A Journal of the Gesellschaft Deutscher Chemiker

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201812222
Angew. Chem. 10.1002/ange.201812222

Link to VoR: http://dx.doi.org/10.1002/anie.201812222
http://dx.doi.org/10.1002/ange.201812222

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COMMUNICATION

A Convergent Synthetic Strategy towards Oligosaccharides Containing 2,3,6-Trideoxypyranoglycosides

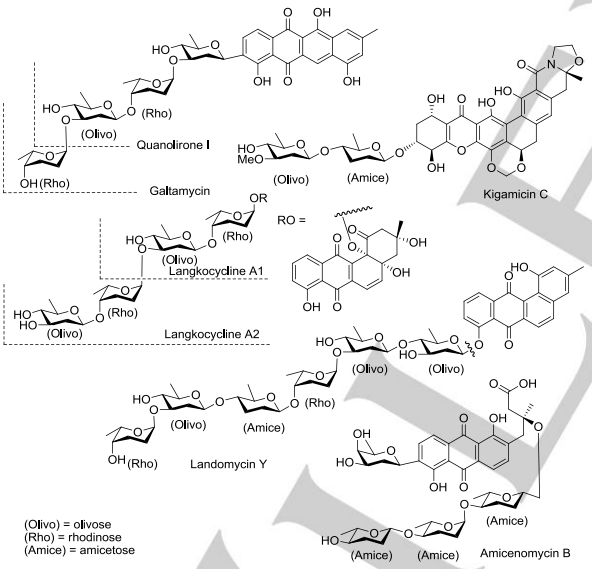
Juyeol Lee,[a] Soyeong Kang, [a] Jungjoon Kim, [a] Dohyun Moon[b] and Young Ho Rhee*[a]

Dedication ((optional))

Abstract: A *de novo* synthetic strategy towards oligosaccharides containing 2,3,6-trideoxypyranoglycoside is reported. A signature event is highlighted by the Pd-catalyzed asymmetric diastereoselective hydroalkoxylation of ene-alkoxyallene linked to glycosidic fragments. The utility of this unique approach was demonstrated by the activation-free, stereodivergent and convergent synthesis of various 2-deoxyoligosaccharides as well as their aglycon conjugates.

2-Deoxyoligosaccharides represent key components found in numerous bioactive natural products.[1] As illustrated by some examples shown in Figure 1, many of these deoxyoligosaccharides contain 2,3,6-trideoxypyranoglycosides (amicetose and rhodinose).[2-5] These moieties are linked to various aglycons as well as to other 2-deoxyglycosides with divergence in sequence and stereochemistry.

Figure 1. Natural products containing 2-deoxyoligosaccharides



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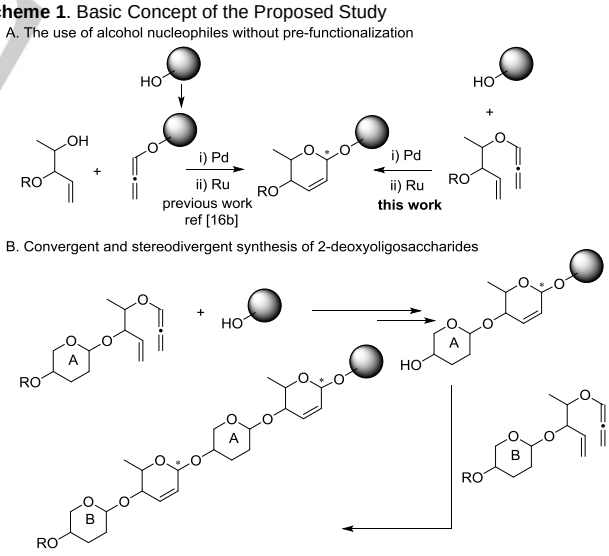
For example, repeating patterns (such as found in Langkocycline congeners) are reported[6] while heterogeneous patterns (such as found in Landomycin Y) are also known.[7] Due to this diverse nature, oligosaccharides containing 2,3,6-trideoxypyranoglycosides have been considered as attractive synthetic targets.[8] Yet, access to these structures has been very limited.[9] This is mainly because of the problems associated with the controlled synthesis of 2-deoxyglycosides. The absence of a directing group at the 2-position makes the stereoselective glycosidic bond formation a particularly difficult task.[10] In addition, anomeric centers in the 2-deoxyoligosaccharides becomes less stable and thus more prone to epimerization/decomposition. These problems become most pronounced with 2,3,6-trideoxypyranoglycosides. In fact, many of the stereoselective (substrate-controlled) methods recently developed for 2,6-dideoxyglycoside showed poorer outcome for 2,3,6-trideoxyglycosides.[11] Due to these problems, classical syntheses of 2-deoxyoligosaccharides rely heavily on the use of removable electron-withdrawing groups at the 2-position.[12] Thus, general and flexible approaches that can provide various 2-deoxyoligosaccharides particularly those possessing 2,3,6-trideoxyglycosides remain underdeveloped. Here, we wish to report a *de novo* synthetic method that allows rapid assembly of complex 2-deoxyglycosides in a convergent and stereodivergent manner based on chemoselective metal catalysis.

Scheme 1. Basic Concept of the Proposed Study



Over the past decades, transition metal catalysis has emerged as a new technique for the oligosaccharide assembly.[13-15] In this context, we recently reported a *de novo* synthesis of mono- and disaccharide form of pyranose glycosides using Pd-catalyzed asymmetric hydroalkoxylation of alkoxyallene as the key strategy, in combination with the ring-closing-metathesis (RCM).[16-18] A salient feature of this method is highlighted by the chiral ligand-driven stereocontrol in the glycosidic bond formation. Also, the chemoselective metal catalysis avoids the need of highly reactive

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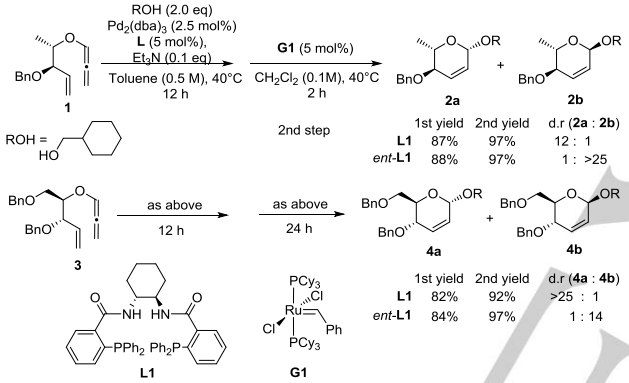
activating groups, which is common in conventional glycochemistry. Based upon these features, we envisioned that the method should be also desirable for the synthesis of oligosaccharides possessing 2,3,6-trideoxyglycosides. At the outset of the study, we reasoned that a new strategy combining ene-alkoxyallene and alcohol nucleophiles should be better suited for the proposed study in many regards (Scheme 1). First, the revised strategy allows for the direct use of the alcohol nucleophiles without conversion into the corresponding alkoxyallenes. This new feature can ease the difficulty in forming the glycon-aglycon conjugates. In addition, employing the alkoxyallene moiety linked to a glycosidic unit will enable a unique convergent synthesis.[19] The complexity and diversity of the glycon portion can rapidly increase by the iterative use of diversely substituted ene-alkoxyallenes. In combination with the ligand-driven stereocontrol discussed previously,[16b] the proposed method can give rise to various oligosaccharides containing 2,3,6-trideoxyglycosides and the related natural products in a highly efficient and well-controlled manner.

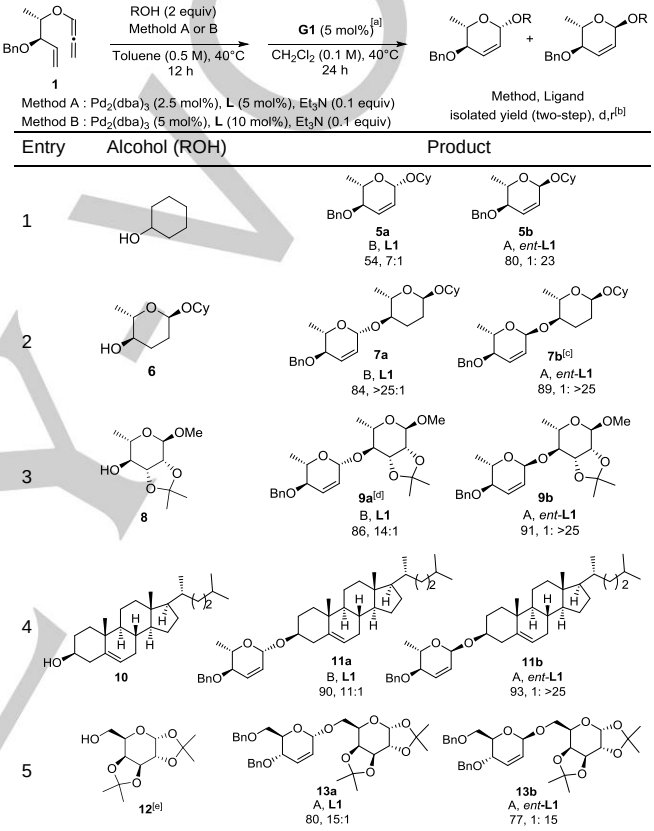
Scheme 2. Preliminary studies for Pd-catalyzed hydroalkoxylation of ene-alkoxyallenes



In order to test the plausibility of the revised strategy, we first examined the reaction of readily available allene **1** and cyclohexylmethyl alcohol (Scheme 2). Using the previously optimized condition[16b] for the asymmetric hydroalkoxylation (2 eq allene **1**/ 1 eq alcohol/ 1.5 eq Et_3N/ 2.5 mol% $Pd_2(dba)_3$/ 5.0 mol% ligand **L1**) in toluene (0.5 M) proceeded very slowly, producing the target compound **2a** in poor yield after the subsequent ring-closing-metathesis (RCM) reaction. After extensive further optimization, the yield was significantly improved (to 84% over two steps) when excess amount of alcohol (2 eq) was reacted with **1** (1 eq) in the presence of catalytic Et_3N (0.1 eq) at 40°C.[20] Simply switching the chiral ligand to the enantiomeric form *ent*-**L1** produced diastereomeric product **2b** in a comparable manner. Following a similar two-step protocol, the monosaccharide glycosides **4a** and **4b** were also obtained from more densely substituted alkoxyallene **3** in high yield and selectivity.

Then, we explored the stereodivergent reaction of various alcohol nucleophiles with allene **1** or **3** using the optimized condition in Scheme 2. As can be seen from Table 1, formation of β-glycosides was in general slower than that of the corresponding α-anomers. Nevertheless, increasing the catalyst loading (to 10 mol%) considerably improved the yield (>80%) without significantly harming the stereoselectiviy. In case when structurally simple cyclohexanol was used, the β-glycoside **5a** was obtained in low 54% yield even with 10 mol% catalyst loading (entry 1). Gratifyingly, monosaccharide alcohol substrates (compounds **6** and **8**) and cholesterol **10**, which are apparently bulkier than cyclohexanol, afforded the β-glycosides (compounds **7a, 9a** and **11a**) in considerably higher yield (entries 2-4). Preparation of the corresponding α-glycosides proceeded much smoother, generating the products in high yield with 5 mol% catalyst loading. Notably, allene **3** also worked well with galactose-derived alcohol **12** to produce the disaccharide **13** in a stereodivergent manner (entry 5). This example verifies the potential utility of the proposed method for future studies involving fully oxygenated oligosaccharides synthesis.

Table 1. Ligand-driven Stereodivergent Synthesis



[a] RCM reaction showed 90~98% yield. [b] Diasteromeric ratio was determined by crude NMR after RCM. [c] The reaction was performed on ~1 mmol scale. [d] 10 mol% Grubbs catalyst in CH_2Cl_2 was used. [e] Alkoxyallene **3** was used.

Having firmly established the generality of this second-generation strategy in the mono- and disaccharide formation, we turned our attention to the convergent synthesis of various oligosaccharides shown in Figure 1. The structural features of these compounds consisting of olivose-rhodinose or olivose-amicetose moiety led us to consider the use of olivose-derived allenes **14** and **15** as a key structural motif. These compounds were readily prepared by using the S_N2 glycosylation method reported by Bennett (For the detailed procedure, see the SI).[21] A preliminary reaction of the cholesterol **10** as the aglycon moiety with alkoxyallene **14** gave the steryl disaccharides **16a** and **16b** in 87 and 92% yield over two steps, respectively (Example A).[22] In addition, coupling of the diastereomeric allene **15** with cyclohexanol proceeded in the presence of ligand *ent*-**L1** to produce β-disaccharide **17a** in 68% yield, which represents the glycosidic framework of kigamicin C (Example B). Again, simply changing the ligand to the enantiomeric form **L1** generated the anomeric α-disaccharide **17b** exclusively in 77% yield. Additional

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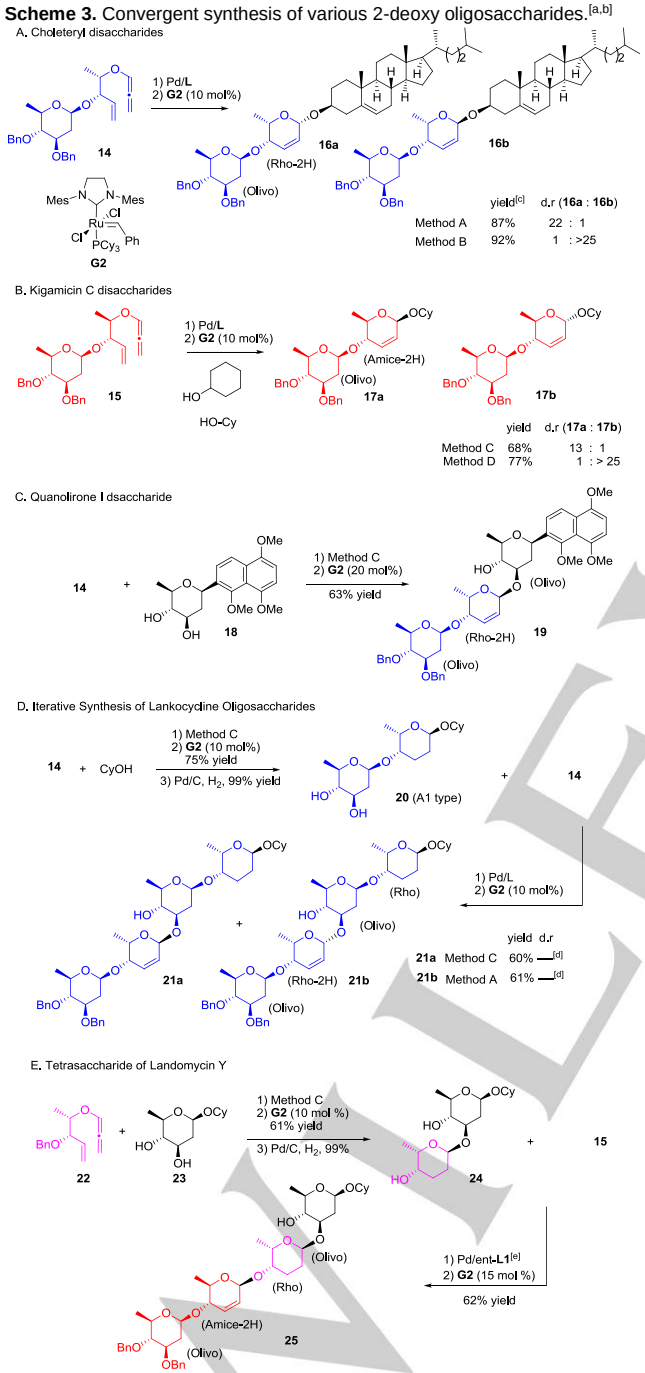
example using unprotected C-glycoside **18** also provided the corresponding α-disaccharide **19** in 63% isolated yield along with its C-4 reigoisomer in 18% yield (Example C). For the determination of the regioselecivity, see below). Thus, the current method can be applied for the synthesis of angucycline natural products such as Quanolirones and Galtamycin without the protection of the C4-OH group.

Scheme 3. Convergent synthesis of various 2-deoxy oligosaccharides.[a,b]



[a] Method A: 5 mol% $Pd_2(dba)_3$, 10 mol% of **L1**. Method B: 2.5 mol% $Pd_2(dba)_3$, 5 mol% of *ent*-**L1**. Method C: 5.0 mol% $Pd_2(dba)_3$, 10 mol% of *ent*-**L1**. Method D: 2.5 mol% $Pd_2(dba)_3$, 5 mol% of ligand **L1**. [b] The yield of RCM reaction in all cases was higher than 90%. [c] Isolated yield of the pure compound. [d] The dr could not be measured because of the complex patterns of the crude NMR. [e] 15 mol% $Pd_2(dba)_3$, 30 mol% of ligand **L1**.

We then pursued preparation of more complex 2-deoxyoligosaccharides. On the basis of the structural pattern found in the Langkocyclines (Figure 1), we reasoned that an iterative use of the allene **14** would pave the road for the collective synthesis of the glycosidic portion of Langkocycline A1 and A2 (Figure 1).[23] As depicted in Example D, the iterative cycle is composed of three-step sequential metal catalysis involving (i) Pd-catalyzed asymmetric hydroalkoxylation followed by (ii) Ru-catalyzed RCM and (iii) Pd-catalyzed hydrogenation (and the concomitant removal of the benzyl group). Remarkably, two glycosidic residues can be introduced by each iteration. Initial subjection of **14** and cyclohexanol to this cycle using ligand *ent*-**L1** as a stereocontrol element led to the formation of Lankocycline A1 cyclohexyl glycoside **20** in 75% yield (over three steps). Additional cycle employing sequential Pd-Ru catalysis and allene **14** in the presence of *ent*-**L1** produced the tetrasaccharides **21a** in 60% yield. (In this case, C4-regioisomer was also obtained in ~20% yield). X-ray crystalographic analysis of this compound unambiguously confirmed the stereo- and regioselectivity of the reaction (For detailed information, see the SI). Furthermore, switching to enantiomeric ligand **L1** gave an unnatural derivative of the tetrasaccharide (compound **21b**) in comparable 61% yield. As a final example, we explored the synthesis of a tetrasaccharide moiety in Landomycin Y (compound **25**), which is highly heterogeneous in terms of the sequence and stereochemistry (Example E). For this purpose, the disaccharides **24** was first prepared from allene **22** and β-D-olivose derivative **23** via the three-step protocol in 61% overall yield. Then, synthesis of tetrasaccharide **25** was pursued by the coupling of **24** and the repeating unit **15**. As described in Scheme 3, Pd-catalyzed asymmetric hydroalkoxylation in this case needed higher loading of $Pd_2(dba)_3$ (15 mol%) to provide the acyclic acetal in 67% yield. After the RCM reaction, the target tetrasaccharide **25** was obtained in 92% yield (62% over two steps). As illustrated by these examples, a number of natural and non-natural oligosaccharides can arise by simply conjugating diverse ene-alkoxyallene fragments. It should be also noted that the proposed method can be easily expanded to the convergent synthesis of natural products possessing oligomeric 2,3,6-trideoxysaccharides (such as Amicenomycins and Cervimycins[24]).

In conclusion, we developed a Pd-catalyzed asymmetric diastereoselective hydroalkoxylation of highly substituted ene-alkoxyallenes. This reaction opens up a new paradigm in the synthesis of oligosaccharides containing 2,3,6-trideoxyglycosides. The future direction of the work is directed to examining automation of the process and to studying the relationship between the stereochemistry of the various monomeric units and the potential bioactivities. The results of these future studies will be reported in a due course.

Acknowledgements

Financial support for this work was provided by the Samsung Science and Technology Foundation. (STF-BA-1502-08).

Keywords: Oligosaccharides • Carbohydrates • Palladium • Diastereoselectivity • Asymmetric synthesis

[1] For selected reviews on carbohydrate-containing natural product: a) S. I. Elshahawi, K. A. Shaaban, M. K. Kharel, J. S. Thorson, *Chem. Soc. Rev.* **2015**, *44*, 7591-7697; b) L. Morelli, L. Poletti, L. Lay, *Eur. J. Org. Chem.* **2011**, 5723-5777; c) A. C. Weymouth-Wilson, *Nat. Prod. Rep.* **1997**, *14*, 99-110.

[2] T. Someno, S. Kunimoto, H. Nakamura, H. Naganawa, D. Ikeda, *J. Antibiot.* **2005**, *58*, 56-60.

[3] J. Qian-Cutrone, J. M. Kolb, K. McBrien, S. Huang, D. Gustavson, S. E. Lowe, S. P. Manly, *J. Nat. Prod.* **1998**, *61*, 1379-1382.

[4] K. Ströch, A. Zeeck, N. Antal, H.-P. Fiedler, *J. Antibiot.* **2005**, *58*, 103-110.

[5] N. Kawamura, R. Sawa, Y. Takahashi, T. Sawa, N. Kinoshita, H. Naganawa, M. Hamada, T. Takeuchi, *J. Antibiot.* **1995**, *48*, 1521-1524.

[6] B. Kalyon, G. Y. A. Tan, J. M. Pinto, C. Y. Foo, J. Wiese, J. F. Imhoff, R. D. Süssmuth, V. Sabaratnam, H. P. Fiedler, *J. Antibiot.* **2013**, *66*, 609-616.

[7] K. A. Shaaban, C. Stamatkin, C. Damodaran, J. Rohr, *J. Antibiot.* **2010**, *64*, 141.

[8] L. Zhu, A. Luzhetskyy, M. Luzhetska, C. Mattingly, V. Adams, A. Bechthold, J. Rohr, *ChemBioChem.* **2007**, *8*, 83-88.

[9] For selected reviews on *2*-deoxy-glycoside synthesis*:* a) C. S. Bennett, M. C. Galan, *Chem. Rev.* **2018**, *118*, 7931-7985l b) C. S. Bennett, *Selective Glycosylations: Synthetic Methods and Catalysts*, Wiley-VCH Weinheim, **2017**; c) A. Z. Aljahdali, P. Shi, Y. Zhong, G. A. O'Doherty, *Adv. Carbohydr. Chem. Biochem*. **2013**, 69, 55-123; d) A. Borovika, P. Nagorny, *J. Carbohydr. Chem.* **2012**, *31*, 255-283; e) D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911-1940.

[10] Y. Guo, G. A. Sulikowski, *J. Am. Chem. Soc.* **1998**, *120*, 1392-1397.

[11] For selected examples that introduce new strategies based upon substrate-controlled glycosylations, see: a) D. Lloyd, C. S. Bennett, *Chem. Eur. J.* **2018**, *24*, 7610-7614; b) S. Kusumi, S. Tomono, S. Okuzawa, E. Kaneko, T. Ueda, K. Sasaki, D. Takahashi, K. Toshima, *J. Am. Chem. Soc.* **2013**, *135*, 15909-15912; c) H. Tanaka, S. Yamaguchi, A. Yoshizawa, M. Takagi, K. Shin-ya, T. Takahashi, *Chem. - Asian J.* **2010**, *5,* 1407–1424; d) Y. Li, Y. Yang, B. Yu, *Tetrahedron Lett.* **2008**, *49*, 3604-3608.

[12] For selected examples describing the total synthesis of deoxyglycoside natural products using this strategy, see: a) X. Yang, B. Fu, B. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 12433-12435; b) B. Yu, P. Wang, *Org. Lett.* **2002**, *4*, 1919-1922; c) W. R. Roush, C. E. Bennett, *J. Am. Chem. Soc.* **2000**, *122*, 6124-6125.

[13] For selected review on transition metal catalyzed glycosylation: a) X. Li, J. Zhu, *Eur. J. Org. Chem.* **2016**, 4724-4767; b) M. J. McKay, H. M. Nguyen, *ACS Catal.* **2012**, *2*, 1563-1595.

[14] For selected examples on the transition metal-catalyzed glycosylation: a) C. Palo-Nieto, A. Sau, M. C. Galan, *J. Am. Chem. Soc.* **2017**, *139*, 14041-14044; b) H. Y. Wang, C. J. Simmons, S. A. Blaszczyk, P. G. Balzer, R. Luo, X. Duan, W. Tang, *Angew. Chem. Int. Ed.* **2017**, *56*, 15698-15702; *Angew. Chem.* **2017**, *129*, 15904-15908; c) H. Yao, S. Zhang, W.-L. Leng, M.-L. Leow, S. Xiang, J. He, H. Liao, K. Le Mai Hoang, X.-W. Liu, *ACS Catal.* **2017**, *7*, 5456-5460; d) A. Sau, M. C. Galan, *Org. Lett.* **2017**, *19*, 2857-2860; e) R. S. Babu, M. Zhou, G. A. O'Doherty, *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429; f) H. Kim, H. Men, C. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 1336-1337.

[15] For selected examples on the total synthesis using transition metal catalysis: a) X. Zhang, Y. Zhou, J. Zuo, B. Yu, *Nat. Commun.* **2015**, *6*, 5879-5888; b) S. O. Bajaj, E. U. Sharif, N. G. Akhmedov, G. A. O'Doherty, *Chem. Sci.* **2014**, *5*, 2230-2234; c) B. Wu, M. Li, G. A. O'Doherty, *Org. Lett.* **2010**, *12*, 5466-5469.

[16] a) M. Kim, S. Kang, Y. H. Rhee, *Angew. Chem. Int. Ed.* **2016**, *55*, 9733-9737; *Angew. Chem.* **2016**, *128*, 9885-9889; b) W. Lim, J. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2014**, *136*, 13618-13621; c) For a related reference introducing *N*,*O*-acetal formation, see: H. Kim, Y. H. Rhee, *Synlett.* **2012**, *23*, 2875-2879.

[17] For our recent studies using ene-alkoxyallenes with *N*-heterocycle nucleophiles, see: a) S. Kang, S. H. Jang, J. Lee, D. G. Kim, M. Kim, W. Jeong, Y. H. Rhee, *Org. Lett.* **2017**, *19*, 4684-4687; b) S. H. Jang, H. W. Kim, W. Jeong, D. Moon, Y. H. Rhee, *Org. Lett.* **2018**, *20*, 1248-1251.

[18] For a related report on the Pd-catalyzed asymmetric alkylation of gem-diacetate, see: B. M. Trost, C. B. Lee, *J. Am. Chem. Soc.* **2001***, 123, 3671-3686.*

[19] For recent examples using Achmatowicz rearrangement for the linear synthesis of 2,3,6-trideoxyoligosaccharides, see: a) M. Zhou, G. A. O'Doherty, *Org. Lett.* **2008***, 10, 2283-2286*; b) W. Song, Y. Zhao, J. C. Lynch, H. Kim, W. Tang, *Chem. Commun.* **2015***, 51, 17475-17478.*

[20] When smaller amount of alcohol was used, the reaction was slower presumably due to the dual coordination of the Pd to the allene and olefin.

[21] J. P. Issa, C. S. Bennett, *J. Am. Chem. Soc.* **2014**, *136*, 5740-5744.

[22] For the complex oligosaccharides shown in Scheme 3, the 2nd generation Grubbs catalyst (**G2**) showed higher yield than the 1st generation Grubbs catalyst (**G1**).

[23] This structural pattern is also found in natural product of the Saquayamycin family. For a reference, see: T. Uchida, M. Imoto, Y. Watanabe, K. Miura, T. Dobashi, N. Matsuda, T. Sawa, H. Naganawa, M. Hamada, T. Takeuchi, H. Umezawa, *J. Antibiot.* **1985***, 38,* 1171–1181.

[24] K. Herold, F. A. Gollmick, I. Groth, M. Roth, K.-D. Menzel, U. Möllmann, U. Gräfe, C. Hertweck, *Chem. Eur. J.* **2005**, *11*, 5523-5530.

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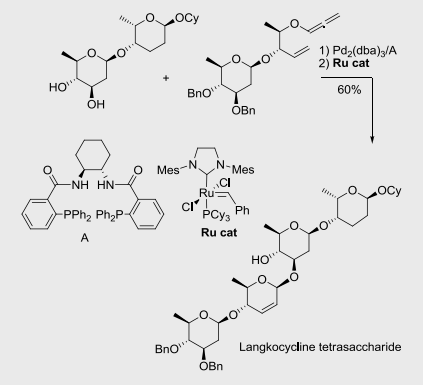
Layout 1:

COMMUNICATION

A new synthetic strategy towards 2,3,6-trideoxyoligosaccharide is described. The key event is the use of ene-alkoxyallene moiety possessing a glycosidic unit. The utility of the reaction was demonstrated by a number of well-controlled synthesis of 2,3,6-trideoxyoligosaccharides, including a tetrasaccharide moiety found in Landomycin Y.



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