HYDROLYSIS OF ISOMERIC TRICYCLIC ORTHOESTERS AND AM1 MOLECULAR MODELLING OF THE REACTION PATHWAY. FURTHER EVIDENCE FOR STEREOELECTRONIC CONTROL‡

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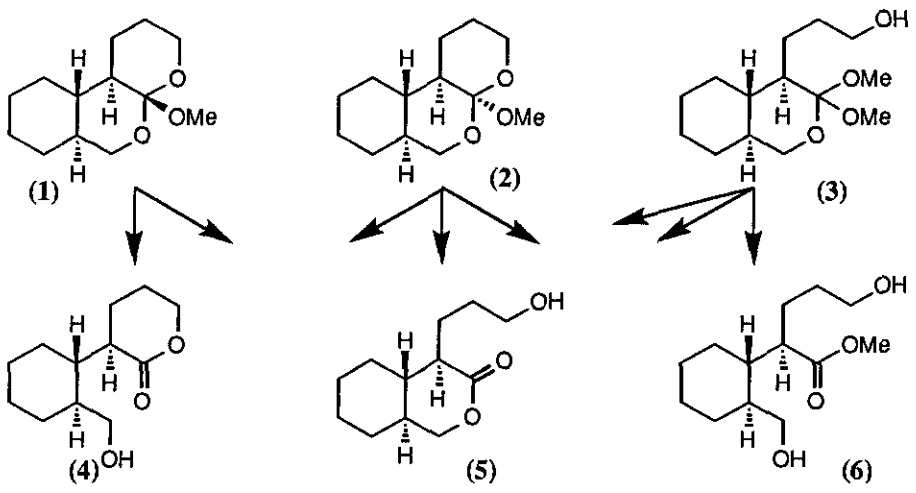
Abstract - Two tricyclic orthoesters and three other orthoesters have been submitted to acid hydrolysis conditions to yield mixtures of lactones and esters. The ratios of different products have been rationalized in terms of stereoelectronic, steric and entropy effects at the various steps. A quantitative AM1 investigation has been carried out, starting from the only tricyclic hemi-orthoester intermediate of the whole system, in order to compare the hydrolysis routes leading to the kinetic and thermodynamic lactone products.

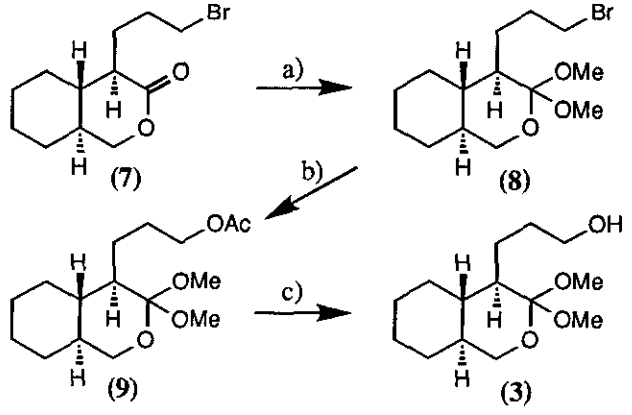
The mild acid hydrolysis of cyclic orthoesters is a powerful technique to demonstrate the importance of stereoelectronic effects in the cleavage of tetrahedral intermediates derived from esters.[1-3] For example, we have reported the synthesis of *cis* and *trans* tricyclic orthoesters (**1**) and (**2**) (Scheme 1) and carried out a preliminary investigation of their hydrolytic behaviors.[4] Recently, we have used with success the semi-empirical Hamiltonian AM1 to better define the reaction pathway in the hydrolysis of acetals and ketals.[5,6] We have therefore reinvestigated the hydrolysis of orthoesters (**1**) and (**2**) along with the corresponding dimethoxy orthoester (**3**) and completed this work by a molecular modelling study of the various reaction pathways. We wish to report this investigation.

Synthesis. Orthoesters (**1**) and (**2**) were prepared following our published experimental procedure.[4] The synthesis of dimethoxy orthoester (**3**) was carried out as shown in Scheme 2. The known bromolactone (**7**)[4] was treated with trimethyloxonium tetrafluoroborate followed by reaction of the intermediate dioxocarbenium ion with sodium methoxide to yield the bromo orthoester (**8**). Displacement of the bromine group by potassium acetate gave the corresponding acetate (**9**) which upon basic hydrolysis provided the hydroxy dimethoxy orthoester (**3**).

‡ This paper is dedicated to the memory of the late Dr. Yoshio Ban.



Scheme 1



Scheme 2 a) **i** Me_3OBF_4, CH_2Cl_2, 20 °C. **ii** MeONa, MeOH, -78 °C to 20 °C (61%)
b) $MeCO_2K$, 18-crown-6, MeCN, 20 °C (90%)
c) 4N NaOH, MeOH, 20 °C. (92%).

Results and discussion

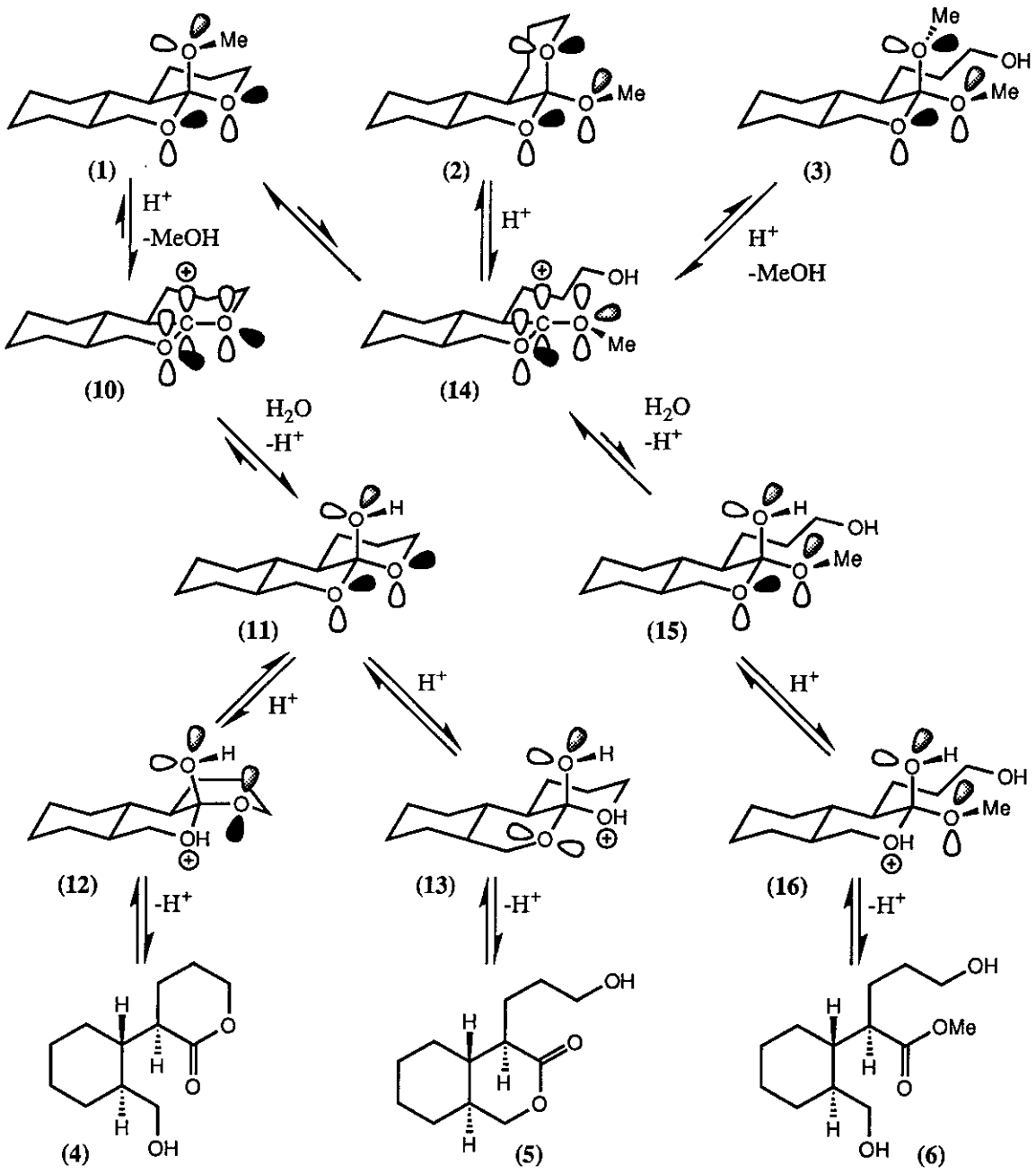
The hydrolyses of orthoesters (**1**) and (**2**) were reinvestigated using a catalytic amount of HCl in a CD_3CN-H_2O mixture. Under these new reaction conditions, the water which is necessary for hydrolysis is present in larger quantities than in the previously reported conditions[4] using acetone only. The hydrolysis of orthoester (**3**) was also carried out under the same conditions. The results (Scheme 1 and Table) are very similar to those previously published. The hydrolysis of *trans*-orthoester (**1**) is very fast, being completed in less than 2 min to produce a 79:21 mixture of lactones (**4**) and (**5**), the less stable lactone (**4**) is then slowly converted into the lactone (**5**) in the reaction medium. As previously described, the hydrolysis of *cis*-orthoester (**2**) is much slower, yielding first a mixture of dihydroxy ester (**6**) and the two lactones (**4**) and (**5**); (**4**) being again slowly converted into (**5**) in the reaction medium.

Table. Acid hydrolysis of orthoesters (1, 2 and 3)*

Orthoester (1)	Time (min)	Orthoester (1) (%)	Lactone (4) (%)	Lactone (5) (%)	Ester (6) (%)
	2	0	79	21	0
	5	0	71	29	0
	10	0	68	32	0
	15	0	64	36	0
	25	0	57	43	0
	60	0	37	63	0
	90	0	27	73	0
	240	0	0	100	0
Orthoester (2)	Time (min)	Orthoester (2) (%)	Lactone (4) (%)	Lactone (5) (%)	Ester (6) (%)
	2	80	10	0	10
	5	61	15	10	14
	10	53	20	10	17
	15	29	30	16	25
	25	12	36	21	31
	60	0	40	24	36
	90	0	35	29	37
	240	0	0	63	37
Orthoester (3)	Time (min)	Orthoester (3) (%)	Lactone (4) (%)	Lactone (5) (%)	Ester (6) (%)
	2	64	16	9	11
	5	46	26	13	15
	10	32	31	16	21
	15	23	32	22	23
	30	0	35	38	27
	40	0	33	40	27
	360	0	0	74	26

* Reaction conditions: orthoester (~3 mg), D_2O (100 ml), CD_3CN (400 ml), and 0.1 N HCl (3 ml).

The non-production of dihydroxy methyl ester (**6**) from the *trans* isomer (**1**) comes from the fact that the starting product (**1**) can only loose the axial methoxy group due to stereoelectronic control, the ring oxygens having each one electron lone pair oriented antiperiplanar to the methoxy group (Scheme 3). The alternative route leading to **14** is geometrically disfavored since it requires ring B to adopt a very strained boat conformation [geometry similar to **13** , H = Me]. Moreover, the step leading from **1** to **10** yields 2 molecules [**10** +MeOH]; as a result the **1** : **10** equilibrium mixture is entropically displaced toward the cation (**10**); such entropy gain does not take place in the transformation of **1** into **14** . Thus, protonation of **1** produces tricyclic dioxocarbenium ion (**10**) which upon hydration yields the hydroxyl tetrahedral intermediate (**11**). This intermediate cannot break down directly due to improper oxygen orbital orientations in the all chairs tricycle. However, it can produce the two isomeric lactones (**4**) and (**5**) if ring C and B undergo respectively conformational changes to the boat-like conformations (**12**) and (**13**). A boat-like conformation is more easily reached in ring C than in ring B, because the latter experiences more steric distortion due to the presence of the *trans* AB ring junction. Therefore, the lactone (**4**) should be the kinetic product and should be observed to a larger extent at the beginning of the hydrolysis process, in complete agreement with the experimental results.



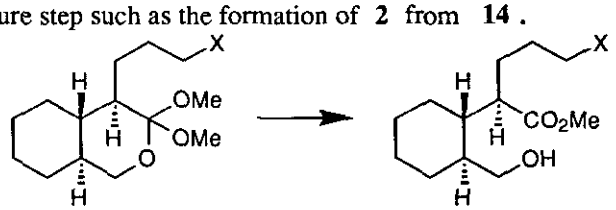
Scheme 3

In the *cis*-orthoester (**2**) too, only one C—O bond is properly oriented to undergo cleavage (Scheme 3) with a stereoelectronically controlled chair-like transition state. Thus, upon protonation (**2**) provides the dioxocarbenium ion (**14**) from which three different stereoelectronically controlled reactions can take place. It can give back **2** ,

yield the *trans*-orthoester (**1**) or undergo an intermolecular reaction with water to give the intermediate (**15**) with an axial OH group which can then lead to the dihydroxy methyl ester (**6**). The reclosure step from **14** to **2** is favored geometrically (a chair-like transition state), whereas the closure step to **1** is geometrically very disfavored (a boat-like transition state); both steps are equally entropically favored. On the other hand, the reaction with water to give **15** is favored geometrically (chair-like transition state) but disfavored entropically being an intermolecular process. The reclosure step from **14** to **2** does not influence the reaction products but slows down the overall rate of hydrolysis. The dihydroxy ester (**6**) comes from **16** , which is itself formed from **15** and the two lactones (**4**) and (**5**) result from an isomerization of *cis*-orthoester (**2**) into *trans*-orthoester (**1**). Thus in agreement with experiments, the relative percentages of the two lactones (**4**) and (**5**) must be essentially the same starting either from **1** or **2** and the large difference in rate of hydrolysis between **1** and **2** is readily explained. Furthermore, we have previously shown that the acid isomerization of **2** into **1** in anhydrous methanol is a fast process (<5 min).[4]

The hydrolysis of dimethoxy orthoester (**3**) gives essentially the same results than *cis*-orthoester (**2**) except that the rate of hydrolysis of **3** is faster than that of **2** . This result can be explained from the fact that **3** forms the dioxocarbenium ion (**14**) also produced from *cis*-orthoester (**2**). Since these two processes [**2** → **14** and **3** → **14**] are stereoelectronically very similar, we may assume that their reaction enthalpies are also similar. However a major entropy difference exists between these two reactions: there is no major entropy gain in going from 2 to **14** (unimolecular process) whereas **3** undergoes a cleavage to yield methanol and **14** resulting in a dramatic entropy gain. As a result, **3** is hydrolyzed faster than **2** .

The formation of dihydroxy methyl ester (**6**) from the hydration of **14** was confirmed indirectly by studying the mild acid hydrolysis of the orthoesters (**8**) and (**9**) (Scheme 4) under the same conditions as for compounds (**1-3**). The hydrolyses of **8** and **9** are completed in less than 2 min to give the hydroxy methyl esters (**17**) and (**18**) respectively. Thus, these compounds must have produced a dioxocarbenium ion [like **14** where the OH group is replaced by Br or OAc] which upon hydration and cleavage gave the corresponding hydroxy esters (**17**) and (**18**) [i.e., *via* **15** → **16** → **6** where CH_2OH is replaced by CH_2Br or CH_2OAc]. Interestingly, the rates of hydrolysis of **8** and **9** are faster than that of *cis*-orthoester (**3**) because the overall hydrolysis rate is not slowed down by a competing closure step such as the formation of **2** from **14** .



Scheme 4

(8) X=Br
(9) X=OAc

(17) X=Br
(18) X=OAc

Theoretical investigation at the AM1 level of theory[7, 8]

We have already shown that the Hamiltonian AM1 is a marvelous tool to quickly explore the potential energy surfaces of protonated acetals and ketals.[5] In the present context dealing with orthoesters, the chemical fate of the

species (**11**) (Scheme 3) is particularly interesting, since it can produce two distinct lactones (**4**) and (**5**). Experimentally, these two lactones (**4**) and (**5**) are the kinetic and the thermodynamic products respectively.
Thus, the neutral species (**11**) (Figure) can be protonated at 2 positions when omitting the hydroxyl group.

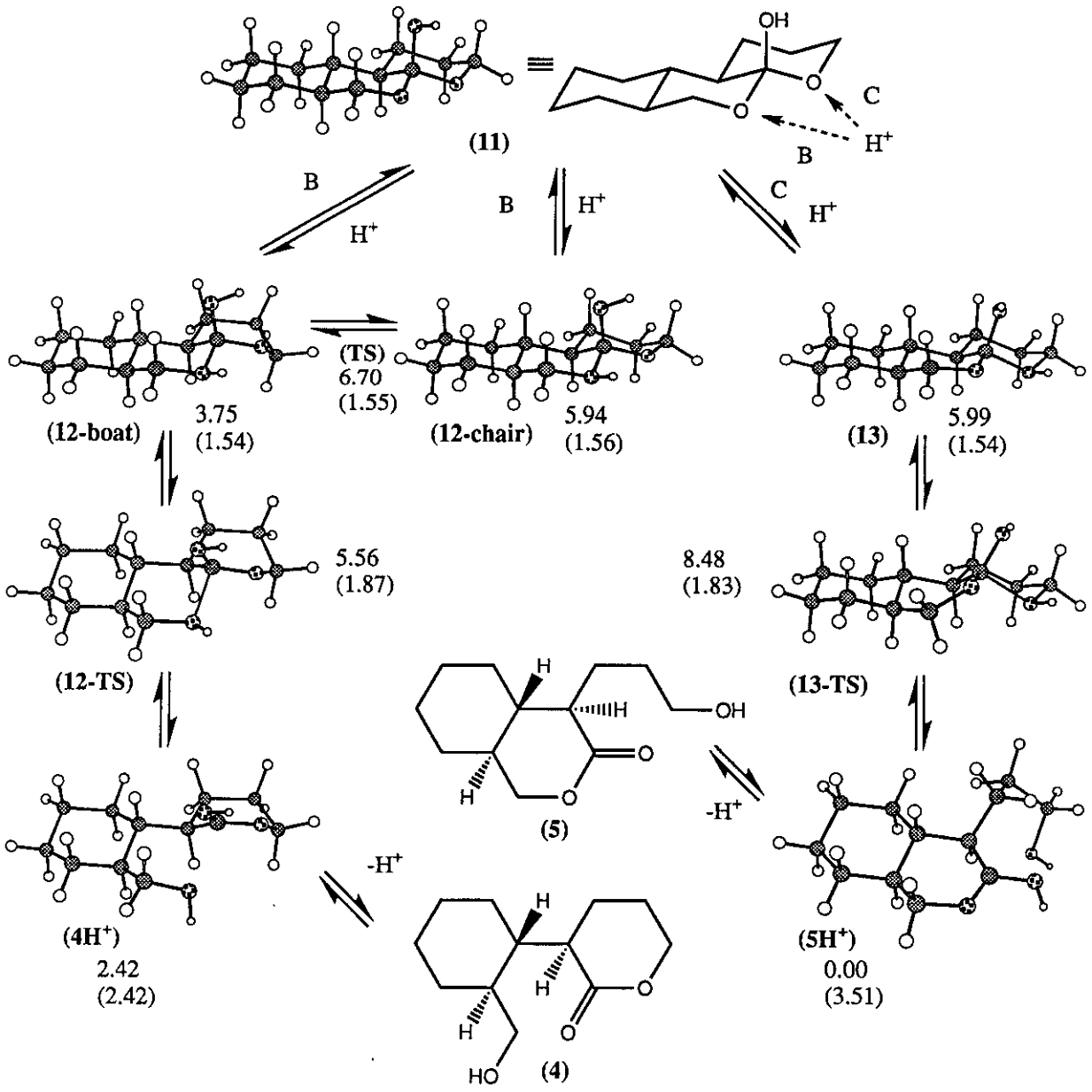


Figure. Relative energies are indicated in kcal/mol and the corresponding breaking C-O bond length reaction coordinates are displayed between brackets in Å.

Both, the B ring oxygen and the C ring oxygen atoms were found to be better protonated at the equatorial lone pair positions, although the axial protonation enthalpy values are close. For simplicity the following discussion will concentrate on the paths arising from the more favored equatorial protonations, the energies quoted are relative to the most stable structure (**5H**$^+$), whose true AM1 energy is -20.44 kcal/mol.

Protonation at the B ring oxygen gives 2 stable structures (**12**-boat) and (**12**-chair) having chair-chair-boat and chair-chair-chair tricyclic structures respectively; their relative energies, 3.75 kcal/mol and 5.94 kcal/mol, indicate that **12**-boat is favored over **12**-chair by 2.19 kcal/mol [**12**-boat is more stable than **12**-chair because of a strong anomeric effect].[5] The low activation enthalpy, 0.76 kcal/mol (6.70-5.94 kcal/mol), required to transform **12**-chair into **12**-boat indicates that the latter product should be the only one present in the reaction medium. **12**-Boat is then opened up to yield **4H**$^+$, the protonated form of the lactone (**4**), *via* the transition structure (**12**-TS) having a chair-chair-boat conformation, a distance of 1.87 Å along the breaking C—O bond length reaction coordinate and a relative energy of 5.56 kcal/mol.

Protonation at the C ring oxygen yields only one stable chair-chair-chair compound (**13**) whose energy, 5.99 kcal/mol, is close to **12**-chair 's. No stable chair-boat-chair structure could be found at the ground state level indicating how difficult it is for **13** to adopt such a conformation despite a potentially strong anomeric effect. However, the calculations clearly show that **13** can be transformed into **5H**$^+$ [protonated form of **5**] only *via* a chair-boat-chair transition geometry (**13**-TS) (relative energy = 8.48 kcal/mol, breaking C—O bond length reaction coordinate: 1.83 Å), since no chair-chair-chair transition structure was found. These interesting results confirm that two periplanar oxygen orbitals are required to eject the third protonated oxygen atom in orthoesters, in excellent agreement with stereoelectronic effects.

In conclusion, the AM1 calculations identify **4** as the kinetic product since the corresponding transition structure (**12**-TS) is favored over **13**-TS [leading to **5**] by 2.92 kcal/mol (8.48-5.56 kcal/mol). As regards the thermodynamic product, **5** is now favored because its protonated form (**5H**$^+$) has a relative energy of 0 kcal/mol, whereas the competing product (**4H**$^+$) has an energy of 2.42 kcal/mol. All these figures match completely with the experiments, and show that AM1 calculations are also very successful with orthoesters.

Experimental

The solvents used were dried and purified by the usual methods. The flash chromatography purifications were carried out on silica gel Merck 60, 230-400 mesh. The ir spectra were taken on a Perkin-Elmer 1600 series FTIR. The nmr spectra were recorded on a Brüker AC 300 instrument and the ms on a ZAB-1F spectrometer.

Synthesis of orthoester (8). The bromo lactone (**7**) (55 mg, 0.2 mmol) was mixed with Me_3OBF_4 (80 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) and left for 18 h at 20 °C. The reaction mixture was then cooled to -78 °C, a methanolic solution of NaOMe (50 mg of Na in 2 ml of MeOH) was added and stirred for 1 h before being warmed up to 20 °C. Water (5 ml) was added and the mixture was extracted with ether (3 x 15 ml). The ether phase was dried over K_2CO_3, concentrated *in vacuo* and the residue was purified by flash column chromatography (hexane/EtOAc/NEt_3 = 85/14/1) to give the title compound (**8**) (39 mg, 61%). Ir (film): 2926, 1446, 1067 cm^{-1}. ^{1}H Nmr (CD_3Cl): 3.59 (1H, dd, J = 11 Hz, 4 Hz, C<u>H</u>HO), 3.37 (2H, t, J = 7 Hz, C<u>H</u>$_2$Br),

3.31 (3H, s, OCH_3), 3.26 (1H, t, J = 11 Hz, CHHO), 3.23 (3H, s, OCH_3), 2.05-0.75 (15H, m, CH, CH_2). ^{13}C Nmr (CD_3Cl): 113.94 (CO_3), 68.30 (OCH_2), 50.77 (CH_2Br), 46.86, 43.42 (OCH_3), 41.88, 41.25, 34.26, 31.63, 29.84, 27.44, 26.10, 25.81, 25.50 (CH, CH_2). Ms (m/z): 322, 320 (M^+), 291, 289 (M^+ - OCH_3).

Orthoester (9). A mixture of orthoester (**8**) (321 mg, 1 mmol), KOAc (300 mg, 3 mmol) and 18-crown-6 (300 mg, 1 mmol) in MeCN (10 ml) was stirred for 40 h at 20 °C. Most of the solvent was evaporated and ether (60 ml) was added. The resulting solution was washed with brine (2 x 15 ml), dried over Na_2SO_4-K_2CO_3 (5:1) and concentrated; the residue was purified by flash column chromatography (hexane/EtOAc/NEt_3 = 85/14/1) to yield the title compound (**9**) (243 mg, 90%). Ir (film): 2927, 1740, 1239 cm^{-1}. ^1H Nmr (C_6D_6): 4.03 (2H, t, J = 6.4 Hz, CH_2OAc), 3.44 (1H, dd, J = 11 Hz, 4.4 Hz, CHHO), 3.27 (6H, s, OCH_3), 3.19 (1H, t, J = 11 Hz, CHHO), 1.8-1.7 (4H, m, CH_2), 1.68 (3H, s, $COCH_3$), 1.65-0.95 (11H, m, CH, CH_2). ^{13}C Nmr (C_6D_6): 170.16 (CO), 114.26 (CO_3), 68.28 (CH_2OAc), 65.08 (CH_2O), 50.65, 46.89 (OCH_3), 44.00, 42.37, 41.51, 30.13, 28.02, 27.69, 26.46, 25.84, 20.53 (CH, CH_2, CH_3). Ms (m/z): 300 (M^+), 269 (M^+ - OCH_3).

Orthoester (3). Orthoester (**9**) (20 mg, 0.07 mmol) was hydrolyzed in a mixture of aqueous NaOH (1N, 1 ml) and MeOH (1.5 ml) for 2 h. The crude product was purified by flash column chromatography with silica gel (hexane/EtOAc/NEt_3 = 50/50/1) to yield the title compound (**3**) (16 mg, 92%). Ir (film): 3410, 1447, 1068 cm^{-1}. ^1H Nmr (C_6D_6): 3.55-3.4 (3H, m, CH_2OH, CHHO), 3.30 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.20 (1H, t, J = 11.0 Hz, CHHO), 1.9-0.55 (15H, m, CH, CH_2). ^{13}C Nmr (C_6D_6): 114.49 (CO_3), 68.37 (CH_2OH), 63.20 (OCH_2), 50.71, 46.91 (OCH_3), 44.32, 42.72, 41.61, 32.40, 30.23, 27.74, 26.53, 25.91, 23.80 (CH, CH_2). Ms (m/z): 258 (M^+), 227 (M^+ - OCH_3).

General procedure of hydrolysis. The orthoesters (0.01 mmol) were hydrolyzed in mixtures of deuterated acetonitrile (0.4 ml), deuterium oxide (0.1 ml) and hydrochloric acid (0.1 N, 3 µl) in nmr tubes. The reactions were monitored by ^1H nmr at different times and the product compositions were determined by the ratio of integrations of appropriate ^1H nmr peaks as previously reported.[4]

References and notes

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8 Computational procedure: All the calculations were done at the RHF level. The first input files for MOPAC 6.00 were created by means of SYBYL 6.01 (Tripos Associates, Inc., 16995 Hanley Rd, Suite 303, St. Louis, Missouri 63144-2913) for IBM RS/6000 computers. The gradient norms of these draft structures were then fully optimized using EF or TS subroutines. Finally, all the transition structures were characterized by only one negative force constant.

9 Financial support of this work by NSERCC Ottawa is gratefully acknowledged.

Received, 4th April, 1995