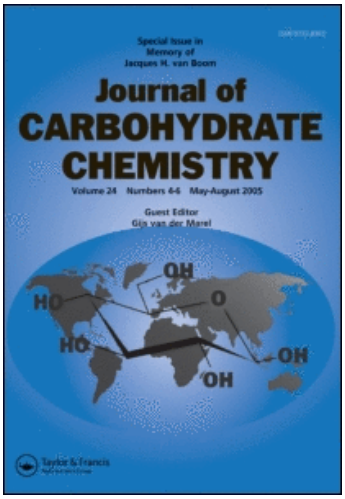

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthetic, Fungicidal Unsaturated-γ-lactones Attached to Furanosidic Systems. Configurational Determination by Nuclear Overhauser Effect[1]

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To cite this Article Rauter, A. P. , Ferreira, M. J. , Font, J. , Virgili, A. , Figueredo, M. , Figueiredo, J. A. , Ismael, M. I. and Canda, T. L.(1995) 'Synthetic, Fungicidal Unsaturated-γ-lactones Attached to Furanosidic Systems. Configurational Determination by Nuclear Overhauser Effect[1]', Journal of Carbohydrate Chemistry, 14: 7, 929 — 948

To link to this Article: DOI: 10.1080/07328309508005386

URL: http://dx.doi.org/10.1080/07328309508005386

J. CARBOHYDRATE CHEMISTRY, 14(7), 929–948 (1995)

SYNTHETIC, FUNGICIDAL UNSATURATED-γ-LACTONES ATTACHED TO FURANOSIDIC SYSTEMS. CONFIGURATIONAL DETERMINATION BY NUCLEAR OVERHAUSER EFFECT[1]

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Received September 19, 1994 - Final Form April 25, 1995

ABSTRACT

Stereoselective synthesis of a butenolide sugar derivative was possible by reaction of the appropriate sugar epoxide with the dilithium salt of phenylselenoacetic acid, followed by oxidation of the α-phenylselenobutanolide obtained with hydrogen peroxide in the presence of catalytic amounts of acetic acid. On the other hand, synthesis of an exocyclic α,β-unsaturated lactone was accomplished by Reformatsky reaction on the appropriate sugar carbonyl groups with ethyl bromomethylacrylate and activated zinc, leading to the introduction of this ring at position 2 or 4 of a furanose ring. Nuclear Overhauser effect studies led to the unambiguous determination of the configuration of the new chiral centre formed by the Reformatsky reaction. The fungicidal efficacy of some unsaturated lactone sugar derivatives is given.

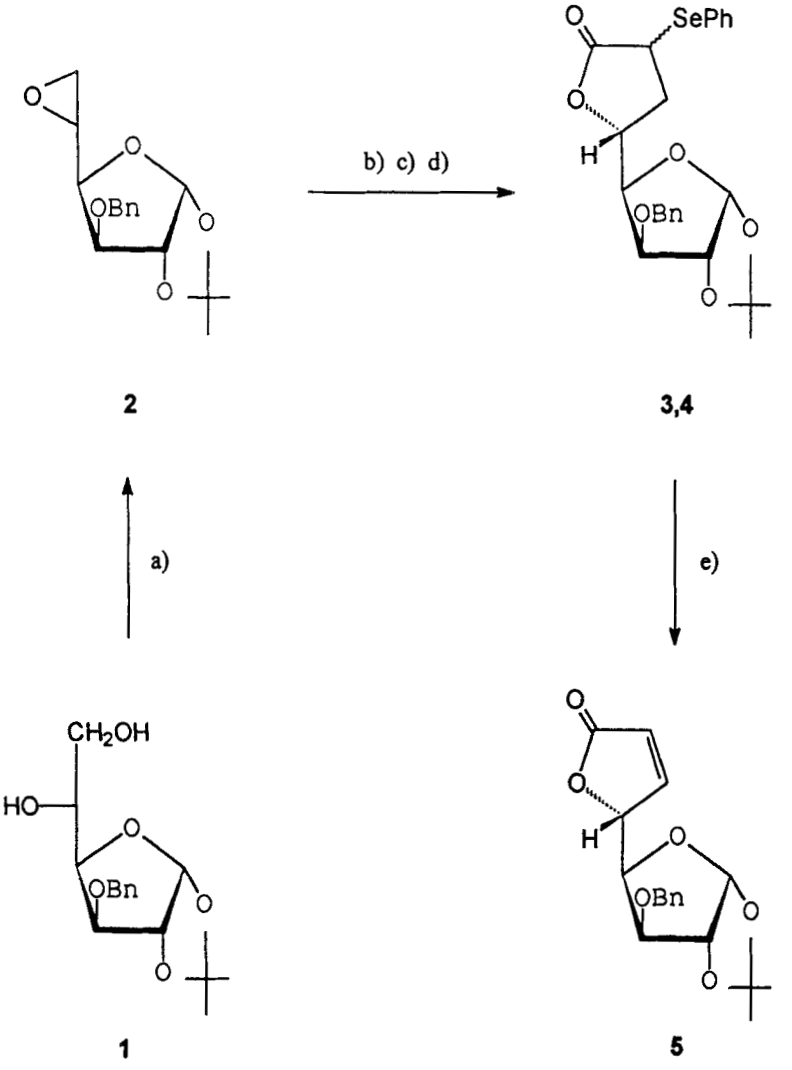
INTRODUCTION

In a previous publication,[2] we reported the synthesis of the sugar derivatives **8**, **9**, **15** and **16**, which contain the α-methylene-γ-lactone moiety in order to study their structure/bioactivity relationship. This structural unit is known to confer a great diversity of bioactivities in naturally occurring sesquiterpenes, some of which possess, among others, antitumor or fungicidal activities. Only a few other sugar derivatives containing this structural feature are described in the literature, among these are a monocyclic derivative synthesized from D-xylose,[3] a bicyclic derivative obtained from D-galactose[4] and a tricyclic derivative prepared from a hexofuranose derivative.[5]

In order to investigate the bioactivity of the previously synthesized compounds, their antitumor activity[6] was tested as well as their fungicidal efficacy.[7] Although these compounds did not show any particularly interesting antitumor activity against Leukemia (3PS31) in rats, they presented considerable fungicidal efficacy against *Botrytis cinerea*, *Plasmopara viticola* (a plant pathogen of commercial interest) and *Puccinia recondita*, thus controlling to some extent grey mould on green pepper leaves, downy mildew on grape wine and brown rust on wheat. These results encouraged us to synthesize new related derivatives in order to be able to correlate their structure, including stereochemistry, with the fungicidal efficacy.

RESULTS AND DISCUSSION

Synthesis of compound **5** was accomplished in two steps, following the procedure previously described by Font et al.[1] Reaction of the epoxide **2** with the dilithium salt of phenylselenoacetic acid, obtained by its treatment with lithium diisopropylamide in tetrahydrofuran at 0 °C, followed by overnight reflux with a saturated ammonium chloride solution afforded a complex mixture, from which the expected epimeric α-phenylselenobutanolides **3** and **4** were isolated in 25% yield. Lactonization of recovered hydroxy acid by heating it in benzene under reflux in the presence of a trace of *p*-toluenesulfonic acid, allowed the recovery of an additional 17.5% of the corresponding butanolides. The overall yield was thus 42.5% (Scheme 1).



a) DEAD, Ph_3P, benzene, reflux, 72% yield. b) $PhSeCH_2COOH$, LDA, THF, 0 °C.
c) NH_4Cl/H_2O, reflux, 25% yield. d) Benzene/*p*-TsOH, reflux, 17.5% yield.
e) H_2O_2 30%, CH_3COOH (cat.), 0 °C, 75% yield.

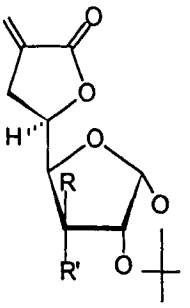
Scheme 1

Treatment of the epimeric mixture of **3** and **4** with hydrogen peroxide in the presence of catalytic amounts of acetic acid at 0 °C afforded the butenolide derivative **5** in 75% yield. This methodology constitutes an important approach to the stereoselective synthesis of new potentially fungitoxic carbohydrates embodying endocyclic unsaturated lactone functionality; the configuration of the single diastereomer produced is determined by that of the epoxide starting material.

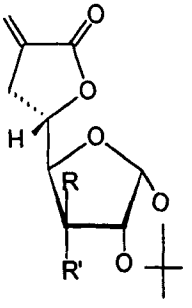
Synthesis of the epoxide **2** was accomplished in 72% yield by a Mitsunobu reaction[9] of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**)[10] with diethyl azodicarboxylate and triphenylphosphine.

The new derivatives **6**, **7**, **11** and **12** (Scheme 2) containing an exocyclic α,β-unsaturated lactone were prepared in moderate yields by Reformatsky reaction of the appropriate carbonyl compounds with ethyl bromomethylacrylate and activated zinc, following the procedure previously reported[2] to give compounds **8**, **9** and **15** - **17**. The starting materials used were 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose (**10**)[11] and the ketosugar **13**, which was synthesized by oxidation of methyl 3,5-*O*-isopropylidene-α-D-xylofuranoside (**14**)[3] with pyridinium chlorochromate /molecular sieves 4Å, in 81% yield. In the first case, the expected epimeric compounds **6** and **7** were isolated in 50% and 28% yields, respectively. In the second case, spirolactones **11** and **12** were isolated in 35% and 60% yields, respectively, from **13**. The formation of **12** is due to the influence of the acidic workup conditions, which hydrolysed the isopropylidene group. This compound will help us to determine the influence of polarity on fungicidal efficacy. To confirm the proposed structure, **11** was submitted to acid hydrolysis leading to formation of the expected derivative **12**. Physical and spectroscopic data for these compounds are given in Tables 1, 2, 3 and 4.

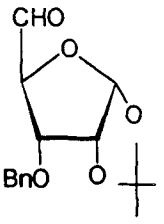
In this work, we report the elucidation by means of the nuclear Overhauser effect (NOE) of the stereochemistry of the new chiral centres formed in the Reformatsky reaction, which under the conditions used affords a mixture of two epimeric lactones. Assignment of stereochemistry is important, in order to determine its influence on bioactivity. Also the stereochemistry previously given[2] for lactones **8**, **9**, **15** and **16** is revised. NOE measurements for compounds **6** and **7** led to the conclusion that



6 R=H, R'=OBn
8 R=OBn, R'=H



7 R=H, R'=OBn
9 R=OBn, R'=H



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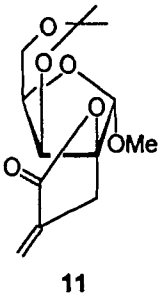

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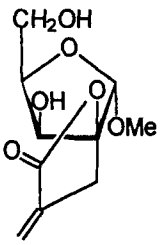

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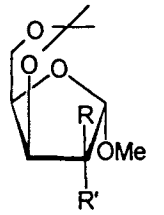
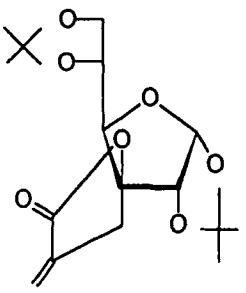


13 R, R'=O
14 R=H, R'=OH



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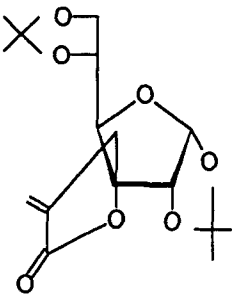

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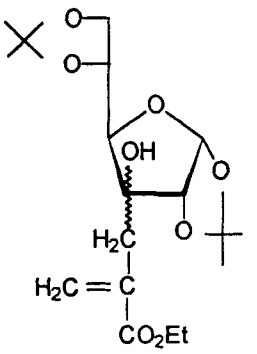

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Scheme 2

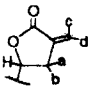
Table 1. Yield, Physical Properties, IR Spectra and Elemental Analysis for Compounds **6**, **7**, **11** and **12**.

Compound	Yield %	R_f^a	$[\alpha]_D^{20}$ ($CHCl_3$)	mp. (°C)	IR (cm^{-1})	Elemental Analysis Calcd	Found
6	28	0.62	+55[b] (*c* 2)	82-84	1760[c] (C=O) 1670 (C=C)	C 65.88 H 6.40	65.62 6.41
7	50	0.66	+165[b] (*c* 1)	94-96	1750[c] (C=O) 1660 (C=C)	C 65.88 H 6.40	65.79 6.36
11	35	0.48	+87.8 (*c* 1.6)	139-141	1775[d] (C=O) 1669 (C=C)	C 57.75 H 6.72	57.30 6.68
12	60	0.36[e]	+94.8 (*c* 2)	101-102	1776[d] (C=O) 1667 (C=C) 3499 (OH)	C 52.17 H 6.13	51.99 6.37

a. 1:1 Ethyl acetate/toluene. b. θ = 25 °C. c. KBr. d. Chloroform. e. Ethyl acetate.

configuration at C-5 is *R* in **6** and *S* in **7**. A staggered arrangement of groups attached to C-4/C-5 bond is revealed by this method (see Tables 2, 3 and Scheme 3), together with examination of the corresponding models. The coupling constants observed, $J_{4,5}$ = 2.2 and 2.4 Hz for **6** and **7**, respectively (Table 3), indicate that the H-4 C-4 C-5 H-5 dihedral angles have values that are slightly larger than 60° or slightly less than 120° from the Karplus equation. The latter angle is unlikely because substituents would be close to

Table 2. ^{1}H NMR Spectroscopic Data - Chemical Shifts (δ in ppm) for Compounds **5**, **6**, **7**, **8**, **9**, **11**, **12**, **15** and **16**.

Cpd. No.	H-1	H-2	H-3	H-4	H-5	Ph	CH_2 Ph	Others, 
5[e]	5.92 d	4.63 d	4.15 d	3.97 dd	5.30 dd	7.33 m	4.73-4.65 m	H-6, 7.71, dd H-7, 6.15, dd CH_3 isop., 1.29, s CH_3 isop., 1.43, s
6[f]	5.79 d	4.84 t	3.80 dd	4.24 dd	4.78 ddd	7.40-7.30 m	4.74, 4.53 AB syst.	H-a, 2.93, m H-b, 2.93, m H-c, 6.04, t H-d, 5.61, t CH_3 isop., 1.32, s CH_3 isop., 1.50, s
7[f]	5.72 d	4.83 t	3.97 dd	4.05 dd	4.72 ddd	7.45-7.30 m	4.77, 4.61 AB syst.	H-a, 3.14, m H-b, 2.97, m H-c, 6.02, t H-d, 5.63, t CH_3 isop., 1.33, s CH_3 isop., 1.52, s
8[f]	5.92 d	4.78 d	4.10 d	4.28 dd	4.87 ddd	7.40-7.30 m	4.76, 4.62 AB syst.	H-a, 3.06, m H-b, 3.06, m H-c, 6.05, t H-d, 5.65, t CH_3 isop., 1.25, s CH_3 isop., 1.43, s
9[f]	5.96 d	4.82 d	4.15 d	4.26 dd	4.74 ddd	7.40-7.30 m	4.75, 4.56 AB syst.	H-a, 3.08, m H-b, 2.78, m H-c, 6.04, t H-d, 5.61, t CH_3 isop., 1.28, s CH_3 isop., 1.42, s

(continued)

Table 2. ^{1} H NMR Spectroscopic Data - Chemical Shifts (δ in ppm) (Cont.).

Cpd. No.	H-1	H-2	H-3	H-4	H-5	Ph	CH_2 Ph	Others
11[e]	5.22 s	-	4.07 d	4.00 m	3.97 Part A AB syst.	-	-	H-5', 3.90, Part B - AB syst. OCH_3, 3.46, s H-a, 3.41, dt H-b, 2.56, dt H-c, 6.26, t H-d, 5.70, t CH_3 isop., 1.38, s CH_3 isop., 1.43, s
12[e]	4.85 s	-	4.40 dd	4.18 dt	3.94 dt	-	-	H-5', 3.82, ddd OH-3, 3.72, d OCH_3, 3.30, s H-a, 3.19, dt H-b, 2.94, dt H-c, 6.21, t H-d, 5.66, t OH-5, 2.82, dd
15[f]	5.94 d	4.55 d	-	3.87-4.18 m	3.87-4.18 m	-	-	H-6, 3.87-4.18, m H-6', 3.87-4.18, m H-a, 3.27, dt H-b, 3.15, dt H-c, 6.11, t H-d, 5.73, t CH_3 isop., 1.23, s CH_3 isop., 1.31, s CH_3 isop., 1.36, s CH_3 isop., 1.47, s

eclipsed and it is also inconsistent with the large H-4/H-5 NOE's observed for these compounds. Thus, it is concluded that the conformations about the C-4/C-5 bond pictured in Scheme 3 are favored in solution. When H-4 and H-5 are *gauche*, the compound with the *R* configuration at C-5 has C-6 *gauche* to C-3, but *anti* to H-4 leading to prediction of NOE's between C-6 protons and H-3 but not between C-6 protons and H-4. In the same

Table 2. ^{1}H NMR Spectroscopic Data - Chemical Shifts (δ in ppm)(Cont.).

Cpd. No.	H-1	H-2	H-3	H-4	H-5	Ph	CH_2 Ph	Others
16[f]	5.81 d	4.55 d	-	4.0-4.2 m	4.0-4.2 m	-	-	H-6', 4.0-4.2, m H-6, 3.85, m H-a, 3.25, dt H-b, 2.83, dt H-c, 6.08, t H-d, 5.69, t CH_3 isop., 1.20, s CH_3 isop., 1.30, s, 6H CH_3 isop., 1.50, s

a, b, c, d. Assignment of protons in the lactone ring of compounds **6** - **9**, **11**, **12**, **15** and **16.**
e. In chloroform-*d*. f. In acetone-d_6.

way, the compound with the *S* configuration at C-5 has C-6 *gauche* to H-4, but *anti* to C-3, leading to prediction of NOE's between C-6 protons and H-4, but not to H-3. For **6**, an H-3/H-6' NOE of 3.5% was observed, but none was observed between C-6 protons and H-4. For **7**, an H-4/H-6' NOE of 4.6% was observed, but none between H-3 and C-6 protons. Thus **6** has the *R* configuration at C-5 while **7** has the *S* configuration.

The structures previously reported[2] for compounds **8** and **9** have now been confirmed by NOE experiments. Null values for 3/5 and 4/5 NOEs in **9** indicate that H-4 and H-5 are in *anti* relationships. The size of $J_{4,5}$, 8.3 Hz, confirms this relationship. Irradiation at H-3 of **9** produced an NOE of 3.5% at H-2, of 8.5% at H-4 and of 3.6% at H-6', but no NOE at H-5 and H-6. Thus H-3 is not close to H-5 and the configuration for C-5 is assigned as *S* in **9**, which adopts a conformation in which H-4 and H-5 are *anti* and the oxygen atoms of the furanosidic and lactone rings are *gauche*. On irradiation at H-1, NOE effects of 6.3% and 3.3% for H-2 of **8** and **9** were observed, respectively. For **8**, $J_{4,5}$

Table 3. ^{1}H NMR Spectroscopic Data - Coupling Constants in Hz - for Compounds **5**, **6**, **7**, **8**, **9**, **11**, **12**, **15** and **16**.

Cpd. No.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{A,B}(CH_2Ph)$	Others
5	3.5	-	3.5	6.7	11.0	$J_{5,6} = 1.5$; $J_{6,7} = 5.9$; $J_{5,7} = 1.5$
6	3.7	3.9	9.2	2.2	11.8	$J_{5,a} = 6.2^e$; $J_{5,b} = 8.2^e$; $J_{a,c} = J_{b,c} = 2.9$; $J_{a,d} = J_{b,d} = 2.7$
7	3.7	4.2	8.8	2.4	11.6	$J_{5,a} = 8.8$; $J_{5,b} = 4.9$; $J_{a,c} = J_{b,c} = 3.0$; $J_{a,d} = J_{b,d} = 2.7$ $J_{a,b} = 17.5$
8	3.8	-	3.4	5.8	11.6	$J_{5,a} = 5.9^f$; $J_{5,b} = 7.5^f$; $J_{a,c} = J_{b,c} = 2.9$; $J_{a,d} = J_{b,d} = 2.6$
9	3.8	-	3.5	8.3	11.5	$J_{5,a} = 7.9$; $J_{5,b} = 6.8$; $J_{a,c} = J_{b,c} = 2.7$; $J_{a,d} = J_{b,d} = 2.9$ $J_{a,b} = 17.6$
11	-	-	3.0	3.0	-	$J_{4,5'} = 3.7$; $J_{5,5'} = 13.4$ $J_{a,c} = J_{b,c} = 3.0$; $J_{a,d} = J_{b,d} = 2.4$; $J_{a,b} = 17.3$
12	-	-	8.0	2.5	-	$J_{3,OH} = 11.7$; $J_{4,5} = 2.5$; $J_{4,5'} = 2.3$; $J_{5,5'} = 12.5$; $J_{5,OH} = 2.5$; $J_{5',OH} = 10.6$; $J_{a,c} = 2.9$; $J_{b,d} = 2.7$; $J_{a,d} = J_{b,d} = 2.5$; $J_{a,b} = 18.1$

Table 3. ^{1}H NMR Spectroscopic Data - Coupling Constants in Hz (Cont.).

Cpd. No.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{A,B}(CH_2Ph)$	Others
15	3.7	-	-	*g*	-	$J_{a,c} = J_{b,c} = 3$; $J_{a,d} = J_{b,d} = 2.5$; $J_{a,b} = 18.3$
16	3.2	-	-	*g*	-	$J_{a,d} = J_{a,c} = 2.7$; $J_{b,d} = J_{b,c} = 2.7$; $J_{a,b} = 17.3$

a, b, c, d. Assignment given for protons such as in Table 2. e, f. It is not possible to distinguish between protons a and b. g. It could not be determined.

= 5.8 Hz and irradiation of H-5 induced a 4.5% NOE at H-4. Both results indicate that H-4 and H-5 are approximately *gauche* in the most populated conformation. The proximity between H-3 and H-5 detected by an NOE effect of 2.1% at H-5 on irradiation of H-3 allows us to confirm the *5R* configuration for **8.** These assignments confirmed the configurations previously reported for these compounds.[2]

Stereochemical elucidation of **11** (Scheme 4) was easily accomplished by irradiation of H-3, which produced NOEs of 7.7% at H-4, of 4% at one methyl group of the isopropylidene group and of 5.7% at H-6. This last observation allowed us to conclude that H-3 and H-6 are on the same side of the molecule, thus imposing *S* configuration for C-2. This assignment was confirmed by irradiation of H-6, which produced an NOE at H-6' of 29% and confirmed the NOE at H-3. On irradiation of H-1, a 9% NOE was observed at the methoxyl group and of 1.5% was observed at H-6'.

Irradiation of **12** at H-3 produced an NOE of 7.2% at H-4 as expected and of 4.7% at H-6, indicating that H-6 and H-3 are on the same side of the furanosidic ring, thus confirming the *S* configuration proposed for C-2. Irradiation at H-6' produced an NOE of 22.9% at H-6 and of 2.7% at H-1. This was confirmed after irradiation of H-1, which

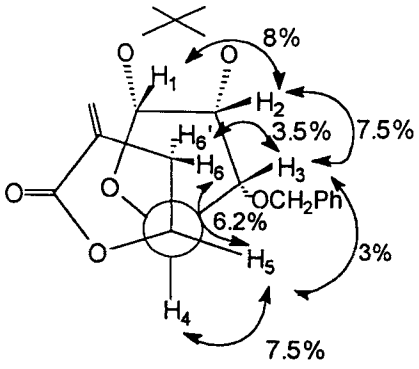
Table 4. ^{13}C NMR Spectroscopic Data (δ in ppm, in Chloroform-*d*) for Compounds **5**, **6**, **7**, **11** and **12**.

	5[a]	**6**	**7**	**11**	**12**
CH_3 -isop.	26.15	26.42	26.52	20.43	-
	26.77	26.89	26.80	28.63	-
H_2 C-6	-	29.69	27.65	31.00	31.27
OCH_3	-	-	-	57.66	55.57
H_2 C-Ph	72.85	72.55	72.17	-	-
HC-5	79.23	73.41	72.42	-	-
H_2 C-5	-	-	-	61.05	61.94
HC-2	81.14[b]	77.54[b]	76.92	-	-
C-2	-	-	-	87.40	87.32
HC-3	81.79[b]	77.49[b]	76.56	74.75	77.57[b]
HC-4	82.24[b]	79.72	78.74	70.94	77.51[b]
HC-1	105.38	104.17	103.92	106.08	105.07
C-isop.	112.32	113.20	113.34	98.56	-
H_2 C=	-	121.92	122.37	123.05	123.37
HC(Ph)	128.14	128.05	128.14	-	-
	128.29	128.15	128.28	-	-
	128.56	128.50	128.57	-	-
C-7	-	133.70	133.53	133.46	133.99
HC-6	156.47	-	-	-	-
HC-7	121.73	-	-	-	-
C(Ph)	137.03	137.27	136.85	-	-
C=O	172.73	170.16	169.76	169.23	169.48

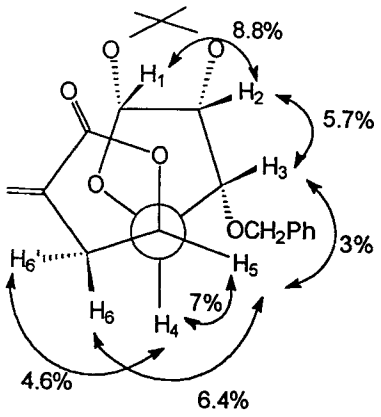
a. This spectrum was performed with a BRUKER AM-400WB spectrometer. b. These assignments might be interchanged.

produced an NOE at H-6', as expected, and also NOE of 3.3% at the methoxyl group. Irradiation of H-6 also produced an NOE at H-3. Finally, H-4 was also submitted to irradiation from which an NOE at H-3 was observed, as well as at H-5, H-5' of 4.7%. These measurements confirm the structure given for **12**.

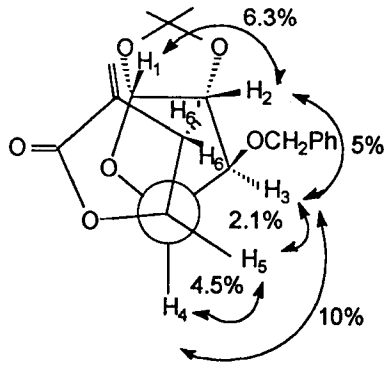
The stereochemistry of the chiral centre at C-3 in compounds **15** and **16** was also determined by this method. Irradiation at H-2 of **15** produced an NOE of 8% at H-1 and



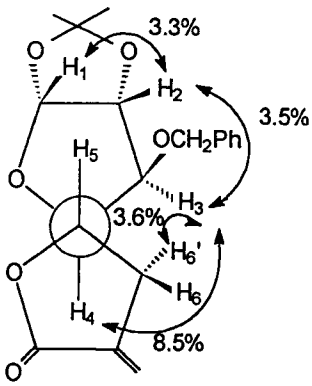
6 (3*R*, 5*R*)



7 (3*R*, 5*S*)



8 (3*S*, 5*R*)

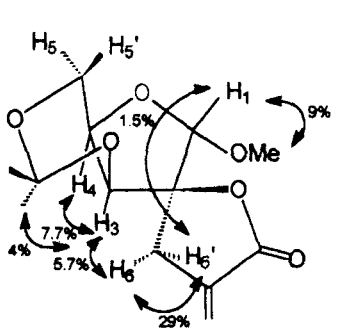


9 (3*S*, 5*S*)

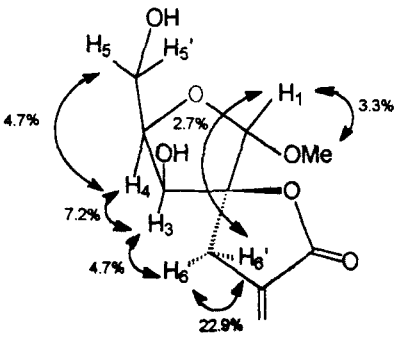
Scheme 3

1.3% at H-7. On irradiation of the nearly coincident signals of H-7 and H-7', no NOE was detected. Thus, H-7 and H-7' are distant from H-2 leading to the assignment of the *S* configuration for C-3. This experiment corrects the *R* configuration previously reported for this compound.[2]

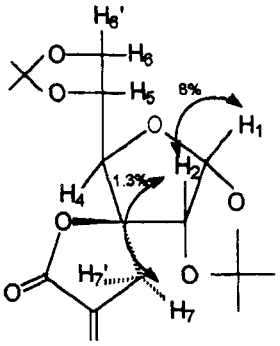
NOE experiments with compound **16** confirmed the expected *R* configuration for C-3. Irradiation at H-7' gave NOEs of 20% for H-7 and of 6.5% for the multiplet due to



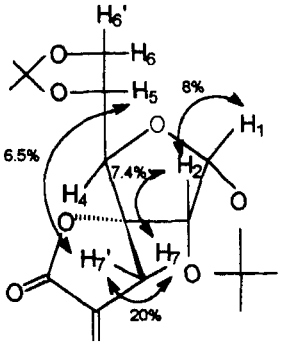
11 (1S, 2S)



12 (1S, 2S)



15 (3S)



16 (3R)

Scheme 4

H-5 and H-6. The enhancement is probably to the H-5 signal. Irradiation at H-2 produced an NOE of 7.4% at H-7 and of 8% at H-1. A final irradiation at H-7 confirmed the NOEs with H-7' and H-2 and allowed assignment of the structure of **16**, correcting that given in the original publication.[2]

^{13}C NMR spectroscopic data for compounds **5**, **6**, **7**, **11** and **12** (see Table 4) are consistent with the proposed structures.

The fungicidal efficacy of compounds **7**, **8**, **9**, **15**, **16** and **17** was tested (Table 5) and the best results were obtained against *Puccinia recondita*, *Plasmopara viticola* and

Table 5. Fungicidal Efficacy of Compounds **7**, **8**, **9**, **15**, **16** and **17**.[7]

	ppm	**7**	**8**	**9**	**15**	**16**	**17**
Phytophtora inf.	500	-	-	-	-	-	-
Tomato	250	-	4	3	4	2	2
protective	125	-	-	-	-	-	-
Pyricularia	500	5	-	-	-	-	-
oryzae	250	5	-	-	-	-	-
Rice protective	125	4	-	-	-	-	-
Sphaerotheca	500	-	-	-	-	-	-
fulig.	250	-	4	4	4	4	5
Cucumber	125	-	-	-	-	-	-
curative							
Pyrenophora	500	5	2	2	2	2	2
teres	250	4	-	-	-	-	-
Barley	125	3	-	-	-	-	-
protective							
Botrytis cinerea	500	7	0	0	0	2	0
Pepper	250	3	-	-	-	-	-
protective	125	**6**	-	-	-	-	-
Plasmopara	500	**7**	**6**	3	2	2	-
viticola	250	5	-	-	-	-	-
Wine protective	125	4	4	-	-	-	-
Fusarium	500	5	-	-	-	-	-
culmorum	250	4	-	-	-	-	-
Wheat	125	3	-	-	-	-	-
protective							
Puccinia	500	2	-	-	-	-	-
recondita	250	2	**6**	**7**	3	**6**	4
Wheat curative	125	2	-	-	-	-	-
	60	-	3	3	-	-	-
Erysiphe	500	4	-	-	-	-	-
graminis	250	4	3	3	3	3	3
Wheat	125	3	-	-	-	-	-
protective							

"-" - Not tested. 0 - No effect (total infection). 2 - Hardly any effect (heavy infection). 3 - Moderate/heavy infection. 4 - Slight efficacy (moderate infection). 5 Moderate efficacy (light/moderate infection). 6 - Good efficacy (light infection). 7 - Intermittent infection. 8 - Very good efficacy (no infection).

Botrytis cinerea.[7] Compounds **7**, **8** and **9** were the most active ones and some conclusions can be drawn from examination of their structures. The higher activity of **7** against *Plasmopara viticola*, when compared to that of **8** may be explained by the conformations given in Scheme 3. The double bond in **8** is more hindered than in that in **7** for the Michael-type reaction, known to be responsible for the bioactivity of many α,β-unsaturated lactones. Also the bulky benzyl group may play a role in producing some steric hindrance in **8**, which is absent in **7**, due to the reversed configuration at C-3. The higher bioactivity of **9** against *Puccinia recondita* when compared to that of **8** may be explained by the conformation of **8** in which the reactive double bond is more hindered than the one in the antiperiplanar conformation of **9.**

The results obtained so far for the limited number of compounds tested do not allow further correlation between stereochemistry and bioactivity. However they do show that activity is affected by the configurations at both C-3 and C-5 and that different configurations result in activity against different species. Some of the compounds are quite active, with **7**, for example controlling grey mould, **8**, **9** and **16** inhibiting brown rust on wheat, and **7** and **8** showing activity against downy mildew on grape wine.

EXPERIMENTAL

General methods. Melting points were determined with a melting point apparatus (Tottoli) and are uncorrected. Optical rotations were measured with a Atago Polax-D polarimeter and IR spectra were recorded with a Biorad FTS 25 PC spectrophotometer. ^{1}H NMR spectra and NOE experiments were run with a Bruker AM-400 WB. Chemical shifts are expressed in parts per million downfield from TMS. Homonuclear ^{1}H{^{1}H} experiments were performed at 400 MHz in acetone-d_6 or chloroform-*d*, using a low decoupler setting (typically 40 L, 5 mW approximately) with a total presaturation time of 6 s. The FIDs were acquired using 16 K points and a sweep width of 5000 Hz in alternate groups of eight, irradiating on/off resonance. A 90^{0} pulse was used during acquisition. The ^{13}C NMR spectra were recorded with a Bruker AC-250 P spectrometer at 62.90 MHz. The progress of all reactions was monitored by thin layer chromatography (TLC)

using aluminum sheets precoated with silica gel $60F_{254}$ to a thickness of 0.2 mm (Merck). Preparative TLC was performed with aluminum plates coated with silica gel $60F_{254}$ to a thickness of 0.5 mm (Merck). Compounds were detected with UV light (254 nm) and/or by spraying the sheets with a 3% vanillin-sulfuric acid solution. Column chromatography was conducted under medium pressure by elution of columns of silica gel (0.040-0.063 mm, Merck).

5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (2). Triphenylphosphine (2.96 g, 11.3 mmol) was added to a solution of **1** (1.33 g, 4.29 mmol) in anhydrous benzene (75 mL). After stirring at room temperature for 15 min, diethylazodicarboxylate (1.74 mL, 10 mmol) was introduced dropwise. Finally, molecular sieves powder 3 Å (3.4 g) was added and the mixture was heated at 80 °C under stirring for two days, being monitored by TLC. After filtration and concentration under reduced pressure, the obtained residue was purified by column chromatography (ethyl acetate/toluene 1:3 v/v) to give **2** (0.90 g, 72%): R_f = 0.47 (ethyl acetate/hexane 1:3), which had physical and spectroscopic data in full agreement with those given in the literature.[10]

(7*R*)- and (7*S*)-3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-7-phenylselenyl--α-D-*gluco*-octofuranurono-8,5-lactone (3,4). A solution of diisopropylamine (2.49 mmol, 0.35 mL) in anhydrous THF (4.7 mL) under argon was cooled to 0 °C. BuLi (1.6 M in hexane, 1.55 mL, 2.49 mmol) was added to the stirred solution. After 20 min, phenylselenoacetic acid (253 mg, 1.17 mmol) in THF (1.2 mL), was added and a white precipitate formed, indicating the formation of the dianion. A solution of the epoxide **2** (171 mg, 0.59 mmol) in anhydrous THF (0.6 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. A saturated ammonium chloride solution was added and the mixture was boiled under reflux overnight. It was cooled, neutralized with a saturated sodium hydrogen carbonate solution, then extracted with ether (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated. The crude mixture was purified by chromatography under medium pressure on a column of silica gel with ethyl acetate/toluene (1:5 v/v) as eluent to give a mixture of **3** and **4** (73.1 mg, 25%). The recovered hydroxy acid was heated in benzene under reflux in the presence of a trace of *p*-toluenesulfonic acid in a

Dean-Stark apparatus. Neutralization and extraction according to the procedure described afforded a mixture of compounds **3** and **4** (51.2 mg, 17.5%). The mixture of epimers (42.5% overall yield) was used in the next step without further characterization. Syrup; R_f = 0.42 (ethyl acetate/hexane 1:3); IR (chloroform), 1772 (C = O) cm^{-1}.

3-*O*-Benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-oct-6-enofuranurono-8,5-lactone (5). To a solution of **3,4** (112 mg, 0.23 mmol) in THF (0.7 mL), cooled to 0 °C, one drop of glacial acetic acid then 30% hydrogen peroxide (0.2 mL, 1.56 mmol) were added. The reaction mixture was stirred for 30 min at 0 °C, neutralized with a saturated solution of sodium hydrogen carbonate and extracted with dichloromethane (3 x 15 mL). The extract was dried over sodium sulfate and concentrated. The residue was purified by preparative TLC with the eluent ethyl acetate/hexane 1:2 to give **5** (57.4 mg, 75%): mp. 66-70 °C; $[\alpha]_D^{20}$ + 0.2 (*c* 1.5, chloroform); IR (chloroform) 1758 (C = O) cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_6$ (332.33): C, 65.06; H, 6.06. Found: C, 64.79; H, 6.20.

Methyl 3,5-*O*-isopropylidene-α-D-*threo*-pentofuranoside-2-ulose (13). A solution of **14** (1.00 g, 4.9 mmol) in dichloromethane (25 mL), previously dried over molecular sieves 4Å, was added to a suspension of pyridinium chlorochromate (3.41 g, 15.9 mmol) and 4Å molecular sieves powder, previously activated at 300 °C (5.54 g), in dichloromethane (24 mL). The reaction mixture was boiled under reflux for 2 h , then cooled, added to a suspension of celite (36 g) in dichloromethane (150 mL) and stirred vigorously for 30 min. Toluene (15 mL) was added to the slushy mixture, which was concentrated in vacuo. Ethyl acetate (25 mL) was added and the mixture was stirred overnight, then filtered. The filtrate was concentrated and the residue was purified by column chromatography (eluent ethyl acetate) to afford **13** (801.7 mg , 81%). Its physical and spectroscopic data were in perfect agreement with those given in the literature.[3]

General procedure for the Reformatsky reaction. Granulated zinc 20 mesh (700 mg, 10.7 mmol) was activated[12] and added to a solution of carbonyl compound (7.2 mmol) in anhydrous THF (4 mL). A solution of ethyl bromomethylacrylate[13] (1.93 g, 10 mmol for the synthesis of **6** and **7** and 3.1 g, 16.1 mmol for the preparation of **11** and **12**) in THF (5 mL) was added dropwise under nitrogen at room temperature. The mixture was

heated at 50 °C, the reaction being monitored by TLC (ca. 1 h for **6**, **7** and 3 h for **11**, **12**). The reaction mixture was cooled to room temperature and a 10% hydrochloric acid solution (20 mL), previously cooled to 0 °C, was added. After extraction with dichloromethane (3x25 mL), the organic phase was neutralized with a 2.5% sodium hydrogen carbonate solution, dried over sodium sulfate and concentrated. The residue was purified by column chromatography under medium pressure on a column of silica gel with ethyl acetate/toluene (1:4 v/v). For physical and spectroscopic data, see Tables 1 - 4.

ACKNOWLEDGMENTS

The authors thank Junta Nacional de Investigação Científica e Tecnológica for the research grants, Conselho de Reitores das Universidades Portuguesas for partial financial support, BASF-AG., Limburgerhof, Germany for conducting the trials to evaluate fungicidal efficacy and National Cancer Institute for the leukemia screening.

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6. National Cancer Institute conducted the leukemia (3PS31) screening in rats and evaluated T/C% at 200 mg/Kg, 100 mg/Kg and 50 mg/Kg dose levels of **8**, **9** and **15-17**. Only **9** presented some activity producing T/C% of 125 and 124 respectively with dose levels of 200 mg/Kg and 100 mg/Kg. At a dose level of 50 mg/Kg **9** was inactive (T/C% 116). All other compounds tested were inactive (85<T/C%<120) or toxic (T/C% <85), depending on the compound and dose level tried.
7. The fungicidal efficacy results presented in this work were determined by BASF-AG, Limburgerhof, Germany, and were kindly remitted to us. Treatment of suitable plants reared in the greenhouse, with an acetonic solution of the compound, diluted with

water and containing a wetting agent (foliar application - non systemic activity), was performed prior to (protective) or after (curative) an artificial infection with specific fungi. After a given time, the degree of infection was recorded from 0 = no compound activity - total infection, to 8 = excellent activity - complete control.

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