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Total Synthesis of Antitumor *Goniothalamus* Styryllactones

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Abstract : Synthesis of eight enantiopure styryllactones has been achieved from a common precursor : ethyl (2*S*, 3*S*, 4*R*) –4-(*t*-butyldimethylsilyloxy) -2,3-isopropylidenedioxy -4-phenylbutanoate **16**, prepared in five steps and 65 % yield from (*R*)-mandelic acid. Key elements for the synthesis of goniofufurone **3**, goniopypyrone **4**, goniobutenolides A and B (**5**, **6**) and 7-*epi*-goniofufurone **7** were the introduction of the *Z*-acrylate moiety by a Julia coupling between **16** or its epimer in benzylic position and methyl 3-phenylsulfonyl orthopropionate **11** followed by a highly diastereoselective reduction of the resulting β-keto sulfone which sets up the last of the four contiguous asymmetric center. In the case of styryllactones **4** and **7**, prior to the Julia coupling, the benzyl sterocenter of **16** was efficiently inverted by a Mitsunobu reaction. Goniodiol **1** and 9-deoxygoniopypyrone **2** were synthesized *via* an efficient coupling between the primary triflate derived from the common intermediate **16** or its epimer and Ghosez's sulfone **11** followed by lactonization and $PhSO_2H$ elimination. Goniodiol **1** has been efficiently converted to another styryllactone : isogoniothalamin epoxide **41**. Addition of the Ghosez's sulfone to an epoxide derived from the enantiomer of **16** allowed a short synthesis of 8-*epi*-9-deoxygoniopypyrone **8**, thereby establishing that its structure is the following : (1*R*, 5*R*, 7*S*, 8*S*) -8-hydroxy -7-phenyl-2,6- dioxabicyclo[3.3.1] nonan-3-one.

Keywords : Bicyclic aliphatic compounds, Mitsunobu reactions, pyrones, sulfones, styryllactones.

I Introduction

The genus *Goniothalamus* (Annonaceae) comprises some 115 species of shrubs and trees growing in Asia. A number of these plants has been used for timber, as fiber sources [1] and a mosquito repellant [2] and most interestingly in folk medecine. Thus, in southern Taiwan, near the coastal regions, extracts of seeds of *Goniothalamus amuyon* have been used to treat edema and rheumatism.[3] Powdered leaves of *Goniothalamus* species have been used as an abortifacient in rural areas of north Malaysia [4] and by local women during labor pain in the region of Manipur (India).[5] Because of the chemotherapeutic potential of *Goniothalamus* species, several research groups have undertaken bioactivity-directed studies of plants of this genus. In 1972, Geran *et al.* showed that the ethanolic extract of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas was very toxic to mice during the P-388 *in vivo* antileukemic screen. [6] Later on, using brine shrimp lethality – directed fractionation of the ethanolic extract of the stem bark, two major classes of cytotoxic compounds including annonaceous acetogenins [7] and styryllactones have been found.[8a-g] Up until now, more than twenty styryllactones have been isolated from plants. As illustrated in Figure 1, it is really amazing how a simple combination of cinnamic acid (C_6-C_3), resulting from the shikimic acid pathway, with two acetate/malonate units (C_4) has given rise to a large number of compounds possessing such unusual structural features.

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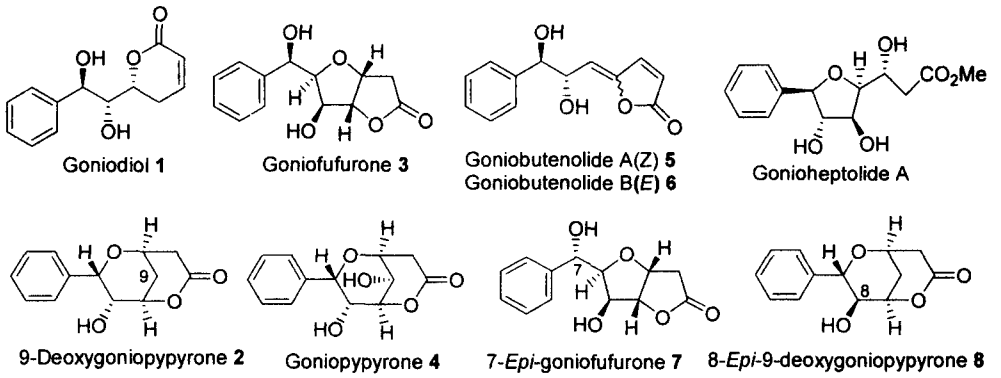


Figure 1

Due to their significant cytotoxicity toward several human tumor lines and fascinating and novel array of structures, styryllactones have attracted the attention of synthetic organic chemists and several syntheses of most of them have appeared in the literature. Because of structural analogies of styryllactones with carbohydrates, most of the synthetic approaches used *D*-glucose or its derivatives as starting materials.[9-15] Other routes to styryllactones utilized as a bulding block 2,3-O- isopropylidene-*D*-glyceraldehyde[16] or are based on asymmetric reactions such as tricarbonyl (η^6-arene) chromium complexes mediated stereoselective carbon-carbon bond formation[17] or Sharpless asymmetric dihydroxylation and epoxidation reactions. [18,19]
In the course of our program directed toward the asymmetric synthesis of styryllactones, we have recently reported in preliminary accounts the total synthesis of styryllactones **1-8**. [20a-d]

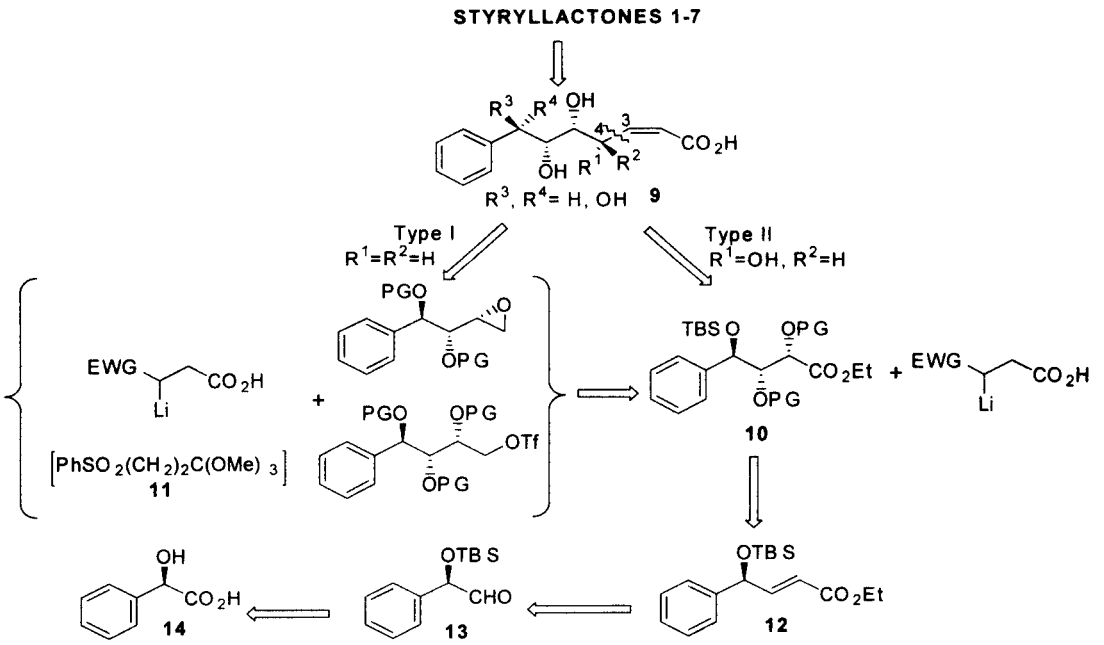
We now report the complete details of this synthetic study as well as of the straightforward preparation of isogoniothalamin epoxide **41** from goniodiol **1**.

Having in mind the use of a common synthetic precursor for the synthesis of most styryllactones, we have divided styryllactones **1-7** into two groups. The main group (Type II styryllactones) consists of compounds **3-7** possessing a substituent or a double bond in γ position in relation to the lactone function, the second group (Type I styryllactones) made up of **1** and **2** have not substituent in the same position.

In our retrosynthetic analysis, we envisioned that tetrahydrofuran and tetrahydropyran ring systems of bicyclic lactones **2-4**, **7** can obviously arise from intramolecular Michael addition of an alcohol group to an α,β-unsaturated lactone (Scheme 1). This antithetic disassembly leads to synthetic intermediates having the same (*Z*)-5,6-dihydroxy-2-hepten-1- oic acid framework **9.** Disconnection of the lactone function of goniodiol **1** and goniobutenolides **5** and **6** also leads to the unsaturated C_7 fragment **9**, assuming that the exocyclic double bond of the γ-alkylidene butenolide moiety of **5** and **6** can be generated by dehydration.

Next, we considered that : (1) C3-C4 of compound **9** for the synthesis of **1** and **2** can be constructed *via* a nucleophilic substitution of an appropriate leaving group (triflate or epoxide) by a β-acrylate anion equivalent; (2) addition of this acrylate anion to an ester functionality will give rise to a keto compound which can be stereoselectively reduced to the required tetrahydroxylated unsaturated acid for the synthesis of compounds **3** – **7**. These retrosynthetic considerations lead to a common potential precursor, the ester **10** and to an homoenolate equivalent bearing a group possessing both carbanion-stabilizing and nucleofugal properties as a masked double bond. Ghosez's sulfone **11** possesses structural features that satisfy this requirement.[21]

Pursuing the retrosynthetic analysis, we anticipated that the 2,3-*syn* diol unit of ester **10** can be obtained by a diastereoselective hydroxylation of a *E*-double-bond with *anti*-selection in agreement with Kishi's rules. [22] The next synthetic objective now becomes the γ-alkoxy-α,β-unsaturated ester **12** which by retrosynthetic scission of the *trans* double bond provides the aldehyde **13**, readily available from mandelic acid **14.**



Scheme 1

II . Results and discussion

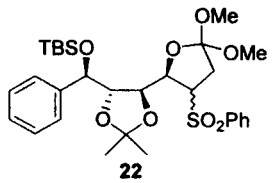
2.1. Synthesis of (+)- goniofufurone 3 and goniobutenolides A and B (5 and 6)

These three styryllactones have been recently isolated from the ethanol extract of the stem bark of *Goniothalamus giganteus*. [8c,e] Goniofufurone **3** and goniobutenolide A **5** showed moderate cytotoxic activity against several human cell lines whereas goniobutenolide B **6** exhibited a significant and selective toxicity against human lung carcinoma A-549 (ED_{50} 0.9 μg/ml). [8e]

The relative and absolute stereochemistries of **3**, **5**, **6** were determined by combined NMR [8c,e] and synthetic studies. [18,23a,b]

As shown in Scheme 2, synthesis of styryllactones **3**, **5**, **6** commences by a double diastereoselective catalytic asymmetric *cis*-hydroxylation (AD)[24] of the conjugated double bond of ester **12** [25] to give exclusively **15** in 97 % yield. After protection of the 1,2-*syn* diol as an acetonide, the resulting compound **16**, treated by an excess of the lithium salt of methyl 3-phenylsulfonyl orthopropionate **11**, [26] afforded the β-keto sulfone **17** in 85 % yield as an unseparable mixture of diastereomers. The stage was now set up for the introduction of the C4 stereogenic center of goniofufurone **3** through reduction of ketone functionality of **17**. $NaBH_4$ - $CeCl_3$ reduction [27] of **17**, at –78 °C, gave the expected compound **18** but with a poor level of diastereoselectivity (3 :1). The best results were obtained by using $LiAlH_4$ in ether, at –78 °C, which afforded **only** the β-hydroxysulfone **18** as an equal mixture of epimers at C3. The stereochemical assignment for sulfone **18** was established by chemical correlation with (+)- goniofufurone.

Attempted purification of **18** on silica gel gave cleanly the cyclic orthoester **22** in 88 % yield, via an intramolecular orthoetherification.



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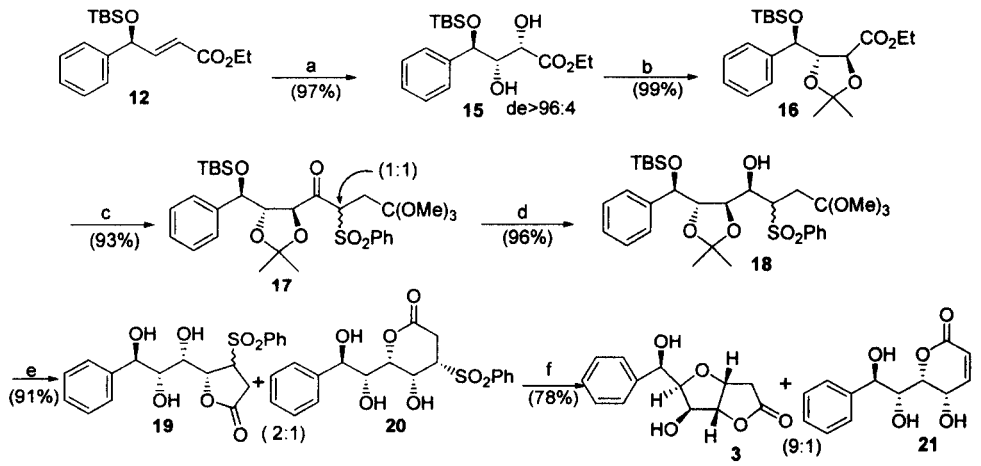
However, compound **18** could be obtained in pure form in 96 % yield by chromatography on neutral alumina.The completion of the synthesis of goniofufurone **3** only required a few functional group manipulations. Complete removal of the hydroxyl protecting groups as well as orthoester hydrolysis and lactone formation were effected in acetic acid-1N HCl – THF (1 :1 :1) at 65 °C to provide an unseparable mixture of sulfones **19** and **20** in 2 :1 ratio and 91 % yield.

Structural assignment of **19** and **20** was established from IR, ^{13}C and ^{1}H – ^{1}H spectra of the mixture. The IR spectrum presented two carbonyl bands, the major one at 1786 cm^{-1} suggested the presence of a saturated γ-lactone whereas the other one at 1743 cm^{-1} indicated the existence of a δ-lactone. [8c,d] ^{13}C NMR spectrum revealed the presence of two carbon signals at 170.9 and 175.8 ppm (ratio 1:2) which chemical shifts are characteristic respectively of saturated δ-and γ-lactones. [8c,d] The relative stereochemistry of the three stereogenic centers in the δ-lactone ring of **20** was evidenced by examination of ^{1}H-^{1}H coupling constants obtained from 2D ^{1}H- NMR spectroscopy. Indeed, coupling constants $J_{3,4}$ = 9.2Hz, $J_{4,5}$ = 5.8 Hz and $J_{5,6}$ = 2.5 Hz indicated the equatorial nature of the hydroxyl group and the side chain and that the SO_2Ph group occupied an axial position.

Finally, exposure of the mixture of γ- and δ-lactones **19** and **20** to DBU furnished, by elimination of $PhSO_2H$ and concomitant intramolecular Michael addition, pure goniofufurone **3** in 70 % yield along with goniotriol **21** [8b] (8 % yield). Synthetic styryllactone **3** showed spectroscopic data in perfect accord with those of the natural compound.

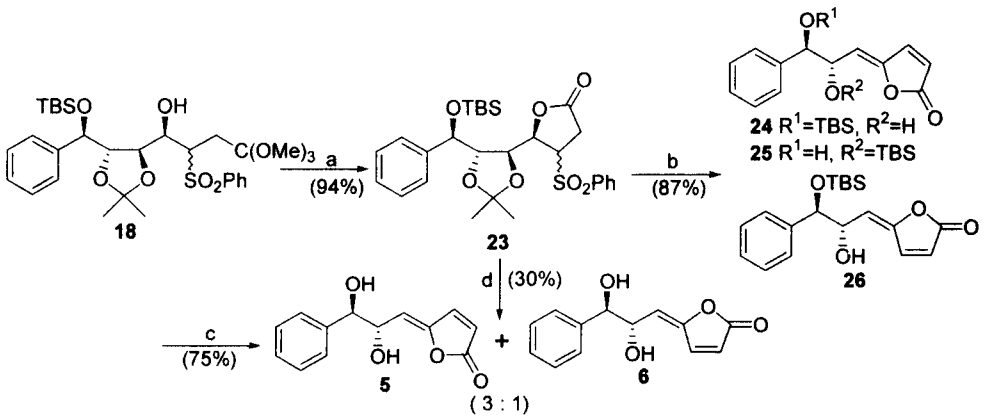


Scheme 2

Reagents and conditions : (a) AD-mix-β, *t*-BuOH-H_2O (1:1), $CH_3SO_2NH_2$, RT,14 h ; (b) 2-methoxypropene, camphorsulfonic acid, CH_2Cl_2, RT,10 min ; (c) methyl 3-phenylsulfonyl orthopropionate **11**, *n*-BuLi, THF, -78 °C, 30 min then add 2,3 –acetonide **16**, -78 °C to RT ; (d) $LiAlH_4$, Et_2O, -78 °C, 2 h (e) AcOH -1NHCl-THF (1 :1 :1); (f) DBU, CH_2Cl_2, 0 °C, 50 min.

Having completed the synthesis of goniofufurone **3**, in six steps and 54 % yield from the unsaturated ester **12**, we then turned our attention to the synthesis of goniobutenolides **5** and **6** starting from the C7 functionalized orthoester **18**. The first task of this synthesis was the construction of the α, β-unsaturated -γ-

butyrolactone ring unit. As outlined in Scheme 3, this goal was readily attained by heating **18** in boiling toluene in the presence of anhydrous camphorsulfonic acid which furnished the lactone **23** in 94 % yield as a 1:2 mixture of diastereomers. Interestingly, treatment of **23** by DBU, at 0 °C, effected concomitant elimination of $PhSO_2H$ and acetone to give, beside the desired diastereomers **24**, **26**, compound **25** corresponding to a 1,2-O-*t*-butyldimethylsilyl group migration in compound **24**. The position of *t*-butyldimethylsilyl group and the configuration of C5-C6 double bond of **24-26** was established by ^{1}H-NMR spectroscopy. Finally, exposure of compounds **24-26** to hot aqueous acetic acid effected cleavage of the *t*-butyldimethylsilyl group to give a 1:1 mixture of goniobutenolides A and B (75 % yield) which could be further separated from each other by flash chromatography . The use of tetrabutylammonium fluoride as a base allowed the direct transformation of **23** to styryllactones **5** and **6** in the same ratio as above but in low yield (30%). Spectra data of synthetic goniobutenolides A and B (**5**, **6**) are in accord with those of natural materials. [8e]



Scheme 3

Reagents and conditions : (a) cat. camphorsulfonic acid, toluene, reflux, 90 min ; (b) DBU (3 equiv), CH_2Cl_2, 0 °C, 1 h ; (c) AcOH-THF-H_2O (3:1:1), 60 °C, 14 h ; (d) NBu_4F, THF, 0 °C, 30 min.

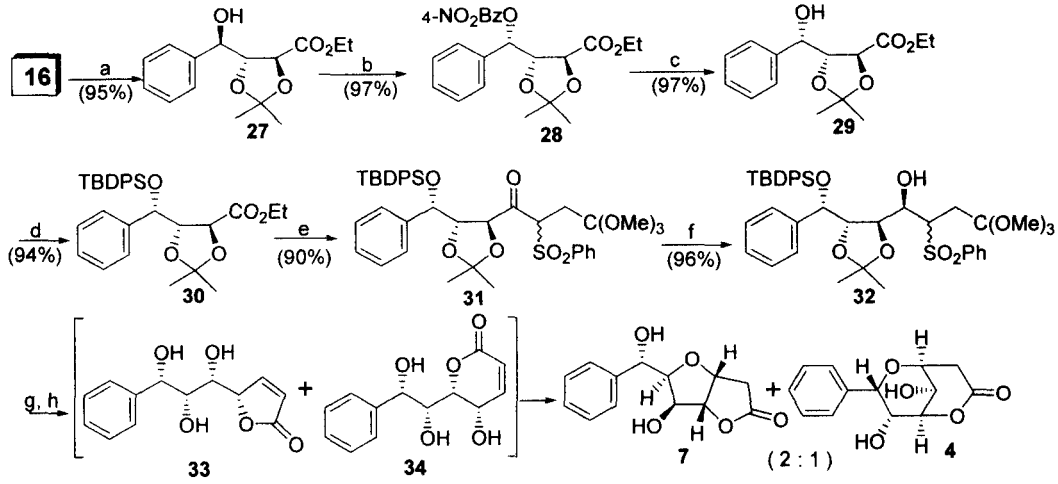
2.2. *Synthesis of (+)-goniopypyrone 4 and (+)-7-epi-goniofufurone 7*

As most styryllactones, goniopypyrone **4** and 7-*epi*-goniofufurone **7** have been isolated from the stem bark of *Goniothalamus giganteus* by McLaughlin and co-workers.[8c,d] The structure and the relative configuration of **4**[8c] and **7**[8d] have been established by X-ray cristallography. The absolute configuration has been determined on the basis of the total synthesis of the natural material for **4** [28] and of the corresponding enantiomer for **7**. [29,30] In contrast to 7-*epi*-goniofufurone **7** which has no significant cytotoxicity, goniopypyrone **4** is the most bioactive styryllactone, exhibiting non selective cytotoxic activity against several human tumor lines (ED_{50} 0.65 μg/ml) at one- tenth of the potency of adriamycin. Because the absolute configuration of **4** and **7** at the benzylic position is the opposite than that of styryllactones **3**, **5**, **6** of which synthesis has been described above, inversion of the C4 stereogenic center of their common precursor : compound **16** was required.

After cleavage of the C4 *t*- butyldimethylsilyl group of **16** with $Et_3N.3HF$, [31] the resulting alcohol **27** was submitted to Mitsunobu reaction conditions[32] using 4- nitrobenzoic acid as a O- nucleophile to afford **28** in 92 % yield from **16**. Sequential saponification of the benzoate ester and protection of the resulting alcohol in the form of a *t*-butyldiphenyl ether gave **30** in 82 % yield from the alcohol **28**. Transformation of the ester **30** to lactones **33**, **34** was effected according to the same protocol than that described for the goniofufurone **3** synthesis (Scheme 2) : (1) introduction of the homoenolate equivalent *via* Julia coupling ; (2) 1,2-*syn*

stereoselective reduction of the ketone functionality of the resulting adduct **31** ; (3) lactonization reaction induced by refluxing acetic acid. The resulting crude reaction mixture (at least four compounds as determined by ^{13}C NMR spectroscopy) was treated by two equivalents of NBu_4F at room temperature which induced removal of the *t*-butyldiphenylsilyl protecting group, $PhSO_2H$ elimination and intramolecular Michael addition, to afford after chromatographic separation pure goniopypyrone **4** (19 % yield) and 7-*epi*-goniofufurone **7** (38 % yield) from **31** in three steps.

Spectral and physical data of styryllactones **4** and **7** were found identical with those of natural compounds. Formation of both bicyclic lactones **4** and **7** shows that the α-pyrone **34** in constrast to its corresponding C7 epimer (Scheme 2) did not isomerize to the α,β-unsaturated-γ-lactone **33**. This result dismisses the hypothesis of Shing *et al.*[14] that 7-*epi*-goniotriol **34** was one of the possible biogenetic precursor of 7-*epi*-goniofufurone **7**.



Scheme 4

Reagents and conditions : (a) $Et_3N.3HF$, CH_3CN, RT, 6 days ; (b) DEAD, PPh_3, 4. NO_2-$PhCO_2H$, THF, 0 °C to RT, 2 h ; (c) K_2CO_3, EtOH-CH_2Cl_2 (3 :1), RT, 90 min ; (d) *t*-$BuPh_2SiCl$, imidazole, DMF, RT, 4 days ; (e) **11**, *n*-BuLi, THF, -78 °C, 30 min then add **29**, -78 °C to RT ; (f) $LiAlH_4$, Et_2O, -78 °C, 90 min ; (g) 80 % AcOH, reflux, 7 h ; (h) NBu_4F, RT,1 h.

2.3 Synthesis of (+) –goniodiol 1 and (+) 9-deoxygoniopypyrone 2

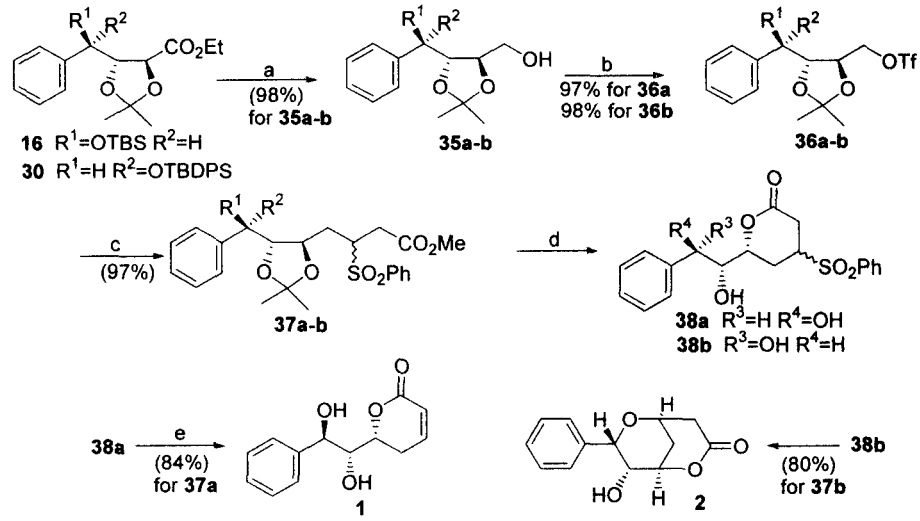
Goniodiol **1** exhibited potent and selective cytotoxicity against human lung carcinoma (A-549, ED_{50}=0.12 μg/ml) with no significant toxicity against brine shrimp (LC_{50}>500 μg/ml).[8d] On the contrary, 9-deoxygoniopypyrone **2** was shown to be only marginally cytotoxic against human tumor cells tested (ED_{50}> 7.4 μg/ml). [8d] The structure and relative configurations of **1** and **2** were determined by NMR spectra studics and X-ray crystallographic analysis [8d] and absolute stereochemistries on the basis of total synthesis of natural materials.[33] As mentioned earlier in our general synthetic plan, we envisioned that the displacement of a triflate by the carbanion of the sulfone **11** would be a good method for the introduction of the *Z*-acrylate surrogate for type I stytyllactone synthesis.

Armed with ample precedents, [34-36] we confidently explored this route by $LiAlH_4$ reduction of the ester function of **16** and triflation of the resulting alcohol **35a**, according to the protocol desribed by Ambrose and Binkley, [37] which furnished compound **36a** in 97 % yield (Scheme 5). As expected, coupling between the lithiated Ghosez's sulfone **11** and the triflate **36a**, in the presence of HMPA, worked beautifully at -78 °C to give after mild acid treatment the ester **37a** in 97 % yield as an equal and unseparable mixture of diastereomers. Exposure of **37a**, for a short reaction time, to trifluoroacetic acid effected cleavage of silyl and acetal protecting groups and lactone formation to give **38a**, which, without purification was treated with DBU

to afford goniodiol **1** in 84 % yield from **37a**. Synthetic goniodiol displayed physical and spectroscopic data in perfect agreement with those of the natural compound. [8d]

We next turned our attention to the synthesis of 9-deoxygoniopypyrone **2**. According to the same reaction sequence than for the goniodiol synthesis, the ester **30** was transformed to the triflate **36b** in 97 % yield. Surprisingly, unlike the coupling reaction between **36a** and **11**, the union of the triflate **36b** and the sulfone **11** was effected in a better yield at room temperature and in the absence of HMPA (94 % yield). Treatment of the β-sulfonyl ester **37b** by trifluoroacetic acid led to the δ-lactone **38b** which by exposure to an excess of DBU furnished 9-deoxygoniopypyrone **2** in 80 % yield from **37b**.

By means of the triflate-sulfone coupling, a powerful carbon-carbon bond forming process, 9-deoxygoniopypyrone **2** was synthesized in five steps and 75 % yield from **30**.



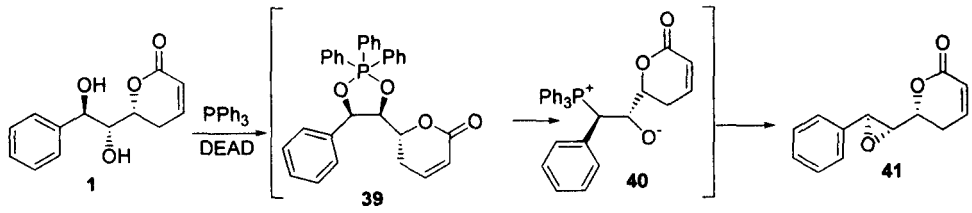
Scheme 5

Reagents and conditions : (a) $LiAlH_4$, Et_2O, 0° C, 5 min ; (b) $(CF_3SO_2)_2O$, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, -10 °C, 30 min ; (C) **11**, *n*-BuLi, solvent (see text) ; (d) CF_3CO_2H-H_2O (4 :1), RT, 18 h ; (e) DBU, CH_2Cl_2, 0 °C, 1 h.

*2.4 Synthesis of (-)-isogoniothalamin epoxide **41** from goniodiol **1***

Our synthetic strategy for goniodiol **1**, using the triflate –sulfone coupling, allowed its preparation, on gram quantities, in 51 % overall yield from mandelic acid. Because of its readily availability, we thought that goniodiol could be a good starting material for the synthesis of several members of its family particularly isogoniothalamin epoxide **41**. This epoxide, which is supposed to be the biosynthetic precursor of goniodiol **1**, has not been yet isolated from *Goniothalamus* plant extracts.[4,13,14] It has been synthesized by epoxidation of (*R*)-(+) –goniothalamin with MCPBA and separation from its diastereomer, goniothalamin epoxide by TLC after multiple developments.[4]

Goniodiol **1** was readily transformed in 75 % yield, by a one-step procedure, to the epoxide **41** *via* a phosporane-promoted cyclodehydration of diols (Scheme 6).[38] Interestingly, in contrast to (+)-phenylethane – 1,2-diol, [38] Mitsunobu epoxidation of the 1,2 –diol system of goniodiol occurred with a complete inversion of stereochemistry at the benzylic center. This cycloetherification must involve the formation of the 1,3,2λ^5-dioxaphospholane **39** which undergoes a highly chemoselective ring opening to the betaine **40** that collapses to **41**.



Scheme 6

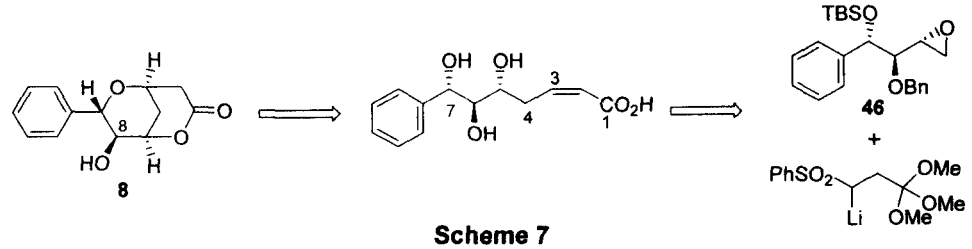
Reagents and conditions : PPh_3 (3 equiv), DEAD (3 equiv), THF, RT, 3 h.

The spectral and physical data for the synthetic isogoniothalamin oxide **41** were in good agreement with those described in the literature except for the sign of the optical rotation. [4,39]

2.5. Synthesis of (-)-8-epi-9-deoxygoniopypyrone 8

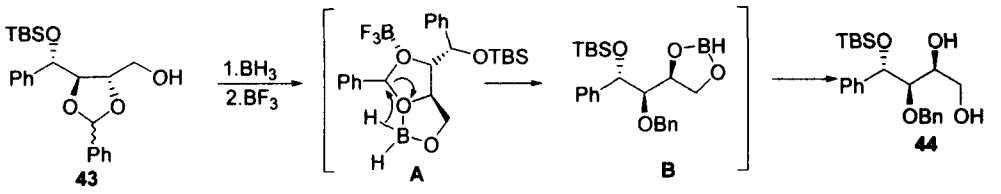
In 1995, 8-*epi*-9-deoxygoniopypyrone **8** was isolated along with other styryllactones of *Goniothalamus dolichocarpus*.[2] Compound **8** was found to have significant larvicidal activity (*Aedes aegypti*, LC_{50} 15-20 μg/ml). The gross structure of **8** was determined as (1*R**, 5*R**, 7*R**, 8*R**) -8-hydroxy-7-phenyl-2,6-dioxabicyclo [3.3.1]nonan-3-one based on two-dimensional NMR studies as well as by comparison with those of its epimer, (+)-9-deoxygoniopypyrone **2**.[2]

We have devised a synthetic strategy for **8** which was traced from that of type I styryllactones (Scheme 1) and involves the assembly of the C1-C3 an C4-C7 fragments of **8** by the opening of the epoxide **46** with the anion of the sulfone **11** (Scheme 7).



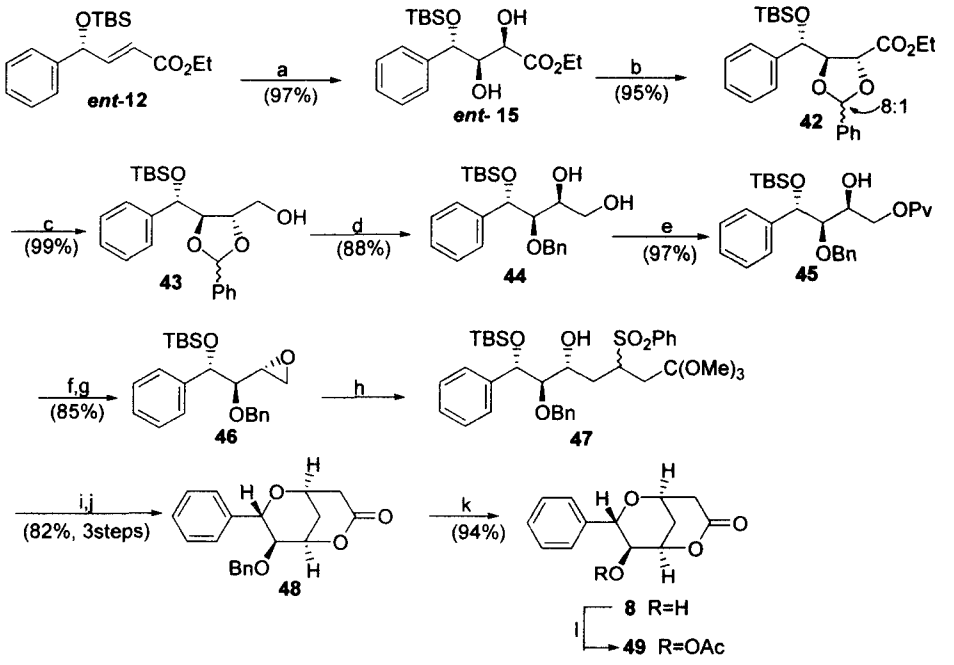
Scheme 7

The starting point of the synthesis of **8** was the (*E*) -α,β-unsaturated ester *ent*-**12**, prepared in four steps and 72 % yield from (*S*)-mandelic acid (Scheme 9).[25] Sharpless asymmetric dihydroxylation of *ent*-**12** proceeded with high diastereofacial stereoselectivity to give exclusively the desired diol *ent*-**15** in 97 % yield. After protection of the *cis*-diol as a benzylidene acetal, reduction of the ester function with $LiAlH_4$ provided the primary alcohol **43** in quantitative yield. Regioselective reductive benzylidene cleavage with the mixture $BH_3.Me_2S$ and $BF_3.Et_2O$ in 1 :1 molar ratio gave cleanly the benzyl ether **44** in 88 % yield. This hydroxy-directed acetal cleavage involves very likely the intermediate **A** which by 1,3 –hydride shift facilitated by $BF_3.Et_2O$, led to **B** (Scheme 8).[4]



Scheme 8

At this stage of the synthesis our plan called for the installation of the epoxide functionality. Regioselective pivaloylation of the primary alcohol group followed by mesylation and finally oxirane ring formation mediated by sodium methoxide afforded the α-epoxide **46** in 82 % yield for the three –reaction sequence. Addition of the lithium salt of **11** to the epoxide **46** in the presence of $BF_3.Et_2O$ gave diastereomeric β-hydroxysulfones **47**.



Scheme 9

Reactions and conditions : (a) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH-H_2O (1 :1), RT, 36 h ; (b) $PhCH(OMe)_2$, camphorsulfonic acid, benzene, reflux, 1 h, (c) $LiAlH_4$, Et_2O, 0°C, 5 min, (d) $BH_3.Me_2S$ then $BF_3.Et_2O$, CH_2Cl_2, 0 °C, 15 min ; (e) *t*-BuCOCl, DMAP, CH_2Cl_2, RT, 15 min ; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, RT, 30 min ; (g) MeONa, Et_2O-MeOH, RT, 5 h ; (h) **11**, *n*-BuLi, $BF_3.Et_2O$, THF, -78 °C, 1 h ; (i) CF_3CO_2H-H_2O (9 :1), RT, 3 h ; (j) DBU, CH_2Cl_2, 0 °C, 1 h ; (k) $TiCl_4$, CH_2Cl_2, RT, 30 min ; (l) Ac_2O, DMAP, CH_2Cl_2, RT, 1 h.

Transformation of **47** to the protected styryllactone **48** was effected according to the same reaction sequence than for 9-deoxygoniopypyrone **2** synthesis (Scheme 5) : (1) cleavage of the silyl protecting group and lactonization induced by acid treatment ; (2) $PhSO_2H$ elimination and concomitant intramolecular Michael addition mediated by DBU. Finally, debenzylation of **48** with $TiCl_4$[41,42] provided 8-*epi*-9-deoxygoniopypyrone

8 in 94 % yield. The spectra and physical data of the acetate of synthetic **8** (compound **49**) are in agreement with those of the natural compound thereby confirming its structure and absolute stereochemistry.[2]

III Conclusion

We have divised a short and efficient syntheses of a number of styryllactones with various structural complexities. A major goal was to develop an effective strategy which allowed the synthesis of most of the members of the styryllactone family from a common precursor. Ethyl (*2S, 3R, 4R*)-4-(*t*-butyldimethylsilyloxy)-2,3-isopropylidenedioxy-4-phenylbutanoate **6**, obtained in five steps from mandelic acid, greatly helped to fulfill this objective . The combination of this « ideal » retron with valuable Ghosez's homoenolate reagent **11** (methyl 3-phenylsulfonyl orthopropionate) authorized the synthesis of styryllactones **1-7** in four to nine steps and with an overall yield ranging from 13 to 78 %. Efficient epoxide – sulfone coupling allowed the synthesis of 8-*epi*-9-deoxygoniopypyrone **8** in nine steps and 62 % yield from *ent*-**15** thereby establishing its absolute stereochemistry (1*R*, 5*R*, 7*S*, 8*S*). Moreover, because of the commercially availability of both enantiomers of mandelic acid, the unnatural enantiomers of all these styryllactones can be prepared for biological evaluation.

IV Experimental section

General procedures. ^{1}H NMR spectra were recorded in $CDCl_3$ (δ_H = 7.25) at ambient probe temperature on a Bruker AC 200 (200 MHz) spectrometer. Data are presented as follows : chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), integration, coupling constant and interpretation. ^{13}C NMR spectra were recorded at ambient probe temperature on a Brucker AC 200 (50.3 MHz) in $CDCl_3$ used as a reference (δ_C = 77.0). IR were recorded on a Perkin-Elmer 298 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at the sodium D line (589 nm). Melting points were determined on a Büchi 530 apparatus and are uncorrected. Combustion analyses were performed by the Service Central de Microanalyse, CNRS, Solaize.

Reagents and solvents were purified by standard means. Diethyl ether and tetrahydrofuran were distilled from sodium wire/ benzophenone and stored under a nitrogen atmosphere. Acetonitrile, boron trifluoride-etherate, dichloromethane, dimethylformamide, toluene and triethylamine were distilled from calcium hydride . Ethanol and methanol were distilled from magnesium metal. All other chemicals were used as received . Unless otherwise stated, all experiments were performed under anhydrous conditions in an atmosphere of nitrogen.

Ethyl (2*S*,3*S*,4*R*)-4-(*t*-butyldimethylsilyloxy)-2,3-dihydroxy-4-phenylbutanoate 15. A mixture of *tert*-butyl alcohol (64 ml) and water (64 ml), AD-mix-β (18 g) and methanesulfonamide (1.23 g) was stirred for a few minutes at room temperature until two clear phases were produced. After addition of the α,β-unsaturated ester **12** (4.2 g, 13.1 mol), the reaction mixture was stirred at room temperature for 14 h. Sodium metabisulfite (20 g) was added and after stirring for 1h the mixture was dilued wtih 50 ml of water and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (Et_2O-petroleum ether, 1:1) to give **15** as an oil (4.5 g, 97 % yield). $[\alpha]^{20}_D$ -33 (*c* 2.5 $CHCl_3$) ; IR (film) 3500, 2960, 1740 cm^{-1} ; ^{1}H NMR : -0.2 (s, 3H, $SiCH_3$), 0.1 (s, 3H, $SiCH_3$),0.9 (s, 9H, $SiC(CH_3)_3$), 1.27 (t, 3H, J = 7.1Hz, $OCH_2C\underline{H}_3$), 2.0 (d, 1H, J = 7.8Hz, OH), 3.3 (d, 1H, J = 5.5Hz, OH), 4.0 (td, 1H, J = 1.3 and 7.8 Hz, C<u>H</u>OH-CHOSi), 4.3 (q, 2H, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.6 (dd, 1H, J = 1.2 and 5.5 Hz, C<u>H</u>OHCO$_2$Et), 4.80 (d, 1H, J = 7.96 Hz, PhC<u>H</u>OSi), 7.34 – 7.48 (m, 5H, Ph) ; ^{13}C NMR : -5.0, -4.5, 14.2, 18.1, 25.8 (3C), 61.9, 70.2, 76.0, 76.6, 128.0 (2C), 128.2, 128.4 (2C), 141.7, 173.8; anal. calcd for $C_{18}H_{30}O_5Si$: C, 60.71 ; H, 8.75. Found : C, 60.98 ; H, 8.53.

Ethyl (2*S*,3*S*,4*R*)-4-(*t*-butyldimethylsilyloxy)-2,3-isopropylidenedioxy-4-phenyl butanoate 16. To a solution of the diol **15** (5 g), 14.1 mmol) in CH_2Cl_2 (25 ml) was added camphorsulfonic acid (0.19 g , 0.81 mmol) followed by 2-methoxypropene (3 ml, 34.5 mmol). After stirring for 15 min at room temperature, the solution was filtered on a pad of silica gel, eluted with Et_2O and the filtrate concentrated *in*

vacuo. Flash chromatography of the residue (Et_2O –petroleum ether, 1:9) gave the acetonide **16** as an oil (5.5 g, 99 % yield). $[\alpha]^{20}_D$ –14 (*c* 1.9, $CHCl_3$) ; IR (film) 2980, 1740 cm^{-1}; ^1H NMR : -0.1 (s, 3H, $SiCH_3$), -0.11 (s, 3H, $SiCH_3$) ; 1.01 (s, 9H, $SiC(CH_3)_3$), 1.1 (t, 3H, J = 7.1Hz, $OCH_2\underline{C}H_3$), 1.42 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.85-4.1 (m, 2H, $OC\underline{H}_2CH_3$), 4.42 (dd, 1H, J = 4.3 and 6.4 Hz, C<u>H</u>OR-CHOSi), 4.57 (d, 1H, J = 6.4Hz, C<u>H</u>OR-CO_2Et), 4.90 (d, 1H, J = 4.3Hz, PhC<u>H</u>OSi), 7.36-7.49 (m, 5H, Ph) ; ^{13}C NMR : -4.8 (2C), 13.9, 18.2, 25.9 (3C), 26.0, 27.1, 61.3, 74.2, 75.3, 83.9, 111.5, 126.7 (2C), 127.7, 128.1 (2C), 140.7, 171.2 ; anal. calcd for $C_{21}H_{34}O_5Si$: C, 63.92 ; H, 8.68. Found : C, 63.89 ; H, 8.51.

Trimethyl (3*R*and3*S*,5*S*,6*S*,7*R*)-7-(-*t*-butyldimetylsilyloxy)-5,6-isopropylidenedioxy-4-oxo-3-phenyl sulfonyl-7-phenylorthoheptanoate 17. To a cooled solution (-78 °C) of trimethyl 3-phenylsulfonyl orthopropionate **11** (4.4 g, 18 mmol) in THF (30 ml) was added dropwise *n*-BuLi (2.3 M in hexanes, 7.5 ml, 1 equiv.). After stirring for 30 min at – 78 °C, a solution of the ester **16** (2.4 g, 6 mmol) in THF (20 ml) was added. The reaction was stirred for 2 h at –78 °C and allowed to warm up to room temperature (1 h). Water (30 ml) and CH_2Cl_2 (60 ml) were added and the pH was adjusted to 6 by addition of 1N HCl solution. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (Et_2O-petroleum ether, 1:2) to give the β-keto sulfone **17** as an equal mixture of diastereomers (3.53 g, 93 % yield). IR (film) 3060, 2960, 1730, 1450, 1330 cm^{-1} ; ^{13}C NMR (diastereomeric mixture) : -4.9, -4.6, -4.5, 18.2, 25.87, 26.05, 26.5, 27.3, 27.33, 28.4, 29.8, 49.5, 49.7, 64.9, 65.4, 75.3, 76.3, 81.4, 82.1, 82.3, 84.2, 111.4, 112.6, 113.6, 113.7, 127.6 -141.1 , 200.0, 200.9 ; anal. calcd for $C_{31}H_{46}O_9SSi$: C, 59.78 ; H, 7.44 ; S, 5.14. Found : C, 59.64 ; H, 7.43 ; S, 5.05.

Trimethyl (3*R*and 3*S*, 4*R*,5*R*,6*S*,7*R*)-7-(*t*-butyldimethylsilyloxy-5,6-isopropylidenedioxy -3-phenyl sulfonyl -7-phenylorthoheptanoate 18. To a cooled solution (-78 °C) of the ketone **17** (3.17 g, 5.1 mmol) in Et_2O (50 ml) was added by portions lithium aluminium hydride (0.47 g, 12.4 mmol). After stirring at –78 °C for 1 h, the mixture was diluted with Et_2O (50 ml) and the excess of $LiAlH_4$ was destroyed by saturated Na_2SO_4 solution. The mixture was filtered on a sintered funnel and evaporated to dryness. The residue was purified by flash chromatography on neutral alumina (Et_2O-petroleum ether, 2:3) to afford the β-hydroxysulfone **18** as a foam (3.06 g) 96 % yield). IR (film) 3410, 2940, 1450, 1380 ; ^{13}C NMR (diastereomeric mixture) : -4.6, -4.5, -4.4, 18.7, 26.3, 26.4, 27.2, 27.3, 27.5, 27.7, 27.9, 28.2, 49.8, 49.9, 62.7, 64.5, 67.5, 68.6, 75.1, 75.3, 78.0, 80.3, 82.2, 82.8, 106.0, 109.6, 124.0-142.1.

[1'*R*,2'*R*,3'*R*,3(*S*or*R*),4*S*]-4-(3-Phenyl-1',2',3'-trihydroxypropyl)-3-phenylsulfonylbutan-4-olide 19 and (1'*R* , 2'*R*, 3*S*, 4*S*, 5*R*) -5-(1',2' –dihydroxy-2-phenylethyl) –4-hydroxy 3-phenylsulfonylpentan –5-olide 20. A solution of the sulfone **18** (1.1 g, 1.76 mmol) in an equal mixture of THF-AcOH-1N HCl (24 ml) was refluxed for 150 min. After evaporation, the residue was partitioned between CH_2Cl_2 (30 ml) and brine (10 ml). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 ml). The organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was filtered on a pad of silica gel (EtOAc –petroleum ether, 3:1) to give a 2:1 mixture of lactones **19** and **20** (0.624 g, 91 % yield) as a foam. IR (film) 3459, 1786, 1743, 1620, 1580, 1308, 1050 cm^{-1} ; ^1H NMR (CD_3OD, compound **19**) :3.0 (dd, 1H, J = 3.2 and 18.6 Hz, $C\underline{H}_a$-C=O), 3.24 (dd, 1H, J = 9.6 and 18.6 Hz, $C\underline{H}_b$-C=O), 3.9 (dd, 1H, J = 4.8 and 7Hz, PhCHOH-C<u>H</u>OHR), 3.98 (dd, 1H, J = 3.4 and 4.8 Hz, C<u>H</u>OH-C<u>H</u>OCO), 4.52 (ddd, 1H, J = 2.6, 3.2, 9.6 Hz, C<u>H</u>SO_2Ph), 4.78 (d, 1H, J = 7Hz, PhC<u>H</u>OH), 5.35 (q, 1H, J = 2.6 and 3.4 Hz, C<u>H</u>-O-C=O), 7.45 – 8.16 (m, 5H, Ph) ; ^{13}C NMR (CH_3OD, compound **19**) 30.5, 62.3, 73.0, 74.4, 75.8, 80.4, 127.9 – 130.8 (9C), 135.8, 137.6, 143.4, 175.6. ^1H NMR (CD_3OD, compound **20**) : 2.96 (dd, 1H, J = 7 and 16.3Hz, $C\underline{H}_a$-C=O), 3.11 (dd, 1H, J = 9.2 and 16.3 Hz, $C\underline{H}_b$-C=O), 4.07 (ddd, 1H, J = 5.8, 7, 9.2 Hz, CHSO_2Ph), 4.27 (dd, 1H, J = 2.3 and 8Hz, PhCHOH-C<u>H</u>OH), 4.78 (d, 1H, J = 8Hz, PhC<u>H</u>OH), 4.8 (m, 1H, C<u>H</u>OHSO_2Ph), 4.98 (m, 1H, C<u>H</u>OC=O), 7.45-8.16 (m, 5H, Ph) ; ^{13}C NMR (CD_3OD, compound **20**) : 28.7, 63.2, 66.1, 74.0, 74.7, 78.9, 127.9-130.8 (9C), 135.8, 137.6, 143.4, 170.9.

Goniofufurone 3 and goniotriol 21. To an ice-chilled solution of the mixture of lactones **19** and **20** (0.624 g, 1.6 mmol) in CH_2Cl_2 (20 ml) was added dropwise DBU (0.75 ml, 5 mmol). After stirring the solution for 50 min at 0 °C, the reaction mixture was filtered on a pad of silica gel (Et_2O). Goniofufurone **3** was first eluted (0.28 g, 70 % yield) as a white solid. Mp 147-149 °C ; $[\alpha]^{20}_D$ + 10 (*c* 0.6, EtOH) [lit.[8c] mp 152-154 °C, $[\alpha]^{20}_D$ + 9 (c 0.5, EtOH)] ; ^1H NMR : 2.68 (dd, 1H, J = 1.8 and 18.8 Hz, $C\underline{H}_aC$=O), 2.74 (dd, 1H, J = 6.3 and 18.8 Hz, $C\underline{H}_bC$=O), 2.88 (s, 1H, OH), 4.09 (dd, 1H, J = 2.8 and 4.7 Hz, C<u>H</u>-CHOHPh), 4.2 (d,1H, J = 2.5 Hz, OH), 4.4 (s, 1H, C<u>H</u>OH-C<u>H</u>OC=O), 4.86 (d, 1H, J = 4.7 Hz, CHOC=O), 5.12 (ddd, 1H, J = 1.8, 4.6, 6.3 HZ,

CH-CH2), 5.2 (d, 1H, J = 4.7 HZ, PhCHOH)7.35-7.45 (m, 5H, Ph) ; ^{13}C NMR (acetone-d_6) : 36.3, 72.2, 74.6, 77.9, 84.7, 88.4, 127.6 (2C), 128.1, 128.8 (2C), 143.2, 176.2. The next fraction was constitued by goniotriol **21**, obtained as a white solid (0.031g, 8 % yield). Mp 172 °C ; $[\alpha]^{20}_D$ + 116 (c 0.5, MeOH) [lit.[8b]mp 170 °C, $[\alpha]^{20}_D$ + 121 (MeOH)] ; ^{1}H NMR (acetone-d_6) : 4.15 (dd, 1H, J = 3.2 and 8.2 Hz, CHOH-CHOHPh), 4.5 (dd, 1H, J = 3.2 and 5.7 Hz, CHOH-CH=CH), 4.63 (t, 1H, J = 3.5 Hz, CHOC = O), 4.73 (d, 1H, J = 8.2 Hz, PhCHOH), 6.05 (d, 1H, J = 9.7 Hz, CH = CH-C=O), 7.05 (dd, 1H, J = 5.7 and 9.7 Hz, CH = CH-C=O), 7.2-7.45 (m,5H, Ph).

[1'*R*, 2'*S*, 3'*R*, 4(*R*and*S*), 5*R*]-5-[3'-(*t*-Butyldimethylsilyloxy-1',2'-isopropylidenedioxy)-3-phenyl propyl]-2,2-dimethoxy-4-phenylsulfonyltetrahydrofurane 22. This cyclic orthoester was obtained from compound **17** (0.36g, 0.58 mmol) using the same procedure than for the preparation of the β-hydroxysulfone **18** except that its purification was effected by chromatography on silica gel (Et_2O-petroleum ether, 1:1) compound **22** was obtained as a 1:1 diastereomeric mixture (0.3 g, 88 %). IR (film) 3060, 2920, 1590, 1450, 1320 cm^{-1} ; ^{1}H NMR : -0.1 (s, 1.05, CH_3), -0.08 (s, 1.5 H, CH_3), 0.15 (s, 1.5H, CH_3), 0.2 (s, 1.5 H, Si $C(CH_3)_3$), 0.94 (s, 4.5 H, $SiC(CH_3)_3$), 0.95 (s, 4.5 H, $SiC(CH_3)_3$), 1.28 (s, 1.5 H, CH_3), 1.32 (s, 3H, CH_3), 1.36 (s, 1.5 H, CH_3), 2.07 (dd, 0.5 H, J = 6.7 and 12.8 Hz, CH_a-$CHSO_2Ph$), 2.2 (dd, 0.5 H, J = 10 and 13.6 Hz, CH_a-$CHSO_2Ph$) , 2.33 (dd, 0.5 H, J = 8.2 and 13.7 Hz, CH_b-$CHSO_2Ph$), 2.55 (dd, 0.5 H, J = 11.6 and 12.8 Hz, CH_b-$CHSO_2Ph$), 2.93 (s, 1.5 H, OMe), 3.05 (s, 1.5H, OMe), 3.2 (s, 1.5 H, OMe), 3.25 (s, 1H, OMe), 3.83-3.89 (m, 1H), 4.03-4.1 (m , 2H), 4.23-4.26 (m, 1H), 4.67 (d, 0.5 H, J = 7.9 Hz, $CHOC(OMe)_2$), 7.3-8.0 (m, 10H) ; ^{13}C NMR ; -4.6, -4.55, -4.5, -4.4, 18.6, 18.7, 26.3 (3C), 27.0, 27.3, 27.6, 27.7, 34.3, 35.0, 48.8, 49.5, 50.3 , 51.3, 63.2, 65.1, 74.9, 75.8, 76.0, 76.6, 76.9, 77.3, 81.5, 81.9, 109.4, 109.5, 121.4, 121.5, 127.3 – 142.4 (10 C) ; anal. calcd for C_{30} $H_{44}O_8SSi$: C, 60.78; H, 7.48; S, 5.4. Found : C, 60.86; H, 7.45; S, 5.52.

[1'*R*,2'*R*, 3'*R*, 4 (*R* and *S*), 5*R*]-5-[3'-(*t*-Butyldimethylsilyloxy)-1',2'-isopropylidenedioxy -3'-phenyl propyl] -4- phenylsulfonylbutan -4- olide 23. A solution of the lactone **18** (1.01 g, 1.61 mmol) in toluene (15 ml) containing a catalytic amount of camphorsulfonic acid (0.12 g, 0.48 mmol) was refluxed for 1 h. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel (Et_2O -petroleum ether, 1:1) to give the γ-lactone **23** as a mixture of diastereomers (ratio 1:1) (0.83 g, 94 %). IR (film) 3030, 2980, 1795, 1590, 1450, 1380 cm^{-1} ; anal. calcd for $C_{28}H_{38}O_7SSi$: C, 61.5; H,7.0; S, 5.86. Found : C, 61.0; H, 7.2; S, 5.52.

(*E*)-and(*Z*)-(2'*S*,3'*R*)-4-[3'-(*t*-Butyldimethylsilyloxy)-2'-hydroxy-3'-phenylpropylidene]but-2-en-4-olide 26 and 24 and (*Z*) - (2'*S*, 3'*R*) -4 – [2'- (*t*-butyldimethylsilyloxy) –3- hydroxy-3-phenylpropylidene] – but –2-en-4-olide 25. To an ice –chilled solution of the lactone **23** (0.83 g, 1.5 mmol) in CH_2Cl_2 (16 ml) was added dropwise DBU (0.67 ml, 4.5 mmol). After stirring for 90 min at 0 °C, the mixture was concentrated and the residue chromatographed on silica gel (Et_2O-petroleum ether, 2:3) gave **24 – 26** as an unseparable mixture (0.455 g, 87 % yield). ^{1}H NMR (compound **24**) : -0.11 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.9 (9H, $SiC(CH_3)_3$), 2.57 (s, 1H , OH), 4.8 (m, 2H, PhCHOSi), 5.17 (d, 1H, J = 8.1 Hz, CH = C-OCO), 6.17 (d, 1H, J = 5.4Hz, CH = CH-CO), 7.23 – 7.3 (m, 6H, Ph + CH =CH-CO) ; ^{1}H NMR (compound **25**) : -0.01 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$, 2.82 (s, 1H, OH), 4.9 (m, 2H), 5.26 (d, 1H, J = 9.3 Hz, CH = CH-OCO), 6.13 (d, 1H, J = 5.3 Hz, CH=CH-CO), 7.23 –7.3 (m, 6H, Ph + CH = CH-CO) ; ^{1}H NMR (compound **26**) : -0.13 (s, 3H, $SiCH_3$), 0.4 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 2.38 (s, 1H, OH), 4.47 (m, 1H, J = 5.2 and 7.8 Hz, CHOH–CH=CH), 4.72 (d, 1H, J=5.2 Hz, PhCHOSi), 5.79 (dd, 1H, J = 1.3 and 7.8 Hz, CH = CH-OCO), 6.1 (dd, 1H, J=1.7 and 5.6 Hz, CH=CH-CO), 7.23-7.3 (m, 5H, Ph), 7.5 (d, 1H, J = 5 Hz, CH=CH-CO).

(*E*)-and (*Z*)-(2'*S*, 3'*R*)-4-(2',3'-Dihydroxy-3-phenylpropylidene) but-2-en-4-olide 6 (goniobut enolide B) and 5 (goniobutenolide A). A solution of the mixture of alkylidene lactones **24-26** (0.4 g, 1.15 mmol) in a mixture of AcOH-THF-H_2O (3:1:1, 10 ml) was refluxed at 50 °C for 14 h. After coevaporation of the reaction mixture with toluene, the residue was purified by flash chromatography on silica gel (*t*BuOMe-cyclohexane, 7:1). Goniobutenolide B **6** (0.05 g, 19 % yield) was first eluted as a white solid. Mp 142-144°C ; $[\alpha]^{20}_D$ -107 (*c* 0.3 $CHCl_3$). [lit.[42] mp 146-148 °C ; $[\alpha]^{25}_D$ -109 (*c* 0.06, $CHCl_3$)]. IR (film) 3420, 2920, 1780, 1750, 1670 cm^{-1} ; ^{1}H NMR : 3,3 (s, 2H, OH), 4.62 (dd, 1H, J = 4.3 and 8 Hz, CHOH-CH=CH), 4.89 (d, 1H, J = 4.3 Hz, PhCHOH), 5.79 (dd, 1H, J = 1.8 and 8Hz, CH =C-OCO), 6.12 (dd, 1H, J = 1.8 and 5.5 Hz, CH=CH-C=O), 7.27-7.33 (m, 5H, Ph), 7.43 (d, 1H, J = 5.5 Hz, CH=CH-C=O). The second fraction was constituted by goniobutenolide A **5** (0.15 g, 56 % yield) obtained as a yellow oil. $[\alpha]^{20}_D$ + 183 (*c* 0.3, $CHCl_3$) [lit.[42] $[\alpha]^{25}_D$ +

183 (*c* 0.2, $CHCl_3$)]. ^1H NMR : 3.8 (s, 2H, OH), 4.99 (m, 2H), 5.33 (d, 1H, J = 8.3 Hz, C<u>H</u>=C-OCO), 6.13 (d, 1H, J = 5.45 Hz, CH = C<u>H</u>-C=O), 7.24-7.33 (m, 6H, Ph + C<u>H</u> = CH –C=O).

Ethyl (2*S*, 3*R*, 4*R*)-4-hydroxy-2,3-isopropylidenedioxy-4-phenylbutanoate 27. To a solution of the ester **16** (3.2 g, 8.1 *mmol*) in acetonitrile (40 ml) was added commercially available $Et_3N.3HF$ (10 ml, 61 mmol). After stirring for 7 days at room temperature, the solution was diluted with CH_2Cl_2 (40 ml) and a saturated potassium carbonate solution (25 ml) was added dropwise. The aqueous phase was extracted with CH_2Cl_2 (3x50 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica gel (Et_2O-petroleum ether, 1:2) to give the alcohol **27** as an oil (2.15 g, 95 %). $[\alpha]^{20}_D$ + (*c* 1.2, $CHCl_3$) ; IR (film) 3480, 2920, 1740, 1590, 1380 cm^{-1} ; ^1H NMR : 1.06 (t, 3H, J = 6.1 Hz, CH_3), 1.42 (s, 3H, CH_3) 1.47 (s, 3H, CH_3), 2.91 (s, 1H, OH), 3.96 (m, 2H), 4.46 (m, 2H), 4.98 (d, 1H, J = 3.7 Hz, PhC<u>H</u>OH), 7.24-7.41 (m, 5H, Ph) ; ^{13}C NMR : 13.9, 25.8, 26.9, 61.4, 72.5, 74.9, 82.6, 111.7, 126.4 (2C), 127.9, 128.3 (2C), 138.7, 171.0 ; anal. calcd for $C_{15}H_{20}O_5$: C, 64.27 ; H, 7.19. Found : C, 64.31 ; H, 7.19.

Ethyl (2*S*,3*R*,4*S*)-2,3-isopropylidenedioxy-4-(4-nitrobenzyloxy)-4-phenylbutanoate 28. To an ice-chilled solution of the alcohol **27** (2.15 g, 7.67 mmol) in THF (88 ml) were successively added 4-nitrobenzoic acid (2.6 g , 15.3 mmol) , triphenylphosphine (4.1 g, 15.3 mmol) then dropwise ethyl azodicarboxylate (2.4 ml, 15.3 mmol). The reaction mixture was stirred for 15 min at 0 °C and 90 min at room temperature. After concentration *in vacuo*, the residue was chromatographed on silica gel (Et_2O-petroleum ether, 1:5) to furnish the nitrobenzoate **28** (3.2 g 97 % yield) as a white solid. Mp 91-92 °C ; $[\alpha]^{20}_D$ -22 (*c* 0.8, $CHCl_3$) ; IR (KBr) 3030, 2920, 1740-1730, 1590, 1380 cm^{-1} ; ^1H NMR : 1.16 (t, 3H, J = 6.2 Hz, CH_3), 1.45 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 4.06 (m, 2H, $OC\underline{H}_2CH_3$), 4.35 (d, 1H, J = 6.4 Hz, C<u>H</u>OR-CO_2Et), 4.81 (t, 1H, J = 6.3 Hz, C<u>H</u>OR-CHOBz), 6.16 (d, 1H, J = 6 Hz, PhC<u>H</u>OBz), 7.3-7.5 (m, 5H, Ph), 8.28 (m, 4H, Ph) ; ^{13}C NMR : 14.0, 26.1, 27.1, 61.6, 76.1, 77.1, 80.6, 112.7, 123.6 (2C), 127.8 (2C), 128.7 (2C), 129.2, 131.0 (2C), 135.3, 135.5, 150.7, 163.7, 170.3 ; anal. calcd for $C_{22}H_{23}O_8N$: C, 61.53; H, 5.4; N, 3.26. Found : C, 61.77; H, 5.49; N, 3.33.

Ethyl (2*S*,3*R*,4*S*)-4-hydroxy-2,3-isopropylidenedioxy-4-phenybutanoate 29. To a solution of the 4-nitrobenzoate **28** (4.62 g, 10.7 mmol) in a mixture CH_2Cl_2 –EtOH (128 ml, 1:3) was added K_2CO_3 (3 g, 22 mmol). After stirring the reaction mixture for 1 h at room temperature, the mixture was filtered then evaporated. The residue was purified by flash chromatography on silica gel (Et_2O-petroleum ether, 2 :3) to give the alcohol **29** (2.6 g, 87 % yield) as an oil. $[\alpha]^{20}_D$ + 40 (*c* 1.2, $CHCl_3$) ; IR (film) 3480, 2920, 1740, 1590, 1380 cm^{-1} ; ^1H NMR : 1.17 (t, 3H, J = 6.9 Hz, CH_3), 1.45 (s, 3H,CH_3), 1.51 (s, 3H, CH_3), 2.8 (d, 1H, J = 6.5 Hz, OH), 4.08 (m, 2H, $OC\underline{H}_2CH_3$), 4.44 (m, 2H), 4.79 (dd, 1H, J = 3.7 and 6.2 Hz, PhC<u>H</u>OH), 7.26 – 7.38 (m, 5H, Ph) ; ^{13}C NMR : 14.1, 26.0, 27.0, 61.5, 74.0, 76.1, 82.5, 112.1, 126.9 (2C), 128.3, 128.5 (2C), 139.9, 170.7 ; anal. calcd for $C_{15}H_{20}O_5$: C, 64.27 ; H, 7.19. Found : C, 64.28 ; H, 7.21.

Ethyl (2*S*,3*R*,4*S*)-4-(*t*-butyldiphenysilyloxy)-2,3-isopropylidenedioxy-4-phenylbutanoate 30. To solution of the alcohol **29** (2.6g, 9.27 mmol) in DMF (24 ml) were successively added imidazole (1.3 g, 18.5 mmol) and *t*-butyldiphenylchlorosilane (3 ml, 12 mmol). The reaction mixture was stirred for 4 days at room temperature and water (50 ml) and petroleum ether (100 ml) were added. The aqueous phase was extracted with petroleum ether (3x100 ml). The combined organic extract were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Et_2O-petroleum ether, 1:5) to afford the silylated ether **30** as an oil (4.5 g, 94 % yield). $[\alpha]^{20}_D$ + 57 (*c* 1.05, $CHCl_3$) ; IR (film) 3020, 2920, 1750, 1590 cm^{-1} ; ^1H NMR : 1.05 (s, 9H, $SiC(CH_3)_3$, 1.1 (t, 3H, J = 7Hz, CH_3), 1.26 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.96 (m, 2H, $OC\underline{H}_2CH_3$), 4.14 (d, 1H, J = 6.8 Hz, C<u>H</u>ORCO_2Et), 4.5 (dd, 1H, J = 5.6 and 6.8Hz, C<u>H</u>ORCHOSi), 4.78 (d, 1H, J = 5.6 Hz, PhC<u>H</u>OSi), 7.16 – 7.55 (m, 15 H, Ph) ; ^{13}C NMR : 13.9, 19.4, 26.0, 26.7, 26.9, 61.1, 75.7, 76.2, 83.0, 111.6, 127.3 (2C), 127.4 (2C), 127.7 (2C), 127.8 (3C), 129.5, 129.7, 132.2, 133.5, 136.0 (2C), 136.1 (2C), 139.5, 170.8. anal.calcd for $C_{31}H_{38}O_5Si$: C, 71.78; H, 7.38. Found : C, 71.6; H, 7.60.

Trimethyl [3(*R*and*S*),5*S*,6*S*,7*S*]-7-(*t*-butyldiphenylsilyloxy)-5,6- isopropylidenedioxy-4-oxo-7-phenyl-3-phenylsulfonylorthoheptanoate 31. The ester **30** (1.55g, 6.4mmol) was converted to the β-ketosulfone **31** by the procedure described for the preparation of **17.** The oily compound **31** was obtained as an equal mixture of diastereomers (1.43 g, 90 % yield). IR (film) 3020, 2980, 1720, 1590, 1380, 700 cm^{-1} ; ^{13}C NMR (C_6D_6) : 19.6, 26.7, 27.1, 27.2 , 27.3, 27.6, 28.2, 28.4, 29.8, 49.1, 49.3, 65.6, 65.9, 76.7, 77.8, 82.0, 82.3, 82.5, 83.2, 111.3, 112.5, 113.9, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.5, 128.6, 128.7, 129.6, 129.7, 133.5, 133.6, 133.7, 133.8, 133.9, 136.2, 136.3, 136.4, 136.8, 137.9, 140.5, 140.8, 199.0, 201.0 ; anal.calcd for $C_{41}H_{50}O_9SSi$: C, 65.92; H, 6.74; S, 4.29. Found : C, 66.08; H, 6.65; S, 4.45.

Goniopypyrone 4 and 7-*epi*-goniofurone 7. The β-ketosulfone **31** (1.43 g, 1.91 mmol) was reduced to the β-hydroxy sulfone **32** by the procedure described for compound **17**. The diastereomeric mixture of the β-hydroxysulfone was obtained as a foam (1.37 g 96 % yield). Anal.calcd for $C_{41}H_{52}O_9Si$: C, 65.74; H, 6.99; S, 4.28. Found : C, 65.4; H, 6.54;S, 4.44. Acid treatment of **32** under the same conditions than for **18** gave a mixture of four diastereomers (0.77 g) which treated by an excess of NBu_4F (2.7 ml, 1 M in THF) gave two products separated by column chromatography on silica gel (AcOEt-hexane, 3:1). Goniopypyrone **4** was first eluted [0.09 g, 19 % yield (three steps)]. Mp 179-181° C ; $[\alpha]^{20}_D$ + 54 (*c* 0.4, EtOH) [lit.[8c] mp 182-184 °C ; $[\alpha]^{20}_D$ + 54 (*c* 0.4, EtOH)] ; ^{1}H NMR (DMSO –d_6) : 2.92(dd, 1H, J = 1.5 and 18.5 Hz, C$\underline{H}_a$C = O), 314 (dd, 1H, J= 5.2 and 18.5 Hz, C$\underline{H}_b$C = O), 3.9 (s, 1H, C$\underline{H}$OHCHPh), 4.3 (m, 1H, C$\underline{H}$-CH_2), 4.58 (dd, J = 3.7 and 6 Hz, C$\underline{H}$OC =O) , 4.85 (s, 1H, PhCH), 5.14 (s, 1H, OH), 5.94 (s, 1H, OH), 7.25 – 7.42 (m, 5H, Ph) ; ^{13}C NMR (DMSO-d_6) : 34.4, 63.2, 68.8, 69.9, 70.0, 72.8, 126.6 (2C), 126.9, 127.5 (2C), 138.4, 168.1. The next fraction was constituted by 7-*epi*-goniofufurone **7** (0.181g, 38 % yield). Mp 189-191 °C ; $[\alpha]^{20}_D$ + 103 (*c* 1, EtOH) [lit. [8d] mp 190-192 °C ; $[\alpha]^{20}_D$ +108 (*c* 0.2,EtOH)] ; ^{1}H NMR (DMSO-d_6) : 2.46 (d, 1H, J = 18.6 Hz, C$\underline{H}_a$ C=O), 2.90 (dd, 1H, J = 6.3 and 18.6 Hz, C$\underline{H}_b$C=O), 3.65 (dd, 1H, J = 3Hz, C$\underline{H}$OH-CHOC=O), 3.84 (dd, 1H, J = 3 and 7.7 Hz, C$\underline{H}$-CHPh), 4.77 (m, 2H), 4.93 (dd, 1H, J = 4.6 and 6.3 Hz, C$\underline{H}$-CH_2), 5.28 (d, 1H, J = 4.6 Hz, OH), 5.53 (d, 1H, J = 4.7 Hz, OH), 7.25-7.49 (m, 5H, Ph).

(1*R*, 2*S*, 3*R*)-1-(*t*-Butyldimethylsilyloxy)-2,3-isopropylidenedioxy-1-phenybutan-4-ol 35a and (1*S*, 2*S*, 3*R*)-1-(*t*-butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-1-phenybutan-4-ol 35b . To a cooled solution of the ester **16** (1.13 g, 2.87 mmol) in Et_2O (25 ml) was added a solution of lithium aluminium hydride (6 ml, 1M in Et_2O). The reaction mixture was filtered on a funnel and the filtrate evaporated. The residue purified by flash chromatography on silica gel gave **35a** as an oil (1.0g, 98 % yield). $[\alpha]^{20}_D$ – 23 (c 1, $CHCl_3$) ; IR (film) 3500, 3030, 2940, 1380 cm^{-1} ; ^{1}H NMR : -0.14 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.9 (s, 9H, $SiC(CH_3)_3$), 1.45 (s, 3H, CH_3), 2.33 (dd, 1H, J = 5.4 and 7.1 Hz, OH), 3.23 (ddd, 1H, J = 5, 7.1 and 12 Hz, C$\underline{H}_a$OH), 3.50 (ddd, 1H, J = 3, 5.4 and 12 Hz, C$\underline{H}_b$OH), 3.94 (dd, 1H, J = 5.5 and 7.9 Hz, C$\underline{H}$-CHPh), 4.24 (ddd, 1 H, J = 3,5 and 7.9 Hz, C$\underline{H}$-CH_2OH), 4.82 (d, 1H, J = 5.5 Hz, PhC$\underline{H}$), 7.25-7.34 (m, 5H, Ph) ; ^{13}CNMR : -4.7, -4.6, 18.2, 25.9 (3C), 27.2 (2C), 63.3, 75.1, 78.4, 81.2, 109.1, 126.4 (2C) , 127.7, 128.2 (2C), 141.3 ; anal. calcd for $C_{19}H_{32}O_4Si$: C, 64.73, H, 9.14. Found : C, 64.92, H, 9.15.

The alcohol **35b** was prepared from the ester **30** (0.52 g, 1 mmol) by the procedure described for **35a**. Compound **35b** was obtained as an oil (0.465 g, 98 %). $[\alpha]^{20}_D$ + 53 (c 1, $CHCl_3$) ; IR (film) 3450, 3030, 2980 cm^{-1} ; ^{1}H NMR : 1.04 (s, 9H, $SiC(CH_3)_3$), 1.06 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.84 (dd, 1H, J = 5.5 and 7.7 Hz, OH), 3.0 (ddd, 1H, J = 4.8, 7.7 and 11.8 Hz, C$\underline{H}_a$OH), 3.24 (ddd, 1H, J = 3.7, 5.5 and 11.8 Hz, C$\underline{H}_b$OH), 3.68 (ddd, 1H, J = 3.7, 4.8 and 8.4 Hz, C$\underline{H}$-CH_2OH), 4.04 (dd, 1H, J = 6.2 and 8.4 Hz, C$\underline{H}$-CHPh), 4.47 (d, 1H, J = 6.2 Hz, PhCH), 7.2 –7.85 (m, 15H, Ph); ^{13}C NMR : 19.3, 26.6, 27.0 (3C), 27.1, 62.4, 76.9, 77.6, 80.7, 108.8, 127.3 (2C), 127.4 (2C), 127.5 (2C) 127.9, 128.0 (2C), 129.5, 129.6, 133.2, 133.5, 136.0 (2C), 136.1 (2C), 139.4 ; anal.calcd for $C_{29}H_{36}O_4Si$: C, 73.07 ; H, 7.61. Found: C, 73.29; H, 7.54.

(2*R*,3*S*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-2,3-isopropylidenedioxy-4-phenyl-1-trifluoromethanesulfonyloxybutane 36a and (2*R*,3*S*,4*S*)-4-(*t*-butyldiphenylsilyloxy)-2,3-isopropylidene dioxy-4-phenyl-1-trifluoromethanesulfonyoxybutane 36b. To a cooled solution (-15 °C) of the alcohol **35a** (0.9 g, 2.55 mmol) in CH_2Cl_2 (25 ml) were successively added 2,6-di-*tert*-butyl-4-methylpyridine (1.08 g, 5.28 mmol) and trifluoromethanesulfonic anhydride (0.86 ml, 4.75 mmol). After stirring for 30 min at –15 °C, water (25 ml) was added. The reaction mixture was extracted with CH_2Cl_2 (3x25 ml). The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (Et_2O-petroleum ether, 3:97) to give the triflate **36a** as an oil (1.2 g, 97 % yield). $[\alpha]^{20}_D$ – 13 (*c* 1, $CHCl_3$) ; ^{1}H NMR : -0.1 (s, 3H, $SiCH_3$), 0.1 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.37 (s, 3H, CH_3), 1.46 (S, 3H, CH_3), 3.94 (dd, 1H, J = 5.5 and 10.7 Hz, C$\underline{H}_a$-OTf), 3.95 (dd, 1H, J = 4.78 and 7.72 Hz , C$\underline{H}$-CHPh), 4.24 (dd, 1H, J = 2.2 and 10.7 Hz, C$\underline{H}_b$-OTf), 4.38 (ddd, 1H, J = 2.2, 5.5 and 7.7 Hz, C$\underline{H}$-CH_2OTf), 4.9 (d, 1H, J = 4.78 Hz, CHPh), 7.3-7.4(m, 5H, Ph) ; ^{13}C NMR : -4.8, -4.7, 18.2, 25.9 (3C), 26.7, 27.1, 74.1, 74.6, 76.0, 80.6, 110.4, 118.5 (q, J_{CF} = 319 Hz), 126 (2C), 128.2, 128.5 (2C), 140.5 ; anal. calcd for $C_{20}H_{31}O_6SSiF_3$: C, 49.57; H, 6.44; S, 6.61. Found : C, 49.65; H, 6.39, S; 6.47.

The alcohol **35b** (0.344 g, 0.72 mmol) was converted to the triflate **36b** using the same procedure than for the preparation of **36a**. Compound **36b** was obtained as a yellow oil (0.43g, 99 %). $[\alpha]^{20}_D$ + 45 (*c* 1, $CHCl_3$) ; ^{1}H NMR : 1.06 (s, 9H, $SiC(CH_3)_3$), 1.1 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 3.69 (dd, 1H, J = 5.5 and 10.7

Hz, CH$_a$-OTf), 3.78 (ddd, 1H, J = 1.8, 5.5 and 8.5 Hz, CH-CH$_2$OTf), 3.99 (dd, 1H, J = 6.6 and 8.5 Hz, CH-CHPh), 4.11 (dd, 1H, J = 1.8 and 10.7 Hz, CH$_b$-OTf), 4.78 (d, 1H, J = 6.6 Hz, PhCH), 7.2-7.8 (m, 15H, Ph) ; ^{13}C NMR : 19.3, 26.6 (2C), 27.0 (3C), 74.8, 75.3, 76.5, 79.8, 110.5, 118.5 (q, J_{CF} = 320 Hz), 127.3 (2C), 127.5 (2C), 127.6, 127.7 (2C), 128.5 (2C), 130.1, 130.2, 133.0, 133.3, 137.3 (2C), 137.5 (2C), 140.1 ; anal. calcd for $C_{30}H_{35}O_6SSiF_3$: C, 59.2; H, 5.8; S,4.26. Found : C, 59.46 ; H, 5.8 ; S,4.78.

Methyl [3(*R*and*S*),5*R*,6*S*,7*R*]-7-(*t*-butyldimethylsilyloxy)-5,6-isopropylidenedioxy-3-phenylsulfonyl heptanoate 37a and methyl [3(*R* and *S*), 5*R*, 6*S*, 7*S*]-7-(*t*-butyldiphenylsilyloxy)-5,6-isopropylidenedioxy-7-phenyl-3phenylsulfonylheptanoate 37b. To a cooled (-78 °C) solution of trimethyl 3-phenylsulfonylorthopropionate (0.44g, 1.8 mmol) in THF (4 ml) was added *n*-BuLi (0.9 ml, 2 M in hexanes). After stirring for 30 min at –78 °C, were successively added HMPA (0.32 ml) and the triflate **36a** (0.26 g, 0.51 mmol) in THF (3 ml). The reaction mixture was stirred for 20 min at –78 °C and allowed to warm up to room temperature. 0.2 N HCl (10ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 20ml). After drying the combined organic phases ($MgSO_4$) and evaporation *in vacuo*, the residue was chromatographed on silica gel (0.28 g, 97 % yield). IR (film) 2960, 1750, 1590, 1450 cm^{-1} ; ^{13}C NMR (mixture of diastereomers) : -4.8, -4.7 , -4.6 , 18.2 , 25.9 , 27.0 , 27.1, 27.2, 32.9, 33.4, 33.7, 33.9, 51.9, 52.1, 58.4, 59.8, 73.1, 74.4, 74.7, 75.6, 85.4, 85.7, 108.9, 109.2, 126.3-141.1 , 170.4, 170.8; anal. calcd for $C_{29}H_{42}O_7Si$: C, 61.89; H, 7.52. Found : C, 61.82; H, 7.52.

The sulfone **37b** was prepared from the triflate **36b** (0.21g, 0.86 mmol) using the same protocol as for **37a** except that HMPA was omitted and the reaction mixture was stirred at room temperature for 20 min. Compound **37b** was obtained as an equal mixture of diastereomers in 97 % yield. IR (film) 3030, 2980, 1740, 1590 cm^{-1}; ^{13}C NMR : 19.4, 19.44, 26.5, 26.6, 27.05, 27.09, 27.1, 27.2, 32.73, 32.76, 32.8, 34.0, 52.0, 52.1, 58.2, 59.7, 73.2, 75.4, 76.6, 77.6, 84.7, 84.9, 108.8, 109.2, 127.3-139.4, 170.4, 170.8 ; anal.calcd for $C_{39}H_{46}O_7SSi$: C, 68.19; H, 6.75; S, 4.66. Found : C, 68.23; H, 7.05; S, 4.44.

(+) –Goniodiol 1. A solution of the sulfonyl ester **37a** (0.28 g, 0.5 mmol) in 80 % trifluoracetic acid solution (5 ml) was stirred for 10 min at room temperature. After evaporation of the solution in the presence of toluene, the residue was purified on silica gel (Et_2O-MeOH, 99:1). The lactone **38a** was dissolved in CH_2Cl_2 (4 ml) and DBU (0.2 ml, 1.3 mmol) was added. After stirring for 1 h at room temperature, the solution was concentrated *in vacuo* and the residue was purified on silica gel to give pure goniodiol **1** (0.098 g, 84 % yield) as on oil. $[\alpha]^{20}_D$ + 74 (*c* 1, $CHCl_3$) [lit.[8d] $[\alpha]^{20}_D$ + 74.4 (*c* 0.3, $CHCl_3$)]. ^{1}H NMR : 2.18 (ddd, 1H, J = 3.7, 6.4 and 18.5 Hz, CH$_a$ – CH = CH), 2.6 (d, 1H, J = 8 Hz, OH), 2.78 (dddd, 1H, J = 2.3, 2.9, 12.8 and 18.5 Hz, CH$_b$ – CH = CH), 3.1 (d, 1H, J = 4.2 Hz, OH), 3.71 (t, 1H, J = 7 Hz, CHOH-CHPh), 4.77 (ddd, 1H, J = 2.2, 3.7 and 12.8 Hz, CHOC=O), 4.93 (dd, 1H, J = 4.2 and 7Hz, PhCH), 5.98 (dd, 1H, J = 2.9 and 9.8 Hz, CH=CH-CO), 6.91 (ddd, 1H, J = 2.3, 6.4 and 9.8 Hz, CH=CH-CO), 7.2-7.4 (m, 5H, Ph).

(+)-9-Deoxygoniopypyrone 2. A solution of the methyl ester **37b** (0.165 g, 0.24 mmol) in 80 % trifluoroacetic acid solution (10 ml) was stirred at room temperature for 18 h. After coevaporation with toluene, the residue was filtered on a pad of silica gel (Et_2O-MeOH, 99:1). To the purified lactone **38b** in CH_2Cl_2 (2 ml) was added DBU (0.085 ml, 0.59 mmol). Stirring the reaction mixture for 1 h at room temperature and concentration *in vacuo* gave a residue wich was chromatographed on silica gel to afford 9-deoxygoniopypyrone **2** (0.047 g, 80 %) as a white solid. Mp 202-204 °C ; $[\alpha]^{20}_D$ + 11 (*c* 0.2, EtOH) [lit.[8d] mp 203-204 °C ; $[\alpha]^{22}_D$ +11 (*c* 0.1, EtOH)]. ^{1}H NMR : 1.7 (d, 1H, J = 3.2 Hz, OH), 1.84 (dd, 1H, J = 4 and 14.6 Hz, CH$_a$-CHOC=O), 2.60 (ddt, 1H, J = 2, 4.1 and 14.6 Hz, CH$_b$-CHOC=O), 2.88 (dd, 1H, J = 5.2 and 19.4 Hz, CH$_a$-C=0) , 2.99 (dt, 1H, J = 2 and 19.4 Hz, CH$_b$-C=O), 3.96 (q, 1H, J = 3.2 and 4.2 Hz, CH-CHPh), 4.53 (m, 1H, CH-CH$_2$-C=O), 4.87 (tt, 1H, J = 2 and 4.2 Hz, CHOC=O), 4.96 (s, 1H, CHPh), 7.35-7.5 (m, 5H, Ph).

(1'*R*,2'*S*,5*R*)-5-(1',2'-Epoxy-2-phenylethyl)pent-2-eno-5-lactone) (isogoniothalamin epoxide) 41. To an ice-chilled solution of goniodiol **1** (0.05 g, 0.21 mmol) in THF (1 ml) were successively added triphenylphosphine (0.167g, 0.64 mmol) and ethyl diazodicarboxylate (0.125 ml, 0.64 mmol). After stirring for 3 h at room temperature, the reaction mixture was filtered on silica gel (Et_2O) to afford the epoxide **41** (0.035 g, 75 %) as a white solid. Mp 110-112 °C ; $[\alpha]^{20}_D$ + 105 (*c* 1.2, $CHCl_3$) [lit .[40] mp 111-114 °C ; $[\alpha]_D$ - 106 (*c* 1.5, $CHCl_3$)]. IR (KBr) 1715 cm^{-1} ; ^{1}H NMR : 2.52 (ddt, 1H, J = 1.5, 4.8, 5.3 and 18.8 Hz, CH$_a$-CH=CH), 2.64 (ddt, 1 H, J= 2.6, 3.3, 10.3 and 18.8 Hz, CH$_b$-CH=CH), 3.23 (dd, 1H, J = 2.2 and 4 Hz, CH-CHPh), 4.05 (d, 1H, J = 2.2 Hz, CHPh), 4.64 (dd, 1H, J = 4 and 4.8 Hz, CHOC=O), 6.04 (ddd, 1H, J = 1.5, 2.6 and 9.9 Hz,

CH=CHC=O), 6.91(ddd, 1H, J=3.3, 5.3, and 9.9 Hz, CH=CH-C=O), 7.2-7.4 (m, 5H, Ph) ; ^{13}C NMR : 26.2, 55.1, 62.2, 75.4, 121.5, 125.8 (2C), 128.6 (3C), 136.0, 144.3, 163.0.

Ethyl (2*R*, 3*R*, 4*S*)-2,3-benzylidenedioxy-4-(*t*-butyldimethylsilyloxy)-4-phenylbutanoate 42. A solution containing the diol *ent*-**15** (2 g, 5.64 mmol), prepared from (*S*)-mandelic acid using the same protocol as for its enantiomer **15**, camphorsulfonic acid (0.065 g, 0.28 mmol) and benzaldehyde dimethyl acetal (0.9 ml, 6 mmol) in benzene (30 ml) was refluxed for 1 h and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (Et_2O) to give **42** (2.36 g, 95 % yield) as a 1:8 diastereomeric mixture. IR (neat) 3060, 2940, 1750, 1590, 1430, 1100, 700 cm^{-1} ; ^{1}H NMR (major isomer) : -0.17 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.9 (s, 9H, $SiC(CH_3)_3$), 1.15 (t, J = 7 Hz, CH_2CH_3) 4.1 (m, 2H, CH_2-CH_3), 4.39 (t, 1H, J = 5.5 Hz, PhCH-CH), 4.78 (d, 1H, J = 5.5 Hz, CH-CO_2Et), 4.87 (d, 1H, J = 5.5 Hz, PhCHOSi), 6.05 (s, 1H, $PhCH(OR)_2$), 7.23-7.5 (m, 10H, Ph) ; ^{13}C NMR (major isomer) : -4.9, -4.5, 14.0, 18.2, 25.9 (3C), 61.2, 74.7, 75.6, 84.9, 105.1, 126.4 (2C), 127.0 (2C), 127.9, 128.1 (3C), 128.3, 129.5, 136.2, 140.7, 171.4 ; anal. calcd for $C_{25}H_{34}O_5$ Si : C, 67.84; H, 7.74 Found : C, 67.86; H, 7.79.

(1*S*, 2*R*, 3*S*)-2-Benzyloxy-1-(*t*-butyldimethylsilyloxy)-1-phenyl-3,4-butanediol 44. To a cooled solution (0 °C) of the ester **42** (2.35 g, 5.3 mmol) in Et_2O (50 ml) was added lithium aluminium hydride (12 ml, 1 M in Et_2O). After stirring the reaction mixture for 5 min at 0 °C, Na_2SO_4 saturated solution was added carefully. The resulting mixture was filtered on a pad of silica gel (Et_2O) to afford the alcohol **43** (2.1 g, 99 %) as on oil. To an ice-chilled solution of compound **43** (2.1 g, 5.24 mmol) in CH_2Cl_2 (30 ml) was added BH_3-Me_2S (0.66 ml, 7 mmol). After stirring for 20 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and stirred at this temperature for 40 min. The mixture was cooled down to 0 °C and $BF_3.Et_2O$ (0.4 ml, 3.1 mmol) was added. After stirring for 20 min, $NaHCO_3$ (1 g) was added and the solution was diluted with water (40 ml). The aqueous phase was extracted with Et_2O (2 x 30 ml) and the combined organic phases washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (Et_2O-petroleum, 1:1) of the residue provided the desired diol **44** (1.25 g 88 % yield) as a colourless oil. ; $[\alpha]^{20}_D$ + 25 (*c* 0.7, $CHCl_3$) ; IR (film) 3500, 3020, 2960, 1590 cm^{-1} ; ^{1}H NMR : -0.16 (s, 3H $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.89 (s 9H, $SiC(CH_3)_3$), 1.92 (dd, 1H, J = 4.4 and 8.1 Hz, OH), 3.0 (d, 1H, J = 6.7 Hz, OH), 3.45 (dd, 1H, J = 2.2 and 6.6 Hz, CHOBn), 3.6 (m, 2H, CH_2OH), 3.93 (m, 1H, CHOH), 4.05 (d, 1H, J = 11Hz, $PhCH_2O$), 4.15(d, 1H, $PhCH_2O$), 4.88 (d, 1H, J = 6.6 Hz, PhCHOSi), 7.1 (m, 2H, Ph), 7.25-7.41 (m, 8H, Ph) ; ^{13}C NMR : -5.0, -4.5, 18.1, 25.8 (3C) , 64.6, 70.6, 73.8, 74.9, 82.4, 127.2 (2C), 127.6, 127.8, 128.0 (2C), 128.4 (2C), 128.5 (2C), 137.8, 142.0 ; anal.calcd for $C_{23}H_{34}O_4$ Si : C, 68.91, H ; 8.51. Found : C, 68.73, H, 8.52.

(1*S*,2*R*,3*R*)-2-Benzyloxy-4-*t*-butylcarbonyloxy-1-*t*-butyldimethylsilyloxy-4-phenyl-3-butanol 45. To a cooled solution (0 °C) in CH_2Cl_2 (10 ml) containing the diol **44** (1.2 g, 2.98 mmol) and 4-dimethylaminopyridine (0.8 g, 6.5 mmol) was added dropwise pivaloyl chloride (0.4 ml, 3.3 mmol). After stirring for 15 min the reaction mixture was quenched with MeOH (0.5 ml) and concentrated. The residue was purified by flash chromatography (Et_2O-petroleum ether, 1:6) to give the pivaloate **45** (1.41 g, 97 % yield) as a colourless oil. $[\alpha]^{20}_D$ + 31 (*c* 1.1, $CHCl_3$) ; IR (film) 3450, 3010, 2960, 1740, 1590 cm^{-1}. ^{1}H NMR : -0.18 (s, 3H , $SiCH_3$), 0.08 (s, 3H, $SiCH_3$) 0.9 (s, 3H $SiC(CH_3)_3$), 1.18 (s, 9H, $OCOC(CH_3)_3$), 2.8 (d, 1H, J = 8.3 Hz, OH), 3.41 (dd, 1H, J = 1.5 and 7 Hz, CHOBn), 3.98 (d, 1H, J = 10.7 Hz, CH_aPh), 4.02 (d, 1H, J = 10.7 Hz, CH_bPh), 4.09 (m, 1H, CHOH), 4.13 (t, 1H, J = 9.3 Hz, CH_a-OPv), 4.17 (dd, 1H, J= 5.9 and 9.3 Hz, CH_b-OPv), 4.86 (d, 1H, J = 7 Hz, PhCHOSi), 7.2 (m, 2H, Ph), 7.27-7.4 (m, 8H, Ph) ; ^{13}C NMR : -5.1, -4.5, 18.1, 25.8 (3C), 27.2(3C), 38.7, 64.8, 68.1, 74.0, 74.2, 81.9, 127.2 (2C), 128.4 (2C) 127.8, 128.0, 128.2 (2C), 128.4, (2C), 128.5 (2C), 137.2 , 142.1, 178.0 ; anal. calcd for C_{28} H_{42} O_5 Si : C, 69.1; H, 8.69. Found, 68.3; H, 8.60.

(1*S*, 2*R*, 3*S*) - 2 -Benzyloxy -1-(*t*-butyldimethylsilyloxy) - 3,4-epoxy-1-phenylbutane 46. To an ice-cooled solution of the pivaloate (1.3 g, 2.67 mmol) in CH_2Cl_2 (27 ml) were added Et_3N (0.8 ml, 5.8 mmol) and mesyl chloride (0.3 ml, 3.9 mmol). The mixture was stirred at 0 °C for 30 min and quenched with MeOH (1ml). After concentration *in vacuo*, the residue was filtered on a pad of silica gel (Et_2O-petroleum ether, 1:2) to give the mesylate which was used in the next step without further purification. The mesylate (1.43 g) was dissolved in a mixture of Et_2O-MeOH (45 ml, 2:1) and an excess of sodium hydride (0.4 g, 4 equiv ; 60 % dispersion in mineral oil) was added carefully. After stirring at room temperature for 1 h the reaction mixture was filtered through a pad of silica gel and eluted with Et_2O (150 ml). After concentration *in vacuo*, the residue was chromatographed on silica gel (Et_2O-petroleum ether, 1:4) to afford the epoxide **46** (0.87 g, 85 % yield) as an

oil. $[\alpha]^{20}_D$ + 27 (*c* 1.4, $CHCl_3$) ; IR (film) 3020, 2960, 1590 cm^{-1} ; ^1H NMR : -0.15 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 2.71 (dd, 1H, J = 4.4 and 5.8 Hz, $C\underline{H}_a$-CH-CHOBn), 2.78 (dd, 1 H, J = 2.9 and 5.8 Hz, $C\underline{H}_b$-CH-CHOBn), 3.21 (ddd, 1H, J = 2.9 and 3.7 and 4.4 Hz, C<u>H</u>-CHOBn), 3.57 (dd, 1H, J = 3.7 and 5.8 Hz, C<u>H</u>OBn), 4.28 (d, 1H, J = 11 Hz, PhC$\underline{H}_a$O), 4.51 (d, 1H, J = 11 Hz, PhC$\underline{H}_b$O), 4.73 (d, 1H, J = 5.8 Hz, PhC<u>H</u>OSi), 7.1(m, 2H, Ph), 7.23-7.4(m, 8H, Ph) ; ^{13}C NMR : -4.9, -4.6, 18.2, 25.8 (3C), 44.1, 51.7, 73.8, 76.5, 81.4, 127.2 (2C), 127.5, 127.9, 128.0 (3C), 128.2 (3C), 138.2, 141.8 ; anal.calcd for $C_{23}H_{32}O_3Si$: C, 71.83, H, 8.38. Found : C, 71.60, H, 8.41.

(1*R*, 5*R*, 7*S*, 8*S*) -Benzyloxy-7-phenyl -2,6-dioxabicyclo [3.3.1]nonan-3-one 48. To a cooled (-78 °C) solution of methyl 3-phenylsulfonyl orthopropionate (0.57 g, 2.34 mmol) in THF (8 ml) was added *n*-BuLi (1.1 ml, 2.2 M in hexanes). The solution was stirred for 30 min and $BF_3.Et_2O$ (0.3 ml, 2.37 mmol) and the epoxide **46** (0.3 g, 0.78 mmol) in THF (2 ml) were successively added. After stirring for 1 h at –78 °C, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (10 ml) and diluted with Et_2O (20 ml). The aqueous phase was extracted with Et_2O (3 x 20 ml) and the combined organic phases were dried ($MgSO_4$) filtered and concentrated. The crude mixture (compound **47**) was dissolved in a 90 % CF_3CO_2H solution (10 ml) and stirred at room temperature for 3 h. After coevaporation of the solution with toluene, the viscous residue was dissolved in CH_2Cl_2 (7 ml) cooled down to 0 °C, and DBU (0.4 ml, 2.67 mmol) was added. After stirring for 30 min, the solution was concentrated and the residue was chromatographed on silica gel (Et_2O-MeOH, 95:5) to give the bicyclic compound **48** (0.207 g, 82 % yield) as white crystals. Mp 173-174 °C (hexane-AcOEt) ; $[\alpha]^{20}_D$ – 135 (*c* 1.2, $CHCl_3$) ; IR (film) : 3010, 2980, 1735, 1590 cm^{-1} ; ^1H NMR : 2.12 (m, 1H, C$\underline{H}_a$C=O), 2.19 (m, 1H, C$\underline{H}_b$C = O) , 2.86 (dd, 1H, J = 5.1 and 19.2 Hz, C$\underline{H}_a$COC=O), 3.0 (d, 1H, J = 19.2 Hz, C$\underline{H}_b$COC =O), 3.36 (dd, J = 2.2 and 9.6 Hz, C<u>H</u>OBn), 4.24 (d, 1H, J = 12.1 Hz, C$\underline{H}_a$Ph), 4.31 (d, 1H, J = 12.1 Hz, C$\underline{H}_b$Ph), 4.45 (m, 1H, C<u>H</u>CH$_2$C=O), 4.6 (d, 1H, J = 9.6 Hz, PhC<u>H</u>), 4.96 (m, 1H, C<u>H</u>OC=O), 6.96 (m, 2H, Ph), 7.2 (m, 2H, Ph), 7.3-7.45 (m, 6H, Ph) ; ^{13}C NMR : 29.6, 36.5, 65.9, 71.1, 72.7, 73.5, 78.6, 127.6 (2C), 127.7 (2C), 128.3, 128.4 (2C), 128.5, 137.3, 138.6, 168.9 ; anal. calcd for $C_{20}H_{20}O_4$: C, 74.05; H, 6.21. Found : C, 73.93; H, 6.15.

8 - *Epi* - 9-deoxygoniopypyrone 8. To an ice-chilled solution of the benzyl ether **48** (0.245 g, 0.75 mmol) in CH_2Cl_2 (25 ml) was added $TiCl_4$ (5 ml, 1 M in CH_2Cl_2). After stirring at room temperature for 30 min, the reaction was quenched with a saturated $NaHCO_3$ solution , decanted and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were washed once with water (10 ml), dried ($MgSO_4$) and concentrated to give an oil which was crystallized from hexane-AcOEt to give the desired styryllactone **8** (0.14 g) . The mother liquor was purified by flash chromatography on silica gel (AcOEt-petroleum ether, 4:1) to give an additonal 0.027 g of **8** (94 % yield). Mp 130-131 °C, $[\alpha]^{20}_D$ – 90 (*c* 0.7, $CHCl_3$) ; ^1H NMR : 2.08 (m, 2H, C$\underline{H}_2$CHOC=O), 2.84 (dd, 1H, J = 4.8 and 19.5 Hz, C$\underline{H}_a$C = O), 2.95 (d, 1H, J = 19.5 Hz, C$\underline{H}_b$C=O), 3.07 (d, 1H, J = 9.2 Hz, OH) , 3.5 (td, 1H, J = 2.2 and 9.2 Hz, C<u>H</u>OH), 4.42 (s, 1H, C<u>H</u>OC = O), 4.44 (d, 1H, J = 9.2 Hz, C<u>H</u>Ph), 4.87 (m, 1H, C<u>H</u>CH$_2$C=O), 7.2-7.5 (m, 5H, Ph); ^{13}C NMR : 29.6, 36.9, 65.6, 72.3, 74.0, 76.8, 127.3 (2C), 128.4 (2C), 128.5, 138.0, 169.2.

8-*Epi*-9-deoxygoniopypyrone acetate 49. To a solution of compound **8** (0.1 g, 0.43 mmol) in CH_2Cl_2 (4ml) were succesively added DMAP (0.156 g, 1.27 mmol) and acetic anhydride (0.1 ml, 0.85 mmol). After stirring for 15 min, the reaction mixture was quenched with MeOH (2 ml). After concentration *in vacuo*, the residue was purified on silica gel (AcOEt -petroleum ether, 4:1) to afford **49** (0.11 g, 98 % yield) as white crystals. Mp 138-139 °C (hexane-AcOEt) ; $[\alpha]^{20}_D$ – 170 (*c* 1, $CHCl_3$) [lit.[2] mp 140-142 °C ; $[\alpha]^{20}_D$ -170.5 (*c* 1, $CHCl_3$)]. The spectroscopic data of synthetic **49** are indentical with those of the natural.[2]

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