Pergamon

Tetrahedron 55 (1999) 2493–2514

TETRAHEDRON

Stereocontrolled Syntheses of Novel Styryl Lactones, (+)-Goniodiol, (+)-Goniotriol, (+)-8-Acetylgoniotriol, (+)-Goniofufurone, (+)-9-Deoxygoniopypyrone, (+)-Goniopypyrone, and (+)-Altholactone from Common Intermediates and Cytotoxicity of Their Congeners

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Received 11 November 1998; accepted 28 December 1998

Abstract: Concise syntheses of (+)-goniodiol, (+)-goniotriol, (+)-8-acetylgoniotriol, (+)-goniofufurone, (+)-9-deoxygoniopypyrone, (+)-goniopypyrone, and (+)-altholactone and their congeners from chiral lactonic aldehydes **27** and **36** as common intermediates are described. The key features in the syntheses are based on the *in situ* generation of unstable aldehydes **27** and **36** followed by their chemoselective reaction with triisopropoxyphenyltitanium to afford both diastereomers **28**, **29** and **37**, **38** at the C-8 positions. The cytotoxicity of styryl lactone congeners against P388 murine leukemia cells was examined.

Keywords : Furans; Styryl Lactones; Cytotoxicity

Introduction

Since the ethanolic extract of the stem bark of *Goniothalamus giganteus* Hook. f. Thomas (Annonaceae) showed significant cytotoxicity against 3PS murine lymphocytic leukemia cells,[1] there has been considerable interest in identifying the constituents.[2-4] Bioactivity-directed studies by McLaughlin *et al.* have resulted in the isolation of physiologically active styryl lactones (+)-goniodiol (**1**),[3a] (+)-goniotriol (**2**),[3b] (+)-8-acetylgoniotriol (**3**),[3c] (+)-goniofufurone (**4**),[3c] (+)-9-deoxygoniopypyrone (**5**),[3a] (+)-goniopypyrone (**6**),[3c] and (+)-altholactone (**7**).[3d] These styryl lactones exhibited cytotoxicity against human tumor cells. The relative configurations of **1** - **7** were revealed by NMR spectral studies and X-ray crystallographic analyses to have highly

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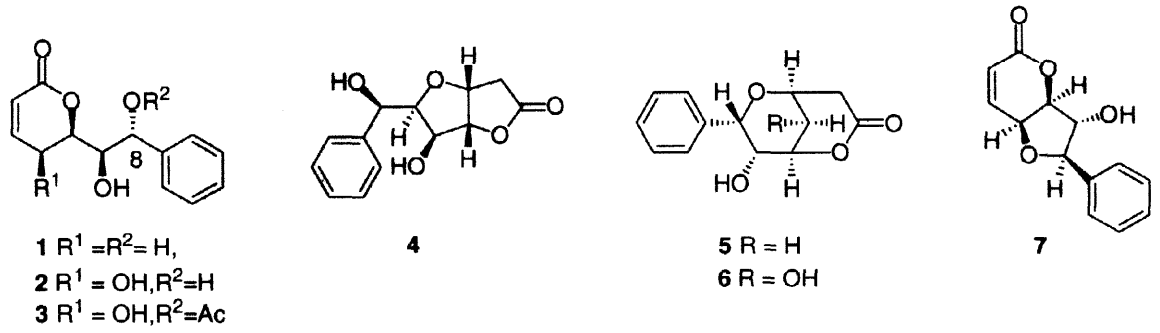


1 $R^1 = R^2 = H$,
2 $R^1 = OH, R^2 = H$
3 $R^1 = OH, R^2 = Ac$

4

5 R = H
6 R = OH

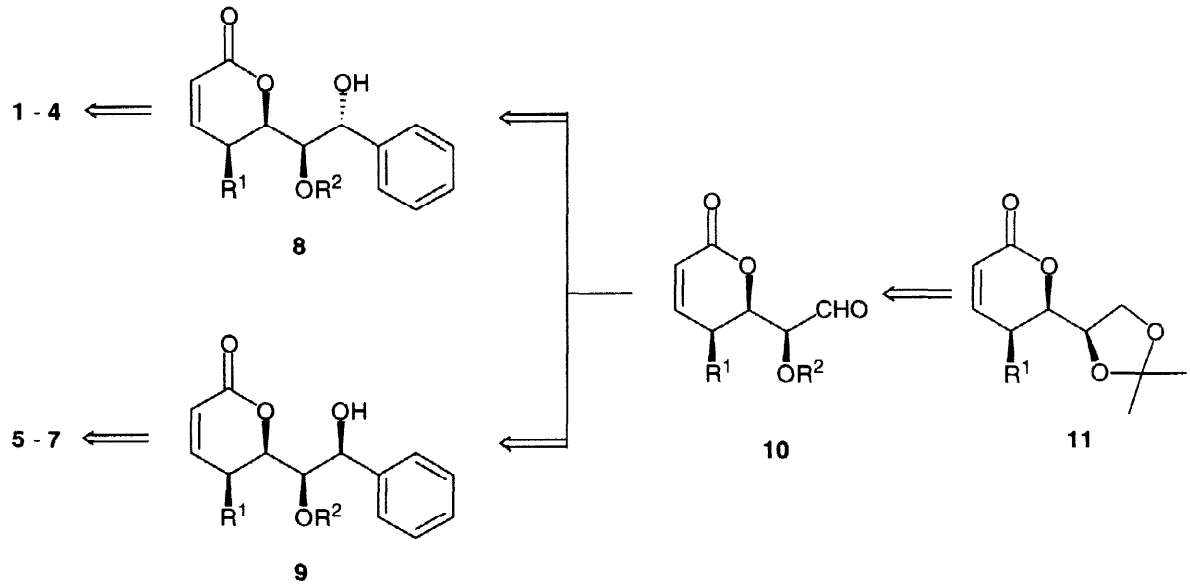
7

Figure 1. Naturally occurring styryl lactones

oxygenated goniothalamin skeletons with contiguous stereogenic centers. Due to the interesting heterocyclic skeletons and the significant cytotoxicities, much attention have been paid to the syntheses of these styryl lactones.[5-15] Among them, the first total syntheses of **1** - **7** by Shing *et al.*[5] and us[15a] led to the confirmation of their absolute configurations as depicted in Figure 1. Herein we report in detail enantio- and stereo-selective syntheses of (+)-goniodiol (**1**), (+)-goniotriol (**2**), (+)-8-acetylgoniotriol (**3**), (+)-goniofufurone (**4**), (+)-9-deoxygoniopypyrone (**5**), (+)-goniopypyrone (**6**), and (+)-altholactone (**7**) from the chiral lactonic aldehydes **27** and **36** as common intermediates and also cytotoxicity of various structural types of styryl lactones congeners prepared in the course of our total syntheses. At the time we started this work, the absolute configurations of these styryl lactones except altholactone were not determined yet. We assumed these stereostructures of **1** - **6** to have the same configurations at the bishomobenzylic positions as goniothalamin based on their biosynthetic pathway.[16]

Results and Discussion

Our plan to address the interesting bicyclic systems in styryl lactones **4** - **7** revolved around preparing suitably protected lactone **8** and its C-8 epimer **9** and cyclizing them site- and stereo-selectively. (Scheme 1) Our

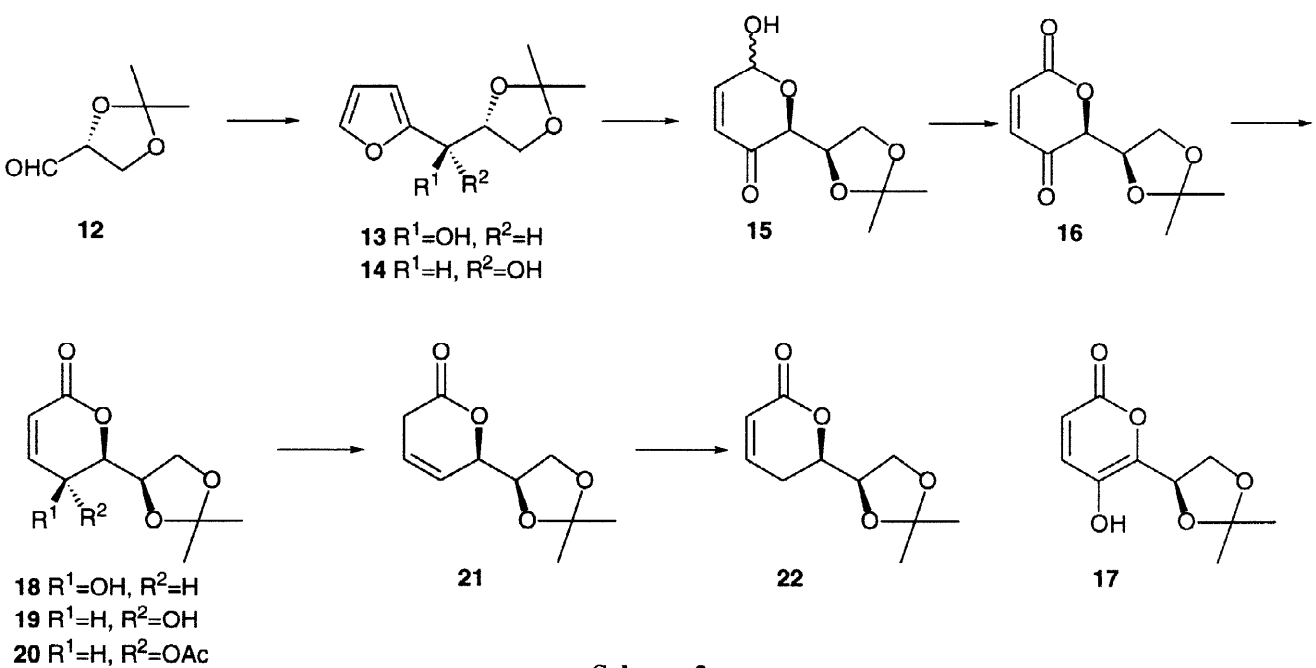


Scheme 1. Synthetic strategy

common intermediate for syntheses was lactonic aldehyde **10**, which could be phenylated to give both diastereomers **8** and **9**. Aldehyde **10** having a *syn*-diol functionality should be available from lactone **11**.

Preparation of (6*R*)-Lactones 18 and 22

Our intial targets, chiral α,β-unsaturated lactones **18** and **22**, were prepared from the known chiral furylmethanol **14**[17] on the basis of our previous work.[18] (Scheme 2) Homochiral furylmethanol **14** was obtained from 2,3-*O*-isopropylidene-D-glyceraldehyde (**12**)[19] as a chiral source according to the procedure described by Jurczak *et al.*[20] Addition of 2-lithiofuran to **12**, gave an inseparable mixture of furylmethanols **13** and **14** in a ratio of 3 : 4. Oxidation of alcohols **13** and **14** with chemical manganese dioxide gave an unstable ketone, which without purification was reduced with L-Selectride to afford the *syn*-diol **14** in 84% yield (2 steps). The 400 MHz ^{1}H NMR spectrum of **14** showed that the diastereomeric excess of **14** was >96%. Ring enlargement of furylmethanol **14** using *N*-bromosuccinimide[21] in aqueous THF furnished lactol **15** quantitatively. Attempts to oxidize **15** to lactone **16** under several conditions, such as pyridinium chlorochromate, DMSO-oxalyl chloride, and TEMPO, failed. When **15** was subjected to Fieser oxidation (chromium (IV) oxide in acetic acid) according to the procedure described by Kuo *et al.*,[22] **16** was monitored on TLC and enol **17** was isolated after workup. Due to the facile enolization of keto lactone **16** to **17**, one-pot conversion of **15** into allylic alcohol **18** was developed. Thus, Fieser oxidation of **15** generated *in situ* **16**, whose reduction with sodium triacetoxyborohydride in *i*-PrOH provided the desired alcohol **18** and its epimer **19** in a ratio of 7 : 1, respectively. The stereochemistry at the C-5 position was determined by the ^{1}H NMR spectrum of **18**, which showed the 5-H signal as a double doublet ($J_{4,5}$=5.5, $J_{5,6}$=2.4 Hz), indicating the presence of pseudoaxial and pseudoequatorial substituents at the C-5 and C-6 positions. The observed selectivity would be explained by assuming that the reduction would occur preferentially from the less hindered side, the *re*-face, to give *syn*-alcohol **18** as a major product. Compound **18** was converted into the deoxygenated lactone **22** by successive

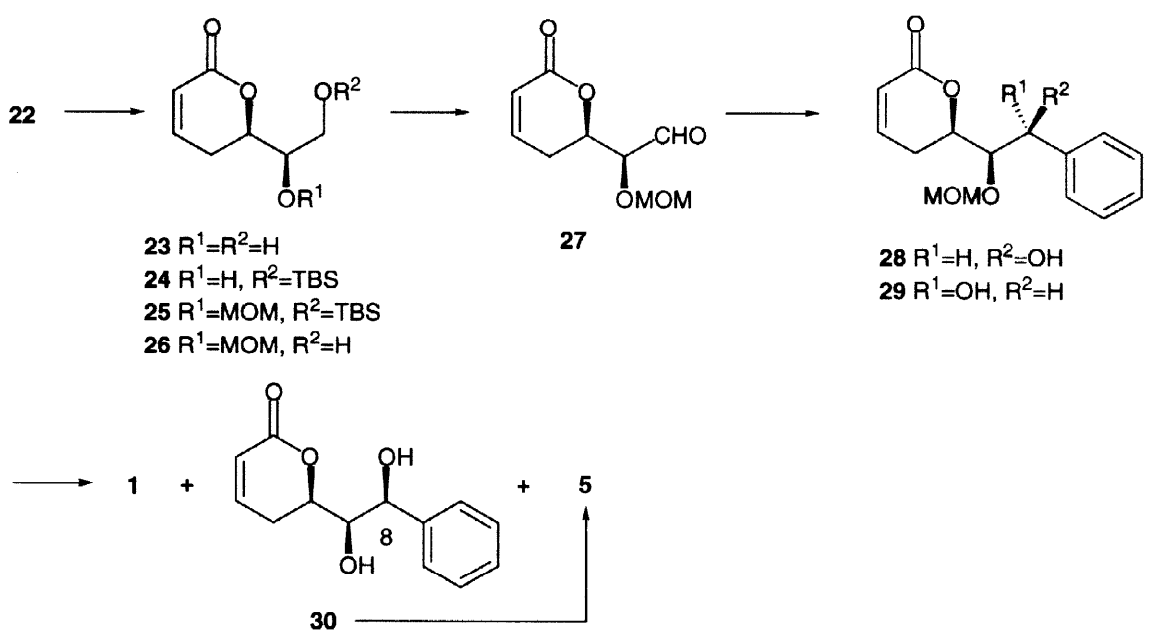


Scheme 2.

acetylation of **18**, reductive deacetoxylation of allylic acetate **20**, and isomerization of the β,γ-unsaturated lactone **21** in 90% overall yield from **18**.

Synthesis of (+)-Goniodiol (1), (-)-8-*epi*-Goniodiol (30), and (+)-9-Deoxygoniopypyrone (5)

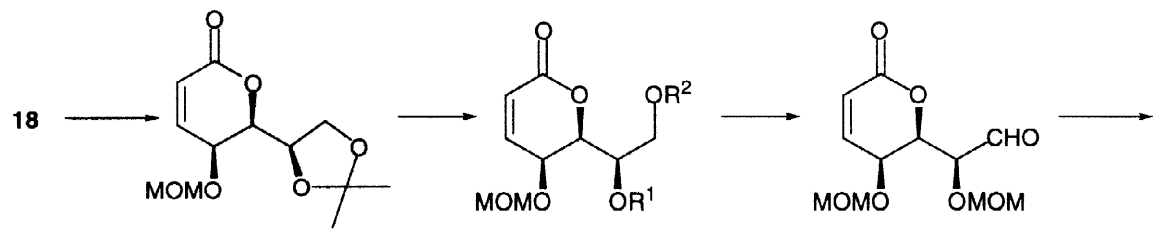
With the requisite α,β-unsaturated lactone **22** in hand, we explored a synthesis of (+)-goniodiol (**1**), (-)-8-*epi*-goniodiol (**30**), and (+)-9-deoxygoniopypyrone (**5**). Deprotection of the acetonide group in **22** afforded diol **23**, which was further converted into alcohol **26** by sequential selective silylation of the primary alcohol in **23**, methoxymethylation of the secondary alcohol in **24**, and removal of the silyl ether in **25** in 86% overall yield from **22**. Swern oxidation[23] of **26** produced *in situ* aldehyde **27** which was detected on TLC, but could not be isolated owing to its instability. Thus, we prepared the unstable aldehyde **27** *in situ* by Swern oxidation of **26** and investigated the introduction of a phenyl moiety into **27**. Although additions to **27** with several organometallics, such as phenyl-lithium, -magnesium bromide, and -cerium dichloride, were tried, the chemoselective addition was achieved only with the use of triisopropoxyphenyltitanium {PhTi(O*i*-Pr)3}.[24a] Aldehyde **27**, generated *in situ*, was treated with PhTi(O*i*-Pr)3, prepared from PhLi and Ti(O*i*-Pr)3Cl, in CH_2Cl_2 - Et_2O to afford an inseparable mixture of diastereomers **28** and **29** in 94% yield as a ratio of 1 : 1. Deprotection of the methoxymethyl group in **28** and **29** with aqueous AcOH gave (+)-goniodiol (**1**) (49%) as a colorless oil, $[\alpha]_D^{25}$+74.8 (*c* 0.7, $CHCl_3$){lit., $[\alpha]_D^{30}$+75.76 ($CHCl_3$)[2] and $[\alpha]_D^{22}$+74.4 (*c* 0.3, $CDCl_3$)[3a]}, and (-)-8-*epi*-goniodiol (**30**) (43%) as a colorless oil, $[\alpha]_D^{25}$-13.7 (*c* 0.7, $CHCl_3$), together with a trace of the bicyclic compound **5** (4.6%). Treatment of **30** with a catalytic amount of DBU in THF resulted in the intramolecular Michael addition reaction to furnish (+)-9-deoxygoniopypyrone (**5**) as a colorless needles, mp 203-204°C, (lit.,[3a] mp 203-204°C); $[\alpha]_D^{26}$+11.1 (*c* 0.3, EtOH) {lit.,[3a] $[\alpha]_D^{22}$+12 (*c* 0.1, EtOH)}. Since the spectroscopic data including the optical rotations of both synthetic goniodiol (**1**) and 9-deoxygoniopypyrone (**5**) are identical with those of natural products,[2,3a] the absolute configurations of goniodiol and 9-deoxygoniopypyrone are unambiguously determined to be **1** and **5**, respectively.

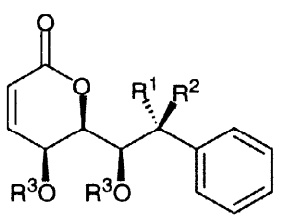


Scheme 3.

Preparation of Key Compounds 37 and 38

Having developed a new synthetic route to (+)-goniodiol (**1**) and (+)-9-deoxygoniopypyrone (**5**), we turned our attention to the synthesis of the highly oxygenated styryl lactones, (+)-goniotriol (**2**) and (+)-8-acetylgoniotriol (**3**), and the bicyclic styryl lactones, (+)-goniofufurone (**4**), (+)-goniopypyrone (**6**), and (+)-altholactone (**7**), from the hydroxy lactone (**18**). Goniotriol derivatives **37** and **38**, pivotal intermediates for the styryl lactones synthesis, were prepared as follows (Scheme 4). Methoxymethylation of the hydroxyl group in **18** gave compound **31** (83%), which was further converted into alcohol **35** by the same sequences as above *via* diol **32**, silyl ether **33**, and MOM ether **34** in 85% overall yield from **31**. Owing to the instability, aldehyde **36**, produced *in situ* by Swern oxidation of **35**, was also used for the next addition reaction. Reactions of **36** with several organometallics were examined and the results are shown in Table 1. In the reaction of PhLi or PhMgBr, none of the desired products were almost obtained (entry 1,2). Aldehyde **37** reacted with PhTi(O*i*-Pr)$_3$,[24a] prepared from PhLi and Ti(O*i*-Pr)3Cl, to give phenylated products **37** and **38** in high yield with moderate diastereoselectivity (entry 3). Addition of PhTi(O*i*-Pr)3,[24a] prepared from PhMgBr and Ti(O*i*-Pr)3Cl, to **36** gave **37** and **38** in moderate yield with relatively low diastereoselectivity (entry 4). In contrast, reaction of PhTiCl$_3$ to **36** yielded only complexed mixtures (entry 5). Unfortunately, we could not obtain **38** as a major product under these conditions. Although the stereochemistries of **37** and **38** could not be determined at this stage, we deduced **37** and **38** to be a Felkin-Anh product and a chleation product, respectively, based on the results reported by Reetz *et al.*[24b]





Scheme 4.

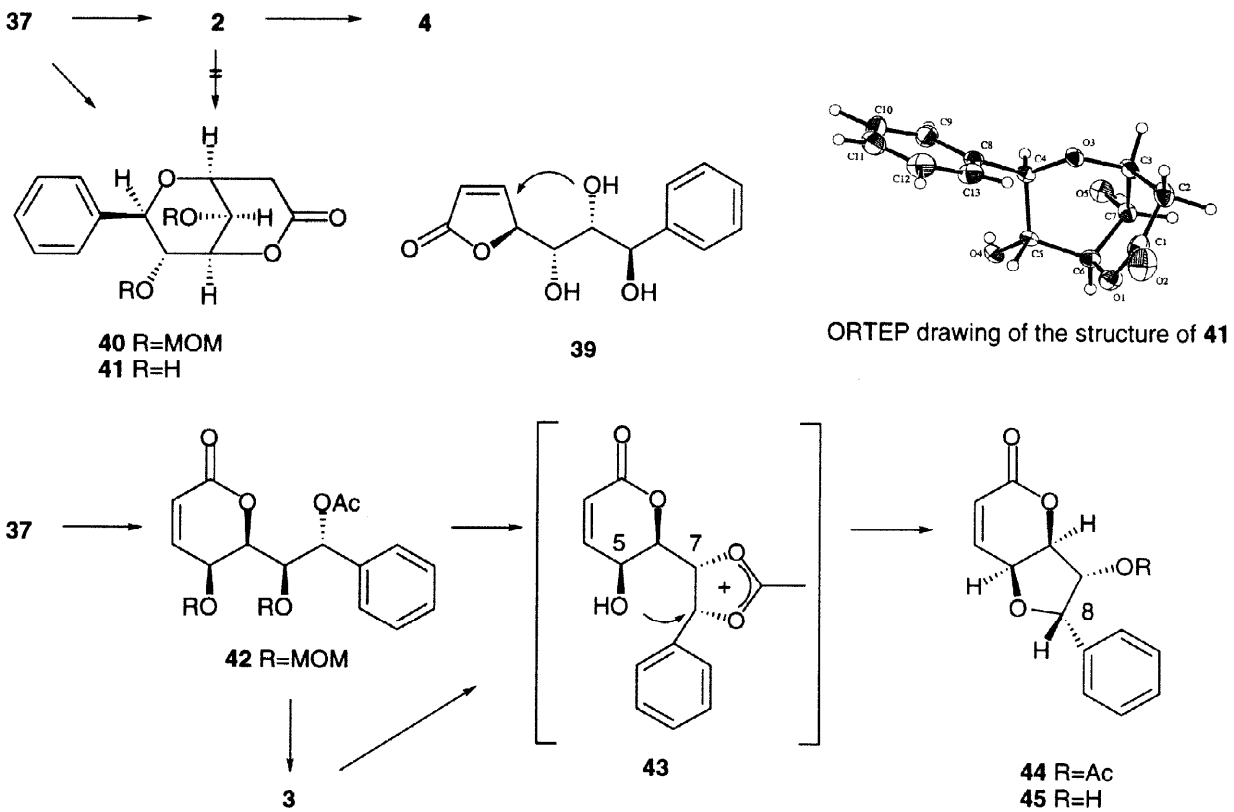
Table 1. Reaction of **36** with Ph-M

entry	Ph-M	yields (%) 37	38
1	PhLi	-	-
2	PhMgBr	trace	
3	PhTi(OiPr) $_3$[a]	78	19
4	PhTi(OiPr) $_3$[b]	34	17
5	PhTiCl$_3$	-	-

[a] Prepared from PhLi and Ti(OiPr)$_3$Cl
[b] Prepared from PhMgBr and Ti(OiPr)$_3$Cl

Synthesis of (+)-Goniotriol (2), (+)-8-Acetylgoniotriol (3), (+)-Goniofufurone (4), (-)-8-*epi*-Goniopypyrone (41), and (+)-8-*epi*-Altholactone (45)

Employing **37**, we synthesized (+)-goniotriol (**2**), (+)-8-acetylgoniotriol (**3**), (+)-goniofufurone (**4**), and their congeners as shown in Scheme 5. Removal of the two MOM groups in **37** with trifluoroacetic acid (TFA) gave (+)-goniotriol (**2**) (88%) as colorless prisms, mp 169.5-170.5°C (lit.,[3b] mp 170°C); $[\alpha]_D^{25}$ +120.2 (*c* 0.4, MeOH){lit., [3b] $[\alpha]_D$ +121 (MeOH)}. Interestingly, treatment of **2** with a catalytic amount of DBU in THF brought about the ring transformation to the bicyclo[3.3.0]octane skeleton providing (+)-goniofufuone (**4**) (60%) as colorless plates, mp 153-154.5°C (lit.,[3c] mp 152-154°C); $[\alpha]_D^{26}$ +9.8 (*c* 0.4, EtOH){lit., [3c] $[\alpha]_D^{22}$ +9 (EtOH)}. Although this transformation pathway is obscure at the present time, butenolide **39** might be produced by the equilibration of the γ-hydroxy δ-lactone moiety in **2** and then the intramolecular Micahel addition of the hydroxyl group at the C-7 position in **39** could proceed to give **4**. Shing *et al.* reported that the DBU mediated cyclization of 8-*epi*-goniotriol resulted in the intramolecular Michael addition of the hydroxyl group at the C-8 position to give goniopypyrone.[5] We, however, could not obtain the expected 8-*epi*-goniopypyrone (**41**) in the cyclization of goniotriol (**2**). (-)-8-*epi*-Goniopypyrone (**41**) was prepared by treatment of **37** with a catalytic amount of DBU followed by deprotection of the MOM group in **40** in 65% (2 steps), colorless prisms, mp 177.5-184.5°C; $[\alpha]_D^{26}$- 63.6 (*c* 0.4, EtOH). The stereostructure of **41** was unambiguously determined by its X-ray crystallographic analysis as depicted.

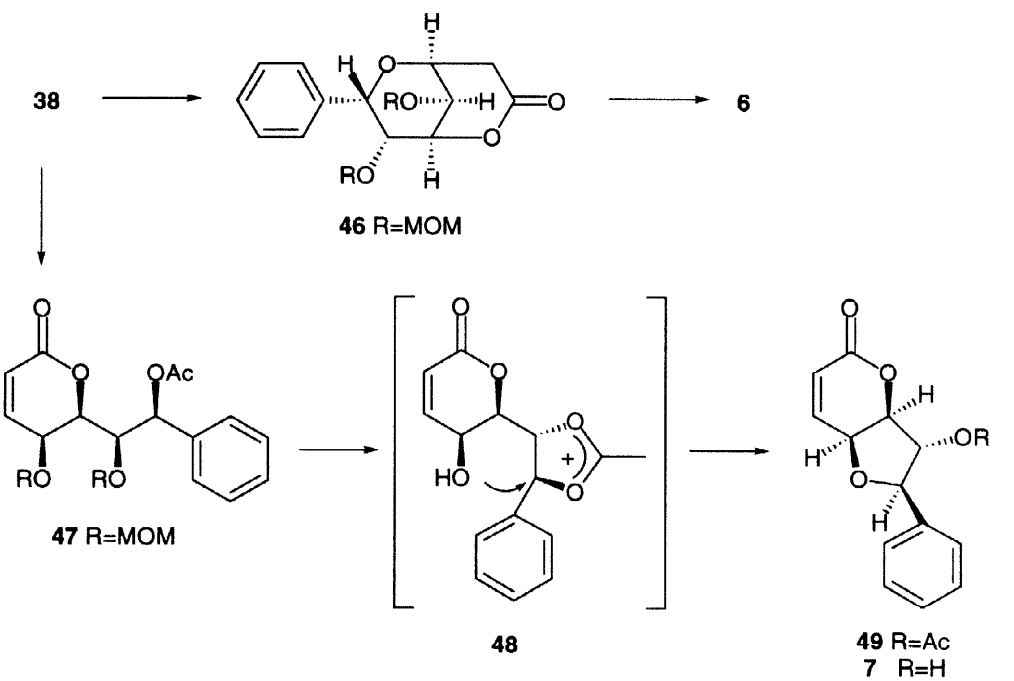


Scheme 5.

(+)-8-Acetylgoniotriol (**3**) and (+)-8-*epi*-altholactone (**45**) were prepared as follows. Acetylation of **37** gave **42**, which on treatment with TFA afforded the desired **3** (59%) as colorless needles, mp 166-167.5°C (lit.,[3c] mp 158-159°C); $[\alpha]_D^{21}$ +41.1 (*c* 0.5, EtOH){lit., [3c] $[\alpha]_D^{22}$ +30 (EtOH)}, together with the bicyclic compound **44** (20%). Long-time exposure of **42** with TFA led to the formation of **44** as a single product. Since treatment of **3** with TFA gave **44** quantitatively, the formation of the bicyclic ring system can be explained by assuming that the participation[25] of the neighboring hydroxyl group at the C-7 position resulted in the generation of the acetoxonium ion intermediate **43**, which could be subsequently cyclized by the nucleophilic attack of the hydroxyl group at the C-5 position with inversion at the benzylic position. Acetate **44** was further converted into the known 8-*epi*-altholactone (**45**)[9,10] by alkaline hydrolysis of the ester portions followed by lactonization in 96% yield, mp 196.5-197°C (lit.,[9] mp 190-191°C; lit.,[10] mp 193.5-194°C); $[\alpha]_D^{24}$ +233.1 (*c* 0.5, EtOH){lit., [9] $[\alpha]_D$ +268 (EtOH); lit., [10] $[\alpha]_D^{26}$ +224 (EtOH)}.

Synthesis of (+)-Goniopypyrone (6) and (+)-Altholactone (7)

We next synthesized (+)-goniopypyrone (**6**) and (+)-altholactone (**7**) from alcohol **38** as shown in Scheme 6. The DBU mediated intramolecular Michael addition of the hydroxyl group in **38** afforded the bicyclic compound **46** (95%), whose treatment with TFA gave (+)-goniopypyrone (**6**) (93%) as colorless needles, mp 174-177°C (lit.,[3c] mp 182-184°C); $[\alpha]_D^{22}$ +42.8 (*c* 0.3, EtOH){lit., [3c] $[\alpha]_D^{22}$ +54 (EtOH)}. (+)-Altholactone (**7**) was prepared similarly as for its 8-epimer **45** by acetylation of the hydroxyl group in **38**, cyclization of acetate **47** with TFA*via* the acetoxonium ion intermediate **48**, and hydrolysis of the ester moieties in **49** followed by lactonization, in 88% overall yield as colorless prisms, mp 113-115°C (lit.,[3d] mp 110°C; lit.,[10] mp 113-114°C); $[\alpha]_D^{24}$ +182.8 (*c* 0.5, EtOH){lit.,[3d] $[\alpha]_D^{25}$ +184.7 (EtOH)}.



Scheme 6.

Biological Evaluation

The biological activities of 16 compounds including several natural styryl lactones (**1**, **4**, **5**, **6**) and their congeners (**23**, **30**, **37**, **38**, **40-42**, **44-47**, **49**) were measured in terms of their cytotoxicity against P388 murine leukemia cells. The IC_{50} are shown in Table 2.

Table 2. *In Vitro* Cytotoxicity of Styryl Lactones and Their Congeners against P 388 Murine Leukemia Cells

compound	IC_{50} (μg/mL)	compound	IC_{50} (μg/mL)
1	4.56	**40**	4.86
4	>100	**41**	14.93
5	13.63	**42**	0.39
6	5.33	**44**	1.30
23	11.37	**45**	1.30
30	7.35	**46**	7.14
37	1.43	**47**	0.41
38	3.55	**49**	0.87

From these results, it is apparent that these styryl lactones except **4** and their congeners are marginally cytotoxic. Goniotriol derivatives (**37**, **38**, **42**, **47**) and altholactone derivatives (**44**, **45**, **49**) inhibited cell growth better than natural styryl lactones (**1**, **4**, **5**, **6**). It is interesting that the most active compounds **42** and **47** have the α,β-unsaturated lactone skeleton and the all hydroxyl groups protected as acetate and MOM ether.

Conclusion

We have succeeded in the stereoselective syntheses of (+)-goniodiol, (+)-goniotriol, (+)-8-acetylgoniotriol, (+)-goniofufurone, (+)-9-deoxygoniopypyrone, (+)-goniopypyrone, and (+)-altholactone from chiral lactonic aldehydes **27** and **36** as pivotal intermediates. The absolute stereochemistries of (+)-goniodiol and (+)-9-deoxygoniopypyrone have been elucidated. Furthermore, their congeners have also been prepared in the course of our total syntheses for biological evaluation.

Experimental Section

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were measured for solutions in $CHCl_3$ on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained on JEOL GSX-270 and JEOL GX-400 instruments for solutions in $CDCl_3$ unless otherwise stated, and chemical shifts are reported on the δ scale from internal TMS. Mass spectra were measured with a JEOL JMS-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

(2*R*)-3-(2'-Furyl)-1,2-*O*-isopropylideneglycerols (13) and (14).

To a stirred solution of furan (23 mL, 0.3 mol) in THF (200 mL) was added dropwise a 1.64M hexane solution of *n*-butyllithium (172 mL, 0.3 mol) at -78°C. After stirring for 3 h at 0°C under argon, a solution of

(*R*)-2,3-isopropylideneglyceraldehyde[19] (20.5 g, 0.2 mol) in THF (150 mL) was added dropwise, and the resulting mixture was stirred for an hour. After addition of a saturated aqueous solution of NH_4Cl, the organic layer was concentrated to leave a residue that was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (5 : 1, v/v) as eluent to afford an inseparable mixture of alcohols **13** and **14** (*anti* : *syn* = 3 : 4) (29 g, 92%) as a colorless oil: ^1H NMR δ 1.37 and 1.44 (each 9/7H, each s, CMe_2), 1.39 and 1.47 (each 12/7H, each s, CMe_2), 2.56 and 2.83 (total 1H, each d, *J* = 4.3Hz, OH), 3.76 and 3.97 (each 4/7H, each dd, *J* = 6.1 and 8.5Hz, 1-H_2), 4.02 and 4.11(each 3/7H, each dd, *J* = 6.1 and 8.5Hz, 1-H_2), 4.40 (1H, m, 2-H), 4.61 (1H, dd, *J* = 4.3 and 6.1Hz, 3-H), 6.34 (2H, m, 3'- and 5'-H) and 7.39 (1H, m, 4'-H).

(2*R*,3*S*)-3-(2'-Furyl)-1,2-*O*-isopropylideneglycerol (14).

A mixture of alcohols **13** and **14** (200 mg, 1 mmol) and chemical manganese dioxide (4 g, 46 mmol) in CH_3CN (4 mL) was stirred vigorously for 3 d at room temperature. After filtration of the mixture through Celite, concentration of the filtrate gave a residue that was then dissolved in THF (2 mL). To this solution was added dropwise a 1M THF solution of L-Selectride (1.1 mL, 1.1 mmol) at -78°C. After stirring for 0.5 h at the same temperature under argon, a 20% aqueous solution of NaOH (0.4 mL) and a 30% aqueous H_2O_2 (0.4 mL) were added to the mixture. Concentration of the organic layer left an oily product that was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (5 : 1, v/v) as eluent to afford alcohol **14** (168 mg, 84%) as colorless needles: mp 62 - 62.5°C (hexane-EtOAc); $[\alpha]_D^{24}$ -10.2 (*c* 1.1, $CHCl_3$); IR 3400 cm^{-1}; ^1H NMR δ 1.40 and 1.48 (each 3H, each s, CMe_2), 2.71 (1H, d, *J* = 4.3Hz, OH), 3.78 and 3.98 (each 1H, each dd, *J* = 6.1 and 8.5Hz, 1-H_2), 4.43 (1H, q, *J* = 6.1Hz, 2-H), 4.60 (1H, dd, *J* = 4.3 and 6.1Hz, 3-H), 6.35 (2H, d, *J* = 1.8Hz, 3'- and 5'-H) and 7.40 (1H, t, *J* = 1.8Hz, 4'-H); HRMS calcd for $C_{10}H_{14}O_4$ (M^+) 198.0892, found (M^+) 198.0892. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.53; H, 7.33.

(2S)-2-[(4'*R*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-6-hydroxy-6*H*-pyran-3(2*H*)-one (15).

To a stirred solution of alcohol **14** (21.5 g, 0.1 mol) and anhydrous sodium acetate (9.8 g, 0.1 mmol) in aqueous THF (220 mL; THF : H_2O = 4 : 1) was added portionwise *N*-bromosuccinimide (21.3 g, 0.1 mol) at 0°C, and stirring was continued for 30 min at the same temperature. After adition of a 10% aqueous solution of KI and a saturated aqueous solution of sodium thiosulfate, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (3 : 2, v/v) as eluent to afford lactol **15** (22.6 g, 97%) as a colorless oil: IR 3350 and 1680 cm^{-1}; ^1H NMR δ 1.37 and 1.49 (each 0.75H, each s, CMe_2), 1.39 and 1.45 (each 2.25H, each s, CMe_2), 3.31 (1H, d, *J* = 4.9Hz, OH), 3.39-4.45 (3H, m, 4'- and 5'-H), 4.59 (1H, d, *J* = 6.7Hz, 2-H), 5.59 (0.25H, dd, *J* = 2.4 and 9.8Hz, 6-H), 5.79 (0.75H, t, *J* = 3.1Hz, 6-H), 6.14 (0.75H, d, *J* = 10.4Hz, 4-H), 6.20 (0.25H, d, *J* = 10.4Hz, 4-H), 6.94 (0.75H, dd, *J* = 3.1 and 10.4Hz, 5-H) and 6.98 (0.25H, dd, *J* = 2.4 and 10.4Hz, 5-H); HRMS calcd for $C_{10}H_{14}O_5$ (M^+) 214.0842, found (M^+) 214.0848.

(5*S*,6*R*)-6-[(4'*R*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-5-hydroxy-5,6-dihydro-2*H*-pyran-2-one (18) and (5*R*,6*R*)-6-[(4'*R*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-5-hydroxy-5,6-dihydro-2*H*-pyran-2-one (19).

To a stirred solution of lactol **15** (100 mg, 0.5 mmol) in acetic acid (0.3 mL) was added dropwise a solution of CrO_3 (164 mg, 1.6 mmol) in acetic acid (0.7 mL), and the resulting mixture was stirred for 0.5 h at room temperature. After addition of isopropyl alcohol (3 mL) to the mixture, sodium triacetoxyborohydride (300 mg, 1.4 mmol) was added portionwise at -20°C and stirred for 5 h at the same temperature. Conentration of the solvent left an oily product, that was dissolved in CH_2Cl_2. The solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (3 : 2, v/v) as eluent to afford the *syn*-alcohol **18** (36 mg, 36%) as colorless needles: mp 106.5 - 108°C (hexane-Et_2O); $[\alpha]_D^{25}$ +97.6 (*c* 0.6, $CHCl_3$); IR 1740 and 3460 cm^{-1}; ^1H NMR δ 1.41 and 1.49 (each 3H, each s, CMe_2), 3.6-3.85 (1H, br s, OH), 4.13 and 4.18 (each 1H, each dd, *J* = 6.1 and 9.2Hz, 5'-H_2), 4.32 (1H, dd,*J* = 2.4 and 5.5Hz, 5-H), 4.36 (1H, dd, *J* = 2.4 and 6.1Hz, 6-H), 4.57 (1H, q, *J* = 6.1Hz, 4'-H), 6.13 (1H, d, *J* = 9.8Hz, 3-H) and 6.99 (1H, dd, *J* = 9.8 and 5.5Hz, 4-H); HRMS calcd for $C_{10}H_{15}O_5$ (M^+ + 1) 215.0917, found (M^+ + 1) 215.0914. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.07; H, 6.78. Further elution with the same solvent system provided the *anti*-alcohol **19** (5 mg, 5%) as a colorless oil: $[\alpha]_D^{22}$ +23.8 (*c* 0.3, $CHCl_3$); IR 1740 and 3350 cm^{-1}; ^1H NMR δ 1.40 and 1.48 (each 3H, each s, CMe_2), 2.87 (1H, d, *J* = 4.3Hz, OH), 4.14 and 4.14 (each 1H, each d, *J* = 6.7Hz, 5'-H_2), 4.42 (1H, dd, *J* = 3.7 and 9.8Hz, 6-H), 4.54 (1H, dt, *J* = 3.7 and 6.7Hz, 4'-H), 4.67 (1H, dt, *J* = 2.4 and 9.8Hz, 5-H), 5.99 (1H, dd, *J* = 2.4 and 9.8Hz, 3-H) and 6.83 (1H, dd, *J* = 2.4 and 9.8Hz, 4-H); HRMS calcd for $C_{10}H_{15}O_5$ (M^+ + 1) 215.0917, found (M^+ + 1) 215.0916.

(5*S*,6*R*)-5-Acetoxy-6-[(4'*R*)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-5,6-dihydro-2*H*-pyran-2-one (20).

To a stirred solution of the *syn*-alcohol **18** (50 mg, 0.2 mmol) in CH_2Cl_2 (0.5 mL) were added 4-dimethylaminopyridine (DMAP) (3 mg, 0.02 mmol) and pyridine (80 μL, 0.9 mmol), followed by acetic anhydride (70 μL, 0.7 mmol) at 0°C, and the resulting mixture was stirred for 3 h at room temperature. After addition of a saturated aqueous solution of $NaHCO_3$ and brine, the mixtire was extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (4 : 1, v/v) as eluent to afford acetate **20** (58 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ +233.7 (*c* 1.2, $CHCl_3$); IR 1740 cm^{-1}; ^1H NMP δ 1.37 and 1.43 (each 3H, each s, CMe_2), 2.10 (3H, s, Ac), 4.04 (2H, d, *J* = 6.7Hz, 5'-H_2), 4.45 (1H, q, *J* = 6.7Hz, 4'-H), 4.55 (1H, dd, *J* = 3.1 and 6.7Hz, 6-H), 5.38 (1H, dd, *J* = 3.1 and 5.5Hz, 5-H), 6.23 (1H, d, *J* = 9.8Hz, 3-H) and 6.94 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H); HRMS calcd for $C_{12}H_{17}O_6$ (M^+ + 1) 257.1024, found (M^+ + 1) 257.1021. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 55.69; H, 6.27.

(6*R*)-6-[(4'*R*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-3,6-dihydro-2*H*-pyran-2-one (21).

To a stirred suspension of Zn powder (460 mg, 7 mmol), copper(II) sulfate•5H_2O (9 mg, 0.4 mmol) and anhydrous sodium acetate (29 mg, 0.4 mmol) in aqueous acetic acid (1 mL, AcOH : H_2O = 1 : 1), was added

dropwise a solution of acetate **20** (90 mg, 0.4 mmol) in THF (0.5 mL) at 0°C, and the resulting mixture was stirred at room temperature for 1 h. After filtration of the mixture through Celite, the filtrate was washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (4 : 1, v/v) as eluent to afford lactone **21** (64 mg, 92%) as a colorless oil: IR 1750 cm^{-1}; ^1H NMR δ 1.37 and 1.42 (each 3H, each s, CMe_2), 3.01-3.23 (2H, m, 3-H_2), 4.01 and 4.08 (each 1H, each dd, J = 6.7 and 8.6Hz, 5'-H_2), 4.29 (1H, dt, J = 2.4 and 6.7Hz, 4'-H), 4.95-5.00 (1H, m, 6-H) and 5.85-6.04 (2H, m, 4- and 5-H); HRMS calcd for $C_{10}H_{15}O_4$ (M^+ + 1) 199.0969, found (M^+ + 1) 199.0968. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.39; H, 7.26.

(6*R*)-6-[(4'*R*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-5,6-dihydro-2*H*-pyran-2-one (22).

To a stirred solution of **21** (60 mg, 0.3 mmol) in THF (0.6 mL) was added DBU (4.5 μL, 0.03 mmol) at room temperature, and the resulting mixture was stirred for 1.5 h at the same temperature under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (3 : 1, v/v) as eluent to afford acetate **22** (60 mg, 99%) as a colorless oil: $[\alpha]_D^{22}$ +134.3 (*c* 1.5, $CHCl_3$); IR 1735 cm^{-1}; ^1H NMR δ 1.38 and 1.45 (each 3H, each s, CMe_2), 2.27-2.63 (2H, m, 5-H_2), 4.05 and 4.09 (each 1H, each dd, J = 6.1 and 8.5Hz, 5'-H_2), 4.33 (1H, dt, J = 4.3 and 6.1Hz, 4'-H), 4.54 (1H, dt, J = 4.3 and 12.2 Hz, 6-H), 6.04 (1H, dd, J = 2.4 and 9.8Hz, 3-H) and 6.93 (1H, ddd, J = 2.4, 6.1 and 9.8Hz, 4-H); HRMS calcd for $C_{10}H_{14}O_4$ (M^+) 198.0891, found (M^+) 198.0876. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.53; H, 7.33.

(6*R*)-6-[(1'*R*)-1',2'-Dihydroxyethyl]-5,6-dihydro-2*H*-pyran-2-one (23).

A mixture of **22** (1.3 g, 6.6 mmol) in aqueous acetic acid (12 mL, AcOH : H_2O = 3 : 1) was stirred at 40°C for 2 h. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using EtOAc as eluent to afford diol **23** (1.0 g, 99%) as colorless leaflets: mp 84 - 84.5 °C (hexane-CH_2Cl_2); $[\alpha]_D^{28}$ +101.3 (*c* 1.5, MeOH); IR 1735 and 3450 cm^{-1}; ^1H NMR δ 2.36 (1H, ddd, J = 4.3, 6.1 and 18.9Hz, 5-Ha), 2.67 (1H, ddt, J = 2.4, 12.8 and 18.9Hz, 5-Hb), 3.7-3.85 (3H, m, 1'-H and 2'-H_2), 3.9-4.5 (2H, br s, 2 × OH), 4.56 (1H, dt, J = 4.3 and 12.8Hz, 6-H), 5.98 (1H, dd, J = 2.4 and 9.8Hz, 3-H) and 6.98 (1H, ddd, J = 2.4, 6.1 and 9.8Hz, 4-H); HRMS calcd for $C_7H_{11}O_4$ (M^+ + 1) 159.0657, found (M^+ + 1) 159.0662. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.98; H, 6.51.

(6*R*)-6-[(1'*R*)-2'-(*tert*-Butyldimethylsiloxy)-1'-hydroxyethyl]-5,6-dihydro-2*H*-pyran-2-one (24).

To a stirred solution of diol **23** (315 mg, 2 mmol) in CH_2Cl_2 (3.5 mL) were added triethylamine (0.7 mL, 5 mmol), DMAP (24 mg, 0.2 mmol), and *tert*-butyldimethylsilyl chloride (601 mg, 4 mmol) at 0°C, and the resulting mixture was stirred at room temperature for 5 h under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with $CHCl_3$. The extract was washed with brine and dried over

Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (3 : 1, v/v) as eluent to afford the silyl ether **24** (54 mg, 99%) as colorless plates: mp 62 - 63°C (hexane-EtOAc); $[\alpha]_D^{24}$ +64.3 (*c* 0.9, $CHCl_3$); IR 1720 and 3450 cm^{-1}; 1H NMR δ 0.09 (6H, s, $SiMe_2$), 0.90 (9H, s, ^tBu), 2.33 (1H, ddd, *J* = 3.7, 6.1 and 18.3Hz, 5-Ha), 2.45 (1H, br s, OH), 2.71 (1H, ddt, *J* = 2.4, 12.8 and 18.3 Hz, 5-Hb), 3.7-3.8 (3H, m, 1'-H and 2'-H_2), 4.58 (1H, dt, *J* = 3.7 and 12.8Hz, 6-H), 6.03 (1H, dd, *J* = 2.4 and 9.8Hz, 3-H) and 6.95 (1H, ddd, *J* = 2.4, 6.1 and 9.8Hz, 4-H); HRMS calcd for $C_{12}H_{21}O_4Si$ (M^+ – 15) 257.1207, found (M^+ – 15) 257.1204. Anal. Calcd for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.88. Found: C, 57.34; H, 9.10.

(6*R*)-6-[(1'*R*)-2'-(*tert*-Butyldimethylsiloxy)-1'-(methoxymethoxy)ethyl]-5,6-dihydro-2*H*-pyran-2-one (25).

To a stirred solution of ether **24** (89 mg, 0.3 mmol) in CH_2Cl_2 (0.9 mL) were added *N*,*N*-diisopropylethylamine (1.44 mL, 8.3 mmol), DMAP (4 mg, 0.03 mmol), and methoxymethyl chloride (0.5 mL, 6.6 mmol) at 0°C, and the resulting mixture was stirred for 5 h at room temperature under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (5 : 1, v/v) as eluent to afford ether **25** (103 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ +36.5 (*c* 1.4, $CHCl_3$); IR 1730 cm^{-1}; ^1H NMR δ 0.08 (6H, s, $SiMe_2$), 0.89 (9H, s, ^tBu), 2.34 (1H, ddd, *J* = 4.3, 6.1 and 18.3Hz, 5-Ha), 2.66 (1H, ddt, *J* = 2.4, 12.2 and 18.3Hz, 5-Hb), 3.42 (3H, s, OMe), 3.68-3.74 (1H, m, 1'-H), 3.80 (1H, dd, *J* = 5.5 and 10.4Hz, 2'-Ha), 3.88 (1H, dd, *J* = 6.1 and 10.4Hz, 2'-Hb), 4.64 (1H, dt, *J* = 4.3 and 12.2Hz, 6-H), 4.72 and 4.82 (each 1H, each d, *J* = 6.7Hz, OCH_2OMe), 6.03 (1H, dd, *J* = 2.4 and 9.8Hz, 3-H) and 6.93 (1H, ddd, *J* = 2.4, 6.1 and 9.8Hz, 4-H).

(6*R*)-6-[(1'*R*)-2'-Hydroxy-1'-(methoxymethoxy)ethyl]-5,6-dihydro-2*H*-pyran-2-one (26).

A solution of ether **25** (410 mg, 1.3 mmol) in THF-AcOH-H_2O (1.2 mL-3.9 mL-1.3 mL) was stirred at 40°C for 5 h. Concentration of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (1 : 4) as eluent to afford alcohol **26** (230 mg, 89%) as a colorless oil: $[\alpha]_D^{25}$ +148.6 (*c* 0.9, $CHCl_3$); IR 3450 and 1730 cm^{-1}; ^1H NMR δ 1.7-2.8 (1H, br, OH), 2.36 (1H, ddd, *J* = 4.3, 6.1 and 18.3Hz, 5-Ha), 2.61 (1H, ddt, *J* = 2.4, 12.2 and 18.3Hz, 5-Hb), 3.46 (3H, s, OMe), 3.7-3.9 (3H, m, 1'-H and 2'-H_2), 4.64 (1H, dt, *J* = 4.3 and 12.2Hz, 6-H), 4.77 and 4.83 (each 1H, each d, *J* = 6.7Hz, OCH_2OCH_3), 6.04 (1H, dd, *J* = 2.4 and 9.8Hz, 3-H) and 6.93 (1H, ddd, *J* = 2.4, 6.1 and 9.8Hz, 4-H). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.35; H, 7.11.

(6*R*,7*R*,8*S*)-6-[7,8-Dihydro-8-hydroxy-7-(methoxymethoxy)styryl]-5,6- dihydro-2*H*-pyran-2-one (28) and (6*R*,7*R*,8*R*)-6-[7,8-Dihydro-8-hydroxy-7-(methoxymethoxy)styryl]-5,6-dihydro-2*H*-pyran-2-one (29).

To a stirred solution of oxalyl chloride (40 μL, 0.5 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of DMSO (42 μL, 0.6 mmol) in CH_2Cl_2 (0.5 mL) at -65°C under argon. After stirring for 15 min at the same

temperature, a solution of alcohol **26** (60 mg, 0.3 mmol) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 30 min. Triethylamine (0.2 mL, 1.5 mmol) was added, and stirring was continued for 15 min at the same temperature. Addition of $PhTi(O^iPr)_3$[24a] (9 mL; 0.4M ethereal solution) to the mixture at -20°C, the solution was further stirred for 1 h at 0°C. After addition of a saturated aqueous solution of NH_4Cl, the precipitate was filtered off and the filtrate was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (1 : 1,v/v) as eluent to afford a diastereomeric mixture of alcohols **28** and **29** (77 mg, 94%) as a colorless oil: ^1H NMR δ 1.4-2.0 (1H, br s, OH), 2.14-2.28 (1H, m, 5-Ha), 2.62-2.84 (1H, m, 5-Hb), 3.26 (1.5H, s, OMe), 3.39 (1.5H, s, OMe), 3.66 and 3.73 (each 0.5H, each dd, J = 3.1 and 6.7Hz, 7-H), 4.18-4.25 (0.5H, m, 6-H), 4.19 and 4.38 (each 0.5H, each d, J = 6.7Hz, OCH_2OCH_3), 4.75-4.85 (0.5H, m, 6-H), 4.76 and 4.80 (each 0.5H, each d, J = 4.8Hz, OCH_2OCH_3), 5.04 and 5.07 (each 0.5H, each d, J = 6.7Hz, 8-H), 5.93-6.03 (1H, m, 3-H), 6.82-6.94 (1H, m, 4-H) and 7.27-7.46 (5H, m, Ph).

Goniodiol (1), 9-Deoxygoniopypyrone (5) and 8-*epi*-Goniodiol (30).

A mixture of alcohols **28** and **29** (77 mg, 0.3 mmol) in aqueous acetic acid (1 mL, AcOH : H_2O = 3 : 1) was stirred for 4 h at 65°C. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 2, v/v) as eluent to afford 9-deoxygoniopypyrone (**5**) (3 mg, 5 %) as colorless needles: mp 203 - 204°C (hexane-EtOAc) {lit.,[3a] mp 203 - 204°C}; $[\alpha]_D^{26}$ +11.1 (*c* 0.3, $CHCl_3$) {lit.,[3a] $[\alpha]_D^{22}$ +12 (*c* 0.1, EtOH)}; IR 3350 and 1740 cm^{-1}; ^1H NMR δ 1.67 (1H, d, J = 3.1Hz, OH), 1.84 (1H, dd, J = 3.7 and 14.0Hz, 9-Ha), 2.54-2.65 (1H, m, 9-Hb), 2.86 (1H, dd, J = 4.9 and 19.5Hz, 4-Ha), 2.98 (1H, br d, J = 19.5Hz, 4-Hb), 3.95 (1H, br s, 8-H), 4.48-4.56 (1H, m, 5-H), 4.83-4.9 (1H, m, 1-H), 4.95 (1H, br s, 7-H) and 7.3-7.44 (5H, m, Ph); HRMS calcd for C13H14O4 (M^+) 234.0890, found (M^+) 234.0889. Further elution with the same solvent system afforded goniodiol (**1**) (32 mg, 49%) as a waxy oil: $[\alpha]_D^{25}$ +74.8 (*c* 0.7, $CHCl_3$) {lit.,[3a] $[\alpha]_D^{22}$ +74.4 (*c* 0.3, $CDCl_3$), lit.,[2] $[\alpha]_D^{30}$ +75.76 ($CHCl_3$)}; IR 3400 and 1725 cm^{-1}; ^1H NMR δ 2.17 (1H, ddd, J = 4.3, 6.7 and 18.3Hz, 5-Ha), 1.8-3.0 (2H, br s, OH × 2), 2.78 (1H, ddt, J = 2.4, 12.8 and 18.3Hz, 5-Hb), 3.71 (1H, dd, J = 2.4 and 7.3Hz, 7-H), 4.79 (1H, ddd, J = 2.4, 4.3 and 12.8Hz, 6-H), 4.93 (1H, d, J = 7.3Hz, 8-H), 5.98 (1H, dd, J = 2.4 and 9.8Hz, 3-H), 6.92 (1H, ddd, J = 2.4, 6.7 and 9.8Hz, 4-H) and 7.29-7.43 (5H, m, Ph); FABMS found $C_{13}H_{15}O_4$ 235.2 (M^+ + 1). Further elution with the same solvent system afforded 8-*epi*-goniodiol (**30**) (28 mg, 43%) as a waxy oil: $[\alpha]_D^{25}$ -13.7 (*c* 0.8, $CHCl_3$); IR 3400 and 1725 cm^{-1}; ^1H NMR δ 2.14 (1H, ddd, J = 4.3, 6.1 and 18.3Hz, 5-Ha), 2.83 (1H, ddt, J = 2.4, 12.8 and 18.3Hz, 5-Hb), 2.9-3.6 (2H, br s, OH × 2), 3.65 (1H, dd, J = 2.4 and 7.3Hz, 7-H), 4.22 (1H, ddd, J = 2.4, 4.3 and 12.8Hz, 6-H), 4.97 (1H, d, J = 7.3Hz, 8-H), 5.96 (1H, dd, J = 2.4 and 9.8Hz, 3-H), 6.87 (1H, ddd, J = 2.4, 6.1 and 9.8Hz, 4-H) and 7.27-7.44 (5H, m, Ph). FABMS found $C_{13}H_{15}O_4$ 235.2 (M^+ + 1).

9-Deoxygoniopypyrone (5).

To a stirred solution of 8-*epi*-goniodiol (**30**) (33 mg, 0.1 mmol) in THF (0.6 mL) was added DBU (4 μL, 0.03 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 15h under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with EtOAc. The

extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (1 : 1,v/v) as eluent to afford 9-deoxygoniopypyrone (**5**) (27 mg, 82%) as colorless needles. Further elution with the same solvent system recovered 8-*epi*-goniodiol (**30**) (6 mg, 18%) as a waxy oil.

(5*S*,6*R*)-6-[(4'*R*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (31).

To a stirred solution of alcohol **18** (100 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) were added diisopropylethylamine (2 mL, 12 mmol) and DMAP (11 mg, 0.1 mmol), and methoxymethyl chloride (0.7 mL, 9 mmol) at 0°C, and the resulting mixture was stirred for 10 h at room temperature under argon. After addition of a saturated aqueous solution of $KHSO_4$, the mixture was extracted with CH_2Cl_2. The extract was washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (3 : 2,v/v) as eluent to afford ether **31** (100 mg, 83%) as a colorless oil: $[\alpha]_D^{26}$ +134.5 (*c* 1.5, $CHCl_3$); IR 1730 cm^{-1}; ^1H NMR δ 1.40 and 1.44 (each 3H, each s, CMe_2), 3.36 (3H, s, OMe), 3.88 and 4.12 (each 1H, each dd, *J* = 6.7 and 8.6Hz, 5'-H_2), 4.17 (1H, dd, *J* = 3.7 and 5.5Hz, 5-H), 4.43 (1H, dd, *J* = 3.7 and 6.7Hz, 6-H), 4.58 (1H, q, *J* = 6.7Hz, 4'-H), 4.66 and 4.71 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 6.15 (1H, d, *J* = 9.8Hz, 3-H) and 6.98 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H); HRMS calcd for $C_{11}H_{15}O_6$ (M^+ – 15) 243.0869, found (M^+ – 15) 243.0870. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.81; H, 7.22.

(5*S*,6*R*)-6-[(1'*R*)-1',2'-Dihydroxyethyl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (32).

A solution of ether **31** (140 mg, 0.54 mmol) in AcOH - H_2O - THF (0.9 mL - 0.3 mL - 0.3 mL) was stirred for 8 h at 40°C. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using EtOAc as eluent to afford diol **32** (104 mg, 88%) as colorless needles: mp 89 - 90°C (EtOAc); $[\alpha]_D^{27}$ +188.1 (*c* 1.2, MeOH); IR 3500 and 1740 cm^{-1}; ^1H NMR δ 3.36 (3H, s, OMe), 3.74 and 3.89 (each 1H, each dd, *J* = 4.3 and 11.6Hz, 2'-H2), 4.20 (2H, m, 5- and 1'-H), 4.51 (1H, dd, *J* = 2.4 and 7.3Hz, 6-H), 4.69 and 4.73 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 6.20 (1H, d, *J* = 9.8Hz, 3-H) and 7.08 (1H, dd, *J* = 6.1 and 9.8Hz, 4-H); HRMS calcd for $C_9H_{13}O_5$ (M^+ – 17) 201.0761, found (M^+ – 17) 201.0761. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.39; H, 6.58.

(5*S*,6*R*)-6-[(1'*R*)-2'-(*tert*-Butyldimethylsiloxy)-1'-hydroxyethyl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (33).

To a stirred solution of diol **32** (700 mg, 3.2 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (0.9 mL, 6.4 mmol), DMAP (40 mg, 0.32 mmol), and *tert*-butyldimethylsilyl chloride (725 mg, 4.8 mmol) at 0°C, and the resulting mixture was stirred at room temperature for 5 h under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel

using hexane-EtOAc (2 : 1,v/v) as eluent to afford the silyl ether **33** (1.1 g, 99%) as a colorless oil; $[\alpha]_D^{29}$ +113.2 (*c* 3.2, $CHCl_3$); IR 3550 and 1730 cm-1; ^1H NMR δ 0.09 (6H, s, $SiMe_2$), 0.89 (9H, s, ^tBu), 3.37 (3H, s, OMe), 3.77 and 3.86 (each 1H, each dd, *J* = 4.9 and 10.4Hz, 2'-H_2), 4.09 (1H, q, *J* = 4.9Hz, 1'-H), 4.24 (1H, dd, *J* = 3.1 and 5.5Hz, 5-H), 4.53 (1H, dd, *J* = 3.1 and 4.9Hz, 6-H), 4.70 and 4.73 (each 1H, each d, *J* = 7.9Hz, OCH_2OMe), 6.18 (1H, d, *J* = 9.8Hz, 3-H) and 7.05 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H). Anal. Calcd for $C_{15}H_{28}O_6Si$: C, 54.19; H, 8.49. Found: C, 54.10; H, 8.73.

(5*S*,6*R*)-6-[(1'*R*)-2'-(*tert*-Butyldimethylsiloxy)-1'-(methoxymethoxy)ethyl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (34).

To a stirred solution of the silyl ether **33** (1.1 g, 3.2 mmol) in CH_2Cl_2 (10 mL) were added diisopropylethylamine (14 mL, 79 mmol), DMAP (39 mg, 0.3 mmol), and methoxymethyl chloride (4.8 mL, 63 mmol) at 0°C, and the resulting mixture was stirred for 10 h at room temperature under argon. After addition of a saturated aqueous solution of $KHSO_4$, the mixture was extracted with CH_2Cl_2. The extract was washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane-EtOAc (4 : 1,v/v) as eluent to afford dimethoxymethyl ether **34** (1.1 g, 99%) as a colorless oil. $[\alpha]_D^{24}$ +127.9 (*c* 1.1, $CHCl_3$); IR 3550 and 1730 cm^{-1}; ^1H NMR δ 0.08 and 0.09 (each 3H, each s, $SiMe_2$), 0.89 (9H, s, ^tBu), 3.35 and 3.44 (each 3H, each s, 2 × OMe), 3.82 and 3.92 (each 1H, each dd, *J* = 3.7 and 11.6Hz, 2'-H_2), 4.06 (1H, dt, *J* = 3.7 and 7.3Hz, 1'-H), 4.24 (1H, dd, *J* = 3.1 and 5.5Hz, 5-H), 4.60 (1H, dd, *J* = 3.1 and 7.3Hz, 6-H), 4.67 and 4.70 (each 1H, each d, *J* = 6.7Hz, OCH_2OMe), 4.76 and 4.82 (each 1H, each d, *J* = 6.7Hz, OCH_2OMe), 6.14 (1H, d, *J* = 9.8Hz, 3-H) and 7.02 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H). Anal. Calcd for $C_{17}H_{32}O_7Si$: C, 54.23; H, 8.57. Found: C, 54.14; H, 8.78.

(5*S*,6*R*)-6-[(1'*R*)-2'-Hydroxy-1'-(methoxymethoxy)ethyl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (35).

A solution of ether **34** (1.6 g, 4.3 mmol) in AcOH - H_2O - THF (12 mL - 4 mL - 2 mL) was stirred at 40°C for 5 h. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using EtOAc as eluent to afford alcohol **35** (1.1 g, 98%) as a colorless oil; $[\alpha]_D^{26}$ +209.9 (*c* 0.9, $CHCl_3$); IR 3450 and 1730 cm^{-1}; ^1H NMR δ 2.20-2.80 (1H, br s, OH), 3.35 and 3.47 (each 3H, each s, 2 × OMe), 3.72 (1H, dd, *J* = 4.2 and 12.1Hz, 2'-Ha), 3.90 (1H, dd, *J* = 3.1 and 12.1Hz, 2'-Hb), 4.10 (1H, ddd, *J* = 3.1, 4.2 and 8.5Hz, 1'-H), 4.18 (1H, dd, *J* = 3.1 and 6.1Hz, 5-H), 4.56 (1H, dd, *J* = 3.1 and 8.5Hz, 6-H), 4.67 and 4.71 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 4.81 and 4.86 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 6.17 (1H, d, *J* = 9.8Hz, 3-H) and 7.06 (1H, dd, *J* = 6.1 and 9.8Hz, 4-H). Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.37; H, 6.92. Found: C, 50.10; H, 7.05.

(5*S*,6*R*,7*R*,8*R*)-6-[7,8-Dihydro-8-hydroxy-7-(methoxymethoxy)styryl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (37) and (5*S*,6*R*,7*R*,8*S*)-6-[7,8-Dihydro-8-hydroxy-7-(methoxymethoxy)styryl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (38).

With PhTi(O^{i}Pr)$_3$ {prepared from ClTi(O^{i}Pr)$_3$ and PhLi}:

To a stirred solution of oxalyl chloride (31 μL, 0.4 mmol) in CH_2Cl_2 (0.6 mL) was added a solution of DMSO (34 μL, 0.5 mmol) in CH_2Cl_2 (0.6 mL) at -70°C under argon. After stirring for 15 min at the same temperature, a solution of alcohol **35** (62 mg, 0.2 mmol) in CH_2Cl_2 (1.3 mL) was added, and stirred for 30 min. Triethylamine (0.2 mL, 1.2 mmol) was added, and stirring was continued for further 15 min at the same temperature. After addition of PhTi(O^{i}Pr)$_3$, prepared from ClTi(O^{i}Pr)$_3$ (0.6 mL, 2.6 mmol) and a 1.05M Et_2O solution of PhLi (2.3 mL, 2.4 mmol) (4.5 mL), to the reaction mixture at -20°C, the mixture was stirred for further 2 h at 0°C. After addition of a saturated aqueous solution of NH_4Cl, the precipitate was filtered off, and the filtrate was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford the *anti*-alcohol **37** (62 mg, 78%) as colorless prisms: mp 97.5 - 98°C (hexane-EtOAc); $[\alpha]_D^{25}$ +141.5 (*c* 1.0, $CHCl_3$); IR 3430 and 1735 cm^{-1}; ^{1}H NMR δ 2.6-3.2 (1H, br s, OH), 3.30 and 3.33 (each 3H, each s, 2 × OMe), 4.04 (1H, dd, *J* = 3.1 and 4.9Hz, 5-H), 4.28 and 4.51 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 4.36 (1H, dd, *J* = 3.7 and 7.3Hz, 7-H), 4.41(1H, dd, *J* = 3.1 and 7.3Hz, 6-H), 4.74 and 4.80 (each 1H, each d, *J* = 6.7Hz, OCH_2OMe), 4.89 (1H, d, *J* = 3.7Hz, 8-H), 6.05 (1H, d, *J* = 9.8Hz, 3-H), 6.90 (1H, dd, *J* = 4.9 and 9.8Hz, 4-H) and 7.27-7.47 (5H, m, Ph); HRMS calcd for $C_{15}H_{17}O_6$ (M^+ – 45) 293.1025, found (M^+ – 45) 293.1026. Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.41; H, 6.66. Further elution with the same solvent system afforded the *syn*-alcohol **38** (15 mg, 19%) as a colorless oil: $[\alpha]_D^{24}$ +133.3 (*c* 0.6, $CHCl_3$); IR 3550 and 1730 cm^{-1}; ^{1}H NMR δ 1.7-2.0 (1H, br s, OH), 3.06 and 3.34 (each 3H, each s, 2 × OMe), 4.32 (1H, dd, *J* = 3.1 and 7.3Hz, 7-H), 4.35 (1H, dd, *J* = 3.1 and 4.9Hz, 5-H), 4.36 and 4.69 (each 1H, each d, *J* = 6.7Hz, OCH_2OMe), 4.61 (1H, dd, *J* = 3.1 and 7.3Hz, 6-H), 4.67 and 4.75 (each 1H, each d, *J* = 6.7Hz, OCH_2OMe), 4.94 (1H, d, *J* = 3.1Hz, 8-H), 6.16 (1H, d, *J* = 9.8Hz, 3-H), 7.03 (1H, dd, *J* = 4.9 and 9.8Hz, 4-H) and 7.3-7.43 (5H, m, Ph); HRMS calcd for $C_{15}H_{17}O_6$ (M^+ – 45) 293.1025, found (M^+ – 45) 293.1027. Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.14; H, 6.74.

With PhTi(O^{i}Pr)$_3$ {prepared from ClTi(O^{i}Pr)$_3$ and PhMgBr}:

To a stirred solution of oxalyl chloride (10 μL, 0.1 mmol) in CH_2Cl_2 (0.4 mL) was added a solution of DMSO (11 μL, 0.2 mmol) in CH_2Cl_2 (0.3 mL) at -70°C under argon. After stirring for 15 min at the same temperature, a solution of alcohol **35** (20 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added, and stirred for 30 min. Triethylamine (53 μL, 0.38 mmol) was added, and stirring was continued for further 15 min at the same temperature. After addition of PhTi(O^{i}Pr)$_3$, prepared from ClTi(O^{i}Pr)$_3$ (0.2 mL, 0.8 mmol) and a 2M THF solution of PhMgBr (0.4 mL, 0.8 mmol) in THF (3 mL), to the reaction mixture at -20°C, the mixture was stirred for further 2 h at 0°C. After addition of a saturated aqueous solution of NH_4Cl, the precipitate was filtered off, and the filtrate was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford the *anti*-alcohol **37** (9 mg, 34%) as colorless prisms. Further elution with the same solvent system afforded the *syn*-alcohol **38** (4 mg, 17%) as a colorless oil.

Goniotriol (2).

To a stirred solution of the *anti*-alcohol **37** (100 mg, 0.3 mmol) in CH_2Cl_2 (2.5 mL) was added CF_3CO_2H (2.5 mL), and the resulting mixture was stirred for 2.5 h at room temperature under argon. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 3, v/v) as eluent to afford goniotriol (**2**) (65 mg, 88%) as colorless prisms: mp 169.5 - 170.5°C (MeOH) {lit.,[3b] mp 170°C, lit.,[2] mp 173°C}; $[\alpha]_D^{22}$ +120.2 (*c* 0.4, MeOH) {lit.,[3b] $[\alpha]_D$ +121 (MeOH)}; ^{1}H NMR (CD_3OD) δ 4.17 (1H, dd, *J* = 3.7 and 7.9Hz, 7-H), 4.43 (1H, dd, *J* = 3.7 and 5.5Hz, 5-H), 4.60 (1H, t, *J* = 3.7Hz, 6-H), 4.74 (1H, d, *J* = 7.9Hz, 8-H), 6.08 (1H, d, *J* = 9.8Hz, 3-H), 7.06 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H) and 7.25-7.48 (5H, m, Ph); HRMS calcd for $C_{13}H_{14}O_5$ (M^+) 250.0842, found (M^+) 250.0848.

Goniofufurone (4).

To a stirred solution of goniotriol (**2**) (50 mg, 0.2 mmol) in THF (1.5 mL) was added DBU (3 μL, 0.02 mmol), and the resulting mixture was stirred for 10 h at room temperature under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 2, v/v) as eluent to afford goniofufurone (**4**) (30 mg, 60%) as colorless plates: mp 153 - 154.5°C (hexane-EtOAc) {lit.,[3c] mp 152 - 154°C}; $[\alpha]_D^{26}$ +9.8 (*c* 0.4, EtOH) {lit.,[3c] $[\alpha]_D^{22}$ +9 (*c* 0.5, EtOH)}; IR 3400 and 1790 cm^{-1}; ^{1}H NMR δ 2.66 (1H, br d, *J* = 18.3Hz, 3-Ha), 2.76 (1H, dd, *J* = 5.5 and 18.3Hz, 3-Hb), 2.95 (1H, br s, OH), 4.09 (1H, dd, *J* = 2.4 and 4.9Hz, 7-H), 4.22 (1H, br s, OH), 4.39 (1H, br s, 6-H), 4.86 (1H, br d, *J* = 3.7Hz, 5-H), 5.07-5.13 (1H, m, 4-H), 5.19 (1H, br d, *J* = 4.9Hz, 8-H) and 7.30-7.42 (5H, m, Ph); HRMS calcd for $C_{13}H_{12}O_4$ (M^+ – 18) 232.0734, found (M^+ – 18) 232.0726.

8-*epi*-Goniopypyrone-5,7-*O*-dimethoxymethyl Ether (40).

To a stirred solution of the *anti*-alcohol **37** (100 mg, 0.3 mmol) in THF (3 mL) was added a catalytic amount of DBU at room temperature, and the resulting mixture was stirred at 40°C for 30 h under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford the bicyclic lactone **40** (80 mg, 80%) as a colorless oil: $[\alpha]_D^{20}$ -32.2 (*c* 0.8, $CHCl_3$); IR 1740 cm^{-1}; ^{1}H NMR δ 2.77 and 3.05 (each 1H, each dd, *J* = 3.1 and 18.3Hz, 3-H_2), 2.94 and 3.49 (each 3H, each s, 2 × OMe), 4.12 (1H, br d, *J* = 9.8Hzπ, 7-H), 4.29 (2H, m, 5-H and OCH_2OMe), 4.56-4.58 (1H, m, 4-H), 4.63 (1H, d, *J* = 6.7Hz, OCH_2OMe), 4.76 (1H, dd, *J* = 2.4 and 4.3Hz, 6-H), 4.86 and 4.90 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 5.01 (1H, d, *J* = 9.8Hz, 8-H) and 7.28-7.44 (5H, m, Ph); HRMS calcd for $C_{15}H_{17}O_6$ (M^+ – 45) 293.1025, found (M^+ – 45) 293.1030. Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.05; H, 6.63.

8-*epi*-Goniopypyrone (41).

To a stirred solution of the bicyclic lactone **40** (30 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added CF_3CO_2H (1.5 mL), and the solution was stirred for 10 h at room temperature under argon. Concentration of the

solvent left a residue that was purified by column chromatography on silica gel using hexane - EtOAc (2 : 5, v/v) as eluent to afford 8-*epi*-goniopypyrone (**41**) (18 mg, 81%) as colorless prisms: mp 177.5 - 184.5°C (hexane-EtOAc); $[\alpha]_D^{26}$ -63.6 (*c* 0.4, EtOH); IR 3350 and 1740 cm^{-1}; ^1H NMR (CD_3OD) δ 2.82 and 2.87 (each 1H, each dd, *J* = 3.1 and 18.3Hz, 3-H_2), 3.87 (1H, br d, *J* = 9.2Hz, 7-H), 4.37-4.44 (2H, m, 4- and 5-H), 4.55 (1H, dd, *J* = 2.4 and 4.3Hz, 6-H), 5.06 (1H, d, *J* = 9.2Hz, 8-H) and 7.23-7.42 (5H, m, Ph); HRMS calcd for $C_{13}H_{14}O_5$ (M^+) 250.0839, found (M^+) 250.0837. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.62; H, 5.71.

X-ray crystallographic analysis of 8-*epi*-Goniopypyrone (41).

X-ray measurement was carried out on a Rigaku AFC 5R diffractometer. The structure was solved by the direct method using SHELXS-86 and refined by a full-matrix least-squares routine where the quantity $\Sigma\omega$ - $(Fo - Fc)^2$ was minimized. The unit cell parameters were obtained from a least-squares fit to ±2θ values of 25 reflections. Crystal data: $C_{13}H_{14}O_5$, FW=250.25, trigonal, *P* 3_2, *a*=12.713(1) Å, *c*=6.226(2) Å, V=871.3(3) $Å^3$, Z=3, μ(CuKα)=9.32 cm^{-1}, D(calc)=1.431 g/cm^3. The intensity data were measured at 23°C employing ω-2θ scan technique. A total of 1031 reflections (2θmax=120.2°) were measured of which 819 were considered observed (I>3σ(I)). The hydrogen atoms were located from a difference Fourier map, and they were refined with isotropic temperature factors. *R*=3.4%, *Rw*=5.2%, S=0.03, Δρ(max)=0.16 $eÅ^{-3}$.

(5*S*,6*R*,7*R*,8*R*)-6-[8-Acetoxy-7,8-dihydro-7-(methoxymethoxy)styryl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (42).

To a stirred solution of the *anti*-alcohol **37** (170 mg, 0.5 mmol) in pyridine (2 mL) was added acetic anhydride (1 mL), and the resulting mixture was stirred for 3 h at room temperature uner argon. After addition of a saturated aqueous solution of $KHSO_4$, the mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford acetate **42** (183 mg, 96 %) as colorless prisms: mp 111°C (hexane-EtOAc); $[\alpha]_D^{26}$ +91.2 (*c* 0.4, $CHCl_3$); IR 1730 cm^{-1}; ^1H NMR δ 2.13 (3H, s, Ac), 3.34 and 3.45 (each 3H, each s, 2 × OMe), 4.11 (1H, dd, *J* = 3.1 and 5.5Hz, 5-H), 4.23 (1H, dd, *J* = 3.7 and 7.9Hz, 7-H), 4.52 (1H, dd, *J* = 3.1 and 7.9Hz, 6-H), 4.43 and 4.59 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 4.78 and 4.90 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 6.01 (1H, d, *J* = 3.7Hz, 8-H), 6.07 (1H, d, *J* = 9.8Hz, 3-H), 6.93 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H) and 7.30-7.50 (5H, m, Ph). Anal. Calcd for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 60.31; H, 6.44.

8-Acetylgoniotriol (3) and 8-*epi*-Altholactone-7-*O*-acetate (44).

To a stirred solution of acetate **42** (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added CF_3CO_2H (0.4 mL) at 0°C, and the mixture was stirred for 1.5 h at room temperature under argon. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using hexane - EtOAc (3 : 2, v/v) as eluent to afford the bicyclic lactone **44** (3 mg, 20%) as colorless flakes: mp 86.5 - 87°C (MeOH); $[\alpha]_D^{24}$ +131.2 (*c* 0.5, $CHCl_3$); IR 1740 cm^{-1}; ^1H NMR δ 1.76 (3H, s, Ac), 4.88 (1H, t, *J* = 4.9Hz, 5-H), 5.10 (1H, dd, *J* = 1.8 and

4.9Hz, 6-H), 5.39 (1H, d, J = 3.7Hz, 8-H), 5.70 (1H, dd, J = 1.8 and 3.7Hz, 7-H), 6.23 (1H, d, J = 9.8Hz, 3-H), 6.98 (1H, dd, J = 4.9 and 9.8Hz, 4-H) and 7.28-7.36 (5H, m, Ph). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.51; H, 5.14. Further elution with the same solvent system gave 8-acetylgoniotriol (**3**) (9 mg, 59%) as colorless needles: mp 166 - 167.5°C (hexane-EtOAc) {lit.,[3c] mp 158 - 159°C}; $[\alpha]_D^{21}$ +41.1 (*c* 0.5, EtOH) {lit.,[3c] $[\alpha]_D^{22}$ +30 (*c* 0.4, EtOH)}; ^{1}H NMR (CD_3OD) δ 2.06 (3H, s, Ac), 4.32 (1H, dd, J = 3.7 and 4.9Hz, 6-H), 4.42 (1H, dd, J = 3.7 and 5.5Hz, 5-H), 4.43 (1H, dd, J = 4.9 and 6.7Hz, 7-H), 5.86 (1H, d, J = 6.7Hz, 8-H), 6.05 (1H, d, J = 9.8Hz, 3-H), 6.98 (1H, dd, J = 5.5 and 9.8Hz, 4-H) and 7.25-7.53 (5H, m, Ph); FABMS found $C_{15}H_{16}O_6$ 235.2 (M^+ + 1).

8-*epi*-Altholactone-7-*O*-acetate (44) from 42.

To a stirred solution of acetate **42** (170 mg, 0.45 mmol) in CH_2Cl_2 (1 mL) was added CF_3CO_2H (5.2 mL) at 0°C, and the mixture was stirred for 10 h at room temperature under argon. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using hexane - EtOAc (3 : 2, v/v) as eluent to afford the bicyclic lactone **44** (119 mg, 97.1%) as colorless flakes.

8-*epi*-Altholactone-7-*O*-acetate (44) from 8-acetylgoniotriol (3).

To a stired solution of 8-acetylgoniotriol (**3**) (19 mg, 0.07 mmol) in CH_2Cl_2 (0.15 mL) was added CF_3CO_2H (0.58 mL) at 0°C, and the mixture was stirred for 10 h at room temperature under argon. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (3 : 2, v/v) as eluent to afford the bicyclic acetate **44** (18 mg, 99%) as colorless flakes.

8-*epi*-Altholactone (45).

To a stirred solution of the bicyclic acetate **44** (80 mg, 0.3 mmol) in THF (1.5 mL) was added a 1M aqueous solution of LiOH (0.9 mL, 0.9 mmol) at 0°C, and stirring was continued for additional 2 h at the same temperature. After acidification with 2*N* HCl, the mixture was extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated to give a white powder. The crude mixture was dissolved in CF_3CO_2H (1.5 mL) and stirred for 2 h at room temperature under argon. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford 8-*epi*-altholactone (**45**) (65 mg, 96%) as colorless prisms: mp 196.5 - 197°C (hexane-EtOAc) {lit.,[10] mp 193.5 - 194°C, lit.,[9] mp 190 - 191°C}; $[\alpha]_D^{24}$ +233.1 (*c* 0.5, EtOH) {lit.,[10] $[\alpha]_D^{26}$ +224 (*c* 0.5, EtOH), lit.,[9] $[\alpha]_D$ +268 (*c* 0.5, EtOH)}; IR 3550 and 1730 cm^{-1}; ^{1}H NMR δ 1.26 (1H, br s, OH), 4.51 (1H, br d, J = 3.4Hz, 7-H), 4.88 (1H, t, J = 4.9Hz, 5-H), 5.09 (1H, dd, J = 1.8 and 4.9Hz, 6-H), 5.36 (1H, d, J = 3.4Hz, 8-H), 6.20 (1H, d, J = 9.8Hz, 3-H), 7.00 (1H, dd, J = 4.9 and 9.8Hz, 4-H) and 7.32-7.45 (5H, m, Ph); HRMS calcd for $C_{13}H_{12}O_4$ (M^+) 232.0734, found (M^+) 232.0728. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.99; H, 5.13.

Goniopypyrone-5,7-*O*-dimethoxymethyl Ether (46).

To a stirred solution of the *syn*-alcohol **38** (117 mg, 0.4 mmol) in THF (3 mL) was added a catalytic amount of DBU at room temperature, and the mixture was stirred for 24 h at 40°C under argon. After addition of a saturated aqueous solution of NH_4Cl, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford bicyclic lactone **46** (111 mg, 95%) as a colorless oil: $[\alpha]_D^{25}$ +8.2 (*c* 0.9, CHCl3); IR 1740 cm^{-1}; ^1H NMR δ 2.93 and 3.45 (each 3H, each s, 2 × OMe), 3.01 (1H, dd, *J* = 4.9 and 19.5Hz, 3-Ha), 3.10 (1H, dd, *J* = 2.4 and 19.5Hz, 3-Hb), 3.97-4.05 (2H, m, 5- and 7-H), 4.02 and 4.39 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 4.55-4.60 (1H, m, 4-H), 4.77 (1H, dd, *J* = 3.7 and 5.5Hz, 6-H), 4.84 and 4.87 (each 1H, each d, *J* = 7.3Hz, OCH_2OMe), 5.02 (1H, d, *J* = 2.4Hz, 8-H) and 7.24-7.44 (5H, m, Ph); HRMS calcd for $C_{15}H_{17}O_6$ (M^+ – 45) 293.1025, found (M^+ – 45) 293.1033. Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.09; H, 6.63. Further elution with the same solvent system recovered the starting material **38** (5 mg, 4%) as a colorless oil.

Goniopypyrone (6).

To a stirred solution of the bicyclic lactone **46** (87 mg, 0.3 mmol) in CH_2Cl_2 (1 mL) was added CF_3CO_2H (5 mL), and the mixture was stirred for 6 h at room temperature under argon. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford goniopypyrone (**6**) (60 mg, 93%) as colorless needles. mp 174 - 177°C (hexane- EtOAc) {lit.,[3c] mp 182 - 184°C}; $[\alpha]_D^{26}$ +42.8 (*c* 0.3, EtOH) {lit.,[3c] $[\alpha]_D^{22}$ +54 (*c* 0.4, EtOH)}; IR 3500 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.00 (1H, dd, *J* = 1.8 and 19.5Hz, 3-Ha), 3.14 (1H, dd, *J* = 5.5 and 19.5Hz, 3-Hb), 4.00-4.05 (1H, m, 7-H), 4.17-4.23 (1H, m, 5-H), 4.38-4.44 (1H, m, 4-H), 4.64 (1H, dt, *J* = 2.4 and 3.7Hz, 6-H), 4.70 (1H, d, *J* = 7.9Hz, OH), 4.95 (1H, d, *J* = 1.2Hz, 8-H), 5.13 (1H, d, *J* = 7.3Hz, OH) and 7.23-7.42 (5H, m, Ph); HRMS calcd for $C_{13}H_{14}O_5$ (M^+) 250.0839, found (M^+) 250.0832.

(5*S*,6*R*,7*R*,8*S*)-6-[8-Acetoxy-7,8-dihydro-7-(methoxymethoxy)styryl]-5-(methoxymethoxy)-5,6-dihydro-2*H*-pyran-2-one (47).

To a stirred solution of the *syn*-alcohol **38** (170 mg, 0.5 mmol) in pyridine (2 mL) was added acetic anhydride (1 mL) at 0°C, and the mixture was stirred for 3 h at room temperature under argon. After addition of a saturated aqueous solution of $KHSO_4$, the mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford acetate **47** (190 mg, 99%) as colorless plates: mp 104.5 - 105°C (hexane-Et_2O); $[\alpha]_D^{23}$ +129.1 (*c* 0.6, $CHCl_3$); IR 1730 cm^{-1}; ^1H NMR δ 2.20 (3H, s, Ac), 3.00 and 3.39 (each 3H, each s, 2 × OMe), 4.16 (1H, dd, *J* = 3.1 and 5.5Hz, 5-H), 4.28 and 4.67 (each 1H, each d, *J* = 6.7Hz, OCH_2OMe), 4.42 (1H, dd, *J* = 2.4 and 7.9Hz, 7-H), 4.49 (1H, dd, *J* = 3.1 and 7.9Hz, 6-H), 4.79 (2H, s, OCH_2OMe), 6.09 (1H, d, *J* = 2.4Hz, 8-H), 6.17 (1H, d, *J* = 9.8Hz, 3-H), 7.05 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H) and 7.28-7.41 (5H, m, Ph); Anal. Calcd for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 59.70; H, 6.38.

Altholactone-7-*O*-acetate (49).

To a stirred solution of acetate **47** (33 mg, 0.1 mmol) in CH_2Cl_2 (0.3 mL) was added CF_3CO_2H (1 mL) at 0°C, and the mixture was stirred for 3 h at room temperature under argon. Concentration of the solvent left a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford the bicyclic ether **49** (22 mg, 93%) as colorless needles: mp 143 - 143.5°C (hexane-EtOAc); $[\alpha]_D^{25}$ +166.5 (*c* 0.4, EtOH); IR 1740 cm^{-1}; ^1H NMR δ 2.16 (3H, s, Ac), 4.63 (1H, dd, *J* = 4.3 and 5.5Hz, 5-H), 4.95 (1H, dd, *J* = 1.2 and 4.3Hz, 6-H), 4.98 (1H, d, *J* = 3.7Hz, 8-H), 5.39 (1H, dd, *J* = 1.2 and 3.7Hz, 7-H), 6.23 (1H, d, *J* = 9.8Hz, 3-H), 7.04 (1H, dd, *J* = 5.5 and 9.8Hz, 4-H) and 7.29-7.37 (5H, m, Ph); HRMS calcd for $C_{13}H_{11}O_3$ (M^+ – 59) 215.0716, found (M^+ – 59) 215.0698. Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.40; H, 5.11.

Altholactone (7).

To a stirred solution of the bicyclic acetate **49** (50 mg, 0.2 mmol) in THF (0.9 mL) was added a 1M aqueous solution of LiOH (0.6 mL, 0.6 mmol) at 0°C, and stirring was continued for additional 1 h at the same temperature. After acidification with 2*N* HCl, the mixture was extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated to give a white powder. The crude mixture was dissolved in CH_2Cl_2 (1.5 mL) containing CF_3CO_2H (0.15 mL) and stirred for 2 h at room temperature under argon. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel using hexane - EtOAc (1 : 1, v/v) as eluent to afford altholactone (**7**) (42 mg, 99%) as colorless prisms: mp 113 - 115°C (MeOH-H_2O) {lit.,[3d] mp 110°C, lit.,[10] mp 113-114°C}; $[\alpha]_D^{24}$ +182.8 (*c* 0.6, EtOH) {lit.,[4] $[\alpha]_D^{20}$ +188 (*c* 0.5, EtOH), lit.,[3d] $[\alpha]_D^{25}$ +184.7 (EtOH)}; IR 3350 and 1730 cm^{-1}; ^1H NMR δ 2.20-2.60 (1H, br s, OH), 4.46 (1H, dd, *J* = 2.4 and 6.1Hz, 7-H), 4.64 (1H, t, *J* = 4.9Hz, 5-H), 4.74 (1H, d, *J* = 6.1Hz, 8-H), 4.94 (1H, dd, *J* = 2.4 and 4.9Hz, 6-H), 6.23 (1H, d, *J* = 9.8Hz, 3-H), 7.00 (1H, dd, *J* = 4.9 and 9.8Hz, 4-H) and 7.30-7.37 (5H, m, Ph); HRMS calcd for $C_{13}H_{12}O_4$ (M^+) 232.0734, found (M^+) 232.0729.

Evaluation of *in vitro* cytotoxicity

Murine P388 cells (1 x 10^4/mL) were seeded in the RPMI 1640 medium. Compounds to be tested were added in graded concentrations, and the cultures were incubated for 72 h at 37 °C in a humidified atmosphere of 5% carbon dioxide. The tumor cells were counted by MTT method, and the IC_{50} value (concentration required for 50% inhibition of the cell growth) was determined by means of the growth curve.

Acknowledgment

The present research is supported by a Grant-in-Aid for Scientific Reseach (No 04671315) from the Ministry of Education, Science and Culture, Japan.

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