Carbohydrate Synthesis

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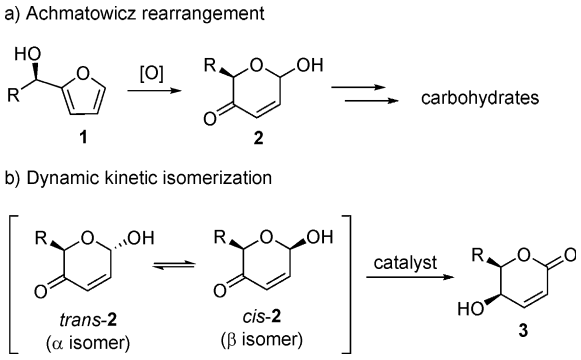
Iridium-Catalyzed Dynamic Kinetic Isomerization: Expedient Synthesis of Carbohydrates from Achmatowicz Rearrangement Products**

Hao-Yuan Wang, Ka Yang, Scott R. Bennett, Sheng-rong Guo, and Weiping Tang**

Abstract: *A highly stereoselective dynamic kinetic isomerization of Achmatowicz rearrangement products was discovered. This new internal redox isomerization provided ready access to key intermediates for the enantio- and diastereoselective synthesis of a series of naturally occurring sugars. The nature of the de novo synthesis also enables the preparation of both enantiomers.*

Biogenic furans are considered to be among the most promising sustainable raw materials for the production of fine chemicals.[1] Besides the defunctionalization methods developed for the synthesis of simple chemicals from furans,[2] the Achmatowicz rearrangement occupies a unique position as it efficiently converts a feedstock furan **1** into a much more structurally complex dihydropyranone **2** (Scheme 1a).[3] The potential of the Achmatowicz rearrangement for the de novo synthesis of carbohydrates was immediately recognized after its initial discovery in the 1970s.[4] Later, the research groups of Feringa[5] and O'Doherty[6] reported that esters of hemiacetal **2** could undergo palladium-catalyzed stereospecific allylic alkylation, thus establishing a unique glycosidation method.[7] The Achmatowicz rearrangement has also been applied to the synthesis of diverse libraries[8] and complex natural products,[9] including hexacyclic harringtonolide, the synthesis of which we recently completed.[10]

Because of the importance of the Achmatowicz rearrangement, a variety of oxidation conditions have been developed for the conversion of **1** into **2**,[11] including recently reported practical catalysts based on vanadium[12] and monooxygenase.[13] Efforts have also been devoted to the manipulation of hemiacetal and ketone groups in **2**, such as protection or oxidation of the hemiacetal and reduction of the ketone group.[14] However, most transformations involving the anomeric center are not highly stereoselective.



Scheme 1. Achmatowicz rearrangement and dynamic kinetic isomerization.

We herein report a highly stereoselective synthesis of lactones **3** from the epimeric mixtures of Achmatowicz rearrangement products **2** through an internal redox isomerization process (Scheme 1b), and its application to the synthesis of naturally occurring sugars.[15] The protection of the hemiacetal and reduction of the ketone were accomplished in one step. More importantly, a dynamic kinetic stereoselective transformation of both epimers of **2** into product **3** was possible because two prerequisites were fulfilled: the rate of equilibration between the *trans* and *cis* hemiacetals **2** was much faster than the isomerization, and the rate of redox isomerization was faster for one hemiacetal than for the other.

Substrate **2a** was prepared from acetylfuran by reduction and Achmatowicz rearrangement. The hemiacetal exists as a mixture of two epimers, and the diastereomeric ratio is around 3:1 in favor of the *cis* isomer (Table 1). We first screened a number of transition-metal catalysts, such as $[\{Ru(cod)Cl_2\}_n]$, $[Cp^*Ru(CH_3CN)_3]$, $[\{Rh(cod)Cl\}_2]$, $[Rh(cod)]BF_4$, $[Ir(cod)]BF_4$, $[\{Ir(cod)Cl\}_2]$, $Pd(OAc)_2$, $[Pd_2(dba)_3]$, $[NiCl_2\{P(C_6H_{11})_3\}_2]$, AgOAc, and CuBr. Interestingly, only iridium-based catalysts provided the desired isomerization product **3a**. Cationic $[Ir(cod)]BF_4$ only yielded a trace amount of product **3a**. We obtained compound **3a** in nearly quantitative yield by using a catalytic amount of the complex $[\{Ir(cod)Cl\}_2]$ (Table 1, entry 1). The diastereomeric ratio of product **3a** was also around 3:1 in favor of the *cis* isomer, thus indicating that the rate of iridium-catalyzed isomerization is much faster than the equilibration of the two epimers. The

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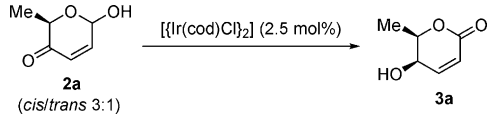
Table 1: Screening of conditions for the isomerization of **2a** to **3a**.



2a (*cis*/*trans* 3:1) → **3a**

Entry	Reaction conditions	Yield [%][a]	d.r.[a]
1	DCE, 50 °C	96	3:1
2	$C_6H_4CO_2H$ (50 mol %), DCE, 50 °C	97	12:1
3	*p*-$NO_2C_6H_4CO_2H$ (50 mol %), DCE, 50 °C	99	9:1
4	*p*-$CH_3C_6H_4CO_2H$ (50 mol %), DCE, 50 °C	97	10:1
5	$C_6H_4CO_2H$ (50 mol %), DCE, RT	97	14:1
6	$C_6H_4CO_2H$ (100 mol %), DCE, RT	88	14:1
7	$C_6H_4CO_2H$ (5 mol %), DCE, RT	86	14:1
8	CH_3CO_2H (50 mol %), DCE, RT	89	16:1
9	CF_3CO_2H (50 mol %), DCE, RT	82	14:1
10	2,6-$Cl_2C_6H_3CO_2H$ (50 mol %), DCE, RT	99	18:1
11	2,6-$Cl_2C_6H_3CO_2H$ (50 mol %), $CHCl_3$, RT	98	>20:1
12	2,6-$Cl_2C_6H_3CO_2H$ (50 mol %), CH_2Cl_2, RT	87	20:1

[a] Yields and diastereomeric ratios (*cis*/*trans*) were calculated on the basis of ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard. cod = 1,5-cyclooctadiene, DCE = dichloroethane.

Table 2: Scope of the iridium(I)-catalyzed dynamic kinetic isomerization.[a]

Entry	Substrate	Product (d.r.)	Yield [%][b]
1	**2a**, R = Me (d.r. 3:1)	**3a** (>20:1)	91
2	**2b**, R = H	**3b**	96
3	**2c**, R = *n*Pr	**3c** (>20:1)	93
4	**2d**, R = *i*Pr	**3d** (>20:1)	90
5[c]	**2e**, R = *t*Bu	**3e** (>20:1)	63
6	**2f**, R = cyclopropyl (d.r. 3:1)	**3f** (>20:1)	94
7[d]	**2g**, R = CH_2OTBS	**3g** (>20:1)	84
8	**2h**, R = phenyl (d.r. 5:1)	**3h** (>20:1)	93
9	**2i**, R = *p*-FC_6H_4	**3i** (>20:1)	95
10	**2j**, R = *p*-$MeOC_6H_4$	**3j** (>20:1)	88
11[e]	**2k**, R = *p*-$CF_3C_6H_4$	**3k** (>20:1)	60
12	**2l**, R = *o*-$CH_3C_6H_4$	**3l** (>20:1)	75

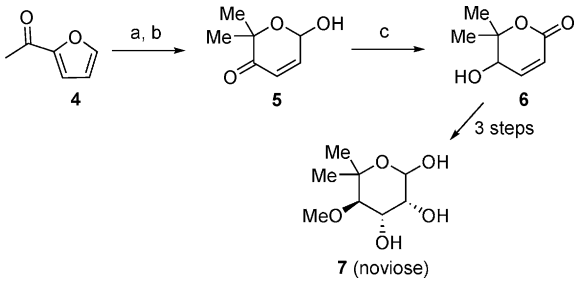
[a] Reactions conditions: [{Ir(cod)Cl}$_2$] (2.5 mol %), $CHCl_3$, room temperature, 8–12 h, unless noted otherwise. [b] Yield of the isolated product. [c] Substrate **2e** was used without purification, and 63 % was the yield after three steps from furan and pivalaldehyde. [d] The reaction was carried out at 50 °C. [e] Substrate **2k** was used without purification, and 60 % was the yield after three steps from furan and 4-(trifluoromethyl)benzaldehyde. TBS = *tert*-butyldimethylsilyl.

configuration of **3a** and its *trans* isomer was assigned by comparing their spectra with previously reported spectral data.[16]

We next screened different Brønsted acids in an attempt to accelerate the rate of equilibration between epimers *cis*-**2a** and *trans*-**2a** (Table 1, entries 2–12). To our delight, the *cis*/*trans* ratio immediately increased to 12:1 upon the addition of benzoic acid (50 mol %; Table 1, entry 2). This result clearly indicates that the rate of equilibration between the two epimeric hemiacetals is accelerated by an acid additive, and that a dynamic kinetic transformation is possible. The use of benzoic acids with either an electron-withdrawing nitro group or an electron-donating methyl group led to a slight decrease in the diastereomeric ratio (Table 1, entries 3 and 4). The diastereomeric ratio was increased slightly by carrying out the reaction at room temperature (Table 1, entry 5). The yield was slightly lower when the amount of benzoic acid was increased to 100 mol % or decreased to 5 mol %, but the diastereomeric ratio remained the same (Table 1, entries 6 and 7). By screening several other carboxylic acids and different solvents (Table 1, entries 8–12), we found that the *cis* isomer could be obtained exclusively in nearly quantitative yield when 2,6-dichlorobenzoic acid was used as the cocatalyst (Table 1, entry 11).

The scope of the iridium-catalyzed redox isomerization is shown in Table 2. Product **3a** was isolated in 91 % yield (Table 2, entry 1) when the reaction was carried out under the optimized conditions given in entry 11 of Table 1. The R group in substrate **2** can also be a hydrogen atom (Table 2, entry 2). Product **3e** with a *tert*-butyl substituent was isolated in 63 % yield over three steps from furan and pivalaldehyde (Table 2, entry 5). Substrate **2e** was not stable and was subjected to isomerization immediately after its preparation by the addition of furanyl lithium to pivalaldehyde and subsequent Achmatowicz rearrangement. Cyclopropyl and silyl ether groups were also tolerated (Table 2, entries 6 and 7). Product **3g** is a key intermediate in the synthesis of a number of carbohydrate lactones, such as gulonolactone and allonolactone.[17] Neither electron-withdrawing nor electron-donating groups on the aryl group impacted the yield significantly (Table 2, entries 8–10). The trifluoromethyl-substituted substrate **2k** was not stable and needed to be used immediately after its preparation (Table 2, entry 11). An *ortho*-substituted phenyl group was also compatible with the transformation (Table 2, entry 12). In all cases, the *cis* isomer was observed exclusively.

A *gem*-dimethyl substituent was also tolerated in the isomerization reaction (Scheme 2). Substrate **5** was prepared in two steps from commercially available 2-acetylfuran (**4**).

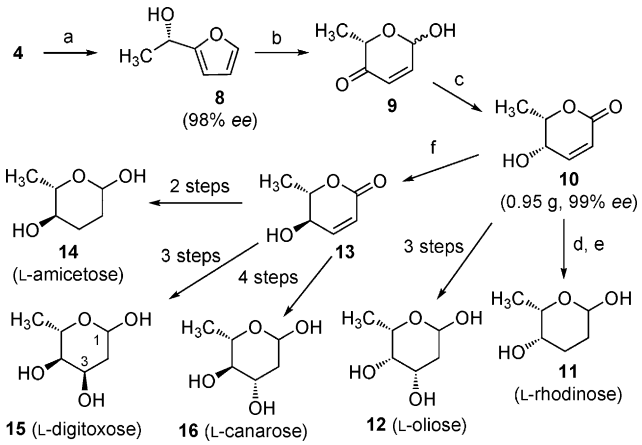


4 → **5** → **6** → **7** (noviose)

Scheme 2. Formal synthesis of noviose: a) MeMgBr; b) NBS, 66 % over 2 steps; c) [{Ir(cod)Cl}$_2$] (2.5 mol %), 50 °C, 89 %. NBS = *N*-bromosuccinimide.

The isomerization product **6** has been converted into noviose in three steps through methylation, reduction, and dihydroxylation.[18] The combination of the Achmatowicz rearrangement and iridium-catalyzed isomerization provides a concise de novo synthesis of noviose.[19]

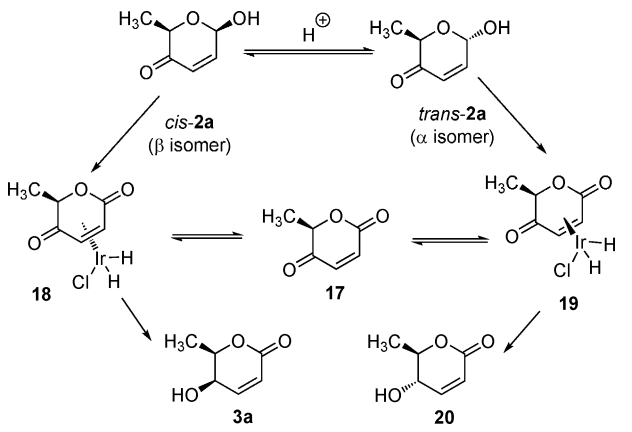
The secondary alcohol **8** could be prepared in 98 % yield with 98 % *ee* according to known protocols (Scheme 3).[20]



Scheme 3. Catalytic asymmetric synthesis of deoxysugars: a) $[\{Cp^*RhCl_2\}_2]$ (0.05 mol%), (*R*,*R*)-TsDPEN (0.12 mol%), HCO_2Na, 40°C, 98%; b) NBS, 85%; c) $[\{Ir(cod)Cl\}_2]$ (2.5 mol%), room temperature, 76%; d) H_2, Pd/C; e) DIBAL-H, 40% over 2 steps; f) PPh_3, *p*-$NO_2C_6H_4CO_2H$, DEAD, then MeOH, Et_3N, 75% over 2 steps. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, DEAD = diethyl azodicarboxylate, DIBAL-H = diisobutylaluminum hydride, TsDPEN = *N*-*p*-tosyl-1,2-diphenylethylenediamine.

The stereochemical integrity was retained under the isomerization conditions in a gram-scale synthesis. Reduction of the key intermediate **10** completed the enantioselective synthesis of L-rhodinose (**11**).[21] The same intermediate has been converted into L-oliose (**12**) in three steps.[16] Mitsunobu inversion of allylic alcohol **10**, followed by hydrolysis,[14a] afforded osmundalactone (**13**).[16,22] The synthesis of L-amicetose (**14**), L-digitoxose (**15**), and L-canarose (**16**) from intermediate **13** has been reported previously.[14b,23] Intermediates **10** and **13** have also been converted into amino sugar derivatives, such as daunosamine and ristoamine.[24]

A trace amount of ketolactone **17**[25] was isolated when the isomerization was conducted on a larger scale (Scheme 4). This intermediate decomposes quickly at room temperature. A mechanism for the dynamic kinetic isomerization is proposed in Scheme 4. Thus, the dehydrogenation of *cis*-**2a** and *trans*-**2a** is thought to afford metal complexes **18** and **19**, from which products **3a** and **20**, respectively, are formed upon hydrogenation. Overall, this transformation is a rare example of stereoselective internal transfer hydrogenation. In the absence of an acid, the ratio of **3a** to **20** is around 3:1, which is similar to the ratio of *cis*-**2a** to *trans*-**2a**. This observation suggests that the rate of equilibration between the two hemiketals is slower than the rate of internal transfer hydrogenation in the absence of an acid. The rate of interconversion between the two hemiacetals became significantly faster than the internal transfer hydrogenation in the presence of an acid additive, thus making the stereoselective dynamic kinetic isomerization possible.



Scheme 4. Proposed mechanism for the iridium-catalyzed isomerization.

In summary, we have discovered a novel iridium-catalyzed stereoselective dynamic kinetic internal transfer hydrogenation reaction. This new method provides a practical and unified approach to the synthesis of deoxy- and amino sugars from simple furan derivatives.

Keywords: carbohydrates · deoxysugars · furans · iridium · isomerization

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