Functionalization of GlucoPyranosides at position 5 by 1,5 C–H insertion of Rh(II)-Carbenes: Dramatic influence of the anomeric configuration

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Functionalization of GlucoPyranosides at Position 5 by 1,5 C-H Insertion of Rh(II)-Carbenes: Dramatic Influence of the Anomeric Configuration

Jana Hammoud, Antoine Joosten, Thomas Lecourt*

E-mail address: Thomas.lecourt@insa-rouen.fr

Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA UMR 6014, 76000 Rouen, France

Abstract

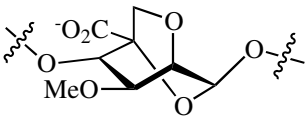
Herein, a C-H bond functionalization approach is reported as a new route towards non-natural glycosides having a quaternary position 5. The development of this transformation furthermore reveals that insertion of Rh(II)-carbenes into the C_5-H bond is controlled by remote stereoelectronic effects induced by the axial or equatorial orientation of the aglycone.

Keywords: C-H bond functionalization; Rh(II)-carbene; Quaternarization; Stereoelectronic effects.

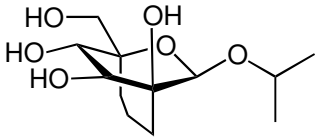
1. Introduction

Non-natural carbohydrate derivatives are key players to elucidate the complex roles of sugars in numerous physiological and pathological processes [1]. Introduction of quaternary centers is more particularly useful to investigate the binding mode of carbohydrates to their biological targets by locking their conformation [2], or to design inhibitors of carbohydrate-active enzymes [3]. For instance, non-natural sugars with a quaternary position 5 were designed to prove the ^2S_O conformation of iduronic acid in heparin [4], or to reduce the conformational freedom of the *exo*cyclic primary alcohol [5]. These compounds have also

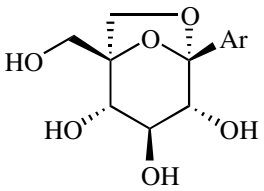
shown great promises to study the mechanism of glycosidases [6], and design inhibitors of the glucose transporter SGLT2 [7] (Fig. 1).



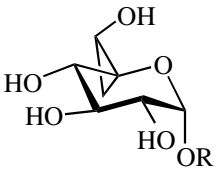
Conformational probe



Mannosidase inhibitor



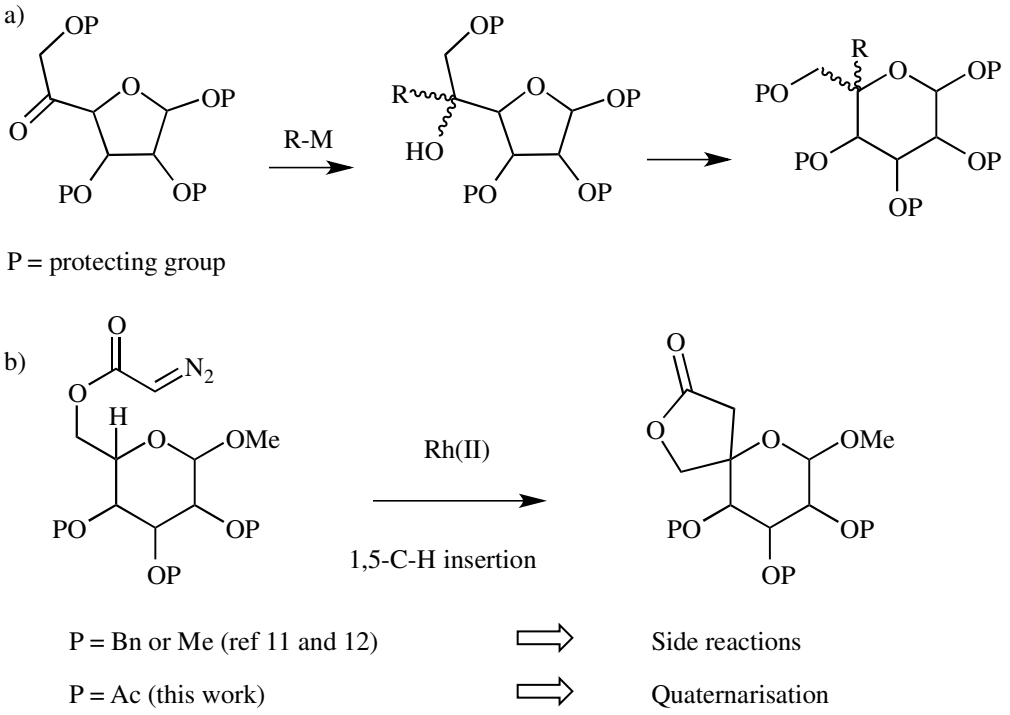
SGLT2 inhibitor



Conformational probe

Fig. 1. Pyranosides with a quaternary position 5 as chemical tools for glycobiology.

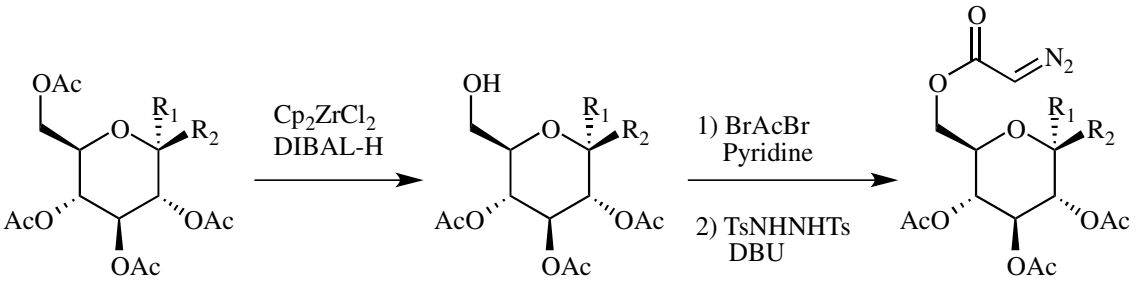
Carbohydrates with a quaternary position 5 are usually obtained following time consuming synthetic routes that rely on (Scheme 1a): 1) the multi-step preparation of a selectively protected furanoside with a keto functionality at position 5; 2) addition of an organometallic reagent to create the quaternary center; 3) ring-expansion into the pyranoside [8,9]. Having recently shown that 1,5-insertion of Rh(II)-carbenes into the anomeric position represents an efficient alternative route towards ketopyranosides [10], we wondered if a similar C-H bond functionalization approach might be amenable to the quaternarization of position 5 (Scheme 1b). Transition metal-catalyzed decomposition of diazoesters grafted at position 6 has already been considered by Peters [11], and later Zhang [12], but these reactions only gave rise to adventitious side reactions into protecting groups and dimerization of the transient metal-carbene. In this context, acetate was chosen to protect positions 2,3 and 4, since it should be inert toward Rh(II)-carbenes and would furthermore deactivate the adjacent C-H bonds of the pyranosidic scaffold thanks to its strongly electron withdrawing character [13].



Scheme 1. Synthetic approaches towards carbohydrates with a quaternary position 5.

2. Results and discussion

In order to install a carbene precursor at position 6 on polyacetylated methyl α- and β-glucopyranosidic scaffolds, the primary alcohols **3** and **4** were first prepared by site-selective de-*O*-acetylation of **1** and **2** with DIBAL-H and Cp_2ZrCl_2 in THF, as recently reported by our group [14]. Bromoacetylation, followed by diazo transfer with TsNHNHTs and DBU in THF [15], then delivered the carbene precursors **5** and **6**, in 45 and 88 % yield respectively (Scheme 2). Decomposition of **5** and **6** was next performed by drop-wise addition of the diazo sugar to a highly diluted suspension of the Rh(II) salt in refluxing 1,2-dichloroethane (1,2-DCE).

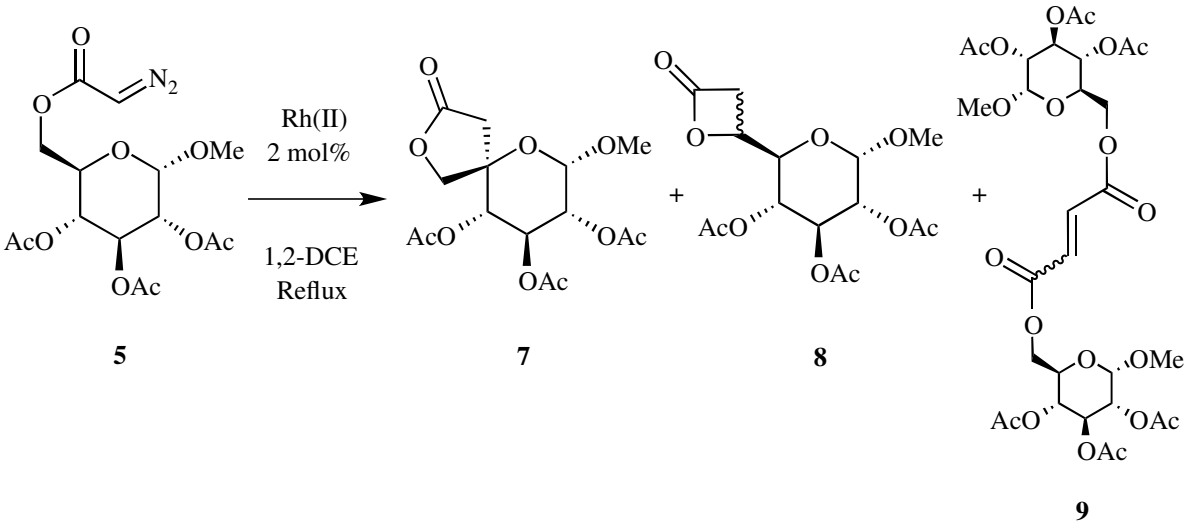


1 R_1= OMe, R_2= H **3** **5** 45 %

2 R_1= H, R_2= OMe **4** **6** 88 %

Scheme 2. Preparation of carbene precursors **5** and **6**.

In the *α-gluco* series, decomposition of **5** with 2 mol% of $Rh_2(OAc)_4$ delivered a very complex mixture, from which two fractions could be isolated after careful chromatography. In a first one, the desired compound **7** could be identified together with a diastereiosomeric mixture of β-lactones **8** resulting from competitive 1,4-C-H insertions into the *exo*cyclic methylene unit. In the second fraction, *Z* and *E* olefins **9** were obtained in mixture with compounds whose structure could not be elucidated (Scheme 3).



5 **7** **8** **9**

Scheme 3. Decomposition of **5** by $Rh_2(OAc)_4$.

Careful NMR analysis of the crude revealed that dimerization of the Rh(II) carbene mainly took place instead of intramolecular insertion processes (Table 1, entry 1). Unfortunately, decreasing the rate of addition of the diazo sugar only slightly diminished dimerization

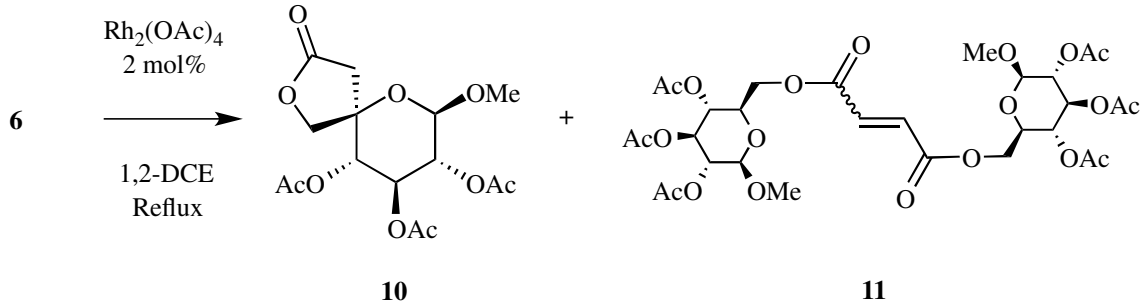
(entries 2-3). Modulation of the reactivity of the transient Rh(II)-carbene [16] by using $Rh_2(acam)_4$ or $Rh_2(tfa)_4$ did not improve the desired 1,5-C-H insertion process (entries 4-5).

Table 1. Decomposition of **5** by Rh(II) catalysts.

Entry	Rh(II)	Rate (μmol/h)	**7** : **8** : **9** : undefined[a]
1	$Rh_2(OAc)_4$	20	6 : 11 : 68 : 15
2	$Rh_2(OAc)_4$	10	5 : 14 : 56 : 25
3	$Rh_2(OAc)_4$	5	15 : 21 : 42 : 22
4	$Rh_2(acam)_4$	20	8 : 5 : 43 44
5	$Rh_2(tfa)_4$	20	9 : <1 : 41 : 50

[a] Ratios were determined by ^{1}H NMR analysis of the crude.

In the *β-gluco* series, the decomposition of **6** with 2 mol% of $Rh_2(OAc)_4$ gave a clean reaction mixture only containing γ-lactone **10** and dimers **11** (Scheme 4).



10 **11**

Scheme 4. Decomposition of **6** by $Rh_2(OAc)_4$

Whereas addition of the substrate at 20 μmol/h first gave an almost 1:1 mixture of **10** and **11** (Table 2, entry 1), decreasing the rate of addition of the substrate (entries 2 and 3) markedly reduced the competitive dimerization process as expected. Addition of diazosugar **6** at a rate of 10 μmol/h to a suspension of 2 mol % of $Rh_2(OAc)_4$ in refluxing 1,2-dichloroethane (3 mM) finally delivered the desired compound **10** in a highly satisfactory 70 % yield after purification by silica gel flash chromatography (entry 4). This compound has been identified on the basis of its ^{1}H NMR spectra where two AB systems at 2.85 and 4.28 ppm were attributed to the methylene unit of the lactone and to H-6 respectively.

Table 2. Decomposition of **6** by $Rh_2(OAc)_4$.

Entry	Rate (µmol/h)	Concentration (mM)	**10** : **11**[a]
1	20	6	46 : 54
2	10	6	70 : 30
3	5	6	72 : 28
4[b]	10	3	81 : 19

[a] Ratios were determined by ^{1}H NMR analysis of the crude; [b] 70 %isolated yield.

As expected, electron-withdrawing acetates prevented competitive insertion into C-H bonds of the sugar frameworks, as well as side reactions into protecting groups previously observed by Pieters and Zhang[11,12]. Additionally, quaternarization of position 5 by functionalization of the axial C-H bond proved to highly depend on configuration of the anomeric position. Indeed, 1,5 C-H insertion of the Rh(II)-carbene grafted at the primary *exo*cyclic position nicely delivered the desired compound **10** in the *β-gluco* series, whereas competitive dimerization and a highly unfavored 1,4-C-H insertion process were mostly observed with the corresponding α-glucoside.

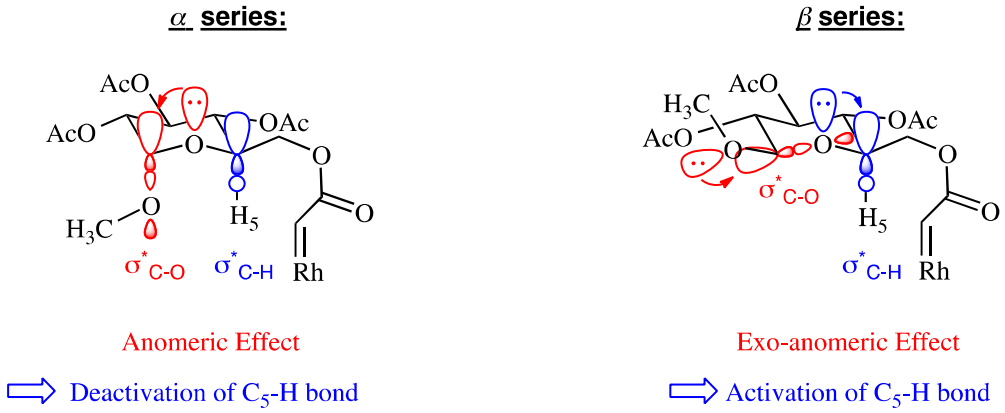


Fig. 2. Potential stereoelectronic effects controlling the insertion of Rh(II)-carbenes into C_5-H bond.

Those contrasting results can be interpreted by the strong and opposite electronic effects [17] exerted on position 5 depending on orientation of the aglycone (Fig. 2). In the *α* series, delocalization of the axial lone pair of the endocyclic oxygen atom into the antibonding $\sigma^*_{C\text{-}O}$

orbital of the aglycone (anomeric effect) deactivates the C_5-H bond and prevents insertion of the electrophilic Rh(II)carbene. In contrary, the *exo*-anomeric effect reinforce the electron density of the endocyclic oxygen atom in the case of β-glucosides. The axial lone pair is then strongly delocalized into the antibonding $\sigma^*_{C5\text{-}H}$ orbital, and induces a strong activation of the antiperiplanar C-H bond. Reaction of the transient metal-carbene is thus driven toward the desired 1,5 insertion process, despite the unfavorable axial orientation of the C_5-H bond.

3. Conclusion

In conclusion, a new route based on a C-H bond functionalization has been developed herein to prepare a methyl glucopyranoside with a quaternary position 5. Thanks to the use of acetate as protecting groups, this approach, relying on the 1,5 C-H insertion of a Rh(II)-carbene grafted at position 6, gave rise to the desired compound in the β-*series*. This C-H functionalization process is dramatically influenced by remote stereoelectronic effects arising from configuration of the anomeric position, since quaternarization could not be performed with the corresponding α-methyl glucoside because of the strong anomeric effect that deactivate the targeted C_5-H bond.

4. Experimental

4.1 General Methods

Anhydrous dichloromethane and tetrahydrofuran were purified and dried on a solvent dispensing system MBRAUN MB-SPS-800. Technical grade solvents were used for quantitative flash chromatography. HPLC grade solvents purchased from Sigma-Aldrich or freshly distilled solvents were used for flash chromatography for compounds undergoing full characterization. For reactions, pyridine was purchased anhydrous. Anhydrous 1,2-dichloroethane, stored in sealed 1 L bottles, was purchased from Sigma-Aldrich (ref. 284505), and dried additionally over molecular sieves (4Å, 8-12 mesh) before use. $Rh_2(OAc)_4$ was purchased from Sigma-Aldrich. All other commercially available reagents were used without any further purification. Flash chromatography was performed on silica gel (60-240 mesh) unless otherwise specified. Analytical thin layer chromatography (TLC) was performed

on silica gel plates (Merck 60F254) visualized either with a UV lamp (254 nm) or by using PMA stain (Phosphomolybdic acid). Organic extracts were dried over anhydrous $MgSO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-III, at 300 MHz (^1H value) or 75 MHz (^{13}C value) in $CDCl_3$. Spectra were referenced to residual chloroform (7.26 ppm, ^1H; 77.16 ppm, ^{13}C) or TMS. Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qt (quintet), and m (multiplet or unresolved), br (broad signal). Coupling constants, *J*, are reported in hertz (Hz). All NMR spectra were obtained at 300K unless otherwise specified. Carbene insertion reactions were performed in flame-dried glassware. *N*,*N*'-ditosylhydrazine was prepared following Fukuyama's procedure [15a]. Compounds **3** and **4** were prepared according to our own procedures [14].

4.2 Experimental Procedures

4.2.1 Methyl 2,3,4-tri-*O*-acetyl-6-*O*-diazoacetyl-α-D-glucopyranoside **5**

To a solution of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside **3** (660 mg, 2.06 mmol, 1 equiv.) and anhydrous pyridine (0.415 mL, 5.15 mmol, 2.5 equiv.) in anhydrous dichloromethane (10 mL) at 0 °C was quickly added bromoacetyl bromide (0.359 mL, 4.15 mmol, 2 equiv.). After being stirred for 10 minutes at 0 °C, the reaction mixture was quenched with methanol (0.5 mL) while TLC (cyclohexane / ethyl acetate 80:20) showed complete consumption of the starting material. The organic layer was diluted with dichloromethane (30 mL), and washed with a saturated aqueous solution of ammonium chloride (20 mL) and a 0.2 M hydrochloric acid solution (20 mL). After drying of the organic phase over anhydrous magnesium sulfate, filtration and concentrated under reduced pressure gave a residue (573 mg, 1.3 mmol) which was used without further purification in the next step. To a solution of this residue (1 equiv.) and *N*,*N*'-ditosylhydrazine (883 mg, 2.6 mmol, 2 equiv.) in distilled tetrahydrofuran (13 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.987 mL, 6.5 mmol, 5 equiv.). The reaction was stirred for 10 minutes at 0 °C, and quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). After addition of diethyl ether (15 mL), the aqueous phase was extracted with diethyl ether (2×15 mL), and the combined organic layers were dried (anhydrous magnesium sulfate), filtered and concentrated under vacuum. The residue was then triturated in diethyl ether and set all night. Filtration and concentration of the filtrate

under vacuum gave **5** (359 mg, 45% over 2 steps). Yellow oil; $[\alpha]_D^{20}$ +140 (*c* 1.0, $CHCl_3$); R_f 0.36 (toluene/acetone 88:12); IR (neat): ν 2958, 2114, 1746, 1698, 1366, 1215, 1030, 734, 487, 469; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.47 (t, 1H, $J_{2,3} = J_{3,4}$ 9.8 Hz, H-3), 5.03 (t, 1H, $J_{3,4} = J_{4,5}$ 9.8 Hz, H-4), 4.95 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.88 (dd, 1H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.8 Hz, H-2), 4.81 (br s, 1H, H-7), 4.28-4.26 (m, 2H, H-6), 4.03-3.97 (m, 1H, H-5), 3.40 (s, 3H, OMe), 2.08 (s, 3H, C(O)*CH*$_3$), 2.04 (s, 3H, C(O)*CH*$_3$), 2.01 (s, 3H, C(O)*CH*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3 (C=O), 170.2 (C=O), 169.7 (C=O), 96.8 (C-1), 70.9 (C-2), 70.2 (C-3), 68.7 (C-4), 67.3 (C-5), 62.4 (C-6), 55.5 (OMe), 46.5 (C-7), 20.9 (C(O)*CH*$_3$), 20.8 (C(O)*CH*$_3$), 20.7 (C(O)*CH*$_3$); HRMS (ESI+): m/z calculated for $C_{15}H_{24}N_3O_{10}$ $[M + NH_4]^+$: 406.1456; found: 406.1441.

4.2.2 Methyl 2,3,4-tri-*O*-acetyl-6-*O*-diazoacetyl-β-D-glucopyranoside **6**

To a solution of methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside **4** (480 mg, 1.50 mmol, 1 equiv.) and anhydrous pyridine (0.302 ml, 3.75 mmol, 2.5 equiv.) in anhydrous dichloromethane (7.5 mL) at 0 °C was quickly added bromoacetyl bromide (0.261 ml, 3 mmol, 2 equiv.). After being stirred for 10 minutes at 0 °C, the reaction mixture was quenched with methanol (0.5 mL) while TLC (cyclohexane / ethyl acetate 80:20) showed complete consumption of the starting material. The organic layer was diluted with dichloromethane (25 mL), and washed with a 0.2 M hydrochloric acid solution (7 mL). After drying of the organic phase over anhydrous magnesium sulfate, filtration and concentrated under reduced pressure gave a residue (600 mg, 1.36 mmol) which was used without further purification in the next step. To a solution of this residue (1 equiv.) and *N*,*N'*-ditosylhydrazine (925 mg, 2.72 mmol, 2 equiv.) in distilled tetrahydrofuran (13 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.034 mL, 6.8 mmol, 5 equiv.). The reaction was stirred for 10 minutes at 0 °C, and quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). After addition of diethyl ether (15 mL), the aqueous phase was extracted with diethyl ether (2×15 mL), and the combined organic layers were dried (anhydrous magnesium sulfate), filtered and concentrated under vacuum. The crude was purified by silica gel chromatography (toluene / acetone 88:12) to give **6** (512 mg, 88% over 2 steps). Yellow solid; mp 126-128 °C; $[\alpha]_D^{20}$ +4 (*c* 1.0, $CHCl_3$); R_f 0.33 (toluene/acetone 88:12); IR (neat): ν 2961, 2115, 1748, 1693, 1366, 1215, 1032, 738, 486; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.20 (t, 1H, $J_{2,3} = J_{3,4}$ 9.1 Hz, H-3), 5.05 (t, 1H, $J_{3,4} = J_{4,5}$ 9.1 Hz, H-4), 4.97 (t, 1H, $J_{1,2} = J_{2,3}$ 9.1 Hz, H-2), 4.81 (br s, 1H, H-7), 4.42 (d, 1H, $J_{1,2}$ 9.1 Hz, H-1), 4.36-4.22

(m, 2H, H-6), 3.71 (dt, 1H, $J_{5,6}$ 3.7 Hz, $J_{4,5}$ = $J_{5,6'}$ 9.1 Hz, H-5), 3.50 (s, 1H, OMe), 2.05 (s, 3H, C(O)*CH*$_3$), 2.03 (s, 3H, C(O)*CH*$_3$), 2.00 (s, 3H, C(O)*CH*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4 (C=O), 169.9 (C=O), 169.5 (C=O), 101.7 (C-1), 73 (C-3), 72 (C-5), 71.3 (C-2), 68.6 (C-4), 62.4 (C-6), 51.2 (OMe), 46.6 (C-7), 20.9 (C(O)*CH*$_3$), 20.8 (C(O)*CH*$_3$); HRMS (ESI+): m/z calculated for $C_{15}H_{24}N_3O_{10}$ $[M + NH_4]^+$: 406.1456; found: 406.1472.

4.2.3 Rh(II)-catalyzed decomposition of **5**

To a suspension of $Rh_2(OAc)_4$ (2.21 mg, 5 µmol, 2 mol%) in refluxing anhydrous 1,2-dichloroethane (100 mL) was added a solution of **5** (100 mg, 0.25 mmol, 1 equiv.) in anhydrous 1,2-dichloroethane (1 mL) dropwise *via* syringe pump (14 µmol/h). At the end of the addition, the reaction mixture was cooled to room temperature, and the residue was concentrated under vacuum. From a very complex mixture (91 mg), fraction 1 (4 mg) and fraction 2 (13 mg) were isolated after careful column chromatography (cyclohexane/ethyl acetate, 70:30 to 50:50). Extensive characterization (MS and NMR) revealed that fraction 1 was containing several products from which γ-lactone **7** and diastereoisomeric β-lactones **8** could be identified. Fraction 2 was shown to contain *cis*-and *trans*-dimers **9**.

4.2.3.1 Fraction 1: mixture of γ-lactone **7** and β-lactones **8**

R_f: 0.42 (petroleum ether / ethyl acetate 45:55); IR (neat): ν 2921, 1746, 1369, 1217, 1034, 930, 600, 488; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.54-5.37 (m, 1H, H-3), 5.24-4.75 (m, 3H, H-1, H-2, H-4), 4.33-4.06 (m, 1.72 H, 2×H-6 of **7**), 4.05-3.93 (m, 0.84 H, H-5 of **8**), 3.92-3.81 (m, 0.6 H, H-6 of **8**), 3.51-3.35 (m, 3H, OMe), 3.04 (d, 0.2 H, $J_{7,7'}$ 17.7 Hz, H-7 of **7**), 2.87 (d, 0.2H, $J_{7,7'}$ 17.7 Hz, H-7' of **7**), 2.69-2.57 (m, 0.6H, H-7 of **8**), 2.47-2.36 (m, 0.6H, H-7' of **8**), 2.13-1.92 (m, 9H, C(O)*CH*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.4-169.4 (C=O), 96.8-96.6 (C-1), 71.7 (C-6 of **8**), 70.9-70.6 (C-4), 70.2-70 (C-3), 68.9-68.3 (C-2), 67.2-67.0 (C-5), 62.1-61.8 (C-6 of **7**), 55.6-55.4 (OMe), 41.72 (C-7 of **8**-dia1), 41.66 (C-7 of **8**-dia2), 29.7 (C-7 of **7**), 21.0-20.5 (m, C(O)*CH*$_3$); HRMS (API+): m/z calculated for $C_{15}H_{21}O_{10}$ $[M + H]^+$: 361.1129; found: 361.1135.

4.2.3.1 Fraction 2: mixture of *cis* and *trans* dimers **9**

R_f: 0.31 (petroleum ether/ ethyl acetate 45:55); IR (neat): ν 2970, 1368, 1215, 1032, 929, 731, 488; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.90 (s, 0.27H, H-7 of **9**-*cis*), 6.29 (s, 0.21H, H-7 of **9**-*trans*), 5.53-5.41 (m, 1H, H-3), 5.14-4.97 (m, 1H, H-4), 4.99-4.82 (m, 2H, H-1, H-2), 4.46-4.09 (m, 2H, H-6), 4.09-3.93 (m, 1H, H-5), 3.50-3.25 (m, 3H, OMe), 2.16-1.92 (m, 9H, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.5-169.5 (C=O), 164.7 (C=O), 164.4 (C=O), 133.6 (C-7 of **9**-*cis*), 129.9 (C-7 of **9**-*trans*), 97.0-96.7 (C-1), 71.2-70.6 (C-2), 70.4-69.7 (C-3), 69.5-67.8 (C-4, C-5), 67.3-66.8 (C-6), 55.9-55.4 (OMe), 21.1-20.5 (C(O)CH_3); MS (ESI+): m/z 738 $[M + NH_4]^+$.

4.2.4 (*5R*,*7R*,*8R*,*9S*,*10S*)-7-methoxy-3-oxo-2,6-dioxaspiro[4.5]decane-8,9,10-triyl triacetate **10**

To a suspension of $Rh_2(OAc)_4$ (3.40 mg, 7.72 µmol, 2 mol%) in refluxing anhydrous 1,2-dichloroethane (150 mL) was added a solution of **6** (150 mg, 0.386 mmol, 1 equiv.) in anhydrous 1,2-dichloroethane (2.5 mL) dropwise *via* syringe pump (10 µmol/h). After the end of the addition, the reaction mixture was concentrated under vacuum, and purified by silica gel chromatography (cyclohexane / ethyl acetate 70:30) to give γ-lactone **10** (97 mg, 70%). White foam; $[\alpha]_D^{20}$ = - 14.2 (*c* 0.2, $CHCl_3$); R_f 0.37 (cyclohexane / ethyl acetate 50:50); IR (neat): ν 2945, 1787, 1749, 1370, 1210, 1035, 903; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.26-5.11 (m, 2H, H-4, H-3), 4.97 (t, 1H, $J_{1,2} = J_{2,3}$ 7.7 Hz, H-2), 4.51 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1), 4.35 (d, 1H, $J_{6,6'}$ 10.2 Hz, H-6), 4.22 (d, 1H, $J_{6,6'}$ 10.2 Hz, H-6'), 3.47 (s, 3H, OMe), 2.96 (d, 1H, $J_{7,7'}$ 17.5 Hz, H-7), 2.73 (d, 1H, $J_{7,7'}$ 17.5 Hz, H-7'), 2.07 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.02 (s, 3H, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.0 (C=O), 170.0 (C=O), 169.5 (C=O), 169.4 (C=O), 99.1 (C-1), 78.7 (C-5), 75.2 (C-6), 71.2 (C-2), 70.2 (C-3), 70.1 (C-4), 57.2 (OMe), 34.1 (C-7), 20.8 (C(O)CH_3), 20.7 (C(O)CH_3), 20.6 (C(O)CH_3).

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