JOC The Journal of Organic Chemistry



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*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b00080 • Publication Date (Web): 27 Mar 2017



## Just Accepted



ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

# The Synthetic Access Toward Cycloastragenol Glycosides

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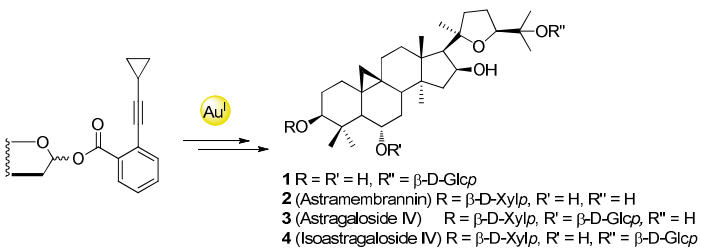



**1** R = R' = H, R'' = β-D-Glc*p*
**2** (Astramembrannin) R = β-D-Xyl*p*, R' = H, R'' = H
**3** (Astragaloside IV) R = β-D-Xyl*p*, R' = β-D-Glc*p*, R'' = H
**4** (Isoastragaloside IV) R = β-D-Xyl*p*, R' = H, R'' = β-D-Glc*p*

**Abstract:**

The first efficient synthetic approach toward four types of the cycloartane glycosides, the cycloastragenol 25-*O*, 3-*O*, 3,6-*O*-bis, and 3,25-*O*-bisglycoside, have been established, which featured the PPY-mediated, concentration-controlled acetylation and Au(I)-catalyzed Yu glycosylation. Through the synthetic investigation, the reactivity sequence of the four OHs in cycloastragenol was fixed for the first time and a detour strategy for the highly efficient removal of bulky pivaloyl protecting groups was discovered.

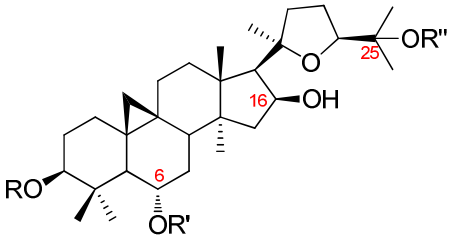
## Introduction

Astragali Radix (Huangqi), the root of *Astraglus membranaceus*, has long been used as one of the most important tonic herbs in traditional Chinese medicine. Studies regarding its pharmacological and clinical use demonstrated that Astragali Radix has many biological functions, including hepatoprotection,[1] neuroprotection,[2]

immunomodulating activity,[3] antitumoral effects.[4] The major active principles responsible for the above mentioned activities are recognized to be the cycloartane glycosides, which indeed have shown numerous pharmaceutical activities, including immunostimulatory,[5] cardioprotective,[6] anticarcinogenic,[7] neuroprotective,[8] and antiflammatory activities.[9] Cycloartane glycosides occur in Astragali Radix in such a heterogeneous manner that more than 30 members, mainly the cycloastragenol glycosides, have been isolated and characterized. Therefore, to access ample amounts of homogeneous cycloartane glycosides from natural resources for detailed pharmaceutical investigation is a formidable task. As a result, all biological studies regarding pure cycloartane glycoside have been limited to astragaloside IV, a congener with the highest natural content. Chemical synthesis could provide homogeneous cycloartane glycosides. However, due to the lack of methods for OHs discrimination and glycosidic linkage construction, no synthetic investigation toward these biologically important compounds has been reported.[10a] Especially, the construction of C-25 tertiary OH glycosidic linkage poses considerable synthetic challenge.[10b-e]

Structurally, the main cycloartane glycosides isolated from *Astraglus membranaceus* can be categorized into three types, *i.e.*, the cycloastragenol 3-*O*-glycoside, cycloastragenol 3,6-*O*-bisglycoside, as well as the cycloastragenol 3,25-*O*-bisglycoside, as exemplified by astramembrannin II (**2**),[11] astragaloside IV (**3**),[12] and isoastragaloside IV (**4**),[12] respectively (Figure 1). As an representative of cycloastragenol 25-*O*-glycoside, although (**1**) has not yet been isolated directly from

the natural resources, as an enzymatic hydrolysis product of astragaloside V it has already been characterized.[13] Thus, there is no reason to doubt its existence in *Astraglus membranaceus*, and the low natural content is responsible for the temporary absence. In fact, as the richest ingredient, astragaloside IV only accounts for 1.17% of the whole Astragali Radix weight, not to mention the minor components (0.42% and 0.017% for **2** and **4**, respectively). To facilitate the following reactivity study of astragaloside IV as well as the searching for new pharmaceutically important cycloartane glycosides, a reliable chemical synthetic approach is urgently needed. Leveraging on the judicious differentiation of the four inert hydroxyl groups of cycloastragenol as well as the Yu glycosylation[14,15] featuring the mild glycosylation conditions and impressive glycosylation potential, the first and efficient approach toward cycloartane glycosides have been discovered, through which the representative members **1**-**4** have been successfully synthesized.




**1** R = R' = H, R" = β-D-Glc*p*
**2** (Astramembrannin II) R = β-D-Xyl*p*, R' = H, R" = H
**3** (Astragaloside IV) R = β-D-Xyl*p*, R' = β-D-Glc*p*, R" = H
**4** (Isoastragaloside IV) R = β-D-Xyl*p*, R' = H, R" = β-D-Glc*p*

**Figure 1.** Representative cycloastragenol glycosides.

**Results and discussion**

The first problem that should be solved en route to the establishment of an efficient approach toward the four target molecules is the discrimination of the four OHs in

cycloastragenol **5** (Scheme 1). The low reactivity of 6,16,25-OHs makes the most simple protecting group manipulation, the acetylation, become sluggish and difficult. It has been reported that even under the harsh acetylation conditions, that is, large excess of acetylating reagents ($Ac_2O$/pyridine: v/v = 1 : 1.2), elevated temperature (60 $^oC$), and prolonged reaction time (50 days), the peracetylated cycloastragenol product was obtained only in 56% yield. Shortened reaction time or decreased reaction temperature resulted in a complex mixture of mono- and diacetate.[16] These precedented results indicate that the hydroxyl groups discrimination of cycloastragenol **5** is by no way a trivial problem.

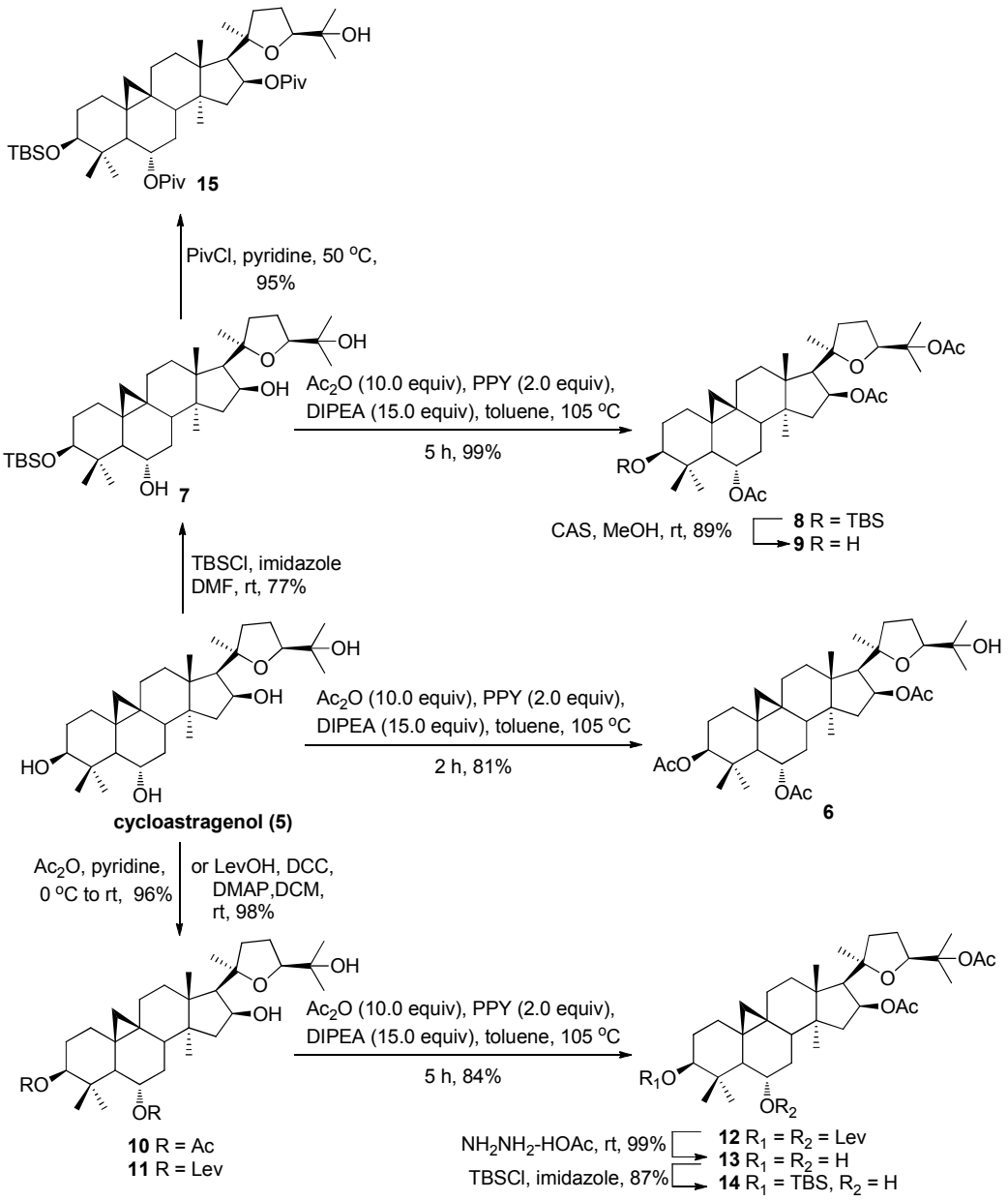
Given the low reactivity of OHs in cycloastragenol, the acetylation was tried with 4-(1-pyrrolidino)-pyridine (PPY) as promoter, as it has been demonstrated to be the most effective catalyst for the acylation of bulky and inert tertiary OHs.[17a,b] Pleasantly, after extensive screening, it was found that under the combined effects of $Ac_2O$ (10.0 equiv), PPY (2.0 equiv), and *N*,*N*-diisopropylethylamine (DIPEA, 15.0 equiv), cycloastragenol **5** was fluently acetylated in toluene at 105 $^oC$, delivering the triacetate **6** which is ready for the due 25-OH sugar residue installation in a good 81% yield. In sharp contrast to the previous reports,[16] under the PPY mediated acetylation conditions, the triacetylation proceeded so rapidly that only 2 hours were required for the completion of the reaction. Thus, the first efficient method for acetylation of cycloastragenol was established, laying firm foundation for the following thorough differentiation of the four OHs of cycloastragenol. It also should be pointed out that the Lewis acid-catalyzed acylation conditions which have been proved to be powerful

for the acylation of inert hydroxyl groups could not work well in our hand.[17c] Encouraged by this promising result, the discrimination of 3-OH from the other three OHs was investigated subsequently. In order to secure satisfactory selectivity, the bulky and easily-cleavable TBS was selected. At the outset, in order to avoid the over-silylation side reaction, **5** was exposed to the conventional silylation conditions, that is, 1.2 equivalents of TBSCl and 2.0 equivalents of imidazole in DMF at room temperature. However, only 40% yield of **7** was isolated with the major starting material being recovered. Further investigation proved that the reactivity disparity between 3-OH and the remaining 6,16,25-OHs was so huge that only trace amount of the over-silylated product was detected even when 4.0 equivalents of TBSCl and 6.0 equivalents of imidazole were applied. The modified conditions brought about a dramatic improvement in the chemical yield, and 77% yield of **7** was obtained. With **7** in hand, full acetylation of resting free OHs including the tertiary 25-OH was required so as to realize the final discrimination of the 3-OH. Although the $Ac_2O$/PPY/DIPEA system has showcased impressive potential in the transformation of **5** to **6**, the conditions could only acetylate the secondary OHs with the tertiary 25-OH left untouched. To realize the acetylation of all free OHs of **7**, further optimization of the $Ac_2O$/PPY/DIPEA conditions was required. Extensive investigation revealed that the concentration of cycloastragenol derivatives had a profound effect on the acetylation potential of the $Ac_2O$/PPY/DIPEA system, and the full acetylation of **7** was efficiently realized with $Ac_2O$/PPY/DIPEA under a high concentration condition (above 50 mg/mL) to afford **8** in almost quantitative yield. To release the 3-OH for the

subsequent glucosyl residue incorporation, the selective cleavage of 3-OTBS in **8** was achieved with CAS in MeOH, furnishing 3-OH free intermediate **9** (89%). Interestingly, the conventional TBS cleavage conditions such as TBAF and HF/pyridine could not effect the transformation. At this junction, the efficient differentiation of 3- and 25-OH of cycloastragenol was achieved, which was heavily dependent on the PPY mediated and concentration-controlled acetylation conditions.

Alternatively, in compound **7** the 25-OH could also be discriminated with the bulky pivaloyl group. Thus, treated with PivCl and pyridine, the two secondary OHs in **7** were esterified to generate **15**, an acceptor suitable for the synthesis of 3,6-*O*-bisglycoside, efficiently (95%). Excess amounts of acylating reagent (10.0 equivalents of PivCl) as well as high reaction concentration are the prerequisites for high pivaloylation yield. For the preparation of cycloastragenol 3,6-*O*-bisglycosides, the discrimination between 3- and 6-OHs in **5** is entailed. To this end, the acetylation of **5** under the conventional conditions ($Ac_2O$, pyridine) was conducted as a model reaction, and the diacetylated cycloastragenol **10** was isolated in an excellent yield (96%).[16] This result indicated that the four OHs could be divided into two groups by esterification, which would facilitate following discrimination between 3- and 6-OH of cycloastragenol. Inspired by the result of the model reaction, attempt to direct levulination of 3,6-OHs of **5** under the effect of LevOH, DCC, and DMAP was made. While 2.5 equivalents of DCC and LevOH afforded a mixture of mono and dilevulinated cycloastragenols, increasing the amounts of DCC and LevOH to 10.0 equivalents resulted in the clean formation of 3,6-dilevulinated cycloastragenol **11**

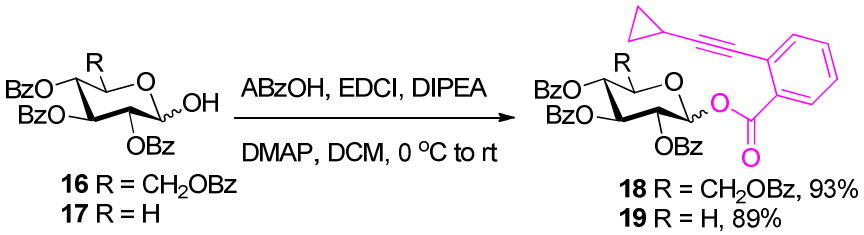
(98%), which was subsequently subjected to the PPY mediated full acetylation conditions to yield **12** (84%). $NH_2NH_2$/HOAc mediated delevulination resulted in the diol intermediate **13** smoothly (99%). With TBS as a temporary protecting group, the differentiation of 3-OH at the presence of 6-OH was realized to afford **14** (87%), which could act as a suitable acceptor for the synthesis of cycloastragenol 3,6-*O*-bisglycoside. Thus far, with acetyl, *tert*-butyldimethyl, pivaloyl, and levulinyl as protecting groups, all four acceptors **6**, **9**, **14**, and **15** needed for the synthesis of the target molecules were obtained successfully. Meanwhile, the detailed protecting group manipulations let to the determination of the reactivity sequence of the four OHs in cycloastraginol **5** as 3-OH > 6-OH > 16-OH > 25-OH. Theoretically, applying the devised hydroxyl group differentiation strategy, all cycloastrgenol acceptors with different patterns of free OH could be obtained, thus paving the way for the highly efficient synthesis of other types of cycloartane glycosides.




**Scheme 1**. Differentiation of the four hydroxyl groups on cycloastragenol (**5**)

With all acceptors equipped with appropriate protecting groups in hand, the synthesis of Yu donors was conducted following the known procedures (Scheme 2). Thus, treated with EDCI, DIPEA, and DMAP, the condensation between hemiacetals **16**,[10c] **17**[15b] and *ortho*-alkynylbenzoic acid proceeded efficiently to afford glycosyl

donors **18**[10c] and **19** (93% and 89% yield respectively). To secure the desired 1,2-*trans*-glycosidic linkages, the donors were equipped with benzoyl groups whereby the stereocontrol of the glycosidic linkages could be guaranteed through the reliable neighboring group participation effect.




**Scheme 2**. Synthesis of glycosyl *ortho*-alkynylbenzoate donors **18** and **19**.

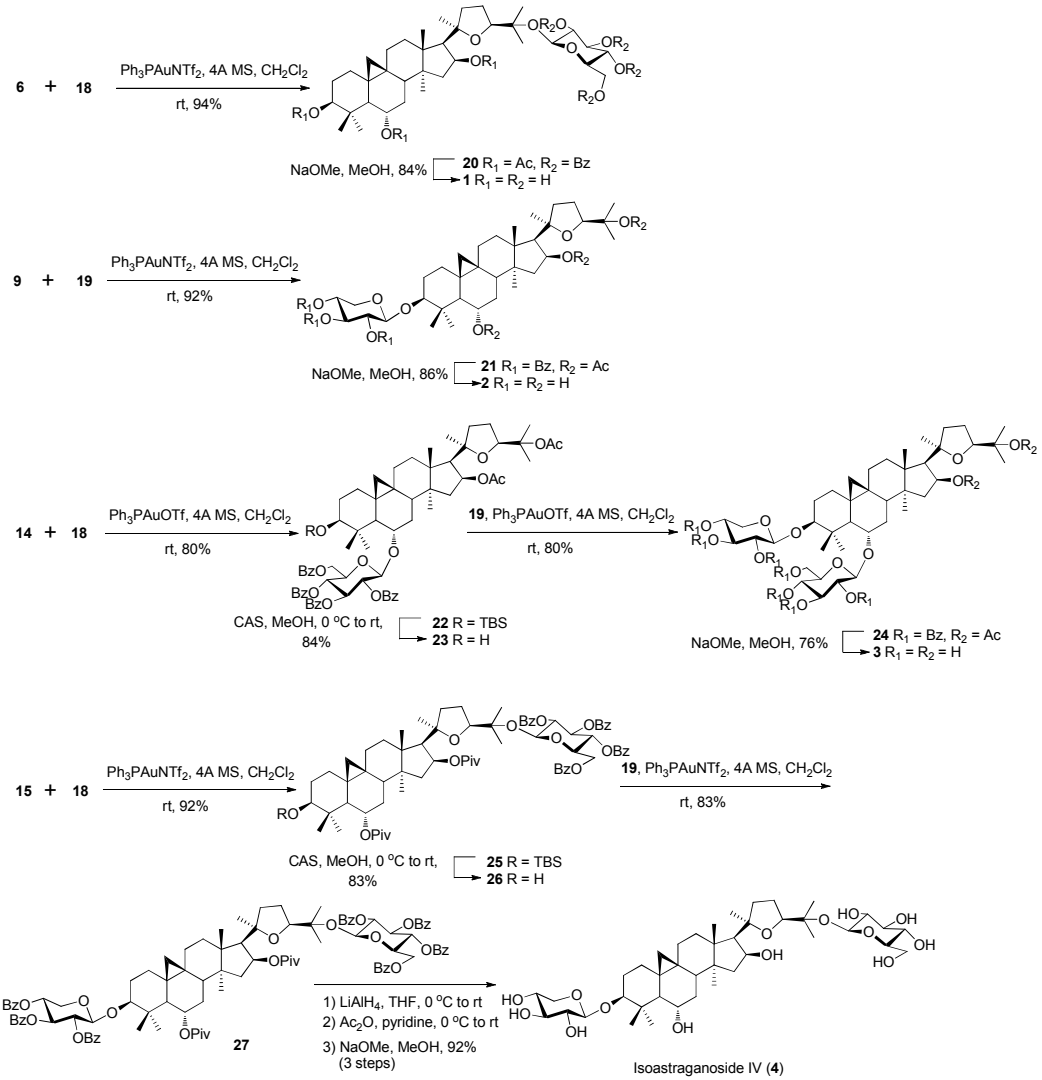
With both donors and acceptors in hand, now the stage was set for the critical glycosidic linkages constructions and the completion of the syntheses of all target molecules (Scheme 3). Thus, under the catalysis of $Ph_3PAuNTf_2$ (0.5 equiv), glycosylation of the tertiary 25-OH acceptor **6** with glucosyl donor **18** proceeded fluently, and the desired monoglycoside **20** was isolated in 94% yield. Under the identical conditions, the condensation between 3-OH acceptor **9** with xylosyl donor **19** proceeded without any problem to afford cycloastragenol 3-*O*-glycoside **21** efficiently (92%). Surprisingly, when the 6-OH acceptor **14** was subjected to the same glycosylation conditions, its condensation with donor **18** proceeded so sluggishly that the conjugating product **22** was isolated in only moderate yield after stirring for 48 h at room temperature (54%), although the 6-OH of cycloastragenol was originally determined to be the second most reactive OH in the differentiation investigations. Replacing $Ph_3PAuNTf_2$ with more reactive $Ph_3PAuOTf$ (0.5 equiv) resulted in a evident enhancement in the glycosylation yield and 80% yield of **22** was obtained.

The abnormal reactivity could presumably be attributed to the double stereodifferentiation effect.[19] With the 6-*O*-glucosyl residue settled, further glycosylation of 3-OH in **23**, obtained by CAS mediated desilylation of **22**, with xylosyl donor **19** was proved to be even more difficult. Both $Ph_3PAuNTf_2$ (0.5 equiv) and $Ph_3PAuOTf$ (0.5 equiv) delivered the cycloastragenol bisglycoside **24** with moderate yields (around 58%). The extremely lowered reactivity of the 3-OH of **23** was caused by the closely located and bulky 6-*O*-glucosyl residue, which probably blocked the attack of active donor species toward 3-OH from the originally less hindered α-face. Systematic screenings resulted in the establishment of the optimal glycosylation conditions in which 2.5 equivalents of donor **19** and 1.0 equivalents of $Ph_3PAuOTf$ were involved, through which 80% yield of **24** were recorded. To further examine the potential of the Yu glycosylation in the synthesis of cycloartane glycosides, the reaction between **15** and **18** under the catalysis of reduced amounts of $Ph_3PAuNTf_2$ (0.2 equiv) was checked. Pleasantly, no evident drop in chemical yield was observed, and **25** was obtained in a comparable 92% yield (vs 94.2% of **20**). Because the detrimental steric effect exerted by the 6-*O*-glucosyl residue was eliminated in monosaccharide acceptor **26**, derived from **25** via selective 3-OTBS cleavage, even under the catalysis of 0.2 equivalents of $Ph_3PAuNTf_2$, the 3-OH glycosylation of **26** with donor **19** proceeded so efficiently that 83% yield of cycloastragenol 3,25-*O*-bisglycoside **27** was isolated. Benefited from the anchimeric effect of benzoyl groups in donors **18** and **19**, all glycosidic linkages were fashioned in a stereoselective manner and only β-isomers were detected, as verified by $^1$H NMR

spectra (for anomeric protons: 5.20 ppm, dd, $J$ = 8.0 Hz for **20**; 4.85 ppm, dd, $J$ = 5.6 Hz for **21**; 4.86 ppm, d, $J$ = 7.6 Hz and 4.20 ppm, d, $J$ = 6.4 Hz for **24**; 5.30 ppm, d, $J$ = 7.6 Hz and 4.80 ppm, d, $J$ = 6.4 Hz for **27**). In addition, the evident upfield shift of the xylosyl anomeric proton from 4.80 ppm to 4.20 ppm in **24** provided a convincing evidence to verify the spatial proximity between 3-*O*-xylosyl and the 6-*O*-glucosyl residues.

With fully protected target molecules **20**, **21**, **24** and **27** in hand, the global deprotection was then investigated. NaOMe mediated Zemplén saponification worked quite well to transform **20**, **21**, and **24** to the corresponding target molecules **1**, astramembrannin II (**2**), and astragaloside IV (**3**) in 84%, 86%, and 76% yields, respectively. However, when **27** carrying two Pivs was exposed to the identical saponification conditions, the desired isoastraganoside IV (**4**) was not obtained as expected, instead, the partially deprotected intermediate with the 6,16-OPivs intact was isolated. The bulky characteristics of pivaloyl group renders Piv to enjoy a quite broad scope of regioselectivity in OH protections, however, in some cases, the same property brings about problems for its removal.[20] In order to cleave the two pivaloyl protecting groups, different conditions including elevated temperature and various bases such as LiOH, KOH, and hydrazine were tried. Unfortunately, all trials met with failure uniformly, and no clean conversion was obtained. Finally, a detour strategy was devised to fulfill the global deacylation goal, wherein the sequential lithium aluminum hydride (LAH) mediated reductive acyl group cleavage, reacetylation with $Ac_2O$ and pyridine (to facilitate the removal of aluminum salts),

and NaOMe promoted Zemplén saponification were involved. Although an indirect strategy was adopted, the whole deprotection efficiency was not compromised and 92% yield of isoastraganoside IV (**4**) was isolated (3 steps). The spectroscopic data of all synthetic compounds were in good accordance with those either reported in literature or recorded with authentic sample,[21] verifying the correctness of synthetic compounds.[18]




**Scheme 3**. Synthesis of the target molecules **1**-**4**.

## Conclusion

In summary, compounds **1**–**4** represent the four types of cycloastragenol glycosides isolated from *Astraglus membranaceus*, which bear the sugar moieties at the 25-OH, 3-OH, 3,6-OHs, and 3,25-OHs, respectively. The synthetic approach features not only the full differentiation of the hydroxyl groups on cycloastragenol but also the highly efficient construction of glycosidic linkages via the Yu glycosylation protocol. With the present approach in hand, access to the diverse cycloastragenol glycosides and their analogs has become feasible. The availability of these homogeneous glycosides will greatly facilitate studies of their biological and pharmacological activities, so that their therapeutic effects can finally be deciphered.

## Experimental section

**General Comments**. All reactions were monitored by thin-layer chromatography over silica-gel-coated TLC plates (Yantai Chemical Industry Research Institute). The spots on TLC were visualized by warming 5% $H_2SO_4$ (5% $H_2SO_4$ in ethanol) sprayed plates on a hot plate. Column chromatography was performed using silica gel (Qingdao Marine Chemical Inc., China), and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden). NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz). Optical rotations were measured at 25 °C with a Rudolph Autopol IV automatic polarimeter using a quartz cell with 2 mL capacity and a 1 dm path length. Concentrations (*c*) are given in g/100 mL. High resolution mass spectra were recorded on a Bruker micrOTOF II spectrometer using electrospray ionization (ESI).

**3,6,16-Tri-*O*-acetyl-cycloastragenol (6).** To a solution of cycloastragenol **5**[22] (180 mg, 0.37 mmol), PPY (108 mg, 0.74 mmol), and DIPEA (0.91 mL, 5.6 mmol) in dry toluene (10 mL) was added $Ac_2O$ (0.35 mL, 3.7 mmol) dropwise at 0 $^oC$ under $N_2$ atmosphere. After the addition was completed, the reaction mixture was heated to 105

°C, and the stirring was continued at the same temperature for 2 h. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate. The resulting mixture was washed successively with water, 1N HCl, aqueous saturated $NaHCO_3$, and brine, and then dried over anhydrous $Na_2SO_4$. Filtration was followed by concentration under reduced pressure to give the crude product which was further purified by silica gel chromatography (PE/EA = 5 : 1) to afford **6** (184 mg, 81%) as a white solid: $[\alpha]_D^{25}$ = 73.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.44-5.39 (m, 1 H), 4.75 (td, *J* = 4.4, 9.2 Hz, 1 H), 4.60 (dd, *J* = 4.4, 11.2 Hz, 1 H), 3.72 (dd, *J* = 6.8, 8.4 Hz, 1 H), 2.50 (d, *J* = 8.4 Hz, 1 H), 2.38 (td, *J* = 5.2, 11.6 Hz, 1 H), 2.17 (dd, *J* = 8.0, 13.6 Hz, 1 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.30 (s, 3 H), 1.29 (s, 3 H), 1.20 (s, 3 H), 1.09 (s, 3 H), 0.99 (s, 3 H), 0.98 (s, 3 H), 0.85 (s, 3 H), 0.61 (d, *J* = 4.8 Hz, 1 H), 0.38 (d, *J* = 4.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.6, 170.4, 85.6, 81.9, 79.5, 75.6, 70.9, 70.2, 57.1, 49.7, 46.2, 46.1, 45.3, 45.0, 40.1, 36.5, 32.9, 32.5, 31.4, 29.7, 29.2, 28.4, 27.8, 27.7, 26.6, 26.0 (2 C), 24.5, 21.8, 21.6, 21.2, 20.7, 20.4, 20.0, 16.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{36}H_{57}O_8$ 617.4048; found 617.4049.

**3-*O-tert*-Butyldimethylsilyl-cycloastragenol (7).** To a solution of cycloastragenol **5** (400 mg, 0.82 mmol) and imidazole (333 mg, 4.9 mmol) in dry DMF (0.6 mL) was added TBSCl (489 mg, 3.3 mmol) at 0 °C. Then the reaction mixture was warmed to room temperature and stirring was continued at the same temperature for 8 h, at which time TLC showed that all starting material disappeared. Ethyl acetate was added to dilute the reaction and the resulting mixture was washed successively with water, 1N HCl, aqueous saturated $NaHCO_3$, and brine, and then was dried over anhydrous $Na_2SO_4$. Filtration and concentration afforded the crude product which was further purified by silica gel chromatography (petroleum ether/ethyl acetate = 1 : 1) to deliver **7** (376.5 mg, 77%) as a white solid: $[\alpha]_D^{25}$ = 30.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.67 (dd, *J* = 7.6, 14.4 Hz, 1 H), 3.72 (dd, *J* = 6.0, 8.0 Hz, 1 H), 3.51 (td, *J* = 3.6, 9.6 Hz, 1 H), 3.25 (dd, *J* = 4.8, 10.0 Hz, 1 H), 2.59 (dd, *J* = 10.4, 21.6 Hz, 1 H), 2.31 (d, *J* = 8.0 Hz, 1 H), 2.00-1.92 (m, 4 H), 1.76 (dd, *J* = 4.0, 12.0 Hz, 1 H), 1.25 (s, 3 H), 1.21 (s, 3 H), 1.17 (s, 3 H), 1.13 (s, 3 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 0.91 (s, 3

H), 0.89 (s, 3 H), 0.85 (s, 9 H), 0.47 (d, *J* = 4.0 Hz, 1 H), 0.31 (d, *J* = 4.4 Hz, 1 H), 0.00 (s, 3 H), -0.005 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 87.1, 81.4, 78.8, 73.4, 71.8, 68.9, 57.5, 53.7, 46.9, 46.5, 46.0, 45.0, 42.1, 37.7, 34.4, 33.0, 32.1, 31.4, 30.8, 29.4, 28.6, 27.9, 27.7, 26.4, 25.9 (2 C), 25.8, 21.4, 20.5, 20.0, 18.1, 15.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{36}H_{65}O_5Si$ 605.4596; found 605.4599.

**3-*O*-*tert*-Butyldimethylsilyl-6,16,25-tri-*O*-acetyl-cycloastragenol (8).** Except for the concentration of **7**, similar procedure as that used for the synthesis of **6** was applied to afford **8** (139.7 mg, 99%) as a white solid: $[\alpha]_D^{25}$ = 78.3 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.31 (m, 1 H), 4.70 (td, *J* = 4.8, 8.8 Hz, 1 H), 3.96 (t, *J* = 7.2 Hz, 1 H), 3.24 (m, 1 H), 2.40 (d, *J* = 8.0 Hz, 1 H), 2.14 (m, 1 H), 2.13 (dd, *J* = 8.0, 13.6 Hz, 1 H), 1.98 (s, 3 H), 1.95 (s, 3 H), 1.93 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.29 (s, 3 H), 0.92 (s, 3 H), 0.85 (s, 15 H), 0.84 (s, 3 H), 0.54 (d, *J* = 4.8 Hz, 1 H), 0.27 (d, *J* = 4.8 Hz, 1 H), 0.00 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.4 (2 C), 170.2, 85.6, 83.1, 81.3, 78.4, 75.8, 70.6, 57.5, 49.6, 46.5, 46.3, 45.4, 44.6, 41.8, 37.3, 32.8, 32.3, 31.6, 30.6, 28.8, 28.4, 27.0 (2 C), 26.2, 26.0, 25.9, 22.8, 22.5, 21.8, 21.6, 21.5, 20.5, 20.2, 19.9, 18.1, 15.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{42}H_{71}O_8Si$ 731.4913; found 731.4912.

**6,16,25-Tri-*O*-acetyl-cycloastragenol (9).** To a solution of **8** (20 mg, 0.03 mmol) in MeOH (2.0 mL) was added CAS (26 mg, 0.11 mmol) at 0 $^o$C. Then the reaction mixture was warmed to room temperature, and the stirring was continued for another 3 h. $Et_3N$ was added to quench the reaction, then the volatile solvent was removed under reduced pressure to yield the crude product which was further purified by silica gel chromatography (petroleum ether/ethyl acetate = 4 : 1) to afford **9** (15 mg, 89%) as a white solid: $[\alpha]_D^{25}$ = 162.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.35-5.30 (m, 1 H), 4.76 (td, *J* = 4.4, 9.2 Hz, 1 H), 4.02 (t, *J* = 7.6 Hz, 1 H), 3.32 (dd, *J* = 3.6, 10.8 Hz, 1 H), 2.43 (d, *J* = 8.0 Hz, 1 H), 2.18-2.12 (m, 2 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.324 (s, 3 H), 1.319 (s, 3 H), 0.99 (s, 3 H), 0.96 (s, 3 H), 0.91 (s, 3 H), 0.59 (d, *J* = 4.8 Hz, 1 H), 0.36 (d, *J* = 4.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 85.5, 83.1, 81.3, 77.8, 75.8, 70.7, 57.5, 49.7, 46.4, 46.3, 45.5, 45.1, 41.2, 37.3, 33.1, 32.3, 31.7, 30.2, 29.2, 28.6, 27.0,

26.6, 26.2, 26.0, 22.8, 22.5, 21.8, 21.6, 21.5, 20.6, 20.3, 20.0, 15.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{36}H_{57}O_8$ 617.4048; found 617.4048.

**3,6-Di-*O*-acetyl-cycloastragenol (10).** To a solution of **5** (300 mg, 0.61 mmol) in dry pyridine (2.0 mL) was added $Ac_2O$ (2.0 mL) dropwise via a syringe at 0 $^oC$ under $N_2$ atmosphere. The ice-bath was then removed and the stirring was continued overnight. Ethyl acetate was added to dilute the reaction, the resulting solution was washed with water, 1N HCl, aqueous saturated $NaHCO_3$, and 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 (petroleum ether/ethyl acetate = 3 : 1) to deliver **10**[16] (337 mg, 96%) as a white solid. For comparison purpose, the $^1H$ NMR was recorded: $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.78 (td, *J* = 4.0, 9.2 Hz, 1 H), 4.71-4.66 (m, 1 H), 4.59 (dd, *J* = 4.4, 10.8 Hz, 1 H), 3.78 (td, *J* = 2.4, 7.2 Hz, 1 H), 2.61 (q, *J* = 10.4 Hz, 1 H), 2.34 (d, *J* = 7.6 Hz, 1 H), 2.05 (s, 3 H), 1.99 (s, 3 H), 1.31 (s, 3 H), 1.24 (s, 6 H), 1.16 (s, 3 H), 1.00 (s, 3 H), 0.95 (s, 3 H), 0.85 (s, 3 H), 0.62 (d, *J* = 4.8 Hz, 1 H), 0.36 (d, *J* = 4.8 Hz, 1 H).

**3,6-Di-*O*-levulinyl-cycloastragenol (11).** To a solution of **5** (300 mg, 0.61 mmol), DMAP (160 mg, 1.22 mmol), and levulinic acid (350 mg, 3.1 mmol) in dry $CH_2Cl_2$ (9 mL) was added DCC (630 mg, 3.1 mmol) under $N_2$ atmosphere at 0 $^oC$. The reaction mixture was then warmed to room temperature and the stirring was continued until TLC showed that all the starting material disappeared. After diluted with $CH_2Cl_2$, the resulting solution was washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine, then was dried over anhydrous $Na_2SO_4$. Filtration and concentration afforded a residue which was then subjected to purification by silica gel chromatography (petroleum ether/ethyl acetate = 1 : 2) to deliver **11** (413 mg, 98%) as a white solid: $[\alpha]_D^{25}$ = 39.6 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.78 (td, *J* = 4.8, 9.2 Hz, 1 H), 4.71 (dd, *J* = 7.6, 14.4 Hz, 1 H), 4.60 (dd, *J* = 4.4, 10.8 Hz, 1 H), 3.77 (t, *J* = 7.2 Hz, 1 H), 3.52-3.45 (m, 1 H), 2.77-2.70 (m, 4 H), 2.59 (t, *J* = 6.4 Hz, 2 H), 2.51 (t, *J* = 6.8 Hz, 2 H), 2.34 (d, *J* = 7.6 Hz, 1 H), 2.19 (s, 3 H), 2.18 (s, 3 H), 2.01-1.88 (m, 6 H), 1.30 (s, 3 H), 1.24 (s, 3 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 0.99 (s, 3 H), 0.94 (s, 3 H), 0.87 (s, 3 H), 0.60 (d, *J* = 4.8 Hz, 1 H), 0.34 (d, *J* = 4.4 Hz, 1 H); $^{13}C$ NMR (100 MHz,

$CDCl_3$) δ 206.6, 206.4, 172.4, 172.0, 87.0, 81.4, 79.9, 73.3, 71.7, 70.7, 57.3, 49.7, 49.2, 45.9, 45.8, 45.1, 44.7, 40.2, 38.1, 37.8, 34.4, 33.9, 33.0, 32.7, 31.4, 29.8, 28.8, 28.4, 28.2, 27.8, 27.7, 26.5 (2 C), 25.8, 25.6 (2 C), 24.9, 20.8, 20.7, 19.7, 16.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{40}H_{62}O_9Na$ 709.4286; found 709.4288.

**3,6-Di-*O*-levulinyl-16,25-di-*O*-acetyl-cycloastragenol (12).** Similar procedure as that used for the synthesis of **8** was adopted to convert **11** to **12** (349 mg, 84%) as a white solid: $[\alpha]_D^{25}$ = 63.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.35-5.30 (m, 1 H), 4.74 (td, *J* = 4.4, 9.2 Hz, 1 H), 4.60 (dd, *J* = 4.8, 11.2 Hz, 1 H), 4.02 (t, *J* = 7.6 Hz, 1 H), 2.77-2.69 (m, 4 H), 2.59 (t, *J* = 6.4 Hz, 2 H), 2.50 (t, *J* = 6.8 Hz, 2 H), 2.43 (d, *J* = 8.0 Hz, 1 H), 2.19 (s, 3 H), 2.18 (s, 3 H), 2.01 (s, 3 H), 1.96 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.323 (s, 3 H), 1.316 (s, 3 H), 0.98 (s, 3 H), 0.96 (s, 3 H), 0.88 (s, 3 H), 0.60 (d, *J* = 4.8 Hz, 1 H), 0.37 (d, *J* = 4.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.5, 206.3, 172.3, 172.1, 170.4, 170.2, 85.5, 83.0, 81.2, 79.8, 75.8, 70.7, 57.4, 49.8, 46.4, 46.2, 45.4, 45.1, 40.2, 38.0, 37.8, 37.3, 32.8, 32.2, 31.3, 29.8, 29.3, 28.7, 28.4, 28.3, 26.9, 26.6, 26.5, 26.1, 26.0, 22.8, 22.5, 21.6, 21.5, 20.7, 20.3, 20.0, 16.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{44}H_{66}O_{11}Na$ 793.4497; found 793.4496.

**16,25-Di-*O*-acetyl-cycloastragenol (13).** To a solution of **12** (530 mg, 0.69 mmol) in a mixed solvent of pyridine and HOAc (7.5 mL, v/v = 1.5 : 1) was added the freshly prepared $NH_2NH_2$/HOAc (0.9 mL, 18.6 mmol) at room temperature. The resulting mixture was stirred at the same temperature for another 12 h. Ethyl acetate was added to dilute the reaction, the resulting solution was washed with water, 1N HCl, aqueous saturated $NaHCO_3$, and brine and then was dried over anhydrous $Na_2SO_4$. Filtration and concentration gave a residue which was further purified by silica gel chromatography (petroleum ether/ethyl acetate = 2 : 1) to furnish **13** (355 mg, 99%) as a white solid: $[\alpha]_D^{25}$ = 59.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.36-5.30 (m, 1 H), 4.02 (t, *J* = 7.2 Hz, 1 H), 3.56 (td, *J* = 3.2, 9.2 Hz, 1 H), 3.33 (dd, *J* = 4.8, 11.2 Hz, 1 H), 2.43 (d, *J* = 8.0 Hz, 1 H), 2.26-2.13 (m, 2 H), 2.02 (s, 3 H), 1.97 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.25 (s, 3 H), 0.98 (s, 3 H), 0.96 (s, 3 H), 0.52 (d, *J* = 4.0 Hz, 1 H), 0.37 (d, *J* = 4.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.3, 85.6, 83.1, 81.3, 78.3, 75.9, 68.8, 57.6, 53.6,

46.6, 46.4, 46.3, 41.5, 37.6, 37.3, 32.3, 32.0, 30.8, 30.2, 29.4, 28.0, 27.0, 26.2, 26.0, 22.8, 22.5, 21.6, 20.8, 20.6, 20.2, 15.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{34}H_{54}O_7Na$ 597.3762; found 597.3764.

**3-*O*-*tert*-Butyldimethylsilyl-16,25-di-*O*-acetyl-cycloastragenol (14).** Similar procedure as that used for the synthesis of **7** was applied to convert **13** to **14** (271 mg, 87%) as a white solid: $[\alpha]_D^{25}$ = 81.8 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.36-5.31 (m, 1 H), 4.02 (t, *J* = 7.2 Hz, 1 H), 3.55 (td, *J* = 4.0, 9.2 Hz, 1 H), 3.28 (dd, *J* = 4.8, 10.0 Hz, 1 H), 2.44 (dd, *J* = 7.6 Hz, 1 H), 2.58-2.15 (m, 2 H), 2.02 (s, 3 H), 1.97 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.33 (s, 6 H), 1.15 (s, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.89 (s, 9 H), 0.50 (d, *J* = 4.4 Hz, 1 H), 0.33 (d, *J* = 4.4 Hz, 1 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 85.6, 83.1, 81.4, 78.8, 75.9, 68.6, 57.6, 53.7, 46.5, 46.3, 46.2, 45.6, 42.0, 37.4, 37.2, 32.3, 31.9, 30.8, 30.4, 29.7, 29.2, 28.4, 26.9, 26.1, 26.0, 25.9, 22.8, 22.5, 21.6, 20.7, 20.5, 20.1, 18.1, 15.7, -3.8, -4.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{40}H_{69}O_7Si$ 689.4807; found 689.4808.

**3-*O*-*tert*-Butyldimethylsilyl-6,16-di-*O*-pivaloyl-cycloastragenol (15).** To a solution of **7** (300 mg, 0.5 mmol) in dry pyridine (1 mL) was added PivCl (50 μL, 4.96 mmol) via a syringe at 0 $^oC$ under $N_2$ atmosphere. After the addition was finished, the ice-bath was removed and the mixture was heated to 50 $^oC$. The stirring was continued at the same temperature until TLC showed that all starting material disappeared. Ethyl acetate was added to dilute the reaction, the resulting solution was washed successively with water, 1N HCl, aqueous saturated $NaHCO_3$, and brine, and then was dried over $Na_2SO_4$. Filtration was followed by evaporation under reduced pressure afforded the crude product which was further subjected to silica gel chromatography (petroleum ether/ethyl acetate = 10 : 1) to give **15** (383.3 mg, 95%) as a white solid: $[\alpha]_D^{25}$ = 72.9 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.31-5.26 (m, 1 H), 4.74-4.69 (m, 1 H), 3.74 (t, *J* = 7.2 Hz, 1 H), 3.24 (dd, *J* = 4.8, 10.0 Hz, 1 H), 2.37 (d, *J* = 8.0 Hz, 1 H), 2.08-2.00 (m, 2 H), 1.36 (s, 3 H), 1.31 (s, 3 H), 1.18 (s, 3 H), 1.16 (s, 9 H), 1.13 (s, 9 H), 1.07 (s, 3 H), 0.96 (s, 3 H), 0.85 (s, 12 H), 0.80 (s, 3 H), 0.54 (d, *J* = 4.8 Hz, 1 H), 0.21 (d, *J* = 4.8 Hz, 1 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.2, 177.7, 85.5, 83.3, 78.5, 75.7, 71.2, 69.7, 57.5, 49.2, 46.7, 46.2,

45.1, 43.0, 41.9, 38.6, 38.2, 32.5, 31.9, 31.4, 27.8, 27.4, 27.3, 27.2, 27.1 (2 C), 26.6, 26.2, 26.0, 25.9, 25.4, 24.5, 20.7, 19.8, 19.6, 18.1, 15.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{46}H_{81}O_7Si$ 773.5746; found 773.5743.

**2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranosyl *ortho*-cyclopropylethynylbenzoate (18).**

Compound **16**[10c] (100 mg, 0.17 mmol) was dissolved in anhydrous $CH_2Cl_2$ (4 mL) at room temperature. To which *ortho*-alkynylbenzoic acid (ABzOH) (37.4 mg, 0.2 mmol), DMAP (28.1 mg, 0.23 mmol), EDCI (43.9 mg, 0.23 mmol), and DIPEA (74 μL) was added. After being stirred overnight at room temperature, the mixture was diluted with $CH_2Cl_2$, and washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine, respectively. The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 5 : 1) to provide **18**[10c] (121 mg, 93%) as a white foam. For comparison purpose, an aliquot of pure α isomer was obtained and the $^1H$ NMR was acquired. $^1H$ NMR (400 MHz, $CDCl_3$) δ $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.07 (d, $J$ = 7.5 Hz, 2 H), 7.92-7.87 (m, 6 H), 7.44-7.28 (m, 17 H), 6.94 (d, $J$ = 3.3 Hz, 1 H), 6.38 (dd, $J$ = 9.6, 9.9 Hz, 1 H), 5.94 (dd, $J$ = 9.9, 10.2 Hz, 1 H), 5.76 (dd, $J$ = 3.3, 9.9 Hz, 1 H), 4.80-4.66 (m, 2 H), 4.54 (dd, $J$ = 3.3, 6.0 Hz, 1 H), 1.56 (m, 1 H), 0.84 (d, $J$ = 6.6 Hz, 4 H).

**2,3,4-Tri-*O*-benzoyl-D-xylopyranosyl *ortho*-cyclopropylethynylbenzoate (19).**

Similar procedure as that used for the synthesis of **18** was adopted to convert **17**[15b] to **19** (612 mg, 89%) as a white foam. An aliquot of pure α isomer was obtained for detailed characterization: $[\alpha]_D^{25}$ = 0.02 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.04-7.98 (m, 6 H), 7.90 (dd, $J$ = 1.2, 8.0 Hz, 1 H), 7.58-7.51 (m, 3 H), 7.49-7.42 (m, 2 H), 7.38-7.30 (m, 6 H), 7.21 (td, $J$ = 1.6, 7.6 Hz, 1 H), 6.42 (d, $J$ = 7.6 Hz, 1 H), 5.81 (t, $J$ = 5.2 Hz, 1 H), 5.58 (dd, $J$ = 4.0, 5.2 Hz, 1 H), 5.36-5.32 (m, 1 H), 4.63 (dd, $J$ = 3.6, 12.8 Hz, 1 H), 4.06 (dd, $J$ = 4.8, 12.4 Hz, 1 H), 1.54-1.47 (m, 1 H), 0.90-0.84 (m, 4 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 164.9, 164.4, 164.3, 163.3, 133.7, 132.8, 129.9, 129.7, 129.4, 129.3, 128.5, 128.3, 127.8 (2 C), 126.3, 124.7, 99.7, 91.4, 73.6, 67.8, 67.6, 67.2, 60.9, 8.2, -0.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{38}H_{31}O_9$

631.1968; found 631.1966.

**3,6,16-Tri-*O*-acetyl-25-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-cycloastragenol (20).** To a solution of **6** (12 mg, 0.02 mmol) and **18** (31 mg, 0.05 mmol) in dry $CH_2Cl_2$ (2.0 mL) was added 4Å MS under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 minutes and then $Ph_3PAuNTf_2$ (7.0 mg, 0.01 mmol) was added. The stirring was continued at room temperature for 3 h (until **6** was consumed as monitored by TLC). The mixture was filtered, the filtrate was concentrated under reduced pressure to yield a residue, which was further purified by silica gel column chromatography (petroleum ether/ethyl acetate 5 : 1) to provide **20** (22 mg, 94%) in only β-isomer as a white solid: $[\alpha]_D^{25}$ = 72.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00-7.95 (m, 4 H), 7.91 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.85 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.56-7.48 (m, 3 H), 7.44-7.33 (m, 7 H), 7.30-7.27 (m, 2 H), 5.92 (t, *J* = 9.6 Hz, 1 H), 5.58 (t, *J* = 10.0 Hz, 1 H), 5.50 (dd, *J* = 8.0, 10.0 Hz, 1 H), 5.29-5.26 (m, 1 H), 5.20 (d, *J* = 8.0 Hz, 1 H), 4.74 (td, *J* = 4.0, 9.2 Hz, 1 H), 4.60-4.56 (m, 2 H), 4.47 (dd, *J* = 6.8, 12.0 Hz, 1 H), 4.16-4.11 (m, 1 H), 3.70 (t, *J* = 7.2 Hz, 1 H), 2.41 (d, *J* = 8.0 Hz, 1 H), 2.18 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.05 (s, 3 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.30 (s, 3 H), 1.22 (s, 3 H), 1.16 (s, 3 H), 1.12 (s, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.86 (s, 3 H), 0.60 (d, *J* = 4.8 Hz, 1 H), 0.38 (d, *J* = 4.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.4, 170.2, 166.0, 165.9, 165.3, 164.9, 133.4, 133.2, 133.1, 129.8 (2 C), 129.7 (2 C), 129.6, 128.9 (2 C), 128.4 (2 C), 128.3, 96.1, 85.8, 82.7, 80.0, 79.6, 76.0, 73.2, 72.1, 72.0, 70.5, 70.3, 63.8, 57.6, 49.8, 46.4, 46.3, 45.6, 45.4, 40.1, 37.4, 33.2, 32.2, 31.4, 29.8, 29.7, 28.6, 26.7, 26.6 (2 C), 25.9, 23.2, 22.2, 21.8, 21.5, 21.2, 20.6, 20.4, 20.1, 16.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{70}H_{82}O_{17}Na$ 1217.5444; found 1217.5447.

**3-*O*-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)-6,16,25-tri-*O*-acetyl-cycloastragenol (21).** Similar procedure as that used for the synthesis of **20** was applied for the glycosylation between **9** (12 mg, 0.02%) and **19** (25 mg, 0.04%), product **21** (22 mg, 92%) was isolated as a white solid: $[\alpha]_D^{25}$ = 29.4 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01-7.94 (m, 6 H), 7.56-7.47 (m, 3 H), 7.40-7.31 (m, 6 H), 5.78 (t, *J* = 7.6 Hz, 1 H), 5.45 (dd, *J* = 5.6, 7.6 Hz, 1 H), 5.34-5.28 (m, 2 H), 4.85 (d, *J* = 5.6 Hz, 1 H),

4.64 (td, *J* = 4.4, 8.8 Hz, 1 H), 4.46 (dd, *J* = 4.4, 12.0 Hz, 1 H), 4.02 (t, *J* = 7.2 Hz, 1 H), 3.68 (dd, *J* = 7.6, 12.0 Hz, 1 H), 3.25 (dd, *J* = 4.4, 11.6 Hz, 1 H), 2.42 (d, *J* = 8.0 Hz, 1 H), 2.00 (s, 3 H), 1.96 (s, 3 H), 1.90 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 0.95 (s, 3 H), 0.80 (s, 3 H), 0.78 (s, 3 H), 0.55 (d, *J* = 4.4 Hz, 1 H), 0.34 (d, *J* = 4.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.3 (2 C), 165.6, 165.5, 165.2, 133.4, 133.3, 133.2, 129.9, 129.8, 129.4, 129.2, 129.1, 128.4 (2 C), 128.3, 102.5, 88.3, 85.6, 83.1, 81.2, 75.8, 70.8, 70.7, 70.3, 69.5, 61.5, 57.4, 49.7, 46.4, 46.3, 45.4, 44.6, 41.5, 37.2, 32.8, 32.3, 31.6, 29.7, 28.9, 28.8, 28.1, 27.1, 26.2, 26.0, 22.8, 22.6, 21.8, 21.6, 20.6, 20.2, 20.0, 15.8; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{62}H_{80}O_{15}N$ 1078.5522; found 1078.5530.

**3-*O*-*tert*-Butyldimethylsilyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-16, 25-di-*O*-acetyl-cycloastragenol (22).** Except for the catalyst and amounts ($Ph_3PAuOTf$, 0.5 equivalents), similar procedure as that used for the synthesis of **20** was adopted to synthesize **22** (11.7 mg, 80%) as a white solid: $[\alpha]_D^{25}$ = 10.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 1.2, 8.0 Hz, 2 H), 8.28-8.25 (m, 4 H), 8.17 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.93-7.88 (m, 1 H), 7.86-7.81 (m, 2 H), 7.56-7.52 (m, 1 H), 7.50-7.45 (m, 2 H), 7.44-7.30 (m, 7 H), 7.27-7.23 (m, 2 H), 5.90 (t, *J* = 9.2 Hz, 1 H), 5.61 (t, *J* = 9.6 Hz, 1 H), 5.57 (dd, *J* = 8.0, 9.6 Hz, 1 H), 5.39-5.34 (m, 1 H), 4.96 (d, *J* = 8.0 Hz, 1 H), 4.60 (dd, *J* = 3.2, 12.0 Hz, 1 H), 4.49 (dd, *J* = 7.2, 12.0 Hz, 1 H), 4.18-4.13 (m, 1 H), 3.98 (t, *J* = 7.2 Hz, 1 H), 3.55 (dd, *J* = 5.2, 12.4 Hz, 1 H), 3.02 (dd, *J* = 4.8, 9.6 Hz, 1 H), 2.41 (d, *J* = 8.0 Hz, 1 H), 2.32 (dd, *J* = 8.0, 13.2 Hz, 1 H), 1.98 (s, 3 H), 1.95 (s, 3 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 1.29 (s, 3 H), 1.11 (s, 3 H), 0.98 (s, 3 H), 0.75 (s, 12 H), 0.61 (s, 3 H), 0.45 (d, *J* = 4.8 Hz, 1 H), 0.05 (d, *J* = 4.8 Hz, 1 H), -0.13 (s, 3 H), -0.36 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 165.8 (2 C), 165.2, 165.0, 133.4, 133.1 (2 C), 133.0, 129.9, 129.8, 129.7 (2 C), 129.6, 129.4, 129.0, 128.9, 128.4, 128.3, 128.2, 101.9, 85.8, 83.2, 81.8, 78.6, 78.4, 75.5, 73.4, 72.4, 72.2, 70.1, 63.9, 57.5, 50.4, 46.6, 46.1, 44.0, 42.4, 41.7, 37.8, 32.6, 31.9, 31.1, 30.4, 28.1, 27.7, 26.7, 26.1, 26.0, 25.9, 22.8, 22.6, 21.6, 21.5, 21.0, 19.2, 19.1, 18.0, 15.6, -4.0, -5.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{74}H_{95}O_{16}Si$ 1267.6384; found 1267.6406.

**6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-16,25-di-*O*-acetyl-cycloastragenol (23).** Similar procedure as that used for the synthesis of **9** was used to convert **22** to **23** (7.6 mg, 84%) as a white solid: $[\alpha]_D^{25}$ = 21.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.57-7.46 (m, 4 H), 7.43-7.32 (m, 7 H), 7.28 (m, 1 H), 5.90 (t, *J* = 9.6 Hz, 1 H), 5.62 (t, *J* = 10.0 Hz, 1 H), 5.54 (dd, *J* = 8.0, 9.6 Hz, 1 H), 5.36-5.31 (m, 1 H), 4.98 (d, *J* = 8.0 Hz, 1 H), 4.60 (dd, *J* = 2.8, 12.0 Hz, 1 H), 4.50 (dd, *J* = 6.8, 12.0 Hz, 1 H), 4.19-4.14 (m, 1 H), 3.99 (t, *J* = 7.2 Hz, 1 H), 3.56-3.51 (m, 1 H), 3.11 (dd, *J* = 4.4, 10.4 Hz, 1 H), 2.38 (d, *J* = 8.0 Hz, 1 H), 2.26 (dd, *J* = 8.0, 13.6 Hz, 1 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.29 (s, 3 H), 1.26 (s, 3 H), 1.14 (s, 3 H), 0.92 (s, 3 H), 0.78 (s, 3 H), 0.76 (s, 3 H), 0.45 (d, *J* = 4.4 Hz, 1 H), 0.15 (d, *J* = 4.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 165.8, 165.2, 165.0, 133.4, 133.1 (2 C), 129.9, 129.8, 129.7 (2 C), 129.4, 128.9, 128.4, 128.2, 101.3, 85.6, 83.2, 81.7, 78.8, 78.0, 75.5, 73.8, 72.5, 72.4, 70.0, 63.8, 57.5, 50.7, 46.5, 46.1, 44.5, 44.0, 41.2, 38.8, 32.8, 32.4, 31.3, 29.8, 29.7, 28.3, 27.4, 26.7, 26.9, 26.7, 26.0 (2 C), 22.9, 22.6, 21.6, 21.5, 21.0, 19.6, 19.5, 15.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{68}H_{81}O_{16}$ 1153.5519; found 1153.5523.

**3-*O*-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-16,25-di-*O*-acetyl-cycloastragenol (24).** Except for the catalyst and amounts ($Ph_3PAuOTf$, 1.0 equivalents), similar procedure as that used for the synthesis of **20** was adopted to synthesize **24** (10.0 mg, 80%) as a white solid: $[\alpha]_D^{25}$ = -4.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00-7.90 (m, 12 H), 7.84 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.67-7.63 (m, 1 H), 7.61 (m, 1 H), 7.56-7.51 (m, 4 H), 7.48-7.33 (m, 13 H), 7.30 (m, 2 H), 5.90 (t, *J* = 9.6 Hz, 1 H), 5.65 (t, *J* = 8.0 Hz, 1 H), 5.60 (t, *J* = 10.0 Hz, 1 H), 5.55 (dd, *J* = 8.0, 10.0 Hz, 1 H), 5.40-5.34 (m, 1 H), 5.30 (dd, *J* = 6.4, 8.0 Hz, 1 H), 5.25-5.20 (m, 1 H), 4.86 (d, *J* = 7.6 Hz, 1 H), 4.58 (dd, *J* = 3.2, 12.0 Hz, 1 H), 4.49 (dd, *J* = 7.2, 12.0 Hz, 1 H), 4.35 (dd, *J* = 4.8, 11.6 Hz, 1 H), 4.20 (d, *J* = 6.4 Hz, 1 H), 4.16-4.11 (m, 1 H), 3.99 (t, *J* = 7.2 Hz, 1 H), 3.40 (dd, *J* = 8.0, 11.6 Hz, 1 H), 3.01 (dd, *J* = 4.4, 11.2 Hz, 1 H), 2.43 (d, *J* = 8.0 Hz, 1 H), 2.31 (dd, *J* = 8.0, 13.6 Hz, 1 H), 1.98 (s, 3 H), 1.96 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.30 (s, 3 H), 1.12 (s, 3 H), 0.98 (s, 3 H), 0.56 (s, 3 H), 0.55 (s, 3 H), 0.37 (d, *J* = 4.4 Hz, 1 H), 0.03 (d, *J* = 4.8 Hz,

1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 165.9, 165.8, 165.6, 165.5, 165.2, 164.9 (2 C), 102.4, 101.6, 87.3, 85.8, 83.2, 81.8, 77.7, 75.5, 73.1, 72.2, 70.9, 70.7, 70.2, 69.7, 63.9, 61.7, 57.4, 50.6, 46.6, 46.0, 43.8, 41.6, 37.8, 32.5, 31.9, 31.1, 31.0, 29.7 (2 C), 29.4, 28.7, 27.1, 26.9, 26.7, 26.0, 23.9, 22.9, 22.7, 22.6, 21.6, 21.5, 21.0, 19.0, 18.9, 15.6, 14.1; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{94}H_{104}O_{23}N$ 1614.6994; found 1614.7008.

**3-*O*-*tert*-Butyldimethylsily-6,16-di-*O*-pivaloyl-25-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-cycloastragenol (25).** Except for the catalyst amounts ($Ph_3PAuNTf_2$, 0.2 equivalents), similar procedure as that used for the synthesis of **20** was applied to afford **25** (160 mg, 92%) as a white solid: $[\alpha]_D^{25}$ = 40.3 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02-7.96 (m, 4 H), 7.91 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.86 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.54-7.48 (m, 4 H), 7.43-7.34 (m, 7 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 5.90 (t, *J* = 9.6 Hz, 1 H), 5.53 (dd, *J* = 9.2, 10.0 Hz, 1 H), 5.48 (dd, *J* = 7.6, 9.2 Hz, 1 H), 5.35 (d, *J* = 8.0 Hz, 1 H), 5.23-5.18 (m, 1 H), 4.76 (dd, *J* = 6.8, 14.4 Hz, 1 H), 4.60 (dd, *J* = 2.8, 12.0 Hz, 1 H), 4.44 (dd, *J* = 7.2, 12.0 Hz, 1 H), 4.13-4.08 (m, 1 H), 3.72 (dd, *J* = 4.8, 8.4 Hz, 1 H), 3.20 (m, 1 H), 2.42 (d, *J* = 7.6 Hz, 1 H), 2.14-2.06 (m, 2 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.18 (s, 9 H), 1.17 (s, 9 H), 1.16 (s, 3 H), 1.13 (s, 3 H), 0.98 (s, 3 H), 0.86 (s, 12 H), 0.80 (s, 3 H), 0.56 (d, *J* = 4.8 Hz, 1 H), 0.27 (d, *J* = 4.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.0, 177.7, 165.9, 165.8, 165.4, 164.9, 134.2, 134.1, 133.5, 133.2, 133.1 (2 C), 129.8 (2 C), 129.7 (2 C), 129.6, 129.3, 129.2, 129.0, 128.8, 128.4, 128.3 (2 C), 96.2, 86.0, 84.1, 80.1, 78.3, 76.1, 73.1, 72.1 (2 C), 70.5, 69.8, 63.9, 57.8, 49.1, 46.8, 46.3, 45.2, 43.2, 41.9, 38.6, 38.5, 38.2, 32.6, 32.1, 31.2, 30.5, 27.8, 27.4, 27.2 (2 C), 25.9, 25.5, 24.0, 21.7, 20.6, 19.7, 19.6, 18.1, 15.4, -3.9, -4.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{80}H_{107}O_{16}Si$ 1351.7323; found 1351.7331.

**6,16-Di-*O*-pivaloyl-25-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-cycloastragenol (26).** Similar procedure as that used for the synthesis of **9** was adopted to convert **25** to **26** (91 mg, 83%) as a white solid: $[\alpha]_D^{25}$ = 20.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00-7.96 (m, 4 H), 7.91 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.85 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.54-7.49 (m, 3 H), 7.45-7.33 (m, 7 H), 7.31-7.27 (m, 2 H), 5.91 (t, *J* = 9.6 Hz, 1 H), 5.54 (t, *J* = 10.1 Hz, 1 H), 5.48 (dd, *J* = 8.0, 9.6 Hz, 1 H), 5.27 (d, *J*

= 8.0 Hz, 1 H), 5.23-5.18 (m, 1 H), 4.78-4.73 (m, 1 H), 4.59 (dd, *J* = 3.2, 12.0 Hz, 1 H), 4.44 (dd, *J* = 7.2, 11.6 Hz, 1 H), 4.14-4.08 (m, 1 H), 3.72 (dd, *J* = 4.8, 8.4 Hz, 1 H), 3.24 (dd, *J* = 4.8, 11.6 Hz, 1 H), 2.43 (d, *J* = 8.0 Hz, 1 H), 2.16 (dd, *J* = 7.6, 13.6 Hz, 1 H), 2.05-2.01 (m, 1 H), 1.36 (s, 3 H), 1.33 (s, 3 H), 1.18 (s, 12 H), 1.17 (s, 9 H), 1.11 (s, 3 H), 1.00 (s, 3 H), 0.91 (s, 3 H), 0.89 (s, 3 H), 0.56 (d, *J* = 4.8 Hz, 1 H), 0.30 (d, *J* = 4.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.1, 177.7, 166.0, 165.8, 165.4, 164.9, 133.5, 133.2 (2 C), 133.1, 129.8 (2 C), 129.7 (2 C), 129.6 (2 C), 128.9, 128.8, 128.4, 128.3 (2 C), 96.2, 86.0, 84.1, 80.1, 77.9, 76.1, 73.1, 72.1, 72.0, 70.4, 69.9, 63.9, 57.8, 49.2, 46.8, 46.3, 45.4, 43.7, 41.3, 38.6, 38.5, 38.3, 32.3 (2 C), 31.3, 30.0, 28.0, 27.3, 27.2, 27.1, 26.9, 26.1, 25.9, 25.6, 23.8, 22.0, 20.8, 19.8, 19.7, 15.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{74}H_{93}O_{16}$ 1237.6458; found 1237.6468.

**3-*O*-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)-6,16-di-*O*-pivaloyl-25-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-cycloastragenol (27).** Except for the catalyst amounts ($Ph_3PAuNTf_2$, 0.2 equivalents), similar procedure as that used for the synthesis of **20** was applied to afford **27** (361 mg, 83%) as a white solid: $[\alpha]_D^{25}$ = 25.2 (*c* 0.3, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02-7.94 (m, 10 H), 7.92 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.86 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.55-7.43 (m, 7 H), 7.41-7.27 (m, 14 H), 5.91 (t, *J* = 10.0 Hz, 1 H), 5.80 (t, *J* = 8.0 Hz, 1 H), 5.52-5.42 (m, 3 H), 5.32-5.27 (m, 2 H), 5.23-5.18 (m, 1 H), 4.80 (d, *J* = 6.4 Hz, 1 H), 4.65-4.58 (m, 2 H), 4.42-4.33 (m, 2 H), 4.14-4.09 (m, 1 H), 3.73 (dd, *J* = 4.8, 8.4 Hz, 1 H), 3.62 (dd, *J* = 7.6, 12.0 Hz, 1 H), 3.15 (dd, *J* = 4.4, 11.2 Hz, 1 H), 2.44 (d, *J* = 7.6 Hz, 1 H), 2.13-2.03 (m, 2 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.19 (s, 3 H), 1.17 (s, 9 H), 1.13 (s, 3 H), 1.08 (s, 9 H), 0.97 (s, 3 H), 0.78 (s, 3 H), 0.64 (s, 3 H), 0.52 (d, *J* = 4.8 Hz, 1 H), 0.26 (d, *J* = 4.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.0, 177.5, 166.0, 165.9, 165.6 (2 C), 165.4, 165.1, 164.9, 133.6, 133.4, 133.3, 133.2 (2 C), 133.1, 129.9, 129.8, 129.7 (2 C), 129.6 (2 C), 129.4, 129.2, 129.1, 128.9, 128.8, 128.5, 128.4 (2 C), 128.3 (2 C), 102.6, 96.2, 88.6, 86.1, 84.2, 80.2, 76.1, 73.1, 72.1 (2 C), 71.2, 71.0, 70.4, 69.6, 69.3, 63.9, 61.7, 57.8, 49.2, 46.8, 46.3, 45.2, 42.9, 41.4, 38.5, 38.3, 32.5, 31.8, 31.1, 28.6, 27.4, 27.2, 27.1, 26.6, 26.2, 25.9, 25.6, 24.0, 21.9, 20.7, 19.7, 19.6, 15.6; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{100}H_{116}O_{23}N$ 1699.7967; found 1699.7990.

**Cycloastrgenol 25-*O*-glucoside (1).** To a solution of **20** (20 mg, 0.017 mmol) in dry MeOH (2 mL) was added freshly prepared NaOMe (Na was dissolved in dry MeOH at 0 $^{o}$C) at room temperature. The resulting solution was stirred at the same temperature for 15 h, at which time TLC showed that the reaction reached completion. The pH value of the reaction mixture was adjusted with $H^+$ resin to 6-7. Filtration and concentration yield a residue which was further subjected to silica gel chromatography ($CH_2Cl_2$/MeOH = 5 : 1) to deliver **1** (9.2 mg, 84%) as a white solid: $[\alpha]_D^{25}$ = 21.4 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $C_5D_5N$) δ 5.10 (d, *J* = 8.0 Hz, 1 H), 4.95-4.88 (m, 2 H), 4.47 (dd, *J* = 2.8, 11.6 Hz, 1 H), 4.34 (dd, *J* = 4.8, 11.6 Hz, 1 H), 4.25-4.16 (m, 2 H), 4.09 (dd, *J* = 9.2, 16.0 Hz, 1 H), 3.93-3.89 (m, 2 H), 3.83-3.77 (td, *J* = 4.4, 10.0 Hz, 1 H), 3.70 (dd, *J* = 4.4, 11.2 Hz, 1 H), 2.87-2.80 (m, 1 H), 2.47 (d, *J* = 7.6 Hz, 1 H), 1.92 (s, 3 H), 1.68 (s, 3 H), 1.43 (s, 3 H), 1.38 (s, 6 H), 1.30 (s, 3 H), 0.96 (s, 3 H), 0.62 (d, *J* = 4.8 Hz, 1 H), 0.34 (d, *J* = 3.6 Hz, 1 H); $^{13}$C NMR (100 MHz, $C_5D_5N$) δ 98.6, 87.0, 81.8, 78.3, 78.0, 77.8, 75.0, 73.3, 71.1, 68.0, 62.5, 57.9, 53.7, 46.8, 45.9, 45.8, 44.9, 42.2, 38.5, 34.8, 33.2, 32.5, 31.2, 30.7, 29.6, 29.2, 27.6, 26.0, 25.7, 25.4, 22.8, 21.4, 20.6, 19.9, 15.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{36}H_{61}O_{10}$ 653.4259; found 653.4260.

**Astramembrannin (2).** Similar procedure as that used for the synthesis of **1** was applied to convert **21** to **2** (25.3 mg, 86%) as a white solid: $[\alpha]_D^{25}$ = 57.2 (*c* 0.5, $CH_3OH$); $^1$H NMR (400 MHz, $C_5D_5N$) δ 6.55 (bs, 1 H), 5.68 (bs, 1 H), 5.05 (dd, *J* = 6.8, 14.0 Hz, 1 H), 4.93 (d, *J* = 7.2 Hz, 1 H); 4.40 (dd, *J* = 4.8, 11.2 Hz, 1 H), 4.27-4.22 (m, 1 H), 4.19 (t, *J* = 8.4 Hz, 1 H), 4.09-4.05 (m, 1 H), 3.91 (dd, *J* = 5.6, 8.8 Hz, 1 H), 3.81-3.72 (m, 2 H), 3.66 (dd, *J* = 4.0, 11.6 Hz, 1 H), 3.15 (dd, *J* = 10.8, 20.4 Hz, 1 H), 2.55 (d, *J* = 7.6 Hz, 1 H), 2.45-2.42 (m, 1 H), 2.35-2.28 (m, 1 H), 2.00 (s, 3 H), 1.58 (s, 3 H), 1.43 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.01 (s, 3 H); 0.58 (d, *J* = 4.0 Hz, 1 H), 0.30 (d, *J* = 4.0 Hz, 1 H); $^{13}$C NMR (100 MHz, $C_5D_5N$) δ 107.4, 88.5, 87.0, 81.5, 78.3, 75.4, 73.2, 71.0, 67.8, 66.8, 58.1, 53.8, 46.8, 46.4, 45.9, 44.8, 42.5, 38.4, 34.7, 33.2, 32.3, 30.4, 30.1, 29.3, 28.7, 28.3, 28.0, 26.9, 26.2, 26.0, 21.3, 20.8, 20.0, 16.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{35}H_{58}O_9Na$ 645.3973; found 645.3974.

**Astragaloside IV (3).** Similar procedure as that used for the synthesis of **1** was applied to convert **24** to **3** (12.97 mg, 76%) as a white solid: $[\alpha]_D^{25}$ = 16.3 (*c* 0.4, $CH_3OH$); $^1H$ NMR (400 MHz, $C_5D_5N$) δ 6.55 (bs, 1 H), 5.81 (d, *J* = 2.8 Hz, 1 H), 4.93 (d, *J* = 8.0 Hz, 1 H), 4.88 (d, *J* = 7.2 Hz, 1 H), 4.52 (dd, *J* = 2.8, 11.6 Hz, 1 H), 4.39-4.31 (m, 2 H), 4.27-4.21 (m, 3 H), 4.19 (t, *J* = 8.8 Hz, 1 H), 4.06 (m, 2 H), 3.94-3.87 (m, 2 H), 3.83 (td, *J* = 3.6, 8.4 Hz, 1 H), 3.74 (t, *J* = 10.4 Hz, 1 H), 3.56 (dd, *J* = 4.0, 11.6 Hz, 1 H), 3.18 (dd, *J* = 11.2, 20.8 Hz, 1 H), 2.55 (d, *J* = 7.6 Hz, 1 H), 2.41-2.27 (m, 4 H), 2.06 (s, 3 H), 1.60 (s, 3 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.31 (s, 6 H), 0.95 (s, 3 H), 0.61 (d, *J* = 3.6 Hz, 1 H), 0.22 (d, 4.0 Hz, 1 H); $^{13}C$ NMR (100 MHz, $C_5D_5N$) δ 107.5, 105.0, 88.3, 87.0, 81.4, 79.1, 79.0, 78.3, 77.9, 75.4, 73.2, 71.6, 71.0, 66.8, 62.9, 58.0, 52.3, 46.0, 45.5, 44.8, 42.4, 34.7, 34.4, 33.2, 32.0, 30.0, 28.8, 28.6, 28.4, 28.0, 26.9, 26.2, 26.0, 20.9, 19.6, 16.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{41}H_{69}O_{14}$ 785.4682; found 785.4675.

**Isoastragaloside IV (4).** To a solution of **27** (70 mg, 0.042 mmol) in dry THF (2.0 mL) was added $LiAlH_4$ (25 mg, 0.67 mmol) under $N_2$ atmosphere at 0 °C. After the addition was completed, the ice bath was removed and the stirring was continued for another 3.7 h at room temperature. The reaction mixture was then chilled to 0 °C, and $H_2O$ was added slowly to quench the reaction. Then the volatile solvent was removed under reduced pressure to yield a residue, which was further co-evaporated with toluene for three times. The resulting residue was dissolved in dry pyridine (2.0 mL), to which $Ac_2O$ (2.0 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature, and the stirring was continued for another 24 h. General procedure was adopted to get the crude product which was further subjected to the silica gel chromatography (petroleum ether/ethyl acetate = 2 : 1) to afford acetylated intermediate. The acetylated intermediate was not characterized and put to the next saponification step directly.

To a solution of above obtained acetylated intermediate in dry MeOH (3 mL) was added freshly prepared MeONa at room temperature. The mixture was stirred at the same temperature for another 18 h, then the reaction was quenched with $H^+$ resin. Filtration and concentration afforded a residue which was further purified by reverse

phase C18 chromatography (MeOH/$H_2O$ = 3 : 1) to afford **4** (30 mg, 92%) as a white solid: $[\alpha]_D^{25}$ = 7.9 (*c* 0.25, $CH_3OH$); $^1H$ NMR (400 MHz, $C_5D_5N$) δ 5.08 (d, *J* = 7.6 Hz, 1 H), 4.93 (d, *J* = 7.2 Hz, 1 H), 4.45 (dd, *J* = 3.6, 11.6 Hz, 1 H), 4.40 (dd, *J* = 4.8, 11.2 Hz, 1 H), 4.32 (dd, *J* = 4.8, 11.6 Hz, 1 H), 4.25-4.15 (m, 4 H), 4.09-4.00 (m, 3 H), 3.92-3.88 (m, 2 H), 3.81-3.72 (m, 2 H), 3.64-3.61 (m, 1 H), 2.85 (dd, *J* = 11.6, 19.6 Hz, 1 H), 2.48 (d, *J* = 7.6 Hz, 1 H), 2.00 (s, 3 H), 1.67 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.29 (s, 3 H), 0.94 (s, 3 H), 0.56 (d, *J* = 3.2 Hz, 1 H), 0.28 (d, *J* = 4.0 Hz, 1 H); $^{13}C$ NMR (100 MHz, $C_5D_5N$) δ 107.4, 98.6, 88.4, 87.0, 81.8, 78.3, 77.8, 75.4, 75.0, 73.3, 71.1, 71.0, 67.7, 66.8, 62.5, 57.9, 53.8, 46.6, 45.9, 45.8, 45.0, 42.5, 38.4, 34.8, 33.2, 32.2, 30.3, 30.1, 29.3, 28.7, 27.6, 26.0, 25.7, 25.4, 22.8, 21.3, 20.7, 19.8, 16.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{41}H_{68}O_{14}Na$ 807.4501; found 807.4498.

**Acknowledgements:**

This work was financially supported by the National Natural Science Foundation of China (21372252 and 21572081). The Scientific Research Fund of Jiangxi Provincial Education Department (GJJ150328) was also appreciated.

**Supporting Information**

$^{13}C$ NMR spectra comparison between synthetic **1**-**4** with those either reported in literatures or acquired with authentic sample, copies of $^1H$ and $^{13}C$ for all new compounds

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21) The authentic sample of astragaloside IV was purchased from Shanghai Yuanye Bio-Technology Co., Ltd, and the website of the company is www.shyuanye.com.

22) Cycloastrogenol **5** is commercially available in above 98% purity, and we purchased it from Chendu Renze Bentu Reagents Co., Ltd. The website of the company is www.rzbtsj.com.