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Access to Diosgenyl Glycoconjugates via Gold(I)-Catalyzed Etherification of Diosgen-3-yl *ortho*-Hexynylbenzoate

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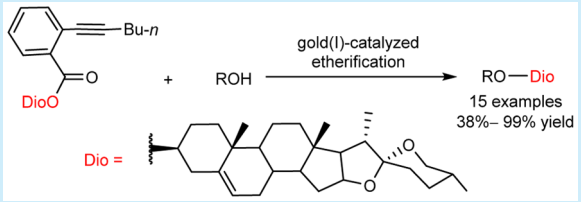
Supporting Information

ABSTRACT: An efficient protocol for the synthesis of diverse diosgen-3-yl glycoconjugates, a class of novel synthetic analogs of natural saponins of biological significance, has been developed. The method relies on gold(I)-catalyzed etherification of diosgen-3-yl *ortho*-hexynylbenzoate with stoichiometric sugar alcohols to afford the corresponding glycoconjugates in 38%−99% yields. The reaction involves the preferential attack of hydroxyl groups to the C3 position of homoallylic carbocation intermediate and displays a broad substrate scope and a good functional group tolerance.



Saponins with diosgenin as a hydrophobic aglycone backbone belong to a subset of spirostan glycosides widely occurring in the plant kingdom.[1] They possess noteworthy broad-spectrum bioactivities including antitumor, antiviral, antifungal, anti-inflammatory, and immunostimulant activities.[2] Isolation of saponins from natural sources usually is a formidable task due to the microheterogeneity of saponins in nature. Moreover, natural saponins are easily subjected to degradation attributable to enzymatic hydrolysis of *O*-glycosidic bonds in tissues and biofluids. To overcome these problems, intensive research efforts have been devoted to the synthesis of natural saponins including diosgenyl glycosides.[3] Meanwhile, a variety of glycomimics resistant to enzymatic hydrolysis has been designed and synthesized.[4] These chemical analogs could be used as molecular probes or enzyme inhibitors.[5] As part of our research on diosgenyl glycosides and their congeners,[6] we aimed to generate novel diosgen-3-yl glycoconjugates by replacing the natural acetal-type glycosidic bond with an ether linkage between diosgenyl and a certain nonanomeric hydroxyl group of a sugar moiety.

In principle, current protocols for synthesis of diosgen-3-yl ethers can be grouped into two large classes. The first involves the treatment of reactive halogenated alkanes or the related species with nucleophilic diosgenin as seen in the synthesis of benzyl ether of diosgenin.[7] The other class relies on the concept of *i*-steroid and retro-*i*-steroid rearrangements that was introduced by Winstein.[8] Following this method, diosgenyl tosylate has been converted into methyl,[9a] 2-azidoethanol,[9b] and 1,6-hexandiol ethers[9c] by capturing the homoallylic carbocation generated from diosgenyl derivatives with an alcohol as the nucleophile. However, this procedure is impractical for employing precious or highly functionalized alcohols because it requires excess alcohol, an elongated reaction time, and a high reaction temperature to obtain the desired diosgen-3-yl ethers in satisfactory yields. Recently, Morzycki and co-workers[10] reported the electrochemical synthesis of diosgen-3-yl galactoside in mere 37% or 30% yield upon treatment of either diosgenyl diphenylphosphate or *i*-steroid thioether with galactosyl diacetonide. Consequently, exploration of new procedures for the efficient and rapid construction of structurally appealing diosgenyl glycoconjugates is highly attractive and desirable.

Recently, there has been an explosion in the study of gold-catalyzed activation of alkynes to exploit the low oxophilic character of gold and the excellent functional group compatibilities these catalysts exhibit.[11] Particularly, gold(I)-catalyzed etherification of alcohols and Friedel−Crafts alkylation of electron-rich aromatics with alkyl *ortho*-alkynylbenzoates,[12a] [4 + 3]-cycloaddition of phenylsulfanyl-substituted allylic *ortho*-alkynylbenzoates with 2,6-disubstituted furans,[12b] and Yu glycosylation with glycosyl *ortho*-alkynylbenzoates as glycosyl donors[13] have proven to be powerful tools for the synthesis of ethers, alkylated aromatics, bridged cyclic compounds, and glycosides. Recently, we reported $(4\text{-MeOPh})_3$PAuCl/AgB$(C_6F_5)_4$-catalyzed stereocontrolled synthesis of β-mannosides using 4,6-*O*-benzylidene-protected mannosyl *ortho*-hexynylbenzoates as glycosyl donors.[14] Herein we describe the $(PhO)_3$PAuCl/AgB$(C_6F_5)_4$-promoted etherification of diosgen-3-yl *ortho*-hexynylbenzoate with stoichiometric sugar alcohols. The reaction is compatible with protecting groups commonly used in carbohydrate chemistry, thus providing a facile route to diverse diosgenyl glycoconjugates as potential analogs of natural saponins.

The coupling of diosgen-3-yl *ortho*-hexynylbenzoate **1** with **2a** was selected as a model reaction to optimize the reaction

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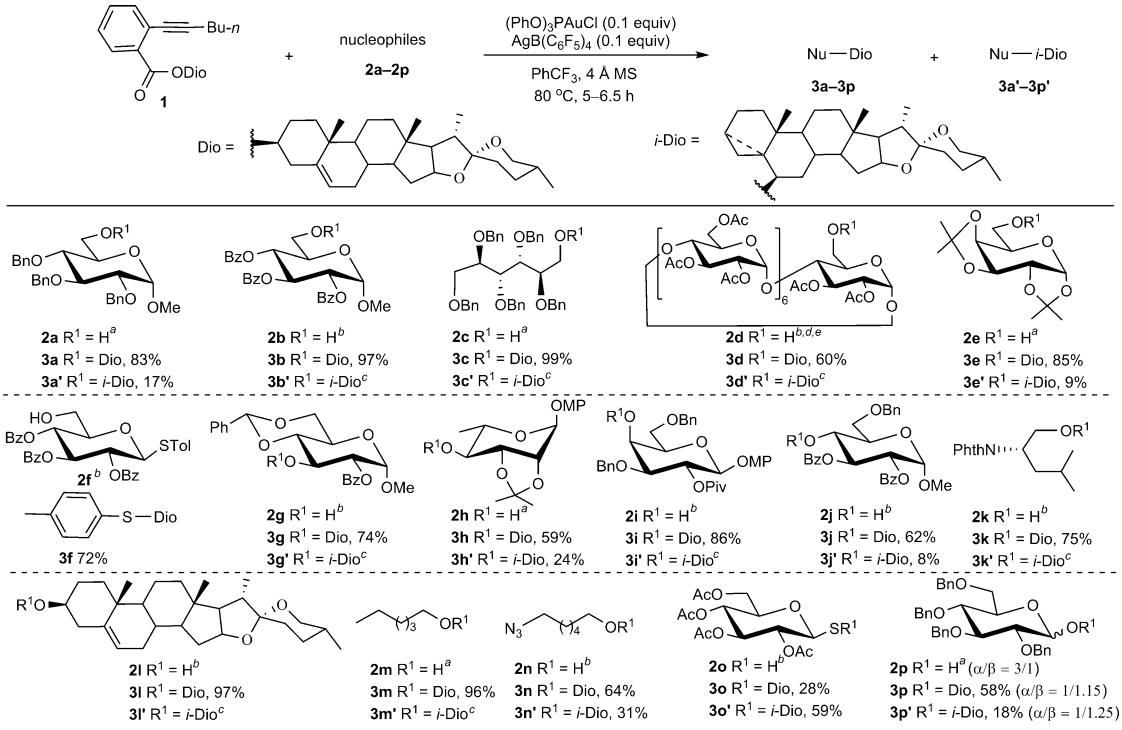
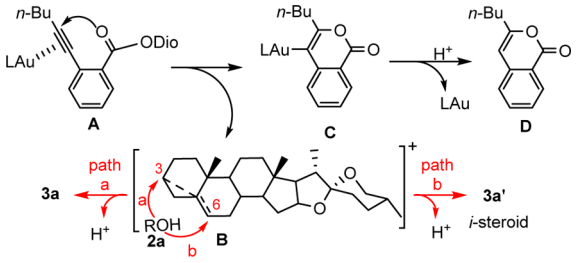
Scheme 1. Synthesis of Diosgenyl Glycoconjugates



[a]2.0 equiv of nucleophile were used. [b]1.2 equiv of nucleophile was used. [c]*i*-Steroid was not isolated. [d]$(PhO)_3PAuCl$ (0.3 equiv) and $AgB(C_6F_5)_4$ (0.3 equiv) were used. [e]28 h.

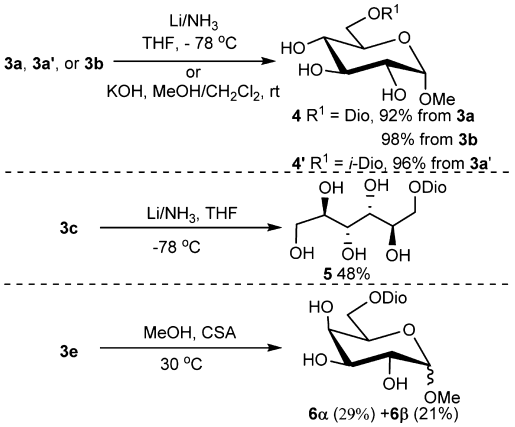
conditions. After evaluating various reaction parameters (see Supporting Information), we found that treatment of **1** (1.0 equiv) with **2a** (2.0 equiv) in solvent $PhCF_3$ at 80 °C in the presence of $(PhO)_3PAuCl$ (0.1 equiv) and $AgB(C_6F_5)_4$ (0.1 equiv) provided the expected glycoconjugate **3a** in 83% yield along with a 17% yield of *i*-steroid **3a′** within 5 h (Scheme 1). This combination stood out as the optimal choice of conditions for the gold-catalyzed etherification of **1**, and the result also suggests that a homoallylic carbocation is involved in the transformation. Based on this observation and literature results,[8,10,12,15] a plausible mechanism is illustrated in Scheme 2. Coordination of the gold(I) catalyst to the triple bond of **1** leads to intermediate **A**, which enhances the electrophilicity of the alkyne group, and the subsequent nucleophilic attack of the carbonyl oxygen to the

Scheme 2. Proposed Reaction Mechanism



activated alkyne generates the homoallylic carbocation intermediate **B** and metallic isocoumarin **C**. The attack of **2a** to the C3 position of carbocation **B** gives ether **3a** as the thermodynamic product (path a), whereas the nucleophilic attack of **2a** to the C6 position affords *i*-steroid **3a′** as the kinetic product (path b). Intermediate **C** is converted by the released proton into

Scheme 3. Deprotection of Diosgenyl Glycoconjugates



isocoumarin **D** with the simultaneous regeneration of the gold catalyst, thus completing the catalytic cycle.

It is well-known that *i*-steroids can be rearranged to 3β-substituted-Δ^5-steroids (retro-*i*-steroid rearrangement) by acid catalysis.[8,10,16] However, in this study, $(PhO)_3PAuCl/AgB(C_6F_5)_4$-catalyzed conversion of *i*-steroid **3a′** to **3a** in $PhCF_3$ at a temperature up to 100 °C hardly occurred, thus indicating that **3a** was exclusively produced by the direct attack of alcohol **2a** to the C3 position of homoallylic carbocation **B** instead of rearrangement of **3a′**.

With the optimized conditions in hand, the scope and limitations of the transformation were systematically examined. As shown in Scheme 1, *ortho*-hexynylbenzoate **1** was treated with various sugar alcohols **2b**–**2m** as competent nucleophiles to provide the corresponding diosgen-3-yl glycoconjugates as the major, even the sole, product. Different from **2a**, the coupling of

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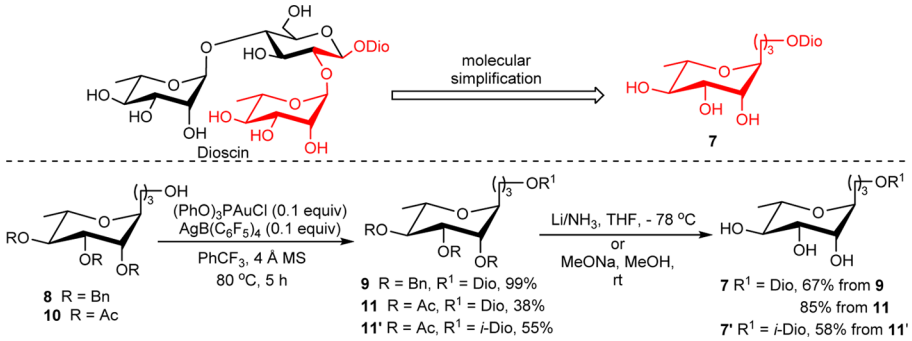
Scheme 4. Design and Synthesis of Diosgenyl Glycoconjugate 7



benzoyl-protected glucosyl derivative **2b** with **1** afforded the expected glycoconjugate **3b** in an excellent 97% yield without the isolation of the corresponding 6-substituted *i*-steroid. Mannitol **2c** is also a suitable nucleophile and reacted with **1** to supply adduct **3c** in quantitative yield.

Amphiphilic cyclodextrins (CDs) with grafted hydrophobic moieties are a new generation of cyclodextrin derivatives compatible with biomembranes.[16] Noteworthy, primary alcohol **2d**, derived from β-cyclodextrin, a cyclic heptamer comprised of α-(1 → 4)-D-glucopyranosyl units, was treated with **1** to smoothly furnish ether **3d** in 60% yield, thus opening up the prospect for modification of CDs. Galactosyl diacetonide **2e** reacted with **1** to afford **3e** and **3e′** in 85% and 9% yields, respectively, thus exhibiting significant improvement in yield compared to the initial synthesis.[8] Thioglycoside **2f** is a challenging nucleophile for the transformation. Treatment of **2f** with **1** led to an unexpected thioether **3f** in 72% yield without the isolation of desired glycoconjugate, indicating the migration of the thioether unit, a common side reaction during glycosylation with thioglycosides as the glycosyl acceptors.[18] This unexpected result could be rationalized by the hypothesis that the thioether moiety outcompetes the primary hydroxyl group as the nucleophile to preferentially attack the C3 position of homoallylic carbocation **B** (Scheme 2) to yield **3f**.

Secondary hydroxyl groups as the nucleophiles were also found to be suitable for the present etherification. Benzylidene- and isopropylidene-protected **2g** and **2h**, respectively, were observed to be viable substrates for the transformation; thus, **3g** and **3h** were obtained in 74% and 59% yields, respectively, with benzylidene and isopropylidene being unaffected. Axial 4-OH of galactoside **2i** was diosgenylated by **1** to give the desired product **3i** in satisfactory 86% yield; however, equatorial 3-OH of glucoside **2j** underwent etherification with **1** to afford a mixture of **3j** and **3j′** in a ratio of 7.8/1 and in an overall 70% yield.

Aliphatic alcohols were also employed for etherification in this study. Amino alcohol **2k** and diosgenin **2l** reacted well with **1** to provide diosgen-3-yl ether **3k** and **3l** in 75% and 97% yields, respectively, without the formation of *i*-steroids. Distinct from hexanol providing ether **3m** in 96% yield, 6-azido-hexanol **2n** afforded **3n** in 64% yield and *i*-steroid **3n′** in 31% yield, which is ascribed to different dielectric constants of **2m** and **2n**.[19]

Glycosyl thiol **2o** as a typical example of sulfur-nucleophiles was tested in the transformation. When it was exposed to the coupling reaction with **1**, thioglycoside **3o** was obtained in 28% yield accompanied by the formation of *i*-steroid **3o′** in 59% yield. Given that **2o** usually reacts with chlorotrialkylphosphine gold(I) to form the complex such as auranofin,[20] this result is interesting and might provide an entry to the synthesis of intriguing thiosaponin as analogs of natural saponins.

Similarly, glucosyl lactol **2p** (β/α = 1:3) was exposed to etherification of **1** under the established conditions to afford saponins **3p**β and **3p**α in 58% yield (β/α = 1.15:1) together with the corresponding *i*-steroids **3p′**β and **3p′**α in 18% yield (β/α = 1.25:1). These outcomes show that the anomeric hydroxy group is a potential nucleophile for the present etherification, thus opening up a new way to synthesize natural saponins. Additionally, compared to **2p**, the enhanced β/α ratio of **3p** and **3p′** is attributed to the stronger nucleophilicity of the **2p**β-isomer than the α-isomer and the rapid equilibrium between them.

With diosgen-3-yl glycoconjugates in hand, deprotection was carried out (Scheme 3). Birch reduction of **3a** and **3a′** with lithium in liquid ammonia cleaved benzyl protecting groups to afford **4** and **4′** in 92% and 96% yields, respectively. Saponification of **3b** was effected using KOH as the base in MeOH/CH_2Cl_2 to furnish **4** in 98% yield. Diosgenylated manitol **3c** readily underwent Birch reduction to deliver **5** in 48% yield. Transacetalization of **3e** with methanol in the presence of camphor-10-sulfonic acid (CSA) supplied **6**$\boldsymbol{\alpha}$ in 29% yield together with anomeric isomer **6**$\boldsymbol{\beta}$ in 21% yield (Scheme 3).

After establishing the protocol for synthesis of diosgenyl glycoconjugates, we applied the method to the synthesis of natural saponin analogs of interest. Dioscin is a representative of diosgenyl saponins and has become an attractive target for drug development (Scheme 4).[21] Studies on its structure−activity relationship (SAR) demonstrate that α-L-rhamnosyl residue appended to the C2 position of the glucosyl unit exerts a pronounced effect on the activities of dioscin.[22] Thus, we attempted to design and synthesize **7** as an analog of dioscin for further SAR research. Between the aglycone and the rhamnosyl moiety, **7** possesses a similar distance and identical stereochemistry of chemical bonds compared to dioscin. However, replacement of α-L-rhamnosyl and β-D-glucosyl linkages with a C−C bond and an ether bond would render **7** more resistant to enzymatic hydrolysis than the parent saponin. These properties might be interesting for medicinal chemistry.

Gold(I)-catalyzed etherification of diosgenyl benzoate **1** was expanded to the synthesis of **7** (Scheme 4). Primary alcohol **8** was converted into ether **9** in quantitative yield. Replacement of benzyl groups in **8** with acetyl groups is deleterious to the transformation; thus, **11** was obtained from **10** in 38% yield along with a 55% yield of *i*-steroid **11′**. Birch reduction of **9** gave **7** in 67% yield. Saponification of **11** and **11′** with MeONa in MeOH proceeded uneventfully to afford **7** and **7′** in 85% and 58% yields, respectively. To the best of our knowledge, *i*-steroids **4′** and **7′** represent the first examples of 6β-substituted 3α,5α-cyclosteroid glycoconjugates.

In summary, an efficient protocol for the synthesis of diosgen-3-yl glycoconjugates has been developed, which relies on gold(I)-

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catalyzed etherification of diosgenyl *ortho*-hexynylbenzoates with diverse sugar alcohols. The reaction has a broad substrate scope and an excellent functional group tolerance. Given the abundance of 3β-hydroxy-Δ^5-steroid-based saponins and their biological relevance, the developed method should be useful in the synthesis of structurally diverse analogs of natural saponins that would provide information regarding the SAR for the related drug development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02963.

Experimental details and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Hostettmann, K.; Marston, A. *Saponins*; Cambridge University Press: Cambridge, U.K., 1995.

(2) (a) Sparg, S. G.; Light, M. E.; van Staden, J. *J. Ethnopharmacol.* **2004**, *94*, 219. (b) Fuchs, H.; Bachran, D.; Panjideh, H.; Schellmann, N.; Weng, A.; Melzig, M. F.; Sutherland, M.; Bachran, C. *Curr. Drug Targets* **2009**, *10*, 140. (c) Man, S.; Gao, W.; Zhang, Y.; Huang, L.; Liu, C. *Fitoterapia* **2010**, *81*, 703. (d) Man, S.; Wang, Y.; Li, Y.; Gao, W.; Huang, X.; Ma, C. *Chin. Herb. Med.* **2013**, *5*, 33. (e) Jeong, G.-S.; Bae, J.-S. *Mini-Rev. Org. Chem.* **2014**, *11*, 316. (f) Munafo, J. P., Jr; Gianfagna, T. J. *Nat. Prod. Rep.* **2015**, *32*, 454.

(3) (a) Yu, B.; Zhang, Y.; Tang, P. *Eur. J. Org. Chem.* **2007**, *2007*, 5145. (b) Yu, B.; Sun, J.; Yang, X. *Acc. Chem. Res.* **2012**, *45*, 1227. (c) Yang, Y.; Laval, S.; Yu, B. *Adv. Carbohydr. Chem. Biochem.* **2014**, *71*, 137. (d) Zu, L.; Zhao, Y.; Gu, G. *J. Carbohydr. Chem.* **2014**, *33*, 269. (e) Yang, Y.; Zhang, X.; Yu, B. *Nat. Prod. Rep.* **2015**, *32*, 1331. (f) Grynkiewicz, G.; Szeja, W. *Curr. Pharm. Des.* **2016**, *22*, 1592.

(4) (a) Stambasky, J.; Hocek, M.; Kocovsky, P. *Chem. Rev.* **2009**, *109*, 6729. (b) Koester, D. C.; Holkenbrink, A.; Werz, D. B. *Synthesis* **2010**, *2010*, 3217. (c) Driguez, H. *ChemBioChem* **2001**, *2*, 311. (d) Witczak, Z. J.; Culhane, J. M. *Appl. Microbiol. Biotechnol.* **2005**, *69*, 237. (e) Risseeuw, M.; Overhand, M.; Fleet, G. W.; Simone, M. I. *Amino Acids* **2013**, *45*, 613.

(5) (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (b) Kiefel, M. J.; von Itzstein, M. *Chem. Rev.* **2002**, *102*, 471.

(6) (a) Chen, P.; Wang, P.; Liu, L.; Qiu, P.; Zhang, L.; Song, N.; Ren, S.; Guan, H.; Li, M. *Asian J. Org. Chem.* **2015**, *4*, 1273. (b) Chen, P.; Wang, P. *Steroids* **2013**, *78*, 959.

(7) (a) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099. (b) Zhao, J. R.; Yuan, X.; Wang, Z.; Chen, S.; Zhang, Z.-X.; Xue, W. *Org. Chem. Front.* **2015**, *2*, 34.

(8) (a) Shoppee, C. W.; Summers, G. H. R. *J. Chem. Soc.* **1952**, 3361. (b) Kosower, E. M.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 4347. (c) Winstein, S.; Kosower, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 4399.

(9) (a) Rosloniec, K. Z.; Wilbrink, M. H.; Capyk, J. K.; Mohn, W. W.; Ostendorf, M.; van der Geize, R.; Dijkhuizen, L.; Eltis, L. D. *Mol. Microbiol.* **2009**, *74*, 1031. (b) Zhang, X.; Yang, X.; Zhang, S. *Synth. Commun.* **2009**, *39*, 830. (c) Yao, D.; Li, P.; Liu, X.; Hu, J.; Yang, L. *Colloid Polym. Sci.* **2015**, *293*, 3049.

(10) (a) Tomkiel, A. M.; Brzezinski, K.; Łotowski, Z.; Siergiejczyk, L.; Wałejko, P.; Witkowski, S.; Kowalski, J.; Płoszyńska, J.; Sobkowiak, A.; Morzycki, J. W. *Tetrahedron* **2013**, *69*, 8904. (b) Tomkiel, A. M.; Kowalski, J.; Płoszyńska, J.; Siergiejczyk, L.; Łotowski, Z.; Sobkowiak, A.; Morzycki, J. W. *Steroids* **2014**, *82*, 60.

(11) (a) Pfläesterer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331 and references cited therein.

(12) (a) Asao, N.; Aikawa, H.; Tago, S.; Umetsu, K. *Org. Lett.* **2007**, *9*, 4299. (b) Topinka, M.; Tata, R. R.; Harmata, M. *Org. Lett.* **2014**, *16*, 4476.

(13) (a) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604. (b) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. - Eur. J.* **2010**, *16*, 1871. (c) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 4933. (d) Ma, Y.; Li, Z.; Shi, H.; Zhang, J.; Yu, B. *J. Org. Chem.* **2011**, *76*, 9748. (e) Li, Y.; Sun, J.; Yu, B. *Org. Lett.* **2011**, *13*, 5508. (f) Yu, J.; Sun, J.; Yu, B. *Org. Lett.* **2012**, *14*, 4022. (g) Xiao, G.; Yu, B. *Chem. - Eur. J.* **2013**, *19*, 7708. (h) Yu, J.; Sun, J.; Niu, Y.; Li, R.; Liao, J.; Zhang, F.; Yu, B. *Chem. Sci.* **2013**, *4*, 3899. (i) Nie, S.; Li, W.; Yu, B. *J. Am. Chem. Soc.* **2014**, *136*, 4157. (j) Zhang, X.; Zhou, Y.; Zuo, J.; Yu, B. *Nat. Commun.* **2015**, *6*, 5879. (k) Zhu, D.; Yu, B. *J. Am. Chem. Soc.* **2015**, *137*, 15098. (l) Li, J.; Yu, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 6618. (m) Liu, H.; Liao, J.-X.; Hu, Y.; Tu, Y.-H.; Sun, J.-S. *Org. Lett.* **2016**, *18*, 1294. (n) Nicolaou, K. C.; Cai, Q.; Sun, H.; Qin, B.; Zhu, S. *J. Am. Chem. Soc.* **2016**, *138*, 3118. (o) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926. (p) Bai, Y.; Shen, X.; Li, Y.; Dai, M. *J. Am. Chem. Soc.* **2016**, *138*, 10838.

(14) Sun, P.; Wang, P.; Zhang, Y.; Zhang, X.; Wang, C.; Liu, S.; Lu, J.; Li, M. *J. Org. Chem.* **2015**, *80*, 4164.

(15) (a) Zhu, Y.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 8329. (b) Tang, Y.; Li, J.; Zhu, Y.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2013**, *135*, 18396. (c) Zhu, Y.; Yu, B. *Chem. - Eur. J.* **2015**, *21*, 8771.

(16) Sun, Q.; Cai, S.; Peterson, B. R. *Org. Lett.* **2009**, *11*, 567.

(17) Cho, E.; Yun, D.; Jeong, D.; Im, J.; Kim, H.; Dindulkar, S. D.; Choi, Y.; Jung, S. *Sci. Rep.* **2016**, *6*, 23740.

(18) (a) Yu, H.; Yu, B.; Wu, X.; Hui, Y.; Han, X. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1445. (b) Zhu, T.; Boons, G. J. *Carbohydr. Res.* **2000**, *329*, 709. (c) Li, Z.; Gildersleeve, J. C. *J. Am. Chem. Soc.* **2006**, *128*, 11612. (d) Chang, S.-S.; Shih, C.-H.; Lai, K.-C.; Mong, K.-K. T. *Chem. - Asian J.* **2010**, *5*, 1152. (e) Bai, S.; Wu, Z.; Huang, Q.; Zhang, L.; Chen, P.; Wang, C.; Zhang, X.; Wang, P.; Li, M. *RSC Adv.* **2016**, *6*, 5442.

(19) Lee, E.; Park, S. K.; Lee, H. Y.; Kim, W. J. *Bull. Korean Chem. Soc.* **1981**, *2*, 105.

(20) Gandin, V.; Fernandes, A. P. *Molecules* **2015**, *20*, 12732. (b) Roder, C.; Thomson, M. J. *Drugs R&D* **2015**, *15*, 13.

(21) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405. (b) Cai, J.; Liu, M.; Wang, Z.; Ju, Y. *Biol. Pharm. Bull.* **2002**, *25*, 193. (c) Liu, M.-J.; Wang, Z.; Ju, Y.; Zhou, J.-B.; Wang, Y.; Wong, R. N.-S. *Biol. Pharm. Bull.* **2004**, *27*, 1059. (d) Kaskiw, M. J.; Tassotto, M. L.; Th'ng, J.; Jiang, Z.-H. *Bioorg. Med. Chem.* **2008**, *16*, 3209. (e) Pérez-Labrada, K.; Brouard, I.; Morera, C.; Estévez, F.; Bermejo, J.; Rivera, D. J. *Tetrahedron* **2011**, *67*, 7713.

(22) (a) Nakamura, T.; Komori, C.; Lee, Y.-y.; Hashimoto, F.; Yahara, S.; Nohara, T.; Ejima, A. *Biol. Pharm. Bull.* **1996**, *19*, 564. (b) Wang, Y.; Zhang, Y.; Zhu, Z.; Zhu, S.; Li, Y.; Li, M.; Yu, B. *Bioorg. Med. Chem.* **2007**, *15*, 2528. (c) Zhu, S.; Zhang, Y.; Li, M.; Yu, J.; Zhang, L.; Li, Y.; Yu, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5629. (d) Hou, S.; Zou, C.; Zhou, L.; Xu, P.; Yu, D. *Chin. Chem. Lett.* **2007**, *18*, 769.

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