

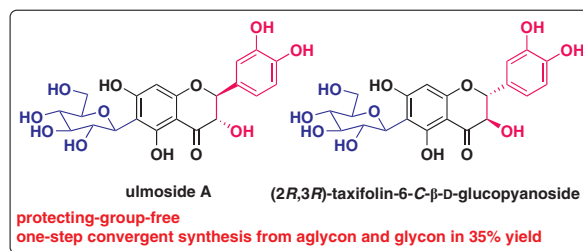
Total Synthesis of the Natural Products Ulmoside A and (2*R*,3*R*)-Taxifolin-6-*C*- β -D-glucopyranoside

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Abstract An efficient first total synthesis of highly polar ulmoside A and (2*R*,3*R*)-taxifolin-6-*C*- β -D-glucopyranoside, useful for the prevention of metabolic disorders, has been described. Key elements of the synthesis include a Sc(OTf)₃-catalyzed regio- and stereoselective C-glycosidation on taxifolin in 35% yield with D-glucose and chiral semipreparative reverse-phase high-performance liquid chromatography (HPLC) for the separation of both taxifolins and the diastereomeric mixture of taxifolin-6-*C*- β -D-glucopyranosides. Correlation of the analytical data of synthetic ulmoside A and its diastereomer with a natural ulmoside A sample confirmed the assigned absolute stereochemistry of the natural products.

Key words flavonoids, C-glycosidation, chiral HPLC, metal triflates, aglycone

Glycosyl flavonoids are ubiquitously distributed in nature and commonly found as secondary metabolites of plant or bacteria. They exhibit a wide range of very interesting biological activities. The glycosyl flavonoids are mostly present in nature as *O*-glycosides and rarely as *C*-glycosides.¹ In general, *C*-glycosides show excellent and different bioactivity when compared to the corresponding *O*-glycosides and aglycons. The C–C bond in these glycosides that links the sugar to aglycon appears to be of great importance, because the *C*-glycosyl bond is stable to enzymatic hydrolysis under physiological conditions, unlike the corresponding *O*-glycosides.^{1c} Therefore, some aryl *C*-glycosides are on the market as SGL₂ inhibitors for treating diabetes.^{1d}

Mourya and co-workers, in 2009, discovered and identified three new *C*-glycosylated flavonoids that were considered as stable glycosides in the biological system, namely (2*S*,3*S*)-taxifolin-6-*C*- β -D-glucopyranoside (or) K058 (or) ulmoside A, (2*S*,3*S*)-aromadendrin-6-*C*- β -D-glucopyranoside, and quercetin-6-*C*- β -D-glucopyranoside from *Ulmus*

wallichiana plant^{2a–c} (Figure 1). The bark of this plant is known in practice in some parts of India to treat bone fractures.^{2b} Mourya and co-workers evaluated their activity in stimulating osteoblast differentiation, which is a bone anabolic function needed for osteoporosis therapy. They also developed a composition for osteoporosis therapy with these compounds. Among them, ulmoside A (**1**) shows excellent bone deflecting activity and efficacy in treating steroid-induced metabolic disorders.^{2d} Interestingly, it has shown excellent adiponectin agonist activity, useful for the cure and prevention of diabetes, and also antioxidative and antiapoptotic activity.^{2e} Stark et al. also isolated ulmoside A (**1**) and (2*R*,3*R*)-taxifolin-6-*C*- β -D-glucopyranoside (**2**) and other flavonoid *C*-glycosides from the bark of medicinal plant *Garcinia buchananii*.^{2c,3a} The H₂O₂ scavenging and oxygen radical absorbance capacity (ORAC) assays demonstrated that compounds **1** and **2** show extraordinary antioxidative power. Earlier, (2*R*,3*R*)-taxifolin-6-*C*- β -D-glucopyranoside (**2**) was also isolated from *Garcinia epuntata* (Figure 1).^{3b}

The above compounds can only be obtained from natural sources in very small quantities. Moreover, evaluation of their biological activity and their development into a drug requires more quantities of the compounds. Therefore, a simple, short, and scalable strategy is indeed essential. To meet the above requirements we have undertaken the total synthesis of those compounds. Interestingly, these two compounds show similar chemical shifts in their NMR spectra, and both have a positive optical rotation. They are only distinguished by their CD spectra. So far, there are no reports on the synthesis of these compounds in the literature. Hence, their total synthesis also helps confirming the assigned stereochemical structures. The important issue to be addressed for designing a synthesis for this class of compounds is the C–C bond formation between the aglycon and carbohydrate moiety to give corresponding aryl *C*-glycosides.

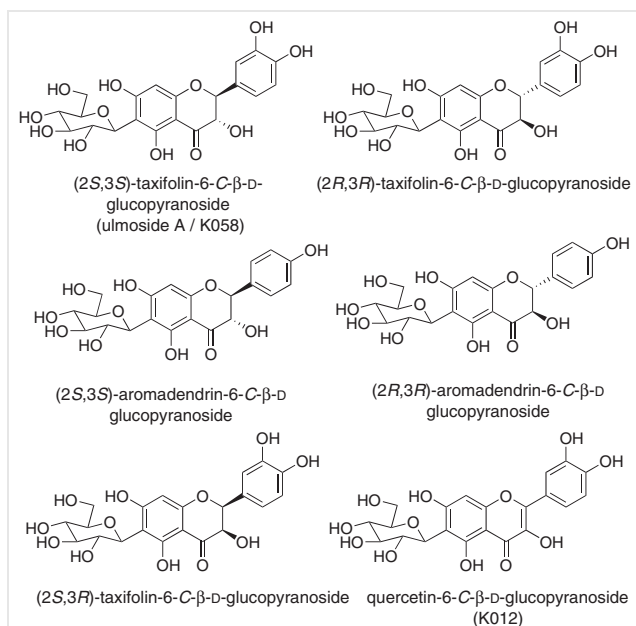
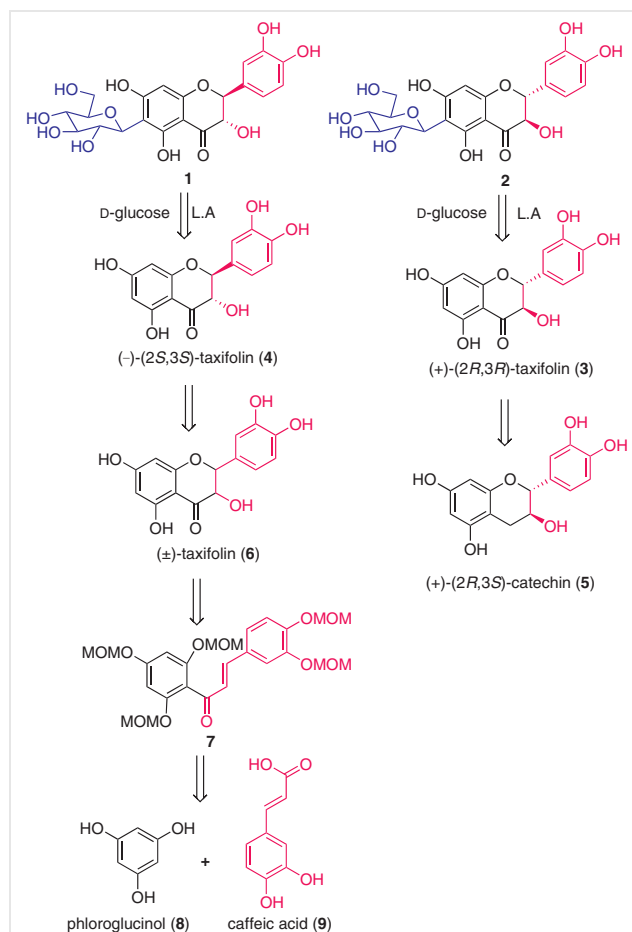


Figure 1 Structures of some natural flavonoid C-glycosides

Formation of the C–C bond between carbohydrate units and electron-rich aromatic moieties was first achieved by Friedel–Crafts reaction.⁴ Later, Suzuki and co-workers⁵ and Kometani et al.⁶ developed a methodology for the C-glycosylation of phenols by a Lewis acid-catalyzed rearrangement of *O*-glycoside to a C-glycosyl derivative, known as a Fries-type reaction. In all these general methods, protected sugar and aromatic moieties have been used for glycosidation that, finally, have to be deprotected to obtain the target compounds. Recently, Sato and others reported the C-glycosidation of unprotected flavonoids with unprotected sugars using metal triflates.^{7–9} Although the yields obtained with use of this method are lower and although the method was applied on simpler systems, we wanted to apply this method for the synthesis of chiral polyphenolic compounds **1** and **2**.

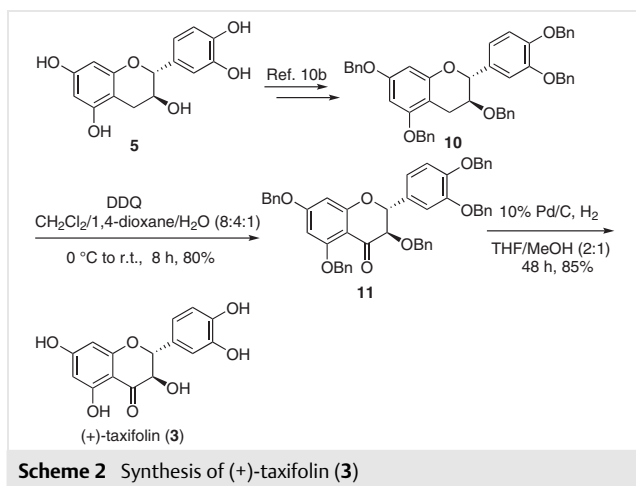
On the basis of the assigned stereochemistry, the retrosynthetic route for ulmoside A (**1**) and (2*R*,3*R*)-taxifolin-6-*C*-β-*D*-glucopyranoside (**2**) has been designed (Scheme 1). We envisioned a one-step synthesis of the target molecules **1** and **2** from corresponding taxifolins **3** and **4** by protecting-group-free C-glycosidation with *D*-glucose in the presence of metal triflates. The (+)-taxifolin (**3**) required for the synthesis of (2*R*,3*R*)-taxifolin-6-*C*-β-*D*-glucopyranoside (**2**) is commercially available but it is expensive; rather it can be prepared from (+)-catechin hydrate (**5**) by using a reported procedure.¹⁰ In the case of (–)-taxifolin (**4**), the aglycon part of compound **1**, to the best of our knowledge, neither its isolation nor its synthesis is reported in the literature. Only the racemic synthesis of taxifolin **6** is reported in the literature.¹¹ Therefore, we decided to synthesize both



Scheme 1 Retrosynthetic analysis

the taxifolins **3** and **4** from the chalcone compound **7** using epoxidation followed by a cyclization approach. Compound **7** could be obtained from commercially available phloroglucinol (**8**) and caffeic acid (**9**) (Scheme 1).

In order to prepare (+)-taxifolin (**3**), the hydroxy groups of (+)-catechin hydrate (**5**) were benzylated by treatment with *BnBr* and K_2CO_3 to give 5,7,3',4'-tetra-*O*-benzyl-(+)-catechin, which, on further treatment with *BnBr* and *NaH*, afforded 3,5,7,3',4'-pent-*O*-benzyl-(+)-catechin **10** in 73% yield (over two steps) (Scheme 2).¹⁰ In the previous report,^{10b} oxidation of 3,5,7,3',4'-pent-*O*-benzyl-(+)-catechin **10** by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a mixed solvent of $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ afforded desired keto compound **11** in 15% yield. To improve the yields in the oxidation, compound **10** was subjected to excess DDQ in a mixed solvent of $\text{CH}_2\text{Cl}_2/1,4$ -dioxane/ H_2O (8:4:1), which afforded the desired keto compound **11** in 80% yield.¹² Further, hydrogenolysis of keto compound **11** in the presence of H_2 and 10% *Pd/C* in MeOH/THF afforded (+)-taxifolin (**3**) in 85% yield.¹⁰



Having synthesized the required (+)-taxifolin (**3**), we next turned our attention to a regio- and stereoselective protecting-group-free C-glycosidation between (+)-taxifolin (**3**) and D-glucose. Thus, experiments were carried out with different catalysts under different solvent ratios as shown in Table 1. The highest yield (35%) of compound **2** was obtained with scandium triflate (0.4 equiv) with a 2:1 ratio of acetonitrile and water heated to reflux for 48 hours (Table 1, entry 4).¹³ All analytical data including ¹H and ¹³C NMR spectra of the synthetic (2*R*,3*R*)-taxifolin-6-C-β-D-glucopyranoside (**2**) were in agreement with reported values.³

Then, we decided to synthesize (±)-taxifolin (**6**) from chalcone **7** as shown in Scheme 3. For this purpose, a new and biomimetic approach was developed to obtain **7**. Treatment of phloroglucinol (**8**) with methoxymethyl chloride (MOMCl) and NaH in dry DMF gave compound **12** in 90% yield. Esterification of caffeic acid (**9**) with MeOH in the presence of H₂SO₄ as a catalyst and protection of the phenolic groups with MOMCl provided the ester compound. Hydrolysis of the resultant ester with NaOH in MeOH/THF afforded the acid compound **13** in 90% yield. Further, acylation of compound **12** with acid **13** in the presence of trifluoroacetic anhydride (TFAA) in CH₂Cl₂ afforded chalcone **7** in 85% yield. Treatment of compound **7** with alkaline hydrogen peroxide led to the formation of racemic epoxide **14**, which was subjected to concd HCl in MeOH/THF to afford (±)-taxifolin (**6**) in 85% yield (Scheme 3).¹¹ Our procedure gave better overall yields (72%) when compared to the earlier reported procedure¹¹ (40%) from MOM-protected intermediates, and also it involves cheaply available starting materials. Our approach has an additional advantage: The caffeic acid can be converted into a chiral epoxy or dihydroxy derivative, which, upon acylation on **12** followed by cyclization, can lead to chiral taxifolins.

Having (±)-taxifolin (**6**) in hand, our next step was to resolve it to obtain enantiomers **3** and **4**. Chiral semipreparative reverse-phase high-performance liquid chromatogra-

Table 1 Optimization of C-Glycosidation Reaction Conditions

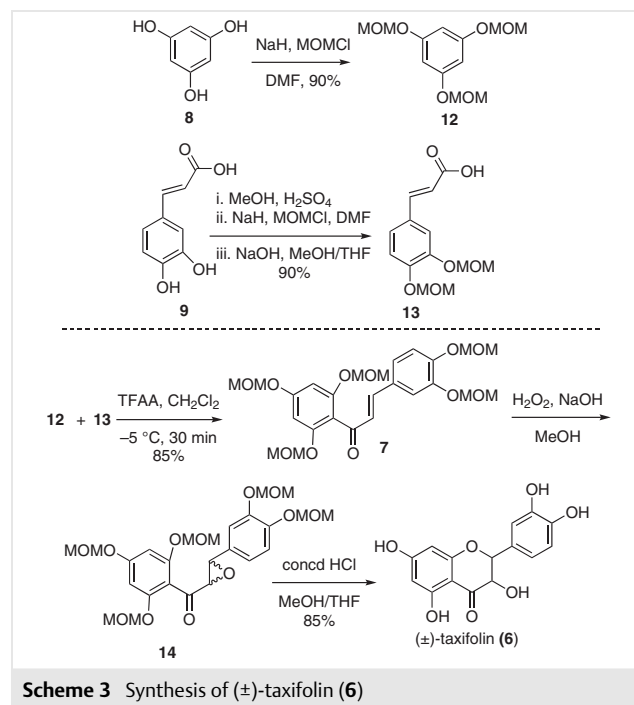
Entry	Catalyst	Equiv.	MeCN/H ₂ O	Time (h)	Yield (%) ^b
1	Sc(OTf) ₃	0.2	1:1	24	10
2	Sc(OTf) ₃	0.2	1:1	48	15
3	Sc(OTf) ₃	0.2	2:1	48	20
4	Sc(OTf)₃	0.4	2:1	48	35
5	Sm(OTf) ₃	0.4	2:1	48	8
6	Bi(OTf) ₃	0.4	2:1	48	5
7	Yb(OTf) ₃	0.4	2:1	48	no reaction ^c

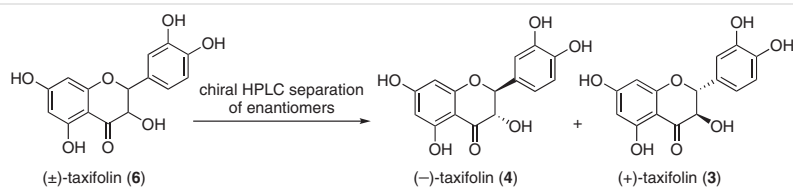
^a Reaction conditions: (+)-taxifolin (**3**) (1 equiv), D-glucose (2.5 equiv), M³⁺(OTf)₃, solvent, reflux.

^b Isolated yield.

^c Based on TLC analysis.

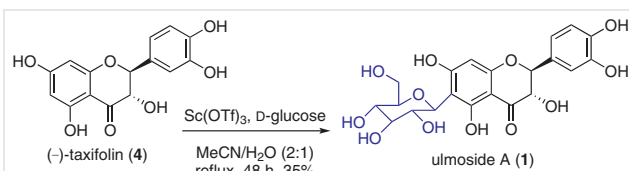
phy (HPLC) allowed us to successfully separate **3** and **4** (Scheme 4). The separated enantiomers have the same physical data with opposite optical rotation values. The spectral and analytical data of **3** and **4** were in full agreement with the literature values, and also the values of the product obtained from (+)-catechin hydrate (**5**) in Scheme 2.^{10c}





Scheme 4 Chiral HPLC separation of racemic taxifolins **6**

To accomplish the second target molecule ulmoside A (**1**), we initiated our synthesis from the $(-)$ -taxifolin (**4**) as shown in Scheme 5. Thus, C-glycosidation of $(-)$ -taxifolin (**4**) with D-glucose in the presence of $\text{Sc}(\text{OTf})_3$ in $\text{MeCN}/\text{H}_2\text{O}$ furnished ulmoside A (**1**) in 35% yield.¹¹ Conducting the reaction for 48 hours helped us to obtain 35% yield of **1**, whereas Sato's conditions gave 25% yield of the product in glycosidation. During the column purification of the product, the unreacted starting material was also recovered. Based on the recovery the yield of the product is around 93%. All analytical data including ^1H and ^{13}C NMR spectra of the synthetic ulmoside A (**1**) were in full agreement with the data of a natural sample of ulmoside A (**1**).^{2a,13,14}



Scheme 5 Total synthesis of ulmoside A (**1**)

Next, we proceeded with similar conditions as mentioned in Scheme 5, to obtain the mixture of ulmoside A (**1**) and $(2R,3R)$ -taxifolin-6-C- β -D-glucopyranoside (**2**) from (\pm) -taxifolin (**6**) and D-glucose (Scheme 6). Chiral semipreparative reverse-phase HPLC allowed us to separate successfully both ulmoside A (**1**) and its diastereomer **2** without any loss of compound. The HPLC chromatogram of synthetic ulmoside A (**1**) revealed a peak at 23.6 min, which was very well correlated with that of natural ulmoside A (see Supporting Information). The complete analysis of HPLC data clearly confirmed that the absolute configuration of the aglycon part of ulmoside A (**1**) is $2S,3S$ and that of its diastereomer is $2R,3R$.

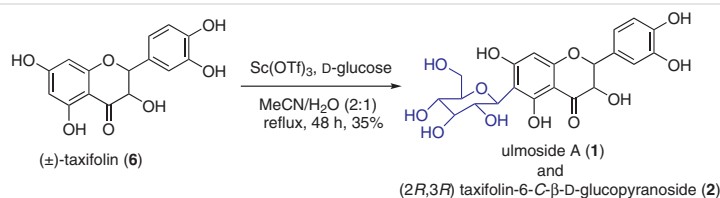
A simple and scalable first synthesis of highly polar ulmoside A (**1**) and $(2R,3R)$ -taxifolin-6-C- β -D-glucopyranoside (**2**), useful for the prevention of metabolic disorders, has been described. Scandium triflate proved to be a suitable catalyst for the regio- and stereoselective C-glycosylation on taxifolins (**3**) and (**4**) in 35% yield with unprotected D-glucose. Despite this, an achiral semipreparative HPLC method was developed for the separation of both (\pm) -taxifolin (**6**) and the diastereomeric mixture of taxifolin-6-C- β -D-glucopyranosides **1** and **2**. The absolute configuration of aglycon of ulmoside A (**1**) and its diastereomer (**2**) was confirmed as $2S,3S$ and $2R,3R$. This strategy is also useful to build a library of compounds with different sugars and polyphenols for better therapeutic activity. Most of these flavonoid C-saccharides are present in dietary supplements and also in the extracts used in Indian traditional medicines. These compounds are less toxic and have a high probability to become drugs. Therefore, we are planning to apply this approach to the synthesis of other flavonoid C-saccharides. Further, chiral epoxidation of chalcone **7** or converting caffeic acid into chiral epoxy or hydroxy derivatives for acylation can lead to a chiral synthesis of taxifolins.

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Scheme 6 Direct C-glycosidation on (\pm) -taxifolin (**6**)

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1707971>.

References and Notes

- (1) (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742. (b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (c) Rauter, A. P.; Lopes, R. G.; Martins, A. *Nat. Prod. Commun.* **2007**, *11*, 1175. (d) Wang, Q.; Shuang, A.; Deng, Z.; Zhu, W.; Huang, Z.; Gang, H.; Chen, G. *Nat. Catal.* **2019**, *2*, 793. (e) Xiao, J.; Capanoglu, E.; Jassbi, A. R.; Miro, A. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, S29.
- (2) (a) Rawat, P.; Kumar, M.; Sharan, K.; Chattopadhyay, N.; Maurya, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4684. (b) Maurya, R.; Rawat, P.; Sharan, K.; Siddiqui, J. A.; Swarnkar, G.; Mishra, G.; Manickavasagam, L.; Jain, G. K.; Arya, K. R.; Chattopadhyay, N. PCT Patent PCT/IN2009/000146, **2009**; (WO2009110003A1, WO200911000, **2009**). (c) Stark, T. D.; Germann, D.; Balemba, O. B.; Wakamatsu, J.; Hofmann, T. *J. Agric. Food Chem.* **2013**, *61*, 12572. (d) Sabyasachi, S.; Chattopadhyay, N.; Maurya, R.; Gayen, J. R.; Bhadauria, S.; Trivedi, A. K.; Singh, A. K.; Mishra, J. Y.; Kumari, R.; Sharan, K.; Khan, M. P.; Khan, K.; Singh, N.; Dwivedi, S. K. D.; Yadav, M.; Dixit, P.; Mishra, D. P.; Sharma, S.; Kamal, R. A. PCT Patent PCT/IN2014/000464, **2014**; (US2016/019324, **2014**). (e) Gupta, P.; Singh, A.; Tiwari, S.; Mishra, A.; Maurya, R.; Singh, S. *Neurotoxicology* **2019**, *73*, 100.
- (3) (a) Stark, T.; Matsutomo, T.; Losch, S.; Boakye, P.; Balemba, O.; Pasilis, S.; Hofmann, T. *J. Agric. Food Chem.* **2012**, *60*, 2053. (b) Mbafor, J. T.; Fomum, Z. T.; Promsattha, B.; Sanson, D. R.; Tempesta, M. S. *J. Nat. Prod.* **1989**, *52*, 417.
- (4) (a) Jaramilo, C.; Knapp, S. *Synthesis* **1994**, *1*. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, **1995**. (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: London, **1995**. (d) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913. (e) Toshima, K.; Matsuo, G.; Nakata, M.; Matsumura, S. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 841. (f) Schmidt, R. R.; Hoffmann, M. *Tetrahedron Lett.* **1982**, *23*, 409.
- (5) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935.
- (6) Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005.
- (7) (a) Sato, S.; Akiya, T.; Nishizawa, H.; Suzuki, T. *Carbohydr. Res.* **2006**, *341*, 964. (b) Van Der Westhuizen, J. H.; Ferreira, D.; Joubert, E.; Bonnet, S. L. WO2011064726A1, **2011**. (c) Sato, S.; Koide, T. *Carbohydr. Res.* **2010**, *345*, 1825.
- (8) Santos, R. G.; Xavier, N. M.; Bordado, J. C.; Rauter, A. P. *Eur. J. Org. Chem.* **2013**, 1441.
- (9) (a) Kitamura, K.; Ando, Y.; Matsumoto, T.; Suzuki, K. *Chem. Rev.* **2018**, *118*, 1495. (b) Yang, Y. *Yu B.* **2017**, *117*, 12281.
- (10) (a) Park, K. D.; Cho, S. J. *Eur. J. Med. Chem.* **2010**, *45*, 1028. (b) Es-Safi, N.-E.; Ducrot, P.-H. *Lett. Org. Chem.* **2006**, *3*, 231. (c) Kikuchi, T.; Nishimura, M.; Hoshino, A.; Mortia, Y.; Saito, N.; Honda, T. *Heterocycles* **2003**, *60*, 1469.
- (11) Yang, L. X.; Huang, K. X.; Li, H. B.; Gong, J. X.; Wang, F.; Feng, Y. B.; Tao, Q. F.; Wu, Y. H.; Li, X. K.; Wu, X. M.; Zeng, S.; Spencer, S.; Zhao, Y.; Qu, J. *J. Med. Chem.* **2009**, *52*, 7732.
- (12) Wu, Z.; Wei, G.; Lian, G.; Yu, B. *J. Org. Chem.* **2010**, *75*, 5725.
- (13) Rao, B. V.; Lingamurthy, M.; Raju, G.; Sarma, V. U. M. US20160362401A1, 2016; (US9611255B2).
- (14) **Ulmoside A (1)**
A solution of (–)-taxifolin (**4**) (0.3 g, 0.98 mmol) and D-glucose (0.44 g, 2.46 mmol) was stirred in a mixture of solvents MeCN/H₂O (2:1, 10 mL) heated to reflux in an oil bath for 48 h in the presence of Sc(OTf)₃ (0.19 g, 0.39 mmol). Then, the reaction mixture was subjected to silica gel column chromatography (acetone/EtOAc/H₂O/AcOH 15:30:2:0.1) to afford ulmoside A (**1**) as a white amorphous powder yield: 0.16 g (35%); [α]_D²⁵ = +1.56 (c = 0.1, MeOH) [lit^{2a} [α]_D²⁵ = +1.33 (c = 0.098, MeOH)]. IR (neat): 3325, 2945, 2833, 1646, 1450, 1413, 1017 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 12.47 (s, 1 H, HO-C(5)), 9.03 (s, 1 H, HO-C(4')), 8.98 (s, 1 H, HO-C(3')), 6.84 (s, 1 H, H-2'), 6.71 (s, 2 H, H-5', 6'), 5.87 (s, 1 H, H-8), 5.78 (s, 1 H, HO-C(3)), 4.92 (d, *J* = 10.9 Hz, 1 H, H-2), 4.82 (br s, 2 H, OH), 4.58 (br s, 1 H, OH), 4.46–4.47 (m, 1 H, H-6''b), 4.45 (d, *J* = 10.0 Hz, 1 H, H-1''), 4.43 (d, *J* = 10.9 Hz, 1 H, H-3), 3.96 (t, *J* = 9.1, 9.3 Hz, 1 H, H-2''), 3.63 (d, *J* = 10.9 Hz, 1 H, H-6''a), 3.04–3.15 (m, 3 H, H-3'', 4'', 5''). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 198.0 (C-4), 166.0 (C-7), 162.6 (C-5), 161.3 (C-9), 145.8 (C-3'), 145.0 (C-4'), 128.0 (C-1'), 119.4 (C-6'), 115.3 (C-2'), 115.1 (C-5'), 106.0 (C-6), 100.2 (C-10), 94.7 (C-8), 82.9 (C-2), 81.6 (C-5''), 79.1 (C-3'''), 72.9 (C-1''), 71.6 (C-3), 70.7 (C-2''), 70.3 (C-4''), 61.6 (C-6''). FAB-MS: *m/z* 467 [M + H]⁺.