Synthesis of the 5,6-Dihydro-2-pyrone Moiety of (+)-Anamarin

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The α,β-unsaturated δ-lactone (+)-goniothalamin (**18***E*) and its *Z*-isomer (**18***Z*), which contain the lactonic moiety of (+)-anamarin (**1**), have been synthesized from the known 1,2-*O*-isopropylidene-3-deoxy-α-D-glucofuranose (**7**). In the key step, methyl 3,5-dideoxy-β-D-glucofuranuronate (**15**) was treated with benzylidenetriphenylphosphorane in dimethyl sulphoxide to give the *E*- and *Z*-β-hydroxy δ-lactones (**17**). These were then transformed into the 5,6-dihydro-2-pyrones (**18**), and also into the aldehyde (**20**), intended for use in a total synthesis of (+)-anamarin (**1**).

(+)-Anamarin (**1**), an unsaturated δ-lactone with a tetra-acetoxylated side-chain, was isolated from a Peruvian unclassified *Hyptis* species by Valverde and his co-workers.[1] Although, to our knowledge, no biological activity has been reported so far for this compound, it is a 6-substituted 5,6-dihydro-2-pyrone, a large number of which exhibit various biological activities.[2]

Retrosynthetic disconnection of the double bond of anamarin (Scheme 1) led us to consider the synthesis of two six-carbon synthons: a lactonic aldehyde (**2**) and a linear tetraoxygenated fragment (**3**) bearing at one end a phosphorus substituent for use in a Wittig reaction. Carbohydrates have proved particularly valuable starting materials for the synthesis of enantiomerically pure compounds.[3] They seemed well suited to our needs and we decided to explore syntheses of the synthons (**2**) and (**3**) respectively from D-glucose and D-gulonolactone.[4] We report here the synthesis of the lactones (**18**) a masked form of the lactonic aldehyde (**2**).†

Results and Discussion

The lactone (**4**), with its protected aldehydic carbonyl group and readily eliminated axial hydroxy group at C-4 seemed a suitable precursor for the lactone (**2**). Scheme 2 shows the modifications required to obtain the open-chain acid (**5**) corresponding to the lactone (**4**) from D-glucose (**6**). The hydroxy groups at C-3 and C-5 have to be removed reductively, and oxidation to a carboxylic acid has to take place at C-6. Furthermore, to allow lactonisation, the aldehydic carbonyl group has to be protected to avoid preferential furanose ring formation.

The synthesis of the lactone (**4**) is summarized in Scheme 3. The 3-deoxy compound (**7**) was obtained from D-glucose (**6**) in four steps in 45% overall yield as follows: formation of the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose according to the procedure of Glen *et al.*;[5] conversion of this into the di-*O*-isopropylideneglucofuranose 3-*O*-(*S*-methyl dithiocarbonate) and subsequent reduction with tributyltin hydride[6] with azoisobutyronitrile as radical initiator;[7] and hydrolysis of the 5,6-*O*-isopropylidene acetal according to the method of Hedgley *et al.*[8] ‡

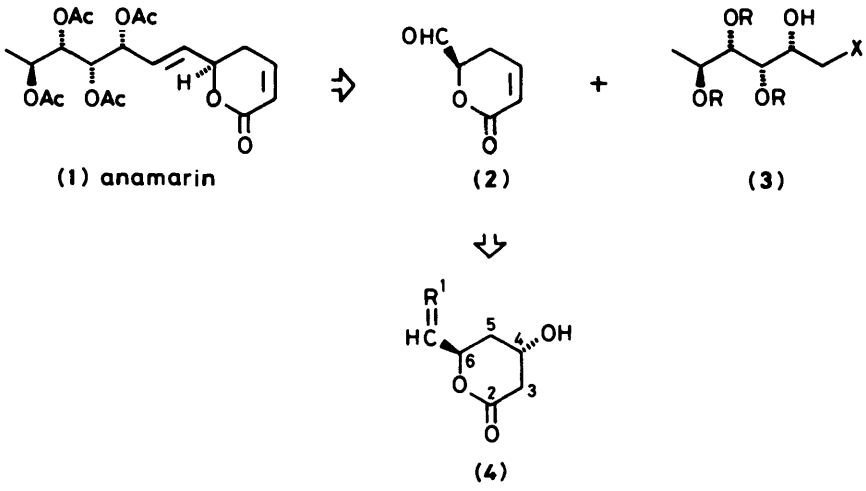
Mesylation of the diol (**7**) with an excess of methanesulphonyl chloride in pyridine afforded quantitatively the dimethanesulphonate (**8**) which, when treated without purification with sodium iodide and zinc powder in dimethylformamide (DMF) under reflux,[9] gave the 5,6-unsaturated furanose (**9**) in 91% yield. Selective hydroboration of the double bond with 9-borabicyclo[3.3.1]nonane,[10] followed by oxidation with alkaline hydrogen peroxide, gave the 3,5-dideoxyfuranose (**10**) (92%), which was oxidized at 18 °C to the glucofuranuronic acid (**11**) by treatment with 6 equiv. of pyridinium dichromate (PDC) in DMF[11] over 24 h. The use of smaller amounts of oxidant or a higher reaction temperature resulted in concomitant formation of up to 10% of the ester (**13**). However, when this happened, this by-product could be extracted with carbon tetrachloride, hydrolysed with aqueous 1M sodium hydroxide, and subjected again to oxidation with PDC to complete the transformation into the acid (**11**). Owing to the high solubility of the acid (**11**) in water its combined aqueous solutions had to be saturated with sodium chloride and extracted five times with ethyl acetate. Evaporation left a DMF solution of the acid (**11**) which was treated directly with ethereal diazomethane, to avoid a rather difficult chromatographic separation. In this way the methyl ester (**12**) was obtained in 62% yield from the alcohol (**10**). Hydrolysis of the remaining isopropylidene acetal with Amberlite IR 120 resin (H^+ form) in water led to the hemiacetal (**15**) in 87% yield.

Lactonisation of the carboxy group with the hydroxy function at C-2, with concomitant unmasking of the aldehyde group, was then required. The first attempts were made on the acid (**11**) in acidic aqueous solutions, and resulted only in removal of the acetonide group to give the acid (**14**), which was treated with Mukaiyama's lactonisation reagent (2-chloro-1-methylpyridinium iodide)[12] without success.

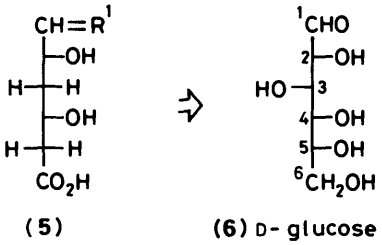
We decided then to protect the aldehydic carbonyl group so as to open the furanose ring. This could be achieved by treating the acid (**11**) or (**14**) with ethanethiol, ethane-1,2-dithiol, or propane-1,3-dithiol in concentrated hydrochloric acid at 0 °C[13] to give the thioacetals (**16a**—**c**) in 60—70% yield. However, subjection of these compounds to the following procedures did not result in lactonisation: treatment with dicyclohexylcarbodiimide in pyridine,[14] Mukaiyama's method,[12] treatment with carbonyldi-imidazole followed by base,[15] and treatment of a mixed anhydride with base.[16] Mild acidic treatment with azeotropic removal of water[17] led only to slow decomposition or, in the case of methanol-hydrogen chloride,[18] to the formation of the methyl esters (**16d** and **e**) in 90—95% yield. When treated with toluene-*p*-sulphonic acid in benzene,[19] these esters (**16d** and **e**) did not lactonise, but decomposed slowly; the same result

† While a revised version of this paper was being prepared, two related communications were published: B. O'Connor and G. Just, *Tetrahedron Lett.*, 1986, **27**, 5201; F. W. Lichtenthaler, K. Lorenz and Wei-Yong Ma, *ibid.*, 1987, **28**, 47.

‡ In this hydrolysis a modified work-up was used: the neutralised aqueous solution was extracted twice with ether, then the aqueous layer was evaporated under reduced pressure, and the residual solid was extracted overnight with chloroform in a Soxhlet apparatus.



Scheme 1.



Scheme 2.

was obtained with sodium methoxide in methanol. Molecular models led us to assume that steric hindrance by the bulky thioacetal group was the reason for these failures.

Selective reduction of the aldehyde function to an alcohol followed by δ-lactonisation was then envisaged. Treatment of compound (**14**) with sodium borohydride–lithium chloride in bis-(2-methoxyethyl) ether at 100 °C[20] gave a carboxylic acid, but treatment with toluene-*p*-sulphonic acid in refluxing benzene or with Corey's reagent [bis(2-pyridyl) disulphide][21] did not afford the expected lactone. Selective reduction of the hemiacetal function of (**15**) could not be achieved although attempts were made with sodium borohydride in water or ethanol, and with zinc borohydride in 1,2-dimethoxyethane–tetrahydrofuran.[22] With sodium cyanoborohydride in water,[23] reduction of the hemiacetal was so slow that hydration of the aldehyde occurred, preventing reduction.

Since we were unable to effect lactonisation as originally planned, we decided to test the feasibility of a Wittig reaction on the furanuronic ester (**15**) in order to achieve coupling with the side-chain of anamarin as well as to open the furanose ring irreversibly. In our mind, there was also a chance that lactonisation might occur in the basic medium of the Wittig reaction. This actually happened when the ester (**15**) was treated with benzylidenetriphenylphosphorane in dimethyl sulphoxide.[24] In this way a 65:35 mixture of the *Z*- and *E*-β-hydroxy lactones (**17**)* was obtained in 45% yield. However treatment of the ester (**15**) with methylenetriphenylphosphorane under the same conditions resulted essentially in no reaction. Furthermore, a two-fold excess of benzylidenetriphenylphosphorane was required to obtain the β-hydroxy lactones (**17**). This precluded use of the valuable side-chain ylide (**3**) to the same end. Therefore we decided to use the benzylidenetriphenylphosphorane to construct a protected form of the masked formyl group of the furanuronic ester (**15**), and to effect lactonisation of the resulting protected aldehyde.

Mesylation of the β-hydroxy lactones (**17**) under standard conditions[26] resulted in the elimination of methanesulphonic acid and led to the α,β-unsaturated lactones (**18**) in 85% yield. The *E*-isomer was identified with the known dihydropyrone (+)-goniothalamin[27,28] by comparison of physical and spectroscopic data (m.p., $[\alpha]_D$, i.r., and n.m.r.). Furthermore, its n.m.r. spectrum revealed absorptions for the vinyl and allyl protons of the lactone ring in remarkably good agreement with the corresponding absorptions of authentic anamarin.

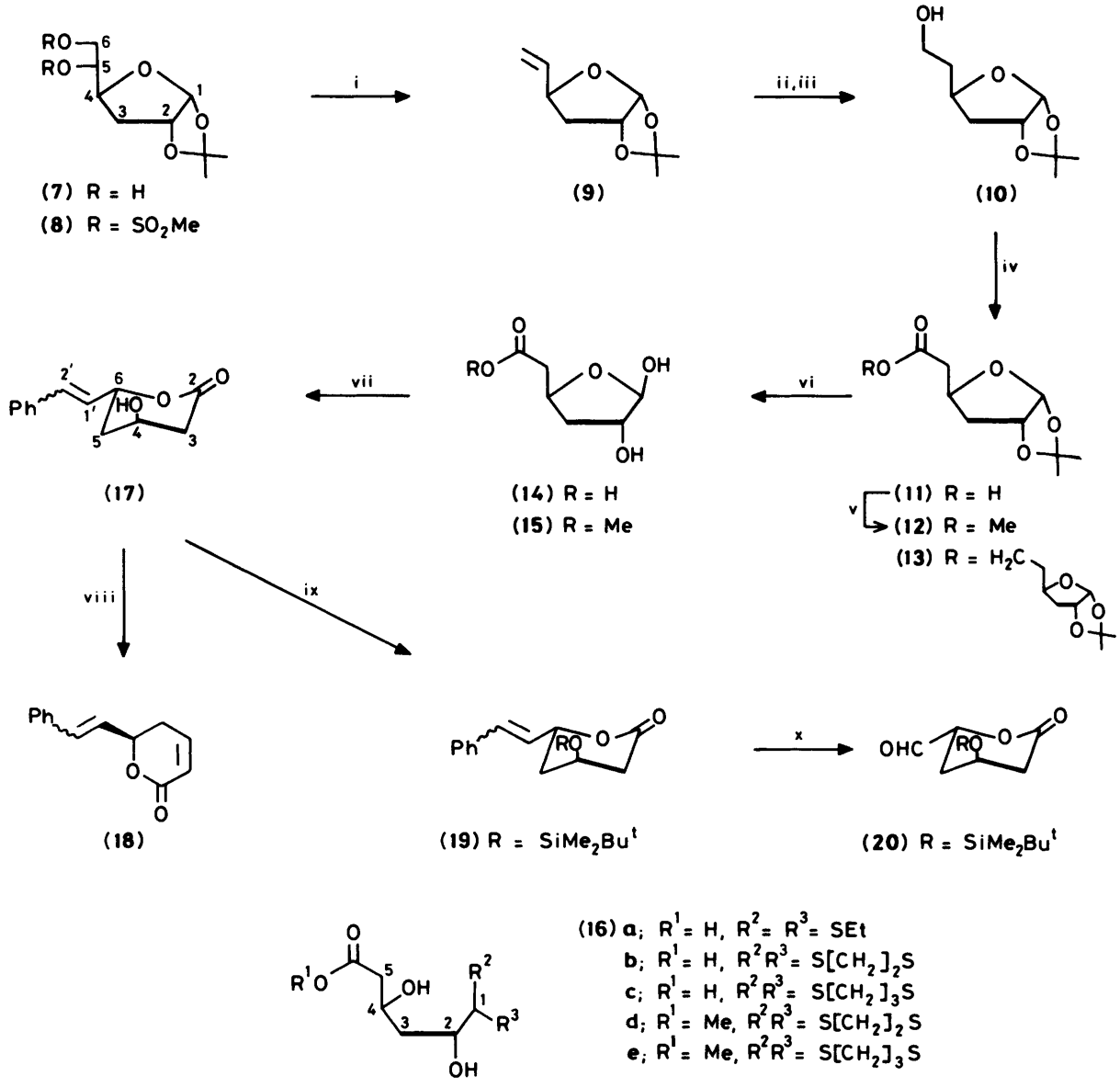
Attempts were made to cleave the exocyclic double bond of the α,β-unsaturated lactones (**18**) selectively to obtain the aldehydic lactone (**2**). These included ozonolysis at low temperature in chloroform–pyridine, which showed no selectivity, and *cis*-hydroxylation with a catalytic amount of osmium tetraoxide and trimethylamine *N*-oxide,[29] in which the endocyclic double bond reacted first. This led us to conclude that the oxidative cleavage of the benzylidene group had to be performed prior to the introduction of a second double bond. Therefore, we transformed the β-hydroxy lactones (**17**) into their *O*-dimethyl-t-butylsilyl derivatives[30] (**19**), which when treated with a catalytic amount of osmium tetraoxide and an excess of sodium metaperiodate[31] in dry methanol gave the aldehyde (**20**). Since this compound is prone to hydration it was identified as its semicarbazone.

Experimental

M.p.s were determined with a Büchi SMP-20 apparatus. Optical rotations were determined with a Perkin-Elmer 141 or 241MC polarimeter. Elemental analyses were performed at the Département de Chimie, Strasbourg. I.r. spectra were recorded with a Perkin-Elmer 257, 597, or 1310 spectrophotometer. N.m.r. spectra were recorded with a Hitachi-Perkin-Elmer R-24A (60 MHz) or a Bruker WP-200SY (200 MHz) instrument, with tetramethylsilane as internal standard. Mass spectra were run on an LKB-9000S or Thomson THN-208 spectrometer.

Column chromatography was carried out with Merck 9385 silica gel (Kieselgel 60; 40—63 μm particle size). T.l.c. was performed with Merck 5715 plates (Kieselgel 60 F_{254}; 0.25 mm

* The β-hydroxy δ-lactones (**17**) display the same relative stereochemistry as the lactone moiety of the hypocholesterolemic agents mevinolin and compactin,[25] two prime synthetic targets.



Scheme 3. *Reagents*: i, NaI, Zn, DMF, reflux; ii, 9-borabicyclo[3.3.1]nonane, THF; iii, 6M NaOH, 30% H_2O_2; iv, PDC, DMF; v, CH_2N_2, Et_2O; vi, Amberlite IR 120 (H^+), H_2O; vii, $Ph_3P{=}CHPh$, Me_2SO; viii, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C; ix, Bu^tMe_2SiCl, NEt_3, DMAP, DMF; x, $NaIO_4$, OsO_4, MeOH

layers); spots were located by spraying with *p*-anisaldehyde–sulphuric acid followed by heating on an electric plate.

Carbohydrate numbering is used for compounds (**7**)—(**16**), and pyran numbering for the lactones (**2**), (**4**), and (**17**)—(**20**).

1,2-O-*Isopropylidene*-3-*deoxy*-5,6-*di*-O-*methylsulphonyl*-α-D-*glucofuranose* (**8**).—Methanesulphonyl chloride (3.4 ml, 43.6 mmol) was slowly added to a stirred solution of the diol (**7**) (1.112 g, 5.44 mmol) in pyridine (30 ml) at 0 °C under nitrogen. After 3 h, water (30 ml) was added and the mixture was extracted with chloroform. To the stirred organic extracts an equal volume of water was added and the pH of the aqueous layer was adjusted to 6 (pH paper) by adding 10M hydrochloric acid. The organic layer was separated, washed successively with aqueous copper nitrate and water, dried ($MgSO_4$), and evaporated. Chromatography on a silica gel column with chloroform–ethanol (19:1) as eluant yielded the *dimethanesulphonate* (**8**) as a syrup which crystallised (1.878 g, 96%), m.p. 84.5—85.5 °C (from ether–pentane); $[\alpha]_D^{26}$ −1.0° (*c* 2.46 in $CHCl_3$) (Found: C, 36.4; H, 5.7; S, 18.1. $C_{11}H_{20}O_9S_2$ requires C, 36.7; H, 5.6; S, 17.8%); $\nu_{max.}$($CHCl_3$) 1 360 and 1 180 cm^{-1}; δ(60 MHz; $CDCl_3$) 1.32 and 1.50 (6 H, 2 s, 2 Me), 3.08 and 3.12 (6 H, 2 s, 2 Me), and 5.80 (1 H, d, *J* 3.8 Hz, 1-H); *m*/*z* 361 (M^+ + 1, 3%), 345 (85), 143 (66), 111 (44), 85 (47), and 43 (100).

1,2-O-*Isopropylidene*-3,5-*dideoxy*-5-*methylene*-α-D-*xylo*-*furanose* (**9**).—A mixture of sodium iodide (7.2 g, 48.0 mmol) and zinc powder (720 mg, 11.0 mmol) was added to a solution of compound (**8**) (1.642 g, 4.56 mmol) in DMF (40 ml) at 70—80 °C under nitrogen. This mixture was then refluxed until completion of the reaction (30—40 min). After cooling to room temperature and addition of water (10 ml) the solution was extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography on a silica gel column with chloroform–ethanol (19:1) as eluant gave the *olefin* (**9**) as an oil (736 mg, 95%), $[\alpha]_D^{21}$ −39.7° (*c* 1.18 in $CHCl_3$) (Found: C, 63.4; H, 8.45. $C_9H_{14}O_3$ requires C, 63.5; H, 8.3%); $\nu_{max.}$(neat) 3 080, 3 000, 1 645, 1 380, 1 370, 1 215, and 1 160 cm^{-1}; δ(200 MHz; $CDCl_3$) 1.33 (3 H, s, Me), 1.53 (3 H, s, Me), 1.61 (1 H, ddd, *J* 13.4, 10.9, and 4.7 Hz, 3-H), 2.18 (1 H, dd, *J* 13.4 and 4.3 Hz, 3-H), 4.63 (1 H, ddd, *J* 10.9, 6.6, and 4.3 Hz, 4-H), 4.75 (1 H, apparent t, *J* 4.2 Hz, 2-H), 5.18 (1 H, dt, *J* 10.3 and 1.2 Hz, 6-H), 5.33 (1 H, dt, *J* 17.2 and 1.2 Hz, 6-H), 5.84 (1 H, ddd, *J* 17.2, 10.3, and 6.6 Hz, 5-H), and 5.85 (1 H, d, *J* 3.7 Hz, 1-H); *m/z* 155 (*M* − 15, 58%), 113 (*M* − 57, 11), 95 (44), 85 (34), 67 (58), 59 (55), and 43 (100).

1,2-O-*Isopropylidene*-3,5-*dideoxy*-α-D-*glucofuranose* (**10**).—A 0.5M solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (THF) (5.8 ml, 2.9 mmol) was added dropwise to a stirred solution of the olefin (**9**) (225 mg, 1.32 mmol) in THF (9 ml) and the mixture was kept at 45 °C for 3 h under nitrogen. Ethanol (2.4 ml) was then added, followed 15 min later by 6M NaOH (0.4 ml) and 30% H_2O_2 (0.8 ml). The mixture was refluxed for 1 h and concentrated under reduced pressure. The residue was diluted with water (10 ml), and the solution was extracted three times with pentane; the aqueous layer containing compound (**10**) was saturated with sodium chloride and extracted five times with ethyl acetate. The ethyl acetate extracts were dried ($MgSO_4$) and evaporated to leave a syrup which was chromatographed on a silica gel column with chloroform–ether (4 : 6) as eluant to afford the alcohol (**10**) as a thick syrup (229 mg, 92%); $[\alpha]_D^{21}$ −7.8° (*c* 1.34 in $CHCl_3$); $\nu_{max.}$(neat) 3 430, 1 385, 1 375, 1 215, and 1 160 cm^{-1}; δ(200 MHz; $CDCl_3$) 1.32 (3 H, s, Me), 1.52 (3 H, s, Me), 1.56 (1 H, ddd, *J* 13.3, 10.9, and 4.7 Hz, 3-H), 1.7—2.0 (3 H, m, 5-H and OH), 2.14 (1 H, dd, *J* 13.3 and 4.1 Hz, 3-H), 3.80 (2 H, t, *J* 5.8 Hz, 6-H), 4.37 (1 H, ddt, *J* 10.9, 8.2, and 4.1 Hz, 4-H), 4.73 (1 H, apparent t, *J* 4.3 Hz, 2-H), and 5.82 (1 H, d, *J* 3.8 Hz, 1-H); *m/z* 173 (*M* − 15, 67%), 131 (*M* − 57, 3), 85 (36), 59 (51), and 43 (100).

Methyl 1,2-O-*Isopropylidene*-3,5-*dideoxy*-α-D-*glucofuranuronate* (**12**).—Pyridinium dichromate (30.0 g, 79.7 mmol) was added to a solution of the alcohol (**10**) (2.52 g, 13.4 mmol) in DMF (200 ml). The solution was stirred at room temperature for 24 h, then water (300 ml) was added and the mixture was extracted twice with carbon tetrachloride to remove the ester (**13**). The aqueous layer containing the acid (**11**) was saturated with sodium chloride and extracted five times with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated to give a solution of the acid (**11**) in DMF. This solution was diluted with anhydrous ether (120 ml), cooled to 0 °C, and treated under nitrogen with ethereal diazomethane until completion of the esterification. Water (50 ml) was then added to the vigorously stirred solution; the organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic phases were washed twice with brine, dried ($MgSO_4$), and evaporated, and the residue was purified on a silica gel column with hexane–ether (4:6) as eluant to give the *ester* (**12**) as an oil (1.80 g, 62%); $[\alpha]_D^{21}$ −20.5° (*c* 1.25 in $CHCl_3$) (Found: C, 55.3; H, 7.5. $C_{10}H_{16}O_5$ requires C, 55.5; H, 7.5%); $\nu_{max.}$(neat) 1 745, 1 440, 1 385, 1 375, 1 215, and 1 160 cm^{-1}; δ(200 MHz; $CDCl_3$) 1.32 (3 H, s, Me), 1.52 (3 H, s, Me), 1.58 (1 H, ddd, *J* 13.3, 10.8, and 4.8 Hz, 3-H), 2.26 (1 H, dd, *J* 13.3 and 4.3 Hz, 3-H), 2.62 (2 H, AB of ABX, *J* 15.4 and 6.5 Hz, 5-H), 3.70 (3 H, s, Me), 4.56 (1 H, ddt, *J* 10.8, 4.3, and 6.5 Hz, 4-H), 4.74 (1 H, apparent t, *J* 4.2 Hz, 2-H), and 5.81 (1 H, d, *J* 3.8 Hz, 1-H).

Methyl 3,5-*Dideoxy*-β-D-*glucofuranuronate* (**15**).—The ester (**12**) (593 mg, 2.74 mmol) was stirred at room temperature with water (24 ml) and Amberlite IR 120 resin (H^+ form) (2.5 g). After completion of the reaction (24—48 h, depending on the room temperature) the resin was filtered off and carefully washed with water. The water was evaporated off under reduced pressure and the residue was chromatographed on silica gel with chloroform–ethanol (9:1 to 7:1) as eluant to afford the *diol* (**15**) as a solid (421 mg, 87%), m.p. 73.5—74 °C (from acetone–hexane); $[\alpha]_D^{21}$ −32.3° (*c* 0.88 in Me_2CO); (Found: C, 48.0; H, 6.6. $C_7H_{12}O_5$ requires C, 47.7; H, 6.9%); $\nu_{max.}$(KBr) 3 310, 1 725, 1 445, 1 235, 1 155, and 1 035 cm^{-1}; δ(200 MHz; CD_3COCD_3) 1.82—2.08 (2 H, m, *J* 13.2, 8.9, 4.2, 6.3, and 1.0 Hz, 3-H), 2.60 (2 H, AB of ABX, *J* 15.2, 7.1, and 6.2 Hz, 5-H), 3.64 (3 H, s, Me), 4.08 (1 H, dd, *J* 4.0 and 0.7 Hz, OH), 4.12 (1 H, br t, *J* 4.0 Hz, 2-H), 4.61 (1 H, apparent ddt, *J* 8.9, 6.3, and 6.6 Hz, 4-H), 5.05 (1 H, d, *J* 4.4 Hz, OH), and 5.13 (1 H, d, *J* 4.4 Hz, 1-H); *m/z* 145 (M^+ − MeO, 24%), 127 (100), and 103 (46).

3,5-*Dideoxy*-D-*glucuronic Acid Trimethylene Dithioacetal* (**16c**).—Propane-1,3-dithiol (220 μl, 2.6 mmol) was added to a stirred solution of the acid (**11**) (103 mg, 0.509 mmol) in concentrated hydrochloric acid (1 ml of 10M solution) at 0 °C. Stirring was continued for 90 min, until completion of the reaction. Sodium chloride was added and the mixture was extracted four times with chloroform. The organic extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with chloroform–ethanol (9:1) as eluant to give the dithioacetal (**16c**) as an oil (89 mg, 70%), $\nu_{max.}$($CHCl_3$) 3 660—3 400, 1 710, and 1 670 cm^{-1}; δ(60 MHz: $CDCl_3$) 1.95 (2 H, m, *J* 6.0 Hz, dithiane), and 2.72 (4 H, m, *J* 6.0 Hz, dithiane).

(4S,6R)-3,4,5,6-*Tetrahydro*-4-*hydroxy*-6-(2-*phenylethenyl*)-2H-*pyran*-2-*one* (**17**).—To a suspension of benzyltriphenylphosphonium chloride (1.75 g, 4.50 mmol) in Me_2SO (20 ml) was added 1.0M sodium methylsulphinylmethanide in Me_2SO (4.0 ml, 4.0 mmol). The mixture was heated until a deep red homogeneous solution was obtained. The solution (9.2 ml, 1.54 mmol) was added dropwise to a stirred solution of the diol (**15**) (135 mg, 0.77 mmol) in Me_2SO (3 ml) under nitrogen, and the mixture was kept at room temperature for 3 h. It was then quenched quickly with cold 1M hydrochloric acid (10 ml) and extracted three times with ethyl acetate. The combined organic phases were washed twice with water and once with brine, dried ($MgSO_4$), and evaporated; the residue was chromatographed on a silica gel column with chloroform–ethanol (39:1) as eluant to give the oily lactone (**17**) (76 mg, 45%) as an inseparable mixture of *E*- and *Z*-isomers; $\nu_{max.}$($CHCl_3$) 3 430, 1 725, 1 600, 1 245, 1 065, and 1 035 cm^{-1}; δ(200 MHz; $CDCl_3$) 2.01 (2 H, m, 5-H), 2.71 (2 H, m, *J* 17.7, 5.1, 3.8, and 1.4 Hz, 3-H), 4.43 (1 H, m, $J_{apparent}$ 4.2 Hz, 4-H), 5.34 (0.4 H, m, 6-H *E*), 5.60 (0.6 H, dt, *J* 3.6 and 9.3 Hz, 6-H *Z*), 5.71 (0.6 H, dd, *J* 10.7 and 9.3 Hz, 1′-H *Z*) 6.20 (0.4 H, dd, *J* 15.9 and 6.3 Hz, 1′-H *E*), 6.70 and 6.71 (1 H, dd and d, *J* 15.9 and 1.3 Hz and *J* 10.7 Hz, 2′-H *E* and 2′-H *Z*), and 7.17—7.38 (5 H, m, Ph).

(6R)-5,6-*Dihydro*-6-(2-*phenylethenyl*)-2H-*pyran*-2-*one* (**18**).—To a stirred solution of the lactone (**17**) (70 mg, 0.32 mmol) in dichloromethane (3 ml) at 0 °C under nitrogen were added successively triethylamine (0.18 ml, 1.3 mmol) and methanesulphonyl chloride (0.075 ml, 0.96 mmol). After 30 min the reaction medium was diluted with dichloromethane (10 ml), washed with 1M hydrochloric acid and water, dried ($MgSO_4$), and evaporated to dryness. Chromatography on a silica gel column with hexane–ethyl acetate (8:2) as eluant afforded the *Z*- and *E*-unsaturated lactones (**18**) (55 mg, 85%): *Z-isomer*, m.p. 55—55.5 °C (from hexane); $[\alpha]_D^{21}$ −358° (*c* 0.75 in $CHCl_3$) (Found: C, 77.9; H, 5.9. $C_{13}H_{12}O_2$ requires C, 78.0; H, 6.0%); $\nu_{max.}$($CHCl_3$) 1 723, 1 385, 1 250, 1 060, and 1 020 cm^{-1}; δ(200 MHz; $CDCl_3$) 2.48 (2 H, m, 5-H), 5.30 (1 H, ddt, *J* 5.7, 1.0, and 9.3 Hz, 6-H), 5.84 (1 H, dd, *J* 11.5 and 9.3 Hz, 1′-H), 6.05 (1 H, ddd, *J* 9.8, 2.2, and 1.5 Hz, 3-H), 6.78 (1 H, br d, *J* 11.5 Hz, 2′-H),

6.88 (1 H, ddd, *J* 9.8, 5.1, and 3.4 Hz, 4-H), and 7.20—7.40 (5 H, m, Ph); *m/z* 200 (M^+, 35%); *E*-isomer, (+)-goniothalamin, m.p. 79.5—80 °C (from ether–hexane) (lit.,[27] 85—86 °C); $[\alpha]_D^{21}$ +137° (*c* 0.74 in MeOH) (lit.,[27] +135°); $\nu_{max.}$($CHCl_3$) 1 723, 1 380, 1 250, 1 060, 1 020, and 965 cm^{-1}; δ(200 MHz; $CDCl_3$) 2.55 (2 H, m, 5-H), 5.11 (1 H, m, *J* 8.7, 6.3, and 1.2 Hz, 6-H), 6.10 (1 H, dt, *J* 9.8 and 1.9 Hz, 3-H), 6.28 (1 H, dd, *J* 16.0 and 6.3 Hz, 1′-H), 6.73 (1 H, dd, *J* 16.0 and 1.2 Hz, 2′-H), 6.93 (1 H, ddd, *J* 9.8, 4.4, and 4.1 Hz, 4-H), and 7.20—7.40 (5 H, m, Ph).

(4S,6R)-3,4,5,6-*Tetrahydro*-6-(2-*phenylethenyl*)-4-*dimethyl*-t-*butylsilyloxy*-2H-*pyran*-2-*one* (**19**).—To a stirred solution of the lactone (**17**) (45 mg, 0.21 mmol) in DMF (1 ml), triethylamine (0.17 ml, 1.2 mmol), 4-(dimethylamino)pyridine (8 mg, 0.06 mmol), and dimethyl-t-butylsilyl chloride (93 mg, 0.62 mmol) were successively added at room temperature under nitrogen. The mixture was set aside for 8 h and then poured into vigorously stirred hexane (30 ml). A solid precipitated which was separated and washed twice with hexane (10 ml). The combined hexane solutions were then washed three times with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column with hexane–ether (6:4) as eluant to give the ethers (**19**) (61 mg, 89%): *E*-isomer, m.p. 60.5—63 °C (from hexane); $[\alpha]_D^{21}$ −20.5° (*c* 0.60 in $CHCl_3$); $\nu_{max.}$(CCl_4) 3 030, 1 750, 1 345, 1 260, 1 230, 1 080, 1 040, and 965 cm^{-1}; δ(200 MHz; $CDCl_3$) 0.10 (6 H, s, 2 Me), 0.91 (9 H, s, Bu^t), 1.95 (2 H, m, *J* 14.0, 10.8, 3.8, and 2.7 Hz, 5-H), 2.65 (2 H, m, *J* 17.5 and 3.8 Hz, 3-H), 4.36 (1 H, m, *J* 3.8 Hz, 4-H), 5.35 (1 H, m, *J* 10.8, 6.4, 3.8, and 1.3 Hz, 6-H), 6.22 (1 H, dd, *J* 15.9 and 6.4 Hz, 1′-H), 6.70 (1 H, dd, *J* 15.9 and 1.3 Hz, 2′-H), and 7.22—7.45 (5 H, m, Ph); *Z-isomer*, m.p. 65—65.5 °C (from hexane); $[\alpha]_D^{21}$ −93.4° (*c* 0.66 in $CHCl_3$) (Found: C, 68.7; H, 8.3. $C_{19}H_{28}O_3Si$ requires C, 68.6; H, 8.5%); $\nu_{max.}$(CCl_4) 3 030, 1 750, 1 255, 1 230, 1 085, and 1 040 cm^{-1}; δ(200 MHz; $CDCl_3$) 0.008 (3 H, s, Me), 0.05 (3 H, s, Me), 0.82 (9 H, s, Bu^t), 1.91 (2 H, m, *J* 14.0 and 10.2 Hz, 5-H), 2.62 (2 H, m, *J* 17.5, 4.3, and 3.2 Hz, 3-H), 4.33 (1 H, m, $J_{apparent}$ 3.8 Hz, 4-H), 5.71 (2 H, m, *J* 9.4 Hz, 6-H and 1′-H), 6.68 (1 H, d, *J* 10.2 Hz, 2′-H), and 7.23—7.40 (5 H, m, Ph).

(4S,6R)-6-*Formyl*-3,4,5,6-*tetrahydro*-4-*dimethyl*-t-*butylsilyloxy*-2H-*pyran*-2-*one* (**20**).—Sodium metaperiodate (38 mg, 0.18 mmol) was added to a solution of the *O*-dimethyl-t-butylsilyl derivatives (**19**) (20 mg, 0.060 mmol) and osmium tetraoxide (4 mg, 0.016 mmol) in dry methanol (4 ml), and the suspension was stirred at 45 °C for 20 h under nitrogen. More sodium metaperiodate (25 mg, 0.12 mmol) was then added and the mixture was stirred for an additional 4 h. After addition of anhydrous ether (5 ml), the slurry was filtered and the solvent and the benzaldehyde were evaporated off under reduced pressure to give the crude oily aldehyde (**20**) (17 mg), which was homogeneous on t.l.c. The *semicarbazone*, prepared according to Fieser,[32] (10 mg, 53%), had m.p. 204—206 °C (decomp.) (from ethanol); $[\alpha]_D^{22}$ −22° (*c* 0.38 in EtOH) (Found: C, 49.2; H, 8.5; N, 13.3. $C_{13}H_{25}N_3O_4Si$ requires C, 49.5; H, 8.0; N, 13.3%); $\nu_{max.}$(KBr) 3 400, 1 730, 1 700, 1 670, 1 630, 1 355, 1 245, 1 165, 1 075, and 1 040 cm^{-1}; δ(200 MHz; CD_3OD) 0.17 (6 H, s, 2 Me), 0.95 (9 H, s, Bu^t), 2.11 (2 H, m, 5-H), 2.70 (2 H, AB of ABX, *J* 17.6, 3.9, and 3.2 Hz, 3-H), 4.49 (1 H, m, $J_{apparent}$ 3.5 Hz, 4-H), 5.29 (1 H, dt, *J* 9.4 and 5.5 Hz, 6-H), and 7.28 (1 H, d, *J* 5.5 Hz, –CH=N–); *m/z* (NH_3; chemical ionization) 333 ($M + NH_4^+$, 53%), 316 ($M + H^+$, 100), and 258 (47).

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