Catalytic Carbohydrate Epimerization

Epimerization of Glycal Derivatives, by a Cyclopentadienyl-ruthenium Catalyst: Application to Metalloenzymatic DYKAT

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Abstract: Epimerization of a non-anomeric stereogenic center in carbohydrates is an important transformation in the synthesis of natural products. In this study an epimerization procedure of the allylic alcohols of glycas, by cyclopentadienylruthenium catalyst 1, is presented. The epimerization of 4,6-O-benzylidene-D-glucal 4 in toluene is rapid and an equilibrium with its α-allyl epimer 5 is established within 5 min at room temperature. Exchange rates for allal and glucal formation were determined by 1D 1H EXSY NMR experiments to 0.055 s⁻¹ and 0.075 s⁻¹, respectively. For 4-O-benzyl-L-rhamnal 8 the epimerization was less rapid and three days of epimerization was required to achieve equilibration of the epimers at room temperature. The epimerization methodology was subsequently combined with acylating enzymes in a dynamic kinetic asymmetric transformation (DYKAT), giving stereoselective acylation to the desired stereoisomers 12, 13 and 15. The net effect of this process is an inversion of a stereogenic center on the glycal and yields ranging from 71% to 83% of the epimer were obtained.

Introduction

Bacterial polysaccharides and other natural products commonly contain rare carbohydrates with different stereochemistry compared to the most common monosaccharides. Such molecules are synthetically accessible through stereocontrolled de novo synthesis[1], [2] or modifications of readily available carbohydrates.[3], [4] The latter methodology frequently involves stereochemical inversions of secondary alcohols, which regularly follow two-step procedures: triflation followed by nucleophilic displacement or oxidation and subsequent stereoselective reduction.[5], [6], [7] An alternative method would be to use a dynamic kinetic asymmetric transformation (DYKAT) approach utilizing a redox epimerization catalyst to epimerize the alcohol and subsequently trap the inverted alcohol in a transesterification reaction catalyzed by a stereoselective enzyme (Figure 1).

The enzymatic selectivity in a transesterification of secondary alcohols is governed by the size of the substituents residing at the stereogenic center. Assuming that the largest group has a higher priority than the medium group according to the CIP rule, lipases show (R)-stereoselectivity, whereas serine proteases show (S)-stereoselectivity.[6], [9]

Figure 1. Schematic picture of the epimerization of a carbohydrate molecule and the subsequent trapping of one epimer by an enzyme-catalyzed stereoselective acylation.

Chemoenzymatic dynamic kinetic resolution (DKR) and DYKAT have been applied in asymmetric synthesis of a wide range of secondary alcohols and primary amines with various transition metal complexes as racemization catalysts (examples are given in Figure 2).[10] Of these catalysts, cyclopentadienylruthenium complex 1, activated by i-BuOK, is one of the most efficient catalysts for racemization of sec-alcohols[11] and it has been used in combination with both (R)-selective lipases[11] and (S)-selective proteases.[12] Catalyst 1 has been thoroughly investigated with both IR and NMR techniques giving valuable insight into its activation and catalytic mechanisms.[13],[14]

Transition metal-catalyzed epimerization of secondary alcohols in carbohydrates, utilizing catalyst 1, has been studied previously. [15] By subjecting partially protected glucose, mannose
and allose derivatives to activated 1 in p-xylene at 120 °C, it was possible to determine the thermodynamic equilibrium between the non-anomeric epimers of the carbohydrates. Typically, catalyst 1 is able to epimerize secondary alcohols at ambient temperature at a rapid rate; however in the case of these protected carbohydrates, where the secondary alcohol is in close proximity to several electron-withdrawing groups the oxidation step of the racemization is much harder to achieve. Moreover, the neighboring groups increase the bulk around the secondary alcohol, which further decreases the efficiency of the epimerization. We envisioned that by performing the epimerization on a protected glycal derivative, the influence of both of these factors would be lowered and thereby enable a more rapid epimerization. With a faster reaction rate it would be possible to study the epimerization by NMR spectroscopic methods. Furthermore, lower temperatures would allow combination of the transition metal-catalyzed epimerization with an enzymatic resolution, thus giving a DYKAT that would yield an inversion of a stereogenic center.

Results and Discussion

Epimerization

Initially, a suitable racemization catalyst was needed and therefore screening of ruthenium-based catalysts 1 – 3 was conducted. All three catalysts have previously been used successfully in combination with enzymes yielding enatioenriched allylic acetates.[19] Epimerization experiments of 4,6-O-benzylidene-D-glucal, 4, employing catalysts 2 and 3, under standard conditions, only showed traces of epimerized products after 18 h at 60 °C.[17] Compound 1, on the other hand, was able to rapidly epimerize 4 at room temperature: aliquots retrieved and analyzed by 1H NMR spectroscopy after 30 and 60 minutes showed a 2:1 mixture of the glucal and allal derivatives 4 and 5 (K\text{eq} = 0.504 for 4 \approx 5).

The rapid establishment of an equilibrium inspired an investigation of the reaction kinetics by NMR spectroscopy. Upon treatment of compound 4 with 10 mol% of activated catalyst 1 in toluene-d\textsubscript{8} solution, the equilibrium between 4 and 5 was established within five minutes at 25 °C. In addition to the C3-epimer, allal 5, the catalyst-substrate complexes\textsuperscript{[18]} 4* and 5* were observed in the 1H NMR spectrum (Figure 3), enabling the determination of the equilibrium constant for the equilibrium between 4 and 5* (K\textsubscript{5} in Figure 3). Subsequent additions of activated catalyst did not increase the complex concentration significantly.

At a sample temperature of 90 °C, the ratio between compounds 4 and 5 was 4:3 and the equilibrium constants were determined to K\textsubscript{1} · K\textsubscript{5} = 0.71 and K\textsubscript{2} = 1.10 by 1H NMR. 1D 1H EXSY NMR experiments\textsuperscript{[19]} were performed at 90 °C with selective excitation of the H2 signals of epimers 4 and 5. With a 3 s mixing period exchange peaks were obtained (Figure 4), which showed that a fast equilibrium between 4 and 5 occurred and enabled establishment of the exchange rates. Full exchange matrix analysis gave the exchange rates k\textsubscript{t} = 0.055 s\textsuperscript{-1} and k\textsubscript{t} = 0.075 s\textsuperscript{-1} (Table 1). No significant exchange peaks were observed at lower temperatures. At elevated temperatures 1H NMR data showed a buildup of two ketones, 6\textsuperscript{[20]} and its suggested saturated analog 7 (Figure 5); both irreversibly formed through oxidation and redox isomerization processes, respectively\textsuperscript{[21]}

Epimerization of the 6-deoxygenated compound, 4-O-benzyl L-rhamnal 8, proceeded at a much lower rate. Equilibration of the epimers 8 and 9 required 4 days of reaction time at room temperature (Figure 6). Rate constants for the epimerization could be extracted through a least-sum-square fitting of the experimental concentrations at different times to a kinetic model. The kinetic model is based on first order kinetics regarding the disappearance and formation of 8 and 9, respectively (Table 1).

Figure 2. Three examples of ruthenium-based racemization catalyst used in combination with enzymes in DKR protocols.

Figure 3. Equilibrium between compounds 4 and 5 using 10 mol% of 1; part of the 1H NMR spectrum at 25 °C of the equilibrium mixture, showing the H2 resonances. Peaks arising from the catalyst-substrate complexes ([Ru] = catalyst 1) are marked with asterisks (*). K\textsubscript{1}, K\textsubscript{t} = 0.90, K\textsubscript{2} = 0.56.

Figure 4. Equilibrium between 4 and 5, facilitated by treatment with t-BuOK activated 1 in toluene-d\textsubscript{8} solution at 90 °C and detected by: a) 1D 1H EXSY NMR with selective excitation of the H2 resonance at 4.52 ppm in 4, b) 1D 1H NMR with selective excitation of the H2 resonance at 4.74 ppm in 5 and c) the corresponding 1D 1H NMR spectrum.

Figure 5. Ketones formed at elevated temperature in the epimerization reaction of compound 4.

Figure 6. Rate constants for the epimerization could be extracted through a least-sum-square fitting of the experimental concentrations at different times to a kinetic model. The kinetic model is based on first order kinetics regarding the disappearance and formation of 8 and 9, respectively (Table 1).
treating the equilibrium between Ru-alkoxide complexes of H5 atoms. The conformational assignments rely on the large antiperiplanar relationship between the axially oriented H4 and the 1H NMR spectrum of the reaction mixture, suggesting that the oxidation by-products are formed in small amounts. Solid lines are drawn through the data points as an aid to the eye. Populations are obtained by integration of 1H NMR spectra.

Oxidation by-products of Table 1. Determined by integration of the epimers peaks in 1H NMR.

Notably, catalyst-substrate complexes were not observed in the 1H NMR spectrum of the reaction mixture, suggesting that the Ru-alkoxide complexes of 8 and 9 are less favored compared to the free Ru-OtBu complex. Disfavored formation of the Ru-alkoxide complexes may be ascribed to steric bulk created by the adjacent freely rotating protecting group that could interfere in the interaction between the ruthenium and hydroxyl group. The equilibrium mixture consisted of 8 and 9 in a 1:1.3 ratio, accompanied by 10% of ketones 10 and 11 combined.

Ring conformation and equilibrium

The D-glycals, compounds 4 and 5 were assigned to occupy the 1H4 conformation, while the 6-deoxy-L-glycals 8 and 9 occupy the 3H4 conformation; in both cases this results in an antiperiplanar relationship between the axially oriented H4 and H5 atoms. The conformational assignments rely on the large JH4,H6 coupling constants (9.6 – 10.2 Hz) and are supported by previous reports on similar compounds (Figure 7). Compound 4, in which the OH group is equatorially oriented, dominated the equilibrium between 4 and 5, while compound 9, in which the OH group is axially oriented, was the most populated epimer in the equilibrium between 8 and 9.

In compound 9 the OH proton displayed signs of hydrogen bonding in the 1H NMR spectrum: The downfield chemical shift (δOCH (9) ≫ δOCH (8)) and coupling constant JHOCCH = 3.1 (Table 2) indicates hydrogen bonding to the benzyl ether oxygen. Analysis of molecular models of compounds 8 and 9 revealed a favorable geometry for hydrogen bonding in the latter compound, but not in the former. An intramolecular hydrogen bond could thus stabilize epimer 9. This hypothesis was tested by adding a competitive hydrogen bond donor (t-BuOH) to the epimerization reaction, that potentially could interfere with this internal hydrogen bond. When t-BuOH was added the equilibrium shifted towards epimer 8 (to give Keq = 1.08) which further supports the existence of an intramolecular hydrogen bond in 9. A similar trend, although of smaller magnitude, is present in compounds 4 and 5, where δOCH (5) > δOCH (4). The coupling constant JHOCCH = 1.9 Hz in 5 indicates restricted motion around the C3-O3 bond, with a probable alignment towards O4 since the distance to the OH group is short in the molecular model.

Dynamic kinetic asymmetric transformation

Inspired by the efficient redox epimerization of glycals 4 and 8 at moderate temperatures we were interested in achieving a DYKAT by coupling this process with a stereoselective biocatalyst. By choosing an (R)-selective lipase, favoring the transesterification of L-rhamnal epimer 9, an inversion of the C3 alcohol stereocenter would be obtained (Figure 8). Owing to its known stability and activity over prolonged reaction times the lipase Candida Antartica Lipase B, CALB, was considered suitable as a transesterification catalyst.

![Figure 7](image-url)

Figure 7. Equilibria of compounds 4 and 5, and 8 and 9, respectively, under catalysis of 1. The dihydropyran rings are schematically depicted in their preferred conformations.

![Figure 8](image-url)

Figure 8. a) Empirical enantiopreference for a lipase and a protease. L = Large-sized substituent, M = Medium-sized substituent. b) Glycals preferred in transesterifications.

Table 1. Exchange rates and energies of the epimerizations of 4 at 90 °C and 8 at 25 °C.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Keq [k]</th>
<th>k⁺/10⁻² (s⁻¹)</th>
<th>k⁻/10⁻² (s⁻¹)</th>
<th>ΔG‡ (kJ mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 ≈ 5</td>
<td>0.77</td>
<td>55</td>
<td>75</td>
<td>95.7</td>
</tr>
<tr>
<td>8 ≈ 9</td>
<td>1.3</td>
<td>0.13</td>
<td>0.086</td>
<td>93.9</td>
</tr>
</tbody>
</table>

[a] Determined by integration of the epimers peaks in 1H NMR.

Table 2. Experimental chemical shifts and coupling constants in ppm and Hz, respectively, and interatomic distances from molecular models, in Å, of the glycal hydroxyl groups.

<table>
<thead>
<tr>
<th></th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>δOCH</td>
<td>1.434  ppm</td>
<td>1.991 ppm</td>
<td>1.130 ppm</td>
<td>2.113 ppm</td>
</tr>
<tr>
<td>JHOCCH</td>
<td>4.51 Hz</td>
<td>1.87 Hz</td>
<td>6.38 Hz</td>
<td>3.09 Hz</td>
</tr>
<tr>
<td>fO4-OH3</td>
<td>2.6 Å</td>
<td>2.1 Å</td>
<td>3.1 Å</td>
<td>2.4 Å</td>
</tr>
</tbody>
</table>
The biocatalyst was mixed with t-BuOK-activated 1, isopropenyl acetate and Na₂CO₃ in toluene at 40 °C and the reaction reached full conversion after 6 days, transforming 81% (75% isolated yield) of L-rhamnal into 12. The remaining 19% consisted of ketones 10 (8%) and 11 (11%) (Figure 9). These compounds arise from the ruthenium alkoxide of 8 (or its epimer 9), where ketone 10 is formed via dehydrogenation and ketone 11 via isomerization. Notably, enzymatic acylation of (S)-alcohol 8 was not observed, showing that CALB is highly selective for transesterification of the corresponding (R)-alcohol.

In order to achieve a similar inversion at C3 of the D-glucal derivative, 4, to acetylated D-allal, a lipase is unsuitable since the stereogenic center at C3 already possesses the configuration preferred in a lipase-catalyzed transesterification. This was verified by subjecting 4 to CALB and isopropenyl acetate in dry toluene, which afforded 78% (71% isolated) of acetylated D-glucal derivative 13 after 18 h (Figure 10). At this point only 13 and 4 could be observed by ¹H NMR indicating that the enzyme was highly selective for transesterification of 5, but that the epimerization had ceased. This was further confirmed by adding racemic 1-phenylethanol after 18 h of reaction time and observing acylation with 16% conversion within 2 h. In order to achieve a higher conversion, the epimerization catalyst was added in three portions at 2.5 mol% at 18 h intervals. Utilizing this protocol the conversion of 4 to 13 was increased to 78% (71% isolated) with a small fraction of the glucal ester 14, arising from a background chemical acylation. About 15% of starting material 4 remained unconverted.

Also the reverse reaction, i.e., the transformation of D-allal 5 to acetylated D-glucal derivative 15, was performed. CALB was used as acylating enzyme and full conversion was achieved within 18 h of stirring yielding 15 in 83% yield (Figure 11). The possibility of obtaining carbohydrates with both axial and equatorial hydroxyl groups highlights the viability of the protocol and makes it an interesting method for the preparation of various carbohydrate isomers.

Conclusion

The epimerization of glycals 4 and 8 with cyclopentadienylruthenium catalyst 1, studied by NMR spectroscopic methods, was found to be significantly more efficient compared to that of saturated carbohydrates. The epimerization rates varied with the substitution pattern of the glycal; the 4,6-di-O-benzylidene-protected compounds (4 and 5) reacted faster than the 4-O-benzyl-6-deoxy compounds (8 and 9). Thanks to the efficacy of the epimerization, which occurred at ambient temperatures, the combination of the epimerization protocol with an enzymatic resolution was possible, resulting in a DYKAT. Due to excellent selectivity for acylation of the axial hydroxyl groups at C3, when employing Subtilisin Carlsberg for the D-glucal system 4/5 and CALB for the L-glucal system 8/9, we
were able to achieve a net inversion of a sterogenic center on the carbohydrate derivatives. Also by changing from Subtilisin Carlsberg to CALB the reverse reaction was achieved, transforming axial substrate S to its equatorial epimer ester T. To the best of our knowledge this is the first DYKAT on glycosals of this type. The acyl derivatives 12 and 13 could be employed in syntheses towards α,β-unsaturated-containing natural products[20] such as Jadomycin B[30] and Kijanimicin[21] (from syntheses towards surfactant-treated with a Na lamp. HR-MS was recorded on an ESI-MS. Ruthenium complex obtained from commercial suppliers and used without further purification/drying.

**Experimental Section**

**General methods**

Unless otherwise noted, all reagents and reactants were used as received from commercial suppliers. Isopropenyl acetate was dried over CaCl₂ and distilled before use. Dry toluene was obtained from a VAC-solvent purifier system and dry THF through distillation over sodium/benzophenone. All other solvents were obtained from commercial suppliers and used without further purification/drying.

For reactions conducted under dry/ inert conditions standard Schlenk techniques were used (unless otherwise noted). All reactions were monitored by thin-layer chromatography using E. Merck silica gel 60 F254 plates (TLC analysis). Flash chromatography was carried out with 60A (particle size 35-70 μm) normal phase silica gel. Optical rotation was measured with a polarimeter equipped with a Na lamp. HR-MS was recorded on an ESI-MS. Ruthenium complex (1H, 5.38 (1H, d, J = 17.1 Hz); HRMS (ESI): calc. for [M+Na] C₁₃H₁₄NaO₃: 241.0831, found 241.0835. 193.0, 162.1, 137.4, 128.4 (2C), 128.0, 105.0, 78.66, 78.65, 73.9, 56.0, 52.0, 21.5, 17.8; HRMS (ESI): calc. for [M+Na] C₁₅H₁₈NaO₄: 285.1097, found: 285.1089; [α]D²5 = 163° (0.2, CDCl₃). NMR measurements. Temperatures were calibrated from H² peak separation of neat ethylene glycol.[22] Chemical shifts were referenced to intrinsic tunicol-δ1 (δ6, 7.90). H² chemical shifts and Jα coupling constants were determined with aid of the PERCH NMR spin simulation software (PERCH Solutions Ltd., Kuopio, Finland). Chemical shifts and coupling constants were altered iteratively until the simulated and experimental spectra appeared highly similar according to visual inspection and the total root-mean-square value was close to or below 0.1%. NMR chemical shift assignments for alcohols were done by 1D 1H,1H-EXSY (with a mixing time of 3 s and total relaxation delay of 10.7 s). Exchange matrix was recorded. The establishment of equilibrium was monitored by subsequent experiments. 1D 1H NMR (CDCl₃, 400 MHz) was recorded. The system was entered to the NMR spectrometer, and the system was tuned, matched, locked and shimmed at 25 °C. The 1H NMR spectrum was recorded. The establishment of equilibrium was monitored by subsequent recordings of 1H NMR spectra. The 1D 1H, 1H-EXSY spectra of compound 4 were acquired at 90 °C, with a mixing time of 3 s and total relaxation delay of 10.7 s. The exchange matrix analysis of the EXSY spectra was performed by employing the EXSYCalc software, version 1.0 (Mestrelab Research).[23] The three-dimensional models of compounds 4, 5 and 9 were built using the Vega ZZ software (release 3.0.1.22)[24]

**General procedure for NMR spectroscopic studies of epimerization mixtures by NMR**

**1.5-anhydro-4,6-benzylidene-3-butanol-2-deoxy-o-ribo-hex-1-enitol (13)**

To a flame-dried Schlenk flask was added (tBuOK (15 µL, 0.5 M in dry THF), 7.9 mg in 0.2 ml distilled -BuOK (tBuOK (7.9 mg in 0.2 ml distilled). Two batches of activated T-BuOK (15 µL, 0.5 M in dry THF, 0.0125 mmol) giving rise to color change from yellow to red. After 6 min stirring the cap was removed and 4-0-benzylidene-4-glucal (117 mg, 0.5 mmol) was added in one portion as a solid. After an additional 4 min 2,2,2-trifluoroethanol butylate (150 µL, 1 mmol) was added. Two batches of activated 1 (7.9 mg in 0.2 ml distilled and dried THF activated by T-BuOK as previously described) were added, and the reaction mixture was stirred at 0 °C for 3 h, and 36 h, thereafter the reaction was stirred for additionally 4 h. The reaction mixture was filtered through Celite® with EIOAc evaporated onto SiO₂ (0.2 g) and purified by column chromatography (SiO₂, gradient from pentane to pentane/EtOAc 9:1) yielding 29 mg (75%) of 12 in the second fraction.

**Dynamic Kinetic Asymmetric Transformations**

3-O-Acetyl-1,5-anhydro-4-O-benzyl-2,6-dideoxy-o-ribo-hex-1-enitol (12) To a flame-dried 5 mL micro-vial were added (γCD₃PO(CH₂)₃CO)Cl (1.47 mg, 0.0075 mmol), Na₂CO₃ (16 mg, 0.15 mmol) and CALB (8 mg). The system was purged with three argon-vacuum cycles. The vial was transferred to an Ar filled glove box and dry, degassed toluene (0.6 mL) was added. tBuOK (15 µL, 0.5 M in dry THF, 0.0075 mmol) was added and a color change from yellow to red was observed. After 6 min of stirring the cap was removed and 4-o-benzylidene-4-mannal (8 (33 mg, 0.15 mmol)) was added in one portion as a solid and the system was quickly sealed with a teflon septum cap. After an additional 4 min isopropenyl acetate (45 µL, 0.45 mmol) was added and the vial was taken out of the glove box and stirred at 40 °C for 6 days. When full conversion was attained the reaction mixture was filtered through Celite® with EIOAc as eluent and the solvent was subsequently evaporated. The residue was purified by column chromatography (SiO₂, gradient from pentane to pentane/EIOAc 9:1) yielding 29 mg (75%) of 12 in the second fraction.

**1.5-anhydro-4,6-benzylidene-3-butanol-2-deoxy-o-ribo-hex-1-enitol (13)**

To a flame-dried Schlenk flask was added (γCD₃PO(CH₂)₃CO)Cl (1.79 mg, 0.0125 mmol), Na₂CO₃ (53 mg, 0.5 mmol) and surfactant-treated Subtilisin Carlsberg (9 mg). The system was purged with three argon-vacuum cycles. Distilled and degassed THF (1 mL) was added followed by T-BuOK (25 µL, 0.15 M in dry THF, 0.0125 mmol) giving rise to color change from yellow to red. After 6 min stirring the cap was removed and 4-0-benzylidene-4-glucal (117 mg, 0.5 mmol) was added in one portion as a solid. After an additional 4 min 2,2,2-trifluoroethanol butylate (150 µL, 1 mmol) was added. Two batches of activated 1 (7.9 mg in 0.2 ml distilled and dried THF activated by T-BuOK as previously described) were added, and the reaction mixture was stirred at 0 °C for 3 h, and 36 h, thereafter the reaction was stirred for additionally 4 h. The reaction mixture was filtered through Celite® with EIOAc evaporated onto SiO₂ (0.2 g) and purified by column chromatography (4 g SiO₂, eluent pentane to pentane/EIOAc 10:1) yielding 107 mg (71%) of 13 as a white solid.

1H NMR (CDCl₃, 400 MHz) δ: 7.47–7.42 (2H, m, ArH), 7.38–7.32 (3H, m, ArH), 6.50 (1H, δJ, δJ = 6.0 Hz, H1), 5.61 (1H, s, CHPh), 5.46 (1H, δJ, δJ = 5.9 Hz, J9, 4.0 Hz, H3), 5.01 (1H, δJ, δJ = 6.0 Hz, J5, 5.9 Hz, H2), 4.46 (1H, δJ, δJ = 5.3 Hz, J9, 10.7 Hz, H6), 4.18 (1H, δJ, δJ = 5.0 Hz, J5, 5.9 Hz, H3), 3.88 (1H, δJ, δJ = 4.0 Hz, H10, 5.9 Hz, H4), 3.34 (1H, at, J9, 3.9 Hz, J5, 5.9 Hz, 56'), 2.33 (2H, 1J, 7.5 Hz, 7.5 Hz, -CH₂CH₂OH), 1.68 (2H, t, 7.9 Hz, 7.5 Hz, -CH₂CH₂OH), 0.93 (3H, 3J, 7.5 Hz, -CH₂CH₂OH), 1.20 (1H, 3J, 7.5 Hz, -CH₂CH₂OH). 1H NMR (CDCl₃, 100 MHz) δ: 173.3, 147.3, 137.2, 129.4, 128.6 (2C), 126.2 (2C), 126.1, 97.3, 71.7, 71.9, 70.5, 68.2, 21.0, 17.8; HRMS (ESI): calc for [M+Na⁺] C₁₇H₂₁NO₃Na: 285.1097, found: 285.1089; [α]D²5 = 163° (0.2, CDCl₃).
purged with three argon-vacuum cycles after which degassed toluene (1 mL) was added. t-BuOK (32 µL, 0.5 M in dry THF, 0.0016 mmol) was added and a color change from yellow to red was observed. After 6 min of stirring the cap was removed and 4.0-benzyloxy-benzone-β (78 mg, 0.33 mmol) was added in one portion as a solid and the system was quickly sealed with a teflon septum cap. After an additional 4 min isopropanol acetate (110 µL, 1 mmol) was added and the reaction was stirred at 40 °C for 18 h. When full conversion was reached the reaction mixture was filtered through celite with EtOAc and the solvent was subsequently evaporated. The residue was purified by column chromatography (SiO2, gradient from pentane to pentane/EtOAc 9:1) yielding 76 mg (83 %) of 15 in the second fraction. Experimental data were in accordance with those previously reported.\(^{10}\) H NMR (CDCl3, 400 MHz): 6: 7.52–7.47 (2H, m, ArH), 7.41–7.35 (3H, m, ArH), 6.39 (1H, dd, Jα 6.2 Hz, Jβ 1.5 Hz, H1), 5.60 (1H, s, C5–C7). \(^{11}\) 13C NMR (CDCl3, 100 MHz): 170.9, 145.6, 137.1, 129.4, 128.5 (2C). 101.6, 100.9, 77.1, 69.03, 69.0, 21.4; HRMS (ESI): calc. for [M+Na] \(\text{C}_{24}\text{H}_{26}\text{NaO}_{2}\): 399.0890, found 399.0894; \([\text{M}^{+}]^{–}\) 95° (c 0.8, CDCl3).

Acknowledgements

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Keywords: Dynamic kinetic asymmetric transformation • carbohydrates • NMR • inversion • enzyme catalysis


[3] Epimerization reactions where 6 equivalents of dry t-BuOH were added at the start of the reaction resulted in a 48:52 mixture of 8 and 9 at 25 °C (K\(_{\text{eq}}\) = 1.08).

[4] A slight increase in reaction temperature, from 25 °C to 40 °C, gave a more rapid epimerization, decreasing the reaction time from eight to six days.


Selective inversion of stereogenic centers in carbohydrates is obtained through a dynamic kinetic asymmetric transformation. The latter process is a combination of a ruthenium-catalyzed epimerization and an enantioselective enzyme-catalyzed acylation. The epimerization was studied by NMR spectroscopy, making it possible to determine rates and equilibria of the processes.