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Synthesis of Δ^{20}-Ginsenosides Rh_4, (20*E*)-Rh_3, Rg_6 and Rk_1: A General Approach to Access Dehydrated Ginsenosides

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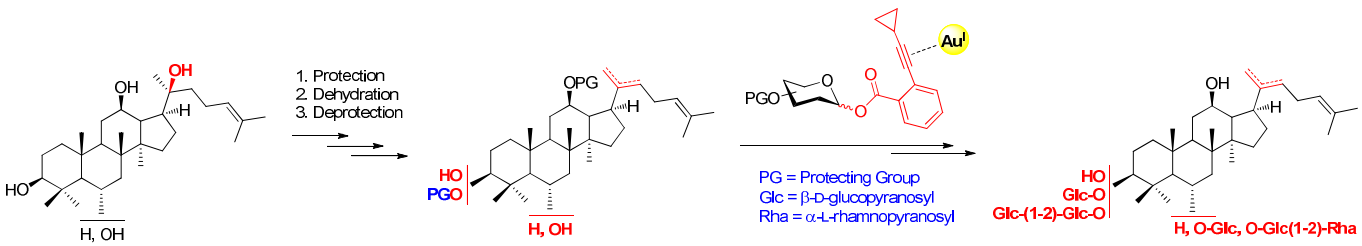


ABSTRACT: Four representative Δ^{20}-ginsenosides, namely ginsenosides Rh_4 (**1**), (20*E*)-Rh_3 (**2**), Rg_6 (**3**) and Rk_1 (**4**) from *Panax* Ginseng were chemically synthesized for the first time. Dehydration of the naturally occurring 20(*S*)-protopanaxatriol and 20(*S*)-protopanaxadiol provided all type of Δ^{20}-sapogenins, which were separated due to a judicious choice of protecting groups. The Δ^{20}-sapogenins were then directly glycosylated with glycosyl *ortho*-alkynylbenzoate donors under the catalysis of $Ph_3PAuNTf_2$ as key steps. The neutral conditions of the glycosylations were crucial to prevent the acid-labile$\Delta^{20,21}$ double bond from isomerization.

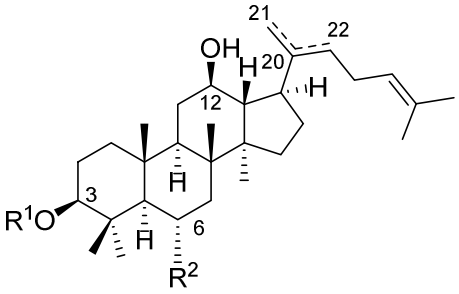
INTRODUCTION

Ginseng is a slow-growing perennial plant belonging to the genus *Panax* of the family Araliaceae which has

been used as an herbal remedy in Asia for its tonic and restorative actions for thousands of years. Its beneficial effects have been widely reported in the literature and are attributed to ginsenosides, triterpenoid saponins present in all parts of the plant.[1] While ginseng can be consumed in its raw form, preliminary treatment is usually applied in order to extend its preservation, reduce or eliminate the toxicity and side effects of the raw material and enhance its medical efficacy. The steam-heating and/or sun-drying of the ginseng's roots are two traditional processes used to produce white and red ginsengs. Such processing methods modify the content of ginsenosides and thus alter the medicinal effects of the plant.[2] Indeed, such operations mainly undergo cleavage of the glycosidic bond at the C-20 of dammarane-type ginsenosides, dehydration of the resulting hydroxyl group at C-20 and epoxidation/hydroxylation of double bonds, resulting in a wide range of dehydrated and polyoxygenated dammarane-type ginsenosides, which are either entirely absent or present only in trace amounts in the raw material.[3] Δ^{20}-ginsenosides are dehydrated saponins in which the side chain of the dammarane-type sapogenins, either 20(*S*)-protopanaxadiol (PPD) or 20(*S*)-protopanaxatriol (PPT), contains a carbon-carbon double bond at the C-20. The double bond can be located between the C20-C21 or between the C20-C22 with *E*- or *Z*-configuration, as exemplified by ginsenosides Rh_4 (**1**), (20*E*)-Rh_3 (**2**), Rg_6 (**3**) and Rk_1 (**4**) (Fig. 1).[3,4,5,6] Among them, Rh_4, Rh_3 and Rk_1 have shown potent anti-tumor activities in different cancer cell lines either by their cytotoxicity or by their capacity to induce apoptosis.[7,8,9] Moreover, Rh_4 demonstrated hepatocytoprotective and nephroprotective activities,[10] as well as immunological adjuvant effect.[11] (20*E*)-Rh_3 exhibited potent inhibitory effect against dermatitis induced by oxazolone,[12] whereas Rk_1 displayed strong anti-vascular permeability and anti-platelet aggregation activities,[13] and a potential atopic dermatitis effect.[14] Recently, Rk_1 and other Δ^{20}-ginsenosides

have also been isolated from *Centella asiatica* (L.) Urban (Apiaceae family),[15] and we believe that novel structures will be reported in the future due to the improvement of analytical techniques.

As plant extracts, ginsenosides are produced in heterogeneous mixtures and in low yields, which renders their isolation difficult and hampers their biological studies. To overcome these difficulties, our group has devoted a persistent effort on the chemical syntheses of all kind of ginsenosides with the aim of producing homogeneous compounds in appreciable amounts and hence, accelerates their structure-activity relationship study.[16,17] More recently, we reported a convenient and effective synthesis of natural and synthetic ocotillol-type ginsenosides.[18] As a part of our continuous effort, we report herein the first chemical syntheses of Δ^{20}-ginsenosides Rh_4 (**1**), (20*E*)-Rh_3 (**2**), Rg_6 (**3**) and Rk_1 (**4**), which, to the best of our knowledge, have never been reported so far. The syntheses were conveniently achieved via a direct glycosylation between the appropriate Δ^{20}-sapogenin acceptor and a glycosyl *ortho*-alkynylbenzoate donor under gold(I)-catalysis. The neutral condition of this protocol, developed in our group, is essential to keep intact the acid-labile C20-C21 double bond.[19]



Name	Δ	R^1	R^2
ginsenoside Rh_4 (**1**)	20,22(*E*)	H	*O*-Glc
isoginsenoside Rh_3 (**2**)	20,22(*E*)	Glc	H
ginsenoside Rg_6 (**3**)	20,21	H	*O*-Glc^2-^{1}Rha
ginsenoside Rk_1 (**4**)	20,21	Glc^2-^{1}Glc	H

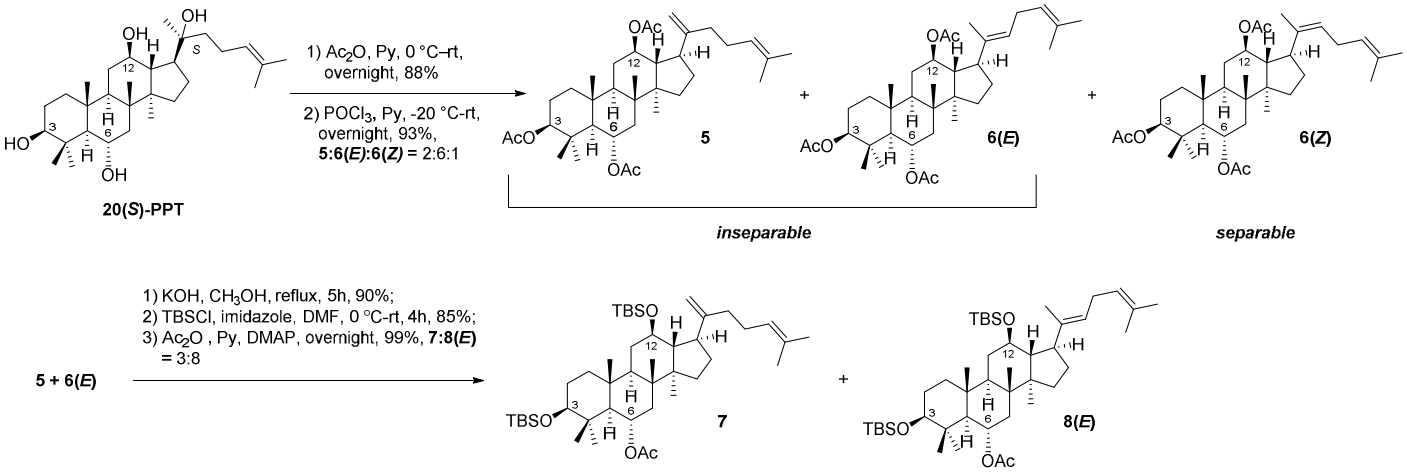
Figure 1. Representative Δ^{20}-ginsenosides (**1-4**). Glc = β-*D*-glucopyranosyl; Rha = α-*L*-rhamnopyranosyl.

RESULTS AND DISCUSSION

The synthesis commenced with the preparation and separation of all type of Δ^{20}-sapogenins via dehydration of the 20-OH of the corresponding partially protected 20(*S*)-PPT and 20(*S*)-PPD. Previously, we reported the reactivity sequence of the four hydroxyl groups of 20(*S*)-PPT to be 12-OH > 3-OH > 6-OH >> 20-OH.[17] Based on this result, the 3-, 6- and 12-OHs of 20(*S*)-PPT were selectively acetylated, providing the corresponding 3,6,12-tri-OAc-20(*S*)-ol PPT in 88% yield, which was then subjected to dehydration (Scheme 1). We have already observed that under glycosylation conditions promoted by TMSOTf or AgOTf/2,6-lutidine,[17b] this alcohol undergoes dehydration with modest stereoselectivity, the three possible Δ^{20}-isomers being isolated in mixture. Aiming to dehydrate in a stereoselective manner, other reaction conditions, including $TsOH.H_2O$,[20] $POCl_3$/pyridine,[21] PPh_3/I_2,[22] and Burgess' reagent,[23] were attempted. However, depending on the conditions, modest stereoselectivity was observed and a mixture of Δ^{20}-sapogenins **5**/**6(*E*)**/**6(*Z*)** was isolated in a comparable ratio, **6(*E*)** being the major isomer. The best yield was obtained using $POCl_3$/pyridine (93%), with a **5**/**6(*E*)**/**6(*Z*)** ^{1}H NMR ratio of 2:6:1, respectively. At this step, a careful column chromatography enabled us to separate and isolate **6(*Z*)** in 11% yield for which the position of the double bond between the C20-C22 with a *Z*-configuration was confirmed by X-ray diffraction analysis (CCDC1414226, Fig. **2**. left). However, olefins **5** and **6(*E*)** remained inseparable at this stage. Consequently, a modification of the protecting group pattern was then carried out in order to separate these two isomers. After full deacetylation under basic conditions (KOH, CH_3OH), the 3- and 12-OHs were selectively protected as *tert*-butyldimethyl-silyl ethers (TBSCl, imidazole, DMF) and the remaining 6-OHs

were acetylated (Ac_2O, Py, DMAP). At this stage, the corresponding 3,12-di-OTBS-6-OAc olefins **7** and **8(*E*)** could be separated and isolated as pure compounds in 21% and 55% yields, respectively, over 3 steps.

Scheme 1. Synthesis of Δ^{20}-PPT sapogenins.



As depicted in Scheme 2, a similar approach was adopted for the synthesis of Δ^{20}-PPD sapogenins. The 3- and 12-OHs of 20(*S*)-PPD were selectively protected as acetates in 82% yield. Then, dehydration using $POCl_3$/pyridine provided a mixture of the three isomers **9**/**10(*E*)**/**10(*Z*)** in 85% yield and in a ^{1}H NMR ratio of 2:6:1, respectively. As previously, the $\Delta^{20,22(Z)}$-isomer **10(*Z*)** could be separated from **9** and **10(*E*)**, inseparable at this stage. In that case, full deacetylation enabled us to separate and isolate **11** and **12(*E*)** in 28% and 65% yields, respectively. A single crystal of **12(*E*)** was subjected to X-ray diffraction analysis and confirmed the position of the double bond between the C20-C22 as well as the *E*-configuration (CCDC1414221, Fig. **2**. right).

Scheme 2. Synthesis of Δ^{20}-PPD sapogenins.

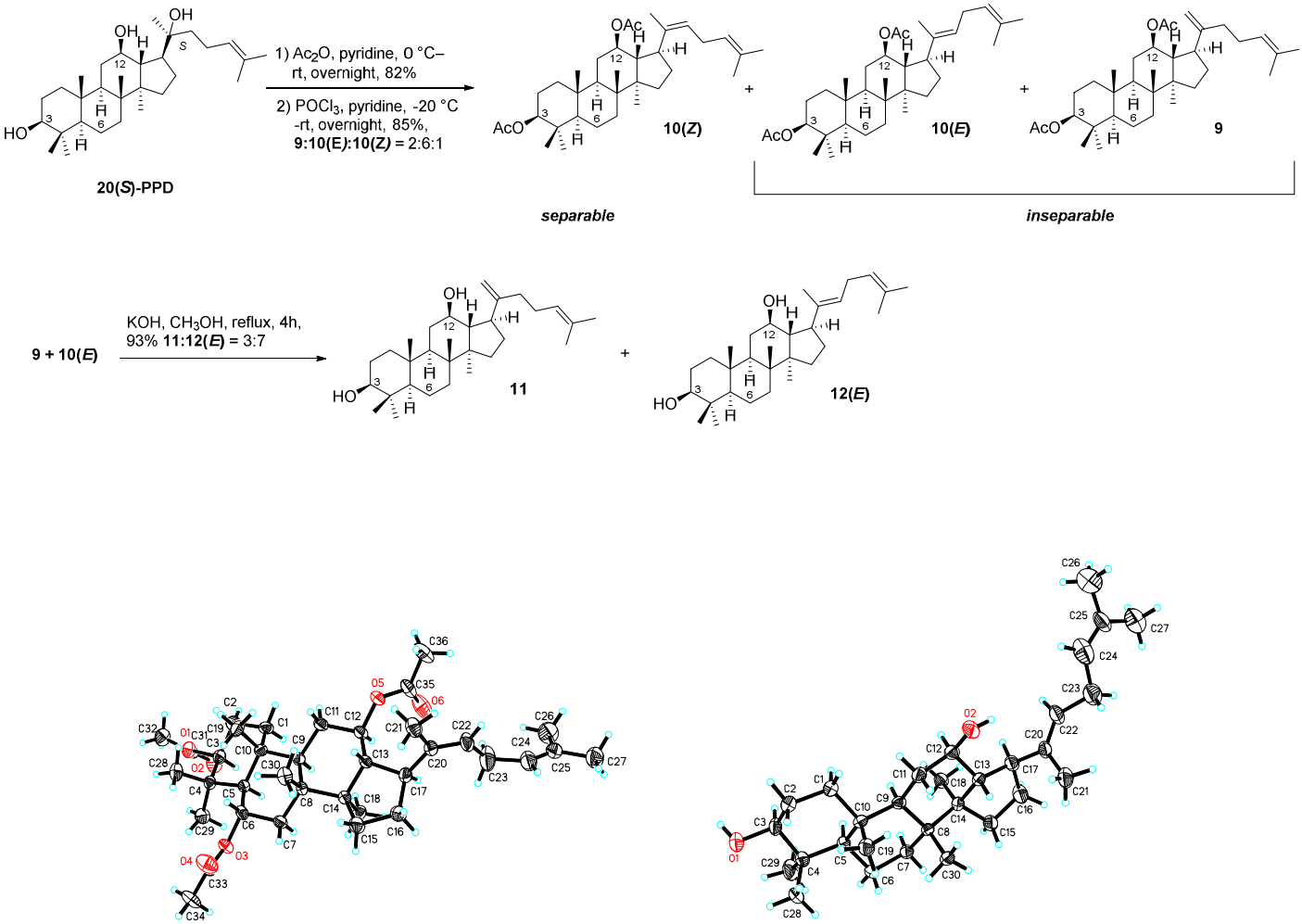


Figure **2**. The ORTEP drawing of **6(*Z*)** (left, CCDC1414226) and **12(*E*)** (right, CCDC1414221) were represented with thermal ellipsoids shown at 30% probability; the solvent of crystallization have been omitted for clarity.

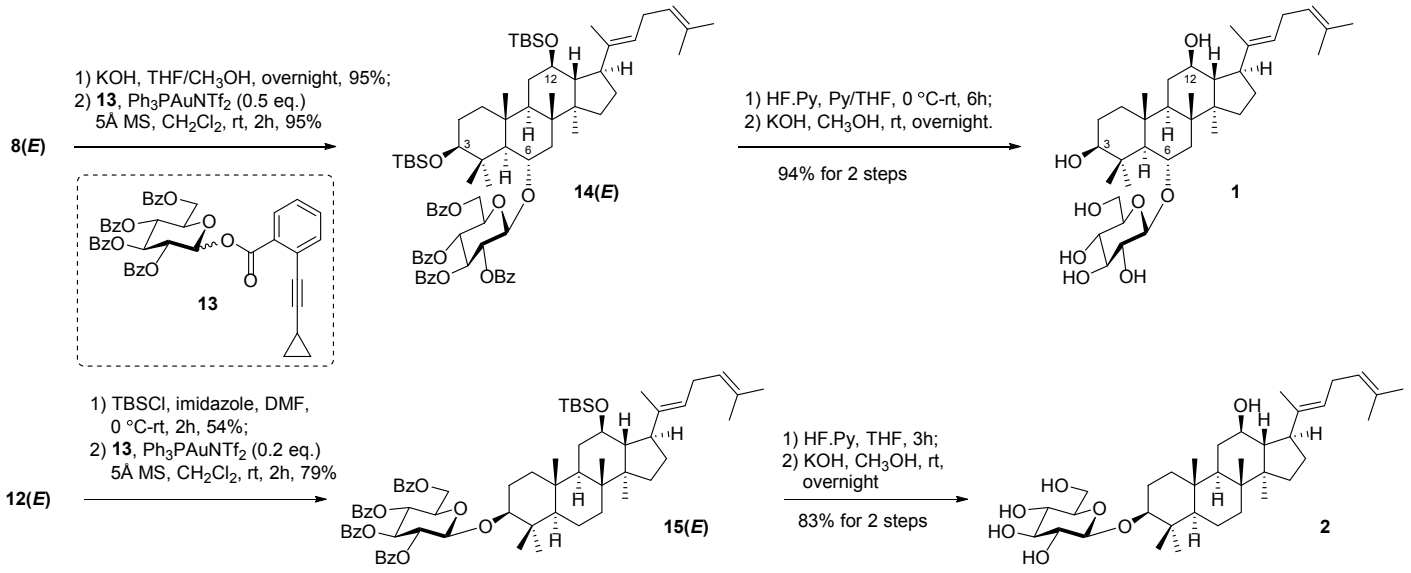
The preparation and separation of all type of Δ^{20}-sapogenins paved the way for the synthesis of Δ^{20}-ginsenosides **1**-**4**. As a key step, the sugar units were attached to the sapogenins by a gold(I)-catalyzed glycosylation with glycosyl *ortho*-alkynylbenzoate donors. A benzoyl group was installed at the 2-position of the donors in order to ensure the required 1,2-trans glycosidic linkage.

As illustrated in Scheme 3, the acetyl group at the 6 position of Δ^{20}-genin **8(*E*)** was removed under basic

condition (95%) and the corresponding 6-OH acceptor was coupled with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl *ortho*-cyclopropylethynylbenzoate donor **13** under the promotion of $Ph_3PAuNTf_2$ in CH_2Cl_2 at room temperature. Given the low reactivity of the 6-OH, in order to increase the glycosylation yield while reducing the orthoester by-product as discovered previously,[17] higher loading of promoter (0.5 eq.) was employed and the desired 6-*O*-glucoside **14(*E*)** was isolated in an excellent 95% yield. It is worth mentioning that this glycosylation could also be performed at 40 ºC without affecting the yield and the stable C20-C22 double bond. Then, desilylation was achieved with a HF·pyridine complex in Py/THF at room temperature. Under these conditions, even the stable 3-OTBS was cleanly removed. Finally, saponification of the benzoyl groups afforded ginsenoside Rh_4 **(1)** in an excellent 94% yield over 2 steps.

Similarly, the 12-OH of **12(*E*)** was protected as silyl ether (54%) and the remaining 3-OH was glycosylated with **13** under the promotion of $Ph_3PAuNTf_2$ in CH_2Cl_2. The 3-OH of PPD-sapogenins being more reactive than the 6-OH of PPT-sapogenins,[17] the glycosylation proceeded smoothly with 0.2 eq. of promoter at room temperature and provided the corresponding 3-*O*-glucoside **15(*E*)** in 79% yield. The TBS group was then cleanly removed with a HF·pyridine complex and subsequent saponification of the benzoyl groups furnished isoginsenoside Rh_3 **(2)** in 83% over 2 steps.

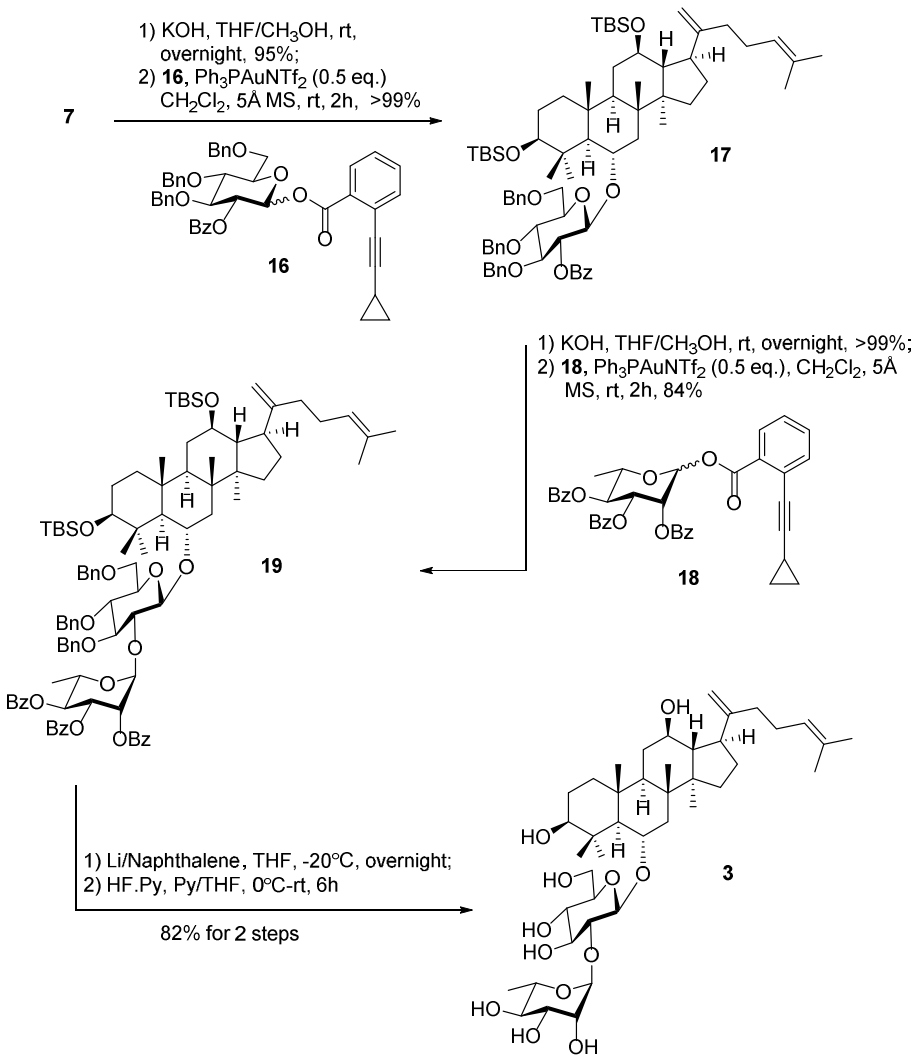
Scheme 3. Synthesis of **1** and **2**



For the synthesis of ginsenosides Rg_6 (**3**) and Rk_1 (**4**), a stepwise glycosylation strategy was adopted in order to control the 1,2-trans configuration of the two glycosidic bonds. As depicted in Scheme 4, the acetyl group of Δ^{20}-genin **7** was firstly removed under basic conditions, yielding the corresponding 3,12-di-OTBS-6-ol (95%). Due to our stepwise glycosylation strategy, the "super armed" 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-*D*-glucopyranosyl *ortho*-cyclopropylethynylbenzoate **16** was used as a donor in order to improve the nucleophilicity of the future 2'-OH acceptor.[17] The coupling between the 3,12-di-OTBS-6-ol sapogenin and **16** proceeded smoothly with 0.5 eq. of $Ph_3PAuNTf_2$ at room temperature and furnished the 6-*O*-glucoside **17** in quantitative yield. It is worth mentioning that heating to 40 ºC resulted in partial isomerization of the C20-C21 double bond, thus decreasing the yield of the desired glycoside. Removal of the benzoyl group under basic conditions (> 99%) afforded the corresponding 2'-OH acceptor, which was effectively coupled with 2,3,4-tri-*O*-benzoyl-*L*-rhamnopyranosyl *ortho*-cyclopropylethynylbenzoate donor **18**. Under the promotion of 0.5 eq. of $Ph_3PAuNTf_2$, the desired

fully protected Δ^{20}-ginsenoside **19** was obtained in 84% yield. At this point, the deprotection sequence rose to be crucial for preserving the C=C bond from isomerization and reduction. Indeed, the usual hydrogenolytic conditions (H_2/Pd cat.) employed to remove benzyl groups would also reduce the C=C bonds.[24] Consequently, other reducing systems such as Li/NH_3 and Li/naphthalene were tested.[25,26] In any order, Li/NH_3 removed the benzyl groups but also reduced the C=C bonds. The system Li/naphthalene did not removed the benzyl groups cleanly if the TBS and benzoyl groups were previously removed. However, the same system worked smoothly at -20ºC on the fully protected Δ^{20}-ginsenoside **19**. Indeed, the reduction of the three benzyl groups occurred first, followed by the cleavage of the three benzoyl groups after a prolonged reaction. Final desilylation with a HF·pyridine complex provided the desired ginsenoside Rg_6 **(3)** in 82% yield over 2 steps.

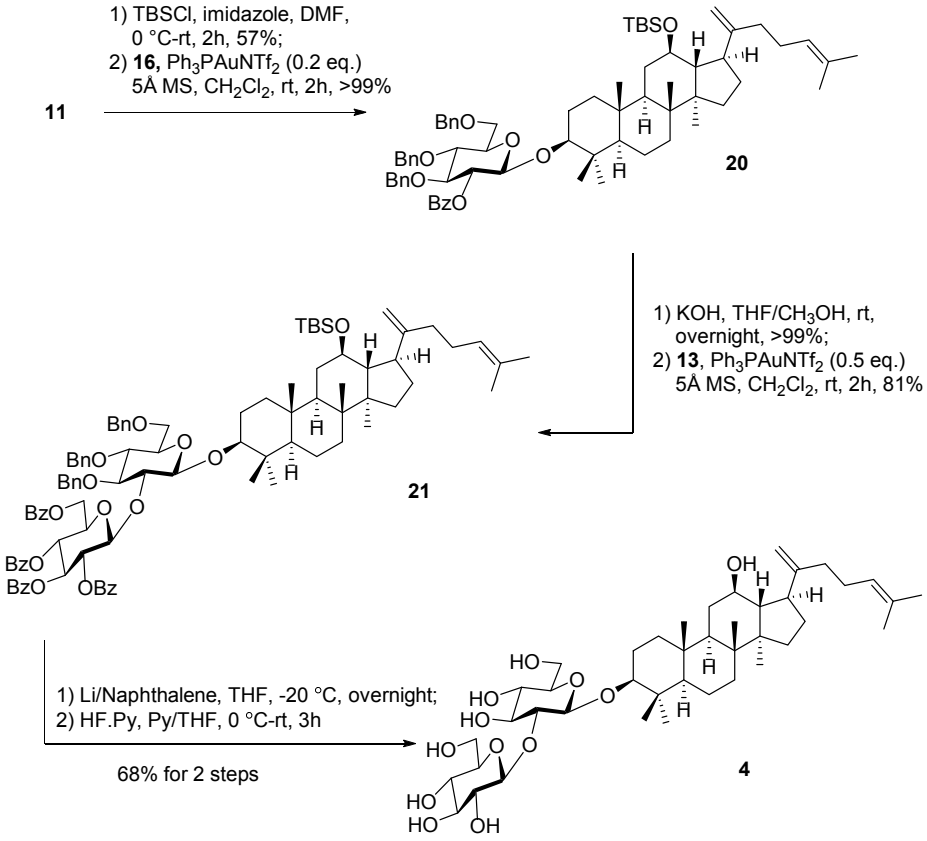
Scheme 4. Synthesis of **3**



Following a similar approach, the 12-OH of Δ^{20}-genin **11** was firstly protected as silyl ether (57%, Scheme 5). The remaining 3-OH was coupled with donor **16** under the promotion of $Ph_3PAuNTf_2$ (0.2 eq.) at room temperature, affording the corresponding 3-*O*-glucoside **20** in quantitative yield. Subsequent saponification provided the corresponding 2'-OH acceptor which was then glycosylated with donor **13** (0.5 eq. of $Ph_3PAuNTf_2$), furnishing the fully protected Δ^{20}-ginsenoside **21** in a good 81% yield (2 steps). Concerning the deprotection sequence, similar results as the ones obtained with **19** were noted with **21**. The three benzyl and four benzoyl groups were smoothly removed with Li/naphthalene at -20 ºC without affecting the C=C

bonds. The TBS group was finally cleaved with a HF·pyridine complex, leading to ginsenosides Rk_1 **(4)** in 68% yield over 2 steps.

Scheme 5. Synthesis of **4**



CONCLUSION

In conclusion, we reported the first chemical syntheses of four representative Δ^{20}-ginsenosides, namely ginsenosides Rh_4 (**1**), (20*E*)-Rh_3 (**2**), Rg_6 (**3**) and Rk_1 (**4**). Our strategy relied on (1) the preparation and separation of all type of Δ^{20}-sapogenins, (2) a gold(I)-catalyzed glycosylation between the Δ^{20}-sapogenins and glycosyl *ortho*-alkynylbenzoate donors, (3) orthogonal deprotection which prevents the C=C bonds

present on the Δ^{20}-sapogenins from isomerization and reduction. Following this rational, syntheses of Δ^{20}-ginsenosides **1-4** were conveniently and effectively achieved in longest 7-11 linear steps. We assume that this strategy represents a general and valuable approach to access dehydrated ginsenosides.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under N_2 or Ar with anhydrous solvents in flame-dried glassware, unless otherwise noted. All glycosylation reactions were performed in the presence of 5Å molecular sieves, which were flame-dried under high vacuum immediately before use in the reaction. Glycosylation solvents were dried using a solvent purification system and used directly without further drying. The chemicals used were reagent grade as supplied, except where noted. Analytical thin-layer chromatography was performed using silica gel 60 F254 glass plates. Compound spots were visualized by UV light (254 nm) and by heating with a solution with 10% H_2SO_4 in ethanol. Flash column chromatography was performed on silica gel and RP-18. NMR spectra were referenced using Me_4Si (0 ppm), residual $CDCl_3$ (^{1}H NMR δ = 7.26 ppm, ^{13}C NMR δ = 77.23 ppm), or C_5D_5N (^{1}H NMR δ = 7.22 ppm, ^{13}C NMR δ = 123.87 ppm). Peak and coupling constant assignments are based on ^{1}H NMR, ^{1}H-^{1}H COSY, and ^{1}H-^{13}C HSQC experiments. Splitting patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet), and brs (broad singlet) for ^{1}H NMR data. High-resolution mass spectra were recorded on ESI-TOF and MALDI-FT spectrometers. Optical rotations were measured on a polarimeter using either $CHCl_3$ or CH_3OH as solvent.

Protopanaxadiol (20(*S*)-PPD) *and protopanaxatriol* (20(*S*)-PPT) were prepared readily from the crude

extract of ginseng following the known procedure.[17,27] Glucosyl donors **13**, **16**, and rhamnosyl donor **18** were synthesized according to literature procedures.[19,28]

General procedure for gold(I)-catalyzed glycosylation with *ortho*-alkynylbenzoate donors. To a flask were added the glycosyl donor, the Δ^{20}-sapogenin acceptor and freshly activated 5Å molecular sieves (weight equal to the combined weight of the donor and acceptor). The flask was evacuated and refilled with Ar and this process was repeated for three times. Then, CH_2Cl_2 was added and the resulting mixture was stirred at room temperature for 30 min. After 30 min, PPh_3AuNTf_2 was added and the mixture was stirred at room temperature until control TLC showed complete consumption of the donor. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated under vacuum. The resulting residue was purified by silica gel column chromatography to provide the coupled glycosides.

General saponification procedure. KOH was added to a solution of the esterified compound in CH_3OH (and/or THF) and the mixture was stirred at room temperature or reflux. When control TLC showed complete consumption of the esterified compound, the reaction mixture was cooled to room temperature and the solvents were evaporated under reduced pressure. The resulting residue was then purified by silica gel column chromatography to provide the corresponding alcohol.

3β,6α,12β-Tri-O-acetyl-5R, *9R*, *13R-dammarane-(Z)-20(22),24(25)-diene* ***(6Z)***. Ac_2O (3.0 mL) was added dropwise to a solution of 20(*S*)-PPT (500 mg, 1.05 mmol) in pyridine (3.0 mL) at 0 ^oC. After complete

addition, the ice bath was removed and the resulting mixture was stirred at room temperature overnight. The mixture was then diluted with EtOAc and successively washed with saturated aqueous $NaHCO_3$, 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to provide the 3β,6α,12β-tri-*O*-acetyl-5*R*, 9*R*, 13*R*-20(*S*)-protopanaxatriol (557 mg, 88%) as a white solid.

3β,6α,12β-Tri-*O*-acetyl-20(*S*)-protopanaxatriol (557 mg，0.92 mmol) was dissolved in pyridine (30 mL) and $POCl_3$ (3.0 mL) was added dropwise at -20 ^oC. The resulting mixture was allowed to warm to room temperature and was stirred overnight. The mixture was then diluted with EtOAc and successively washed with water, 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. At this stage, ^1H NMR analysis showed that the crude residue is composed of a mixture of **5/6(*E*)/6(*Z*)** with a ^1H NMR ratio of 2:6:1. The crude residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 15:1) to provide an inseparable mixture of **5/6(*E*)** (444 mg, 82%) and **6(*Z*)** (57 mg, 11%) as a white solid.

6(*Z*): $[\alpha]^{25}_D$ = +12.2 (*c* 1.0, $CHCl_3$); m.p. 175-178 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40-5.31 (m, 1H), 5.08-4.97 (m, 2H), 4.91 (td, *J* = 11.5, 8.3 Hz, 1H), 4.47 (dd, *J* = 12.1, 4.4 Hz, 1H), 2.98 (dd, *J* = 16.2, 10.1 Hz, 1H), 2.67 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.58 (dd, *J* = 14.9, 7.2 Hz, 1H), 2.05 (s, 6H), 1.87 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.3, 170.2, 137.2, 131.0, 124.0, 123.6, 80.0, 77.2, 73.9, 70.3, 58.6, 50.9, 49.7, 46.5, 42.4, 40.9, 39.3, 38.3, 37.7, 32.0, 30.3, 28.0, 27.8, 26.4, 25.7, 23.1, 22.0, 21.2, 20.8, 17.6, 17.2, 16.84, 16.77,

16.6; IR: $\tilde{\nu}$ = 3444, 2952, 2872, 1732, 1459, 1399, 1370, 1244, 1162, 1147, 1122, 1105, 1071, 1019, 975, 922, 900, 867, 807, 659, 606, 547, 512, 493 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{57}O_6$ $[M+H]^+$ 585.4150, found 585.4151.

3β,12β-Di-O-tert-butyldimethylsilyl-6α-O-acetyl-5R, *9R*, *13R-dammarane-20(21),24(25)-diene (7) and 3β,12β-di-O-tert-butyldimethylsilyl-6α-O-acetyl-5R*, *9R*, *13R-dammarane-(E)-20(22),24(25)-diene (**8E**).* The inseparable mixture of **5/6(*E*)** (1.012 g, 1.76 mmol) was subjected to the general saponification procedure with KOH (146 mg, 2.6 mmol) in CH_3OH (10 mL) at reflux for 5 hours. After workup, purification by silica gel column chromatography (petroleum ether/EtOAc, 3:1) provided the corresponding of 3β,6α,12β-triols (724 mg, 90%) in mixture as a white solid.

The two 3β,6α,12β-triols (724 mg, 1.58 mmol) and imidazole (516 mg, 7.9 mmol) were dissolved in DMF (7.0 mL) and cooled to 0 ^oC (ice bath). TBSCl (1.19 g, 7.9 mmol) was then added and the resulting mixture was stirred at room temperature for 4 hours and TLC showed complete consumption of the 3β,6α,12β-triols. The mixture was then diluted with EtOAc and successively washed with 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 20:1) to provide the corresponding 3β,12β-di-OTBS-6α-ols (922 mg, 85%) in mixture as a white solid.

Ac_2O (2.0 mL) was added dropwise to a solution of the two 3β,12β-di-OTBS-6α-ols (200 mg, 0.29 mmol) and DMAP (17.7 mg, 0.15 mmol) in pyridine (5.0 mL) at 0 ^oC. After complete addition, the ice bath was removed and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with

EtOAc and successively washed with saturated aqueous $NaHCO_3$, 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 250:1) to afford **7** (60 mg, 28%) and **8(*E*)** (155 mg, 72%) separately, as white solids.

7: $[\alpha]^{25}_D$ = +28.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (td, *J* = 10.3, 5.1 Hz, 1H), 5.16 (brs, 1H), 4.75 (s, 1H), 4.60 (s, 1H), 3.53 (td, *J* = 10.1, 4.6 Hz, 1H), 3.17 (dd, *J* = 10.9, 4.5 Hz, 1H), 2.50 (td, *J* = 10.7, 6.1 Hz, 1H), 2.04 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.83 (s, 9H), 0.80 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), -0.00 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 152.5, 131.1, 124.8, 107.6, 78.9, 73.2, 70.9, 58.8, 50.9, 50.1, 49.2, 47.8, 42.8, 40.8, 39.4, 39.2, 38.6, 32.7, 32.5, 32.1, 30.7, 30.6, 27.4, 26.2, 26.0, 25.9, 25.7, 22.0, 18.13, 18.08, 17.7, 17.3, 16.93, 16.87, 16.1, -3.6, -4.3, -4.7, -5.0; IR: $\tilde{\nu}$ = 2957, 2933, 2855, 1724, 1637, 1472, 1463, 1387, 1362, 1248, 1191, 1101, 1061, 1023, 969, 937, 921, 896, 884, 836, 774, 670, 630, 614, 574, 512, 478 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{80}O_4Si_2Na$ $[M+Na]^+$ 751.5487, found 751.5481.

8(*E*): $[\alpha]^{25}_D$ = +29.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (td, *J* = 10.5, 4.6 Hz, 1H), 5.11 (t, *J* = 6.8 Hz, 1H), 5.03 (t, *J* = 6.6 Hz, 1H), 3.55 (td, *J* = 10.2, 4.8 Hz, 1H), 3.18 (dd, *J* = 11.2, 4.7 Hz, 1H), 2.75-2.65 (m, 1H), 2.64-2.56 (m, 1H), 2.44 (td, *J* = 10.7, 6.4 Hz, 1H), 2.04 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.99 (s, 3H), 0.90 (s, 12H), 0.84 (s, 9H), 0.81 (s, 3H), 0.06 (s,3H), 0.05 (s, 3H), 0.00 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 138.3, 130.8, 123.9, 122.3, 79.0, 73.1, 70.9, 58.8, 50.9, 50.1, 49.3, 49.0, 42.8, 40.8, 39.4, 39.2, 38.6, 32.7, 32.0, 30.7, 30.1, 27.4, 27.0, 26.0, 25.9, 25.7, 22.0, 18.13, 18.06, 17.7, 17.3, 17.02, 16.95, 16.1, 13.0, -3.6, -4.4, -4.6, -5.0; IR: $\tilde{\nu}$ = 2958,

2934, 2855, 1723, 1471, 1462, 1386, 1364, 1248, 1192, 1100, 1070, 1023, 967, 936, 922, 896, 886, 849, 835, 815, 773, 669, 618, 567, 516, 437 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{80}O_4Si_2Na$ $[M+Na]^+$ 751.5487, found 751.5482.

*3β,12β-Di-O-acetyl-5R, 9R, 13R-dammarane-(Z)-20(22),24(25)-diene (**10Z**).* Ac_2O (7.5 mL) was added dropwise to a solution of 20(*S*)-PPD (1.0 g, 2.17 mmol) in pyridine (7.5 mL) at 0 °C. After complete addition, the ice bath was removed and the resulting mixture was stirred at room temperature overnight. The mixture was then diluted with EtOAc and successively washed with saturated aqueous $NaHCO_3$, 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 7:1) to provide the 3β,12β-di-*O*-acetyl-20(*S*)-protopanaxadiol (967 mg, 82%) as a white solid.

3β,12β-Di-*O*-acetyl-20(*S*)-protopanaxadiol (300 mg，0.55 mmol) was dissolved in pyridine (15 mL) and $POCl_3$ (1.5 mL) was added dropwise at -20 °C. The resulting mixture was allowed to warm to room temperature and was stirred overnight. The mixture was then diluted with EtOAc and successively washed with water, 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. At this stage, ^{1}H NMR analysis showed that the crude residue is composed of a mixture of **9/10(*E*)/10(*Z*)** with a ^{1}H NMR ratio of 2:6:1. The crude residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 30:1) to furnish an inseparable mixture of **9/10(*E*)** (225mg, 77%) and **10(*Z*)** (24 mg, 8%) as a white solid.

10(*Z*): $[\alpha]^{25}_D$ = -28.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06-4.99 (m, 2H), 4.93 (td, *J* = 11.0,

5.3 Hz, 1H), 4.49 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.99 (dd, *J* = 17.5, 10.7 Hz, 1H), 2.69 (dt, *J* = 15.0, 7.3 Hz, 1H), 2.61-2.53 (m, 1H), 2.05 (s, 3H), 1.87 (s, 3H), 1.68 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.3, 137.5, 130.9, 123.8, 123.7, 80.6, 74.4, 55.8, 51.1, 50.3, 47.0, 40.0, 38.7, 37.9, 37.2, 34.8, 32.1, 28.1, 28.0, 27.9, 26.4, 25.7, 23.6, 21.3, 20.8, 18.1, 17.6, 16.7, 16.5, 16.2, 15.6; IR: $\tilde{\nu}$ = 2962, 2852, 1731, 1653, 1463, 1392, 1362, 1246, 1199, 1144, 1106, 1022, 983, 955, 926, 900, 859, 803, 657, 609, 597, 554, 501 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{55}O_4$ $[M+H]^+$ 527.4095, found 527.4093.

5R, 9R, 13R-Dammarane-20(21),24(25)-diene-3β,12β-diol ***(11)*** *and 5R, 9R, 13R-dammarane-(E)-20(22),24(25)-diene-3β,12β-diol* ***(12E)***. The inseparable mixture of **9/10(*E*)** (912 mg, 1.77 mmol) was subjected to the general saponification procedure with KOH (495 mg, 8.85 mmol) in CH_3OH (10 mL) at reflux for 4 hours. After workup, purification by silica gel column chromatography (petroleum ether/EtOAc, 10:1) provided **11** (215mg, 28%) and **12(*E*)** (500 mg, 65%) as white solids.

11: $[\alpha]^{25}_D$ = +22.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (t, *J* = 5.8 Hz, 1H), 5.03 (s, 1H), 4.79 (s, 1H), 3.70 (td, *J* = 10.5, 5.1 Hz, 1H), 3.20 (dd, *J* = 11.4, 4.8 Hz, 1H), 2.69-2.54 (m, 1H), 1.70 (s, 3H), 1.63 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 131.9, 124.1, 109.2, 78.8, 73.3, 55.9, 50.81, 50.78, 50.4, 48.0, 40.1, 39.0, 38.9, 37.2, 35.0, 32.3, 30.9, 29.1, 28.0, 27.4, 26.8, 25.7, 18.3, 17.8, 16.7, 16.2, 15.7, 15.4; IR: $\tilde{\nu}$ = 3424, 3080, 2961, 2870, 2726, 1635, 1450, 1387, 1295, 1262, 1189, 1118, 1080, 1026, 958, 930, 872, 802, 647, 578, 503 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{50}O_2Na$ $[M+ Na]^+$ 465.3703, found 465.3704.

12(*E*): $[\alpha]^{25}_{D}$ = -9.3 (*c* 1.0, $CHCl_3$); m.p. 112-114 ^{o}C ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (t, *J* = 7.0 Hz, 1H), 5.05 (t, *J* = 7.0 Hz, 1H), 3.72 (td, *J* = 10.4, 5.2 Hz, 1H), 3.19 (dd, *J* = 11.4, 4.7 Hz, 1H), 2.76-2.55 (m, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.61 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.87 (s, 6H), 0.77 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3, 132.1, 124.7, 122.1, 78.8, 73.3, 55.9, 50.5, 50.3, 50.2, 50.1, 40.1, 39.0, 38.9, 37.2, 35.0, 32.4, 30.4, 28.0, 27.4, 27.3, 27.0, 25.6, 18.2, 17.7, 16.7, 16.2, 15.6, 15.3, 12.4; IR: $\tilde{\nu}$ = 3404, 3067, 2958, 1712, 1641, 1452, 1388, 1345, 1296, 1257, 1189, 1118, 1079, 1024, 957, 928, 876, 846, 824, 646, 579, 514 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{50}O_2Na$ $[M+ Na]^+$ 465.3703, found 465.3706.

*3β,12β-Di-O-tert-butyldimethylsilyl-6α-O-(2',3',4',6'-tetra-O-benzoyl-β-D-glucopyranosyl)-5R, 9R, 13R-dammarane-(E)-20(22),24(25)-diene (**14E**).* **8(*E*)** (135 mg, 0.18 mmol) was subjected to the general saponification procedure with KOH (31 mg, 0.56 mmol) in a solvent mixture of CH_3OH (1.0 mL)/THF (1.0 mL) at room temperature overnight. After workup, purification by silica gel column chromatography (petroleum ether/EtOAc, 20:1) yielded the corresponding 3β,12β-di-OTBS-6α-ol (121 mg, 95%) as a white solid.

The aforementioned 3β,12β-di-*O*-TBS-6α-ol (86 mg, 0.12 mmol) was subjected to the general glycosylation procedure with donor **13** (191 mg, 0.25 mmol), PPh_3AuNTf_2 (46 mg, 0.062 mmol) and CH_2Cl_2 (2.0 mL) at room temperature for 2 hours. After work-up, purification by silica gel column chromatography (petroleum ether/EtOAc, 20:1) afforded **14(*E*)** (150 mg, 95%) as a white solid.

14(*E*): $[\alpha]^{25}_{D}$ = +20.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.91 (t, *J* = 7.5 Hz, 4H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.59-7.17 (m, 12H), 5.92 (t, *J* = 9.6 Hz, 1H), 5.68-5.58 (m, 2H),

5.21-5.06 (m, 2H), 5.00 (t, J = 6.4 Hz, 1H), 4.66-4.55 (m, 1H), 4.52 (dd, J = 12.1, 5.4 Hz, 1H), 4.29-4.22 (m, 1H), 4.07-4.00 (m, 1H), 3.52-3.44 (m, 1H), 2.99 (dd, J = 11.3, 4.4 Hz, 1H), 2.76-2.65 (m, 1H), 2.64-2.56 (m, 1H), 2.44-2.29 (m, 1H), 2.06-2.00 (m, 1H), 1.70 (s, 3H), 1.63 (s, 3H), 1.49 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.82 (s, 12H), 0.71 (s, 9H), 0.66 (s, 3H), -0.02 (s, 3H), -0.07 (s, 6H), -0.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 165.8, 165.2, 165.1, 138.4, 133.4, 133.14, 133.11, 133.0, 130.7, 129.82, 129.79, 129.7, 129.6, 129.4, 128.84, 128.81, 128.4, 128.3, 128.2, 128.1, 123.9, 122.2, 102.6, 80.9, 79.6, 73.5, 73.2, 72.2, 69.7, 63.6, 60.2, 50.8, 50.0, 49.2, 49.0, 45.3, 41.0, 39.3, 39.2, 38.6, 32.7, 31.7, 30.4, 30.0, 27.14, 27.06, 26.0, 25.9, 25.7, 18.1, 18.0, 17.7, 17.4, 16.9, 16.0, 13.0, -3.7, -4.4, -4.6, -5.2; IR: $\tilde{\nu}$ = 3063, 2957, 2855, 1739, 1603, 1585, 1472, 1452, 1390, 1362, 1316, 1262, 1178, 1104, 1068, 1027, 1004, 972, 934, 898, 886, 851, 835, 804, 773, 708, 686 cm^{-1}; HRMS (MALDI) calcd for $C_{76}H_{104}O_{12}Si_2Na$ $[M+Na]^+$ 1287.6959, found 1287.6982.

*6α-O-β-D-Glucopyranosyl-5R, 9R, 13R-dammarane-(E)-20(22),24(25)-diene-3β,12β-diol (**1**).* HF·Py (1.0 mL) was added to a solution of **14(*E*)** (50 mg, 0.040 mmol) in pyridine (1.0 mL) and THF (4.0 mL) at 0 ^{o}C. After addition, the mixture was stirred at room temperature for 6 hours and TLC showed complete consumption of **14(*E*)**. Then saturated aqueous $NaHCO_3$ was added to quench the reaction. The two layers were separated and the aqueous one was extracted with EtOAc. The organic layers were combined and successively washed with 1M aqueous HCl and brine, and dried over Na_2SO_4. The solvents were evaporated under vacuum and the resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2:1) to provide the corresponding 3β,12β-diol intermediate as a white solid.

The aforementioned 3β,12β-diol intermediate was subjected to the general saponification procedure with KOH (8.8 mg, 0.16 mmol) in CH_3OH (2.0 mL) at room temperature overnight . After workup, purification by RP-18 column chromatography (CH_3OH/H_2O, 5:1) yielded **1** (23 mg, 94% over 2 steps) as a white solid.

1: $[\alpha]^{25}_D$ = +21.0 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, pyridine-d_5 + one drop D_2O) δ 5.46 (t, *J* = 6.7 Hz, 1H), 5.19 (t, *J* = 6.5 Hz, 1H), 4.98 (d, *J* = 7.7 Hz, 1H), 4.48 (m, 1H), 4.40 (td, *J* = 10.4, 2.3 Hz, 1H), 4.32 (dd, *J* = 11.5, 5.3 Hz, 1H), 4.26 (t, *J* = 8.9 Hz, 1H), 4.17 (t, *J* = 9.2 Hz, 1H), 4.05 (t, *J* = 8.3 Hz, 1H), 3.97-3.83 (m, 2H), 3.49 (dd, *J* = 11.3, 4.5 Hz, 1H), 2.77-2.67 (m, 2H), 2.52-2.46 (m, 1H), 2.02 (s, 3H), 1.80 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.54 (s, 3H), 1.21 (s, 3H), 0.99 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, pyridine-d_5) δ 140.0, 131.2, 123.8, 123.4, 105.9, 80.0, 79.6, 78.5, 78.0, 75.4, 72.5, 71.7, 63.0, 61.4, 50.8, 50.6, 50.5, 50.3, 45.2, 41.2, 40.3, 39.7, 39.4, 32.4, 32.2, 31.6, 28.7, 27.8, 27.4, 25.6, 17.65, 17.63, 17.3, 16.7, 16.3, 13.0; HRMS (MALDI) calcd for $C_{36}H_{60}O_8Na$ $[M+Na]^+$ 643.4180, found 643.4151.

*3β-O-(2',3',4',6'-Tetra-O-benzoyl-β-D-glucopyranosyl)-12β-di-O-tert-butyldimethylsilyl-5R, 9R, 13R-dammarane-(E)-20(22),24(25)-diene (**15E**).* **12(*E*)** (112 mg, 0.25 mmol) and imidazole (34 mg, 0.51 mmol) were dissolved in DMF (1.0 mL) and cooled to 0 ^oC (ice bath). TBSCl (76 mg, 0.51 mmol) was then added and the resulting mixture was stirred at room temperature for 2 hours and TLC showed complete consumption of **12(*E*)**. The mixture was then diluted with EtOAc and successively washed with 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 50:1 to 5:1) to provide the corresponding 12β-OTBS-3β-ol (77 mg, 54%) as a white solid.

The aforementioned 12β-OTBS-3β-ol (85 mg, 0.15 mmol) was subjected to the general glycosylation procedure with donor **13** (175 mg, 0.23 mmol), PPh_3AuNTf_2 (22 mg, 0.030 mmol) and CH_2Cl_2 (2.0 mL) at room temperature for 2 hours. After work-up, purification by silica gel column chromatography (petroleum ether/EtOAc, 20:1) yielded **15(*E*)** (137 mg, 79%) as a white solid.

15(*E*): $[\alpha]^{25}_D$ = +33.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 7.7 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.57-7.48 (m, 3H), 7.45-7.37 (m, 6H), 7.33-7.24 (m, 3H), 5.93 (t, *J* = 9.7 Hz, 1H), 5.66-5.57 (m, 2H), 5.12 (t, *J* = 6.6 Hz, 1H), 5.04 (t, *J* = 6.6 Hz, 1H), 4.89 (d, *J* = 7.9 Hz, 1H), 4.65 (dd, *J* = 11.9, 2.8 Hz, 1H), 4.51 (dd, *J* = 11.9, 6.4 Hz, 1H), 4.19-4.12 (m, 1H), 3.56 (td, *J* = 9.9, 4.7 Hz, 1H), 3.15 (dd, *J* = 11.7, 4.3 Hz, 1H), 2.75-2.65 (m, 1H), 2.67-2.57 (m, 1H), 2.46 (td, *J* = 10.6, 6.5 Hz, 1H), 1.70 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 0.98 (s, 3H), 0.86 (s, 12H), 0.84 (s, 3H), 0.70 (s, 3H), 0.67 (s, 3H), 0.03 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.9, 165.3, 165.0, 138.6, 133.4, 133.2, 133.10, 133.08, 130.7, 129.83, 129.75, 129.72, 129.70, 129.68, 129.4, 128.85, 128.81, 128.4, 128.33, 128.28, 124.0, 122.2, 103.2, 90.6, 73.3, 73.0, 72.2, 72.0, 70.2, 63.5, 56.1, 51.0, 50.5, 49.4, 39.8, 39.0, 38.8, 36.8, 34.9, 32.8, 32.0, 30.2, 27.6, 27.1, 26.0, 25.7, 18.1, 17.7, 17.0, 16.2, 16.0, 15.7, 13.1, -4.1, -4.5; IR: $\tilde{\nu}$ = 3063, 2960, 2856, 1735, 1602, 1585, 1452, 1389, 1368, 1315, 1263, 1177, 1093, 1068, 1027, 973, 935, 889, 858, 836, 800, 774, 709, 686, 639, 505 cm^{-1}; HRMS (MALDI) calcd for $C_{70}H_{90}O_{11}SiNa$ $[M+Na]^+$ 1157.6145, found 1157.6153.

*3β-O-β-D-Glucopyranosyl-5R, 9R, 13R-dammarane-(E)-20(22),24(25)-diene-12β-ol (**2**).* HF·Py (0.2 mL) was added to a solution of **15(*E*)** (91 mg, 0.080 mmol) in THF (2.0 mL) at 0 °C. After addition, the mixture

was stirred at room temperature for 3 hours and TLC showed complete consumption of **15(*E*)**. Then saturated aqueous $NaHCO_3$ was added to quench the reaction. The two layers were separated and the aqueous one was extracted with EtOAc. The organic layers were combined and successively washed with 1M aqueous HCl and brine, and dried over Na_2SO_4. The solvents were evaporated under vacuum and the resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 7:1) to provide the corresponding 12β-ol intermediate (81 mg, > 99%) as a white solid.

The aforementioned 12β-ol intermediate (50 mg, 0.049 mmol) was subjected to the general saponification procedure with KOH (27 mg, 0.49 mmol) in CH_3OH (1.0 mL) at room temperature overnight. After workup, purification by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) yielded **2** (25 mg, 83%) as a white solid.

2: $[\alpha]^{25}_D$ = +2.1 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, pyridine-d_5) δ 5.51 (t, J = 6.8 Hz, 1H), 5.22 (t, J = 6.5 Hz, 1H), 4.95 (d, J = 7.7 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 4.40 (dd, J = 11.5, 5.3 Hz, 1H), 4.27-4.17 (m, 2H), 4.07-3.98 (m, 2H), 3.95-3.88 (m, 1H), 3.38 (dd, J = 11.5, 3.9 Hz, 1H), 2.85-2.75 (m, 2H), 2.25-2.15 (m, 1H), 1.82 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H), 1.32 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (126 MHz, pyridine-d_5) δ 140.1, 131.2, 123.7, 123.4, 106.9, 88.7, 78.7, 78.4, 75.8, 72.5, 71.8, 63.0, 56.4, 51.0, 50.9, 50.7, 50.4, 40.2, 39.6, 39.2, 37.0, 35.3, 32.6, 32.2, 28.8, 28.1, 27.4, 26.7, 25.7, 18.4, 17.7, 17.0, 16.8, 16.4, 15.8, 13.1; HRMS (MALDI) calcd for $C_{36}H_{60}O_7Na$ $[M+Na]^+$ 627.4231, found 627.4224.

*3β,12β-Di-O-tert-butyldimethylsilyl-6α-O-(2'-O-benzoyl-3',4',6'-tri-O-benzyl-β-D-glucopyranosyl)-5R, 9R, 13R-dammarane-20(21),24(25)-diene (**17**).* **7** (140 mg, 0.19 mmol) was subjected to the general

saponification procedure with KOH (32 mg, 0.57 mmol) in a solvent mixture of CH_3OH (1.0 mL)/THF (1.0 mL) at room temperature overnight. After workup, purification by silica gel column chromatography (petroleum ether/EtOAc, 20:1) provided the corresponding 3β,12β-di-OTBS-6α-ol intermediate (125 mg, 95%) as a white solid.

The aforementioned 3β,12β-di-OTBS-6α-ol intermediate (88 mg, 0.13 mmol) was subjected to the general glycosylation procedure with donor **16** (185 mg, 0.26 mmol), PPh_3AuNTf_2 (47 mg, 0.064 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for 2 hours. The reaction was quenched by addition of NEt_3 and after work-up, purification by silica gel column chromatography (petroleum ether/EtOAc, 25:1) afforded **17** (152 mg, > 99%) as a white solid.

17: $[\alpha]^{25}_D$ = +24.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.42-7.19 (m, 12H), 7.17-7.03 (m, 5H), 5.36 (t, *J* = 8.1 Hz, 1H), 5.20 (brs, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.8-4.7 (m, 3H), 4.66-4.59 (m, 4H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.95 (t, *J* = 9.3 Hz, 1H), 3.82 (t, *J* = 8.9 Hz, 1H), 3.80-3.73 (m, 2H), 3.69 (d, *J* = 10.2 Hz, 1H), 3.62-3.56 (m, 1H), 3.51 (td, *J* = 10.0, 4.7 Hz, 1H), 2.99 (dd, *J* = 11.3, 4.4 Hz, 1H), 2.50 (td, *J* = 10.7, 6.2 Hz, 1H), 1.73 (s, 3H), 1.65 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.84 (s, 9H), 0.72 (s, 9H), 0.64 (s, 3H), -0.01 (s, 3H), -0.04 (s, 3H), -0.06 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 152.7, 138.1, 138.0, 137.7, 132.9, 131.0, 130.1, 129.9, 128.4, 128.3, 128.2, 128.15, 128.0, 127.8, 127.64, 127.60, 127.59, 124.9, 107.5, 103.0, 83.3, 80.6, 79.6, 78.2, 75.2, 75.0, 74.9, 73.9, 73.3, 69.4, 60.2, 51.0, 50.1, 49.3, 47.9, 45.3, 41.1, 39.3, 39.2, 38.6, 32.8, 32.4, 31.9, 30.6, 30.5, 27.2, 26.2, 26.0, 25.9, 25.8, 18.1, 18.0, 17.7, 17.4, 17.3, 16.8, 15.9, -3.7, -4.3, -4.6, -5.2; HRMS (MALDI) calcd for $C_{76}H_{110}O_9Si_2Na$ $[M+Na]^+$ 1245.7581, found 1245.7642.

*3β,12β-Di-O-tert-butyldimethylsilyl-6α-O-[2'',3'',4''-tri-O-benzoyl-α-L-rhamnopyranosyl-(1→2)-3',4',6'-tri-O-benzyl-β-D-glucopyranosyl)-5R, 9R, 13R-dammarane-20(21),24(25)-diene (**19**).* **17** (120 mg, 0.10 mmol) was subjected to the general saponification procedure with KOH (28 mg, 0.50 mmol) in a solvent mixture of CH_3OH (1.0 mL)/THF (1.0 mL) at room temperature overnight. After workup, purification by silica gel column chromatography (petroleum ether/EtOAc, 25:1) furnished the corresponding 3β,12β-di-OTBS-6α-OGlc-2'-ol intermediate (113 mg, > 99%) as a white solid.

The aforementioned 3β,12β-di-OTBS-6α-OGlc-2'-ol intermediate (77 mg, 0.069 mmol) was subjected to the general glycosylation procedure with donor **18** (88 mg, 0.14 mmol), PPh_3AuNTf_2 (25 mg, 0.034 mmol) in CH_2Cl_2 (1.5 mL) at room temperature for 2 hours. The reaction was quenched by addition of NEt_3 and after work-up, purification by silica gel column chromatography (petroleum ether/EtOAc, 30:1) provided **19** (91 mg, 84%) as a white solid.

19: $[\alpha]^{25}_D$ = +29.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.97 (d, *J* = 7.4 Hz, 2H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 3H), 7.39 -7.19 (m, 14H), 7.04 (t, *J* = 7.4 Hz, 2H), 6.98 (t, *J* = 7.3 Hz, 1H), 5.83-5.77 (m, 2H), 5.62 (t, *J* = 9.8 Hz, 1H), 5.52 (s, 1H), 5.20 (t, *J* = 6.6 Hz, 1H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.88-4.80 (m, 4H), 4.76 (s, 1H), 4.67-4.57(m, 4H), 4.40 (td, *J* = 10.5, 3.4 Hz,1H), 3.90-3.84 (m, 2H), 3.84-3.74 (m, 3H), 3.60-3.55 (m, 1H), 3.51 (td, *J* = 10.2, 4.6 Hz, 1H), 3.23 (dd, *J* = 11.2, 4.7 Hz, 1H), 2.49 (td, *J* = 10.8, 6.0 Hz, 1H), 1.71 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.82 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.03 (s, 3H), -0.07 (s, 3H); ^{13}C NMR (126

MHz, $CDCl_3$) δ 165.8, 165.2, 165.1, 152.6, 138.2, 138.0, 137.9, 133.2, 133.1, 132.8, 131.1, 129.92, 129.86, 129.7, 129.65, 129.57, 129.5, 128.44, 128.39, 128.2, 128.1, 127.9, 127.8, 127.7, 127.67, 127.66, 127.6, 127.4, 124.9, 107.6, 99.8, 97.8, 85.8, 79.9, 78.6, 77.2, 76.2, 75.48, 75.46, 74.8, 74.0, 73.4, 72.6, 72.0, 70.5, 69.7, 69.3, 66.5, 60.7, 51.0, 49.9, 49.3, 47.8, 46.0, 40.8, 39.8, 39.2, 39.0, 32.8, 32.6, 32.2, 31.8, 30.7, 27.5, 26.2, 26.07, 26.05, 25.95, 25.8, 18.15, 18.12, 17.7, 17.4, 17.3, 17.2, 17.0, 16.8, -3.7, -4.3, -4.6, -5.0; IR: $\tilde{\nu}$ = 3064, 3031, 2958, 2855, 1733, 1640, 1603, 1585, 1497, 1471, 1452, 1391, 1361, 1315, 1262, 1206, 1177, 1105, 1068, 1027, 934, 898, 885, 836, 803, 773, 753, 709, 616, 516, 459 cm^{-1}; HRMS (MALDI) calcd for $C_{96}H_{128}O_{15}Si_2Na$ $[M+Na]^+$ 1599.8684, found 1599.8748.

*6α-O-[α-L-Rhamnopyranosyl-(1→2)-β-D-glucopyranosyl]-5R, 9R, 13R-dammarane-20(21),24(25)-diene-3β,12β-diol (**3**).* A solution of **19** (50 mg, 0.032 mmol) in THF (1.0 mL) was added dropwise to a solution of Li (11 mg, 1.6 mmol) and naphthalene (406 mg, 3.2 mmol) in THF (2.0 mL) at -20 ^oC. The resulting mixture was stirred at the same temperature overnight. Saturated aqueous NH_4Cl was then added to quench the reaction and the solvents were evaporated under vacuum. The resulting residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 25:1) to lead to the corresponding debenzylated and debenzoylated glycoside intermediate as a white solid.

HF·Py (0.5 mL) was added to a solution of the aforementioned glycoside intermediate in a solvent mixture of pyridine (0.5 mL)/THF (2.0 mL) at 0 ^oC. After addition, the mixture was stirred at room temperature for 6 hours and TLC showed complete consumption of the glycoside intermediate. NEt_3 was then added to quench the reaction and the solvents were evaporated under vacuum. The resulting residue was purified by RP-18

column chromatography (CH_3OH/H_2O, 3:1) to yield **3** (20 mg, 82% over 2 steps) as a white solid.

3: $[\alpha]^{25}_D$ = -4.3 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, pyridine-d_5) δ 6.56 (s, 1H), 5.37 (t, *J* = 6.8 Hz, 1H), 5.34 (d, *J* = 6.9 Hz, 1H), 5.18 (s, 1H), 5.03 (dt, *J* = 15.5, 6.1 Hz, 1H), 4.95 (s, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 4.78 (dd, *J* = 10.7, 3.3 Hz, 1H), 4.74 (dd, *J* = 9.3, 3.5 Hz, 1H), 4.60 (dd, *J* = 11.4, 2.4 Hz, 1H), 4.49-4.36 (m, 4H), 4.28 (t, *J* = 9.0 Hz, 1H), 4.07-4.01 (m, 1H), 3.97 (td, *J* = 10.3, 5.0 Hz, 1H), 3.55 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.84 (td, *J* = 10.6, 6.0 Hz, 1H), 2.19 (s, 3H), 1.86 (d, *J* = 6.2 Hz, 3H), 1.74 (s, 3H), 1.66 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (101 MHz, pyridine-d_5) δ 155.5, 131.2, 125.4, 108.1, 102.0, 101.8, 79.5, 78. 6, 78.4, 78.3, 74.4, 74.2, 72.6, 72.5, 72.3, 69.5, 63.1, 60.9, 52.1, 51.2, 50.2, 48.3, 46.2, 41.4, 40.0, 39.7, 39.5, 33.7, 32.8, 32.6, 32.2, 30.7, 27.8, 27.1, 25.8, 18.8, 17.8, 17.6, 17.2, 16.9; HRMS (MALDI) calcd for $C_{42}H_{70}O_{12}Na$ $[M+Na]^+$ 789.4760, found 789.4724.

3β-O-(2'-O-Benzoyl-3',4',6'-tri-O-benzyl-β-D-glucopyranosyl)-12β-O-tert-butyldimethylsilyl-5R, 9*R*, 13*R-dammarane-20(21),24(25)-diene (**20**).* **11** (170 mg, 0.39 mmol) and imidazole (52 mg, 0.77 mmol) were dissolved in DMF (1.5 mL) and cooled to 0 ^{o}C. TBSCl (116 mg, 0.77 mmol) was then added and the resulting mixture was stirred at room temperature for 2 hours and TLC showed complete consumption of **11**. The mixture was then diluted with EtOAc and successively washed with 1M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 50:1 to 5:1) to provide the corresponding 12β-OTBS-3β-ol intermediate (123 mg, 57%) as a white solid.

The aforementioned 12β-OTBS-3β-ol intermediate (42 mg, 0.075 mmol) was subjected to the general

glycosylation procedure with donor **16** (82 mg, 0.11 mmol), PPh_3AuNTf_2 (11 mg, 0.015 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for 2 hours. The reaction was quenched by addition of NEt_3 and after work-up, purification by silica gel column chromatography (petroleum ether/EtOAc, 20:1 to 15:1) furnished **20** (82 mg, > 99%) as a white solid.

20: $[\alpha]^{25}_D$ = +42.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.44 (t *J* = 7.7 Hz, 2H), 7.42-7.25 (m, 10H), 7.19-7.13 (m, 5H), 5.37 (t, *J* = 8.7 Hz, 1H), 5.20 (brs, 1H), 4.88 (d, *J* = 10.9 Hz, 1H), 4.78 (d, *J* = 10.8 Hz, 2H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.69-4.61 (m, 4H), 4.59 (d, *J* = 7.9 Hz, 1H), 3.90-3.79 (m, 2H), 3.79-3.69 (m, 2H), 3.65-3.50 (m, 2H), 3.09 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.54 (td, *J* = 10.7, 6.1 Hz, 1H), 1.73 (s, 3H), 1.65 (s, 3H), 1.01 (s, 3H), 0.88 (s, 15H), 0.70 (s, 3H), 0.65 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 152.8, 138.3, 138.0, 137.9, 132.9, 131.1, 130.1, 129.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.61, 127.57, 124.9, 107.5, 103.4, 89.7, 82.9, 78.3, 75.1, 75.04, 75.02, 74.2, 73.5, 73.4, 69.0, 56.2, 51.0, 50.6, 49.6, 47.9, 39.8, 39.0, 36.8, 35.0, 32.8, 32.6, 32.1, 30.7, 27.7, 26.22, 26.16, 26.0, 25.8, 25.4, 18.11, 18.07, 17.7, 16.9, 16.3, 16.0, 15.7, -4.2, -4.6; HRMS (MALDI) calcd for $C_{70}H_{96}O_8SiNa$ $[M+Na]^+$ 1115.6767, found 1115.6807.

*3β-O-[2",3",4",6"-Tetra-O-benzoyl-β-D-glucopyranosyl-(1→2)-3',4',6'-tri-O-benzyl-β-D-glucopyranosyl)-1 2β-O-tert-butyldimethylsilyl-5R, 9R, 13R-dammarane-20(21),24(25)-diene (**21**).* **20** (100 mg, 0.091 mmol) was subjected to the general saponification procedure with KOH (25 mg, 0.46 mmol) in a solvent mixture of CH_3OH (2.0 mL)/THF (1.0 mL) at room temperature overnight. After workup, purification by silica gel column chromatography (petroleum ether/EtOAc, 20:1) provided the corresponding

12β-OTBS-3β-OGlc-2'-ol intermediate (90 mg, > 99%) as a white solid.

The aforementioned 12β-*O*-TBS-3β-*O*-Glc-2'-ol intermediate (64 mg, 0.065 mmol) was subjected to the general glycosylation procedure with donor **13** (98 mg, 0.13 mmol), PPh_3AuNTf_2 (24 mg, 0.032 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for 2 hours. The reaction was quenched by addition of NEt_3 and after work-up, purification by silica gel column chromatography (petroleum ether/EtOAc, 10:1) afforded **21** (82 mg, 81%) as a white solid.

21: $[\alpha]^{25}_D$ = +11.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.3 Hz, 2H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.82 (d, *J* = 7.4 Hz, 2H), 7.54-7.20 (m, 25H), 7.12 (dd, *J* = 6.4, 2.7 Hz, 2H), 5.86 (t, *J* = 9.7 Hz, 1H), 5.71 (t, *J* = 9.7 Hz, 1H), 5.57 (dd, *J* = 9.6, 8.2 Hz, 1H), 5.41 (d, *J* = 8.0 Hz, 1H), 5.21 (t, *J* = 6.7 Hz, 1H), 4.78 (s, 1H), 4.70-4.57 (m, 7H), 4.54 (t, *J* = 11.3 Hz, 1H), 4.45 (dd, *J* = 12.1, 4.8 Hz, 1H), 4.39 (d, *J* = 7.7 Hz, 1H), 4.11-4.02 (m, 1H), 3.94-3.92 (m, 1H), 3.72 (d, *J* = 9.5 Hz, 1H), 3.63 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.60-3.48 (m, 3H), 3.44-3.37 (m, 1H), 3.10 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.55 (td, *J* = 10.9, 5.9 Hz, 1H), 1.73 (s, 3H), 1.65 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H), 0.86 (s, 9H), 0.81 (s, 3H), 0.79 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 165.8, 165.1, 165.0, 152.9, 138.25, 138.17, 137.8, 133.3, 133.13, 133.08, 132.9, 131.0, 129.9, 129.8, 129.7, 129.2, 128.9, 128.8, 128.6, 128.36, 128.35, 128.3, 128.24, 128.22, 127.82, 127.76, 127.59, 127.58, 127.5, 124.9, 107.4, 103.7, 100.6, 90.3, 85.6, 78.6, 78.0, 75.3, 74.8, 74.6, 73.5, 73.4, 73.2, 72.4, 72.0, 69.9, 69.0, 63.2, 56.3, 51.1, 50.6, 49.7, 47.9, 39.9, 39.4, 39.0, 36.8, 35.1, 32.9, 32.6, 32.1, 30.7, 27.7, 26.22, 26.16, 26.0, 25.7, 18.1, 18.0, 17.7, 16.9, 16.3, 16.2, 15.7, -4.2, -4.6; IR: $\tilde{\nu}$ = 3448, 3064, 3032, 2927, 2855, 1964, 1738, 1638, 1602, 1585, 1496, 1452, 1388, 1360, 1315, 1264, 1214, 1178, 1093, 1068, 1026, 937, 889, 862, 836, 801, 773, 735, 709, 502 cm^{-1}; HRMS

(MALDI) calcd for $C_{97}H_{118}O_{16}SiNa$ $[M+Na]^+$ 1589.8081, found 1589.8087.

3β-O-[β-D-Glucopyranosyl-(1→2)-β-D-glucopyranosyl]-5R, 9R, 13R-dammarane-20(21),24(25)-diene-12β-ol (4). A solution of **21** (30 mg, 0.019 mmol) in THF (1.0 mL) was added dropwise to a solution of Li (6.6 mg, 0.95 mmol) and naphthalene (244 mg, 1.9 mmol) in THF (1.0 mL) at -20 °C. The resulting mixture was stirred at the same temperature overnight. Saturated aqueous NH_4Cl was then added to quench the reaction and the solvents were evaporated under vacuum. The resulting residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 8:1) to provide the corresponding debenzylated and debenzoylated glycoside intermediate a white solid.

HF·Py (0.2 mL) was added to a solution of the aforementioned glycoside intermediate in a solvent mixture of pyridine (0.2 mL)/THF (0.8 mL) at 0 °C. After addition, the mixture was stirred at room temperature for 3 hours and TLC showed complete consumption of the glycoside intermediate. NEt_3 was then added to quench the reaction and the solvents were evaporated under vacuum. The resulting residue was purified by RP-18 column chromatography (CH_3OH/H_2O, 4:1) to yield **4** (10 mg, 68% over 2 steps) as a white solid.

4: $[\alpha]^{25}_D$ = +7.3 (*c* 0.5, CH_3OH); ^{1}H NMR (500 MHz, pyridine-d_5 + one drop D_2O) δ 5.37 (d, J = 7.6 Hz, 1H), 5.26 (brs, 1H), 5.15 (s, 1H), 4.89 (s, 1H), 4.87 (d, J = 7.6 Hz, 1H), 4.57-4.43 (m, 2H), 4.38-4.14 (m, 6H), 4.11-4.04 (m, 2H), 3.96-3.82 (m, 3H), 3.26 (dd, J = 11.5, 3.9 Hz, 1H), 2.84-2.74 (m, 1H), 1.63 (s, 3H), 1.57 (s, 3H), 1.22 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, pyridine-d_5) δ 155.6, 131.2, 125.4, 108.1, 106.1, 105.2, 88.9, 83.5, 78.4, 78.3, 78.2, 78.0, 77.2, 72.4, 71.7, 62.9, 62.7, 56.4, 52.5, 51.2, 50.9, 48.3, 40.2, 39.7, 39.3, 37.0, 35.4, 33.9, 32.7, 32.6, 30.8, 28.1, 27.1, 26.8, 25.8, 18.5, 17.8,

17.0, 16.6, 16.5, 15.8; HRMS (MALDI) calcd for $C_{42}H_{70}O_{12}Na$ $[M+Na]^+$ 789.4760, found 789.4757.

ASSOCIATED CONTENT

Supporting Information

NMR spectra and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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