Hydrolysis of α and β -glycosides.

New experimental data and modelling of reaction pathways.

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Experimental

Infrared (ir) spectra were taken on a Perkin-Elmer 1600 series FTIR. Nuclear magnetic resonance (nmr) spectra were recorded on a Brüker AC 300 instrument. Mass spectra (ms) were obtained on a ZAB-IF spectrometer. Flash chromatography was performed on silica gel Merck 60, 230-400 mesh.

Aldehyde **9**: To a solution of DMSO (0.16ml, 2.2mmol) in dichloromethane (3ml) was added oxalyl chloride (0.1ml, 1.1mmol) at -78°C, and the resulting mixture was stirred for 5 min. The alcohol **8** (186mg, 1mmol) in dichloromethane (2ml) was added and the solution was stirred for 30 min; then, triethylamine (0.63ml, 4.5mmol) was introduced. The dry ice-acetone bath was removed after 5 min and the reaction mixture was left to warm up to room temperature and stirred for 10 min. Water (10ml) and dichloromethane (10 ml) were added, the organic phase was separated, the aqueous phase was extracted with dichloromethane (2x10ml), the combined organic phase was dried over magnesium sulfate, the solvent was removed and the residue was purified by flash chromatography (hexane:ethyl acetate,

7:3) to give the aldehyde **9** (170 mg, 92%). ir (film): 1739, 1234, 1040 cm^{-1} . ^1H nmr (CDCl_3): 9.55 (1H, d, $J=4.0\text{Hz}$, CHO), 4.02 (1H, dd, $J=11.0$ and 5.0Hz , CHHO), 3.92 (1H, dd, $J=11.0$ and 6.5Hz , CHHO), 2.2-1.10 (10H, m, CH, CH_2), 2.10 (3H, s, CH_3). ^{13}C nmr (CDCl_3): 203.41, 170.55, 67.21, 52.81, 40.75, 36.07, 27.53, 25.53, 24.43, 20.57. ms (m/e): 185 (M^+-H), 169 (M^+-CH_3), 139 (M^+-COCH_3).

Acetoxy enol ether **10**: To a solution of LDA (1.3M. 7.7ml, 10mmol) in THF (20 ml) was added (methoxymethyl) triphenyl phosphonium chloride (3.43g. 10mmol) at 0°C . The reaction mixture was stirred for 30 min. Aldehyde **9** (0.92g, 5mmol) in THF (10ml) was introduced over a period of 15min and the resulting mixture was stirred for 4h. Saturated aqueous ammonium chloride was added, the two phases were separated and the aqueous phase was extracted with ether (3x30ml). The combined organic phase was dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (hexane:ethyl acetate. 9:1) to give a mixture of Z and E enol ether **10** (0.58g. 56%). ir (film): 1740, 1656, 1241 cm^{-1} . ^1H nmr (C_6D_6): 6.25 (3/5H, d, $J=12.5\text{Hz}$, CH_2OCH_3 E), 5.60 (2/5H, d, $J=6.0\text{Hz}$, CH_2OCH_3 Z), 4.40 (3/5H, dd, $J=12.5$ and 9.5Hz , $\text{CH}=\text{C}$ E), 4.31 (2/5H, dd, $J=11.0$ and 3.5Hz , CHHO Z), 4.26 (3/5H, dd, $J=11.0$ and 3.5Hz , CHHO E), 4.08 (2/5H, dd, $J=9.5$ and 6.0Hz , $\text{CH}=\text{C}$ Z), 4.04 (2/5H, dd, $J=11.0$ and 8.0Hz , CHHO Z), 3.87 (3/5H, dd, $J=11.0$ and 7.5Hz , CHHO E), 3.13 (9/5H, s, OCH_3 E), 3.07 (6/5H, s, OCH_3 Z), 1.86-0.94 (10H, m, CH, CH_2), 1.72 (9/5H, s, CH_3 E), 1.69 (6/5H, s, CH_3 Z). ^{13}C nmr (C_6D_6): 170.15, 170.06, 147.66, 146.56, 111.66, 106.71, 68.13, 67.88, 58.99, 55.38, 42.45, 42.33, 39.69, 35.57, 33.92, 30.09, 29.98, 26.43, 26.36, 26.30, 26.21, 26.12, 20.55, 20.47. ms (m/e): 212 (M^+), 181 (M^+-OCH_3), 169 (M^+-Ac).

Hydroxy enol ethers **11E** and **11Z**: Acetoxy enol ether **10** (104mg, 0.5mmol) was dissolved in a solution of methanol (3ml) and aqueous sodium hydroxide (1ml, 2N) and the resulting mixture was stirred for 1h at room temperature. The solvent was removed under reduced pressure and the residue was purified

by flash chromatography (hexane:ethyl acetate. 7:3) to give **11E** (55mg, 65%) and **11Z** (28mg, 32%). ir (film): **11E**: 3367, 1652, 1448, 1206, 1158cm⁻¹; **11Z** : 3408, 1664, 1450, 1264, 1102cm⁻¹. ¹H nmr (C₆D₆): **11E**: 6.27 (1H, d, 13.0Hz, CHOCH₃), 4.45 (1H, dd, J=13.0 and 9.5Hz, CH=CHO), 3.49 (1H, br, CHHOH), 3.32 (1H, br, CHHOH), 3.14 (3H, s, OCH₃), 1.79-0.97 (10H, m, CH, CH₂); **11Z**: 5.53 (1H, d, J=6.0Hz, CHOCH₃), 4.08 (1H, dd, J=10.0 and 6.5Hz, CH=CHO), 3.72 (1H, m, CHHOH), 3.56 (1H, m, CHHOH), 2.95 (3H, s, OCH₃), 2.55 (1H, m, CH), 2.00 (1H, m, CH), 1.81-0.96 (8H, m. CH₂). ¹³C nmr (C₆D₆-CDCl₃): **11E**: 147.32, 107.58, 66.57, 55.38, 45.57, 35.72, 29.66, 26.52, 26.35; **11Z**: 145.56, 111.43, 66.37, 59.13, 44.79, 34.55, 33.61, 29.35, 26.17, 25.96. ms (m/e): 170 (M⁺), 152 (M⁺-H₂O), 109 (M⁺-CH₂O-OCH₃).

Dimethoxy acetal **12**: Triphenyl phosphine hydrobromide (8mg) was added to acetoxyl enol ether **10** (85mg, 0.5mmol) in methanol (0.5ml) and the resulting mixture was stirred for 20h at room temperature. Two drops of triethylamine were added and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexane:ethyl acetate:triethylamine, 85:14:1) to give the dimethoxy acetal **12** (89mg. 95%). ir (film): 1741, 1240, 1124, 1049cm⁻¹. ¹H nmr (C₆D₆): 4.45 (1H, dd, J=7.0 and 4.0Hz, OCHO), 4.12 (1H, dd, J=11.0 and 3.5Hz, CHHO), 4.00 (1H, dd, J=11.0 and 6.0Hz, CHHO), 3.13 (3H, s, OCH₃), 3.14 (3H, s, OCH₃), 2.02-0.78 (15H, m, CH, CH₂, CH₃). ¹³C nmr (C₆D₆): 170.11, 102.93, 67.14, 52.60, 51.20, 41.84, 36.45, 35.26, 32.33, 30.17, 26.13, 25.94, 20.46. ms (m/e): 243 (M⁺-H), 213 (M⁺-OCH₃), 171 (M⁺-Ac).

Hydroxy dimethoxy acetal **13**: Acetoxyl dimethoxy acetal **12** (48mg, 0.2mmol) was hydrolyzed in a mixture of methanol (1ml) and aqueous sodium hydroxide (1N, 0.5ml) for 30 min at room temperature to give hydroxy dimethoxy acetal **13** (37 mg, 92%) after purification by flash chromatography (hexane:ethyl acetate, 1:1). ir (film): 3402, 1198, 1058cm⁻¹. ¹H nmr (C₆D₆): 4.40 (1H, dd, J=7.5 and 4.0Hz. OCHO), 3.53 (1H, dd, J=11.0 and 5.0Hz, CHHO), 3.40 (1H, dd, J=11.0 and 3.0Hz, CHHO), 3.12 (3H, s, OCH₃), .2.02-0.88 (12H, m, CH,

CH₂). ¹³C nmr (C₆D₆): 103.63, 65.36, 52.50, 45.06, 36.75, 34.51, 33.43, 30.19, 26.54, 26.38. ms (m/e): 201 (M⁺-H), 181 (M⁺-OCH₃). HRMS (m/e): Calcd. for C₁₁H₂₁O₃ (M⁺-H): 201.1491, found: 201.1489.

Methoxy pentenoxy acetal **14**: A solution of acetoxy enol ether **10** (348mg, 1.67mmol), pentenol (222mg, 2.58mmol) and a catalytic amount of trifluoroacetic acid in dichloromethane (10ml) was stirred for 30 h at room temperature. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate:triethylamine, 85:14:1) to give methoxy pentenoxy acetal **14** (75mg, 15%), dimethoxy acetal **12** (55mg, 14%), dipentenoxo acetal (10mg, 2%) and some starting material (85mg, 24%). **14** ir(film): 1741, 1240, 1124cm⁻¹. ¹H nmr (C₆D₆): 5.74 (1H, m, CH=CH₂), 5.00 (2H, m, CH=CH₂), 4.50 (1H, m, OCHO), 4.12 (1H, dd, J=11.0 and 3.0Hz, CHHO), 4.00 (1H, dd, J=11.0 and 6.0Hz, CHHO), 3.48 (1H, m, CHHO), 3.30 (1H, m, CHHO), 3.15 (3H, s, OCH₃), 2.12-0.84 (19H, m, CH, CH₂). ¹³C nmr (C₆D₆): 170.11, 138.56, 114.91, 102.39, 102.04, 67.15, 65.27, 64.14, 52.42, 51.11, 41.83, 36.97, 36.81, 35.30, 35.24, 32.35, 30.83, 30.14, 29.55, 26.14, 25.92, 20.49. ms (m/e): 267 (M⁺-OCH₃), 213 (M⁺-OC₅H₉).

Hydroxy methoxy pentenoxy acetal **15**: Acetoxy mixed acetal **14** (60mg, 0.2mmol) was hydrolyzed in a mixture of methanol (2ml) and aqueous sodium hydroxide (1N, 0.5 ml) during 40min at room temperature to give hydroxy mixed acetal **15** (44mg, 92%) after purification by flash chromatography (hexane:ethyl acetate, 1:1). ir (film): 3441, 1642, 1123, 1049cm⁻¹. ¹H nmr (C₆D₆): 5.74 (1H, m, CH=CH₂), 4.98 (2H, m, CH=CH₂), 4.48 (1H, m, OCHO), 3.58-3.25 (4H, m, OCH₂), 3.15 and 3.14 (3H, 2s, OCH₃ of two isomers), 2.12-0.89 (14H, m, CH, CH₂). ¹³C nmr (C₆D₆): 138.46, 115.26, 114.90, 103.12, 102.99, 65.47, 66.22, 65.11, 52.28, 52.17, 45.07, 37.29, 34.62, 33.62, 30.76, 30.20, 29.57, 26.58, 26.35. ms (m/e): 255 (M⁺-H), 224 (M⁺-CH₃OH), 223 (M⁺-CH₃OH-H). HRMS (m/e): Calcd. for C₁₄H₂₆O₃ (M⁺-H): 255.1960, found: 255.1957, Calcd. for C₁₃H₂₃O₂ (M⁺-CH₃OH): 224.1776, found: 224.1771, Calcd for C₁₃H₂₂O₂ (M⁺-CH₃OH-H): 223.1698, found: 223.1695.

Bicyclic enol ether **19** (trans 4a,5,6,7,8,8a-hexahydro-1H-isochromene): To a solution of bicyclic lactol **18** (2-hydroxy-3-oxa-trans-decalin) (**21**) (154mg, 1mmol) in benzene (60ml) was added paratoluenesulfonic acid (2mg). A large part of benzene (40ml) was gradually distilled off. Triethylamine (20μl) was added to neutralize the reaction mixture. The solvent was evaporated. The residue was purified by silica gel flash chromatography (hexane:ethyl acetate:triethylamine, 95:4:1) to give the title compound as an oily product (84mg, 61%). ir(film): 3024.8, 1652.3, 1448.3, 1306.2cm⁻¹. ¹H nmr (C₆D₆): 5.53 (1H, d, J=6.2 Hz, OCH=CH), 4.08 (1H, dd, J=6.4 and 9.8Hz, OCH=CH), 3.73 (1H, m, OCH=CHCHH), 3.54 (1H, m, OCH=CHCHH), 2.55 (1H, m, CH), 2.00 (1H, m, CH), 1.81-1.43 (4H, m, CH₂), 1.23-0.96 (4H, m, CH₂). ¹³C nmr (C₆D₆): 144.71, 111.42, 65.56, 44.79, 34.55, 33.61, 29.35, 26.17, 25.96. ms (m/e): 138 (M⁺).

Molecular modelling details

The different structures were calculated at the RHF/6-31G* theory level¹ by means of GAMESS.² Since no transition structures could be found for the exocyclic hydrolysis pathways, bond length constraints (see table) were imposed to the C-O bond undergoing cleavage to reconstruct the various competing paths. This procedure indicated the presence of transition structures for the endocyclic cleavage around 1.9Å. No further work was undertaken to precisely locate those transition structures, since the potential energy surfaces are very flat in these cases. Consequently, all transition structures reported in this work have their breaking C-O bond length set at 1.9Å, all other coordinates being optimized. For each

¹ M.W. Schmidt, K.K. Baldrige, J.A. Boatz, S.T. Elbert, M.S. Gordon, J.H. Jensen, S. Koseki, N. Maturaga, K.A. Nguyen, S.J. Su, T.L. Windus, M. Dupuis and J.A. Montgomery. *J. Comput. Chem.* **14**, 1347 (1993).

² P.C. Hariharan and J.A. Pople. *Theoret. Chim. Acta* **28**, 213 (1973).

glycoside **1 α** and **1 β** , there are four lone pairs that can be protonated. The eight entire paths were computed, and only the ones passing through the lower energy transition structures were kept for discussion (the relevant lone pairs are indicated by * in scheme a).

Scheme a

The neutral glycosides **1 α** and **1 β** have relative energies of 0.00Kcal/mol and 1.52Kcal/mol in agreement with other calculations.³ However, these figures suggest that gas phase calculations may overestimate the strength of the anomeric effect, since the energy gap should only be around 0.3 to 0.9Kcal/mol according to known experimental data.⁴ This discrepancy was also found in the case of the charged structures **3** and **6** (Scheme b, Table). The oxocarbenium ions **3** arising from exocyclic cleavage of both **1 α** and **1 β** should be the same. However, there is a calculated energy gap of 1.45 Kcal/mol (1.51 - 0.06) between the two structures **3** + MeOH (one structure **3 α** with methanol on the α face and another structure **3 β** with methanol on the β face as shown in Scheme b) when the bond gap is set to 2.4Å between the oxocarbenium ion and the methanol molecule (C-O bond undergoing cleavage). At such distance, the C-O bond order is 0,⁵ which suggests that electronic interactions between the two partners should be very weak. This is confirmed by single point calculations of the oxocarbenium ions **3** (from **3 α** and **3 β**) alone after removal of the methanol molecule; their energies

³ a) C.W. Andrews, B. Fraser-Reid and J.P.Bowen. *J. Am. Chem. Soc.* **113**, 8293 (1991). b) K.N. Wiberg and M.A. Murcko. *J. Am. Chem. Soc.* **111**, 4821 (1989).

⁴ a) E.V. Eikeren. *J. Org. Chem.* **45**, 4641 (1980). b) A.J. de Hoog, H.R. Buys, C. Altona and C. Havinga. *Tetrahedron* **25**, 3365 (1969). c) A.J. de Hoog. *Org. Magn. Reson.* **6**, 233 (1974). d) G.O. Pierson and O.A. Runquist. *J. Org. Chem.* **33**, 2572 (1968).

being, as expected, very similar (0.03Kcal/mol energy gap). At 2.4Å bond distance again, the structures corresponding to **6α** and **6β** have an energy difference of only 0.03Kcal/mol. On the other hand, when there cannot be interactions between the alcohol and the oxocarbenium ion as in the minimized structures **6α'** and **6β'** (Scheme b), the β-oxocarbenium ion is more stable than the α-oxocarbenium ion by 0.63Kcal/mol. It is therefore obvious that the gas phase calculations crude energies should be calibrated to account for real solution phase reactions, in which stereoelectronic effects might be weakened by the solvent; even more so, when the C-O bond distance increases (as in structures **2**, **3**, **5** and **6**). Since the bond order is nil for all 2.4Å C-O bonds, it appears reasonable to reset the energies of the corresponding structures to represent this fact.

Scheme b. Determination of the corrections to apply according to the fact that **3α** and **3β** should have the same energy and **6α** and **6β** should have the same difference in energy as that found between **6α'** and **6β'** (note the conformational difference with **6α** and **6β**) where there cannot be interactions between the alcohol and the oxocarbenium ion

⁵ I. Mayer. *Chem. Phys. Lett.* **97**, 270 (1983).

The calculated energies of the oxocarbenium ion (minimized **3** without MeOH) added to the energy of methanol (-424.17693au -115.03542au = -539.21236au) yields a relative energy of 0.00Kcal (the two molecules being computed separately, there are no interactions between them) with regards to the interaction free structures **6 α '** (-539.20188au) and **6 β '** (-539.21236au), whose relative energies become 6.58Kcal/mol and 5.95Kcal/mol, respectively. These three relative energies are expected to give a fair estimate of the energies of **3**, **6 α** and **6 β** for C-O bond distances of 2.4Å (having no interactions between the oxocarbenium ion and the alcohol). All calculated energies were therefore corrected accordingly.

d(Å) ↓	E (Kcal/mol)							
	Exocyclic cleavage path via 2				Endocyclic cleavage path via 5			
	Path 1α → 3		Path 1β → 3		Path 1α → 6α		Path 1β → 6β	
	calc	corr	calc	corr	calc	corr	calc	corr
		-0.06		-1.51		+1.35		+0.75
1.6	6.61		11.52		3.99		2.99	
1.7	6.12		10.74		4.41		3.52	
1.8	5.58		9.75		4.86		4.10	
1.9 ts	4.64	4.58	8.35	6.84	4.95$_{max}$	6.30	4.34$_{max}$	5.09
2.0	3.39		6.63		4.76		4.30	
2.1	2.13		4.88		4.52		4.21	
2.12							4.20min	
2.17					4.46min			
2.4 ion	0.06	0.00	1.51	0.00	5.23	6.58$_{min}$	5.20	5.95$_{min}$
2.47	0.00min							
2.59			1.04min					

Table. Calculated and corrected energy values of the paths; shaded rows for transition structures **2** and **5** and oxocarbenium ions **3** (+ MeOH) and **6**.

Underlined figures are energy values of fully optimized **6 α '** and **6 β '**.

9

10

10

11E

11E

11Z

11Z

12

13

13

14

14

15