Carbohydrate Synthesis

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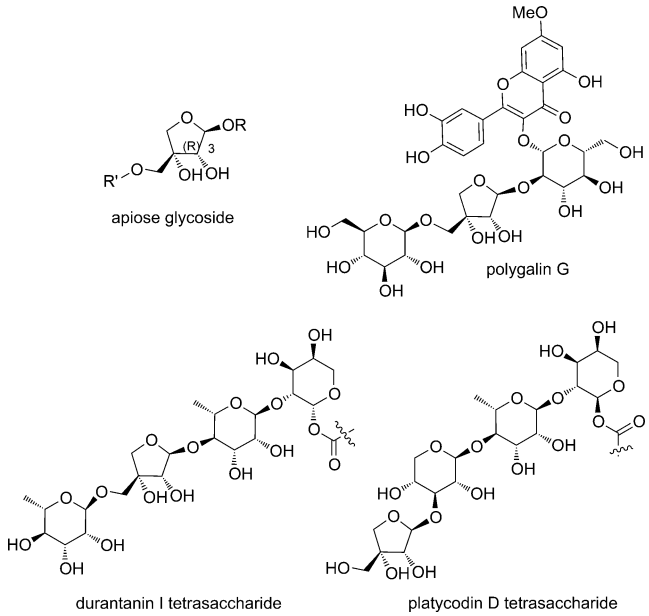
De Novo Synthesis of Furanose Sugars: Catalytic Asymmetric Synthesis of Apiose and Apiose-Containing Oligosaccharides

*Mijin Kim, Soyeong Kang, and Young Ho Rhee**

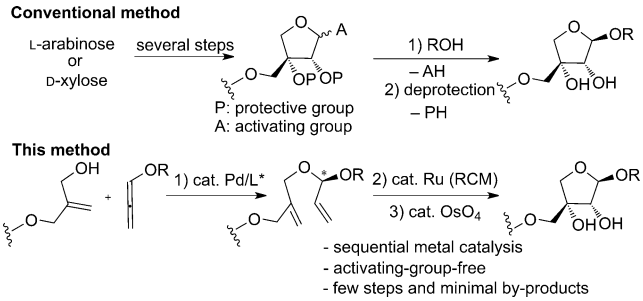
Abstract: *A de novo synthetic method towards apiose, a structurally unusual furanose, is reported. The key feature is sequential metal catalysis consisting of the palladium-catalyzed asymmetric intermolecular hydroalkoxylation of an alkoxyallene and subsequent ring-closing metathesis (RCM). This strategy enabled the efficient synthesis of various apiose-containing disaccharides and a unique convergent synthesis of trisaccharides.*

The stereoselective synthesis of carbohydrates with high chemical efficiency is an important goal in synthetic organic chemistry.[1] In this context, furanose sugars, such as apiose, pose a great synthetic challenge. Apiose is a unique branched furanose, whose naturally occurring form has the 3*R* configuration, as found in various natural products (Scheme 1). It occurs widely as a terminal or internal residue of various polysaccharides.[2] Notably, some natural products containing apiofuranose exhibit interesting biological properties, such as anti-inflammatory and immune-stimulating activity.[3]

In classical syntheses, the introduction of an apiose residue into an oligosaccharide has relied upon a linear method involving the coupling of an activated furanose precursor (glycosyl donor) with an alcohol moiety (glycosyl acceptor; Scheme 2). This conventional method has a number of drawbacks. For example, the furanose precursor must be synthesized from suitable carbohydrates in several steps.[4]

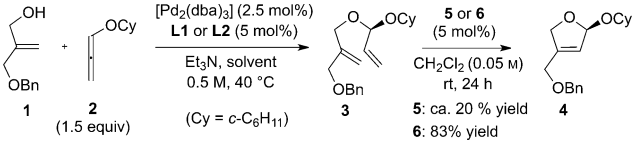


Scheme 1. Apiose-containing oligosaccharides.



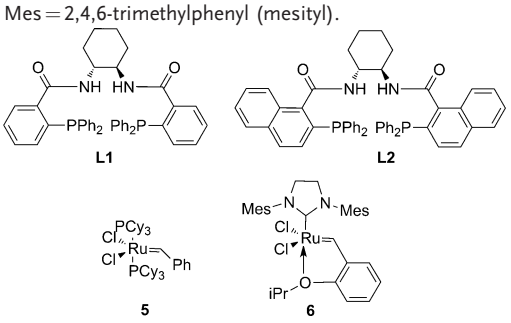
Scheme 2. Methods for the synthesis of apiose.

Table 1: Optimization of reaction conditions.



Entry	Ligand	Amount of Et_3N [equiv]	*t* [h]	Solvent	Yield [%][a]	*ee* [%][b]
1	**L1**	1.5	0.5	toluene	94	96
2	**L1**	1.5	0.5	CH_2Cl_2	94	92
3	**L1**	1.5	24	1,4-dioxane	76	87
4	**L1**	0.1	0.5	toluene	96	97
5	**L2**	1.5	24	toluene	56	88

[a] Yield of the isolated product **3**. [b] The *ee* value of **4** after the ring-closing metathesis reaction. Bn = benzyl, dba = dibenzylideneacetone, Mes = 2,4,6-trimethylphenyl (mesityl).



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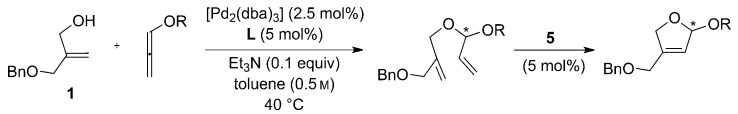
Furthermore, the establishment of the well-defined configuration observed in all natural products containing an apiose moiety has required the use of specific directing protective groups, such as acetyl or benzylidene groups.[5] Moreover, activating groups must be used, and then disposed of as waste after the glycosylation step.

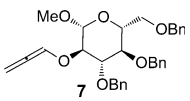
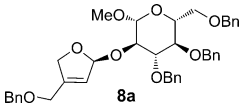
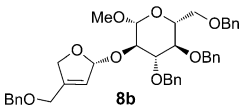
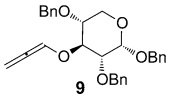
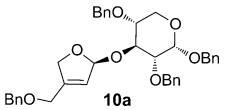
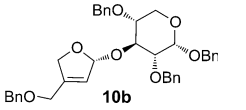
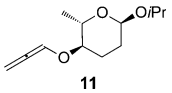
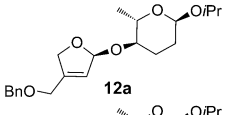
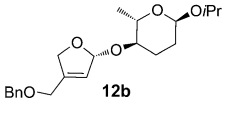
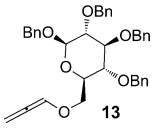
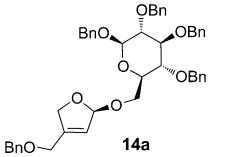
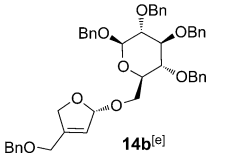
A de novo approach, in which the glycosidic bond is formed by an asymmetric reaction, is considered a powerful alternative to glycosylation reactions.[6,7] However, such methods have been largely limited to pyranose synthesis. Herein, we report a unique de novo approach to apiofuranose on the basis of our previous studies in a related area.[8] In this scenario, an acyclic chiral O,O-acetal is first formed by the palladium-catalyzed asymmetric hydroalkoxylation of an allene (Scheme 2).[9,10] Subsequent ruthenium-catalyzed ring-closing metathesis (RCM) and an osmium-catalyzed dihydroxylation reaction introduce all the stereochemical information present in the apiose residue.[11] A salient feature of this method is the efficient assembly of the apiose sugar from structurally readily available precursors in just three steps, with no need for activating groups and minimal formation of by-products. Furthermore, this new reaction sequence requires no directing protective groups because the stereoselectivity of the dihydroxylation should be dictated by the chiral acetal moiety.

At the beginning of the study, we investigated the synthesis of the simple monosaccharide form of apiose by the coupling reaction of the allylic alcohol **1** and allene **2** derived from cyclohexanol (Table 1). As in our previous studies,[8] the reaction in the nonpolar solvent toluene proceeded smoothly to generate the acyclic acetal **3** in 94% yield in the presence of $[Pd_2(dba)_3]$ (2.5 mol%), chiral ligand **L1** (5 mol%), and triethylamine (1.5 equiv; Table 1, entry 1). Because the product **3** was relatively unstable, we immediately attempted the formation of the cyclic acetal **4** without analysis of the enantiomeric purity. Initial studies with the Ru catalyst **5** gave the product only in poor yield. Notably, the use of catalyst **6** significantly improved the yield of **4** (formed with 96% *ee*) to 83% (Table 1, entry 1). The absolute configuration was tentatively assigned as shown in Table 1 on the basis of our analysis in previous studies.[8] (For the rigorous determination of the absolute configuration, see below). Next, we optimized the reaction conditions for the palladium-catalyzed reaction. The use of more-polar solvents, such as CH_2Cl_2 and 1.4-dioxane, somewhat decreased the enantioselectivity (Table 1, entries 2 and 3), whereas the the reaction still proceeded in high yield (96%) with excellent selectivity (97% *ee*) when the amount of triethylamine was reduced (0.1 equiv; entry 4). However, the use of ligand **L2** significantly slowed down the reaction (entry 5).

Having established optimal conditions for the enantioselective synthesis of the apiose monosaccharide, we turned to

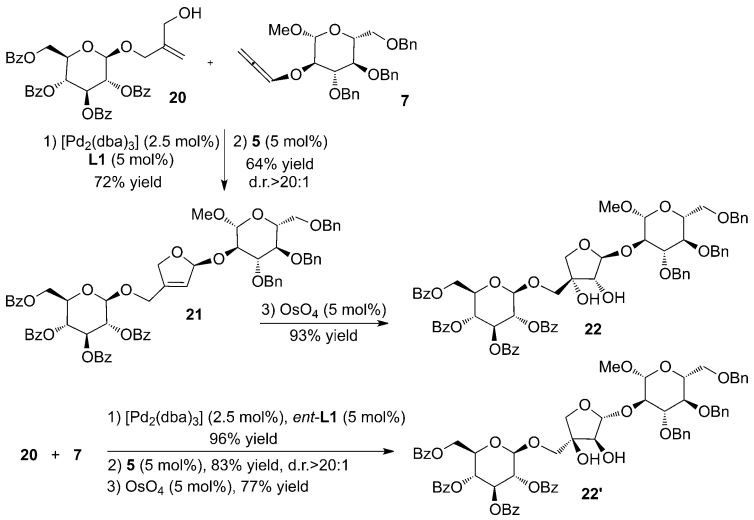
Table 2: Scope of disaccharide synthesis.



Entry	Allene	Method[a]	*t* [h]	Product	Yield [%][b,c] (1st, 2nd)
1	 **7**	A	3	 **8a**	82, 77
2		B	5	 **8b**	87, 77
3	 **9**	A[d]	3	 **10a**	74, 83
4		B[d]	3	 **10b**	90, 74
5	 **11**	A	2	 **12a**	93, 83
6		B	2	 **12b**	95, 86
7	 **13**	A[d]	2	 **14a**	87, 80
8		B[d]	8	 **14b**[e]	99, 77

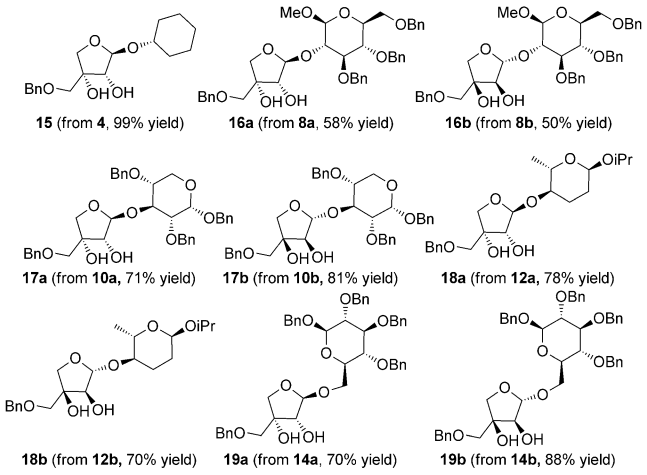
[a] Method A: **L1** was used; method B: *ent*-**L1** was used. [b] Yield of the isolated product for each step. [c] In all cases, the diastereomeric ratio of the first step was determined to be > 10:1 by integration of the ^{1}H NMR spectrum. [d] Ligand: 7.5 mol%. [e] d.r. 8:1.

the stereoselective synthesis of disaccharides by treating the alcohol **1** with pyranose monosaccharides possessing an allene at various positions. In our initial attempt, disaccharide **8a** possessing the furanose moiety at the C2 position of D-glucose was obtained from allene **7** in 63% yield over two steps with high selectivity (Table 2, entry 1). Notably, simply switching the ligand to enantiomeric (*S*,*S*)-**L1** gave the diastereomeric disaccharide **8b** in 67% yield (over two steps, entry 2). The reaction of the 3-allenyloxy xylose derivative **9** with **1** also gave the diastereomeric disaccharides **10a** and **10b** in good yields (Table 2, entries 3 and 4). Furthermore, deoxysugar substrate **11** with an alkoxyallene group at the C4 position gave the disaccharides **12a** and **12b** uneventfully (Table 2, entries 5 and 6). The reaction was successfully extended to substrate **13** with the allene group at the C6 position of the glucopyranoside.[12] Thus, disaccharides **14a** and **14b** were obtained in 70 and 76% yield, respectively (over two steps, entries 7 and 8). Interestingly, the use of Ru catalyst **5** for the RCM step led to much higher conversion than that observed with **6** in all cases.[13] The examples in Table 2 firmly establish the generality of the proposed method in the synthesis of disaccharides possessing the apiose moiety at the terminal position. The diastereomeric dissacharides with the nonnatural form of apiose were obtained with comparable chemical efficiency.



Scheme 4. Convergent synthesis of the trisaccharide unit of polygalin G. Bz = benzoyl.

We next examined the diastereoselective dihydroxylation reaction. The osmium-catalyzed reaction of various substrates afforded the desired mono- and disaccharide products in good to high yield (Scheme 3). In all cases, the product was obtained as single *trans* diastereomer, thus verifying our hypothesis that the stereochemical outcome of the dihydroxylation step is determined by the stereogenic information in the acetal moiety. The structure of **17a** was unambiguously established by X-ray crystallographic analysis, which confirmed our spectroscopic analysis.[14]



Scheme 3. Products of stereoselective osmium-catalyzed dihydroxylation. Typical procedure: 4-Methylmorpholine *N*-oxide (2 equiv) and a solution of OsO_4 (4 wt% in H_2O, 0.003 equiv) in distilled H_2O (total concentration: 1.4 M) were added to a solution of the cyclic O,O-acetal in acetone/THF (1:1 v/v, 1.0 M) at 0°C, and the reaction mixture was stirred at room temperature for 16 h.

Encouraged by the evident utility of the multicatalytic reaction, we then undertook the challenge of a unique convergent synthesis of the apiose-containing trisaccharide moiety **22**, which constitutes the key fragment of polygalin G. To our delight, the palladium-catalyzed coupling reaction of the readily available monosaccharide-containing allyl alcohol **20** and the glucose-derived alkoxyallene **7** produced the desired O,O-acetal intermediate in 72% yield, which was immediately converted into the furanose intermediate **21** by way of a RCM reaction in 64% yield with >20:1 selectivity (Scheme 4). The subsequent dihydroxylation reaction provided the target **22** in 93% yield, again as single diastereomer. Notably, a nonnatural isomer of trisaccharide **22** (compound **22′**) was synthesized with comparable yield and chemical efficiency simply by switching the ligand to *ent*-**L1**. This convergent synthesis highlights the advantage of the current method in terms of chemical efficiency in comparison with the classical linear (sequential) glycosylation reaction.

In summary, we developed a highly efficient synthesis of apiose-containing mono- and oligosaccharides by palladium-catalyzed asymmetric intermolecular hydroalkoxylation. This reaction forms the basis of a unique de novo synthesis of furanose sugars. The utility of the proposed method was demonstrated by the highly efficient synthesis of various disaccharides and the convergent synthesis of a trisaccharide moiety. We are currently working on the extension of the sequential Pd/Ru catalysis to the synthesis of more structurally complex furanose and pyranose oligosaccharides. The results of these studies will be reported in due course.

Experimental Section

Typical procedure: A solution of $[Pd_2(dba)_3]$ (5.8 mg, 6.3 μmol) and **L1** (7.6 mg, 0.011 mmol) in toluene was added to a solution of **7** (104 mg, 0.20 mmol), **1** (56 mg, 0.31 mmol), and triethylamine (2.4 μL, 0.018 mmol) in toluene (total concentration: 0.5 M). The

reaction mixture was stirred at room temperature for 3 h, then purified without a workup procedure by flash column chromatography (eluent: hexane/EtOAc 90:10) to give the acyclic O,O-acetal intermediate as a colorless oil (115.3 mg, 0.16 mmol, 82% yield) with d.r. 20:1, as determined by ^{1}H NMR spectroscopy of the crude mixture. $R_f = 0.37$ (hexane/EtOAc 80:20); $[\alpha]_D^{25} = -24.6$ ($c = 0.76$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.38$–7.11 (m, 20H), 5.82 (ddd, $J = 17.4$, 10.5, 6.2 Hz, 1H), 5.32 (d, $J = 17.4$ Hz, 1H), 5.25–5.21 (m, 4H), 4.90 (d, $J = 11.0$ Hz, 1H), 4.79 (d, $J = 11.0$ Hz, 1H), 4.78 (d, $J = 12.2$ Hz, 1H), 4.62 (d, $J = 12.2$ Hz, 1H), 4.55 (d, $J = 12.2$ Hz, 1H), 4.52–4.50 (m, 3H), 4.29 (d, $J = 7.7$ Hz, 1H), 4.28 (d, $J = 12.8$ Hz, 1H), 4.17 (d, $J = 12.8$ Hz, 1H), 4.07 (s, 2H), 3.74 (dd, $J = 10.9$, 2.0 Hz, 1H), 3.68 (dd, $J = 10.8$, 4.7 Hz, 1H), 3.63–3.56 (m, 2H), 3.51 (s, 3H), 3.53–3.47 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 143.0$, 138.7, 138.6, 138.4, 138.3, 135.4, 128.59, 128.57, 128.53, 128.1, 127.99, 127.96, 127.94, 127.88, 127.82, 127.76, 118.9, 114.0, 104.2, 103.8, 84.8, 78.2, 77.8, 75.9, 75.2, 75.1, 73.7, 72.3, 71.3, 69.1, 67.4, 57.0 ppm; IR (NaCl): $\tilde{\nu} = 3088$, 3064, 3030, 2922, 2860, 1740, 1658, 1606, 1497, 1454, 1361, 1309, 1278, 1215, 1095, 1058 cm^{-1}; HRMS (ESI): m/z calcd for $C_{42}H_{48}O_8Na^+$: 703.3241 $[M+Na]^+$; found: 703.3240.

Catalyst **5** (11 mg, 0.013 mmol) in CH_2Cl_2 was added to a solution of the above acyclic O,O-acetal (87 mg, 0.13 mmol) in CH_2Cl_2 (total concentration: 0.1M) at 40 °C under a nitrogen atmosphere, and the reaction mixture was stirred for 1 h (monitored by TLC). The solvent was removed under reduced pressure, and the resulting crude oil was purified by flash column chromatography on silica gel (deactivated by triethylamine before use) to afford **8a** (63.4 mg, 0.097 mmol, 77% yield) as a colorless oil. $R_f = 0.50$ (hexane/EtOAc 80:20); $[\alpha]_D^{26} = +4.39$ ($c = 0.24$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.34$–7.14 (m, 20H), 6.07 (d, $J = 6.8$ Hz, 1H), 5.68 (s, 1H), 4.88 (d, $J = 11$ Hz, 1H), 4.83–4.78 (m, 2H), 4.74–4.72 (m, 1H), 4.63 (d, $J = 12$ Hz, 1H), 4.56 (d, $J = 12$ Hz, 1H), 4.55 (d, $J = 11$ Hz, 1H), 4.53–4.47 (m, 3H), 4.28 (d, $J = 7$ Hz, 1H), 4.18 (s, 2H), 3.76 (dd, $J = 11.0$, 2.0 Hz, 1H), 3.69 (dd, $J = 11.0$, 4.5 Hz, 1H), 3.62–3.60 (m, 3H), 3.47–3.46 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 143.7$, 139.1, 138.5, 138.4, 138.0, 128.67, 128.63, 128.60, 128.5, 128.27, 128.26, 128.01, 127.96, 127.91, 127.8, 127.7, 122.8, 110.5, 104.5, 84.0, 80.3, 77.9, 75.5, 75.3, 75.2, 74.3, 73.7, 72.8, 69.3, 65.6, 57.3 ppm; IR (NaCl): $\tilde{\nu} = 2924$, 2865, 2844, 1497, 1454, 1359, 1056 cm^{-1}; HRMS (ESI): m/z calcd for $C_{40}H_{44}O_8Na^+$: 675.2928 $[M+Na]^+$; found: 675.2926.

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Keywords: asymmetric synthesis · carbohydrates · de novo synthesis · diastereoselectivity · oligosaccharides

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[1] For selected reviews on the stereoselective synthesis of carbohydrates, see: a) Y. Yang, X. Zhang, B. Yu, *Nat. Prod. Rep.* **2015**, *32*, 1331–1355; b) X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, *48*, 1900–1934; *Angew. Chem.* **2009**, *121*, 1932–1967; c) D. A. Ryan, D. Y. Gin, X. Zhu, R. R. Schmidt in *Handbook of Chemical Glycosylation*, Wiley-VCH, Weinheim, **2008**, pp. 95–185; d) P. Fugedi, *The Organic Chemistry of Sugars*, CRC, Boca Raton, **2006**, pp. 89–179.

[2] a) E. Beck, H. Hopf, *Methods Plant Biochem.* **1990**, *2*, 235–289; b) R. R. Watson, N. S. Orenstein in *Adv. Carbohydr. Chem. Biochem.*, *Vol. 31* (Eds.: R. S. Tipson, H. Derek), Academic Press, New York, **1975**, pp. 135–184.

[3] For selected examples of oligosaccharide natural products containing apiose, see: a) C. Furusawa, S. Yasuda, H. Tsuji, S. Ito, H. Miyashita, H. Yoshimitsu, T. Nohara, M. Ono, *Nat. Prod. Res.* **2015**, 1–5; b) Y.-L. Song, G.-S. Zhou, S.-X. Zhou, Y. Jiang, P.-F. Tu, *Nat. Prod. Res.* **2013**, *27*, 1220–1227; c) J. W. Chung, E. J. Noh, H. L. Zhao, J.-S. Shim, Y. W. Ha, E. M. Shin, E. B. Lee, C. S. Cheong, Y. S. Kim, *Bio. Pharm. Bull.* **2008**, *31*, 2114–2120; d) G. Ragupathi, R. Damani, K. Deng, M. M. Adams, J. Hang, C. George, P. O. Livingston, D. Y. Gin, *Vaccine* **2010**, *28*, 4260–4267.

[4] For examples of the synthesis of apiose, see: a) A. Panda, S. Islam, M. K. Santra, S. Pal, *RSC Adv.* **2015**, *5*, 82450–82459; b) K. S. Toti, M. Derudas, F. Pertusati, D. Sinnaeve, F. Van den Broeck, L. Margamuljana, J. C. Martins, P. Herdewijn, J. Balzarini, C. McGuigan, S. Van Calenbergh, *J. Org. Chem.* **2014**, *79*, 5097–5112; c) M. Koos, J. Micova, B. Steiner, J. Alfoldi, *Tetrahedron Lett.* **2002**, *43*, 5405–5406; d) P.-T. Ho, *Can. J. Chem.* **1979**, *57*, 381–383.

[5] For selected examples of the synthesis of apiose-containing olisaccharides, see: a) S. A. Nepogodiev, M. Fais, D. L. Hughes, R. A. Field, *Org. Biomol. Chem.* **2011**, *9*, 6670–6684; b) M. Kojima, Y. Nakamura, K. Komori, S. Akai, K.-I. Sato, S. Takeuchi, *Tetrahedron* **2011**, *67*, 8276–8292; c) Y. Zhang, K. Wang, Z. Zhan, Y. Yang, Y. Zhao, *Tetrahedron Lett.* **2011**, *52*, 3154–3157; d) X. Zhu, B. Yu, Y. Hui, R. R. Schmidt, *Eur. J. Org. Chem.* **2004**, 965–973; e) M. A. J. Buffet, J. R. Rich, R. S. McGavin, K. B. Reimer, *Carbohydr. Res.* **2004**, *339*, 2507–2513.

[6] For selected pioneering studies on the de novo synthesis of oligosaccharides, see: a) E. U. Sharif, H.-Y. L. Wang, N. G. Akhmedov, G. A. O'Doherty, *Org. Lett.* **2014**, *16*, 492–495; b) A. Z. Aljahdali, P. Shi, Y. Zhong, G. A. O'Doherty, *Adv. Carbohydr. Chem. Biochem.* **2013**, *69*, 55–123; c) R. S. Babu, Q. Chen, S.-W. Kang, M. Zhou, G. A. O'Doherty, *J. Am. Chem. Soc.* **2012**, *134*, 11952–11955; d) R. S. Babu, M. Zhou, G. A. O'Doherty, *J. Am. Chem. Soc.* **2004**, *126*, 3428–3429.

[7] For selected examples of other de novo approaches, see: a) W. Song, Y. Zhao, J. C. Lynch, H. Kim, W. Tang, *Chem. Commun.* **2015**, *51*, 17475–17478; b) S. Xiang, K. L. M. Hoang, J. He, Y. J. Tan, X.-W. Liu, *Angew. Chem. Int. Ed.* **2015**, *54*, 604–607; *Angew. Chem.* **2015**, *127*, 614–617; c) H.-Y. Wang, K. Yang, D. Yin, C. Liu, D. A. Glazier, W. Tang, *Org. Lett.* **2015**, *17*, 5272–5275; d) H. Kim, H. Men, C. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 1336–1337; e) A. C. Comely, R. Eelkema, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 8714–8715; these de novo approaches cannot be readily applied to furanose synthesis.

[8] a) W. Lim, J. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2014**, *136*, 13618–13621; b) H. Kim, W. Lim, D. Im, D.-g. Kim, Y. H. Rhee, *Angew. Chem. Int. Ed.* **2012**, *51*, 12055–12058; *Angew. Chem.* **2012**, *124*, 12221–12224; c) H. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2012**, *134*, 4011–4014; d) H. Kim, Y. H. Rhee, *Synlett* **2012**, *23*, 2875–2879.

[9] For selected examples of metal-catalyzed asymmetric etherification, see: a) D. Kim, J. S. Lee, S. B. Kong, H. Han, *Angew. Chem. Int. Ed.* **2013**, *52*, 4203–4206; *Angew. Chem.* **2013**, *125*, 4297–4300; b) H. He, K.-Y. Ye, Q.-F. Wu, L.-X. Dai, S.-L. You, *Adv. Synth. Catal.* **2012**, *354*, 1084–1094; c) M. Roggen, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 5568–5571; *Angew. Chem.* **2011**, *123*, 5683–5686; d) P. A. Evans, D. K. Leahy, W. J. Andrews, D. Uraguchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 4788–4791; *Angew. Chem.* **2004**, *116*, 4892–4895; e) F. López, T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 3426–3427; f) H. Kim, C. Lee, *Org. Lett.* **2002**, *4*, 4369–4371.

[10] For examples of the palladium-catalyzed asymmetric hydrocarbonation of allenes, see: B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 20611–20622, and references therein.

[11] For selected reviews on the RCM reaction, see: a) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199 – 2238; b) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446 – 452.
[12] For the preparation of allenes, see the Supporting Information.
[13] In the reaction, catalyst **6** seemed to be deactivated faster than **5** in the presence of highly oxygenated substrates. For details of the optimization study, see the Supporting Information.
[14] See the Supporting Information. CCDC 1440078 (**17a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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