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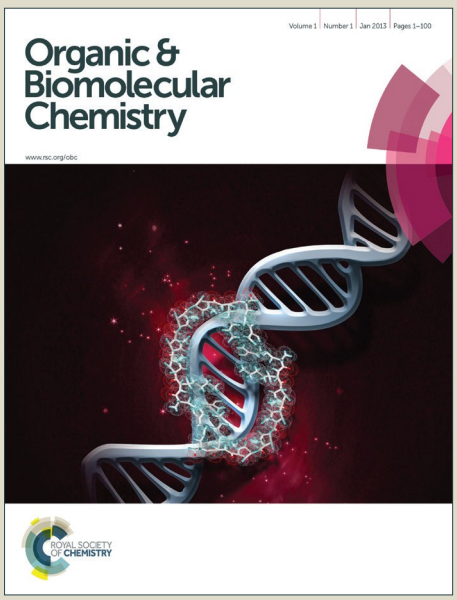

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ARTICLE

Synthetic Investigation toward Apigenin 5-O-glycoside Camellianin B as well as the Chemical Structure Revision

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Yang Hu,[a] Yuan-Hong Tu,[a] De-Yong Liu,[a] Jin-Xi Liao[a] and Jian-Song Sun*[,a]

Capitalizing on Au(I)-catalyzed ortho-alkynylbenzoate glycosylation method, the first total synthesis of the proposed structure of apigenin-5-*O*-glycoside camellianin B was acchieved, wherein three approaches, one linear and two convergent, were established, through which the synthetic structures were firmly corroborated. Meanwhile, through the synthesis of anthentic camellianin B via commercially availlable camellianin A, the misassigned structures of camellianin A and B were revised.

Introduction

Flavonoid glycosides are drawing more and more attention from both the organic synthesis and pharmaceutical communities, since as the major ingredients of fruits, vegetables and beverages they have been demonstrated to exert beneficial effect on the health of humans.[1,2] Big stride has been made in the field of flavonoid glycoside synthesis, nevertheless, great efforts were devoted to the syntheses of flavonoid 3-*O*, 7-*O*, 3,7-di-*O*, as well as *C*-glycosides,[3] and the synthesis of flavonol 5-*O*-glycosides is highly overlooked in spite of the fact that the number of this subclass of flavonoid glycosides is increasing rapidly and some of them have been proved to possess interesting bioactivities.[4] So far, papers regarding flavonoid 5-*O*-glycosides synthesis are quite rare, and all reported methods are heavily hinged on conventional glycosylation methods, making the overall synthetic efficiency far from satisfying.[5] On the contrary, flavonoid 5-*O*-glycosides are highly demanded not only as indispensable reference compounds in flavonoid compound metabolic pathway investigation [5c] but also as ideal leading compounds for flavonoid glycoside medicine development (Figure 1).[6]

As typical representatives of flavonoid 5-*O*-glycosides, camellianin B (**1**) and A (**1'**) were originally isolated from *Camellia sinensis* L in 1987.[7] Thereafter, as ingredients of antihyperglycemic fraction extracted from *Cephalotaxus sinensis*, these two glycosides were also isolated and characterized by Deng et al. during a bioassay-guided fractionation investigation.[8] Although camellianin B has been known for almost three decades, no bioactivity study has been conducted concerning it due to its extremely low content in natural sources. Structurally, as the aglycon of camellianin B, apigenin lacks the 3-hydroxyl group in comparison to kaempferol and quercetin derivatives,[9] which makes the reactivity of 5-OH dramatically decreased due to the enhanced strength of intramolecular H-bond (IHB). As a result, the glycosylation of apigenin 5-OH is more challenging.[9] In addition, the 1→4 linked disaccharide chain of camellianin B further increased the synthetic difficulty because of the low nucleophilicity of 4-OH of glucosyl residue.[10] Fascinated by the synthetic challenges as well as the possible antihyperglycemic effect, we decided to conduct the synthetic investigation of camellianin B, culminating in the first total synthesis of the originally proposed structure of it via three different routes and finally the chemical structures revision of both camellianin B and A.

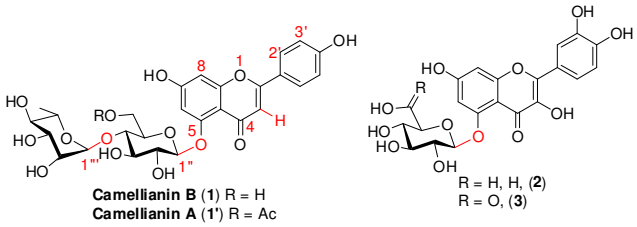

Figure 1. The chemical structures of representative flavonol 5-*O*-glycosides.

RESULTS AND DISCUSSION

Synthesis of camellianin B (1) via Linear Strategy

Given the challenges associated with apigenin 5-*O*-glycosidic linkage construction, we decided to adopt a more reliable synthetic strategy, the linear strategy, to produce camellianin B. As implied in our precedented results, the protecting groups on flavonol acceptors have a profound effect on the reactivity of the 5-OHs. Thus, apigenin acceptors equipped with hexanoyl and benzyl protecting groups were synthesized,

[a] The National Engineering Research Centre for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, China.
E-mail: jssun@jxnu.edu.cn

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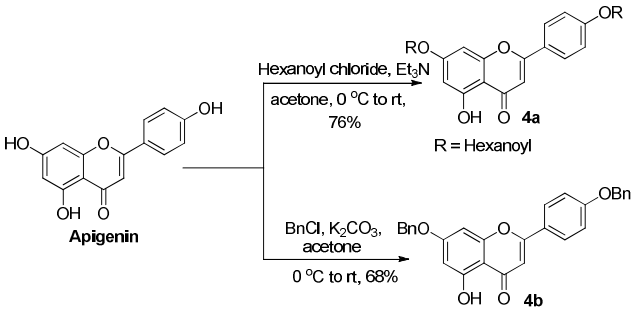
which were directly realized by controlling the equivalents of the employed reagents, furnishing **4a** and **4b** in 76% and 68%, respectively (Scheme 1).

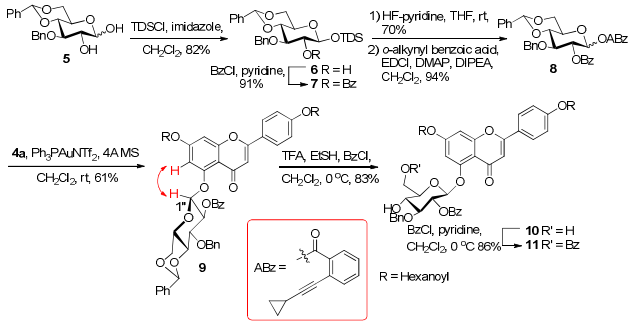


Scheme 1. Synthesis of acceptors **4a** and **4b**.

Interestingly, careful scrutiny of the ^{1}H NMR spectra of **4a** and **4b** shown that apigenin 5-OH acceptor with electron-withdrawing protecting groups on 7,4'-OHs had weakened IHB than that of compound carrying electron-donating protecting groups, as demonstrated by the chemical shifts of apigenin 5-OH protons (for **4a** the proton appeared at 12.68 ppm whereas the corresponding proton for **4b** resonated at 12.80 ppm). The chemical shift of hydroxyl protons involved in formation of IHB is a reliable indicative for the strength of the corresponding IHB,[11] and for flavonoid derivatives reduced IHB strength can facilitate the glycosylation of 5-OH. In consequence, **4a** was chosen as acceptor in the following synthetic study.

With easily available intermediate **5**[12] as starting material, the synthesis of glucosyl *ortho*-alkynylbenzoate **8** and its application in the pivotal glycosidic linkage construction were depicted in scheme 2. Thus, treated with TDSCl and imidazole, the anomeric OH of **5** could be blocked as TDS silyl ether with high regio- and stereo-selectivity, yielding **6** efficiently (82%).[10a] The remaining free 2-OH in **6** was then protected as benzoyl ester so as to ensure the stereoselectivity via anchimeric effect in the ensuing glycosylation step to give **7** (91%). HF•pyridine mediated removal of the anomeric TDS of **7** was followed by esterification of the nascent OH under dehydrative conditions to generate glucosyl *ortho*-alkynylbenzoate donor **8** (66%, 2 steps). With both donor **8** and acceptor **4a** in hand, the challenging glycosylation was then tried under the promotion of catalytic amount of Au(I) complex.[13] Pleasantly, a respectable 61% yield of **9** was isolated, even though donor **8** suffered from diminished reactivity due to the 'torsional effect' exerted by 4,6-*O*-benzylidene protecting group. Only β-isomer was detected, as determined by the anomeric proton of the glucosyl residue (5.47 ppm, J = 7.2 Hz). The sugar attachment position was corroborated by NOE spectrum, which clearly shown that H''-1 had correlation only with one of the two protons assigned to H-6 and H-8.[14] With considerable amount of **9** being available, our attention was then turned to the following acid-catalyzed regioselectively reductive opening of the benzylidene group in **9**. Unexpectedly, this conversion was proved to be extremely problematic due to the acid-sensitivity of the glycosidic linkage.

Upon subjected to conventional acid-promoted reductive conditions (TFA, Et_3SiH),[15] the cleavage of glycosidic linkage competed with the desired reductive opening process to yield the decomposed by-products. To avoid exposure of the vulnerable apigenin 5-*O*-glycosidic linkage to harsh acidic conditions, mild reaction conditions were also tried ($Cu(OTf)_2$, Me_2EtSiH),[16] but no reaction was detected and the starting material was recovered quantitatively. Because efforts to realize the desired benzylidene reductive opening all met with failure, the direct route was abandoned and a detour was adopted in which thoroughly removal of benzylidene group and regioselective protection of the primary 6''-OH were entailed. After extensive tries, the optimal conditions for thorough removal of benzylidene group of **9** were fixed, that is, 5.0 equivalents of TFA, 8.0 equivalents of EtSH, and catalytic amounts of BzCl (0.002 equiv.) at 0 °C (see table 1). Under these conditions, the benzylidene group in **9** was rapidly removed, and the diol intermediate **10** was isolated in a good 83% yield. Selective blocking of the primary 6''-OH of the sugar residue was achieved by treatment of **10** with BzCl at low temperature to afford **11** which is ready for subsequent rhamnosyl moiety installation. The introduction of benzoyl group on the 6''-OH was determined by the down-field shifts of H''-6 protons from 3.98 ppm to 4.67 ppm.



Scheme 2. Synthesis of apigenin 5-*O*-monoglycoside acceptor **11**.

Debenzylidenation is a relatively simple process from protecting group manipulation perspective. Nevertheless, in the case of **9**, to remove it without touching the acid-sensitive apigenin 5-*O*-glycosidic linkage is by no way a trivial problem. Considering that the successful debenzylidenation of **9** could not only facilitate the total synthesis of the target molecule but also offer helpful reference to practioners who will conduct the same transformation on acid-susceptible substrates, we decided to investigate this reaction systematically (Table 1). During the investigation the direct reductive benzylidene opening reaction, we observed that the glycosidic linkage was limited stable to acidic conditions and the maximum tolerant amount to TFA for **9** was determined to be 5.0 equivalents; once the applied TFA amounts exceeded 5.0 equivalents, the decomposition side reaction became serious. Thus, TFA (5.0 equiv.) in dry CH_2Cl_2 at 0 °C was tried first, and after 4 h of stirring, only 30% yield of **10** was obtained, and the remaining **9** was recovered (entry 1). Prolonging the reaction time could not bring about evident

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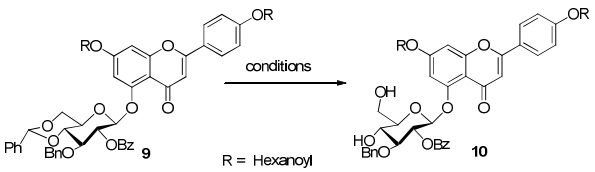
improvement. To expedite the desired process, TFA (5.0 equiv.) water was tried as nucleophilic species in the presence of TFA (5.0 equiv.) at room temperature, but an even lower yield of **10** was recorded (entry 2). In this case, the extended reaction time was detrimental to the desired deprotection process because of evident glycosidic linkage fracture. Replacing TFA with stronger TsOH at the presence of water led to the loss of the Hexanoyl group on 7-OH of apigenin residue and only trace amount of **10** was detected (entry 3).[9] Logically, weaker acids including HOAc[17] and $Er(OTf)_3$[18] were then checked, but these efforts were finally proved to be futile (entries 4-6). In view of the fact that only TFA provided promising results, we decided to fix TFA as the acid of choice while continued to screen other nucleophilic reagents besides water. Fortunately, EtSH (8.0 equiv.) was found to be the best of choice, and under the promotion of TFA (5.0 equiv.) it could afford the desired debenzylidene product **10** in a good 81% yield (entry 7). Although the chemical yield was satisfying, the reaction was sluggish, and at least 4.5 h were required before the reaction reached completion. Serendipitously, catalytic amount of BzCl (0.002 equiv) was demonstrate to be beneficial to the deprotection process, and at the presence of it the reaction time was shortened drastically to 45 min while the yield was maintained at above 80% (entry 8). The accelerating effect of BzCl was ascribed to the trace amount of HCl generated in situ by the reaction between BzCl and EtSH, which could easily activate the oxygen of the benzylidene group.

Table 1. Optimization of the conditions to remove benzylidene group in **9**.

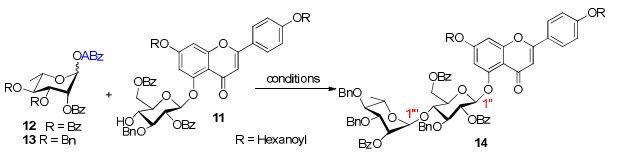


Entry	Solvents	Reagent	Time	Temperature	Yield[a]
1	CH_2Cl_2	TFA[b]	4 h	0 °C	30%
2	CH_2Cl_2 (wet)	TFA[b]	45 min	rt	15%
3	CH_2Cl_2 (wet)	*p*-TsOH	1.5 h	rt	trace
4	THF	AcOH (80%)	4 h	50 °C	trace
5	CH_3CN	$Er(OTf)_3$	2 h	rt	trace
6	CH_3CN/CH_2Cl_2	$Er(OTf)_3$	14 h	rt	trace
7	CH_2Cl_2	TFA, EtSH[c]	4.5 h	0 °C	81%
8	CH_2Cl_2	TFA, EtSH, BzCl (cat)[d]	45 min	0 °C	83%

[a] Isolated yield; [b] TFA (5.0 equiv. to **9**); [c] TFA (5.0 equiv.), EtSH (8.0 equiv.); [d] TFA (5.0 equiv.), EtSH (8.0 equiv.), BzCl (0.002 equiv.).

The optimized debenzylidenation conditions could afford **10** efficiently and reproducibly, paving the way to get diol **10** easily and in turn the monoglycoside acceptor **11**. With **11** in hand, the following rhamnosyl residue incorporation was then investigated. Not unexpectedly, the extremely inert property of acceptor **11** toward glycosylation posed another hurdle en route to produce **1** (Table 2). Easily available donor **12**[19] (1.2 equiv.) was tried first to condense with **11** under the promotion of PPh_3AuNTf_2 (0.2 equiv.). Surprisingly, no desired rhamnosylation product was detected and acceptor **11** was recovered completely (entry 1). Increasing the donor equivalents solely or enhancing the amounts of both donor and catalyst simultaneously is widely adopted strategies to conquest inert glycosylation acceptors.[20] Thus, under the effect of either 0.2 or 0.4 equivalents of PPh_3AuNTf_2, **12** in great excess (3.0 equiv.) were then tried to react with **11** (entries 2 and 3); again, no promising result was obtained. Further screening entailed resorting to more powerful catalyst PPh_3AuOTf,[13a,15b] however, besides considerable amounts of decomposition of **11** (0.4 equivalents of Au(I) complex), no desired glycosylation product were detected (entries 4 and 5). Finally, super-armed donor **13**[14,19] was invoked, and pleasantly we were rewarded by a promising yield of 15% disaccharide **14** under the promotion of PPh_3AuNTf_2 (entries 6 and 7). Switching the catalyst from PPh_3AuNTf_2 to PPh_3AuOTf brought about a dramatic enhancement in chemical yield, and 91% yield of **14** was isolated (entry 8). The structure of **14** was determined by ^1H and ^{13}C NMR spectra (For anomeric protons: H-1'' resided at 5.51 ppm with *J* value being 6.0 Hz, whereas H-1''' resided at 5.21 ppm in a doublet form with *J* = 2.0 Hz; For anomeric carbons: C-1'' and C-1''' had chemical shifts of 99.3 and 97.7 ppm, respectively).

Table 2. Optimization of conditions to form apigenin 5-*O*-disaccharide.



Entry	Donor (equiv.)	Catalyst (equiv.)	Time	Yield[a]
1	**12** (1.2)	$Ph_3PAuNTf_2$ (0.2)	12 h	NR[b]
2	**12** (3.0)	$Ph_3PAuNTf_2$ (0.2)	12 h	NR
3	**12** (3.0)	$Ph_3PAuNTf_2$ (0.4)	12 h	NR
4	**12** (1.2)	$Ph_3PAuOTf$ (0.2)	12 h	NR
5	**12** (1.2)	$Ph_3PAuOTf$ (0.4)	8 h	decomposed
6	**13** (1.2)	$Ph_3PAuOTf$ (0.2)	12 h	NR
7	**13** (6.0)	$Ph_3PAuNTf_2$ (0.6)	12 h	15%
8	**13** (6.0)	$Ph_3PAuOTf$ (0.6)	12 h	91%

[a] Isolated yield. [b] NR = no reaction.

With apigenin 5-*O*-disaccharide **14** in hand, all it took to reach **1** was the global deprotection (Scheme 3). To this end, **14** was subjected to palladium mediated hydrogenolysis and base mediated saponification successively, after purification by C18 RP chromatography, to afford **1** successfully (76%, 2 steps). It should be pointed out that the sequence of the deprotection steps is crucial for the success of producing **1**, since reversed deprotection sequence only afforded a complicated mixture. It is also worth mentioning that in the debenzylation step CH_2Cl_2 is an indispensable solvent ingredient, because without it the debenzylation reaction became extremely sluggish. Subsequently, comparison of the spectra of synthetic **1** with those reported in literature[7,8] was conducted, and unfortunately evident discrepancies were observed. More surprisingly, regarding the target molecule camellianin B, different documents provide contradictory analytic data (see ESI for ^1H NMR data comparison with different origins). Therefore, the reported data could not be used as convincing reference to judge the chemical structure obtained via chemical synthesis is right or not, and further measures have to be taken before a conclusion could be formed.

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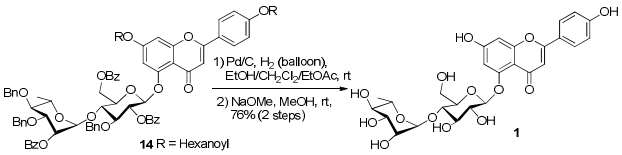
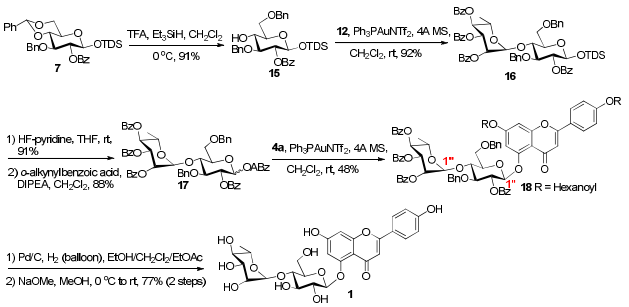


Scheme 3. Completion the synthesis of the proposed camellianin B (**1**).

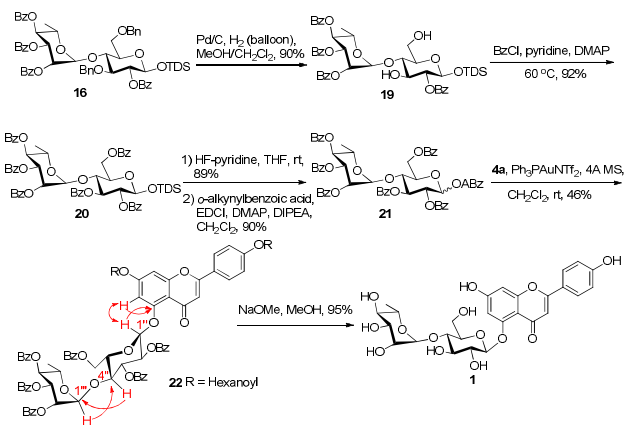
Synthesis of camellianin B (1) via Convergent Strategy

If the same compound as that generated via linear strategy could also be obtained by convergent strategy, then this would provide a convincing evidence to verify the correctness of the chemical structure of the synthetic **1**. Meanwhile, the convergent approaches may avoid the drawbacks inherent to linear route, thereby providing the proposed camellianin B in a more efficient manner. To this end, two convergent synthetic routes have been devised, and the first one is depicted in scheme 4. Thus, treated with TFA and Et_3SiH, the benzylidene group in **7** was reductively opened efficiently, yielding **15** in excellent yield, although the same transformation on **9** was frustrating in the linear approach. Regarding acceptor **15**, because the due to glycosylated 4-OH was flanked by two electron-donating benzyl groups at both 3 and 6-OHs and the adverse effect exerted by the bulky apigenin moiety (cf. **11**) was removed, the reactivity was so high that even disarmed rhamnosyl donor **12** could couple with it to furnish disaccharide **16** in 92% yield. The resultant **16** was then subjected to HF•pyridine mediated desilylation and dehydrative *o*-alkynylbenzoylation successively to produce disaccharide donor **17** (80%, 2 steps). The pivotal glycosylation between donor **17** and acceptor **4a** proceeded fluently to give **18** in a venerable 48% yield. The structure of **18** was confirmed by both ^{1}H NMR spectrum wherein H'' and H''' protons appeared at 5.46 (d, *J* = 6.4 Hz) and 5.32 (d, *J* = 1.6 Hz) and ^{13}C spectrum in which the anomeric carbons of C-1'' and C-1''' resonated at 97.3 and 100.1 ppm, respectively. Finally, similar deprotection procedures as those used for compound **14** was applied to **18**, and identical product **1** was produced, as verified by both TLC and ^{1}H NMR spectrum.



Scheme 4. Convergent synthesis of **1** with **17** as donor.

To further simplify the post-glycosylation manipulations and improve the convergent extent, the more convergent approach wherein disaccharide donor **21** equipped with unified acyl protecting groups was applied was subsequently investigated (Scheme 5). Distinct from the above mentioned convergent route, disaccharide **16** was not immediately transformed to disaccharide donor, instead, protecting groups unification was performed first. Thus, debenzylation of **16** via palladium-catalyzed hydrogenation furnished diol **19** (90%). The accelerating effect of CH_2Cl_2 on hydrogenolysis process was once more detected and utilized. Surprisingly, the free 3-OH in **19** was so inert that conventional benzoylation conditions (BzCl, pyridine, 0 °C to rt) could not benzoylate it, and only 6-OH benzoylated intermediate was isolated. Eventually, harsher reaction conditions were adopted, and the desired perbenzoylated disaccharide **20** was obtained successfully in 92% yield, which was then converted to disaccharide donor **21** without any event. Under the catalysis of $Ph_3PAuNTf_2$, **4a** was fluently glycosylated with donor **21** to afford apigenin 5-*O*-disaccharide **22** (46%). At this junction, the structure of **22** was thoroughly analysed through 1D and 2D NMR spectra. The sugar chain attachment position was definitely confirmed by NOE correlation between H-1'' and H-6 (6.82 ppm, d, *J* = 2.0 Hz) as well as by HMBC correlation of H-1'' and C-5. C-5 (156.2 ppm) was discriminated easily by its strong HMBC correlation with H-6, while the corresponding correlation with H-8 (6.96 ppm, d, *J* = 2.0 Hz) was not detected. The 1→4 inter-sugar linkage pattern of the disaccharide chain was deduced by strong HMBC correlations between H-1''' (5.34 ppm, d, *J* = 1.6 Hz, assigned by ^{1}H NMR) and C-4'' (75.7 ppm, deduced by its HMQC correlation with H-4'' resonating at 4.91 ppm as a triple signal with a *J* value of 9.2 Hz which could be easily discriminated by ^{1}H NMR), as well as HMBC correlation of C-1''' (assigned by HMQC at 98.9 ppm) and H-4'' (Scheme 5).[14] Therefore, the structure of **22** was confidently confirmed. All it takes from **22** to reach **1** is removal of all acyl protecting groups under basic conditions. Thus, treated with NaOMe, **22** was converted to **1** in an as high as 95% yield. Again, the obtained **1** was proved to be identical to those obtained by the former two approaches.



Scheme 5. Convergent synthesis of **1** with **21** as donor.

Revision of the originally proposed chemical structures of camellianin B and A

Although the fact that all synthetic routes resulted in the same product provides a strong support for the correctness of our synthetic compound, problems leading the spectroscopic

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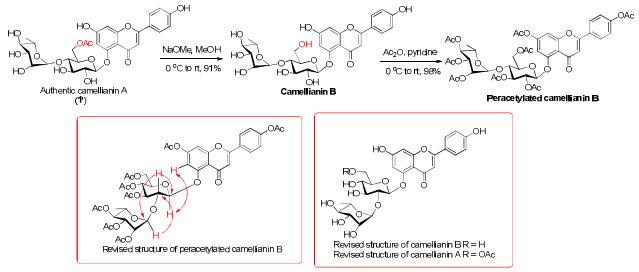
discrepancies between synthetic and authentic samples should be specified. Although the two reported analytic data of **1** are conflicting to each other, consensus is reached in terms of the relationship between camellianin B (**1**) and A (**1'**), that is, camellianin B differentiates from A by losing the acetyl group on 6''-OH of glucose residue. Hence, the authentic camellianin B could be obtained by deacetylation of the commercially available camellianin A (Scheme 6).[21] Treated with NaOMe, camellianin A was fluently converted to the authentic camellianin B (91%). Spectroscopic analysis revealed that the authentic camellianin B was not identical to those obtained by chemical synthesis (the NMR comparison between the synthetic and authentic samples is provided in ESI). To facilitate the reassignment of the chemical structures of camellianin B and A, peracetylation of authentic **1** was performed under conventional conditions (98% yield), and the resultant peracetylated camellianin B was then subjected to thoroughly 1D and 2D NMR analysis. The NOE correlation peak between H-6 and H''-1 indicated that the sugar chain was indeed attached to the 5-OH of the apigenin moiety; while the H-H COSY correlation between H''-1 and H''-2 which resided at 4.22 ppm implied that the sugar chain was 1→2 linked instead of the originally proposed 1→4 linked. This linkage pattern was further corroborated by HMBC spectrum, wherein the correlations of H-1''' and C-2'', H-2'' and C-1''', as well as H-2'' and C-1'' were recognized. Therefore, the architecture of peracetlated camellianin B should be revised to that shown in the red panels of scheme 6, in turn both the chemical structures of camellianin B and A have been assigned incorrectly.



Scheme 6. Synthesis of authentic and peracetylated authentic camellianin B

CONCLUSION

The first total synthesis of proposed camellianin B was achieved via three different routes. In the first route, a linear tactic was adopted. Although the early introduced acid-labile apigenin 5-*O*-glucosidic linkage made the following protecting group manipulations and sugar chain elongation quite difficult, all associated problems were overcome via systematic optimizations. In particular, efficient approaches to remove benzylidene protecting group of acid-sensitive substrate and to construct glycosidic linkage of inert acceptor containing flavonoid moiety were established. To avoid the problems posed by the existence of susceptible apigenin 5-*O*-glycosidic linkage, another two convergent routes were also devised, wherein the challenging apigenin 5-*O*-glycosidic linkages were fashioned with disaccharide *ortho*-alkynylbenzoites as donors under the catalysis of Au(I) complex. All three routes yielded the same products, verifying the correctness of the synthetic compound. The evident discrepancies of spectroscopic data between those of synthetic sample and those reported in literature coupled with the contradictory published analytic data concerning **1** prompted us to synthesize the authentic as well as peracetlylated authentic target molecules, which eventually led to the final structure revision of camellianin B and A.

Acknowledgements

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