Tetrahedron Vol. 45, No. 9, pp. 2627 to 2640, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

ENANTIODIVERGENT SYNTHESIS OF (+) AND (-) ALTHOLACTONE FROM D-GLUCOSE. PREPARATION AND CYTOTOXIC ACTIVITY OF ANALOGS

J.-P. GESSON*, J.-C. JACQUESY and M. MONDON
Laboratoire de Chimie XII, U.A. CNRS 489
40,Avenue du Recteur Pineau
86022, POITIERS (FRANCE)

(*Received in Belgium* 7 *February* 1989)

ABSTRACT: Total synthesis of (+)altholactone (goniothalenol), an antitumor pyrone isolated from an unnamed *polyalthea* species and from *goniothalamus giganteus*, has been completed in 11 steps from D-glucose using the easily available aldehyde **7**. Starting from the same compound or from the related benzoate **24** an enantiodivergent synthesis of (-)**1** has also been completed using as the key step an efficient arylation in anhydrous HF. Under these conditions, epimerization at C-8 occurs partially to give the new 8-epi (+)**1** or its enantiomer. Most of these pyrones show interesting cytotoxicity *in vitro* against L1210 leukemia.

(+)Altholactone **1** has been isolated in 1977 by Loder and Nearn[1] from the bark of an unnamed *polyalthea* species. The unique cis-fused furanopyrone structure has been proposed on the basis of chemical degradation and spectral data.

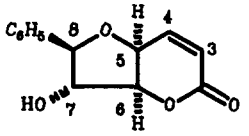
More recently, the same compound has been obtained by McLaughlin and al.[2] (proposed name: goniothalenol) from the stem bark of *goniothalamus giganteus* and the earlier structure confirmed by X-Ray analysis. These authors have also shown that **1** is cytotoxic to BS and 9KB and demonstrate antitumor activity against P388 leukemia in mice (T/C: 118% at 25 mg/kg).

Altholactone is a member of a class of naturally occuring 2-pyrones bearing a functionnalized 2-phenyl ethyl side chain at C-6. The structure of the simplest compound of this series,(+) goniothalamin **2**, isolated from several *goniothalamus* species was originally proposed to have the 6S configuration[3]. However several total syntheses[4] have shown that this material does have the opposite 6R configuration. The corresponding goniothalamin oxide **3**, an embryotoxic compound recently obtained from *goniothalamus macrophyllus* may well be a biogenetic precursor of more functionnalized pyrones such as **1**, as suggested by Sam and al..[5] Accordingly the structures of goniodiol **4** and goniotriol **5** occuring in the leaves and twigs of *goniothalamus sesquipedalis* and in the bark of *goniothalamus grifithii* should probably be 6R as shown and not 6S as proposed by Talapatra[6], goniotriol **5** being therefore a non cyclized form of altholactone **1**.

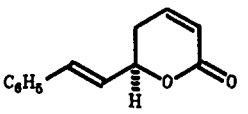
Related pyrones such as dihydrokawain-5-ol **6** *isolated from piper methysticum*[7] *or more* distant ones such as asperlin[8], anamarine[9], olguine[10] are also known, all having in common the same configuration at C-6.

The interesting furanopyrone structure and biological activity of altholactone 1 *and the* ambiguity associated with the absolute stereochemistry at C-6 of some analoguous compounds lead us to propose a total synthesis of both enantiomers of 1.[11] This work will also allow to determine any biological activity in the 6S series.

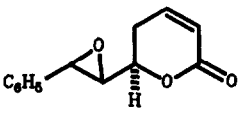
Retrosynthetic analysis shows, obviously, that a carbohydrate may be used for this aim and furthermore that aldehyde 7[12], readily available from D-glucose in only four steps, may be a common intermediate for an enantiodivergent synthesis of (+) and (-) altholactone from D-glucose. The route used to synthetize (+)1 should rely first on the construction of a phenyl substituted furan ring followed by ring closure of the pyrone while the route toward (-)1 should imply the introduction of the phenyl substituent at the last step. These two strategies and the cytotoxic activity of all these pyrones will be successively discussed.



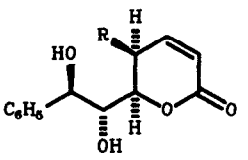
1



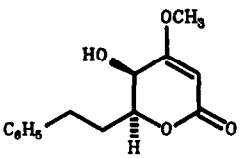
2



3



4 R=H Goniodiol
5 R=OH Goniotriol



6
dihydroKawain-5ol

TOTAL SYNTHESIS OF (+)1:

As stated above this synthesis requires first the preparation of a suitably protected furan followed by formation of the pyrone ring.

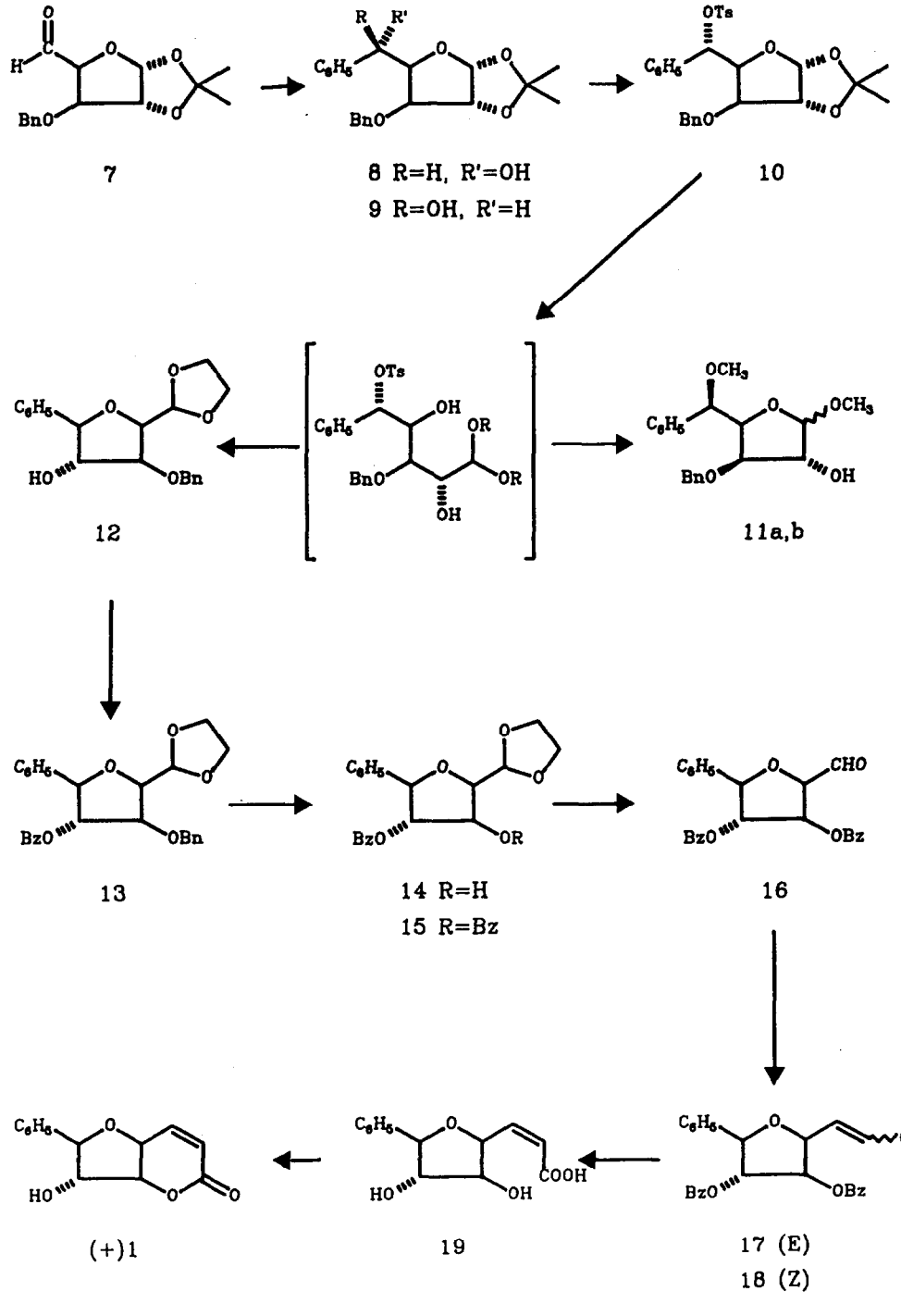
Preparation of furan 12 :

Condensation of phenylmagnesium bromide in ether with aldehyde 7 has been earlier described by Inch.[13] In these conditions a mixture of alcohols **8** (73%) and **9** (4%), easily separated by chromatography over silica gel, is obtained. The expected alcohol **8** arise from a chelation-controlled addition of the Grignard reagent which occurs here in a diastereoisomeric ratio of 16 to 1. This high selectivity is also observed for other Grignard reagents and aldehyde 7 as shown previously by Hanessian.[14]

Alcohol **8** is then converted to the corresponding tosylate **10** (86%) whose internal displacement by the hydroxyl group at C-2 is anticipated to afford the requested furan ring according to the work of Ogawa.[15] However under the conditions used by this author (methanolic HCl) a complex mixture is formed from which only the pure *alpha* and *beta* furanosides **11a,b** can be isolated. These compounds clearly arise from intermolecular displacement of the tosylate by the solvent (methanol) before or after cleavage of the acetonide function. In order to suppress this unwanted process the reaction is carried out in benzene at reflux in the presence of 4 equivalents of ethylene glycol and of a catalytic amount of *para*toluenesulfonic acid. A single compound, furan **12**, is thus isolated in 87% yield . The relative stereochemistry of the phenyl ring with respect to the vicinal hydroxyl group is trans as judged from the value of the coupling constant of the corresponding doublet (J=4.8 Hz) , a figure which is similar to the one observed for the benzylic proton of altholactone (J=5.5Hz) .

Conversion of 12 to (+) altholactone 1:

The elaboration of the pyrone ring requires the use of a Wittig olefination or a Reformatsky reaction (followed by dehydration) on a suitably protected aldehyde. Therefore a primary benzylic group should be cleaved in presence of a secondary one and this appears to be the crucial point in this sequence. No selectivity is observed under hydrogenolysis conditions using different catalysts (Pd/C, $Pd/BaSO_4$, Ni,...) using either the alcohol **12** or the corresponding benzoate **13**. However the use of freshly distilled trimethylsilyl iodide (TMSI) under careful conditions (1.1 eq., -20 to +5°C, 48 hrs) affords the desired alcohol **14** in 58 % yield together with 15.5 % of unreacted **13**. Attempts to bring the reaction to completion by changing the reactions conditions were unsuccessful , complex mixtures being obtained on longer reaction time or at higher temperature. Similarly only extensive decomposition was observed starting from alcohol **12** under any conditions. It should be noted that a general answer to this question has been proposed recently by Just[16] in


7
8 R=H, R'=OH
9 R=OH, R'=H
10
12
11a,b
13
14 R=H
15 R=Bz
16
17 (E)
18 (Z)
19
(+)1

connection with a planned synthesis of altholactone : p,p'-dinitrobenzhydryl ethers (DNB ethers) being selectively cleaved in presence of benzyl ethers.

As before, the free alcohol is protected as a benzoate to give **15** (90%) before hydrolysis of the acetal group (CF_3COOH-H_2O, 80-20) to the sensitive aldehyde **16** (86%). This material is then treated with 3 eq. of Ph_3P=CHCOOMe in anhydrous methanol at 20°C for 3 hours[17] to give a mixture of the E unsaturated ester **17** (11%) and of the requested Z isomer **18**(58%) which are easily separated by chromatography.

Base catalyzed hydrolysis of **18** (1N NaOH, room temperature, 12 hrs.) followed by acidification and continuous extraction with dichloromethane affords dihydroxy-acid **19** which is then converted without further purification to (+)**1** using CF_3COOH in dichloromethane (55 % yield from **18**). This material exhibits a melting point (111-112°C) close to the one reported by McLaughlin[2] (110°C) , which is higher than the value reported initially by Loder[1] (75°C); TLC behaviour in different solvent systems, IR and ^1H NMR spectra are identical to an authentic sample of (+)**1**. Finally, optical rotation does confirm the proposed absolute configuration of (+)**1** ($[\alpha]_D$ +183°,$[\alpha]_D$Litt. +188°[1] and +184.7°[2]).

TOTAL SYNTHESIS OF (-)1:

Following the strategy outlined above, the synthesis of (-)**1** will imply first the preparation of the key pyrone **23** followed by arylation of the hemiacetal function.

Preparation of pyrone 23:

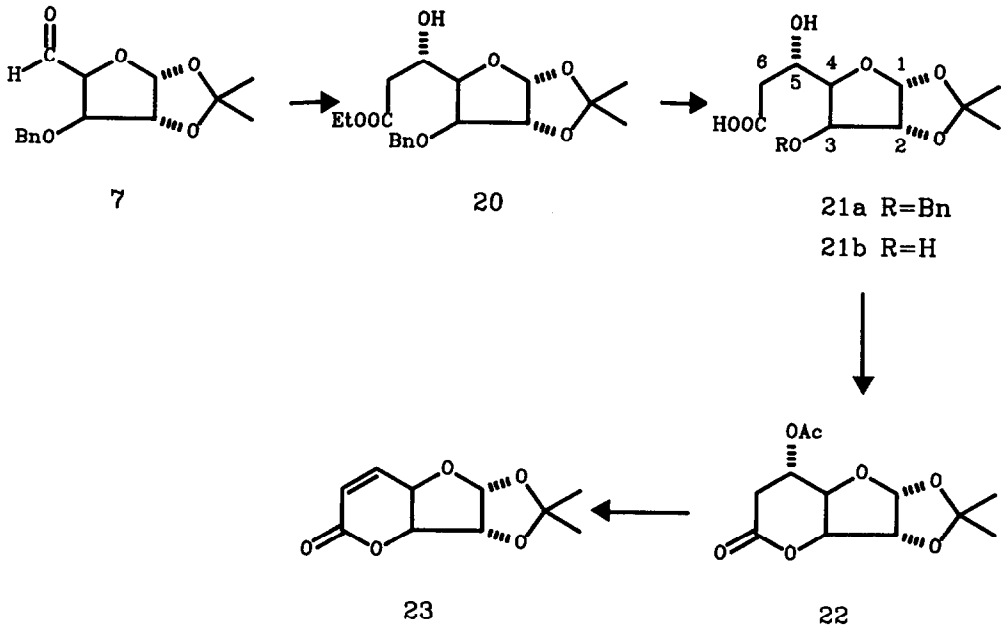
Two routes have been developped starting from aldehyde **7** as for the synthesis of (+)**1** or more rapidly from the corresponding benzoate **24**.

Reformatsky condensation of **7** with ethyl bromoacetate gives almost exclusively a single alcohol **20** in 85 % yield. The stereochemistry at the newly created asymetric carbon can not be determined by NMR but it may be anticipated to be S if the reaction is under chelation-control as expected for such a Reformatsky condensation[18]. This assumption will be confirmed later after cyclisation.

Saponification of the ester group followed, without purification of the intermediate acid, by hydrogenolysis of the benzyl group affords the dihydroxy-acid **21** (85%) which is then lactonized using 1.2 eq. of dicyclohexylcarbodiimide (DCC) in pyridine. Acetylation gives then the lactone **22** (78% from **21**) whose ^1H NMR reveals the presence of an axial acetoxy group, the geminal proton (H-5) giving a doublet ($J_{4,5}$= 2.2Hz) of triplets ($J_{5,6}$= 8.8Hz) as expected for an equatorial orientation. Finally treatment of **22** with 1.1 eq. of diazabicycloundecene (DBU) in CH_2Cl_2 gives the key unsaturated lactone **23** (87%) which is characterized by the presence of vinylic protons in NMR giving signals at 6.24 ppm (d, $J_{5,6}$=9.7Hz) for H-6 and 6.97 ppm (dd, $J_{5,6}$=9.7Hz and $J_{4,5}$=5.7Hz) for H-5.

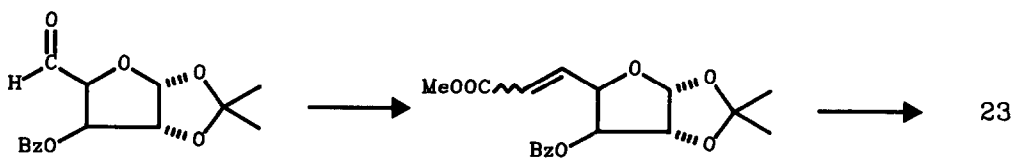
Alternatively a shorter route to **23** has been completed from aldehyde **24**, easily prepared as **7**, from diacetone D-glucose by benzoylation instead of benzylation. Condensation of

Ph_3P=CHCOOMe in methanol with **24** affords a mixture of the Z unsaturated ester **25** (71%) and of the E one **26** (17%) easily separated by chromatography. Conversion of **25** to **23** is then carried out by saponification followed by CF_3COOH induced lactonization (66% overall).



7 20 21a R=Bn 21b R=H

23 22



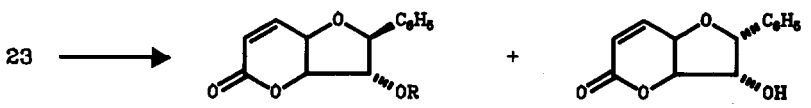
24 25 (Z) 26 (E) 23

Conversion of 23 to (-)1:

This last step requires the introduction of a phenyl group at the anomeric center of **23** and this is reminiscent of the preparation of C-glycosides from carbohydrates.[19] This coupling reaction is carried out after activation of the anomeric position (halide, acetate,...) using generally a Lewis acid and is restricted to activated aromatics. The use of anhydrous HF to promote this reaction has been scarcely reported in the litterature. For exemple the condensation of D-glucose with anisole gives mainly the diarylated compound **27** together with some cyclized products.[20]

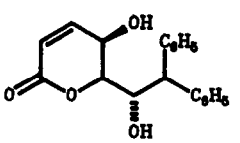
However treatment of **23** with 40 eq. of benzene in HF at 0°C for 10 minutes results in its complete conversion to three compounds which are separated by chromatography: **28** (18.3%), (-)**1** (47.7%) and **29** (3.4%).

The TLC behavior, IR, ^{1}H and ^{13}C NMR spectra of (-)**1** are identical with those of an authentic sample of (+)**1**. This oily material, which could not be induced to crystallize even after extensive purification by TLC (over florisil), exhibits an $[\alpha]_D$ value of -166° instead of +183° for (+)**1**. Acetylation of this material affords cleanly the acetate **30** whose physical (mp:141°C, mp_{Litt}[1]:142°C) and spectral data are similar to those reported by Loder[1] excepted the sign of optical rotation ($[\alpha]_D$ -200°; $[\alpha]_{DLitt}$ +208°).

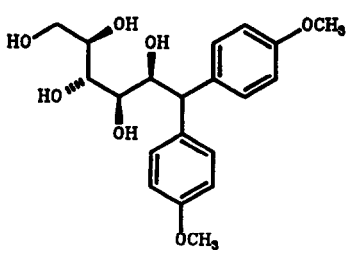


(−)1 R=H
30 R=Ac

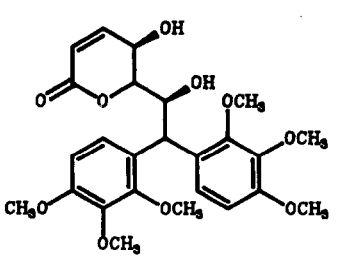
28



29



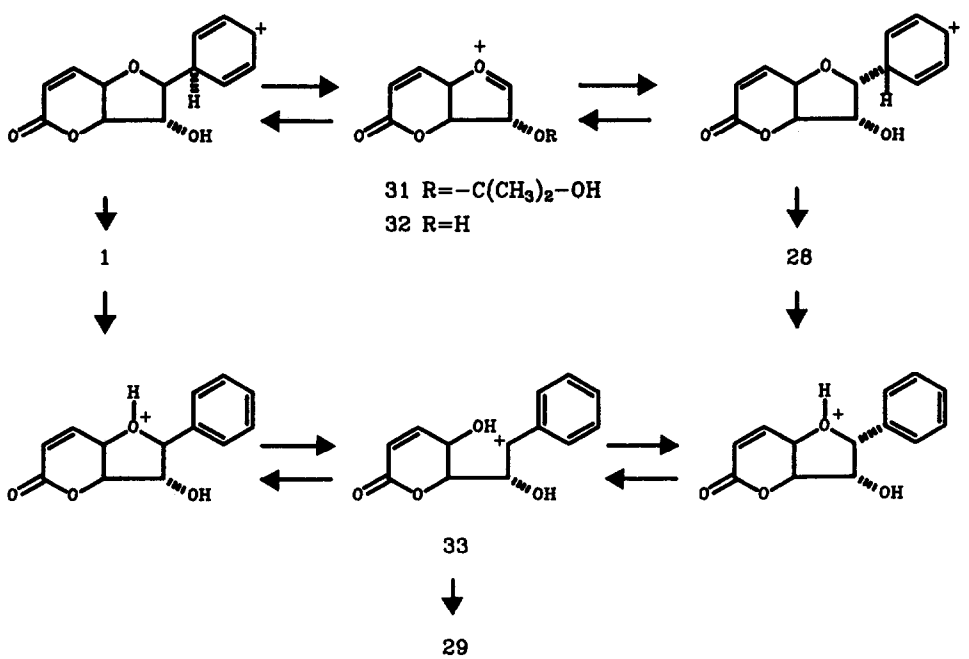
27



34

Compound **28** appears to be 8-epi (-)1 on the basis of MS and NMR data. Examination of the coupling constants between H-5,H-6,H-7 and H-8 and comparison with those of 1 reveals a change in the conformation of the furan ring in order to maintain the phenyl substituent equatorially oriented, the torsion angle between H-6 and H-7 becoming close to 90° ($J_{6,7}$=0). The minor compound **29** results from diarylation as shown by MS and NMR, the benzylic proton giving a doublet (J=8.7Hz) at 4.42 ppm.

The formation of **1**, **28** and **29** may be explained by protonation of the acetonide followed by cleavage to the onium ion **31** or **32** (resulting from acetone elimination). Arylation of such ions may occur preferentially trans to the vicinal substituent leading thus mainly to **1**. However equilibration of **1** and **28** cannot be ruled out either through protonation of the aromatic ring to give back **31** or **32**, or by protonation of the ring oxygen and formation of the benzylic ion **33** (the intermediacy of this latter accounts for the formation of the diarylated product **29**). This mechanism is corroborated by the HF catalyzed equilibration of (+)1 which gives after 1 hour at 0°C a 70/30 mixture of **1** and (+)**28** : this 2.66 ratio corresponds to the thermodynamic equilibrium between the two isomers and is close to the 2.3 ratio observed in the arylation of **23** after 10 minutes in the same conditions. The use of a more reactive aromatic such as 1,2,3-trimethoxybenzene gives only, in the same conditions, the diarylated compound **34** together with traces of two other compounds which are not characterized.



CYTOTOXIC ACTIVITY:

All the arylated pyrones prepared have been tested for their cytotoxicity against L1210 at the Behring Institute (Marburg,FRG) using a methodology already described.[21] The IC_{50}'s (µg/mL) measured in the stem cell assay under continuous exposure are reported in Table I.

TABLE I

Compound:	(+)1	(+)28	(-)1	(-)28	29	34
IC_{50}:	1.3	3.0	3.2	2.2	1.5	4.7

The most interesting compounds in this test are (+)1 which shows an activty in the range of methotrexate and fluorouracil and the diarylated compound **29** which is almost as active. The enantiomer of altholactone, (-)1, is less active but epimerization of the phenyl ring results in an increase of activity in the (-) series and a decrease in the (+) series. This observation suggests that the relative orientation of the phenyl ring with respect to the pyrone ring may play a role in the activity. Finally introduction of three methoxy groups in the diarylated compound results in a lowering of the activity.

The cytotoxicity observed for all these pyrones should be however confirmed in vivo to precise the potential interest as antitumor agents.

CONCLUSION:

The enantiodivergent syntheses of the naturally occuring (+)altholactone **1** and of its enantiomer (-)**1** have been completed from D-glucose. The epimerization of the phenyl substituent at C-8 has been observed in anhydrous HF thus allowing the preparation of the corresponding isomers in both optically active form. Finally it is important to note that most of these pyrones demonstrate cytotoxic activity at concentrations similar to known antitumor agents.

ACKNOWLEDGEMENTS:

We thank CNRS and Laboratoires Hoechst (Paris) for financial support of this work. We express our gratitude to Pr. J.L. McLaughlin (Purdue U.,USA) for a generous gift of (+)altholactone as well as copies of IR and NMR spectra and to Dr. D. Heissler (Strasbourg) for calling our attention to the absolute configuration of goniothalamin. We deeply thank Dr. H.P. Kraemer (Behring Institute, Marburg,FRG) for carrying out the cytoxicity tests.

EXPERIMENTAL:

Melting points were determined on a Tottoli Büchi 510 melting point apparatus and are uncorrected. ^1H NMR were recorded on a Brücker WP200SY, using $CDCl_3$ as a solvent and TMS as an internal standard (C numbering of carbohydrates used for all compounds except pyrones). Low resolution mass spectra were obtained on a Kratos MS 25 spectrometer.I.R. spectra were

recorded on a Beckman Acculab 2. Microanalyses were obtained from the "Service Central de Microanalyses" (CNRS,Lyon). All reactions were run under an inert atmosphere using dry solvents. Separations and purifications were carried out by column chromatography over SiO_2 (Merck Kieselgel 60 (0,063-0,2 mm))or by preparative TLC using silica gel coated plates (60 F254, 1 mm).

ALDEHYDE 7

Sodium periodate (19g, 88.7 mmoles) is added to a solution of 3-O-benzyl 1,2-O-isopropylidene-α-D-glucofuranose (25 g, 80.6 mmoles) in 300 mL of ethanol and 400 mL of water. After stirring at room temperature for 30 min, the mixture is filtered and the filtrate extracted with CH_2Cl_2 to give aldehyde 7 and the corresponding hydrate. This crude mixture is used directly in the next step.

Pure aldehyde 7 may be obtained by refluxing the crude mixture in benzene using a Dean-Stark trap. ^1H NMR : 1.27 (s, 3H); 1.42 (s, 3H); 4.27 (d,J = 3.6 Hz, H-3); 4.38 and 4.53 (2d, J = 11.8 Hz, Ph$\underline{CH_2}$); 4.59 (d, J = 3.4 Hz, H-2); 6.05 (d, J = 3.4 Hz, H-1); 9.61 (s, CHO); MS (CI,isobutane) 279 (M+1).

ALCOOLS 8 AND 9

The crude aldehyde 7 obtained as above is dissolved in Et_2O, and then is added to a solution of phenyl magnesium bromide (350 mmoles) in Et_2O (280 mL). After stirring for 2 hrs at room temperature, the reaction mixture is poured into iced 1N HCl. Usual work up gives compounds 8 (more polar) and 9 separated by column chromatography.

8 (73%, for the 2 steps); $[\alpha]_D$ - 41° (c 0.1, chloroform);$[\alpha]_D$Litt.[13] -33.5° (c 2.0,chloroform);^1H NMR : 1.28 and 1.47 (2s, 2 CH_3), 2.98 (OH), 3.58 (d, J = 3 Hz, H-3), 4.25 and 4.51 (2d, J = 11.5 Hz, Ph$\underline{CH_2}$), 4.32 (dd, J = 3 and 7.7 Hz, H-4), 4.57 (d, J = 3.7 Hz, H-2), 5.04 (d, J = 7.7 Hz, H-5), 5.98 (d, J = 3.6 Hz, H-1), 7.32 (m, 10 H) ppm; IR (CH_2Cl_2) : 3530 and 3600 (OH) cm-1; MS (CI, isobutane) 357 (M+1).

9 (4%) ^1H NMR: 1.30 and 1.46 (2s, 2CH_3), 3.98 (d, J = 3 Hz, H-3), 4.30 (dd, J = 3 and 6.3 Hz, H-4), 4.44 and 4.65 (2d, J = 11.5 Hz, Ph$\underline{CH_2}$), 4.58 (d, J = 4 Hz, H-2), 5.06 (d, J = 6.1 Hz, H_5), 6.00 (d, J = 4 Hz, H-1), 7.36 (10H) ppm.

TOSYLATE 10

A solution of 8 (6.6 g, 18.5 mmoles) and tosyl chloride (4.2 g, 22.2 mmoles) in 50mL pyridine is stirred at room temperature for 24 hrs. After extraction, the crude compound 10 is purified by crystallization (8.1 g, 86%) mp : 117-118°C (dec); $[\alpha]_D$ -12° (c 0.1, chloroform); ^1H NMR: 1.28 and 1.48 (2s, 2CH_3), 3.32 (d, J = 3.2 Hz, H-3), 3.96 and 4.30 (2d, J = 11.4 Hz, Ph$\underline{CH_2}$), 4.48 (d, J = 3.7 Hz, H-2), 4.58 (dd, J = 3.2 and 9 Hz, H-4), 5.70 (d, J = 9 Hz, H-5), 5.91 (d, J = 3.7 Hz, H-1) ppm. Anal. Calcd for $C_{28}H_{30}O_7S$: C, 65.86; H, 5.92. Found : C, 65.86; H, 5.91.

FURAN 12

A mixture of 10 (9.2g, 18 mmoles), p-toluenesulfonic acid (catalytic amount) and ethylene glycol (4.8g, 72 mmoles) in benzene is stirred under reflux for 1 hr using a Dean Stark trap. Usual work up gives compound 12 as an oil purified by flash column chromatography (hexane-ethylacetate, 50-50 v/v)(5.4g, 87%); $[\alpha]_D$ 11° (c 1.3, chloroform); ^1H NMR : 2.40 (OH), 3.90 (m, 4H), 4.06 (H-1, H-2), 4.26 (dd, J = 3 and 4.8 Hz, H-3), 4.56 (Ph$\underline{CH_2}$), 4.64 (d, J = 4.8 Hz, H-4), 5.31 (br,-$\underline{CH}(OR)_2$) ppm; MS (CI, isobutane) 343 (M+1); IR (CH_2Cl_2) 3600, 3480, 1600 cm-1.

BENZOATE 13

A solution of 12 (7.5g, 22 mmoles) and benzoyl chloride (3.7g, 26.3 mmoles) in pyridine (70mL) is stirred overnight at room temperature. After extraction as usual the compound 13 is isolated (as an oil) (98%). $[\alpha]_D$ 44° (c 2, chloroform); ^1H NMR : 3.97 (m, 4H), 4.11 (dd, J = 3.5 and 7 Hz, H-1), 4.24 (d, J = 3.5 Hz, H-2), 4.59 and 4.72 (2d, J = 11.8 Hz,Ph$\underline{CH_2}$), 5.20 (d, J = 2 Hz, H-3), 5.47 (d, J = 7 Hz, $\underline{CH}(OR)_2$), 5.50 (d, J = 2 Hz, H-4) ppm; MS (CI, isobutane) 447 (M+1); IR (CH_2Cl_2) 1725 cm-1.

DEPROTECTION OF 13

To a solution of 13 (1.3g, 2.9 mmoles) in methylene chloride (40 mL) maintained at - 20°C, is added trimethylsilyl iodide (0.47 mL, 3.3 mmoles). The reaction mixture is kept into a refrigerator (+ 5°C) for 2 days, and then washed with a solution of sodium thiosulfate to give after usual work up and separation by column chromatography, the less polar starting

compound **13** (202 mg, 15.5%) and then **14**, oil, (547 mg, 53%). Note : this reaction is only successful if a freshly opened bottle of trimethylsilyl iodide stabilized over Cu is used. $[\alpha]_D$ 28° (c 0.1, chloroform); ^{1}H NMR : 4.1 (m, 4H), 4.26 (t, J = 4.2 Hz, H-1), 4.56 (dd, J = 2 and 4 Hz, H-2), 5.11 (d, J = 3.5 Hz, H-4), 5.29 (dd, J = 2 and 3.5 Hz, H-3), 5.43 (d, J = 4.4 Hz, $\underline{CH}(OR)_2$) ppm; MS (CI, isobutane) 357 (M+1); IR (CH_2Cl_2) 3500, 1725 cm^{-1}; Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.65. Found : C, 67.28; H, 5.75.

DIBENZOATE 15

A solution of **14** (880 mg, 2.47 mmoles) and benzoyl chloride (0.34 mL, 2.9 mmoles) in pyridine(8 mL) is stirred overnight at room temperature. After work up as usual and filtration over florisil compound **15** (90%) is obtained. mp 47-51°C; $[\alpha]_D$ -49° (c 1.3, chloroform); ^{1}H NMR: 4.01 (m, 4H), 4.44 (dd, J = 3.6 and 6 Hz, H-1), 5.31 (broad s, H-4), 5.42 (d, J = 6 Hz, $\underline{CH}(OR)_2$), 5.54 (broad s, H-3), 5.90 (dd, J = 1 and 3.6 Hz, H-2) ppm; MS (CI, isobutane) 461 (M+1); IR (CH_2Cl_2) : 1725 cm^{-1}.

CLEAVAGE OF ACETAL 15

A solution of **15** (300 mg) in CF_3COOH-H_2O (80/20, v/v) is stirred overnight at room temperature. The reaction mixture is then poured onto water and extracted as usual to give aldehyde **16** (86%) which is used without further purification. ^{1}H NMR : 5.04 (d, J = 4.3 Hz, H-1), 5.44 (broad s), 5.60 (broad s), 6.03 (d, J = 4.3 Hz, H-2), 9.94 (s, $\underline{CH}O$) ppm. IR (CH_2Cl_2) 1720 cm-1 (broad).

WITTIG REACTION ON 16

A mixture of aldehyde **16** (1.21g, 2.9 mmoles) and Ph_3P=CH-$COOCH_3$ (2.9g, 8.7 mmoles) in dry methanol (10 mL) is stirred at room temperature for 2-3 hrs. the solvent is evaporated in vacuo and the residue taken up with diisopropylether in order to remove the insoluble Ph_3PO. The filtrate is then concentrated and the residue chromatographied by column chromatography to give successively **18** (790 mg, 58%) and **17** (154 mg, 11,3%).

18 : $[\alpha]_D$ 50° (c 0.6, chloroform); ^{1}H NMR :3.76 (s, 3H), 5.21 (d, J = 2.6 Hz, H-4), 5.54 (d, J = 2.6 Hz, H-3), 6.00 (d, J = 11 Hz, H-6), 6.06 (H-1 and H-2), 6.55 (dd, J = 6 and 11 Hz, H-5) ppm; IR (CH_2Cl_2) : 1720, 1650, 1600 cm-1; MS (CI, isobutane) 473 (M+1).

17 : $[\alpha]_D$ - 56° (c 0.5, chloroform); ^{1}H NMR: 3.70 (s, 3H), 5.18 (m, 1H), 5.28 (d, J = 2.3 Hz, H-4), 5.54 (H-3), 5.79 (d, J = 3.7 Hz, H-2), 6.41 (dd, J = 1.3 and 16 Hz, H-6), 6.41 (dd, J = 4.5 and 16 Hz, H-5) ppm; MS (CI, isobutane) 473 (M+1).

ACID 19 AND (+)ALTHOLACTONE 1

The ester **17** is hydrolyzed in an 1N aqueous solution of sodium hydroxide overnight. After acidification with 1N sulfuric acid, followed by usual work up, there is obtained a mixture of **19** and (+)**1** which is treated with CF_3COOH/H_2O (0.5 mL/10 mL) for 30 min. After evaporation, the residue is purified by column chromatography over florisil to give (+)**1** (55%).

19 ^{1}H NMR :4.09 (dd, J = 3 and 6 Hz, H-3), 4.60 (dd, J = 3.5 and 5 Hz, H-2), 4.68 (d, J = 6 Hz, H-4), 5.53 (t, H-1), 6.01 (dd, J = 1.3 and 12 Hz, H-6), 6.55 (dd, J = 6.4 and 12 Hz, H-5) ppm. (+) **1** mp 111-112°C; mp_{Litt2} 110°C and mp_{Litt1} 75°C; $[\alpha]_D$ 183° (c 0.5, ethanol); $[\alpha]_D$Litt^1 +188° (c 0.5,EtOH) and $[\alpha]_D$Litt^2 +184.7° (EtOH); ^{1}H NMR :4.43 (dd, J =2 and 5.5 Hz, H-7), 4.63 (t, J = 5 Hz, H-5), 4.75 (d, J = 5.5 Hz, H-8), 4.89 (dd, J = 2 and 5 Hz, H-6), 6.21 (d, J = 9.9 Hz, H-3), 6.99 (dd, J = 5 and 9.9 Hz, H-4), 7.4 (5H) ppm.

REFORMATSKY REACTION OF 7

A suspension of freshly activated Zn (successive washings with HCl, 20%, water, acetone, diethyl ether, then drying) (655 mg, 10 mmoles) in benzene (10 mL)is heated under reflux. A solution of aldehyde **7** (2g, 7.2 mmoles), ethylbromoacetate (1.6 mL, 14.4 mmoles) in diethyl ether (3 mL) is then added dropwise to this suspension and the reflux is maintained for 30 min. The reaction mixture is hydrolyzed with a 20% aqueous solution of sulfuric acid and then extracted with methylene chloride. Column chromatography of the crude product gives **20** as an oil (2.24g, 85%). $[\alpha]_D$ -22° (c 2, chloroform); ^{1}H NMR : 1.25 (t, J = 7 Hz, 3H), 1.31 and 1.47 (2s, 2x 3H), 2.51 (dd, J = 9 and 16,7 Hz, H-6a), 2.80 (dd, J = 2.8 and 16.7 Hz, H-6b), 3.20 (OH), 4.1 (m, 2H, H-3, H-4), 4.15 (q, J = 7 Hz, 2H-8), 4.37 (broad t, H-5), 4.59 and 4.71 (2d, J = 11 Hz, $Ph\underline{CH}_2$), 4.60 (H-2), 5.91 (d, J = 3.6 Hz, H-1), 7.34 (5H) ppm; IR (CH_2Cl_2) : 3580, 3500, 1730 cm^{-1}; MS (CI, NH_3) 367 (M+1).

SAPONIFICATION OF 20 TO 21a

On treatment with a 1N aqueous solution of sodium hydroxide the ester **20** gives acid **21a** sufficiently pure for the next step. $[\alpha]_D$ -30° (c 1.1, chloroform); ^1H NMR: 1.30 and 1.47 (2s, 2 x 3H), 2.54 (dd, J = 9 and 16.7 Hz, H-6a), 2.82 (dd, J = 2.8 and 16.7 Hz, H-6b), 4.05 (H-3, H-4) 4.38 (broad t, H-5), 4.60 (H-2), 4.56 and 4.70 (2d, J = 11.8 Hz, $Ph\underline{CH}_2$), 5.90 (d, J = 3.6 Hz), 7.33 (5H) ppm; IR (CH_2Cl_2) : 3580, 3500, 3000 (broad), 1710 cm^{-1}; MS (CI,NH_3) 339 (M+1).

HYDROGENOLYSIS OF 21a

A solution of **21a** (42 mmoles) in ethylacetate (300 mL) is stirred overnight, in presence of Pd/C 10% (300 mg), under an hydrogen atmosphere (1 atm). The reaction mixture is then filtered and after removal of the solvent under reduced pressure the crude product is recrystallized to give **21b** (8.9g, 85% from **20**). mp 142°C, $[\alpha]_D$ - 8° (c 1.2, acetone), ^1H NMR: 1.27 and 1.43 (2s, 2 x 3H), 2.46 (dd, J = 9.4, 16.2 Hz, H-6a), 2.73 (dd, J = 3 and 16.2, H-6b), 3.97 (dd, J = 2.5 and 8.3 Hz, H-4), 4.28 (d, J = 2.5 Hz, H-3), 4.37 (ddd, J = 3, 8.3 and 9.4 Hz, H-5), 4.50 (d, J = 3.5 Hz, H-2), 5.87 (d, J = 3.5 Hz, H-1)ppm; MS (CI, isobutane) 249 (M+1); Anal : Calcd for $C_{10}H_{16}O_7$: C, 48.39; H, 6.50. Found : C, 48.58; H, 6.43.

LACTONIZATION OF 21b

A mixture of **21b** (3g, 12.1 mmoles) and DCC (2.74 g, 13.3 mmoles) in pyridine (30 mL) is stirred, at room temperature, for 6 hrs. The mixture is then filtered and to the filtrate is added acetic anhydride (2.9 mL, 30.4 mmoles) and a catalytic amount of 4-dimethylaminopyridine. After stirring overnight at room temperature and work up as usual, filtration over florisil gives **22** (2.6g, 79%). mp 85-86°C; $[\alpha]_D$ 22° (c 1.2, chloroform); ^1H NMR: 1.35 and 1.54 (2s, 2x3H), 2.15 (s, 3H), 2.88 (d, J = 8.8 Hz, 2H-3) 4.68 (t,J = 2.4 Hz, H-5), 4.74 (d, J = 3.6 Hz, H-7), 4.78 (d, J = 2.6 Hz, H-6), 5.32 (td, J = 2.2 and 8.8 Hz, H-4), 6.00 (d, J = 3.6 Hz, H-8) ppm; IR (CH_2Cl_2) 1755 cm^{-1}; MS (CI, NH_3) 290 ($M+NH_4^+$), 273 (M+1); Anal. Calcd for $C_{10}H_{16}O_7$: C, 52.94; H, 5.92; Found : C, 53.13; H, 6.28.

LACTONE 23

DBU (1.5g, 9.9 mmoles) is added to a solution of **22** (2.45g, 9 mmoles) in methylene chloride (25 mL). The reaction mixture is stirred at room temperature for 1 hr then washed with water, dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude compound by filtration on florisil affords pure **23**. mp 70-71°C, $[\alpha]_D$ 33° (c 1.5, chloroform); ^1H NMR: 1.36 and 1.54 (2s, 2x3H), 4.64 (dd, J = 3.1 and 5.7 Hz, H-5), 4.83 (H-6, H-7), 6.02 (d, J = 3.6 Hz, H-8), 6.24 (d, J = 9.7 Hz, H-3), 6.97 (dd, J = 5.7 and 9.7 Hz, H-4) ppm; IR (CH_2Cl_2) 1740, 1700, 1640 cm^{-1}; MS (CI, NH_3) 230 ($M+NH_4^+$), 213 (M+1); Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H,5.70. Found : C, 56.60; H, 5.90.

WITTIG REACTION OF ALDEHYDE 24

The reaction conditions are the same as those used for the preparation of compound **17**. **25** (71%) and **26** (17%) are similarly separated by column chromatography. **25** mp 89-90°C; $[\alpha]_D$ - 232° (c, 1, chloroform); ^1H NMR : 1.35 and 1.60 (2s, $2CH_3$), 3.74 (s, 3H), 4.70 (d, J = 3.8 Hz, H-2), 5.76 (d, J = 2.8 Hz, H-3), 5.93 (H-4, H-6), 6.04 (d, J = 3.8 Hz, H-1), 6.35 (dd, J = 6.5 and 11.7 Hz, H-5), 7.44 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 6 Hz); MS 348; Anal. Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found : C, 61.89; H, 5.92.

PREPARATION OF LACTONE 23 FROM 25

The reaction conditions are identical to those used to prepare (+)**1** from **17**. **23** is thus obtained in 66% yield over two steps through the intermediate acid whose physical constants are: mp 140°C; $[\alpha]_D$ - 146° (c 1, acetone); ^1H NMR (CD_3COCD_3): 1.27 and 1.42 (2s, $2CH_3$), 4.40 (broad s, H-3), 4.54 (d, J = 3.7 Hz, H-2), 5.58 (broad d, J = 6.7 Hz, H-4), 5.94 (d, J = 3.7 Hz, H-1), 5.96 (dd, J = 1.7 and 11.8 Hz, H-6), 6.32 (dd, J = 6.7 and 11.8 Hz, H-5) ppm; IR (CH_2Cl_2), 3400 (broad), 1730 cm^{-1}; Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found : C, 52.20; H, 6.16.

HF CATALYZED ARYLATION OF 23 TO (-)1, 28 AND 29

To a mixture of HF (3 mL) and benzene (1.5 mL), maintained in a teflon bottle, is added 100 mg (0.47 mmole) of **23**. After stirring for 10 min at 0°C, the reaction mixture is poured into an iced sodium carbonate solution. Extraction with methylene chloride and purified by preparative TLC affords by order of decreasing polarity **28** (20 mg, 18.3%), (-)**1** (52 mg, 47.7%) and **29** (5mg, 3.4%).

28 : mp 190-192°C; $[\alpha]_D$ - 266° (c 0.5, ethanol); ^1H NMR : 4.50 (H-7), 4.88 (t, J = 5 Hz, H-5), 5.10 (d, J = 5 Hz, H-6), 5.35 (d, J = 3.5 Hz, H-8), 6.20 (d, J = 10 Hz, H-3), 7.00 (dd, J = 5 and 10 Hz, H-4), 7.42 (5H) ppm; ^{13}C NMR : 160.9 (C-2), 140.66 (C-4), 134.93 (C-1'), 128.8 (C-3'), 128.5 (C-4'), 126.7 (C-2'), 123.1 (C-3), 84.5, 83.55, 78.01, 68.15 (C-5) ppm; IR (CH_2Cl_2) : 3600, 3460, 1735 cm-1; MS (CI, NH_3) 250 ($M+NH_4^+$), 233 (M+1); Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found : C, 67.38; H, 5.08. (-) **1** : $[\alpha]_D$ - 166° (c 0.5, ethanol); ^1H NMR : 4.42 (dd, J = 2 and 5.5 Hz, H-7), 4.60 (t, J = 5 Hz, H-5), 4.72 (d, J = 5.5 Hz, H-8), 4.89 (dd, J = 2 and 5 Hz, H-6), 6.20 (d, J = 9.9 Hz, H-3), 6.99 (dd, J = 5 and 9.9 Hz, H-4), 7.4 (5H) ppm; ^{13}C NMR = 161.8 (C-2), 140.7 (C-4), 138.3 (C-1'), 128.5 (C-3'), 128.4 (C-4'), 126.1 (C-2'), 123.3(C-3), 86.4 (C-6), 85.9 (C-8), 83.3 (C-7), 68 (C-5) ppm; IR (CH_2Cl_2) 3600, 3420, 1730 cm-1; MS (CI, NH_3) 250 ($M+NH_4^+$) 235 (M+1).
29 mp 201-202°C; $[\alpha]_D$ +53° (c, 0.5, ethanol); ^1H NMR: 4.09 (t, J = 2.9 Hz, H-6), 4.25 (dd, J = 2.9 and 6.4 Hz, H-5), 4.42 (d, J = 8.7 Hz, H-8), 4.88 (dd, J = 2.9 and 8.7 Hz, H-7), 6.02 (d, J = 9.7 Hz, H-3), 6.69 (dd, J = 6.2 and 9.7 Hz, H-4) ppm; MS (CI, NH_3) 328 ($M+NH_4^+$), 311 (M+1); IR (CH_2Cl_2) 3600, 1730, 1600 cm-1.

ACETYLATION OF (-)1 TO (-)30

Standard acetylation of (-)1 with acetic anhydride in pyridine gives acetate **30**. mp 141°C; $[\alpha]_D$ -200° (c 0.5, ethanol) [mp_{Litt}] 142°C and $[\alpha]_D$Litt[1] +208° for **(+)30**]; ^1H NMR: 2.16 (s), 4.63 (dd, J = 4 and 5.2 Hz, H-5), 4.95 (d, J = 4 Hz, H-6), 4.97 (d, J = 3.6 Hz, H-8), 5.39 (dd, J = 1 and 3.8 Hz, H-7), 6.27 (d, J = 9.7 Hz, H-3), 7.03 (dd, J = 5.3 Hz and 9.7 Hz, H-4) ppm.

8-EPI (+)ALTHOLACTONE 28

To 1 mL of HF at 0°C is added 10 mg of (+)1. The solution is stirred 1 hr at 0°. After work up as usual a preparative TLC, affords the starting material (+)1 (70%) and (+) **28** (30%) : mp 190-191°C; $[\alpha]_D$ 268° (c 0.5, ethanol).

PREPARATION OF 34

To a solution of 1,2,3-trimethoxybenzene (907 mg, 5.4 mmoles) in HF (3 mL) at 0°C, is added **23** (115 mg, 0.54 mmole). After stirring for 1 hr at 0°C, work up as usual and chromatography over silica gives **34** together with traces of uncharacterized material.
34 (64%) mp 75-80°C; $[\alpha]_D$ 4° (c 0.5, ethanol); ^1H NMR: 3.74 (s, 3H), 3.82 (s, 6H), 3.84 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.23 (broad t, H-6), 4.35 (dd, J = 2.4 and 5.8 Hz, H-5), 4.67 (dd, J = 3.1 and 8.6 Hz, H-7), 5.14 (d, J = 8.6 Hz, H-8), 6.06 (d, J = 9.8 Hz, H-3), 6.62 (d, J = 8.6 Hz, ArH), 6.65 (d, J = 8.6 Hz, ArH), 6.94 (dd, J = 5.7 and 9.6 Hz, H-4), 7.02 (d, J = 8.6 Hz, ArH) ppm; MS (CI, isobutane) 491 (M+1) 490 (M).

REFERENCES AND NOTES:

1.Loder,J.W.;Nearn,R.H.*Heterocycles***1977**,*7*,113.
2.El-Zayat,A.A.E.;Ferrigni,N.R.;McCloud,T.G.; McKenzie,A.T.;
Byrn,S.R.;Cassady,J.M.;Chang,C.-J.;McLaughlin,J.L. *Tetrahedron Lett.* **1985**,*26*,955.
3.a)Hlubucek,J.R.;Robertson,A.V.Aust.J.Chem.**1967**,20,2199.
b)Jewers,K.;Davis,J.R.;Dougan,J.;Manchada,A.H.;Blunden,G;Kyi,A.;Wetchapinan,S.*Phytochemistry* ,**1972**,*11*,2025.
4.a)Meyer,H.H.*Liebigs Ann. Chem.***1979**,484.
b)O'Connor,B.;Just,G.*Tetrahedron Lett.***1986**,*27*,5201.
c)Gillard,F.;Heissler,D.;Riehl,J.-J.*J.Chem.Soc.Perkin I***1988**,2291.
5.Sam,T.W.;Sew-Yeu,C.;Matsjeh,S.;Gan,E.K.;Razak,D.; Mohamed,A.L. *Tetrahedron Lett.***1987**,*28*,2541.
6.Talapatra,S.K.;Basu,D.;Goswami,T.D.S.;Talapatra,B.*Ind.J.Chem.***1985**,*24B*,29.
7.Achenbach,H.;Wittman,G.*Tetrahedron Lett.***1970**,3259.
8.Argoudelis,A.D.;Zeisserl,J.F.*Tetrahedron Lett.***1966**,1969. For a total synthesis of the enantiomer see: Lesage,S.;Perlin,A.S.*Can.J.Chem.***1978**,*56*,2889.
9.Alemany,A.;Marquez,C.;Pascual,C.;Valverde,S.;Martinez-Ripoll,M.;Fayos,J.;Perales,A. *Tetrahedron Lett.***1979**,3585.
10.Alemany,A.;Marquez,C.;Pascual,C.;Valverde,S;Perales,A.;Fayos,J.;Martinez-Ripoll,M. *Tetrahedron Lett.***1979**,3579.
11.For preliminary communications see:
Gesson,J.-P.;Jacquesy,J.-C.;Mondon,M.*Tetrahedron Lett.***1987**,*28*,3945 and 3949.

For another recently reported synthesis of (+) and (-)altholactone see:
Gillhouley,J.G.;Shing,T.K.M.*J.Chem.Soc.Chem.Commun.***1988**,976.
12.a)Freudenberg,K.;Durr,W.;Von Hochstetter,H.*Chem.Ber.***1928**,*61*,1735.
b)Kakinuma,K.*Tetrahedron Lett.***1977**,4413.
13.Inch,T.D.*Carbohydr.Res.***1967**,*5*,45.
14.Wolfrom,M.L.;Hanessian,S.*J.Org.Chem.***1962**,*27*,1800.
15.Ogawa,T.;Matsui,M.;Ohrui,H.;Kuzahara,H.;Emoto,S.*Agr.Biol.Chem.***1972**,*36*,1449.
16.Just,G.;Wang,Z.Y.;Chan,L.*J.Org.Chem.***1988**,*53*,1030.
17.Tronchet,J.M.;Gentile,B.*Helv.Chem.Acta* **1979**,*62*,2091.
18.For reviews see: Reetz,M.T.*Angew.Chem.Int.Ed.Engl.***1984**,*23*,556. Heathcock,C.H.*Asymetric Synthesis*,Morrison,J.D.Ed.,Academic Press,**1984**,*Vol.3*,111.
19.a)Hanessian,S.;Pernet,G.Adv.*Carbohydr.Chem.Biochem.***1976**,*33*,111.
b)Doyle Daves,G.;Cheng,C.C.*Progress in Medicinal Chemistry*,Ellis,G.P.;West,G.B.Ed.North-Holland Publishing Co.**1976**,*13*,303.
20.Micheel,F.;Stanek,J.*Tetrahedron Lett.***1970**,1609.