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Reinvestigation of the Synthesis of (2R,3R) 2,3-(Cyclohexylidenedioxy)-4-cyclopentenone as Possible Building Block for the Synthesis of Carbocyclic Nucleosides.

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REINVESTIGATION OF THE SYNTHESIS OF (2R,3R) 2,3-(CYCLO-HEXYLIDENEDIOXY)-4-CYCLOPENTENONE AS POSSIBLE BUILDING BLOCK FOR THE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES.

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ABSTRACT : An in depth study of the four-steps synthesis of (2R,3R) 2,3-(cyclohexylidenedioxy)-4-cyclopentenone (5) from D-ribonolactone (1) is described. From these experiments we must conclude that the overall yield reported in the literature (65%) is overestimated. All compounds have been throughly investigated by ^{1}H- and ^{13}C-NMR spectroscopy.

INTRODUCTION.

In the past years our research group has been involved in the synthesis of a series of nicotinamide-C-nucleosides[1-3] some of them showing mild *in vitro* cytostatic activity against murine leukemia (L1210), human B-lymphoblast (RAJI), human T-lymphoblast (MOLT/4F) and human T-lymphocyte (MT-4) cells[4,5].

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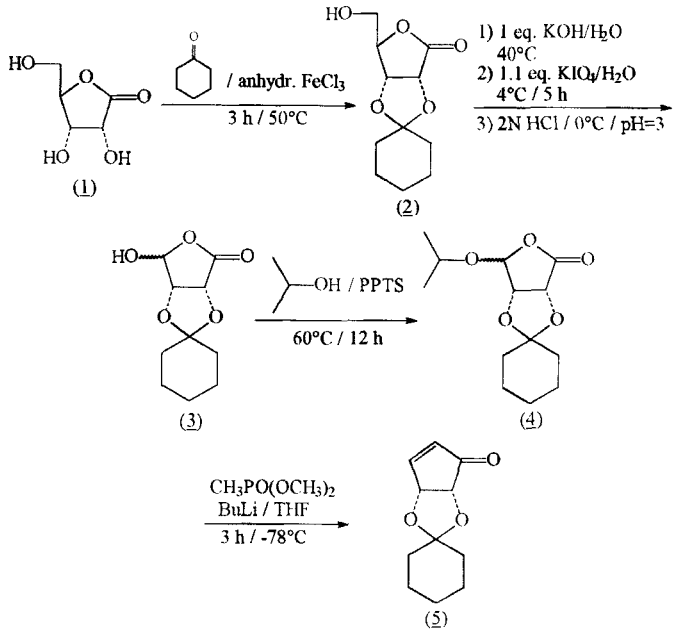
In order to study the effect of structural modifications in the sugar moiety on the biological activity of such compounds several changes have been introduced. An interesting modification, of which ample examples are described in the literature are these nucleosides whereby the traditional D-ribofuranosyl ring was replaced by a 5-membered carbocyclic ring, called carbocyclic nucleosides.

For this purpose the synthesis of (2R,3R) 2,3-(cyclohexylidenedioxy)-4-cyclopentenone (5) was undertaken as possible building block in the synthesis of (1S, 2S, 3R, 4R) 3-carbamoyl-5-(2,3-dihydroxy-4-hydroxymethylcyclopentyl)-pyridine.

RESULTS AND DISCUSSION.

Synthesis of (2R,3R) 2,3-(cyclohexylidenedioxy)-4-cyclopentenone (5).

Cyclopentenone derivatives have enjoyed widespread popularity as precursors to carbocyclic nucleosides. Within these approaches the synthesis of (2R,3R) 2,3-(cyclohexylidenedioxy)-4-cyclopentenone (5) and analogous compounds have been described and ample literature was available[6]. Amongst these, the approach published by Borcherding *et al.*.[7] seemed most convenient because it described a short 4 steps procedure leading to compound 5 in an overall yield of 65%. Although, this procedure was repeated several times by us under carefully controlled conditions, we were not able to reproduce some of the reported yields. Therefore the reactions were reinvestigated, side components were adequately identified and the structures of (2), (3), (4) and (5) were proven by detailed NMR spectroscopy. In SCHEME 1 the different reaction steps are summarized.



SCHEME 1 : *Synthesis of (2R,3R) 2,3-(cyclohexylidenedioxy)-4-cyclopentenone (5) starting from D-ribonolactone (1).*

Treatment of the D-ribonolactone (1) with cyclohexanone in the presence of $FeCl_3$ was done according to the procedure as described by Beer *et al.*[8]

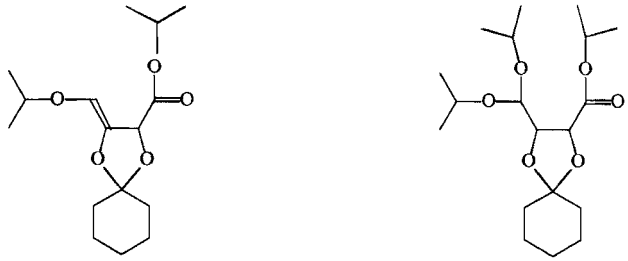
In the next step the sodium salt of compound 2 was treated with $NaIO_4$ for 10 minutes at 4°C[8]. However, no reaction was observed and the starting compound (2) was recovered each time. This was proven by the analysis of the corresponding reaction mixture by desorption chemical ionisation mass spectrometry (DCI-MS) using ammonia as the reagent gas. Each time ions were found at m/z 229 and 246. These correspond to the $[MH]^+$- and $[M+NH_4]^+$-ions of the starting material (2). If reaction

had occured, ions at m/z 215 ($[MH]^+$) and/or 232 ($[M+NH_4]^+$) were expected. A possible explanation of this observation could be the low solubility of the periodate salts ($NaIO_4$, KIO_4) in H_2O at low temperature. However, the solubility of KIO_4 increases in the presence of KOH while the solubility of $NaIO_4$ decreases in the presence of NaOH[9]. In view of this we decided to use a KOH/KIO_4 mixture. This difficulty was also noticed by D.Liu *et al.*[10] who modified this procedure by dissolving the protected D-ribonolactone (2) in dioxane before adding the NaOH solution.

In our methodology a solution of (2) and KOH in H_2O was stirred for 15 minutes at 40°C. Then an ice cooled suspension of 1 eq. KIO_4 in H_2O was added. The mixture was stirred at 4°C and aliquots were taken and analysed by DCI-MS. It was noticed that after 4 hours most of the starting material had disappeared. Further prolongation of the reaction time had no noticeable effect. If the reaction was repeated but using 1.1 eq. KIO_4 no starting material could be detected.

We also want to emphasize that we observed that careful control of the pH was a prerequisite in order to obtain compound (3) in a good yield. Therefore, in addition to the work-up procedure of Beer *et al.* [8] the pH of the aqueous layer was controlled after each extraction and if neccessary acidified to pH 3 with 2N HCl[11]. After evaporation of the solvent compound 3 was isolated as an oil in 85% yield.

One of the methodologies described in the literature for the synthesis of compound 4 was refluxing the L-erythruronolactone (3) in dry 2-propanol in the presence of a catalytic amount of pyridinium p-toluenesulfonate for 1.5 hours[7]. If the reaction was performed under these conditions and the crude reaction mixture (80/20



(7) (6)

FIGURE 1 : *Structures of the side products (6) and (7).*

CH_3OH/NH_4OAc) was analysed by electrospray mass spectrometry (ES-MS) four significant ions : m/z 257, 274, 299 and 376 were detected. The ions at m/z 257 and 274 correspond to the protonated molecule $[MH]^+$ and the $[M+NH_4]^+$-ion respectively of compound (4). Ions at m/z 376 and 299 were assigned to side products (6) and (7) as depicted in figure 1.

The ion at m/z 376 points to the presence of structure (6) and can be explained by its $[M+NH_4]^+$-ion. A product ion scan of m/z 376 gave ions at m/z 299 and 215. These were additional proof of structure (6) because they can be explained by the loss of 1 molecule of isopropanol followed by the loss of 2 molecules isopropene.

The detection of m/z 299 in the ES-MS spectrum of the mixture suggests also the presence of compound (7).

As a result of these analysis we decided to start a more detailed study of the formation of compound 4 in an attempt to avoid the formation of the side compounds described. Therefore, the reaction conditions were changed in terms of temperature and reaction time. First, the reaction was carried out at reflux temperature and aliquots were taken

TABLE 1 : *Gas chromatographic results (3% carbowax 20 M op CHROMOSORB G HP 100/120 mesh, 3 m x 3 mm - 216°C / 15 min) of the synthesis of 2,3-(cyclohexylidenedioxy)-4-hydroxy-4-(2-propyloxy)--butyrolactone (4) at different temperatures and reaction times.*

temp.	time (h)	4 (%)	side products (%)		yield of 4 (%)
reflux	5 min.	79.7	7.1	10.7	
	0.5	81.3	13.0	3.7	
	1	74.5	20.8	2.6	
	1.5	67.6	27.8	2.4	30-35
	3	53.6	42.6	1.8	
60°C	2.5	80.4	8.5	10.6	23.3
	6	86.3	9.3	4.1	29.0
	12	70.3	29.1	---	49.5

after 5, 30, 60, 90 and 180 minutes. Second, the reaction was performed at 60°C and stopped after 2.5, 6 and 12 hours. All these reaction mixtures were then analysed by GC (3% carbowax 20 M on CHROMOSORB G HP 100/120 mesh, 3 m x 3 mm - 216°C / 15 min). The results are summarized in Table 1. The gas chromatogram showed three compounds with retention times of 2.9, 5.1 and 11.0 minutes. On the basis of the NMR results the compound at t_R 5.1 minutes was identified as the butyrolactone (4).

Since the starting material (3) was not eluting from the Carbowax column, the data presented in column 3 and 4 of Table 1 represent the ratio between the formed protected lactone (4) and the side products.

In column 5 the yields are reported obtained after purification of the reaction mixture and isolation of the compound by by column chromatography.

In view of the results summarized in Table 1 we could conclude that at reflux temperature the total amount of side products increased with prolonged reaction time from 7.1 and 10.7 to 42.6 and 1.8 % respectively. The best results were obtained if the reaction mixture was stirred for 12 hours at 60°C. However, the occurrence of one side product could never be completely avoided. Therefore purification of the reaction mixture was necessary. This was done by column chromatography (see experimental). After evaporation pure (97%) 2,3-(cyclohexylidenedioxy)-4-hydroxy-4-(2-propyloxy)-butyrolactone (4) was obtained in 49.5% yield.

Independently from us, Hudlicky[12] and co-workers found that the conversion of (3) to (4) was optimal when the hydroxylactone (3) was stirred in isopropanol with pyridinium p-toluenesulfonate at room temperature for 1 week. They also mentioned the presence of a side component which was separated by column chromatography. The yield (41-51%) they obtained was in good agreement with ours. The structure of the side product was suggested to be analogous to compound (6) (see Figure 1) but no definitive prove was given.

The reaction conditions for the Wittig transformation of (4) to (5) were unchanged and the results were satisfactory in spite of the somewhat lower yield : 66% versus 80%. In 1992 we reported[13] that the yield of (5) as published by Borcherding *et. al* [7] was not reproducible. This was confirmed by these authors in a publication which appeared in the same year[14]. Yields were reported between 35-50%, also by other laboratories[12,15].

We cannot account for this discrepancy but we suspect that the yields obtained by us are higher because of the intensive purification of the starting material (4) which is a prerequisite in organolithium reactions as often was experienced in our laboratory.

NMR results of compounds (2), (3), (4) and (5).

Structure identification of all the synthesised compounds was done by 400 MHz ^{1}H-NMR spectroscopy and 100 MHz ^{13}C-NMR spectroscopy. All the products were recorded in $CDCl_3$ with TMS as internal standard and the results are summarized in TABLES 2,3 and 4[1].

For the compounds (4) and (5) no ^{13}C-NMR data were available in the literature. The ^{1}H- and ^{13}C-NMR data of compounds (2) and (3) were already reported but without assignments. With the aid of homonuclear nuclear Overhauser enhancement (NOE) experiments and 2-D-NMR spectroscopy some additional information was gathered and we were able to assign all the signals unambiguously.

For compound (2) the assignment of the H-2 - H-3 - and H-4 signals was based on coupling constants and nuclear Overhauser enhancement (NOE) experiments.

Although, the coupling constants observed for the lactone protons in compound 2 were in good agreement with the coupling constants found in D-ribonolactone (1)[16,17] the correct assignment of H-2 and H-3 was difficult on the basis of this constants because

[1]The numbering of the atoms of the lactone ring in 3 are reversed with respect to D-ribonolactone. In "uronic acids" (and "uronolactones") the carbon atom of the (potential) aldehydic carbonyl group, and not that of the carboxyl group, must give number 1. To avoid confusion by comparison the NMR-data of compound (3) with the compounds (2) and (4) we haven't used this numbering system in the NMR spectra.

TABLE 2 :*400 MHz ^{1}H-NMR data of (2), (3), (4) and (5) : δ-values in ppm.*

	2	3	4	5
H-2	4.78 (d)	4.95 (d)	4.81 (d)	4.45 (dt)
H-3	4.83 (d)	4.60 (br s)	4.52 (d)	5.26 (ddd)
H-4	4.64 (t)	5.78 (br s)	5.55 (s)	7.61 (ddd)
H-5	---	---	---	6.19 (ddd)
CH'H"OH	3.99 (br d)	---	---	---
CH'H"OH	3.82 (br d)	---		---
H-7				
H-8	1.55 -	1.55 -	1.25 -	1.60 (m)
H-10	1.70 (m)	1.65 (m)		
H-11			1.59 (m)	
H-9	1.41 (m)	1.35 (m)		1.45 (m)
CH'H"OH	2.23 (br s)	7.00 (br s)	---	---
$(CH_3)_2$CHO-	---	---	1.20 (d) and 1.24 (d)	---
$(CH_3)_2$CHO-	---	---	4.03 (h)	---

TABLE 3 : *400 MHz ^{1}H-NMR data of (2), (3), (4) and (5) : coupling constants in Hz.*

	2	3	4	5
$J_{2,3}$	5.6	5.5	5.5	5.4
$J_{2,4}$	---	---	---	0.4
$J_{2,5}$	---	---	---	0.4
$J_{3,4}$	a	a	---	2.3
$J_{3,5}$	---	---	---	0.7
$J_{4,H'}$	2.1	---	---	---
$J_{4,H"}$	2.1	---	---	---
$J_{4,5}$	---	---	---	6.0
$J_{H',H"}$	- 12.7	---	---	---
$J_{CH3,CH3}$	---	---	6.2	---

a : could not be determined.

TABLE 4 : *^{13}C-NMR data of (2), (3), (4) and (5) : δ-values in ppm.*

	2	3	4	5
C-1	175.6	174.4	173.9	203.1
C-2	75.3	74.4	72.5	76.2
C-3	77.8	79.6	74.4	78.3
C-4	83.3	99.4	79.5	159.7
C-5	---	---	---	134.2
CH'H"OH	61.8	---	---	---
C-6	113.8	115.3	115.0	116.4
C-7	36.4 (a)	36.3 (a)	36.4 (a)	37.2 (a)
C-8	23.9 (b)	23.8 (b)	23.9 (b)	23.8 (b)
C-9	24.8	24.7	24.8	24.9
C-10	23.8 (c)	23.6 (c)	23.8 (c)	23.6 (c)
C-11	34.9 (d)	35.1 (d)	35.3 (d)	35.7 (d)
$(CH_3)_2CHO$-	---	---	23.1 and 21.4	---
$(CH_3)_2CHO$-	---	---	102.7	---

(a) and (d) can exchange.
(b) and (c) can exchange.

H-3 appear as a pseudo-doublet. This was also observed in the 2D-COSY-spectrum, where no cross peaks could be detected between H-3 and H-4.

The very small value of $^3J_{3,4}$ as well as the small values of $^3J_{4,H'}$ and $^3J_{4,H''}$ were explained by Horton and Walaszek[16] by the existence of a conformational equilibrium between the two envelope forms ^3E and E_3.

However, with the aid of NOE-experiments it was possible to distinghuish H-2 and H-3. Saturation of H-4 resulted in a 3 times greater NOE-effect for the signal at 4.83 ppm than for the signal at 4.78 ppm. Furthermore, saturation of H' also caused a 4 times greater NOE-effect on the signal at 4.83 ppm than on the signal at 4.78 ppm.

Therefore, the signal at δ = 4.83 ppm was assigned to H-3 and the signal at δ = 4.78 ppm to H-2.

These results were in contrast with a previous postulation. For D-ribonolactone (1)[16], 2,3-O-isopropylidene-D-ribonolactone[18] as well as for some 2',3'-O-isopropylidene-D-ribofuranosyl nucleosides[5] a *chemical* shift order δ(H-2) > δ(H-3) was assumed.

The assignment of the lactone carbon atoms of compound (2) was done on the basis of the 2D-HETCOR-spectrum and found to be :

$$\delta(\text{C-4}) > \delta(\text{C-3}) > \delta(\text{C-2}) >> \delta(\text{CH}_2\text{OH}).$$

Also here the sequence of C-2 and C-3 appeared to be reversed with respect to D-ribonolactone (1)[16,19] .

Because of the broadening of the lactone signals in compound (3) it was difficult to assign H-2, H-3 and H-4 on the basis of the coupling constants. Only the signal at δ = 4.95 ppm appeared as a doublet, the other two signals at δ = 4.60 ppm and δ = 5.78 ppm were broad singlets. The 2D-COSY spectrum gave no additional information and Nuclear Overhauser enhancement (NOE) experiments were in this case difficult because of the broadening of the signals.

In the ^{1}H-NMR spectrum of 4 H-2 and H-3 appeared as doublets. Because of the absence of a coupling between H-3 and H-4, H-4 appeared as a sharp singlet. The protons H-2 and H-3 were assigned unambiguous by the aid of nuclear Overhauser enhancement (NOE) experiments. When H-4 (δ= 5.55 ppm) was irradiated the signal at 4.52 ppm experienced a greater NOE-effect than the signal at 4.81 ppm (almost 10

TABLE 5:

D-ribonolactone (1)	δ(H-2) > δ(H-3)	δ(C-2) > δ(C-3)
compound (2)	δ(H-2)< δ(H-3)	δ(C-2)< δ(C-3)
compound (3)	δ(H-2) > δ(H-3)	δ(C-2) < δ(C-3)
compound (4)	δ(H-2) > δ(H-3)	δ(C-2)< δ(C-3)

times more), or δ(H-2) = 4.81 ppm and δ(H-3) = 4.52 ppm. This is the reverse compared to compound (2).

On the other hand, we observed in the 2D-HETCOR-spectrum of 4 that the sequence of C-2 and C-3 was analogous to the sequence in (2) or : δ(C-3) > δ(C-2).

Because the *chemical shift* values for H-2 and H-3 were nearly the same in compounds (3) and (4) we may assume that the assignment of H-2 and H-3 be similar in both compounds.

For compound (5) the assignment of H-2 (4.45 ppm) and H-3 (5.26 ppm) was more easy than in the previous compounds (2), (3) and (4). In this case the assignment could be done on basis of the coupling constants (Table 3). The signal at δ = 5.26 ppm (H-3) has a coupling constant of 2.3 Hz with H-4, while the signal at δ = 4.45 ppm (H-2) only has a longe-range coupling of 0.4 Hz with H-4.

The assignment of C-2, C-3, C-4 and C-5 was also done in analogy with compound (2) and checked by 2D-HETCOR-spectroscopy (see Table 4).

On the basis of this results we could conclude (see Table 5) that for compound (2) the assignment of H-2 and H-3 as well as the assignment of C-2 and C-3 were reversed with respect to previous postulation for D-ribonolactone or its derivatives. For compound (3) and (4) the assignment of H-2 and H-3 was analogous with D-ribonolactone but the assignments of C-2 and C-3 was the same as in compound (2).

Conclusion.

We can conclude that the synthesis of the enone (5) can be accomplished by the investigated 4-steps synthesis. However, the yields as reported by Borcherding *et al.* were overestimated. Therefore, we explored a more efficient strategie for the synthesis of an appropriate cyclopentenone derivative starting from 3,4-epoxycyclopentene which will be reported in the near future[20].

EXPERIMENTAL.

General methods : ^{1}H-NMR spectra were recorded on a VARIAN-UNITY 400 spectrometer (400 MHz). ^{13}C-NMR spectra were recorded on a Jeol JNM PFT-PS-100 spectrometer (25 MHz) connected to a TI-980 B computer system or on the Varian spectrometer. The 2D-spectra and the NOE experiments were also recorded on a VARIAN-UNITY 400 spectrometer (400MHz). All the NMR spectra were recorded in $CDCl_3$ with TMS as internal reference. DCI-mass spectra were run on a Ribermag-10-10B (Nermag S.A.) quadrupole mass spectrometer equipped with a SIDAR data system. Primary ionisation of the reagent gas (NH_3) was performed by 70 eV electrons.

The ionisation current was 0.08 mA and the pressure in the ion source was 0.1 mm Hg. (+)-Electrospray mass spectra were recorded on a VG Quattro II triple-quadrupole mass spectrometer (Micromass, Manchester, UK) consisting of a Model 325 pump. MS/MS spectra were performed with 3.10^{-3} mbar Ar in the collision cell at a collision energy of 20 eV.

Reactions involving organometallic reagents were performed in oven-dried glassware under a dry N_2 atmosphere. 2-Propanol was dried under reflux for several hours over CaO and was destillated prior to use. THF was dried by distillation from sodium/benzophenone ketyl prior to use. Pyridinium p-toluenesulfonate was prepared by adding 1 mol of p-toluenesulfonic acid to 1 mol of pyridine (mp =114-116°C).

D-Ribonolactone (1) was purchased from Aldrich (Bornem, Belgium), BuLi (1.6 M in hexane) from Janssen Chimica (Beerse, Belgium) and Kieselgel 60, particle size 0.040-0.063 mm (230-400 mesh ASTM) from Merck (Belgolabo, Overijse, Belgium).

Synthesis.

2,3-O-cyclohexylidene-D-ribonolactone (2).

6 g D-ribonolactone (1) was added to a solution of 120 ml freshly distilled cyclohexanone, 300 mg anhydrous $FeCl_3$ and 9 g Drierite (10-20 mesh, Janssen Chimica). Stirring was continued for 3 h at 50°C. The reaction mixture was cooled with an ice-bath, stirred for 10 min with 1.2 g $Na_2CO_3.10H_2O$ and 3 g charcoal, filtered through a Celite filter and evaporated. The residue was evaporated 3 times with 100 ml H_2O and then extracted with ethyl acetate. After evaporation a dark red oil was obtained which after lyophilization was purified by crystallization from CH_2Cl_2/hexane (1/1) : mp = 127°C (yield 60%).

^{1}H-NMR ($CDCl_3$) δ 1.41 (2H, m, H-9), 1.55-1.70 (8H, m, H-7/H-8/H-10/H-11), 2.23 (1H, br s, CH'H'OH), 3.82 (1H, br d, CH'H'OH, $J_{H',H'}$= -12.7 Hz, $J_{H',4}$= 2.1 Hz), 3.99 (1H, br d, CH'H'OH, $J_{H',4}$= 2.1 Hz), 4.64 (1H, t, H-4), 4.78 (1H, d, H-2, $J_{2,3}$= 5.6 Hz), 4.83 (1H, d, H-3).

^{13}C-NMR ($CDCl_3$) δ 23.9 and 23.8 (C-8, C-10), 24.8 (C-9), 34.9 and 36.4 (C-7 ,C-11), 61.8 (CH_2OH), 75.3 (C-2), 77.8 (C-3), 83.3 (C-4), 113.8 (C-6), 175.6 (C-1).

DCI-mass spectrometry (NH_3) : m/z 246 ($[M+NH_4]^+$, 100%), m/z 229 ($[MH]^+$, 19.7%).

2,3-O-cyclohexylidene-L-erythruronolactone (3).

1.5 g (6.58 mmol) 2,3-O-cyclohexylidenedioxy-D-ribonolactone (2) was stirred for 15 min in a solution of 0.44 g (7.90 mmol) KOH and 15 ml H_2O at 40°C. An ice cooled suspension of 1.66 g (7.24 mmol) KIO_4 and 10 ml H_2O was added and the mixture was stirred at 4°C. After 5 h was added 0.5 g $BaCl_2.10H_2O$ in 5 ml H_2O and the white precipitate was filtered through a Celite filter. The filtrate was acidified to pH 3 with 2N HCl at 0°C and extracted several times with ethyl acetate. After each extraction the pH was controlled and again acidified to pH 3. The combined ethyl acetate layers were dried over $MgSO_4$ and evaporated on a rotatory evaporator leaving a white precipitate. The crude L-erythruronolactone (3) was isolated in 85% (1.20 g) yield and used in the next step without any futher purification[2].

[2]It was hard to crystallize the compound by us. However, ^{1}H-NMR analysis of the uncrystallized product had showed that it was pure enough to be used in the following reaction step, and as such no further attempts were made to crystallize the compound.

^{1}H-NMR ($CDCl_3$) δ 1.35 (2H, m, H-9), 1.55-1.65 (8H, m, H-7/H-8/H-10/H-11), 4.60 (1H, br s, H-3), 4.95 (1H, d, H-2, $J_{2,3}$= 5.5 Hz), 5.78 (1H, br s, H-4), 7.00 (1H, br s, HO-C-4).

^{13}C-NMR ($CDCl_3$) δ : 23.6 and 23.8 (C-8, C-10), 24.7 (C-9), 35.1 and 36.3 (C-7, C-11), 74.4 (C-2), 79.6 (C-3), 99.4 (C-4), 115.3 (C-6), 174.4 (C-1).

DCI-mass spectrometry (NH_3) : m/z 232 ($[M+NH_4]^+$,100%), m/z 215 ($[MH]^+$, 22.2%).

2,3-(cyclohexylidenedioxy)-4-hydroxy-4-(2-propyloxy)-butyrolactone (4).

The L-erythruronolactone (3) (5 g, 23.4 mmol) and a catalytic amount of pyridinium p-toluenesulfonate (0.6 g, 2.34 mmol) were dissolved in 250 ml of dry 2-propanol and stirred for 12 h at 60°C. The solution was concentrated in vacuo to a syrup, which was then dissolved in 250 ml diethyl ether, extracted with H_20, dried over $MgSO_4$ and filtered. The filtrate was evaporated leaving a yellow oil which was purified by column chromatography on silica (Kieselgel 60, 230-400 mesh, 55cm x 20mm I.D., hexane/diethyl ether (85/15)).The eluant was collected in 3ml fractions and the fractions were analysed by GLC (3% Carbowax 20 M on CHROMOSORB G HP 100/120 mesh, 3m x 3mm, 8min., 216°C). Compound 4 eluted after a volume of ca. 135 ml. After evaporation of the solvent compound 4 was collected as a yellow oil (2.96 g, 49.5%).

^{1}H-NMR ($CDCl_3$) δ 1.20 and 1.24 (6H, 2d, $(CH_3)_2CHO$-, J= 6.2 Hz), 1.25-1.59 (10H, m. cyclohexyl), 4.03 (1H, heptet, $(CH_3)_2CHO$-), 4.52 (1H, d, H-3, $J_{3,2}$= 5.5 Hz), 4.81 (1H, d, H-2), 5.55 (1H, s, H-4).

^{13}C-NMR ($CDCl_3$) δ 21.4 and 23.1 ($\underline{C}H_3)_2CHO$-), 23.8 and 23.9 (C-8, C-10), 24.8 (C-9), 35.3 and 36.4 (C-7, C-11), 72.5 (C-2), 74.4 (C-3), 79.5 (C-4), 102.7 ($(CH_3)_2\underline{C}HO$), 115.0 (C-6), 173.9 (C-1).

Mass spectrometry : see discussion.

2,3-(cyclohexylidenedioxy)-4-cyclopentenone (5).

In a three-necked flask equipped with a magnetic stirrer, a N_2 inlet tube, a dropping funnel with a $CaCl_2$-tube and a septum was added 1.97 g (15.56 mmol) of dimethyl[3] methylphosphonate and 100 ml dry THF. The phosphonate solution was cooled to -78°C with an acetone/dry ice bath and after 15 min was added via the septum dropwise 9.71 ml (15.56 mmol), precooled at -20°C, BuLi (1.6 M in hexane). Stirring was continued for 15 min at -78°C. A solution of 4 g (15.62 mmol) of compound (4) in 13 ml dry THF was added rapidly via the dropping funnel. The solution was than stirred for 3 h at -78°C after which the dry ice bath was removed and the solution was allowed to warm up to room temperature within 1 h. Then, the reaction mixture was poured into a solution of 250 ml of diethyl ether and 50 ml H_2O, shaken and the organic layer was separated. The aqueous layer was extracted with diethyl ether and the organic layers were combined, washed with a saturated NaCl-solution, dried over $MgSO_4$, filtered and evaporated (<50°C). The oil was purified by chromatography on silica (Kieselgel 60, 230-400 mesh, 20cm x 15mm I.D., hexane/diethyl ether (2/8)) to give 2.0 g (66%) of a colorless oil.

[3]The dimethyl methylphosphonate reagent was prepared by refluxing trimethyl phosphite with a trace iodomethane for 3 hours and the phosphonate was purified by fractional distillation[21,22].

^{1}H-NMR ($CDCl_3$) δ 1.45 (2H, m, H-9), 1.60 (8H, m, H-7/H-8/H-10/H-11), 4.45 (1H, dt, H-2, $J_{2,3}$= 5.4 Hz, $J_{2,4}$= 0.4 Hz, $J_{2,5}$= 0.4 Hz), 5.26 (1H, ddd, H-3, $J_{3,4}$= 2.3 Hz, $J_{3,5}$= 0.7 Hz), 6.19 (1H, ddd, H-5, $J_{5,4}$= 6.0 Hz), 7.61 (1H, ddd, H-4).

^{13}C-NMR ($CDCl_3$) δ 23.6 and 23.8 (C-8, C-10), 24.9 (C-9), 35.7 and 37.2 (C-7, C-11), 76.2 (C-2), 78.3 (C-3), 116.4 (C-6), 134.2 (C-5), 159.7 (C-4), 203.1 (C-1).

DCI-mass spectrometry (NH_3) : m/z 212 ($[M+NH_4]^+$, 100%), m/z 195 ($[MH]^+$, 16.5%).

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