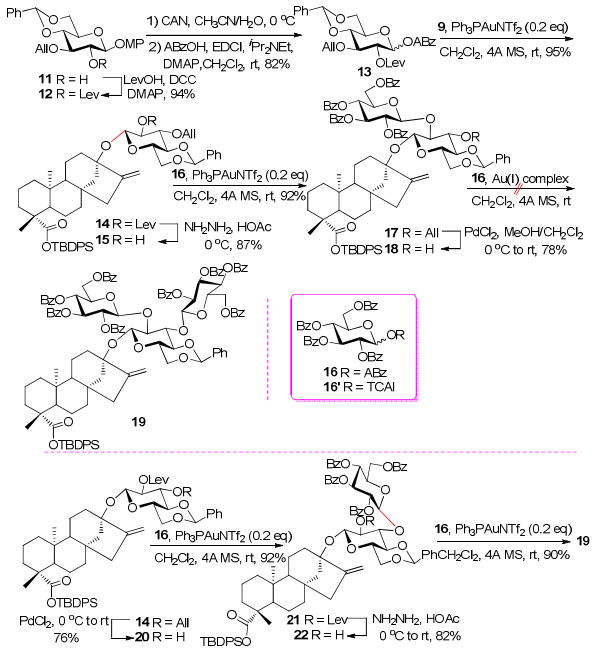
Scheme 1. Acquisition of acceptor **9** via acid hydrolysis of stevioside mixture as well as related derivatizations.

With ample amounts of **9** in hand, the stage was now set for the construction of the common building block **4** (Scheme 2), which was deemed as a challenging task owing to both the acid sensitivity of the aglycone and the less accessible property of the tertiary C-13 hydroxy group. According to the experience gained in our precedent synthetic investigation of ginsenosides, for the generation of the branched sugar chain the glycosylation of 2-OH before 3-OH of the core glucosyl residue was checked first, as for the 2-hydroxy group next to a sterically demanding aglycone at the anomeric position an extremely low reactivity was expected.[19] Taking the acid sensitivity of acceptor **9** into account, the orthogonally protected glycosyl donor **13** with a levulinoyl (Lev) group at 2-O, an allyl (All) group at 3-O and benzylidene protection at 4,6-O was investigated first, as **13** can be activated under mild conditions with a gold catalyst ($Ph_3PAuNTf_2$, 0.2 equiv). The synthesis of **13** commenced with glucoside **11**[20], which was subjected to levulinoylation under standard conditions to

afford **12** (94%). Anomeric 4-methoxyphenyl (MP) hydrolysis was followed by dehydrative *o*-alkynylbenzoylation to provide donor **13** (82%, 2 steps). Although the ensuing glycosylation between **13** and **9** entailed the bulky tertiary C-13 hydroxy group of steviol, the reaction proceeded efficiently under the catalysis of the Au(I) complex to furnish **14** in excellent yield (95%). Hydrazinium acetate mediated cleavage of the Lev group led to glycoside acceptor **15**, which was ready for the introduction of a glucosyl residue at the 2-hydroxy group. Again, Au(I)-catalyzed glycosylation of **15** with known donor **16**[21] furnished disaccharide **17** very efficiently (92%). The liberation of the 3-hydroxy group of the core glucosyl residue in **17** was achieved by the removal of the All group under standard conditions affording acceptor **18** (78%). However, the glycosylation of **18** with donor **16** failed and even the more powerful $Ph_3PAuOTf$ catalyst[22] did not lead to any trace amount of the desired trisaccharide **19**. After all attempts, either by increasing the amounts of donor and promoter or by applying a more reactive 6-O-silylated glycosyl donor, that were all met with failure, this route was abandoned.

In fact, similar problems have been previously encountered by our and other groups.[23] Therefore, the sequence of branch sugar introductions was reversed (Scheme 2). Thus, removal of the 3-O-All group prior to the 2-O-Lev group in **14** was conducted to provide acceptor **20**, which is ready for the glycosylation at the 3-hydroxy group. Glycosylation with donor **16** under standard conditions furnished disaccharide **21** in excellent yield (92%). Finally, the decisive glycosylation of disaccharide acceptor **22**, obtained from **21** by selective cleavage of the 2-O-Lev group, with donor **16** was

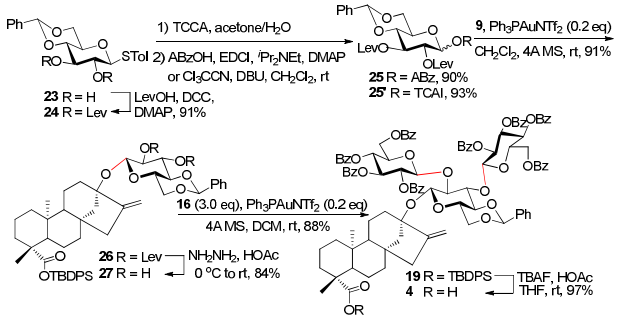
carried out; to our satisfaction, the desired branched trisaccharide **19** was obtained in a respectable 90% yield. Although in **19** two identical sugar moieties are contained, the established stepwise introduction strategy is apparently also applicable to the generation of analogues with different entities that constitute the branched sugars; thus the desired flexibility of the synthetic approach is exhibited.



Scheme 2. The assembly of trisaccharide glycoside **19** via different branch sugar introduction sequence with glycosyl o-alknylbenzote as donors.

As the branched sugar moieties at the C-13 hydroxy group of steviosides contains generally identical residues, the strategy to install the branched sugar residues at the 2- and 3-hydroxy group simultaneously in a one-pot reaction was explored (Scheme 3). As a prerequisite, the glycosylation should follow the sequence of 3-hydroxy group first and then 2-hydroxy group of the diol acceptor **27**; otherwise, the reaction would not continue after the 2-O-glycosylation and only the 1,2-linked disaccharide would be obtained. For this study known glucose derivative **23**[24] was acylated to

deliver **24**, which was then subjected to thioglycoside hydrolysis and *o*-alkynylbenzoylation to generate the Yu donor **25** (90%, 2 steps). The ensuing coupling of **9** with donor **25** went smoothly, affording glycoside **26** in an excellent 91% yield. The following cleavage of the two Lev groups provided the desired acceptor **27** (84%). To our delight, the pivotal Au(I)-catalyzed glycosylation of **27** with donor **16** (3.0 equiv) followed the desired glycosylation sequence to generate trisaccharide **19** (88%) and no premature 1,2-linked disaccharide was detected. Finally, desilylation of the C-19 silyl ester of **19** was performed with TBAF/acetic acid to give the common building block **4** in very good overall yield.

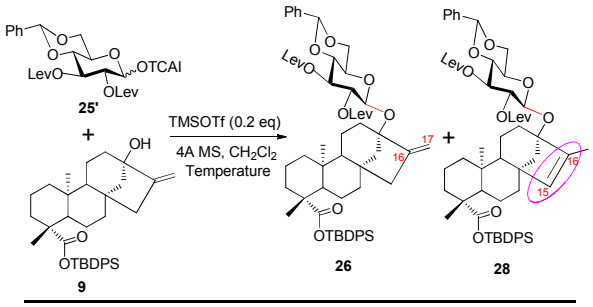


Scheme 3. Synthesis of the common building block **4** via simultaneous branch sugars introduction with Yu donors.

Allured by the dramatic drop in synthetic cost with glycosyl trichloroacetimidate as donors, the fabrication of the key building block **4** with Schmidt donor was tried under the risk of aglycone rearrangement under acidic conditions. To seek for the optimal glycosylation conditions for Schmidt donors, the coupling between **25'**[25] and acceptor **9** was examined systematically (Table 1). Under the effect of TMSOTf at room temperature, the glycosylation delivered monosaccharide glycoside **28** with the double bond of the aglycone migrated from C16,17 to C15,16 (91%, entry 1). A

similar result was recorded when the reaction was conducted at 0 °C (94%, entry 2). In sharp contrast, once the reaction temperature was decreased to -20 °C, the undesired double bond shift reaction was suppressed to such an extent that **26** and **28** were isolated with a ratio of 6 : 1 (93%, entry 3). Further lowering the reaction temperature to -40 °C, the side reaction was prohibited completely, and the desired glycosylation product **26** was isolated in an excellent 96% yield (entry 4). Mechanistically, the double bond migration of the aglycone takes place prior to glycosylation reaction, as the control reaction of **9** with TMSOTf (0.2 eq) in the absence of donor **25'** revealed that the migration reaction proceeded so rapidly that it could reach completion in less than 5 minutes at 0 °C. It deserves further comments that under the effect of TMSOTf, the *ent*-kaurene aglycon **9** only undergoes double bond migration reaction and no Wagner-Meerwein rearrangement byproduct was detected.

Table 1. Optimization of glycosylation reaction between Schmidt donor **25'** and **9**.

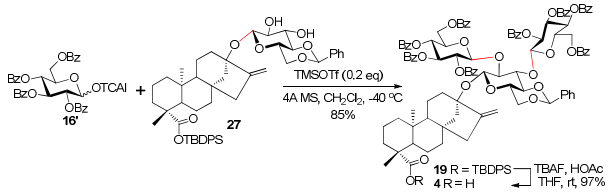


Entry	Temperature	Result[a]	Entry	Temperature	Result[a]
1	rt	only **28** (91%)	3	-20 °C	**26** (80%), **28** (13%)
2	0 °C	only **28** (94%)	4	-40 °C	only **26** (96%)

[a] Isolated yield.

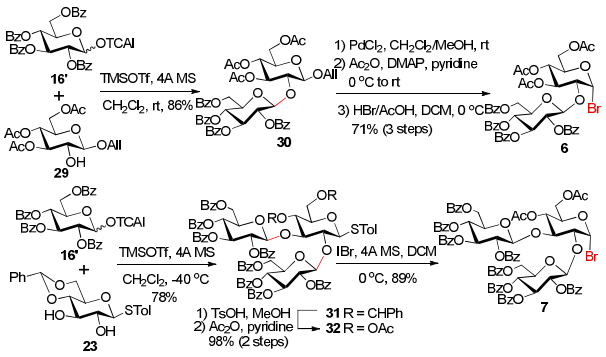
Once the optimal conditions for glycosylation of **9** with Schmidt donor **25'** were settled, they were applied to the challenging coupling of **16'**[26] and diol acceptor **27**

(Scheme 4). Fortunately, the reaction proceeded smoothly so that the desired **19** was obtained in a good yield (85%), as with the Yu donor; the product was then subjected to the conventional desilylaton conditions to yield **4** (97%). Thus far, the synthetic route to common building block **4** featuring both high efficiency and low cost was also established.



Scheme 4. Synthesis of **4** with glycosyl trichloroacetimidate as donors.

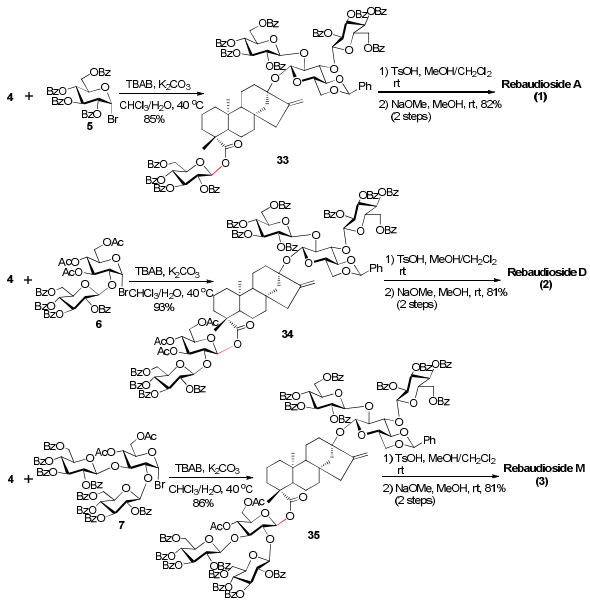
Although the generation of the branched trisaccharide building block **4**, stepwise with Yu donors as well as simultaneously with both Yu and Schmidt donors, has been successfully established, the efficiency, flexibility and economy of the synthetic strategy is finally also determined by the introduction manner of the sugar chain at the C-19 carboxylic group. To this aim, the PTC glycosylation protocol with glycosyl bromides as glycosyl donors was examined. The synthesis of glycosyl bromide **6** contained coupling of Schmidt donor **16'** with known acceptor **29**[27] and the following replacement of the anomeric All group of the obtained disaccharide **30** by an alpha-oriented bromide via the sequence of deallylation, O-acetylation and bromide substitution (**6**, 71%, 3 steps, Scheme 5). Commencing with 2,3-O-unprotected acceptor **23** and Schmidt donor **16'** the trisaccharide **31** was obtained in 78% yield, and no thioglycoside aglycone transfer was detected.[28] Acid-mediated benzylidene cleavage was followed by O-acetylation yielding **32**, which was reacted with IBr to afford trisaccharide bromide **7** (89%).[9c]



Scheme 5. Synthesis of di- and tri-saccharide bromide donors **6** and **7**.

With glycosyl bromide donors **5**-**7** and common building block **4** in hand, investigation of the PTC glycosylation as well as the completion of the synthesis was undertaken (Scheme 6). In the presence of tetrabutylammonium bromide (TBAB) and potassium carbonate, the reaction between **4** and glucosyl bromide **5**[29] proceeded smoothly and the desired glucosylation product **33** (having four sugar residues attached) was obtained in a good 85% yield. Benzylidene group cleavage with *p*-TsOH in a mixture of methanol/dichloromethane worked very well and no isomerization/rearrangement of the aglycone or loss of the trisaccharide residue at C-13 was observed. Following Zemplen saponification led successfully to the target molecule **1**, rebaudienoside A (82%, 2 steps). The PTC glycosylation method was so efficient that both, disaccharide bromide **6** and trisaccharide bromide **7**, afforded good to excellent coupling yields, providing **34** with five sugar residues (93%) and **35** with six sugar residues (86%), respectively. Thus, after debenzylidenation and cleavage of the acetyl and benzoyl groups furnishing both compounds in 81% yield over two steps, a firm methodology for the efficient synthesis of the valuable rebaudiosides D (**2**) and M (**3**) was available. The spectroscopic data of the target compounds **1**-**3** are in good

accordance with those reported in the literature.[30]



Scheme 6. Introduction of C19-COOH sugar chains via PTC protocol and completion synthesis of all three target molecules.

Conclusions:

In summary, based on the large scale acquisition of steviol from the crude extract of *S. rebaudiana* leaves, ample amounts of the aglycone were available for the first efficient, diversity-oriented, and economic protocol to generate steviol glycosides. The diversity was founded on the stepwise introduction of the sugar residues at the C-13 hydroxy group with Yu donors and at the C-19 carboxylic group with glycosyl bromides as glycosyl donors and the cost economy was taken care of by the successful application of Schmidt donors in glycosidic linkage construction. The high overall efficiency has benefited from the judicious choice of suitable glycosylation protocols, mild Yu glycosylation, Schmidt glycosylation that could be conducted at low temperature without any glycosylation potential loss, and PTC glycosylation,

which all kept the fragile steviol aglycone untouched and provided good to excellent glycosylation yields. The established synthesis strategy is obviously applicable to other steviol glycoside congeners and derivatives, thus providing a reliable and robust method to access these valuable natural products. Hence, a firm basis is now available to solve the problems that so far restrict the development of stevioside industry.

Experimental Section:

16,17-α-Epoxyl-steviol *tert*-butyldiphenylsilyl ester (8a) and 15,16-α-epoxyl-steviol tert-butyldiphenylsilyl ester (8b)

To a solution of steviosides mixture (100 g) in water (250 mL) was added HCl (0.04 M, 0.83 mL) at room temperature. Then the reaction mixture was heated to 95 ^{o}C, and the stirring was continued for 28 h, during which time white precipitates appeared. The precipitates were collected by filtration, and then washed thoroughly with water. After drying under reduced pressure, the precipitates was recrystallized from absolute MeOH to afford the crude product containing steviol, isosteviol, and double bond migrated isomer (12.0 g) as a white solid.

The mixture obtained above (12.0 g) was dissolved in dry DMF (50 mL), to which imidazole (3.84 g, 56.5 mmol) and TBDPSCl (14.7 mL, 56.5 mmol) was added successively at room temperature under N_2 atmosphere. The reaction mixture was stirred at the same temperature overnight. Ethyl acetate was added to dilute the reaction mixture, and the resultant solution was washed successively with water and brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration to afford the crude product, which was purified by silica gel

chromatography (PE/EA = 10 : 1) to afford an inseparable mixture of silylated steviol as well as its silylated double bond migrated isomer (12.6 g) as a white foam.

To a solution of above obtained mixture (12.6 g) in dry CH_2Cl_2 (50 mL) was added *m*-CPBA (5.86 g, 34.0 mmol) at 0 ^oC. After the addition was completed, the reaction mixture was warmed up gradually to room temperature, and the stirring was continued at the same temperature for another 2 h. Ethyl acetate was added to dilute the reaction mixture, and the solution was washed successively with saturated aqueous $Na_2S_2O_3$ and brine, and then dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure yielded a residue, which was further purified by silica gel chromatography (PE/EA = 4 : 1) to afford **8a** (6.62 g) as a white foam and **8b** (6.3 g) as a white foam. For **8a**: $[\alpha]_D^{25}$ = -31.6 (*c* 1.0, CHCl3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4 H), 7.45-7.40 (m, 2 H), 7.38-7.34 (m, 4 H), 2.93 (d, *J* = 4.8 Hz, 1 H), 2.78 (d, *J* = 4.8 Hz, 1 H), 2.34 (brs, 1 H), 2.24-2.19 (m, 1 H), 2.14 (dd, *J* = 2.0, 11.2 Hz, 1 H), 1.35 (dd, *J* = 2.8, 11.2 Hz, 1 H), 1.27 (s, 3 H), 1.14 (s, 9 H), 0.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 135.8 (2 C), 132.1 (2 C), 130.1, 127.7, 74.9, 65.4, 57.1, 53.9, 48.8, 46.7, 45.8, 45.2, 41.7, 41.5, 40.8, 39.5, 38.6, 34.8, 29.3, 27.3, 22.3, 19.7, 19.4, 19.3, 16.4, HRMS (ESI) calcd for $C_{36}H_{48}NaO_4Si$ $[M+Na]^+$ 595.3214, found 595.3210. For **8b**: $[\alpha]_D^{25}$ = -61.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4 H), 7.44-7.40 (m, 2 H), 7.37-7.33 (m, 4 H), 2.71 (s, 1 H), 2.25-2.20 (m, 1 H), 1.91-1.87 (m, 1 H), 1.84-1.65 (m, 5 H), 1.57-1.50 (m, 3 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.13 (s, 9 H), 1.07-0.99 (m, 3 H), 0.71 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 135.8, 135.7, 132.1, 132.0, 130.1, 127.6, 78.9, 67.2, 61.9, 61.8,

56.8, 48.4, 45.3, 43.7, 40.9, 39.4, 38.7, 38.5, 36.0, 33.6, 29.3, 27.3, 21.0, 20.4, 19.7, 19.4, 19.2, 15.9, 11.0; HRMS (ESI-TOF) calcd for $C_{36}H_{48}O_4SiNa$ $[M+Na]^+$ 595.3214, found 595.3210.

16,17-α-Epoxyl-steviol 2-napthylmethyl ester (8a') and 15,16-α-epoxyl-steviol 2-napthylmethyl ester (8b')

Similar procedure as that used for the synthesis of **8a**, **8b** was applied to afford **8a'** (3.1 g) as a white foam and **8b'** (2.9 g) as a white solid. For **8a'**: $[\alpha]_D^{25}$ = -59.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 4 H), 7.53-7.46 (m, 3 H), 5.33 (AB, 2 H), 2.92 (d, *J* = 4.4 Hz, 1 H), 2.78 (d, *J* = 4.4 Hz, 1 H), 2.32 (t, *J* = 1.2 Hz, 1 H), 2.26 (td, *J* = 3.6, 13.2 Hz, 1 H), 2.15 (dd, *J* = 2.0, 11.2 Hz, 1 H), 1.92-1.55 (m, 10 H), 1.48-1.42 (m, 3 H), 1.35-1.32 (m, 1 H), 1.21 (s, 3 H), 1.08-0.93 (m, 3 H), 0.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 133.5, 133.3, 133.1, 128.4, 128.1, 127.8, 127.6, 126.4, 126.3, 126.1, 74.8, 66.4, 65.4, 57.1, 53.9, 48.8, 46.6, 45.8, 44.0, 41.7, 41.3, 40.8, 39.4, 38.1, 34.8, 29.0, 22.0, 19.6, 19.2, 15.8; HRMS (ESI) calcd for $C_{31}H_{39}O_4$ $[M+H]^+$ 475.2843, found 475.2849. For **8b'**: $[\alpha]_D^{25}$ = -33.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.82 (m, 4 H), 7.52-7.44 (m, 3 H), 5.31 (AB, 2 H), 2.70 (s, 1 H), 2.25 (td, *J* = 3.2, 12.8 Hz, 1 H), 1.89-1.81 (m, 3 H), 1.78-1.62 (m, 4 H), 1.36 (s, 3 H), 1.22 (s, 3 H), 1.15 (dd, *J* = 3.2, 10.8 Hz, 1 H), 0.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 133.5, 133.3, 133.1, 128.4, 128.1, 127.8, 127.6, 126.4 (2 C), 126.2, 78.9, 67.1, 66.4, 61.8, 56.8, 48.3, 44.1, 43.7, 40.9, 39.3, 38.5, 38.1, 35.9, 33.6, 29.0, 20.7, 20.4, 19.1, 15.3, 11.0; HRMS (ESI-TOF) calcd for $C_{31}H_{39}O_4$ $[M+H]^+$ 475.2843, found 475.2855.

Steviol *tert*-butyldiphenylsilyl ester (9)

To a solution of **8a** (5.5 g, 9.6 mmol) in a mixed solvent of 1,4-dioxane and MeOH (100 mL, v/v = 1 : 1) was added zinc dust (3.58 g, 54.8 mmol), $CuSO_4$ (0.88 g, 5.5 mmol), NaI (2.45 g, 16.3 mmol), and NaOAc (0.82 g, 10 mmol) at room temperature. To the resultant suspension HOAc (5.76 mL, 96 mmol) was then added. The resulting reaction mixture was stirred at the same temperature overnight, at which time TLC showed that all starting material disappeared. Filtration to remove all solids, and the filtrate was diluted with ethyl acetate. The resulting solution was washed successively with water, saturated aqueous $NaHCO_3$, and brine, then dried over anhydrous Na_2SO_4. Filtration was followed by concentration under reduced pressure yielded the crude product, which was further purified by silica gel chromatography (PE/EA = 10 : 1) to afford **9** (5.35 g, 100%) as a white foam: $[\alpha]_D^{25}$ = -55.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4 H), 7.45-7.34 (m, 6 H), 4.97 (t, *J* = 2.4 Hz, 1 H), 4.81 (t, *J* = 2.4 Hz, 1 H), 2.25-2.16 (m, 2 H), 2.09-2.02 (m, 2 H), 1.90-1.38 (m, 12 H), 1.27 (s, 3 H), 1.24 (dd, *J* = 2.4, 11.2 Hz, 1 H), 1.14 (s, 9 H), 1.08-1.04 (m, 1 H), 0.95 (d, *J* = 8.0 Hz, 1 H), 0.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 156.3, 135.8 (2 C), 132.2 (2 C), 130.1, 127.7, 103.0, 80.4, 57.2, 53.9, 47.6, 47.1, 45.3, 41.8, 41.6, 40.8, 39.5, 39.3, 38.7, 29.4, 27.3, 22.4, 20.6, 19.4 (2 C), 16.2; HRMS (ESI-TOF) calcd for $C_{36}H_{48}O_3SiNa$ $[M+Na]^+$ 579.3265, found 579.3257.

Steviol 2-napthylmethyl ester (9')

Similar procedure as that used for the synthesis of **9** was applied to get **9'** (0.97 g, 100%) as a white solid: $[\alpha]_D^{25}$ = -51.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.86-7.83 (m, 4 H), 7.53-7.46 (m, 3 H), 5.32 (AB, 2 H), 4.97 (t, J = 2.4 Hz, 1 H), 4.81 (d, J = 2.4 Hz, 1 H), 2.25-2.00 (m, 4 H), 1.92-1.36 (m, 9 H), 1.25-1.21 (m, 2 H), 1.21 (s, 3 H), 1.08-1.04 (dd, 1 H), 0.95 (d, J = 8.0 Hz, 1 H), 0.90-0.83 (m, 3 H), 0.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 156.2, 133.6, 133.3, 133.2, 128.4, 128.1, 127.8, 127.6, 126.4, 126.3, 126.2, 103.0, 80.3, 66.4, 57.2, 53.8, 47.5, 47.0, 44.1, 41.8, 41.4, 40.8, 39.4, 39.3, 38.2, 29.0, 22.0, 20.5, 19.2, 15.6; HRMS (ESI-TOF) calcd for $C_{31}H_{39}O_3$ $[M+H]^+$ 459.2894, found 459.2894.

15-α-Hydroxyl-isosteviol (10)

To a solution of **8b** (123 mg, 215 mmol) in dry CH_2Cl_2 (2 mL) was added PPh_3 (84.6 mg, 0.32 mmol) and I_2 (55.0 mg, 0.22 mmol) at room temperature. The reaction mixture was then heated to reflux, and the stirring was continued for another 2 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate. The solution was washed successively with saturated aqueous $Na_2S_2O_3$, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration to afford a residue, which was further purified by silica gel chromatography (PE/EA = 1 : 1) to deliver **10** (92 mg, 75%) as a light yellow solid: $[\alpha]_D^{25}$ = -80.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (d, J = 1.2 Hz, 1 H), 2.55 (dd, J = 1.6, 18.8 Hz, 1 H), 2.18-2.13 (m, 2 H), 2.10-2.04 (m, 1 H), 2.00-1.94 (m, 1 H), 1.89-1.58 (m, 6 H), 1.47-1.37 (m, 3 H), 1.26 (s, 3 H), 1.24-1.20 (m, 2 H), 1.14 (dd, J = 2.0, 12.0 Hz, 1 H), 1.04 (s, 3 H), 0.95 (dt, J = 4.4, 13.2 Hz, 1 H), 0.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 88.6, 56.6, 54.4, 54.2, 44.4, 43.7 (2 C), 40.0, 38.4, 37.7, 35.8, 35.5, 29.1, 21.0, 19.9, 19.0, 15.0, 13.8; HRMS (ESI-TOF) calcd for $C_{20}H_{31}O_4$ $[M+H]^+$

335.2217, found 335.2221.

***p*-Methoxyphenyl**

2-*O*-levulinoyl-3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranoside (12)

To a solution of **11** (500 mg, 1.2 mmol) in dry CH_2Cl_2 (5 mL) was added LevOH (560 mg, 0.48 mmol), DMAP (300 mg, 0.25 mmol), DIPEA (0.8 mL, 0.48 mmol), and EDCI (930 mg, 0.48 mmol) at 0 ^oC under N_2 atmosphere. The reaction mixture was warmed up to room temperature and the stirring was continued for another 12 h. Ethyl acetate was added to dilute the reaction mixture, and the obtained mixture was washed successively with water, saturated aqueous $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration to afford the crude product, which was further purified by silica gel chromatography (PE/EA = 3 : 1) to deliver **12** (580 mg, 94%) as a white solid: $[\alpha]_D^{25}$ = -15.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.53-7.51 (m, 2 H), 7.42-7.36 (m, 3 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 9.2 Hz, 2 H), 5.95-5.85 (m, 1 H), 5.71 (s, 1 H), 5.27 (qd, *J* = 2.0, 17.2 Hz, 1 H), 5.16-5.08 (m, 3 H), 4.36-4.29 (m, 2 H), 4.20-4.14 (m, m, 1 H), 3.88-3.80 (m, 3 H), 3.78-3.72 (m, 1 H), 3.75 (s, 3 H), 2.81-2.78 (m, 2 H), 2.62 (t, *J* = 6.8 Hz, 2 H), 2.13 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 171.9, 156.5, 152.3, 138.9, 136.4, 129.6, 128.9, 127.0, 119.4, 116.4, 115.3, 101.8, 101.7, 81.9, 79.5, 73.8, 73.7, 69.0, 67.0, 55.8, 38.1, 28.6; HRMS (ESI-TOF) calcd for $C_{28}H_{33}O_9$ $[M+H]^+$ 513.2119, found 513.2125.

2-*O*-Levulinoyl-3-*O*-allyl-4,6-*O*-benzylidene-D-glucopyranosyl

***ortho*-cyclopropylethynylbenzoate (13)**

To a solution of **12** (1.0 g, 1.95 mmol) in a mixed solvent of toluene, acetonitrile and pH 7.0 buffer (2 mL, v/v/v = 1 : 2 : 1) was added CAN (3.3 g, 5.84 mmol) at 0 ^{o}C. The stirring was continued at the same temperature for another 15 min. Ethyl acetate was added to dilute the reaction mixture, and the solution was washed successively with saturated aqueous $Na_2S_2O_3$, water, and brine, then dried over anhydrous Na_2SO_4. Filtration was followed by concentration to afford a residue, which was further purified by silica gel chromatography (PE/EA = 2 : 1) to afford the hemiacetal residue (0.79 g, 89%) as a light yellow syrup, which was used directly for the next step without detailed characterization.

The above obtained hemiacetal intermediate (0.79 g, 1.37 mmol) was dissolved in dry CH_2Cl_2 (2 mL), to which ABzOH (0.69 g, 3.7 mmol), $^{i}Pr_2NEt$ (1.7 mL, 9.9 mmol), DMAP (575 mg, 4.7 mmol), and EDCI (1.13 g, 5.9 mmol) were added at 0 ^{o}C under N_2 atmosphere. After the addition was completed, the reaction mixture was warmed up to room temperature, and the stirring was continued for another 6 h. Ethyl acetate was added to dilute the reaction mixture, the resulting solution was washed with water, brine, and dried over anhydrous Na_2SO_4. Filtration was followed by concentration gave a residue, which was further purified by silica gel chromatography (PE/EA = 4 : 1) to **13** (0.92 g, 82%) as a mixture of α/β isomers. An aliquot of β-isomer was isolated for detailed characterization: $[\alpha]_D^{25}$ = -37.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.89 (dd, *J* = 1.2, 7.6 Hz, 1 H), 7.57-7.51 (m, 4 H), 7.44-7.38 (m, 4 H), 6.04 (dd, *J* = 1.2, 8.4 Hz, 1 H), 5.97-5.87 (m, 1 H), 5.73 (s, 1 H), 5.29-5.23 (m, 1 H), 5.21-5.16 (m, 1 H), 5.13-5.09 (m, 1 H), 4.37-4.31 (m, 2 H), 4.24-4.18 (m, 1 H),

3.98 (t, *J* = 8.4 Hz, 1 H), 3.89-3.82 (m, 3 H), 2.75 (t, *J* = 6.4 Hz, 2 H), 2.57-2.54 (m, 2 H), 2.05 (s, 3 H), 1.58-1.52 (m, 1 H), 0.97-0.92 (m, 2 H), 0.84-0.80 (m, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.1, 164.1, 138.8, 136.3, 134.8, 133.3, 131.5, 131.2, 129.6, 128.9, 128.1, 127.0, 126.1, 116.5, 101.9, 100.8, 93.7, 81.8, 79.3, 74.8, 73.8, 73.0, 68.9, 67.7, 38.2, 28.6, 9.2 (2 C), 1.1; HRMS (ESI-TOF) calcd for $C_{33}H_{35}O9$ $[M+H]^+$ 575.2276, found 575.2276.

13-*O*-(2-*O*-Levulinoyl-3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-steviol *tert*-butyldiphenylsilyl ester (14)

To a solution of **9** (300 mg, 0.54 mmol) and **13** (470 mg, 0.82 mmol) in dry CH_2Cl_2 (2 mL) was added activated powdered 4A MS under N_2 atmosphere. The suspension was stirred at room temperature for 30 min, to which $Ph_3PAuNTf$ (80 mg, 0.11 mmol) was added. After stirring at room temperature for another 4 h, 4A MS was removed by filtration. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (PE/EA = 5 : 1) to give **14** (480 mg, 92%) as a white foam: $[\alpha]_D^{25}$ = -28.2 (*c* 1.0, CHCl3); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.76-7.71 (m, 4 H), 7.54-7.37 (m, 11 H), 5.94-5.84 (m, 1 H), 5.68 (s, 1 H), 5.26 (qd, *J* = 1.6, 17.2 Hz, 1 H), 5.10-5.07 (m, 1 H), 4.93 (brs, 1 H), 4.90-4.88 (m, 2 H), 4.78 (d, *J* = 2.4 Hz, 1 H), 4.31-4.26 (m, 1 H), 4.18-4.11 (m, 2 H), 3.79-3.65 (m, 3 H), 3.53-3.47 (m, 1 H), 2.90-2.48 (m, 5 H), 2.22-2.10 (m, 6 H), 2.07-2.05 (m, 2 H), 2.02-1.79 (m, 6 H), 1.68-1.34 (m, 5 H), 1.31 (s, 3 H), 1.15 (s, 9 H), 1.09 (dd, *J* = 4, 13.2 Hz, 1 H), 1.02 (d, *J* = 8 Hz, 1 H), 0.86 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 177.1, 171.6, 153.6, 139.0, 136.5, 136.4 (2 C), 136.3, 132.9, 132.8, 130.9, 129.6,

128.9, 128.4, 127.1, 127.0 (2 C), 116.3, 105.0, 101.8, 97.2, 86.3, 82.2, 79.7, 74.2, 73.6, 69.2, 66.8, 57.5, 54.4, 47.9, 45.8, 44.9, 43.1, 42.0, 41.2, 40.1, 39.1, 38.0, 37.3, 28.7, 27.4, 23.0, 20.9, 20.0, 19.7, 16.9; HRMS (ESI-TOF) calcd for $C_{57}H_{73}O_{10}Si$ $[M+H]^+$ 945.4968, found 945.4971.

13-*O*-(3-*O*-Allyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-steviol *tert*-butyldiphenylsilyl ester (15)

To a solution of **14** (320 mg, 0.34 mmol) in a mixed solvent of pyridine and HOAc (28.8 mL, v/v = 51 : 34) was added freshly prepared NH_2NH_2•HOAc (230 μL, freshly prepared by mixing NH_2NH_2 and HOAc with a volume ratio of 1 : 3.28) at 0 °C. The stirring was continued at the same temperature for 30 min. After quenched with acetone, ethyl acetate was added to dilute the reaction mixture. The resulting solution was washed successively with water, saturated $NaHCO_3$, brine, and then dried with anhydrous Na_2SO_4. Filtration was followed by concentration to yield the crude product, which was further purified by silica gel chromatography (PE/EA = 2.5 : 1) to afford **15** (251 mg, 87%) as a white foam: $[\alpha]_D^{25}$ = -36.8 (*c* 1.0, CHCl3); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.77-7.71 (m, 4 H), 7.54-7.33 (m, 11 H), 5.98-5.88 (m, 1 H), 5.63 (s, 1 H), 5.30 (qd, *J* = 1.6, 17.2 Hz, 1 H), 5.12-5.10 (m, 1 H), 5.08 (qd, *J* = 1.6, 10.4 Hz, 1 H), 4.81 (d, *J* = 2.0 Hz, 1 H), 4.67 (d, *J* = 7.6 Hz, 1 H), 4.39 (d, *J* = 4.4 Hz, 1 H), 4.37-4.26 (m, 2 H), 4.13 (dd, *J* = 4.8, 10.0 Hz, 1 H), 3.73 (t, *J* = 10.0 Hz, 1 H), 3.58-3.50 (m, 2 H), 3.42-3.36 (m, 2 H), 2.24-2.20 (m, 1 H), 2.17-2.11 (m, 2 H), 2.00-1.77 (m, 5 H), 1.68-1.41 (m, 5 H), 1.31 (s, 3 H), 1.16 (s, 9 H), 1.03 (d, *J* = 8.4 Hz, 1 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 177.1, 153.9, 139.2, 137.0,

136.5, 136.4, 133.0, 132.9, 130.9 (2 C), 129.5, 128.8, 128.5, 128.4, 127.0, 115.8, 104.9, 101.8 (2 C), 99.6, 86.4, 82.3, 81.9, 75.5, 73.8, 69.5, 66.9, 57.6, 54.5, 48.2, 45.8, 45.1, 42.9, 42.2, 41.3, 40.2, 39.2, 37.7, 27.5, 23.1, 20.9, 20.0, 19.7, 16.9; HRMS (ESI-TOF) calcd for $C_{52}H_{67}O_8Si$ $[M+H]^+$ 847.4600, found 847.4606.

13-*O*-[2-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol *tert*-butyldiphenylsilyl ester (17)

Similar procedure as that used for the synthesis of **14** was applied to conduct the coupling between monosaccharide acceptor **15** and donor **16** to deliver **17** (200 mg, 92%) as a white foam: $[\alpha]_D^{25}$ = -14.5 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.08 (dd, *J* = 1.2, 8.0 Hz, 2 H), 8.01 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.94 (dd, *J* = 1.6, 8.4 Hz, 2 H), 7.82 (dd, *J* = 1.6, 8.4 Hz, 2 H), 7.76-7.70 (m, 4 H), 7.65-7.55 (m, 4 H), 7.51-7.41 (m, 14 H), 7.37-7.31 (m, 5 H), 6.05-5.95 (m, 2 H), 5.82 (t, *J* = 9.6 Hz, 1 H), 5.61 (d, *J* = 8.0 Hz, 1 H), 5.60 (s, 1 H), 5.56 (dd, *J* = 7.6, 9.2 Hz, 1 H), 5.24-5.18 (m, 2 H), 5.09 (qd, *J* = 1.6, 10.4 Hz, 1 H), 4.81 (d, *J* = 7.2 Hz, 1 H), 4.68 (dd, *J* = 2.8, 12.4 Hz, 1 H), 4.65 (d, *J* = 2.4 Hz, 1 H), 4.59 (dd, *J* = 4.4, 12.0 Hz, 1 H), 4.53-4.49 (m, 1 H), 4.29-4.24 (m, 1 H), 4.10 (dd, *J* = 4.8, 10.0 Hz, 1 H), 4.05-4.00 (m, 1 H), 3.81 (t, *J* = 7.6 Hz, 1 H), 3.70 (t, *J* = 10.0 Hz, 1 H), 3.63-3.55 (m, 2 H), 3.44-3.38 (m, 1 H), 2.23 (d, *J* = 12.8 Hz, 1 H), 2.12 (dd, *J* = 2, 11.2 Hz, 1 H), 2.09 (s, 1 H), 2.05 (s, 1 H), 2.02-1.34 (m, 13 H), 1.30 (s, 3 H), 1.15 (s, 9 H), 1.08 (dd, *J* = 5.6, 14.4 Hz, 1 H), 0.97 (d, *J* = 7.6 Hz, 1 H), 0.89-0.84 (m, 1 H), 0.81 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 177.1, 166.4, 166.1, 165.8, 165.6, 154.0, 139.0, 136.7, 136.5, 136.4, 134.4, 134.2 (2 C), 133.9, 132.9 (2 C), 130.9 (3 C), 130.5, 130.4 (2 C), 130.2, 130.1,

130.0, 129.5, 129.4, 129.3 (3 C), 128.8, 128.4, 127.0, 116.1, 105.2, 101.7 (2 C), 97.6, 86.0, 82.5, 82.4, 80.0, 74.4, 73.9, 73.6, 72.5, 70.5, 69.4, 66.2, 63.9, 57.6, 54.6, 47.9, 45.8, 44.7, 43.3, 42.1, 41.2, 40.1, 39.2, 37.0, 27.5, 23.0, 21.0, 20.0, 19.7, 16.9; HRMS (ESI-TOF) calcd for $C_{87}H_{93}O_{19}Si$ $[M+COOH]^-$ 1469.6075, found 1469.6110.

13-*O*-[2-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol *tert*-butyldiphenylsilyl ester (18)

To a solution of **17** (200 mg, 0.14 mmol) in a mixed solvent of MeOH and CH_2Cl_2 (8 mL, v/v = 1 : 1) was added $PdCl_2$ (7.5 mg, 0.04 mmol) at room temperature under N_2 atmosphere. The resulting reaction mixture was stirred at the same temperature for 1 h, at which time TLC showed that all starting disappeared. Filtration through a pad of Celite and silica gel was followed by concentration afford a residue, which was further purified by silica gel chromatography (PE/EA = 2 : 1) to afford **18** (150 mg, 78%) as a white foam: $[\alpha]_D^{25}$ = -5.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.09 (dd, *J* = 1.2, 8.0 Hz, 8.02 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.94 (d, *J* = 1.2, 8.0 Hz, 2 H), 7.82 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.75-7.70 (m, 4 H), 7.65-7.33 (m, 23 H), 6.04 (t, *J* = 9.6 Hz, 1 H), 5.82 (t, *J* = 9.6 Hz, 1 H), 5.69 (d, *J* = 8.0 Hz, 1 H), 5.55 (s, 1 H), 5.54 (dd, *J* = 8.0, 9.6 Hz, 1 H), 5.24 (dd, *J* = 2.4, 4.4 Hz, 1 H), 4.93 (d, *J* = 3.2 Hz, 1 H), 4.77 (d, *J* = 6.8 Hz, 1 H), 4.67-4.64 (m, 2 H), 4.59-4.49 (m, 2 H), 4.08 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.79-3.71 (m, 2 H), 3.68 (t, *J* = 10.0 Hz, 1 H), 3.46-3.32 (m, 2 H), 1.30 (s, 3 H), 1.14 (s, 9 H), 0.78 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 177.2, 166.5, 166.2, 165.9, 165.8, 154.0, 139.1, 136.5, 136.4, 134.3, 134.2, 134.0, 133.9, 133.0, 132.9, 131.0, 130.9, 130.8, 130.5, 130.4, 130.3, 130.2, 130.1, 129.6, 129.4, 129.3 (2

C), 128.8, 128.4, 127.3, 105.1, 102.3, 102.2, 101.9, 97.6, 86.0, 82.2, 81.8, 75.2, 74.6, 73.6, 72.4, 70.6, 69.4, 66.4, 63.8, 57.6, 54.6, 47.9, 45.8, 44.8, 43.3, 42.1, 41.2, 40.1, 39.2, 37.0, 27.5, 23.1, 21.0, 20.3, 19.7, 16.9; HRMS (ESI-TOF) calcd for $C_{83}H_{88}O_{17}SiNa$ $[M+Na]^+$ 1407.5683, found 1407.5683.

13-*O*-(2-*O*-Levulinoyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-steviol *tert*-butyldiphenylsilyl ester (20)

Similar procedure as that used for the synthesis of **18** was applied to convert **14** to **20** (300 mg, 76%) as a white foam: $[\alpha]_D^{25}$ = -35.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4 H), 7.52-7.35 (m, 11 H), 5.54 (s, 1 H), 4.99 (d, *J* = 2.4 Hz, 1 H), 4.98 (dd, *J* = 8.0, 9.2 Hz, 1 H), 4.84 (brs, 1 H), 4.72 (d, *J* = 8.0 Hz, 1 H), 4.24 (dd, *J* = 5.2, 10.8 Hz, 1 H), 3.95 (t, *J* = 9.2 Hz, 1 H), 3.79 (t, *J* = 10.4 Hz, 1 H), 3.63 (t, *J* = 9.2 Hz, 1 H), 3.42-3.36 (m, 1 H), 2.84-2.75 (m, 1 H), 2.72-2.56 (m, 2 H), 2.50-2.43 (m, 1 H), 2.28 (d, *J* = 13.6 Hz, 1 H), 2.14 (s, 3 H), 2.03 (d, *J* = 17.6 Hz, 1 H), 1.95-1.38 (m, 10 H), 1.26 (s, 3 H), 1.14 (s, 9 H), 1.08-0.94 (m, 3 H), 0.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 176.9, 172.0, 152.0, 137.2, 135.7 (2 C), 132.2, 130.1 (2 C), 129.4, 128.4, 127.7, 126.5, 105.2, 102.0, 96.3, 86.4, 80.7, 75.2, 72.6, 68.8, 66.4, 57.0, 53.8, 47.6, 45.3, 44.2, 42.4, 41.4, 40.7, 39.5, 38.7, 38.4, 37.1, 30.0, 29.4, 28.3, 27.3, 22.2, 20.4, 19.4, 16.4; HRMS (ESI-TOF) calcd for $C_{54}H_{69}O_{10}Si$ $[M+H]^+$ 905.4655, found 905.4642.

13-*O*-[2-*O*-Levulinoyl-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol *tert*-butyldiphenylsilyl ester (21)

Similar procedure as that used for the synthesis of **14** was applied to conduct the

condensation of **16** and **20** to afford **21** (510 mg, 92%) as a white foam: $[\alpha]_D^{25}$ = -0.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.01 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.95 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.88 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.80 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.75-7.70 (m, 4 H), 7.61-7.55 (m, 5 H), 7.50-7.39 (m, 14 H), 7.36-7.32 (m, 2 H), 7.30-7.26 (m, 2 H), 6.10-60.5 (m, 1 H), 5.74 (dd, *J* = 8.8, 10.4 Hz, 2 H), 5.49-5.43 (m, 2 H), 4.98 (dd, *J* = 7.6, 8.8 Hz, 1 H), 4.86-4.84 (m, 2 H), 4.72 (d, *J* = 2.4 Hz, 1 H), 4.55 (dd, *J* = 3.2, 12.0 Hz, 1 H), 4.48 (dd, *J* = 4.8, 12.0 Hz, 1 H), 4.37-4.33 (m, 1 H), 4.30 (t, *J* = 9.2 Hz, 1 H), 4.14 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.81-3.76 (m, 2 H), 3.56-3.50 (m, 1 H), 2.64-2.38 (m, 4 H), 2.24 (d, *J* = 13.2 Hz, 1 H), 2.10 (s, 3 H), 2.09 (s, 1 H), 2.03 (d, *J* = 8 Hz, 2 H), 1.98-1.35 (m, 12 H) , 1.30 (m, 4 H), 1.14 (s, 9 H), 1.08 (dd, *J* = 4.0, 8.0 Hz, 1 H), 1.00 (d, *J* = 8.0 Hz, 1 H), 0.89(d, *J* = 4.0 Hz, 1 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 206.4, 177.1, 171.5, 166.4, 166.1, 165.8, 153.4, 138.9, 136.4 (2 C), 134.3, 134.2, 134.1, 133.9, 133.0, 132.9, 130.9, 130.8, 130.6, 130.5, 130.4 (2 C), 130.2, 130.1 (2 C), 129.5, 129.4, 129.3, 128.8, 128.5, 128.4, 127.2, 105.0, 101.9, 100.7, 97.1, 86.4, 80.2, 80.0, 74.4, 74.3, 73.5, 72.5, 70.9, 69.3, 67.0, 64.0, 57.5, 54.4, 48.0, 45.8, 44.8, 43.1, 42.0, 41.2, 40.1, 39.2, 28.2, 37.3, 28.5, 27.5, 23.0, 20.9, 20.0, 19.8, 17.0; HRMS (ESI-TOF) calcd for $C_{88}H_{98}NO_{19}Si$ $[M+NH_4]^+$ 1500.6497, found 1500.6491.

13-*O*-[3-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol *tert*-butyldiphenylsilyl ester (22)

Similar procedure as that used for the synthesis of **15** was applied to convert **21** to **22** (198 mg, 82%) as a white foam: $[\alpha]_D^{25}$ = -6.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz,

acetone-d_6) δ 8.04 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.97 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.92 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.83 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.77-7.72 (m, 4 H), 7.61-7.53 (m, 5 H), 7.51-7.33 (m, 15 H), 7.27-7.23 (m, 3 H), 6.01 (t, *J* = 9.6 Hz, 1 H), 5.78 (t, *J* = 10.0 Hz, 1 H), 5.645 (s, 1 H), 5.638 (d, *J* = 8.0 Hz, 1 H), 5.56 (dd, *J* = 8.0, 9.2 Hz, 1 H), 5.03 (d, *J* = 2.8 Hz, 1 H), 4.78 (d, *J* = 2.4 Hz, 1 H), 4.64 (d, *J* = 7.6 Hz, 1 H), 4.60 (dd, *J* = 3.2, 12.0 Hz, 1 H), 4.54-4.49 (m, 2 H), 4.45-4.40 (m, 1 H), 4.11-4.07 (m, 1 H), 3.74 (t, *J* = 10.0 Hz, 1 H), 3.63 (t, *J* = 9.2 Hz, 1 H), 3.45-3.36 (m, 2 H), 2.24 (d, *J* = 13.2 Hz, 1 H), 2.13-1.99 (m, 3 H), 1.90-1.7 (m, 13 H), 1.31 (s, 3 H), 1.16 (s, 9 H), 1.12-1.10 (m, 1 H), 1.00 (d, *J* = 8.0 Hz, 1 H), 0.90-0.88 (m, 1 H), 0.85 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 177.1, 166.4, 166.1, 165.8 (2 C), 153.6, 139.0, 136.4 (2 C), 134.3, 134.2, 134.0, 133.9, 133.0, 132.9, 130.9 (2 C), 130.8, 130.7, 130.4 (3 C), 130.2, 130.1 (2 C), 129.4, 129.3, 128.7, 128.5, 128.4, 127.1, 105.0, 101.6, 101.5, 99.4, 86.6, 81.2, 79.8, 75.8, 75.7, 74.4, 73.4, 72.5, 70.8, 69.4, 67.2, 64.0, 57.5, 54.5, 48.2, 45.8, 44.9, 42.8, 42.1, 41.2, 40.1, 39.2, 37.7, 27.5, 23.0, 20.9, 20.0, 19.8, 16.9; HRMS (ESI-TOF) calcd for $C_{83}H_{88}O_{17}SiNa$ $[M+Na]^+$ 1407.5683, found 1407.5692.

13-*O*-[2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol *tert*-butyldiphenylsilyl ester (19)

Similar procedure as that used for the synthesis of **14** was applied to conduct the condensation of **16** and **22** to afford **19** (212 mg, 90%) as a white foam: $[\alpha]_D^{25}$ = +25.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.6 Hz, 2 H), 8.15 (d, *J* = 7.6 Hz, 2 H), 7.94 (d, *J* = 8.0 Hz, 2 H), 7.89-7.81 (m, 9 H), 7.68-7.18 (m, 40 H), 5.88 (dd, *J* = 10.4, 20.8 Hz, 2 H), 5.62 (dd, *J* = 8.0, 10.0 Hz, 1 H), 5.50-5.43 (m, 4 H), 5.07

(brs, 1 H), 4.93 (d, *J* = 7.6 Hz, 1 H), 4.82 (d, *J* = 7.6 Hz, 1 H), 4.63 (brs, 1 H), 4.60 (d, *J* = 7.6 Hz, 1 H), 4.31-4.09 (m, 6 H), 4.01 (t, *J* = 8.8 Hz, 1 H), 3.86 (t, *J* = 7.6 Hz, 1 H), 3.69-3.60 (m, 2 H), 3.28-3.22 (m, 1 H), 2.77-2.71 (m, 1 H), 2.30 (d, *J* = 13.2 Hz, 1 H), 1.99 (d, *J* = 11.2 Hz, 1 H), 1.90-1.73 (m, 7 H), 1.58-1.28 (m, 6 H), 1.24 (s, 3 H), 1.14 (s, 9 H), 0.79 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 166.0 (3 C), 165.8, 165.2, 165.1 (2 C), 152.7, 137.5, 135.7, 133.7, 133.5, 133.4, 133.3, 133.1, 133.0, 132.2, 132.1, 130.3, 130.1, 130.0, 129.8 (2 C), 129.7, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0 (2 C), 128.9, 128.5, 128.4 (3 C), 128.3, 128.1, 127.7, 126.2, 105.1, 101.4, 100.2, 100.0, 97.0, 85.6, 80.6, 79.0, 78.6, 73.0, 72.8, 72.7, 71.5, 71.4, 70.2, 69.7, 68.9, 65.9, 63.5, 63.1, 60.5, 57.1, 54.0, 47.2, 45.3, 43.6, 42.9, 41.4, 40.7, 39.5, 38.8, 36.2, 29.4, 27.2, 22.2, 20.4, 19.5, 19.4, 16.5; HRMS (ESI-TOF) calcd for $C_{117}H_{115}O_{26}Si$ $[M+H]^+$ 1964.7473, found 1964.7485.

_p_-Tolyl-2,3-di-_O_-levulinoyl-4,6-_O_-benzylidene-1-thio-β-D-glucopyranoside (24)

Similar procedure as that used for the synthesis of **12** was adopted to convert **23** to **24** (5.5 g, 91%) as a white solid: $[\alpha]_D^{25}$ = -34.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.48-7.43 (m, 4 H), 7.36-7.33 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 5.62 (s, 1 H), 5.42 (t, *J* = 8.8 Hz, 1 H), 5.04-4.95 (m, 2 H), 4.34 (dd, *J* = 3.6, 10.0 Hz, 1 H), 3.83-3.77 (m, 1 H), 3.75-3.72 (m, 2 H), 2.83-2.79 (m, 2 H), 2.76-2.70 (m, 2 H), 2.61-2.57 (m, 2 H), 2.54-2.49 (m, 2 H), 2.33 (s, 3 H), 2.14 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 205.7, 205.6, 171.5, 171.1, 138.1, 137.6, 132.9, 129.7, 128.8, 128.7, 128.0, 126.3, 101.0, 100.9, 86.1, 78.1, 72.6, 70.5, 70.3, 68.0, 37.3 (2 C), 27.8, 27.7, 25.4, 20.4, 20.3; HRMS (ESI-TOF) calcd for $C_{30}H_{35}O_9S$ $[M+H]^+$ 571.1996,

found 571.1995

2,3-Di-*O*-levulinoyl-4,6-*O*-benzylidene-D-glucopyranosyl *ortho*-cyclopropylethenylbenzoate (25)

To a solution of **24** (1.0 g, 1.75 mmol) in a mixed solvent of acetone and H_2O (40 mL, v/v = 3 : 1) was added trichloroisocyanuric acid (TCCA) (610 mg, 2.6 mmol) portionwise at 0 ^oC. After the addition was completed, filtration was followed by dilution of the filtrate with ethyl acetate. The resulting solution was washed successively with water, saturated aqueous $NaHCO_3$, brine, and then dried over Na_2SO_4. Filtration was followed by concentration *in vacuo* gave a residue, which was further purified by silica gel chromatography (PE/EA = 1 : 1) to afford hemiacetal intermediate. The hemiacetal intermediate was used for Yu donor preparation without further characterization. Under the standard conditions, the hemiacetal compound was efficiently converted to Yu donor **25** (1.0 g, 90% for 2 steps) as a mixture of α/β isomers. An aliquot of pure β-isomer was obtained for detailed characterization: $[\alpha]_D^{25}$ = -41.4 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.50-7.43 (m, 4 H), 7.38-7.29 (m, 4 H), 6.02 (d, *J* = 8.0 Hz, 1 H), 5.52 (s, 1 H), 5.49 (t, *J* = 8.8 Hz, 1 H), 5.36 (dd, *J* = 8.0, 9.2 Hz, 1 H), 4.44 (dd, *J* = 3.6, 9.6 Hz, 1 H), 3.83-3.72 (m, 3 H), 2.86-2.44 (m, 8 H), 2.15 (s, 3 H), 2.08 (s, 3 H), 1.58-1.51 (m, 1 H), 0.94-0.89 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 206.1, 171.9, 171.6, 163.4, 136.8, 134.6, 132.7, 131.0, 129.3 (2 C), 128.4, 128.3, 127.3, 126.3, 126.0, 101.7, 100.7, 92.8, 78.4, 74.4, 71.6, 71.0, 68.5, 67.3, 38.0, 37.9, 29.9, 29.7, 28.0 (2 C), 9.2, 9.1, 0.9; HRMS (ESI-TOF) calcd for $C_{35}H_{37}O_{11}$ $[M+H]^+$ 633.2330, found 633.2337.

13-*O*-(2,3-Di-*O*-levulinoyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-steviol *tert*-butyldiphenylsilyl ester (26)

Identical procedure as that used for the synthesis of **14** was adopted to conduct the coupling between **25** and **9** to afford **26** (270 mg, 91%) as a white foam: $[\alpha]_D^{25}$ = -28.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.76-7.71 (m, 4 H), 7.50-7.46 (m, 5 H), 7.45-7.43 (m, 3 H), 7.37-7.35 (m, 3 H), 5.63 (s, 1 H), 5.37 (t, *J* = 9.6 Hz, 1 H), 5.04 (d, *J* = 7.6 Hz, 1 H), 4.96 (dd, *J* = 8.0, 9.6 Hz, 1 H), 4.95-4.94 (m, 1 H), 4.80 (dd, *J* = 1.6, 3.6 Hz, 1 H), 4.18 (dd, *J* = 4.8, 10.0 Hz, 1 H), 3.81-3.73 (m, 2 H), 3.64-3.58 (m, 1 H), 2.77-2.73 (m, 2 H), 2.72-2.69 (m, 2 H), 2.58-2.47 (m, 4 H), 2.23 (d, *J* = 13.2 Hz, 1 H), 2.11-2.08 (m, 7 H), 2.00-1.80 (m, 6 H), 1.68-1.54 (m, 2H), 1.47-1.42 (m, 2H), 1.31 (m, 4 H), 1.15 (m, 12 H), 1.08 (dd, *J* = 4.4, 13.2 Hz, 1 H), 1.03 (d, *J* = 8.4 Hz, 1 H), 0.88 (m, 5 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 177.1, 172.3, 171.7, 153.5, 138.7, 136.4 (2 C), 133.0 (2 C), 130.9, 129.6, 128.8, 128.5 (2 C), 127.2, 105.0, 101.9, 97.2, 86.7, 79.4, 73.1, 72.5, 69.2, 67.0, 57.6, 54.5, 48.1, 45.9, 44.9, 43.1, 42.0, 41.3, 40.2, 39.2, 38.2, 38.1, 37.5, 28.7, 28.6, 27.5, 23.1, 21.0, 20.0, 19.8, 17.0; HRMS (ESI-TOF) calcd for $C_{59}H_{74}O_{12}SiNa$ $[M+Na]^+$ 1025.4842, found 1025.4863.

13-*O*-(4,6-*O*-Benzylidene-β-D-glucopyranosyl)-steviol *tert*-butyldiphenylsilyl ester (27)

Similar procedure as that used for the synthesis of **15** was adopted to convert **26** to **27** (160 mg, 84%) as a white foam: $[\alpha]_D^{25}$ = -42.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (m, 4 H), 7.52-7.36 (m, 11 H), 5.52 (s, 1 H), 5.07 (s, 1 H), 4.89 (s, 1 H), 4.60 (d, *J* = 7.6 Hz, 1 H), 4.22 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.84 (t, *J* = 9.2 Hz, 1

H), 3.77 (t, *J* = 10.0 Hz, 1 H), 3.58-3.50 (m, 2 H), 3.42-3.36 (m, 1 H), 3.00 (brs, 1 H), 2.66 (brd, *J* = 15.6 Hz, 1 H), 2.28 (d, *J* = 13.2 Hz, 1 H), 2.21-2.16 (m, 1 H), 2.06-1.99 (m, 2 H), 1.91-1.74 (m, 6 H), 1.68-1.37 (m, 5 H), 1.28 (s, 3 H), 1.15 (s, 9 H), 1.08-0.99 (m, 2 H), 0.97 (d, *J* = 8.0 Hz, 1 H), 0.74 (s, 3 H); ^{13}C NMR (100 MHz, CDCl3) δ 176.8, 152.4, 137.2, 135.8, 135.7, 132.1, 132.0, 130.1, 129.3, 128.4, 127.7, 126.4, 105.0, 102.0, 98.2, 86.5, 80.7, 74.8, 73.4, 68.8, 66.5, 57.0, 53.7, 47.7, 45.3, 44.3, 42.3, 41.4, 40.7, 39.5, 38.7, 37.3, 29.3, 27.2, 22.2, 20.4, 19.4 (2 C), 16.3; HRMS (ESI-TOF) calcd for $C_{49}H_{63}O_8Si$ $[M+H]^+$ 807.4287, found 807.4287.

13-*O*-[2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol *tert*-butyldiphenylsilyl ester (19) ---Simultaneous branch sugar residues introduction with Yu donors.

Except for the donor amounts, identical procedure was applied to conduct the glycosylation between **16** (3.0 eq) and **27** to deliver **19** (214 mg, 88%).

13-*O*-[2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol (4)

To a solution of **19** (95 mg, 0.048 mmol) in dry THF (1 mL) was added HOAc (6 μL, 0.1 mmol) and TBAF (1N in THF, 0.06 mL) at room temperature. After stirring at the same temperature for 30 min, ethyl acetate was added to dilute the reaction mixture. The resulting solution was washed successively with water, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration *in vacuo* to give a residue, which was further purified by silica gel chromatography (PE/EA = 2.5 : 1) to afford **4** (80 mg, 97%) as a white solid: $[\alpha]_D^{25}$ = -13.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400

MHz, DMSO-d_6) δ 11.96 (s, 1 H), 7.98-7.76 (m, 17 H), 7.65-7.31 (m, 29 H), 6.17 (t, *J* = 9.6 Hz, 1 H), 6.05 (t, *J* = 9.2 Hz, 1 H), 5.93 (t, *J* = 9.2 Hz, 1 H), 5.84 (dd, *J* = 8.4, 9.2 Hz, 1 H), 5.74 (s, 1 H), 5.65 (d, *J* = 7.6 Hz, 1 H), 5.57-5.50 (m, 2 H), 5.35 (dd, *J* = 8.0, 9.6 Hz, 1 H), 4.97 (s, 1 H), 4.75 (d, *J* = 6.8 Hz, 1 H), 4.50 (d, *J* = 10.4 Hz, 1 H), 4.41-4.34 (m, 2 H), 4.26 (t, *J* = 2.4 Hz, 1 H), 4.22-4.12 (m, 3 H), 4.00 (t, *J* = 8.8 Hz, 1 H), 3.91 (t, *J* = 9.2 Hz, 1 H), 3.60-3.47 (m, 2 H), 2.06-1.91 (m, 3 H), 1.85-1.61 (m, 7 H), 1.45-1.26 (m, 6 H), 1.10 (s, 3 H), 0.99-0.91 (m, 1 H), 0.86 (s, 3 H), 0.74-0.70 (m, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.5, 165.5,165.4, 165.2, 164.8, 164.7 (2 C), 152.4, 137.6, 133.8, 133.7, 133.4, 133.2, 133.1, 129.5, 129.4, 129.3, 129.2 (3 C), 129.1, 129.0 (2 C), 128.9 (2 C), 128.8 (2 C), 128.6 (2 C), 128.5 (2 C), 127.9, 126.1, 104.2, 99.9, 98.9, 97.0, 95.9, 84.8, 79.6, 78.4, 75.6, 73.7, 73.3, 72.7, 72.0, 70.9, 70.3, 69.6, 69.4, 68.2, 64.4, 63.4, 62.6, 55.9, 53.2, 46.9, 43.0, 42.8, 42.0, 40.8, 37.6, 36.4, 28.6, 21.6, 19.9, 18.8, 15.4; HRMS (ESI-TOF) calcd for $C_{101}H_{97}O_{26}$ $[M+H]^+$ 1726.6297, found 1726.6312.

13-*O*-(2,3-Di-*O*-levulinoyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-steviol *tert*-butyldiphynylsilyl ester (26) ---With Schmidt donor

To a solution of **25'** (2.29 g, 3.76 mmol) and **9** (1.61 mg, 2.89 mmol) in dry CH_2Cl_2 (10 mL) was added activated powdered 4A MS under N_2 atmosphere at 0 ^oC. After being stirred at the same temperature for 30 min, the suspension was cooled to -40 ^oC, and then treated with TMSOTf (1.0 mL, 0.58 mmol). After stirring at the same temperature for 6 h, Et_3N was added to quench the reaction. Filtration was followed by concentration under reduced pressure afforded the crude product, which was

further purified by silica gel chromatography (PE/EA = 2.5 : 1) to deliver **26** (2.78 g, 96%).

Side-product derived from acid-induced double bond migration of the agycon with Schmidt donor 25' (28)

Similar procedure as that used for the synthesis of **26** with donor **25'** was adopted to conduct the condensation between **25'** and **9** at room temperature to afford **28** (163 mg, 91%) as a white foam: $[\alpha]_D^{25}$ = -40.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.74-7.71 (m, 3 H), 7.52-7.41 (m, 9 H), 7.38-7.34 (m, 3 H), 5.64 (s, 1 H), 5.37 (t, *J* = 9.6 Hz, 1 H), 5.10 (s, 1 H), 5.04 (d, *J* = 7.6 Hz, 1 H), 4.95-4.90 (m, 1 H), 4.22 (dd, *J* = 3.2, 10.4 Hz, 1 H), 3.82-3.73 (m, 2 H), 3.68-3.61 (m, 1 H), 2.76-2.70 (m, 4 H), 2.60-2.44 (m, 4 H), 2.10 (s, 6 H), 1.94-1.67 (m, 5 H), 1.59 (s, 3 H), 1.31 (s, 3 H), 1.15 (s, 9 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 177.1, 172.3, 171.7, 143.6, 138.7, 136.4 (2 C), 135.6, 133.0 (2 C), 130.9 (2 C), 129.6, 128.8, 128.4, 127.2, 101.9, 96.6, 89.6, 79.4, 73.1, 72.4, 69.2, 67.0, 57.3, 49.3, 48.6, 47.7, 45.9, 45.8, 41.5, 40.4, 40.2, 39.2, 38.2, 38.0, 28.6 (2 C), 27.5, 22.0, 21.6, 20.0, 19.8, 16.8, 12.1; HRMS (ESI-TOF) calcd for $C_{59}H_{74}O_{12}SiNa$ $[M+Na]^+$ 1025.4842, found 1025.4832.

13-*O*-[2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol *tert*-butyldiphynylsilyl ester (19)---Simultaneous glycosylation with Schmidt donors.

Except for the donor amounts, the similar procedure as that used for the synthesis of **26** with **25'** as donor was adopted to conduct the coupling of **16'** (3.0 eq) and **27** to afford **19** (3.17 g, 85%).

Allyl

2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (30)

Except for reaction temperature, identical procedure as that used for the synthesis of **26** with **25'** as donor was applied to conduct the condensation of **16'** and **29** at room temperature to afford **30** (3.7 g, 86%) as a white solid: $[\alpha]_D^{25}$ = +38.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.92 (dd, *J* = 1.6, 8.4 Hz, 2 H), 7.90 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.81 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.57-7.46 (m, 3 H), 7.44-7.25 (m, 9 H), 5.97-5.89 (m, 1 H), 5.88 (t, *J* = 9.2 Hz, 1 H), 5.76 (t, *J* = 9.6 Hz, 1 H), 5.50 (dd, *J* = 7.6, 9.6 Hz, 1 H), 5.38 (qd, *J* = 1.6, 17.2 Hz, 1 H), 5.20-5.14 (m, 3 H), 4.95 (t, *J* = 9.6 Hz, 1 H), 4.69 (dd, *J* = 3.2, 12.4 Hz, 1 H), 4.62 (d, *J* = 7.2 Hz, 1 H), 4.45-4.40 (m, 2 H), 4.25 (dd, *J* = 4.8, 12.4 Hz, 1 H), 4.19-4.10 (m, 2 H), 4.08 (dd, *J* = 2.4, 12.4 Hz, 1 H), 3.82 (dd, *J* = 7.2, 8.8 Hz, 1 H), 3.66-3.62 (m, 1 H), 2.06 (s, 3 H), 1.92 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.8, 169.7, 166.2, 165.9, 165.2, 165.1, 133.7, 133.5 (2 C), 133.3, 129.9 (2 C), 129.8 (2 C), 129.6, 129.2, 128.9, 128.8, 128.5 (2 C), 128.4, 117.3, 101.1, 100.7, 78.8, 73.5, 73.3, 72.6, 72.2, 71.4, 70.5, 69.4, 68.7, 62.8, 62.1, 20.8, 20.6, 20.4; HRMS (ESI-TOF) calcd for $C_{49}H_{48}O_{18}Na$ $[M+Na]^+$ 947.2733, found 947.2742.

2-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl bromide (6)

To a solution of **30** (3.2 g, 3.46 mmol) in a mixed solvent of CH_2Cl_2 and MeOH (400 mL, v/v = 1 : 1) was added $PdCl_2$ (185 mg, 1.04 mmol) at room temperature. The

suspension was stirred at the same temperature for another 1.5 h, at which time TLC showed that all starting material disappeared. Filtration through a pad of Celite and silica gel was followed by concentration under reduced pressure yielded the crude hemiacetal intermediate, which was directly used in the next conversion without further purification. The hemiacetal intermediate was then dissolved in dry pyridine (10 mL), to which Ac_2O (2 mL, 8.94 mmol) was added dropwise at 0 ^oC. After the addition was completed, the reaction mixture was warmed up to room temperature gradually, and the stirring was continued at the same temperature for another 2 h. Ethyl acetate was added to dilute the reaction mixture, and the resultant solution was washed successively with water, 1N HCl, saturated aqueous $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration under reduced pressure to afford the disaccharide acetate, which was used directly without further purification. The disaccharide acetate intermediate was then dissolved in dry CH_2Cl_2 (90 mL), to which 30% HBr/HOAc solution (40 mL) was added dropwise at 0 ^oC under N_2 atmosphere. The resulting mixture was stirred at the same temperature for another 15 min, then CH_2Cl_2 was added to dilute the reaction. The resultant solution was washed with water, saturated aqueous NaHCO3, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration under reduced pressure to afford the crude product, which was further purified by flash chromatography (PE/EA = 4 : 1) to afford disaccharide bromide **6** (2.3 g, 71% for 3 steps) as a white solid: $[\alpha]_D^{25}$ = +78.3 (*c* 1.0, $CHCl_3$); 1H NMR (400 MHz, acetone-d_6) δ 8.13 (dd, *J* = 1.6, 7.2 Hz, 2 H), 7.97 (d, *J* = 7.2 Hz, 2 H), 7.95 (d, *J* = 6.8 Hz, 2 H), 7.83 (dd, *J* = 1.6,

7.6 Hz, 2 H), 7.68-7.42 (m, 10 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 6.93 (dd, *J* = 1.2, 2.0 Hz, 1 H), 6.09-6.03 (m, 1 H), 5.82-5.77 (m, 1 H), 5.58-5.52 (m, 1 H), 5.45-5.38 (m, 2 H), 5.09-5.04 (m, 1 H), 4.95 (dd, *J* = 2.4, 12.0 Hz, 1 H), 4.60-4.50 (m, 2 H), 4.34-4.25 (m, 2 H), 4.15 (dd, *J* = 3.6, 10.0 Hz, 1 H), 4.10-4.06 (m, 1 H), 2.00 (s, 3 H), 1.94 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.5, 169.9, 169.5, 166.4, 166.1, 165.8, 165.2, 134.5, 134.3, 134.2, 134.1, 130.8, 130.5 (3 C), 130.4, 130.3 (2 C), 130.2, 130.0, 129.9, 129.4, 129.3, 102.6, 92.4, 78.8, 74.1, 73.2, 72.9, 72.6, 71.6, 70.3, 68.1, 63.1, 62.0, 20.6, 20.5, 19.9; HRMS (ESI-TOF) calcd for $C_{46}H_{43}O_{17}BrNa$ $[M+Na]^+$ 971.1568, found 971.1570.

***p*-Tolyl**

2,3-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (31)

Except for donor amounts, similar procedure as that used for the synthesis of **26** with **25'** as donor was applied to conduct the condensation between **16'** (3.0 eq) and **23** to afford trisaccharide **31** (1.6 g, 78%) as a white solid: $[\alpha]_D^{25}$ = +30.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.15 (d, *J* = 7.6 Hz, 2 H), 8.09 (d, *J* = 7.6 Hz, 4 H), 8.01 (dd, *J* = 1.6, 7.2 Hz, 2 H), 7.95-7.86 (m, 8 H), 7.66-7.37 (m, 26 H), 7.32-7.26 (m, 5 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 6.06 (t, *J* = 9.6 Hz, 2 H), 5.83-5.73 (m, 5 H), 5.66-5.61 (m, 1 H), 5.57 (d, *J* = 8.0 Hz, 1 H), 4.94 (d, *J* = 9.2 Hz, 1 H), 4.62-4.21 (m, 8 H), 3.99-3.86 (m, 2 H), 3.72 (t, *J* = 10.0 Hz, 1 H), 3.60-3.54 (m, 1 H), 2.25 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.4 (2 C), 166.3, 166.2, 165.8 (2 C), 165.7, 138.8, 137.7, 134.5, 134.4 (2 C), 134.3 (2 C), 134.2, 133.9, 132.5, 131.2, 130.8, 130.7, 130.6,

130.5, 130.4 (3 C), 130.3 (2 C), 130.2 (2 C), 130.1, 130.0 (2 C), 129.8, 129.7, 129.4, 129.3, 128.7, 127.2, 101.6 (2 C), 99.8, 99.6, 86.6, 81.8, 78.2, 76.9, 74.3, 74.2, 73.7, 73.4, 72.5, 72.2, 70.9, 70.3, 69.0, 64.4, 63.1, 21.0; HRMS (ESI-TOF) calcd for $C_{89}H_{75}O_{25}S$ $[M+H]^+$ 1575.4313, found 1575.4343.

***p*-Tolyl**

2,3-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-di-*O*-acetyl-1-thio-β-D-glucopyranoside (32)

To a solution of **31** (1.55 g, 1.01 mmol) in a mixed solvent of CH_2Cl_2 and MeOH (100 mL, v/v = 1 : 1) was added TsOH (0.96 g, 5.05 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 12 h, then Et_3N was added to quench the reaction. Ethyl acetate was added to dilute the reaction mixture, and the resultant solution was washed successively with water, saturated aqueous $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration under reduced pressure afforded the diol intermediate, which was directly used for the next step without further purification. The diol intermediate was dissolved in dry pyridine (5 mL), to which Ac_2O was added dropwise at 0 ^oC under N_2 atmosphere. The reaction mixture was then warmed up to room temperature, and the stirring was continued for another 2 h. Ethyl acetate was added to dilute the reaction mixture, the resultant solution was washed with water, 1N HCl, saturated aqueous $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration to give the crude product, which was further purified by silica gel chromatography (PE/EA = 3 : 1) to afford **32** (1.5 g, 98% for 2 steps) as a white solid:

$[\alpha]_D^{25}$ = +71.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 1.2, 9.2 Hz, 2 H), 8.29 (dd, *J* = 1.2, 8.8 Hz, 2 H), 8.01 (dd, *J* = 1.6, 8.4 Hz, 2 H), 7.94-7.87 (m, 10 H), 7.76-7.71 (m, 4 H), 7.62-7.29 (m, 20 H), 7.25-7.23 (m, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 5.85 (dd, *J* = 9.6, 19.6 Hz, 2 H), 5.65-5.57 (m, 2 H), 5.48-5.40 (m, 2 H), 4.92-4.84 (m, 2 H), 4.71 (d, *J* = 7.6 Hz, 1 H), 4.44 (d, *J* = 9.6 Hz, 1 H), 4.33-4.27 (m, 2 H), 4.20-4.13 (m, 2 H), 4.06-3.98 (m, 2 H), 3.94 (t, *J* = 9.2 Hz, 1 H), 3.83 (t, *J* = 9.2 Hz, 1 H), 3.27-3.22 (m, 1 H), 2.51-2.46 (m, 1 H), 2.43-2.38 (m, 1 H), 2.32 (s, 3 H), 2.01 (s, 3 H), 1.92 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.5, 166.0, 165.9, 165.8, 165.1, 165.0, 164.9, 164.6, 137.2, 133.8, 133.7 (2 C), 133.6, 133.5 (2 C), 133.1, 131.9, 130.8, 130.3, 130.2, 129.9 (2 C), 129.8 (2 C), 129.7, 129.6 (3 C), 129.5 (2 C), 129.4, 129.0, 128.8 (2 C), 128.7, 128.6 (2 C), 128.5 (2 C), 128.4, 100.4, 99.5, 86.8, 80.8, 75.7, 75.5, 73.1, 72.6, 72.5, 71.5, 69.5, 68.9, 68.2, 62.8 (2 C), 61.9, 21.2, 20.9 (2 C); HRMS (ESI-TOF) calcd for $C_{85}H_{74}O_{25}SNa$ $[M+Na]^+$ 1549.4132, found 1549.4141.

2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-di-*O*-acetyl-α-D-gluco pyranosyl bromide (7)

To a solution of **32** (350 mg, 0.23 mmol) in dry CH_2Cl_2 (2 mL) was added IBr (66 mg, 0.32 mmol) at 0 ^oC under N_2 atmosphere. After the addition was completed, the reaction mixture was stirred at the same temperature for another 30 min, then CH_2Cl_2 was added to dilute the reaction. The resultant solution was washed successively with saturated $Na_2S_2O_3$, water, brine, and then dried over anhydrous Na_2SO_4. Filtration was followed by concentration under reduced pressure gave a residue, which was further purified by flash chromatography (PE/EA = 2 : 1) to afford 7 (300 mg, 89%) as a

white solid: $[\alpha]_D^{25}$ = +116.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, acetone-d_6) δ 8.34-8.29 (m, 4 H), 8.04-7.98 (m, 6 H), 7.94-7.86 (m, 9 H), 7.82-7.76 (m, 3 H), 7.67-7.61 (m, 4 H), 7.56-7.50 (m, 10 H), 7.43-7.38 (m, 4 H), 6.58 (d, *J* = 3.6 Hz, 1 H), 5.95 (t, *J* = 9.6 Hz, 1 H), 5.77 (t, *J* = 9.6 Hz, 1 H), 5.66-5.59 (m, 2 H), 5.56 (td, *J* = 1.2, 9.6 Hz, 1 H), 5.46-5.41 (m, 1 H), 5.00 (t, *J* = 9.6 Hz, 1 H), 4.92 (d, *J* = 8.0 Hz, 1 H), 4.84 (d, *J* = 8.0 Hz, 1 H), 4.69 (dd, *J* = 2.8, 12.4 Hz, 1 H), 4.46-4.33 (m, 3 H), 4.26-4.15 (m, 3 H), 4.11 (dd, *J* = 4.0, 9.2 Hz, 1 H), 4.03 (dd, *J* = 2.0, 12.8 Hz, 1 H), 3.34-3.30 (m, 1 H), 3.18-3.13 (m, 1 H), 1.99 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.5, 169.8, 166.5, 166.3 (2 C), 166.2, 165.6 (2 C), 165.4, 134.9, 134.7, 134.6, 134.5 (2 C), 134.4, 134.1 (2 C), 130.8, 130.7, 130.6 (2 C), 130.5, 130.4 (3 C), 130.3, 130.2 (2 C), 129.9, 129.8 (2 C), 129.7, 129.6, 129.5, 129.4 (3 C), 100.9, 100.8, 92.9, 77.8, 77.2, 74.4, 73.7, 73.6, 73.2, 73.0 (2 C), 72.2, 69.9, 69.8, 67.5, 63.4, 62.6, 62.2, 20.8, 20.6; HRMS (ESI-TOF) calcd for $C_{78}H_{67}O_{25}BrNa$ $[M+Na]^+$ 1507.3053, found 1507.3034.

13-*O*-[2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol (2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl) ester (33)

To a solution of **4** (110 mg, 0.064 mmol) in a mixed solvent of $CHCl_3$ and H_2O (4 mL, v/v = 1 : 1) was added K_2CO_3 (26.4 mg, 0.19 mmol) and TBAB (41 mg, 0.13 mmol) at room temperature. After being stirred at the same temperature for 10 min, perbenzoylated glucosyl bromide **5** (84 mg, 0.13 mmol) was added. After being stirred at 40 ^oC for another 14 h, then the reaction mixture was cooled to room

temperature. Ethyl acetate was added to dilute the reaction, and the resultant solution was washed successively with water, brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* gave a residue, which was further purified by silica gel chromatography (PE/EA = 1.5 : 1) to deliver **33** (125 mg, 85%) as a white foam: $[\alpha]_D^{25}$ = +34.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.16-8.11 (m, 4 H), 8.04-7.83 (m, 17 H), 7.64-7.28 (m, 44 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 6.11 (t, *J* = 9.6 Hz, 1 H), 6.05-5.99 (m, 2 H), 5.90 (t, *J* = 9.2 Hz, 1 H), 5.81 (dd, *J* = 8.0, 10.0 Hz, 1 H), 5.76-5.66 (m, 4 H), 5.63 (dd, *J* = 7.6, 9.6 Hz, 1 H), 5.52 (d, *J* = 8.0 Hz, 1 H), 5.40 (d, *J* = 7.6 Hz, 1 H), 5.16 (brs, 1 H), 4.75 (d, *J* = 6.4 Hz, 1 H), 4.70-4.59 (m, 3 H), 4.56-4.49 (m, 3 H), 4.43-4.36 (m, 2 H), 4.26 (dd, *J* = 5.2, 10.4 Hz, 1 H), 4.18-4.10 (m, 2 H), 3.89 (t, *J* = 9.2 Hz, 1 H), 3.76-3.66 (m, 3 H), 3.46-3.38 (m, 1 H), 2.20 (dd, *J* = 3.6, 13.6 Hz, 1 H), 2.01-1.68 (m, 5 H), 1.61-1.28 (m, 6 H), 1.00 (s, 3 H), 0.78 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 175.5, 166.4, 166.3 (2 C), 166.2, 166.1, 166.0, 165.9, 165.8 (2 C), 165.7, 153.3, 138.9, 134.5 (2 C), 134.4, 134.3 (2 C), 134.0, 138.8 (2 C), 130.8, 130.7, 130.6, 130.5, 130.4 (5 C), 130.3 (3 C), 130.2 (2 C), 130.1, 130.0 (2 C), 129.9 (2 C), 129.8, 129.5, 129.4 (4 C), 129.3 (2 C), 129.2, 128.7, 127.2, 105.3, 101.6, 100.9, 99.8, 97.6, 92.2, 86.8, 81.2, 79.8, 78.3, 74.2, 74.0, 73.6, 73.5, 73.4, 72.5, 72.3, 72.2, 71.0, 70.9, 70.2, 69.4, 66.5, 64.4, 63.8, 63.3, 57.7, 54.8, 48.4, 44.7, 44.4, 42.9, 42.1, 40.1, 38.3, 38.2, 22.4, 20.9, 20.0, 16.8; HRMS (ESI-TOF) calcd for $C_{135}H_{122}O_{35}Na$ $[M+Na]^+$ 2326.7693, found 2326.7716.

Rebaudioside A (1)

To a solution of **33** (100 mg, 0.043 mmol) in a mixed solvent of CH_2Cl_2 and MeOH (3

mL, v/v = 1 : 1) was added TsOH (41 mg, 0.22 mmol) at room temperature. The resultant solution was stirred at the same temperature overnight, before Et_3N was added to quench the reaction. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel chromatography (PE/EA = 1 : 2) to obtained the diol intermediate, which was not characterized in detailed and applied directly in the next step. Thus obtained diol intermediate was then dissolved in absolute MeOH (2 mL), to which freshly prepared NaOMe (in absolute MeOH, 0.2 mL) was added at room temperature. The reaction mixture was stirred at the same temperature for 6 h, then Amberlite (H^+) was added to adjust the pH value of the reaction mixture to 7. Filtration was followed by concentration under reduced pressure to give the crude product, which was further purified by RP-18 silica gel column chromatography (MeOH/H_2O = 2 : 1) to afford **1** (34 mg, 82% for 2 steps) as a white solid: $[\alpha]_D^{25}$ = -18.1 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.67 (d, *J* = 4.8 Hz, 1 H), 5.27 (d, *J* = 3.2 Hz, 1 H), 5.25 (s, 1 H), 5.17 (d, *J* = 6.8 Hz, 1 H), 5.14 (d, *J* = 4.8 Hz, 1 H), 5.06-5.00 (m, 5 H), 4.93 (t, *J* = 2.4 Hz, 1 H), 4.73-4.69 (m, 2 H), 4.63-4.60 (m, 2 H), 4.53-4.50 (m, 2 H), 4.47 (dd, *J* = 8.4, 17.2 Hz, 1 H), 4.14 (t, *J* = 5.6 Hz, 1 H), 3.70-3.37 (m, 10 H), 3.26-2.94 (m, 15 H), 2.10-1.68 (m, 6 H), 1.46-1.34 (m, 6 H), 1.13 (s, 3 H), 1.06-0.89 (m, 3 H), 0.86 (s, 3 H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 176.85, 153.9, 104.5, 98.0, 95.5, 87.7, 86.3, 80.6, 79.0, 78.7, 78.4, 78.3, 78.1, 78.0, 77.1, 76.0, 75.0, 73.7, 71.6, 71.3, 70.7, 70.4, 62.7, 62.4, 62.1, 61.8, 57.1, 53.8, 47.5, 44.3, 43.8, 42.3, 41.5, 40.5, 39.6, 28.2, 36.7, 28.1, 22.0, 20.4, 19.2, 15.3; HRMS (ESI-TOF) calcd for $C_{44}H_{71}O_{23}$ $[M+H]^+$ 967.4381, found 967.4372.

13-*O*-[2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol

[2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl] ester (34)

Similar procedure as that used for the synthesis of **33** was adopted to conduct the coupling between **4** and **6** to afford **34** (1.2 g, 93%) as a white solid: $[\alpha]_D^{25}$ = +9.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.18-8.12 (m, 6 H), 8.00-7.87 (m, 16 H), 7.80 (dd, *J* = 1.6, 8.8 Hz, 2 H), 7.72-7.28 (m, 41 H), 6.14 (t, *J* = 8.8 Hz, 1 H), 6.03-5.97 (m, 2 H), 5.93 (d, *J* = 8.0 Hz, 1 H), 5.82-5.73 (m, 2 H), 5.68-5.57 (m, 4 H), 5.52-5.46 (m, 2 H), 5.44 (d, *J* = 8.0 Hz, 1 H), 5.31 (d, *J* = 8.0 Hz, 1 H), 5.17-5.12 (m, 2 H), 5.00 (t, *J* = 10.0 Hz, 1 H), 4.80 (dd, *J* = 2.4, 12.0 Hz, 1 H), 4.71-4.64 (m, 3 H), 4.58-4.50 (m, 3 H), 4.42-4.32 (m, 2 H), 4.24-4.19 (m, 2 H), 4.16-4.03 (m, 4 H), 3.85-3.75 (m, 2 H), 3.66-3.54 (m, 3 H), 3.40-3.34 (m, 1 H), 2.49 (d, *J* = 13.2 Hz, 1 H), 2.24 (d, *J* = 11.2 Hz, 1 H), 2.12-2.07 (m, 4 H), 1.96 (s, 3 H), 1.92-1.75 (m, 6 H), 1.65-1.38 (m, 6 H), 1.30 (s, 3 H), 0.96-0.62 (m, 11 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 175.2, 170.5, 170.0, 169.8, 166.5 (2 C), 166.4, 166.3 (2 C), 166.2, 166.0, 165.9, 165.8, 165.7, 165.5, 153.3, 139.0, 134.6, 134.4, 134.3, 134.1, 133.9, 133.8, 130.9, 130.8, 130.7, 130.6, 130.5, 130.4, 130.3, 130.2 (2 C), 130.0 (3 C), 129.9, 129.5, 129.4 (2 C), 129.2 (2 C), 128.7, 127.2, 105.2, 101.6, 101.5, 101.0, 99.9, 97.6, 91.8, 87.3, 80.9, 79.7, 78.4, 76.5, 75.2, 74.4, 74.1, 73.5, 73.2, 72.8, 72.7, 72.5, 72.3, 71.0, 70.8, 70.7, 69.4, 69.1, 66.6, 64.4, 64.1, 63.7, 62.2, 58.0, 54.8, 48.5, 44.7, 44.2, 42.8, 42.3, 41.0, 40.1, 38.7, 37.8, 22.3, 21.0, 20.8, 20.6, 20.2, 17.2; HRMS (ESI-TOF) calcd

for $C_{147}H_{138}O_{43}Na$ $[M+Na]^+$ 2614.8538, found 2614.8538.

Rebaudioside D (2)

Similar procedure as that used for the synthesis of **1** was applied to convert **34** to **2** (260 mg, 81% for 2 steps) as a white solid: $[\alpha]_D^{25}$ = -22.0 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, pyridine-d_5) δ 6.37 (d, *J* = 6.4 Hz, 1 H), 5.83 (s, 2 H), 5.69 (s, 1 H), 5.63 (d, *J* = 7.6 Hz, 1 H), 5.53 (d, *J* = 7.6 Hz, 1 H), 5.45 (d, *J* = 7.6 Hz, 1 H), 5.14 (d, *J* = 7.2 Hz, 1 H), 5.02 (s, 1 H), 4.64-3.89 (m, 23 H), 2.77 (d, *J* = 12.8 Hz, 1 H), 2.54 (d, *J* = 11.2 Hz, 1 H), 2.28-1.68 (m, 13 H), 1.43 (s, 3 H), 1.16 (s, 3 H), 1.01 (d, *J* = 12.0 Hz, 1 H), 0.89 (d, *J* = 6.4 Hz, 1 H), 0.77 (dd, *J* = 10.4, 14.4 Hz, 1 H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 175.8, 154.0, 105.7, 104.8, 104.6, 104.5, 97.8, 93.6, 88.1, 86.6, 81.0, 80.8, 79.0, 78.6, 78.4 (2 C), 78.2, 78.1, 78.0, 77.4, 76.4, 76.2, 75.3, 72.3, 72.0, 71.6, 70.8, 69.9, 63.2, 63.0, 62.3 (2 C), 62.1, 57.4, 53.9, 49.7, 47.6, 44.3, 44.1, 42.2, 41.8, 40.6, 39.7, 37.8, 29.2, 22.2, 20.5, 20.0, 16.8; HRMS (ESI-TOF) calcd for $C_{50}H_{80}O_{28}Na$ $[M+Na]^+$ 1151.4728, found 1151.4740.

13-*O*-[2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranosyl]-steviol

[2,3-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,6-di-*O*-acetyl-β-D-glucopyranosyl] ester (35)

Similar procedure as that used for the synthesis of **33** was applied to conduct the condensation of **4** and **7** to afford **35** (195 mg, 86%) as a white solid: $[\alpha]_D^{25}$ = +45.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.34-8.29 (m, 4 H), 8.17-8.14 (m, 4 H), 7.99-7.86 (m, 27 H), 7.81-7.70 (m, 6 H), 7.68-7.36 (m, 41 H), 7.31-7.28 (m, 3 H),

6.02-5.94 (m, 4 H), 5.76-5.50 (m, 11 H), 5.41 (d, *J* = 8.0 Hz, 1 H), 5.30 (d, *J* = 7.6 Hz, 1 H), 5.12 (brs, 1 H), 5.09 (d, *J* = 7.6 Hz, 1 H), 4.96-4.91 (m, 2 H), 4.73 (dd, *J* = 2.0, 5.2 Hz, 1 H), 4.64 (d, *J* = 2.0 Hz, 1 H), 4.52-4.30 (m, 7 H), 4.27 (dd, *J* = 5.6, 12.4 Hz, 1 H), 4.18-3.98 (m, 8 H), 3.80-3.72 (m, 1 H), 3.64-3.55 (m, 3 H), 3.53 (t, *J* = 10.0 Hz, 1 H), 3.35-3.29 (m, 1 H), 2.35 (d, *J* = 13.6 Hz, 1 H), 2.26 (dd, *J* = 2.0, 10.4 Hz, 1 H), 2.15-2.05 (m, 2 H), 1.99-1.40 (m, 15 H), 1.27 (s, 3 H), 1.21-1.18 (m, 2 H), 0.97-0.84 (m, 6 H), 0.79 (td, *J* = 3.6, 13.6 Hz, 1 H), 0.66 (dd, *J* = 10.4, 14.4 Hz, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ175.4, 170.5, 169.8, 166.6, 166.5, 166.4 (2 C), 166.3 (2 C), 166.2, 165.9 (2 C), 165.8, 165.7 (2 C), 165.5, 165.4, 165.3, 153.4, 139.0, 134.5, 134.4, 134.3, 134.2, 134.1, 133.9, 133.8, 130.8 (3 C), 130.7 (2 C), 130.5 (2 C), 130.4 (3 C), 130.3 (2 C), 130.1 (2 C), 130.0 (2 C), 129.9, 129.8, 129.7 (2 C), 129.5 (3 C), 129.4 (3 C), 129.2, 128.7, 127.2, 105.2, 101.0, 99.9, 97.6, 87.1, 81.0, 80.5, 79.8, 78.4, 77.0, 74.1, 73.9, 73.8, 73.7, 73.5, 73.0, 72.3, 71.0, 70.7, 70.5, 70.3, 68.3, 66.4, 64.4, 64.0, 63.7, 62.4, 58.0, 54.9, 48.5, 44.6, 44.1, 42.9, 42.3, 41.0, 40.1, 38.6, 37.8, 21.0, 20.8, 20.1, 17.1; HRMS (ESI-TOF) calcd for $C_{179}H_{163}O_{51}$ $[M+H]^+$ 3130.3251, found 3130.3266.

Rebaudioside M (3)

Similar procedure as that used for the synthesis of **1** was applied to convert **35** to **3** (55 mg, 81% for 2 steps) as a white solid: $[\alpha]_D^{25}$ = -12.5 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, pyridine-d_5) δ 6.47 (d, *J* = 8.0 Hz, 1 H), 5.86 (d, *J* = 6.8 Hz, 1 H), 5.81 (s, 1 H), 5.73 (d, *J* = 8.0 Hz, 2 H), 5.55 (d, *J* = 7.6 Hz, 2 H), 5.51 (d, *J* = 8.0 Hz, 1 H), 5.34 (d, *J* = 8.0 Hz, 1 H), 5.09 (t, *J* = 8.8 Hz, 1 H), 4.92 (brs, 1 H), 4.72 (d, *J* = 10.8

Hz, 1 H), 4.59 (dd, *J* = 8.4, 9.2 Hz, 3 H), 2.80 (d, *J* = 11.2 Hz, 2 H), 2.48 (dd, *J* = 12.8, 13.6 Hz, 1 H), 2.34 (dd, *J* = 15.6, 16.4 Hz, 1 H), 1.42 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 176.6, 153.0, 104.6, 104.5, 103.9, 103.8, 103.6, 96.0, 94.6, 88.3, 87.6, 87.3, 81.1, 78.4, 78.2 (2 C), 77.8, 77.7, 77.5, 77.4 (2 C), 76.6, 75.5, 75.3, 75.2, 73.3, 72.9, 71.0, 70.8, 70.1, 69.8, 63.7, 62.3, 61.8, 61.5, 57.1, 46.2, 44.0, 43.0, 42.3, 40.9, 40.0, 39.5, 38.2, 28.0, 23.2, 19.9, 19.4, 16.5; HRMS (ESI-TOF) calcd for $C_{56}H_{89}O_{33}$ $[M-H]^-$ 1289.5292, found 1289.5281.

Associated content

The Supporting Information is available free of charge on the ACS Publications website at DOI:.

^{13}C NRM comparison between synthetic samples and authentic samples reported in literature, copies of NMR spectra of all new compounds, and X-ray crystallographic data for **8b'** and **10** (CIF)

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