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A General, Iterative, and Modular Approach toward Carbohydrate Libraries Based on Ruthenium-Catalyzed Oxidative Cyclizations

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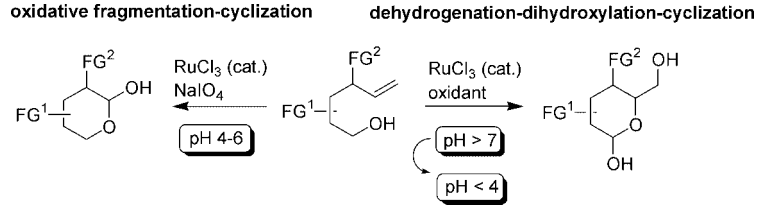

Carbohydrates are an omnipresent class of highly oxygenated natural products. Due to their wide spectra of biological activities, they have been in the center of synthetic organic chemistry for more than 130 years. During the past 50 years non-natural carbohydrates attracted the interest of various chemists in the fields of organic, biological, and medical chemistry. Especially desoxygenated sugars proved to be an important class of compounds. Up to date, most non-natural analogues are synthesized starting from natural, enantiomerically pure carbohydrates in multistep synthesis. In this report, we present a synthetic strategy that allows the selective modular synthesis of natural and non-natural carbohydrates within five synthetic steps starting from readily available starting materials. Due to a sequential introduction of O- or N-functionalities, a regioselective protection of each new functional group is possible. The key step in the carbohydrate synthesis is a RuO_4-catalyzed oxidative cyclization via a pH-dependent dehydrogenation−dihydroxylation−cyclization or an oxidative fragmentation−cyclization, leading to highly substituted new carbohydrates, in which each functional group is orthogonally protected and accessible for further synthetic operations.

Introduction

Carbohydrates belong to the four most important classes of biomolecules (i.e., carbohydrates, lipids, nucleic acids, and proteins).[1] They are involved in a variety of biological processes on a cellular level, such as recognition processes, metabolism, etc. Due to the advent of new and sensitive analytical technologies, biological processes are nowadays studied not only on a cellular but also on a molecular level. These studies have not only led to a deeper understanding of the way biomolecules act and interact but also spurred the interest in biomimetic molecules, such as nucleic acid,[2] amino acid,[3] and carbohydrate[4] analogues and their behavior in biological systems. The increasing demand for small defined libraries of bio- or biomimetic molecules has led to a technological push in organic synthesis, in which parallelization and automation allows for the efficient preparation of a defined set of molecules within a short period of time.[5] However, as compared to the other classes of biological building blocks, a comparable synthesis of substituted carbohydrates in a parallel fashion has yet not been developed.

This fact might be attributed in part to the chemical properties of carbohydrates, in which the ring opening−ring closing leads to mixtures of anomers of different ring sizes. Apart from this structural flexibility, the presence of up to six different hydroxyl groups with different but defined relative and absolute configuration causes problems in subsequent regioselective functional group transformations. The latter aspect has led to the develop-

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ment of sophisticated protecting group strategies that allow for a differentiation between the various hydroxyl groups. However, the use of protecting groups increases the amount of synthetic operations and thus decreases the overall efficiency of the synthesis.

It is in line with these arguments that so far carbohydrate libraries have mainly been prepared by derivatization of the hydroxyl groups within a given carbohydrate core.[6] In the past 10 years, organometallic or organic catalysts have changed the classical field of carbohydrate chemistry. Using these methods, multicomponent couplings between different monosaccharides are performed, giving rise to different substituted polysaccharides in an efficient manner.[7] Although some very efficient de novo carbohydrate syntheses are reported in the literature,[8,9] a broadly applicable, automatable, modular, and parallel synthesis that allows for structural variations within the carbohydrate core itself has not been developed up to date.

Recently, we started a research project aiming to build up small, defined libraries of orthogonally protected carbohydrate and carbohydrate mimic cores that would allow for a variety of further synthetic manipulations. As a first part of this research project, we report here on our initial results in the development of a potentially automatable, iterative approach toward structurally diverse orthogonally protected carbohydrates and analogues applying novel RuO_4-catalyzed oxidative cyclizations as central key steps.

Results and Discussion

Part 1: Development of Ru-Catalyzed Oxidative Cyclizations. Concept. Since the original contribution by Shing in 1994,[10] the selective, nondestructive oxidation of C=C bonds in the presence of RuO_4 gained increasing interest within the past years.[11] This oxidant exhibits a strong dependency of its oxidizing behavior from external parameters such as pH value, temperature, solvents, and reoxidants.[12] Due to this dependency, RuO_4-catalyzed oxidations are often accompanied by side reactions. However, if these parameters are equalized in the correct way, the variety of possible oxidation modes allows for the preparation of different oxygen-containing products out of one common starting material. Within the past 4 years, we were

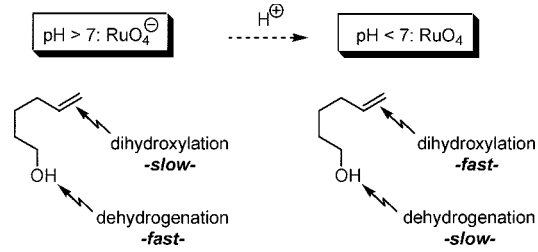

FIGURE 1. The pH-dependent chemoselectivity switch in Ru-catalyzed oxidations.

able to show that a slight modification of the reaction conditions allows for a selective yet totally different product formation.[11] Different from most inorganic oxidation catalysts, RuO_4 exhibits a strong pH-dependent stability[13] that allows for a switch of the oxidation state and chemoselectivity by a simple adjustment of the pH value. Whereas RuO_4 is stable up to pH 7 and oxidizes C=C bonds much faster than, for example, aliphatic primary alcohols,[11f] $RuO_4^{\ominus}$ formed between pH 7 and 10 readily dehydrogenates primary alcohols in the presence of C=C bonds[14] (Figure 1).

We envisioned that this unique pH-dependent mechanistic dichotomy in RuO_4-catalyzed olefin oxidation would pave the way for a new type of carbohydrate synthesis as depicted in Figure 2. Starting from a common precursor **i**, two mechanistically distinct reaction pathways are possible. Under acidic conditions, the stable RuO_4 reacts with olefins in a [3 + 2]-cycloaddition to give cyclic ruthenates. Depending on the pH value, these intermediates undergo different subsequent transformations. Whereas at a slightly acidic pH of 4−6 the electrocyclic fragmentation is fast, addition of Brønsted or Lewis acids accelerates the hydrolysis at pH < 4, leading to the preferred formation of *syn*-diols. If cyclization precursor **i** is oxidized under slightly acidic conditions with RuO_4, fragmentation of the C=C bond occurs. The dehydrogenation of primary aliphatic alcohols is comparably slow. The resulting aldehyde **ii** might undergo a ring closure, forming lactols of type **iii** (path A, Figure 2).[15] However, starting the same sequence under slightly basic conditions would yield perruthenate instead of RuO_4. This metal oxo species is known for its selective dehydrogenation of alcohols even in the presence of olefins. Hence, the dehydrogenation from **i** to **iv** should occur under basic conditions. Acidification of the reaction mixture to pH < 4 would lead to the in situ formation of RuO_4 from perruthenate and sets the stage for a fast dihydroxylation of **iv** to **v**. The cyclization would then lead to lactols of type **vi** (path B, Figure 2).[16]

Investigations on the pH-Dependent Reactivity. With regard to an attempted automatable and parallel synthesis of cyclization precursors, the use of one general protecting group pattern is of importance. The functional group FG^2 at C-4 in **i** is of major importance for the stereoselectivity in the dihydroxylation event. Hence, our investigations started with a

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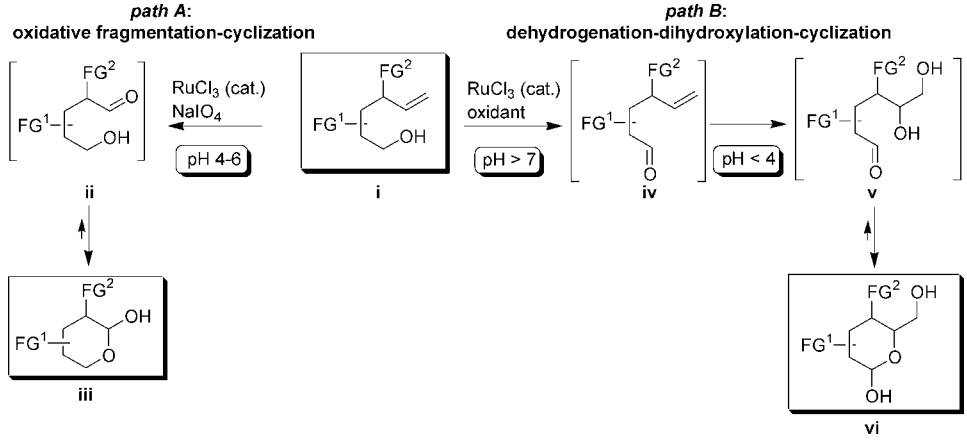
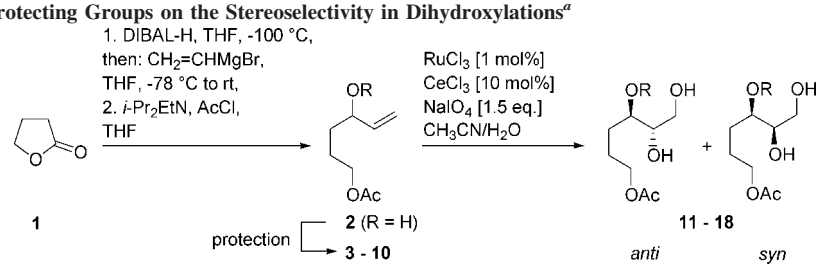


FIGURE 2. Oxidative cyclization pathways toward various carbohydrate skeletons.

TABLE 1. Influence of Protecting Groups on the Stereoselectivity in Dihydroxylations[a]



entry	olefin	R	diol	*anti*:*syn*[b]	yield [%][c]
1	**3**	TBDMS	**11**	82:18	93
2	**4**	TIPS	**12**	81:19	95
3	**5**	TBDPS	**13**	74:26	91
4	**6**	Bn	**14**	82:18	89
5	**7**	Bz	**15**	69:31	92
6	**8**	Ac	**16**	70:30	97
7	**9**	Piv	**17**	76:24	88
8	**10**	C(O)O*i*-Bu	**18**	70:30	87

[a] All reactions were performed on a 2 mmol scale using 1.0 mol % of $RuCl_3$ (as a 0.1 M stock solution in water), 10 mol % of $CeCl_3$, and 1.5 equiv of $NaIO_4$ in a solvent mixture of CH_3CN/H_2O (6 mL/1 mL) at 0 °C and stopped after full conversion. [b] Determined by ^1H NMR integration. [c] Combined isolated yield.

screening of various protecting groups and their directing effect on the stereoselective course in RuO_4-catalyzed dihydroxylation (Table 1).

Among the tested protecting groups, silyl and benzyl ethers induce the highest degree of stereoselectivity (entries 1 and 4, Table 1). However, allyl silyl ethers are susceptible toward acid-assisted cleavage. Hence, the more stable benzyl group was chosen for the protection of the 4-OH group in the subsequent chemoselectivity study.

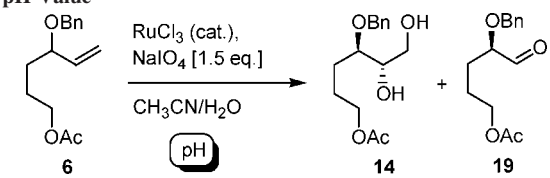
A dramatic change in the reactivity and mechanism depending on the pH value was observed (Table 2), indicating the correct adjustment of this parameter to be of utmost importance for the selective preparation of a single type of carbohydrate mimic.

Knowing the optimum pH range for the fragmentation versus dihydroxylation, we subsequently set out to develop the oxidative cyclizations.

The Ru-Catalyzed Oxidative Fragmentation−Cyclization−Acylation. On the basis of Yang's procedure for RuO_4-catalyzed fragmentations of olefins,[17] various parameters in the oxidation of cyclization precursor **20** (obtained by basic hydrolysis of **6**) were varied. Gratifyingly, a slight modification of the original protocol in combination with an anhydrous workup and in situ acylation allowed for the isolation of the desired cyclization product in good yield (Scheme 1).

Knowing that the pH range of the fragmentation already allowed for the intramolecular cyclization, the more complex

TABLE 2. Fragmentation versus Dihydroxylation−Influence of the pH Value[a]



entry	pH	**14**:**19**[b]	conversion [%][b]
1	6	8:92	81
2	5	12:88	80
3	4	44:56	79
4	3	89:11	86
5	2	96:4	91

[a] All reactions were performed on a 2 mmol scale using 1.0 mol % of $RuCl_3$ (as a 0.1 M stock solution in water), 10 mol % of $CeCl_3$, and 1.5 equiv of $NaIO_4$ in a solvent mixture of CH_3CN/H_2O (6 mL/1 mL) at 0 °C and stopped after 10 min. The pH value was adjusted by titration using a 2 N NaOH solution prior to the addition of starting material. [b] Determined by GC integration.

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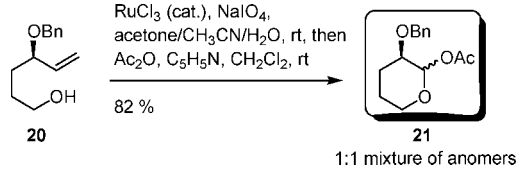
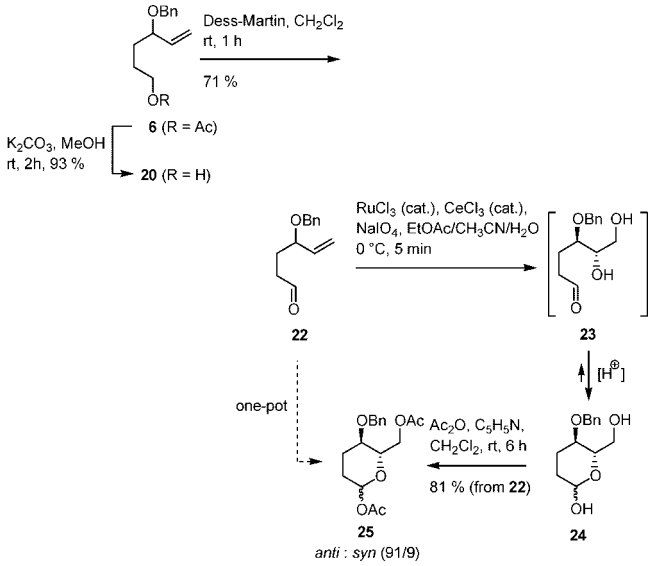
SCHEME 1. Oxidative C=C Bond Cleavage−Cyclization



dehydrogenation−dihydroxylation−cyclization was approached subsequently.

The Ru-Catalyzed Sequential Dehydrogenation−Dihydroxylation−Cyclization−Acylation. Initial efforts focused on the development of a stepwise dehydrogenation of **20** to the corresponding aldehyde **22** and its subsequent dihydroxylation−cyclization to **24**. In order to facilitate the workup, the crude product solution was not isolated but directly subjected to a concomitant acylation to give the bisacylated lactols *syn*- and *anti*-**25** in a ratio of 9:91 in an overall yield of 81% starting from **22** (Scheme 2).

SCHEME 2. RuO_4-Catalyzed Dihydroxylation−cyclization−Acylation sequence



Having elaborated a stepwise protocol for the dehydrogenation and oxidative cyclization, we turned our interest toward the development of a catalytic oxidative sequence. Initial experiments focused on the use of two different reoxidants. On the basis of literature known procedures, alcohol **20** was oxidized at pH 10 using $NaBrO_3$ as the oxidizing agent.[18] After full conversion, simple filtration of the suspension and treatment of the filtrate with aqueous $CeCl_3/NaIO_4$ immediately generated RuO_4 and initiated the final dihydroxylation event. A subsequent filtration−acylation delivered the 2,3-bisdeoxypyranosides **25** in good overall yield with diastereoselectivities comparable to the ones obtained in the stepwise protocol (method A, Scheme 3). Although this method proved successful, further investigations led to the development of a more practical method. We considered the change between two different stoichiometric oxidizing salts and the need for an intermediate removal of one oxidant by filtration to be problematic for large-scale applications. In furtherance of our investigations on the pH-dependent chemoselectivity switch, we found the literature reported aerobic oxidation of alcohol **20** using a combination of $RuCl_3/Al_2O_3$ in ethyl acetate at 80 °C to be a convenient alternative for the in situ formation of aldehyde **22**.[19] The immobilized Ru catalyst is liberated upon addition of acetonitrile and the aqueous slurry of $CeCl_3/NaIO_4$. After full conversion, filtration is followed by acylation (method B, Scheme 3). The desired product **23** was obtained in significantly improved yield and identical diastereoselectivity.

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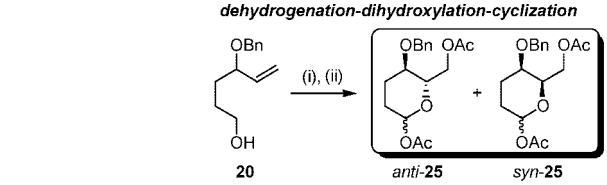
SCHEME 3. One-Pot Ru-Catalyzed Dehydrogenation−Dihydroxylation−Cyclization Sequence



Method A:

(i) $RuCl_3$ (cat.), $NaBrO_3$, pH 10, 50 °C
$EtOAc/CH_3CN/H_2O$, filtration then
(ii) $CeCl_3$ (cat.), $NaIO_4$, 0 °C, filtration then
Ac_2O, C_5H_5N, rt

91 : 9 — 52 % yield

Method B:

(i) $RuCl_3$ (cat.), Al_2O_3, O_2, 80 °C
EtOAc, then:
(ii) $CeCl_3$ (cat.), $NaIO_4$, CH_3CN/H_2O,
0 °C, filtration then:
Ac_2O, C_5H_5N, rt

91 : 9 — 66 % yield

Part 2: Development of a Modular, Potentially Automatable Carbohydrate Library Syntheses. Synthetic Concept. In order to build up a defined library of carbohydrates, we envisioned a three-dimensional matrix of potential carbohydrate precursors **i**, defined by the three major building blocks A, B, and C, to be the optimum base for the development of an efficient carbohydrate library synthesis. From a retrosynthetic point of view, the carbohydrate precursor can be formed via

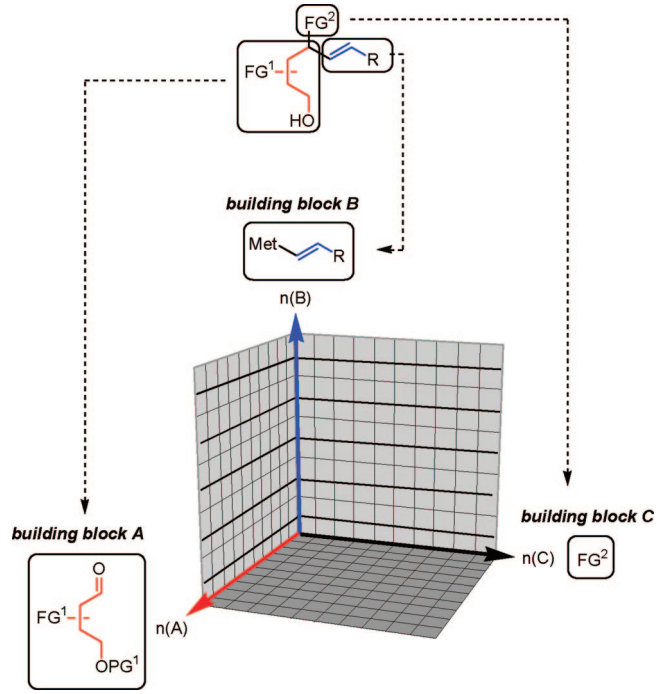
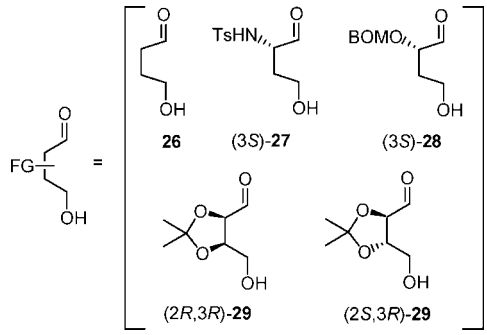


FIGURE 3. Modular, three-dimensional approach toward cyclization precursor **i** (*n*(A,B,C) refers to the number of building blocks).

SCHEME 4. Building Block A Synthons 26−29 (BOM = benzyloxymethoxy)



the combination of building block A, the backbone of the carbohydrate, and a vinyl metal species (building block B) plus a possible functional group transformation (building block C). The variation of these three building blocks against each other allows for a general access toward a matrix that is defined by $[n(A) \times n(B) \times n(C)]$ permutation, as shown in Figure 3.

Moreover, whereas these theoretical arguments account for the preparation of a structural diverse library of compounds, the synthetic approach is of practical use only if (*i*) the number of synthetic and diversifying processes is low and if (*ii*) the transformations can be performed under parallel conditions on a defined matrix of starting materials. Hence, in order to avoid unnecessary synthetic operations (e.g., protecting group manipulations), every heterofunctional group should be introduced iteratively, allowing for its selective and orthogonal protection prior to the introduction of further functionality. This operational simple trick sets the stage for a short synthesis of orthogonally protected cyclization precursors and carbohydrate mimics that can selectively be deprotected for further synthetic applications.

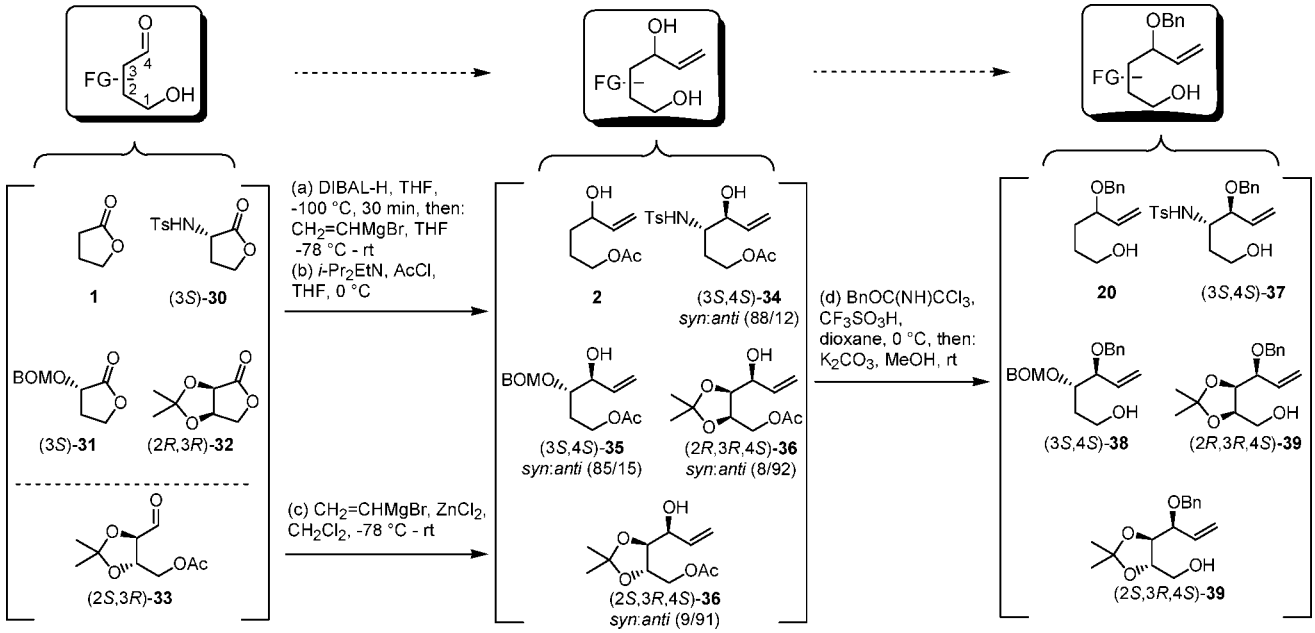
Whereas the requirements mentioned above build the base for an automatable, parallel synthesis, a common "synthetic point of convergence" needs to be defined. Up to this point, the synthetic routes toward the various building blocks A might differ; however, all further preparative manipulations have to be performed in an identical and hence automatable manner.

Variation of Building Block A. A set of five different, chiral pool derived building block A synthons were chosen as initial starting points for the preparation of a carbohydrate library (Scheme 4). With regard to the attempted parallel and automatable synthesis of cyclization precursors, a special emphasis was placed on the use of identical reagents and conditions for the subsequent transformations. Hence readily accessible lactones **1** and **30**−**32** were subjected to a reduction−vinylation−acylation sequence (Scheme 5). The allylic alcohols were directly transformed into the desired cyclization precursors using a one-pot benzylation−saponification protocol.[20] The cyclization precursors **20** and **37**−**39** were obtained in good to excellent diastereoselectivities and yields. For the preparation of benzyl ether (2*S*,3*R*,4*S*)-**39**, a slightly modified synthetic route was chosen. Due to the inaccessibility of the corresponding lactone, the literature known acetate **33** was subjected to a highly selective 1,2-addition using vinyl zinc chloride followed by the one-pot benzylation−saponification as described above (Scheme 5).

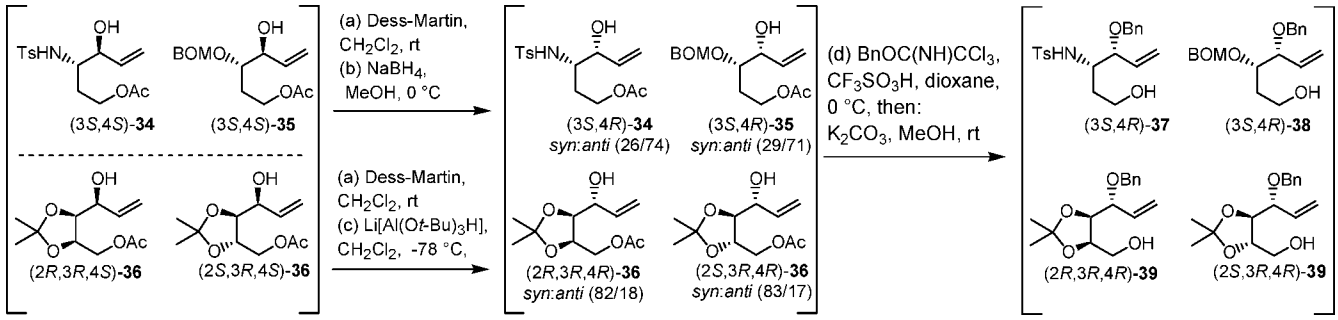
The C-4 epimeric series of cyclization precursors is accessible in a two-step sequence of oxidation−reduction using Li[Al(O*t*-Bu)$_3$H] or $NaBH_4$ as reducing agents. Allylic alcohols **34**−**36**were obtained in moderate to good diastereoselectivities (Scheme 6). Having nine different cyclization precursors in hand, we subsequently turned our attention toward the variation of the remaining building blocks.

Variation of Building Block B. The stereoselective course in RuO_4-catalyzed dihydroxylations of C=C bonds allows for the direct translation of π-bond geometry into relative configuration of two newly introduced C−O bonds. Hence, we were wondering whether the 1,2-addition of a long chain vinyl metal species could be used not only for the preparation of new types of glycolipids but also for the generation of two stereoisomeric carbohydrates formed solely through the double bond geometry. Thus, (*E*)- and (*Z*)-vinyl zinc species **41** were prepared according to literature known procedures[21] and reacted with lactone **1** in analogy to the conditions listed in Scheme 5 to furnish the corresponding (*E*)- and (*Z*)-allyl alcohols (*E*)-**42** and (*Z*)-**42** in good yields (Scheme 7).

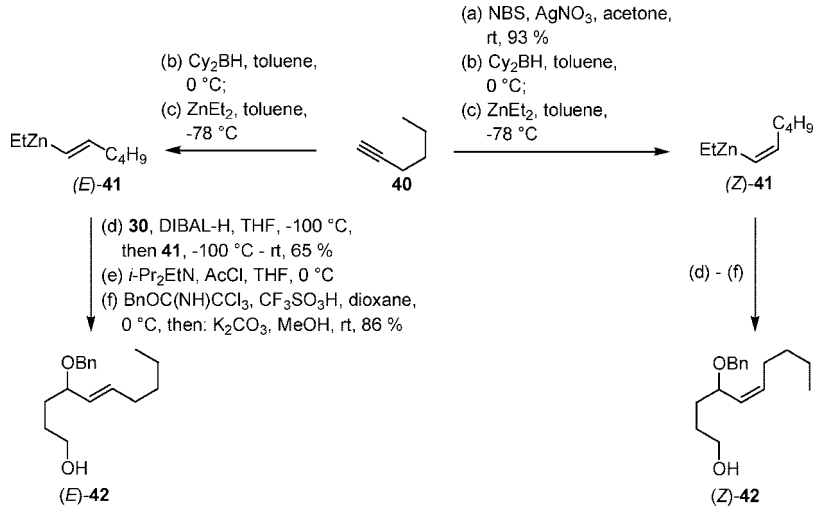
SCHEME 5. Preparation of Cyclization Precursors 20 and 37−39



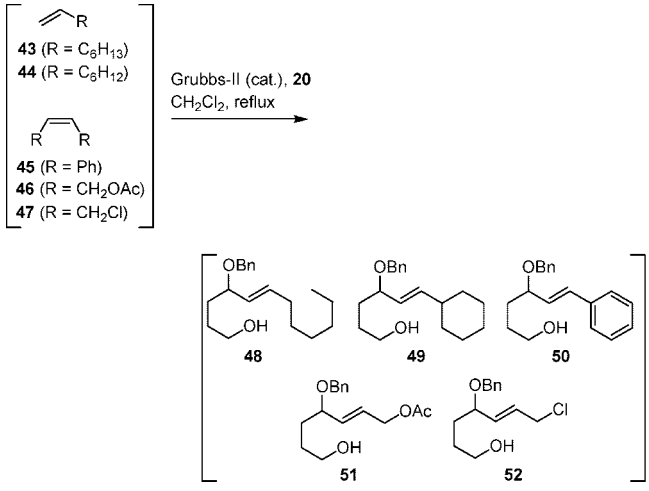
SCHEME 6. Preparation of C-4 Epimeric Cyclization Precursors 35−37



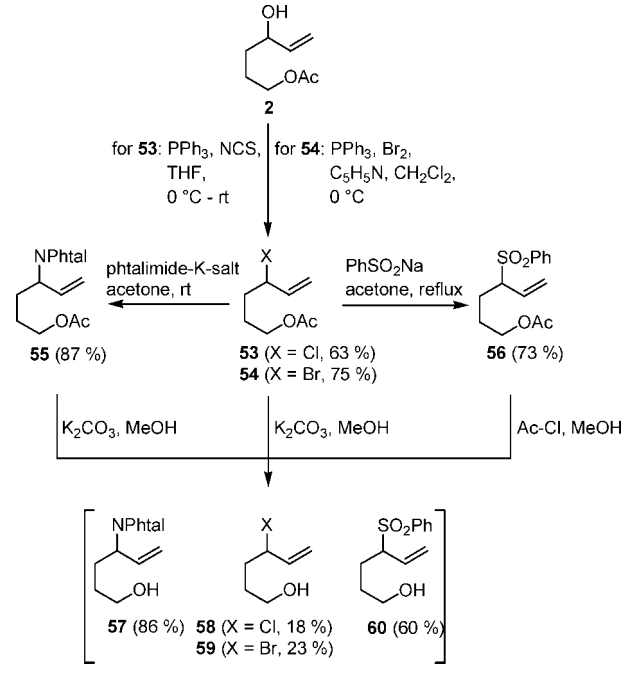
SCHEME 7. Control of π-Bond Geometry in 1,2-Additions—Preparation of (*E*)- and (*Z*)-42



SCHEME 8. Variation of Building Block B via Cross Metathesis



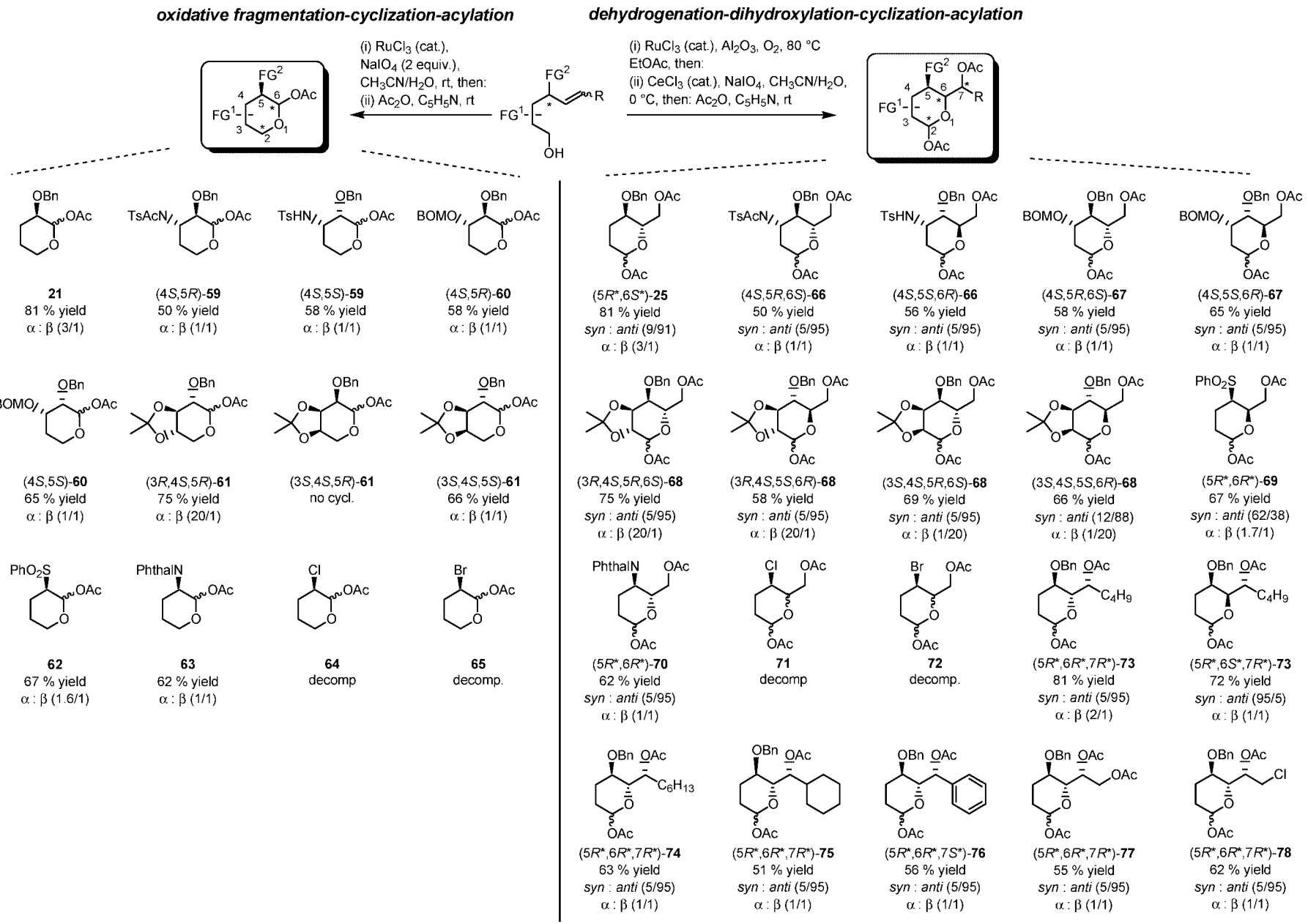
SCHEME 9. Variation of Building Block C by Nucleophilic Substitution



Apart from the 1,2-addition that allows for a control of π-bond geometry, the selective cross metathesis[22] between allyl benzyl ether **20** and various olefins **43**−**47** allows for the fast preparation of a defined set of new cyclization precursors **48**−**52**. The *E*-configured olefins are formed as the sole products (Scheme 8). A permutation of the various building blocks A **20** and **37**−**39** with the five olefins **43**−**47** was not performed in this study; however, it should be mentioned that the nine different precursors can be combined with these olefins to give 45 different cyclization precursors with defined stereochemistry. Taking into account the possibility of controlling the π-bond geometry in the 1,2-addition using either (*E*)- or (*Z*)-**42**, the number of precursors increases already to 63 solely by permutation of the building blocks mentioned in this study.

Variation of Building Block C. The allyl alcohol moiety in the cyclization precursors prepared so far sets the stage for a

TABLE 3. Carbohydrate Library Synthesis via Ru-Catalyzed Oxidative Cyclizations



variety of functional group transformations. Among the various substitution reactions of hydroxyl groups, we envisioned the exchange for a halide atom to be of particular interest. The biological impact of such a functional group appears to be very promising plus it paves the way for the introduction of new C−S or C−N bonds. The general synthetic route is shown in Scheme 9. The permutation of these four structural variations with the synthetic operations presented above increases the amount of potential cyclization precursors from 63 to 252. However, the deprotection of allylic halides **53** and **54** under various conditions proved to be problematic, and the desired alcohols **58** and **59** were obtained as instable liquids in low yield.

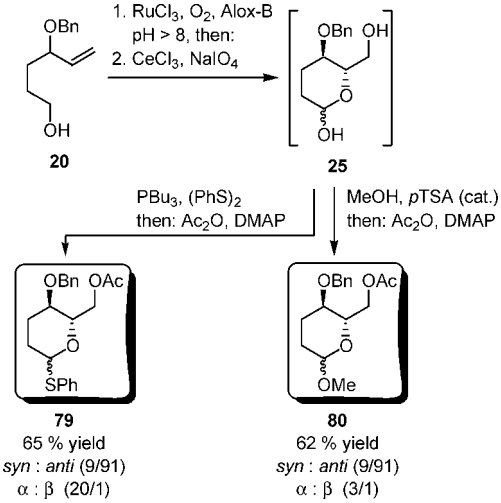
Preparation of a Carbohydrate Library. Having in hand a set of potential carbohydrate precursors, we subsequently turned our attention toward the synthesis of a small defined carbohydrate library (Table 3) by applying the sequential Ru-catalyzed oxidative fragmentation−cyclization−acylation conditions shown in Scheme 1 to a set of cyclization precursors possessing monosubstituted olefins, such as **20**, **37**−**39**, and **57**−**60**. Very much to our delight, the set of functional and protecting groups chosen for this study proved to be stable under the reaction conditions. The desired lactols were obtained in their acylated form in good yields as a mixture of anomers. Only the allylic halides **58** and **59** were unstable under the reaction conditions. These first encouraging results were followed by the successful application of the dehydrogenation−dihydroxylation−cyclization−acylation to the set of cyclization precursors. With the exception of the allylic halides, a set of 18 different carbohydrates and carbohydrate mimics were prepared in a highly diastereoselective manner. The relative configuration for each stereoisomer was investigated and established by intense NMR spectroscopic analysis on the isolated isomerically pure compounds. Several biologically active, fully protected specific carbohydrates are among the member of this library (Table 4).

TABLE 4. Important Known Carbohydrate Structures

entry	number	name
1	(4*S*,5*R*)-**61**	L-2-deoxyarabinose
2	(4*S*,5*S*)-**61**	L-2-deoxyribose
3	(3*R*,4*S*,5*R*)-**62**	L-xylose
4	(3*S*,4*S*,5*S*)-**62**	D-arabinose
5	(4*S*,5*R*,6*S*)-**67**	L-2-deoxyglucose
6	(4*S*,5*S*,6*R*)-**67**	L-2-deoxyallose
7	(3*R*,4*S*,5*R*,6*S*)-**68**	L-altrose
8	(3*R*,4*S*,5*S*,6*R*)-**68**	D-glucose
9	(3*S*,4*S*,5*R*,6*S*)-**68**	L-allose
10	(3*S*,4*S*,5*S*,6*R*)-**68**	L-mannose

Increasing the Synthetic Utility−The Workup. A simple but very important way to increase the synthetic utility of our protocol is the workup procedure. The lactols derived via oxidative cyclization have been acylated during the workup procedure. However, with regard to attempted applications in the synthesis of more complex di- or polysaccharides, the preparation of methyl or thioglycosides by variation of the workup procedure appears to be interesting.[23] Thus, as a proof of principle, allyl benzyl ether **20** was dehydrogenated−dihydroxylated using the standard conditions. The reaction mixture was separated from inorganic salts by simple filtration, and the filtrate was treated with an acidic methanol solution or using Fürstner's disulfide method.[24] The free hydroxyl group was acylated subsequently, and the desired products were obtained in good yield as a mixture of anomers (Scheme 10).

SCHEME 10. Variation of the Work-up Protocol−Preparation of Alkyl and Thioglycosides



Conclusion

In the present report, a new iterative de novo carbohydrate synthesis is described. The synthetic concept is based upon a short, modular, parallel synthesis of various allyl benzyl ethers, which are transformed into the corresponding orthogonally protected carbohydrate mimics via two novel Ru-catalyzed oxidative cyclizations. The overall simplicity of the synthetic operations plus the availability of the starting materials makes this approach especially amenable for the preparation of small, defined carbohydrate libraries in an automatable way. Future work will concentrate on this aspect with the goal to develop glycolipid and peptide libraries and to study their biological activity against various targets.

Experimental Section

The general procedures for the oxidative fragmentation−cyclization and for the dehydrogenation−dihydroxylation−cyclization are given below. The spectroscopic data of all carbohydrates shown above are listed in the Supporting Information.

General Procedure for the Oxidative Fragmentation−Cyclization. The appropriate alkene (1 mmol) was dissolved in acetone (2 mL), acetonitrile (2 mL), and water (1.7 mL). A solution of $RuCl_3$ (0.1 M, 300 μL, 0.03 mmol, 3 mol %) and $NaIO_4$ (428 mg, 2 mmol) was added. After stirring for 20 min, the mixture was diluted with ethyl acetate (10 mL), filtered, and washed with a mixture of $NaSO_3$ solution and $NaHCO_3$ solution (1:1, v/v) (10

(19) Yamaguchi, K.; Mizuno, N. *Chem.−Eur. J.* **2003**, *9*, 4353.

(20) Allylic alcohol **2** was obtained in a racemic way and used as such throughout this study. However, aysmmetric addition of a vinyl zinc reagent in the presence of an enantiomerically pure amino alcohol might be used for the preparation of the isomerically pure alcohol. In the present study, the main focus was placed on the use of the allyl benzyl ethers in the cyclization event.

(21) (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170. (b) Negishi, E.-I.; Williams, R. M.; Lew, G.; Yoshida, T. *J. Organomet. Chem.* **1975**, *92*, C4. (c) Campbell, J. B.; Molander, G. A. *J. Organomet. Chem.* **1978**, *156*, 71. (d) Jeon, S.-J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 9618.

(22) For an excellent and most recent review on the potential of cross metathesis in natural product synthesis, see: Hoveyda, A.; Zhugralin, A. R. *Nature* **2007**, *450*, 243, and references cited therein.

(23) Ogura, H.; Hasegawa, A.; Suami, T. *Carbohydrates: Synthetic Methods and Applications in Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 1998.

(24) Fürstner, A. *Liebigs Ann. Chem.* **1993**, *11*, 1211.

mL). Phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuum (max 30 °C). The obtained crude product was acylated directly. To a solution of the substrate dissolved in dry dichloromethane (2 mL) were added pyridine (815 μL, 10 mmol), acetic anhydride (470 μL, 5 mmol), and DMAP (catalytic amount). After 12 h, the mixture was diluted with ether (20 mL) and hydrolyzed by the addition of 2 N HCl. Phases were separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution dried over Na_2SO_4, filtered, and evaporated in vacuum. The obtained crude product was purified via flash chromatography.

(3*S*,4*S*,5*R*)-**62**: R_f 0.31 (4:1 *iso*-hexanes/ethyl acetate); $[\alpha]^{20}_D = -72$ ($c = 1.7$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 6.10 (d, $J = 6.7$ Hz, 1H), 4.75 (d, $J = 12.6$ Hz, 1H), 4.69 (d, $J = 12.6$ Hz, 1H), 4.58 (dd, $J = 7.5$, 3.0 Hz, 1H), 4.27−4.24 (m, 1H), 3.68 (m, 1H), 3.60 (dd, $J = 6.8$, 3.0 Hz, 1H), 2.05 (s, 3H), 1.55 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 131.2, 128.6, 128.2, 128.1, 107.4, 93.7, 74.1, 73.7, 72.5, 72.2, 64.0, 26.5, 25.6, 25.3 ppm; IR (film) ν 2987 (m), 2934 (m), 1745 (s), 1633 (m), 1455 (w), 1371 (m), 1226 (s), 1166 (w), 1064 (s) 1009 (m) cm^{-1}; *m*/*z* (EI) 322 (1), 219 (5), 156 (5), 141 (10), 91 (100), 65 (5); HRMS (ESI + Na^+) calcd for $C_{15}H_{19}O_4$ 263.1283, found 263.1280.

General procedure for the dehydrogenation-dihydroxylation-cyclization. Step 1: Preparation of Ru−Al_2O_3 Catalyst. Al_2O_3 (2.00 g, 19.6 mmol) was stirred with an aqueous solution of $RuCl_3$ (2 mL, 0.1 M) for 30 min at ambient temperature. The brown aqueous phase became lighter, and the powder turned dark gray. The powder was filtered, washed with water (15 mL), and dried in vacuum. The obtained powder was added into water (30 mL), and the pH value of the solution was slowly adjusted to 13 by addition of an aqueous solution of NaOH (1.0 M). The resulting slurry was stirred for 24 h at ambient temperature. The color of the powder turned from dark gray to dark green-gray. The solid was filtered off, washed with water (20 mL), and dried in vacuum to afford Ru−Al_2O_3 (1.9 g).

Step 2: Sequential Dehydrogenation−Dihydroxylation−Cyclization. A suspension of Ru−Al_2O_3 (250 mg) in ethyl acetate (10 mL) was stirred for 5 min at ambient temperature. Alcohol (0.5 mmol) was added, molecular oxygen was passed through the suspension, and the resulting mixture was stirred at 85 °C for 72 h. After 24 h Ru−Al_2O_3 (250 mg) was added, and heating was continued for further 50 h (100 mg). After cooling to ambient temperature, acetonitrile (10 mL) was added and the slurry was stirred for 20 min. An aqueous solution of H_2SO_4 (100 μL, 2 N) was added while stirring for 20 min. The suspension was cooled to 0 °C. Meanwhile, $NaIO_4$ (161 mg, 0.75 mmol) and $CeCl_3 \cdot 7H_2O$ (18.6 mg. 0.05 mmol, 10 mol %) were stirred in 3 mL of H_2O and gently heated until a bright yellow suspension was formed. The yellow suspension was cooled to 0 °C, added to the aldehyde Ru−Al_2O_3 suspension, and stirred for 5 min. Solid Na_2SO_4 (5 g) was added followed by ethyl acetate (10 mL). The solid was filtered of, the filter cake was washed several times with ethyl acetate, and the filtrate was concentrated in vacuum. The crude product was directly acylated as described above.

(2*S*,3*R*,4*S*,5*R*,6*S*)-**68**: R_f 0.31 (3.1 *iso*-hexanes/ethyl acetate); $[\alpha]^{20}_D = -66$ ($c = 0.1$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5H), 5.90 (d, $J = 7.0$ Hz, 1H), 4.86 (d, $J = 11.5$ Hz, 1H), 4.84 (ddd, $J = 11.0$, 3.0, 3.0 Hz, 1H), 4.71 (dd, $J = 9.6$, 7.0 Hz, 1H), 4.68 (d, $J = 11.5$ Hz, 1H), 4.32 (s, 1H), 4.13 (dd, $J = 12.5$, 11.0 Hz, 1H), 4.09 (d, $J = 9.5$ Hz, 1H), 3.56 (d, $J = 12.5$ Hz, 1H), 2.12 (s, 3H), 1.97 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.7, 138.4, 128.4, 128.2, 128.0, 111.3, 95.3, 76.7, 75.8, 74.5, 74.2, 71.5, 61.1, 26.9, 26.8, 21.4, 20.9 ppm; IR (film) ν 2986 (m), 2936 (m), 1754 (s), 1497 (w), 1455 (w), 1371 (m), 1225 (s), 1156 (m), 1111 (m), 1079 (m), 1058 (m), 1033 (m), 1013 (m) cm^{-1}; *m*/*z* (EI) 335 (5), 276 (5), 229 (5), 173 (5), 127 (10), 115 (10), 105 (10), 91 (100), 81(5), 65 (5); HRMS (FAB + HR) calcd for $C_{18}H_{23}O_6$ 335.1495, found 335.1476. (2*R*,3*R*,4*S*,5*R*,6*S*)-**68**: R_f 0.31 (3:1 *iso*-hexanes/ethyl acetate); $[\alpha]^{20}_D = -45$ ($c = 0.1$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m; 5H), 5.91 (d, $J = 7.0$ Hz, 1H), 4.84 (dd, $J = 3.0$ Hz, 1H), 4.83 (d, $J = 11.5$ Hz, 1H), 4.73 (d, $J = 11.5$ Hz, 1H), 4.60 (dd, $J = 9.5$, 7.0 Hz, 1H), 4.28 (dd, $J = 9.5$, 1.5 Hz, 1H), 4.09 (d, $J = 14.0$ Hz, 1H), 3.95 (s, 1H), 3.77 (d, $J = 14.0$ Hz, 1H), 2.12 (s, 3H), 2.11 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.7, 133.0, 128.5, 128.1, 128.0, 111.1, 94.9, 76.5, 74.9, 74.8, 74.1, 70.8, 61.2, 27.0, 21.4, 21.0 ppm; IR (film) ν 2986 (m), 2935 (m), 1754 (s), 1632 (w), 1496 (w), 1455 (m), 1371 (m), 1226 (s), 1153 (m), 1088 (m), 1061 (m), 1011 (m) cm^{-1}; *m*/*z* (EI) 334 (5), 276 (5), 229 (5), 187 (5), 173 (5), 127 (5), 115 (5), 105 (5), 91 (100), 82 (5), 65 (5); HRMS (FAB + HR) calcd for $C_{18}H_{23}O_6$ 335.1495, found 335.1478.

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Supporting Information Available: Experimental procedures for the preparation and spectral data for all reported compounds plus copies of ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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