Progress in the Total Synthesis of Antitumour Styryl Lactones

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Abstract: During the last years, the stereoselective synthesis of a small group of styryl lactones has increased the interest in synthetic organic chemistry in which many research groups have focused much of their efforts. This review gives an overview of the different approaches for the total synthesis of novel styryl lactones, which were found to possess marginal to significant cytotoxicities against several human tumors reported to date.

Keywords: Stereoselective synthesis, total synthesis, styryl lactones, cytotoxicity.

1. INTRODUCTION

Since the first styryl lactone goniothalamin was isolated from the trees of genus *Goniothalamus* in 1972 [1], a variety of styryl lactones have been isolated and identified within the family Annonaceae based on the bioactivity-directed studies of the Asian trees of the genus *Goniothalamus* [2]. The most common and potential medicinal usage of these trees has traditionally been connected with the treatment of the procurement of abortion [3], edema and rheumatism [4], as a painkiller and a mosquito repellent [5]. Recently, from the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook f., Thomas (Annonaceae), McLaughlin's group discovered, isolated and elucidated a number of novel styryl lactones, (+)-goniofufurone (**1**) [2a], (+)-7-*epi*-goniofufurone (**2**) [2b], (+)-goniopypyrone (**3**) [2a], (+)-deoxygoniopypyrone (**4**) [2b], (+)-altholactone (**5**) [6], (+)-goniotriol (**6**) [7], (+)-7-acetylgoniotriol (**7**) [2a], (+)-goniobutenolide A (**8**) [8] and (-)-goniobutenolide B (**9**) [8]. Some of representative styryl lactones are listed in Fig. (**1**).

The styryl lactones have the common skeleton structure characteristics such as the part of styryl or styryl with functional groups and the part of γ-(or δ-) lactone, which are reported to show significant cytotoxic activities against several human tumour cultured cells of human KB, A-549 lung carcinoma, and HCT-8 colon tumour, as well as murine P-388 and L-1210 lymphocytic leukemia. It is very often found that one enantiomer is normally responsible of the biological activity, while the other results to be inactive or less toxic. For instance, (+)-goniofufurone (**1**) was reported to show significant cytotoxic activity against A-549 (human lung carcinoma, ED_{50} 4.76 μg/ml) [2a], however, (+)-7-*epi*-goniofufurone (**2**) show insignificant cytotoxic activity against A-549 (human lung carcinoma, ED_{50} 27.20 μg/ml) [2b]. Due to the significant bioactivity and the unique structural features, much attention has been paid to synthesis of these compounds. Recently, many new synthetic strategies have been reported starting from commercially available chiral material (such as sugars and tartaric acids) and achiral material using the asymmetric synthesis. Preliminary accounts have been reported [9]. In this review, we would like to describe the progress in the total synthesis of these natural products reported by many research groups worldwide during the last decades. In this context, we will arrange the contents of this review according to the name of compounds.

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A) SYNTHESIS OF (+)-GONIOFUFURONE (1), (+)-7-*EPI*- GONIOFUFURONE (2) AND (-)-GONIOFUFURONE (17)

Recently, a novel styryl lactone goniofufurone has been isolated from the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae) bearing cytotoxic activities against several human tumour cells [2a]. The structure of goniofufurone was elucidated by X-ray crystallography to be **1** or its enantiomer **2** [2a]. Since then, several research groups have been engaged in the stereocontrolled synthesis of these styryl lactones starting from the commercially available chiral material and achiral material using the asymmetric synthesis.

The first total syntheses of styryl lactone goniofufurone and its enantiomer were reported by Shing *et al.* using a chiral synthon from commercially available and inexpensive D-*glycero*-D-*gulo*-*heptono*-γ-*lactone* (D-*glucoheptonic* γ-*lactone*, **10**) involving an intramolecular Michael reaction as the key step [10, 11]. The key intermediates of styryl alcohol **11** and its 6-epi-**12** were prepared *via* diastereoselective 1,2- addition of a phenyl Grignard reagent to the lactone **10,** followed by oxidation with pyridinium chlorochromate and stereo-selective reduction to yield 6-epi-**12**. Acetylation of **12** with acetic anhydride followed by selective hydrolysis and deacetylation with a catalytic amount of NaOMe in methanol to the tetraol **14**. Oxidation of the vicinal diol in **14** followed by immediate Wittig alkenation in methanol afforded stereoselectively the Z-alkene **15**(Z: E = 7:1) in 92% yield from **14**. Removal of the acetone group in **15** with 80% aq. HOAc gave the γ-lactone **16**, m.p. 109-111°C; $[\alpha]_D^{22}$ +72 (*c* 0.9, EtOH). Treatment of 16 with a catalytic amount of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in tetrahydrofuran (THF) occurred the intramolecular Michael addition reaction of **16** to provide the goniofufurone enantiomer **17** as white plates, m.p. 152-154°C; $[\alpha]_D^{22}$ –8.5 (*c* 0.8, EtOH) (Scheme **1**).

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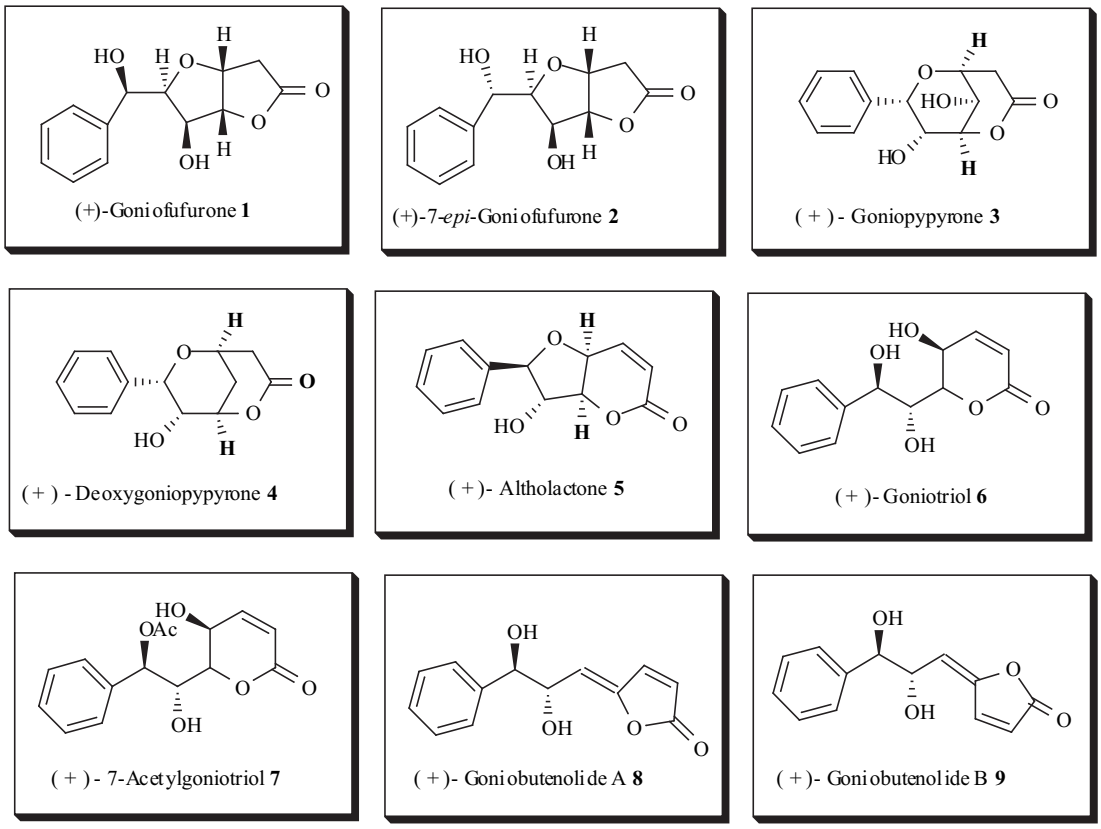
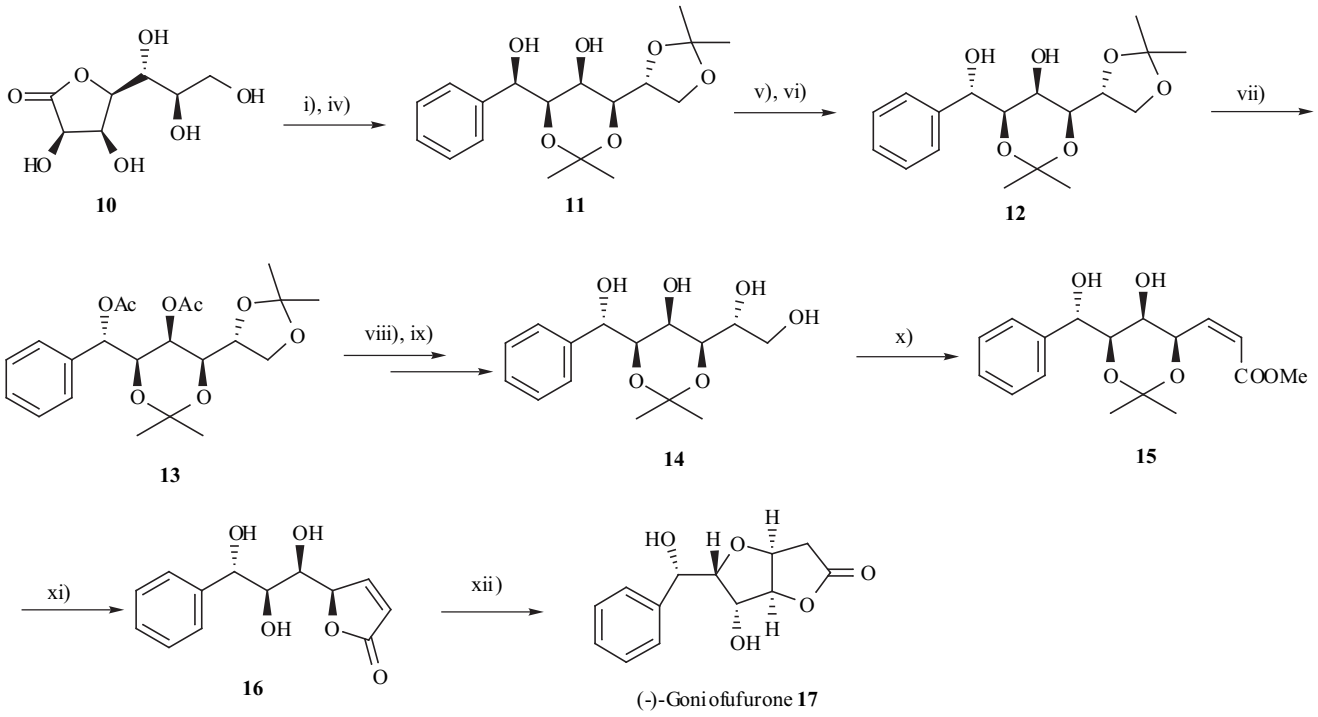


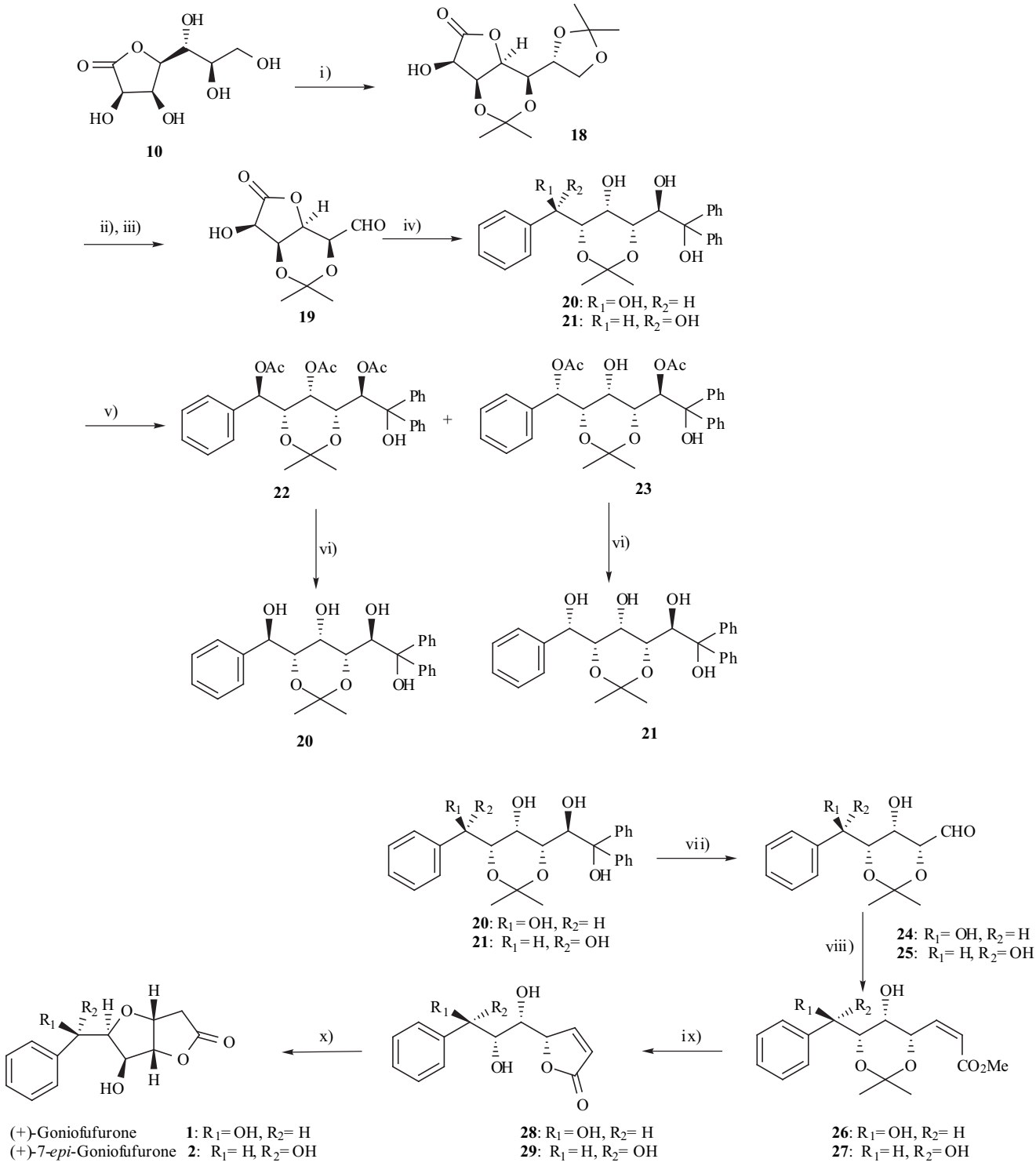
Fig. (1). Styryl lactones.



Scheme 1. Synthesis of (-)-Goniofufurone.

Reagents and conditions: i) Acetone, anhydrous $ZnCl_2$, H_3PO_4, room temperature (r.t.), 1 day, 66%; ii) $NaBH_4$, MeOH, 0°C to r.t., 12h, 98%; iii) $NaIO_4$, MeOH, H_2O, r.t., 3 h, 100%; iv) PhMgBr, THF, 0°C, 74%, **11**:**12** = 8:1; v) Pyridinium chlorochromate, CH_2Cl_2, 4Å molecular sieves, r.t., 3h, 61%; vi) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, -78 °C, 70%; vii) $(MeCO)_2O$, pyridine, cat. N,N-dimethylaminopyridine, CH_2Cl_2, r.t., 1 day, 80%; viii) 50% aq. AcOH, r.t., 15 h, 81%. ix) cat. NaOMe, MeOH, r.t., 2h, 93%; x) $NaIO_4$, MeOH, H_2O, r.t., 30 min; then $Ph_3P{=}CHCO_2Me$, MeOH, r.t., 2h, 92%; xi) 80% aq. HOAc, r.t., 2 days, 83%; xii) 0.05%(v/v) DBU in THF, r.t., 1 day, 71%.

After then, Shing *et al.* reported the total syntheses of the natural goniofufurone **1** and **2** from the same starting material D-*glucoheptonic* γ-*lactone* **10**. The synthetic route to goniofufurone **1** and **2** is shown in Scheme (**2**). Compound **10** was converted to 3,5,6,7-diaceonide **18** by thermodynamically controlled acetonation followed by selective hydrolysis at the terminal isopropylidene group to provide the triol in good yield. Oxidation of the vicinal diol in the triol gave the aldehyde **19** followed by **1,2**- addition of an excess of phenyl Grignard reagent to the aldehyde **19** at



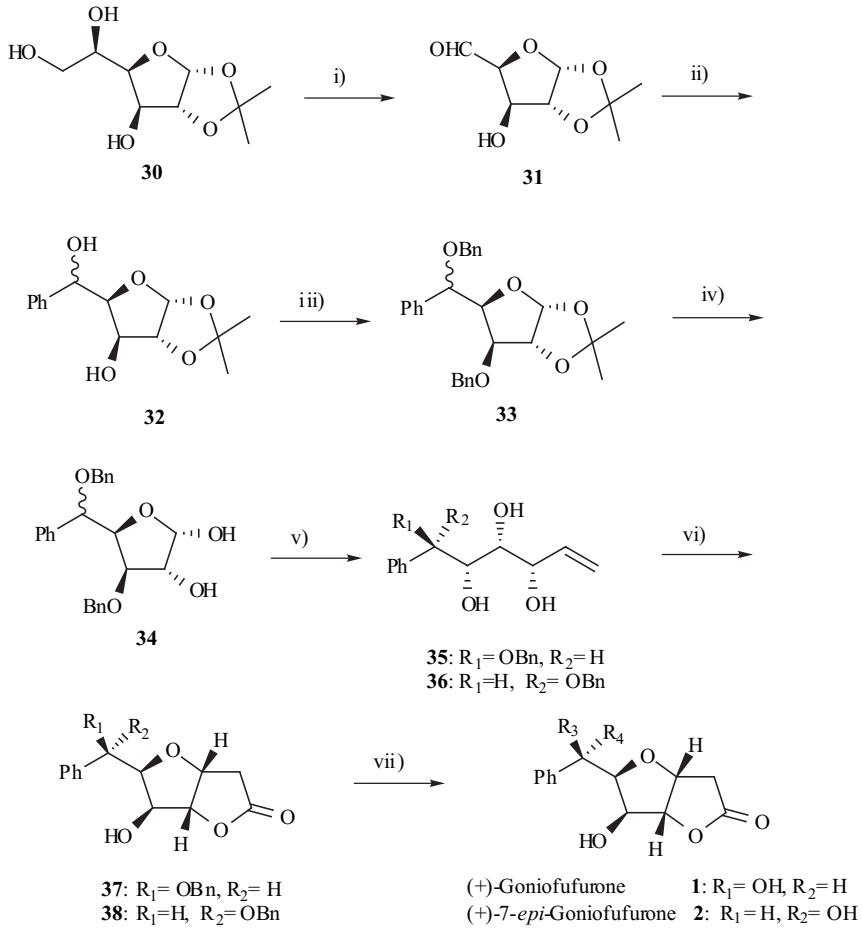
Scheme 2. Synthesis of (+)-Goniofufurone and (+)-7-*epi*-Goniofufurone.

Reagents and conditions: i) Acetone, anhydrous $ZnCl_2$, H_3PO_4, r.t., 1 day, 66%; ii) HOAc, H_2O, r.t., 70%; iii) $NaIO_4$, MeOH, r.t., 30 min; iv) PhMgBr, THF, 0°C, 56% from **18**, **20**:**21** = 1:2; v) Ac_2O, cat. N, N-dimethylaminopyridine, CH_2Cl_2, 36% **22**, 49% **23**; vi) aq. NaOH, r.t., 99% **20**, 98% **21**; vii) $NaIO_4$, MeOH, H_2O, r.t., 30 min; viii) $Ph_3P{=}CHCO_2Me$, MeOH, r.t., 2 h, 79% **26**, 80% **27**; ix) 89% aq. HOAc, r.t., 1 day, 89% **28**, 74% **29**; x) 0.05% (v/v) DBU in THF, r.t., 1 day, 74% **1**, 70% **2**.

0°C to afford the diastereoisomeric **20** and **21** in a ratio of 1 to 2. Acetylating of the mixture of **20** and **21** with acetic anhydride gave the triacetate **22** and **23** separated by chromatography, followed by deactivation with a base of NaOH to regenerate the pure alcohols **20** and **21**, respectively. Oxidation of the vicinal diol in **20**(**21**) using sodium metaperiodate provided the aldehyde **24**(**25**), followed by immediate Wittig alkenation in methanol to afford stereoselectively the Z-alkene **28**(**29**)(Z: E = 10:1) in 79% yield. Then the same sequence of reaction as above mentioned for the Z-alkene **28**(**29**) was carried out to get the natural (+)-goniofufurone **1** or (+)-7-*epi*-goniofufurone **2**, respectively.

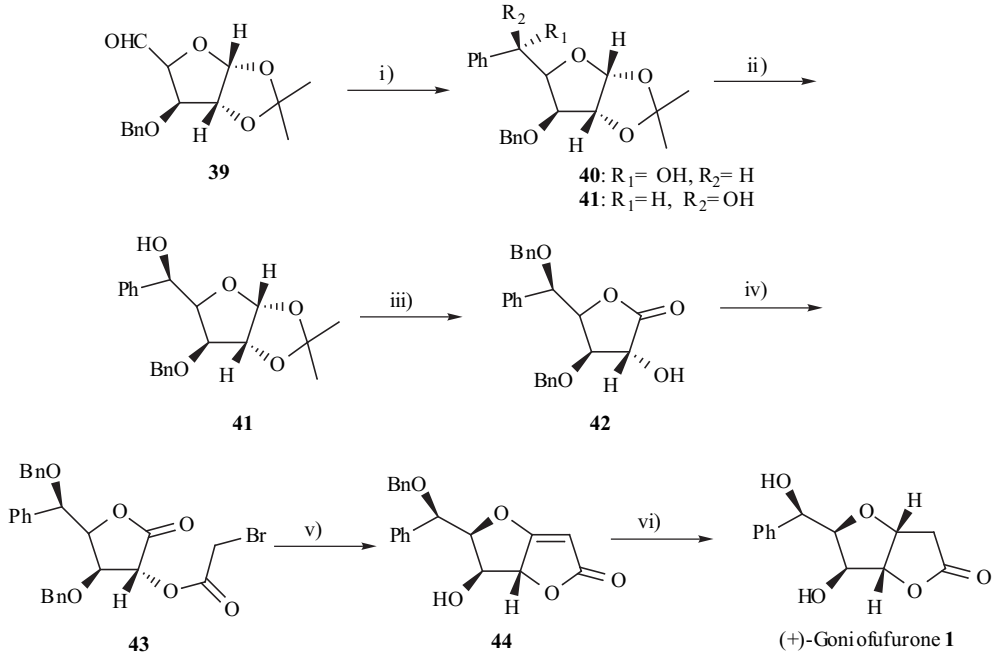
Jäger *et al*. reported the total synthesis of the (+)-goniofufurone **1** and (+)-7-*epi*-goniofufurone **2,** as well as their enantiomers (-)-goniofufurone **1** and (-)-7-*epi*-goniofufurone **2** from D-glucose in short steps [12,13]. The synthetic strategy is shown in (Scheme **3**).

Oxidation of the vicinal diol in the commercially available monoacetone D-glucose **30** by periodate cleavage gave the aldehyde **31** which without purification reacted with excess phenyl magnesium bromide in THF to yield a mixture of **32**. Protection of free OH groups in **32** provided the compound **33**. Then hydrolysis with aqueous acetic acid got the furanose **34** which were treated with an excess of Wittig reagent to afford the phenyl hexenitols of **35** and **36** in 14% and 55% yield after chromatographic separation, followed by palladium (II)-catalysed oxycarbonylation of the resulting phenyl- hexenitols of **35** and **36** to give the corresponding γ-lactone **37** and **38**. The final step, reductive cleavage of the di-O-benzyl group in **37** (**38**) using ca. 5 % palladium catalyst (Pd, 10 % on charcoal) with atmospheric pressure of hydrogen in methanol was employed to produce the natural (+)-goniofufurone **1** or (+)-7-*epi*-goniofufurone **2**. Analogously, Murpy *et al*. used the aldehyde **39** as chiral precursor from D-glucose and succeeded in the synthesis of the (+)-goniofufurone **1** (Scheme **4**) [14]. In this case, the addition of phenyl magnesium bromide to **39** gave a mixture of **40** and **41** in a ratio of 14:1, respectively, followed by oxidation of the mixture of **40** and **41** and reduction to give a separable mixture of **40** and **41** in a ratio of 1:8 in 69% overall yield. Protection of the free hydroxy group in **41** with a benzyl group followed by removal of the acetonide protecting group and oxidation of the resulting hemiacetal provided an α-hydroxy γ-lactone **42**. Then bromoacetylation of **42** gave the corresponding **43** in 87% yield, followed by a key step of Wittig cyclisation of a stabilised phosphorane



Scheme 3. Synthesis of (+)-Goniofufurone and (+)-7-*epi*-Goniofufurone.

Reagents and conditions: i) $NaIO_4$, MeOH, H_2O, 0°C, 2 h; ii) PhMgBr (5eq.), THF, 0°C, 4 h, r.t., 20 h, 69% from **30**; iii) NaH, BnBr, DMF, 0°C- r.t., 5 h, 70%; iv) HOAc/ H_2O (v/v=1:1), 70-90°C, 10 h; v) CH_3PPh_3Br (5eq.), BuLi (5 eq.), THF, 0°C- r.t., 40h, 17% **35**, 55% **36;** vi) CO, $PdCl_2$ (0.1 eq.), $CuCl_2$ (3 eq.), NaOAc (3 eq.), HOAc, r.t., 8 h, 89% **37**, 85% **38**; vii) H_2, Pd/C (10%), MeOH, r.t., 15 h, 84% **1**, 82% **2**.



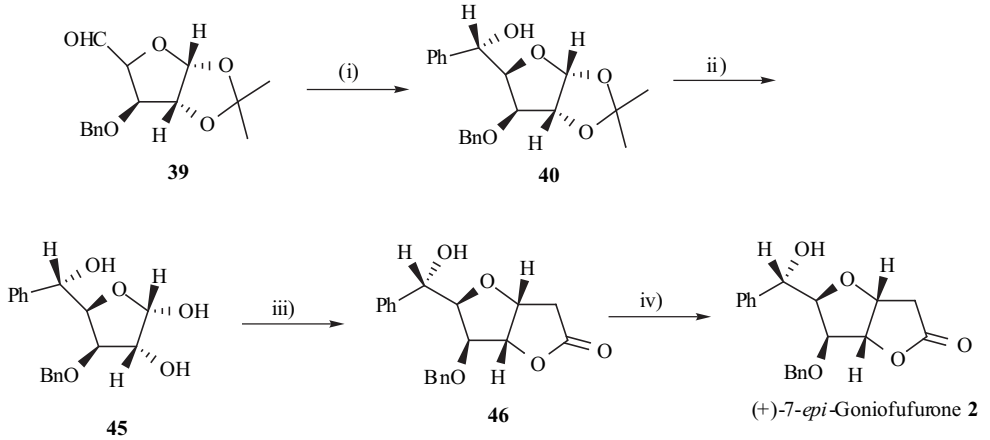
Scheme 4. Synthesis of (+)-Goniofufurone.

Reagents and conditions: i) PhMgBr, Et_2O, reflux, 78%, **40**:**41** = 14:1; ii) 1. pyridinium chlorochromate (PCC), CH_2Cl_2; 2. $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78°C, 67%, **40**:**41** = 1:8; iii) 1. BnBr, NaH, THF, 87%; 2. CF_3COOH-H_2O(v/v =7:3), 85%; 3. Br_2-$BaCO_3$, dioxane, H_2O, 54%; iv) $BrCOCH_2Br$, pyridine, Et_2O, 87%; v) Ph_3P, MeCN, then 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU), THF, reflux, 30 min., 88%; vi) H_2, 10% Pd on C, 58%.

with **43** and catalytic hydrogenation to obtain the natural (+)-goniofufurone **1** in 58% yield as plates, m.p. 151-152°C, $[\alpha]_D^{24}$ + 8.5(*c* 0.8, EtOH), {lit. [2a], $[\alpha]_D^{24}$ + 9.0(*c* 0.5, EtOH)}.

Rao *et al*. had followed a similar approach and efficiently synthesized the (+)-7-*epi*-goniofufurone **2** using the aldehyde **39** as chiral precursor from D-glucose in 6 steps in 30% overall yield [15] (Scheme **5**). Treatment of **39** with phenylmagnesium bromide to give the desired chelation-controlled product **40**. The 1,2-acetonide moiety in **40** was hydrolysed with aq. trifluoroacetic acid to obtain the triol **45** followed by bicyclisation process involving the Wittig reaction to afford the **46** and further hydrogenation by 10% Pd/C to obtain (+)-7-*epi*-goniofufurone **2**.

Another strategy for the synthesis of (+)-goniofufurone **1** was investigated to use a readily available chiral lactone **47**[16] with a syn-triol functionality [17] (Scheme **6**). In this way, the first acid removal of the acetonide group afforded the diol **48** in 73% yield. The alcohol **49** was got by sequential silylation of the primary hydroxy group in **48**, methoxymethylation of secondary alcohol and desilylation of the ether in 96% overall yield. Swern oxidation of **49** provided the unstable aldehyde, which without isolation was further treated with phenyltitanium reagent to furnish the



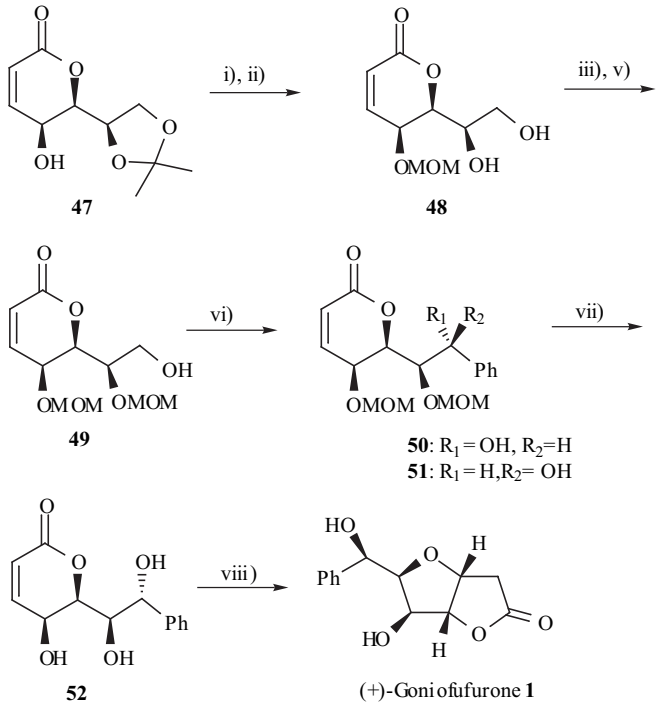
Scheme 5. Synthesis of (+)-7-*epi*-Goniofufurone.

Reagents and conditions: i) PhMgBr, THF, r.t., 83%; ii) CF_3COOH/-H_2O (v/v = 3:2), 88%; iii) $Ph_3P{=}CHCO_2Et$, MeOH, -20°C, 8 h, 60%; iv) H_2, 10% Pd on C, MeOH, 93%.

alcohol **50** and **51** in 78% and 19% yields, respectively. Subsequent acid removal of the protecting group and a catalytic amount of DBU catalysed cyclization afford the (+)-goniofufurone **1.**

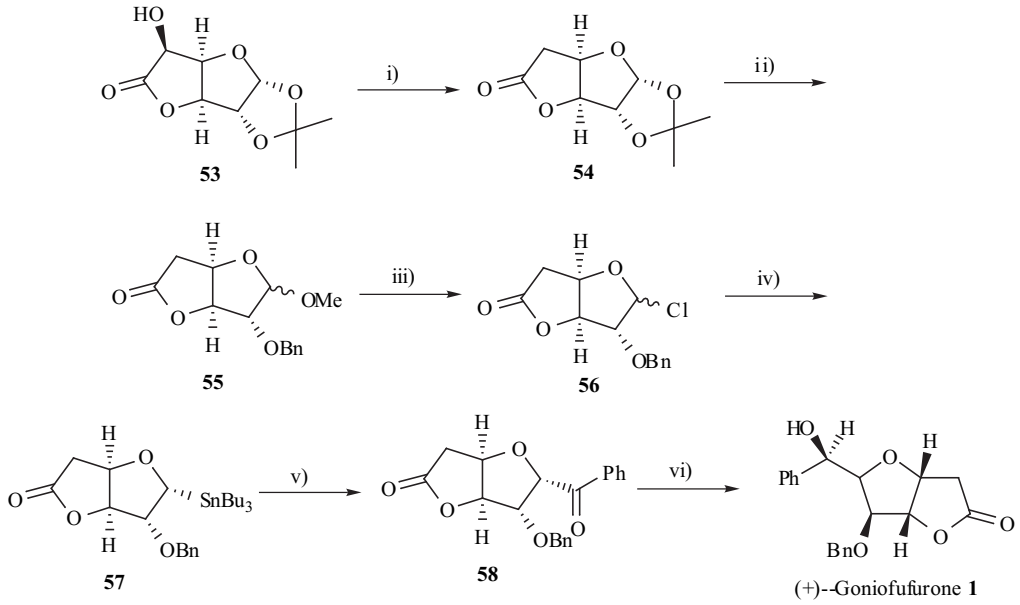
In a different approach, Falck *et al*. reported a novel direct C-glycoside formation *via* Pd/Cu mediated coupling of PhCOCl with cyclic α-alkoxystannane **57** derived from D-glucurono-6, 3-lactone as a key step in a concise route provided the total synthesis of (+)-goniofufurone **1** in a short synthetic sequence [18] (Scheme **7**).

Hanaoka succeeded in an efficient total synthesis (+)-goniofufurone **1** in a highly stereocontrolled fashion from



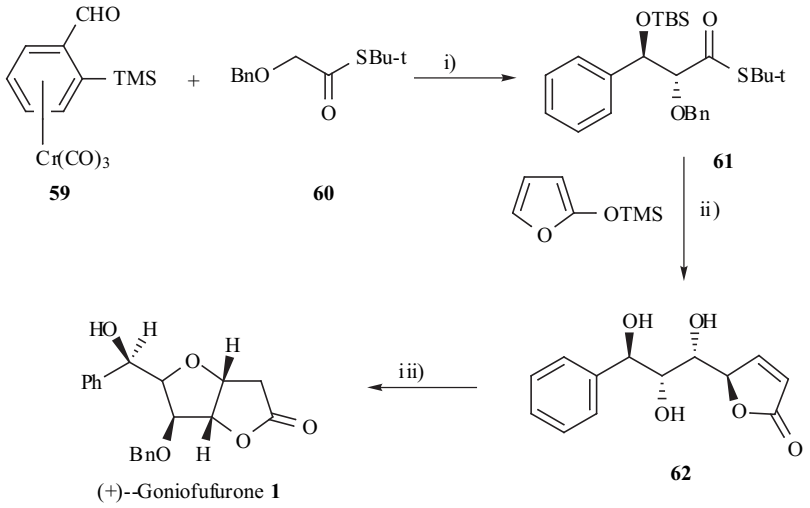
Scheme 6. Synthesis of (+)-Goniofufurone.

Reagents and conditions: i) *i*-Pr_2NEt, MOMCl, DMAP, CH_2Cl_2, 83%; ii) 75% aq. HOAc, THF, 88%; iii) *t*- $BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2; iv) *i*-Pr_2NEt, MOMCl, DMAP, CH_2Cl_2; v) 75% aq. HOAc, THF, 96% from **48**; vi) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, then $PhTi(Oi\text{-}Pr)_3$, 0°C, 78% **50**, 19% **51;** vii) TFA, CH_2Cl_2, 88%; viii) DBU, THF, 60%.



Scheme 7. Synthesis of (+)-Goniofufurone.

Reagents and conditions: i) 1. PhOC(S)Cl, DMAP, CH_3CN, 1 h; 2. Bu_3SnH, AIBN, $PhCH_3$, 110°C, 78% from **53**; ii) 1. DOWEX 50X400, MeOH, 65°C, 5 h; 2. Ag_2O/ $PhCH_2Br$ (3eq.), PhH, 24°C, 36 h, 95%; iii) HCl/ dioxane, 101°C, 5 h; 2. Ph_3P, THF/ CCl_4 (v/v = 3:1), 65°C, 3 h; 2. $Bu_3SnSiMe_3$/ Bu_4NF (1.5eq.), 4Å MS, DMF, -45°C, 4 h; v) PhCOCl, $(Ph_3P)_2PdCl_2$, CuCN, $PhCH_3$, 95°C, 18 h; DCC, DMAP, CH_2Cl_2, 24°C, 8 h; vi) 1. LiAlH (*t*-BuO)$_3$, THF, 0°C, 45 min.; 2. Pd/C, H_2 (1atm), MeOH, 24°C, 16 h.

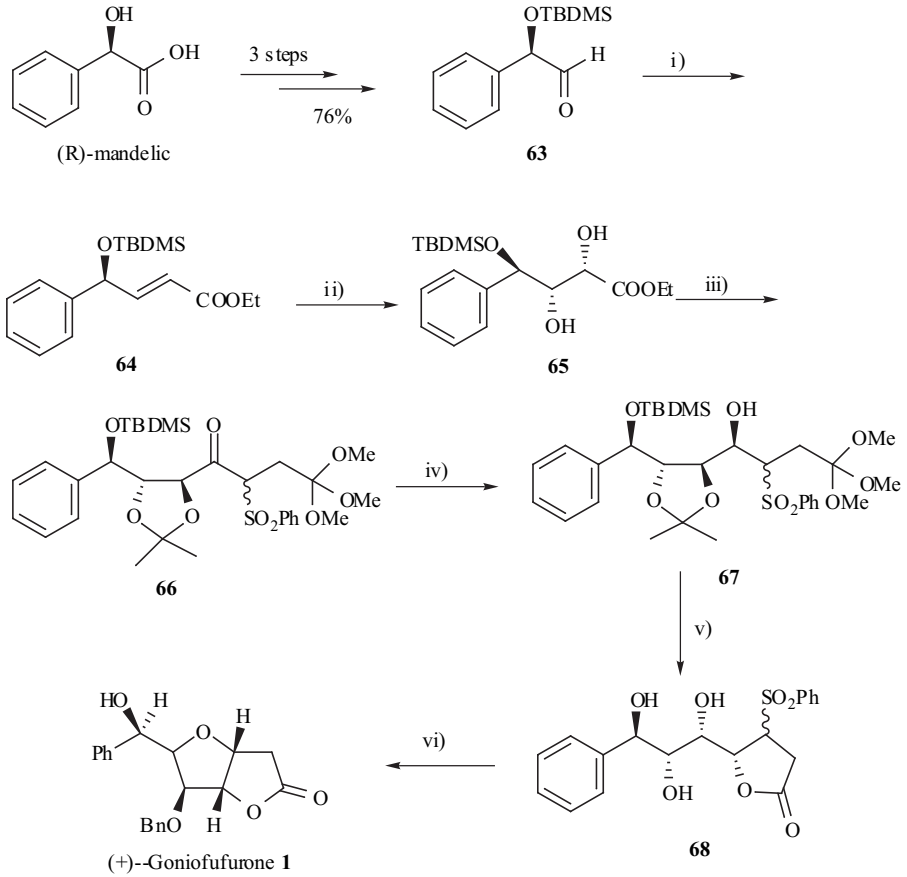


Scheme 8. Synthesis of (+)-Goniofufurone.

Reagents and conditions: i) 1. TTN, MeOH, 27°C; 2. TBSOTf, DMAP, CH_2Cl_2, 0°C; 3. DIBAL-H, PhH, r.t.; 4. Swern Oxidation; ii) 1. Ti(OPr-*i*)$_2Cl_2$, CH_2Cl_2, -78°C; 2. $BF_3.OEt_2$, NaI, CH_3CN, 0°C; iii) TBAF, THF, r.t.

chiral (+)-tricarbonyl (η^6-2-trimethylsilybenzaldehyde) chromium (0) complex **59** through stereoselective aldol reaction as a crucial steps [19,20,21] Scheme **8**). This approach provided a powerful way to prepare the (+)-goniofufurone **1** compared with the chiral synthons using natural sources.

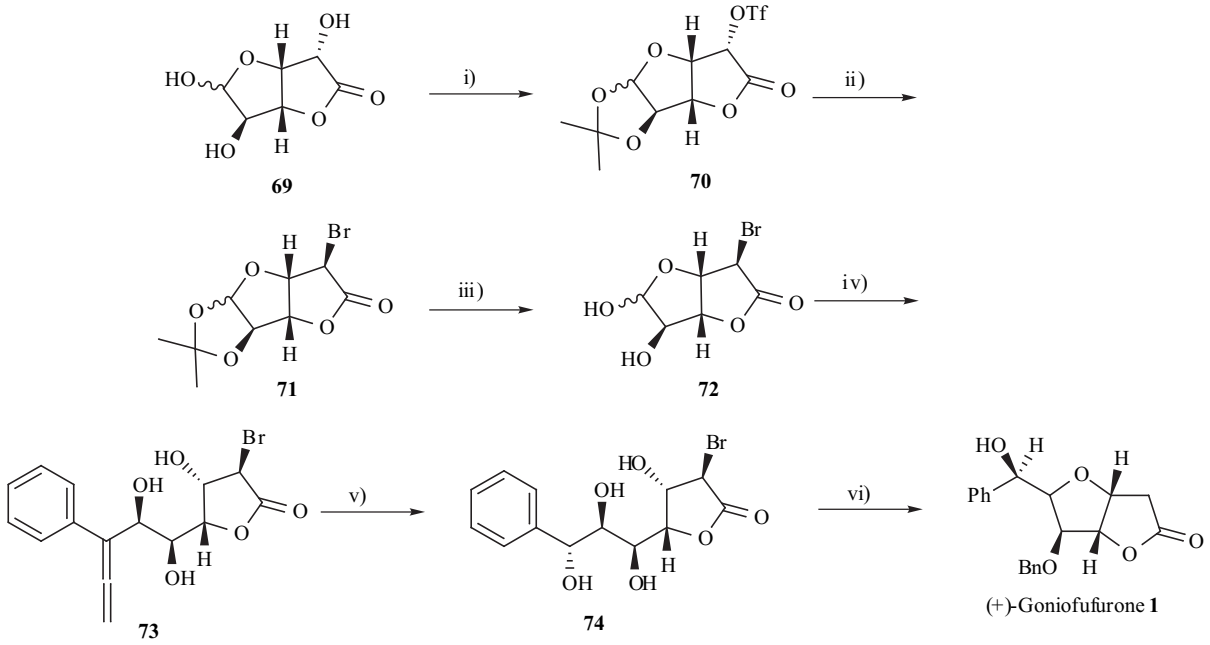
Another short and efficient route to (+)-goniofufurone from commercial D-mandelic acid *via* Julia coupling using



Scheme 9. Synthesis of (+)-Goniofufurone.

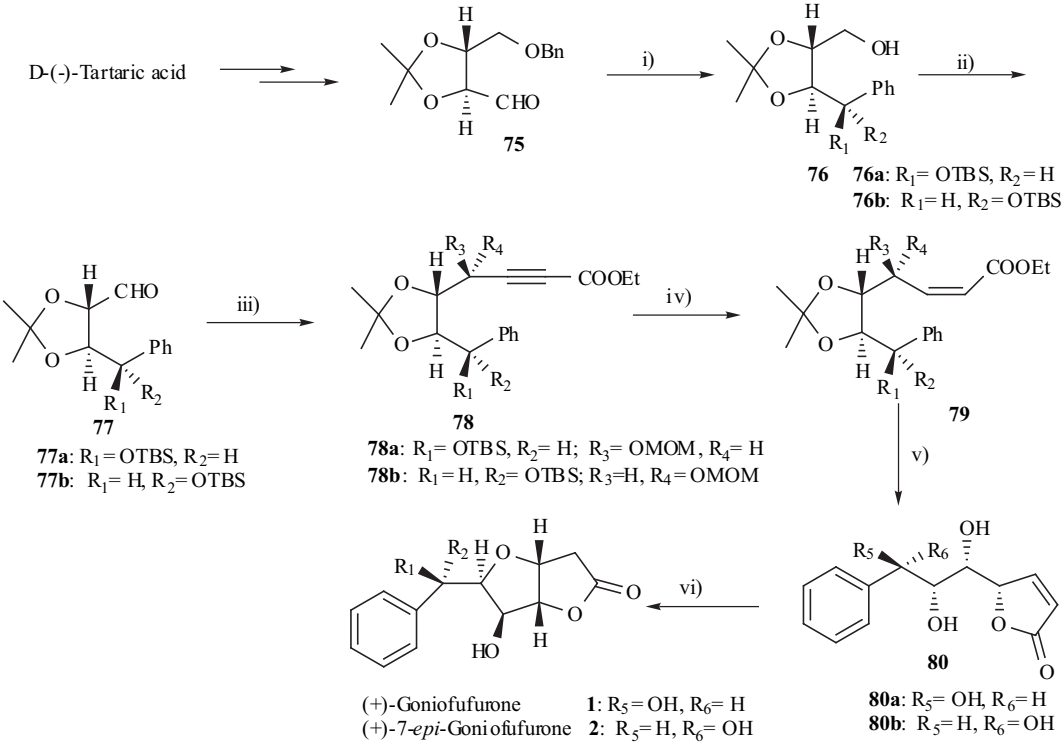
Reagents and conditions: i) Ph_3P=CHCOOEt, toluene, 110°C, 30 min; ii)cat. OsO_4, NMO, acetone, H_2O, r.t., 5 h; iii) 1. 2-methoxypropene, 10-camphorsulfonic acid, CH_2Cl_2, r.t., 10 min; 2. methyl 3-phenylsulfony orthopropinate (3eq.), n-BuLi, -78°C, 2 h; iv) $LiAlH_4$, Et_2O, -78°C, 2 h; v) THF, 1N HOAc, reflux, 3 h; vi) DBU (3eq.), CH_2Cl_2, 0°C, 50 min.

the β-hydroxy sulfone as a common intermediate was described by Vatèle [22]. The chiral aldehyde **63** was prepared from D-mandelic acid in 76% yield. Wittig alkenation of aldehyde **63** in refluxing toluene occurred with high selectivity to afford the (*E*)-ester **64** in 88% yield. Dihydroxylation of (*E*)-ester **64** in the presence of a catalytic amount of OsO_4 and an excess of N-methylmorpholine-oxide in water-acetone (v/v = 4:1) produced the



Scheme 10. Synthesis of (+)-Goniofufurone.

Reagents and conditions: i) 1. con. H_2SO_4, aceton, 86%; 2. Tf_2O, pyridine, CH_2Cl_2, -40°C, 94%; ii) LiBr, acetone, 97%; iii) CF_3COOH, H_2O, r.t., 98%; iv) propargyl bromide, In, 0.1 HCl, EtOH, 32%; v) 1. O_3, MeOH, Me_2S; 2. $NaBH_4$, MeOH, -10°C, H_2SO_4, Ac_2O, 75%; vi) 1. $NaHSO_3$, Na_2SO_3, MeOH, H_2O; 2. HCl(g), MeOH, 44%.



Scheme 11. Synthesis of (+)-Goniofufurone and (+)-7-*epi*-Goniofufurone.

Reagents and conditions: i) 1. PhMgBr, THF, -78°C, 2 h, then r.t, 12 h; 2. TBSCl, imidazole, DMF, r.t. 1 day; 3. H_2, Pd/C, ethyl acetate, 45°C, 6 h; ii) Dess-Martin periodanane, CH_2Cl_2, 1 h; iii) 1. ethyl propiolate, 2 M BuLi, i-Pr_2NH, THF, -78°C, 12 h; 2. MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 40°C, 24 h; iv) Lindlar cat., ethyl acetate, 30°C, 3 days; v) 1M HCl, MeOH, reflux, 12 h; vi) DBU, THF, r.t. 1 day.

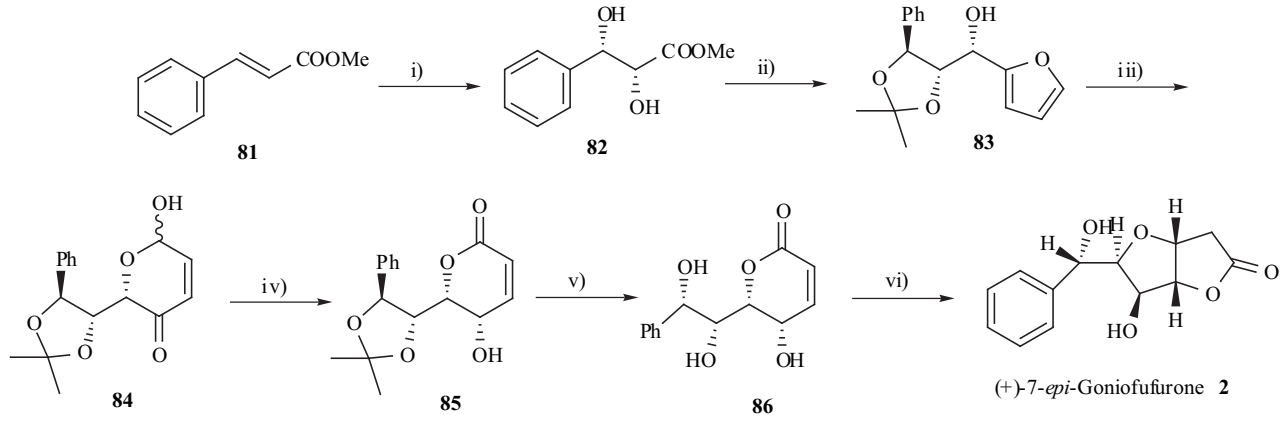
diastereoselectively triol **65** in 84% yield. Protection of 1,2-diol in **65**, which was treated with an excess of the lithium salt of methyl 3-phenylsulfonyl orthopropionate to afford the β-keto sulfone **66** in 83% yield. Subsequent complete removal of the protecting groups in **67** provided the triol lactone **68,** which was treated with DBU *via* elimination and intramolecular Michael addition-cyclization to give the (+)-goniofufurone **1** (Scheme **9**).

Li *et al*. reported a new route to (+)-goniofufurone from a readily available D-glucurono-6,3-lactone by the regio- and diastereoselectivities of indium-mediated allenylation of carbonyl compound bearing free hydroxyl groups in aqueous ethanol solution, which offered the advantage of running the reaction to be performed in aqueous solution reducing the need for extensive protecting group manipulations [23, 24] (Scheme **10**).

We have published the total synthesis of four diastereoisomers of goniofufurone from commercially available D- (-) and L- (+)-tartaric acids by the addition of ethyl lithiopropiolate to the chiral aldehyde intermediate as a key step [25] (Scheme **11**).

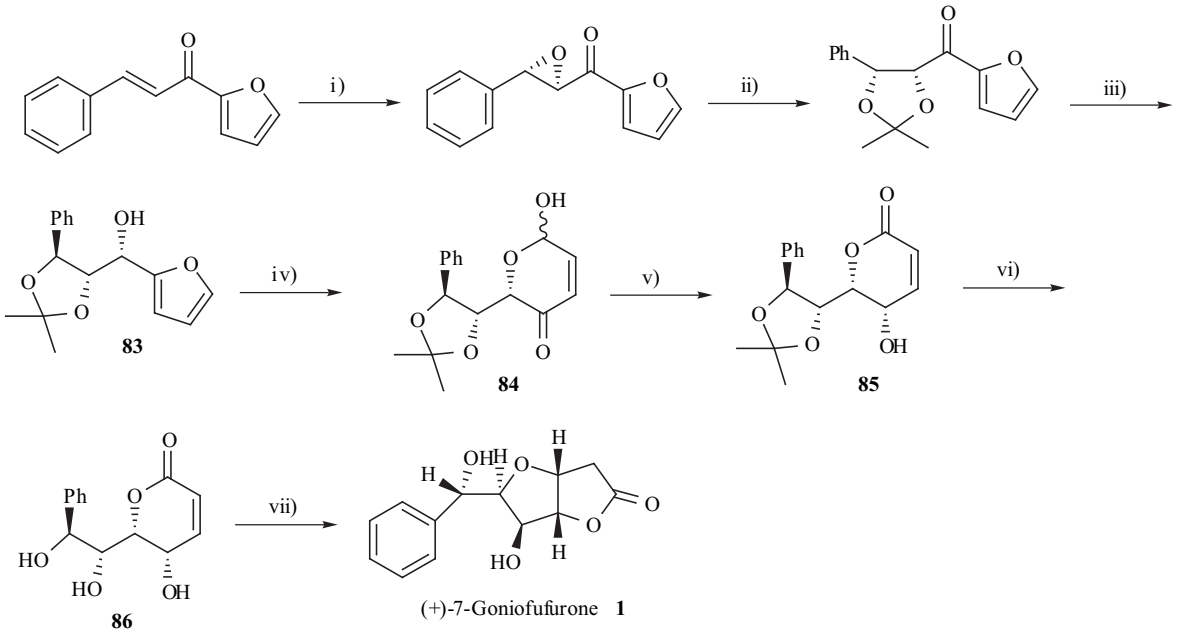
Alternatively, Zhou *et al*. have reported the total synthesis of the natural (+)-goniofufurone **1** or (+)-7-*epi*-goniofufurone **2** based on Sharpless asymmetric dihydroxylation and asymmetric epoxidation starting from achiral material cinnamate and cinnamyl alcohol, respectively [26, 27] (Scheme **12**). This method opened the versatility of the way to prepare many these interesting compounds.

Roberts *et al.* has also published an efficient method for the total synthesis of the natural (+)-goniofufurone **1** using



Scheme 12. Synthesis of (+)-7-*epi*-Goniofufurone.

Reagents and conditions: i) OsO_4, DHQ-CLB, 92%; ii) 1. $Me_2C(OMe)_2$, p-TsOH, 99%; 2. $LiAlH_4$, 3. DMSO, $(COCl)_2$, Et_3N; 4. $(C_4H_3O)MgBr$, CuBr, 54%; iii) TBHP, $VO(acac)_2$, 87%; iv) 1. CrO_3, HOAc; $NaBH(OAc)_3$, 65%; v) CF_3COOH, THF, H_2O 90%; vi) 0.5 M NaOH, r.t. 20 min, then 1 M HCl.



Scheme 13. Synthesis of (+)-7-Goniofufurone.

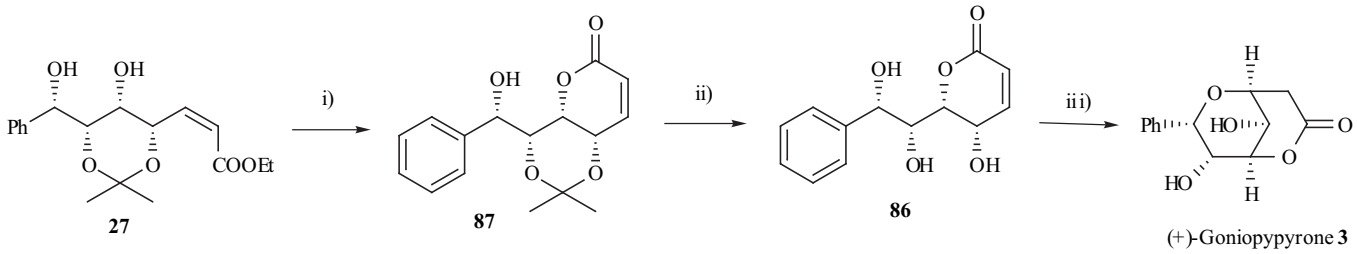
Reagents and conditions: i) urea-hydrogen peroxide, poly-L-leucine, DBU, THF, r.t. 2 h. ii) 1. I_2 (0.5-1.0 mol%), CH_3CN/ H_2O (v/v = 1:1), 40°C, 60 h; 2. $Me_2CH(OMe)_2$, p-TsOH, CH_2Cl_2, r.t. 5 h; iii) $NaBH_4$, $CeCl_3$, MeOH, -78°C; iv) NBS, THF/ H_2O (v/v = 8:2); v) CrO_3, HOAc; $NaBH(OAc)_3$; vi) CF_3COOH, THF, H_2O; vii) DBU, THF, r.t. 2 days, 67%.

Julia-Colonna asymmetric epoxidation of furyl styryl ketone as a key step which allowed a rapid construction of the backbone of the (+)-goniofufurone in a short sequence [28] (Scheme **13**).

B) SYNTHESIS OF (+)-GONIOPYPYRONE(3) AND (+)-9-DEOXY-GONIOPYPYRONE(4)

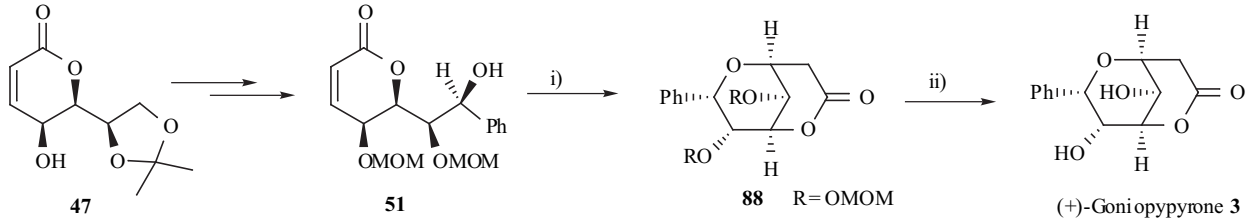
(+)-Goniopypyrone [2a] and (+)-9-deoxygonipypyrone [2b] were recently isolated from the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae). Among the styryl lactones, it was reported that (+)-Goniopypyrone was the most bioactive to show nonselective ED50 values of ~ 0.67 μg/ml in three human tumour cell lines of the A-549 (human lung carcinoma), MCF-7 (human breast adenocarcinoma), and HT-29 (human colon adenocarcinoma). Due to the unique structural features and significant bioactivity, several groups have paid attention to synthesis of them from commercial available chiral starting materials and achiral starting material.

Shing *et al*. has first synthesized the (+)-Goniopypyrone from commercially available and inexpensive D-*glycero*-D-*gulo*-*heptono*-γ-*lactone* (D- *glucoheptonic* γ-*laotone*, **10**) using the same intramolecular Michael strategy for the goniofufurone synthesis [11]. Treatment of the Z-alkene **27** with a catalytic amount of DBU in dry THF under reflux led to the pyrone **87** as coluorless needles in 70% yield, then hydrolysis of the acetonide in **87** by aqueous acetic acid under reflux yielded the trihydroxypyrone **86** in 82% yield as colourless needles followed by intramolecular Michael



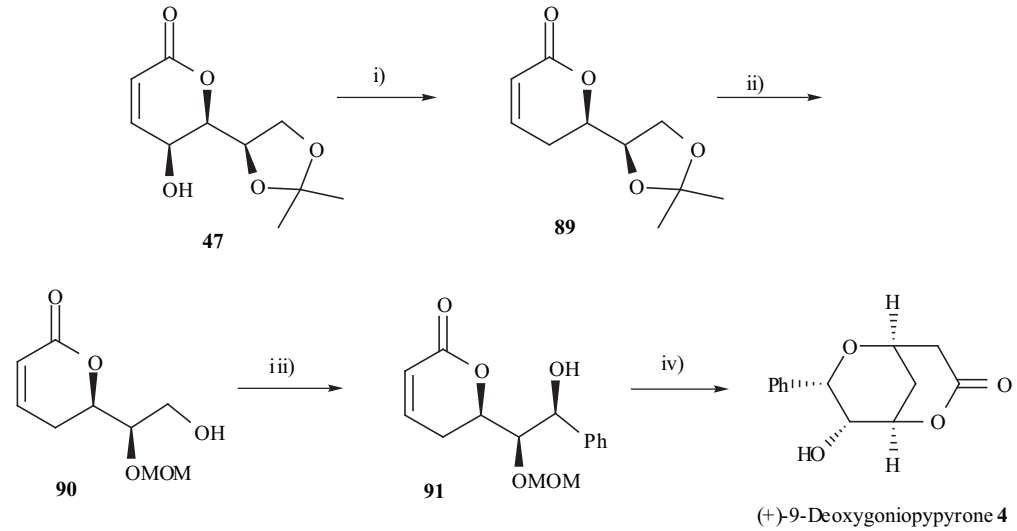
Scheme 14. Synthesis of (+)-Goniopypyrone.

Reagents and conditions: i) cat. DBU, THF, reflux, 70%; ii) AcOH, H_2O, 82%; iii) cat. DBU, THF, r.t. 70%.



Scheme 15. Synthesis of (+)-Goniopypyrone.

Reagents and conditions: i) DBU, THF, 95%; ii) TFA, CH_2Cl_2, 93%.

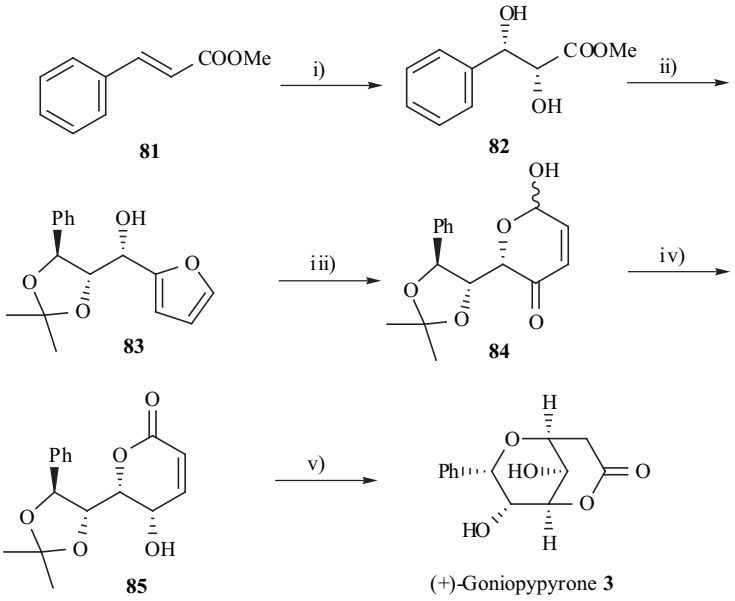


Scheme 16. Synthesis of (+)-9-Deoxygoniopypyrone.

Reagents and conditions: i) 1. Ac_2O, DMAP, CH_2Cl_2, r.t. 99%; 2. Zn, $CuSO_4{\cdot}5H_2O$, AcONa, 50% HOAc, THF, 0°C- r.t. 1 h, 92%; 3. DBU(cat.), THF, r.t., 16 h, 99%; ii) 1.75% aq. HOAc; 2. TBSCl, Et_3N, DMAP(cat.), CH_2Cl_2; 3. MOMCl, *i*-Pr_2NEt, DMAP(cat.); 4. 75% aq. HOAc; iii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, then $PhTi(O\text{-}iPr)_3$, Et_2O, 0°C, 1 h; iv) 1.75% aq. HOAc; DBU(cat.), THF, r.t., 15 h, 82%.

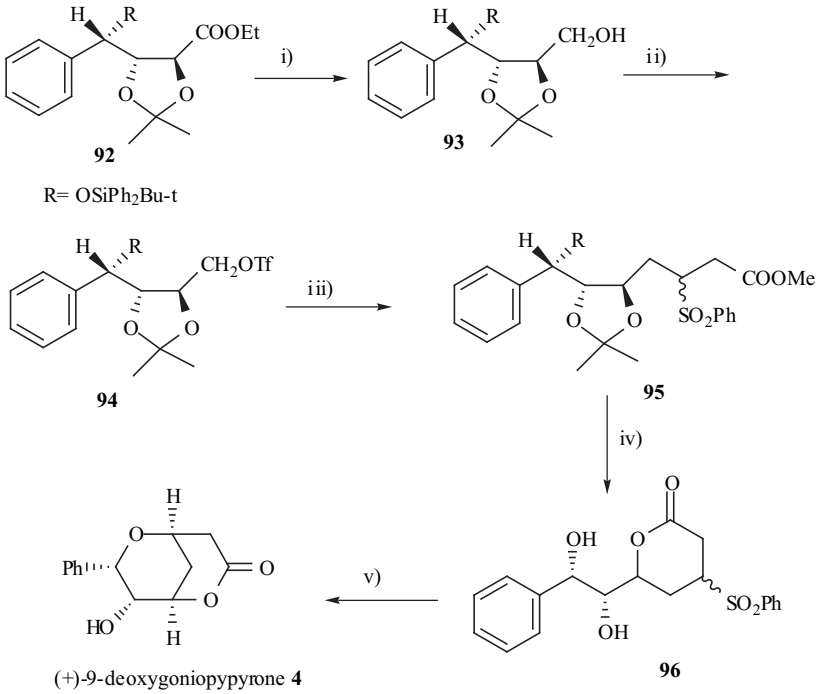
addition catalysed by DBU in dry THF at room temperature to give the (+)-Goniopypyrone **3** (Scheme **14**).

Honda *et al.* has followed a similar approach using a readily available chiral lactone **47** to synthesiz the (+)-Goniopypyrone **3** [17] (Scheme **15**) and (+)-9-deoxygonipypyrone **4** [16] (Scheme **16**). **52** was converted into the corresponding **88** catalysed by DBU in THF, followed by the treatment with TFA to give the (+)-Gonipypyrone **3**. In the same context, Deoxygenation of **47** was carried out by sequential acetylation of **47**, reductive deacetoxylation of the allyl acetate and isomerisation of β,γ-unsaturated lactone to get the lactone **89** in 90% yield from **47**. Acid removal of the acetonide group in **89** afforded the diol, which was further converted into **90**. Swern oxidation of **90** followed by phenylation of the aldehyde in one pot led to **91**. Subsequent deprotection of the methoxymethyl group in **91** with aqueous HOAc and DBU-catalysed the intramolecular



Scheme 17. Synthesis of (+)-Goniopypyrone.

Reagents and conditions: i) OsO_4, DHQ-CLB, 92%; ii)1. $Me_2C(OMe)_2$, p-TsOH, 99%; 2. $LiAlH_4$; 3. DMSO, $(COCl)_2$, Et_3N; 4. CuBr, $(C_4H_3O)MgBr$, 54%; iii) TBHP, $VO(acac)_2$, 87%; iv) 1. CrO_3, HOAc; 2. $NaBH(OAc)_3$, 65%; iv) AcOH, 90%; v) DBU, THF, r.t., 1 day, 85%.



Scheme 18. Synthesis of (+)-9-deoxygoniopypyrone.

Reagents and conditions: i) $LiAlH_4$, Et_2O, 0°C, 5 min; ii) $(CF_3SO_2)_2O$, DMAP, CH_2Cl_2, -10°C, 30 min; iii) $PhSO_2(CH_2)_2C(OMe)_3$ (3 eq.), n-BuLi(3 eq.); iv) CF_3COOH/ H_2O(v/v = 4:1), r.t., 18 h; v) DBU(3 eq.), CH_2Cl_2, 0°C, 1 h.

Michael addition reaction afforded the desired (+)-9-deoxygonipypyrone **4** as colourless needles.

Zhou *et al*. have reported the total synthesis of the natural (+)-goniopypyrone **3** [29] or (+)-9-deoxygoniopypyrone **4** [30] based on Sharpless asymmetric dihydroxylation starting from achiral material cinnamate **82** (Scheme **17**).

Vatèle *et al*. has described a short route which the combination of the availability of the C_4-ester **92** from (*R*)-mandelic acid with the valuable Ghosez's homoenolate reagent and the efficient triflate-sulfone coupling allowed the preparation of the (+)-9-deoxygoniopypyrone **4** [31] Scheme **18**).

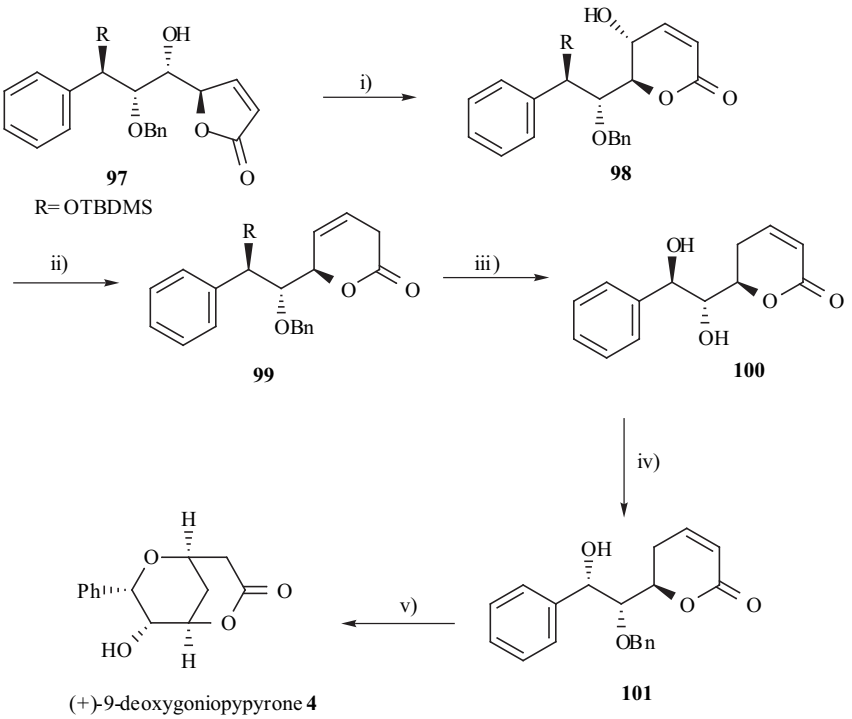
Hanaoka *et al.* succeeded in an efficient total synthesis (+)-goniopypyrone **3** and (+)-deoxy-goniopypyrone **4** in a highly stereocontrolled fashion from chiral (+) tricarbonyl (η^6-2-trimethylsilybenzaldehyde) chromium (0) complex **59** *via* the common key intermediate **97** [20, 21] (Scheme **19**).

C) SYNTHESIS OF (+)-ALTHOLACTONE (5)

The remarkable bioactive features of (+)-altholactone **5** are toxicity against p388 leukemia cell in mice and a lethality to brine shrimp [6]. Up to now, several groups have paid attention to synthesis of it from commercial available chiral starting materials. Ogawa *et al*. [32] disclosed a total synthesis of (+)-altholactone **5** using L- arabinose as an enantiomerically pure starting material. Oxidation of the vicinal diol in the **102** followed by immediate Wittig alkenation in THF to afford stereoselectively the *E*-alkene **103**(Z: E = 1:3). The protection of hydroxy group in **103-*E*** gave the benzoylation **98** in 93% yield, then oxidation of **104** by m-chloroperbenzoic acid in CH_2Cl_2 under reflux provided a mixture of **105**. This mixture was directly debenzoylated by NaOMe. After neutralisation and work-up, the debenzoylated mixture in CH_2Cl_2 was treated with silica gel at r.t. for 32 h to form the mixture of **107**(major) and **108**(minor), then **107** was converted in to the **108** in 3 steps. Collins oxidation of **110** gave the aldehyde **111** followed by Wittig carbon elongation to obtain the mixture of **112-*E*** and **112-*Z*** in 39% and 30% yield. And final hydrolysis of **112-*Z*** led to the (+)-altholactone **5** (Scheme **20**)

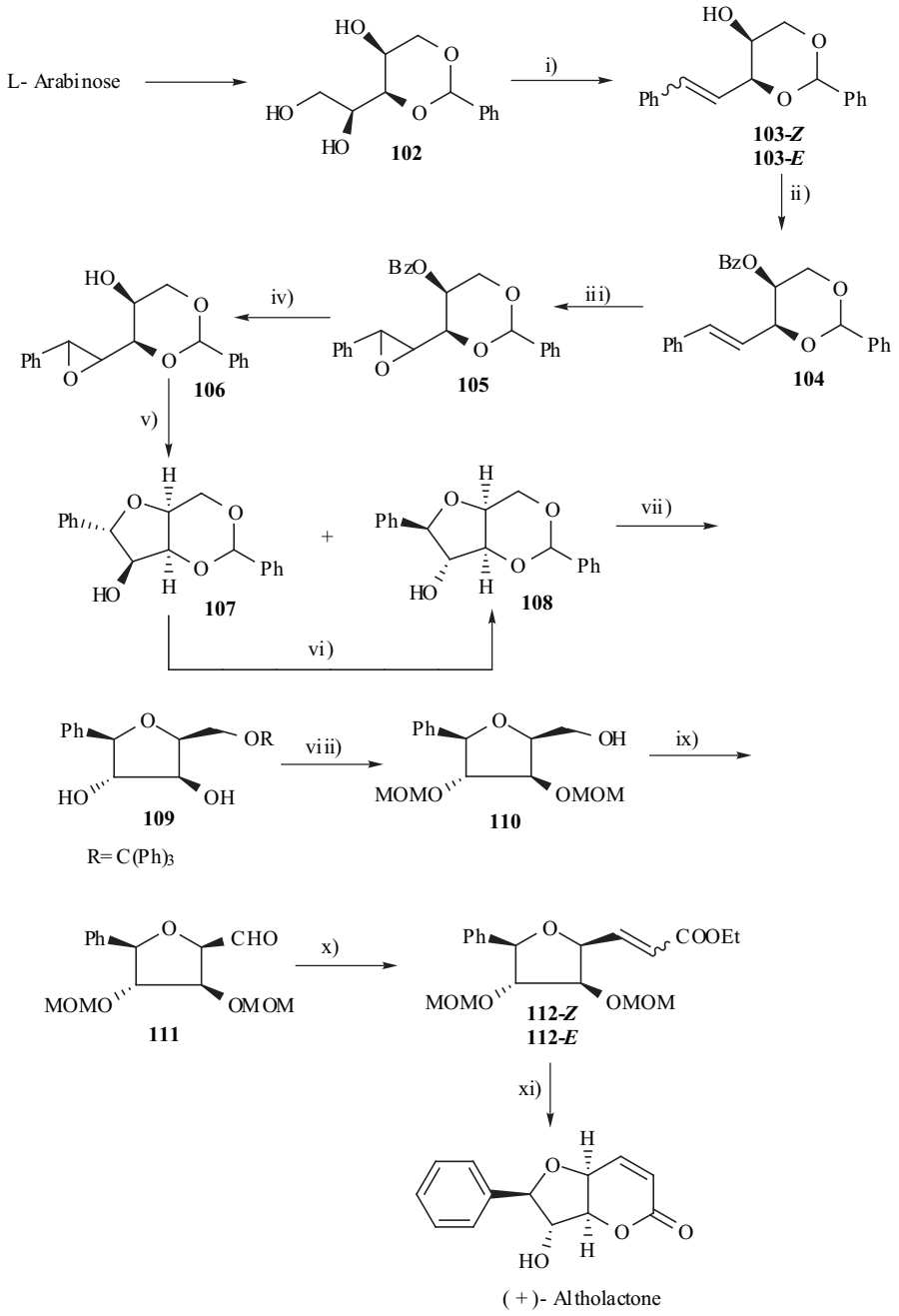
In the same context, Shing *et al*. reported that a stereocontrolled reduction as a key step was employed for the synthesis of (+)-altholactone **5**[33]. In this case, the diacetonide **114** was obtained from the commercially available D-gulonolactone **113**, followed by the addition of phenyl lithium to give the lactol **114**. Stereocontrolled reduction of **113** with Et_3SiH mediated by $BF_3{\cdot}Et_2O$ furnished the α-D-C-phenyl derivative **115**. Oxidation of the diol with periodate, followed by immediate Wittig olefination, led to stereoselective the **116-*Z***-olefin (Z: E = 6:1). Deacetonation of **116** occurred with spontaneous lactonisation to give the 7-epi-altholactone, which was converted into the corresponding (+)-altholactone **5** by nucleophilic displacement (Scheme **21**). Another method for the synthesis of (+)-altholactone **5** was also reported by this group [11].

Analogously, Gesson *et al*. has used D-glucose as a chiral starting for the synthesis of (+)-altholactone **5** [34, 35]. Addition of phenylmagnesium in ether with the



Scheme 19. Synthesis of (+)-9-deoxygoniopypyrone.

Reagents and conditions: i) 1.TMS-imidazole, CH_2Cl_2, 97%,; 2. DIBALH, Et_2O, -78°C; 3. *t*-BuOK, THF, -70°C, 4. PDC, AcONa, CH_2Cl_2; 5. 10% HCl, MeOH; ii) 1. Ac_2O, DMAP, CH_2Cl_2, 100%; 2. Zn-Hg, satd. HCl in Et_2O, -20°C, 88%; iii) 1. DBU, THF, 90%; 2. NaI, $BF_3{\cdot}OEt_2$, CH_3CN, 0°C, 97%; iv) 1. PPh_3, DEAD, p-$NO_2C_6H_4COOH$, C_6H_6; 1N LiOH, THF; 3. TFA, THF; v) 1. DBU, THF; $TiCl_4$, CH_2Cl_2.

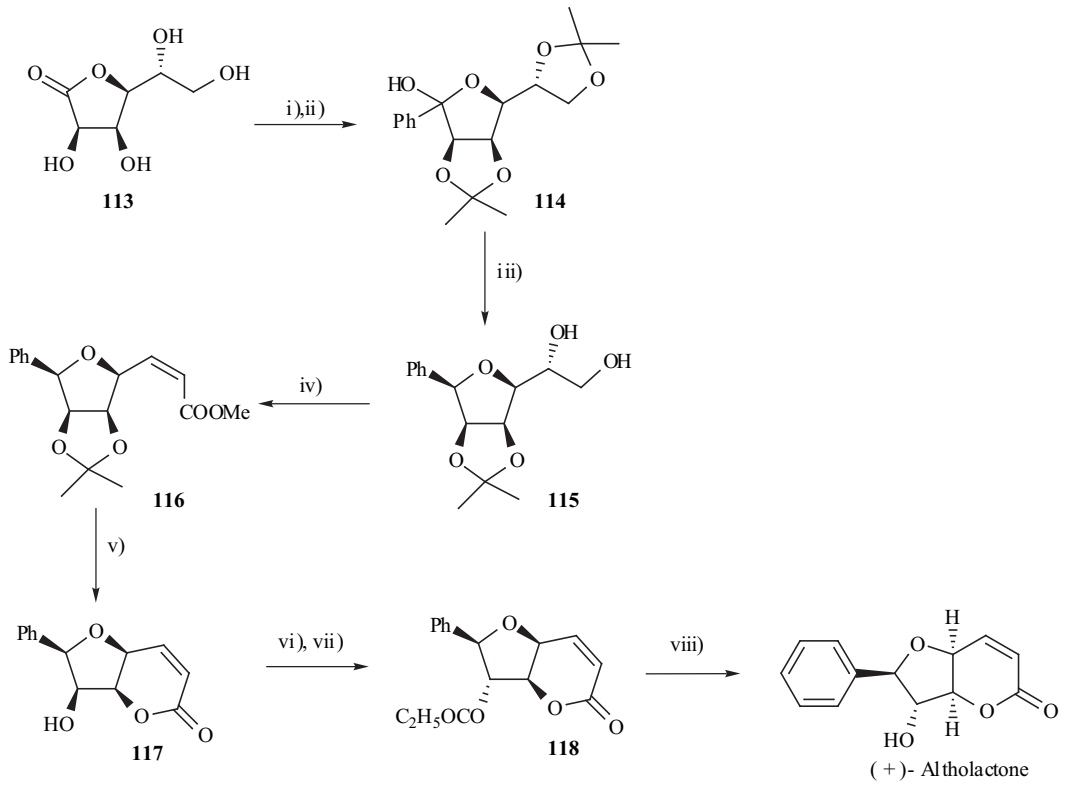


Scheme 20. Synthesis of (+)-Altholactone.

Reagents and conditions: i) 1. $NaIO_4$; 2. $PhCH_2P^+PPh_3Cl^-$, BuLi, THF, r.t.; ii) PhCOCl, base; iii) m-CPBA, CH_2Cl_2, reflux; iv) NaOMe; v) SiO_2, CH_2Cl_2; vi) 1. MsCl, base; 2. *t*-BuOK; 3. B_2H_6, NaOH/ H_2O; vii) 1.HCl, dioxane; TrCl, DMAP, pyridine; viii) 1. MOMCl, *i*-Pr_2NEt, THF; 2. TsOH, MeOH; ix) CrO_3, pyridine, CH_2Cl_2; x) Wittig reagent; xi) TsOH · H_2O, MeOH.

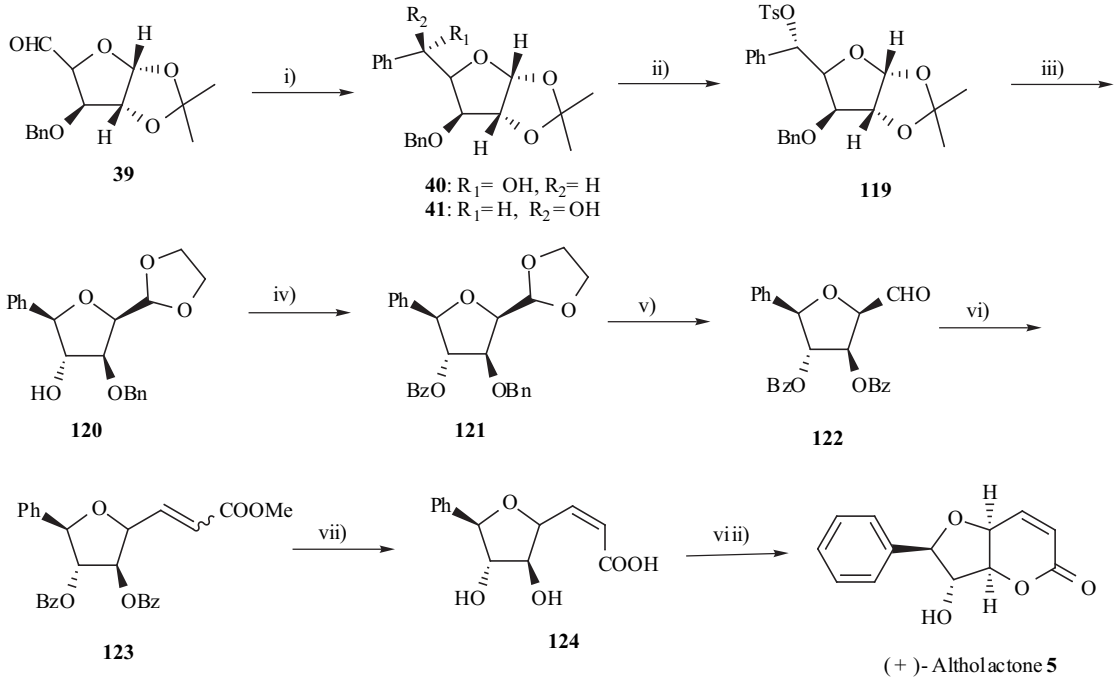
aldehyde **39** as chiral precursor from D-glucose afforded the mixture of **40** and **41** in 73% and 4% yield, respectively. Alcohol **40** was then converted to the corresponding tosylate **119**, Treatment of **119** with 4 eq. Ethylene glycol in the presence of catalytic amount of p-toluenesulfonic acid to obtain the single compound **120** in 87% yield, then followed a similar approach to (+)-altholactone **5** (Scheme **22**).

Kang *et al*. reported an enantiocomplementary total synthesis of (+)-altholactone **5** from L-glyceraldehyde acetonide [36]. In this case, first addition reaction of lithium phenylacetylide to L-glyceraldehyde **125** gave a mixture of alcohol of **126** and **127**. **126** was treated with Mitsunobu condition and lithium aluminum hydride (LAH) reduction in sequence, and **127** was reduced with LAH to give the alcohol **128**. Acid-mediated equilibration of **128** in acetone produced a 5:1 mixture of **129** and **128**. Swern oxidation of **129** followed by Wittig reaction gave the desired trans-allylic diol **130** in 88% yield. Epoxidation of **130** with MMPP followed by acid-catalysed cyclisation furnished a 1:3.5 mixture of **131** and **131**. As a sequence, ozonolysis of **132** and the resulting aldehyde was olefinated with t-butyl (triphenylphosphoranylidene)-acetate in methanol to get the



Scheme 21. Synthesis of (+)-Altholactone.

Reagents and conditions: i) Me_2CO, H_2SO_4; ii) PhLi, THF, -78°C; iii) Et_3SiH, $BF_3 \cdot Et_2O$, MeCN, -20°C; iv) $NaIO_4$, aq. MeOH; then Ph_3P=CHCOOMe; v) aq. CF_3COOH; vi) $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine, -10°C; vii) $EtCO_2Cs$, $HCONMe_2$; viii) aq. NaOH; then TFA.

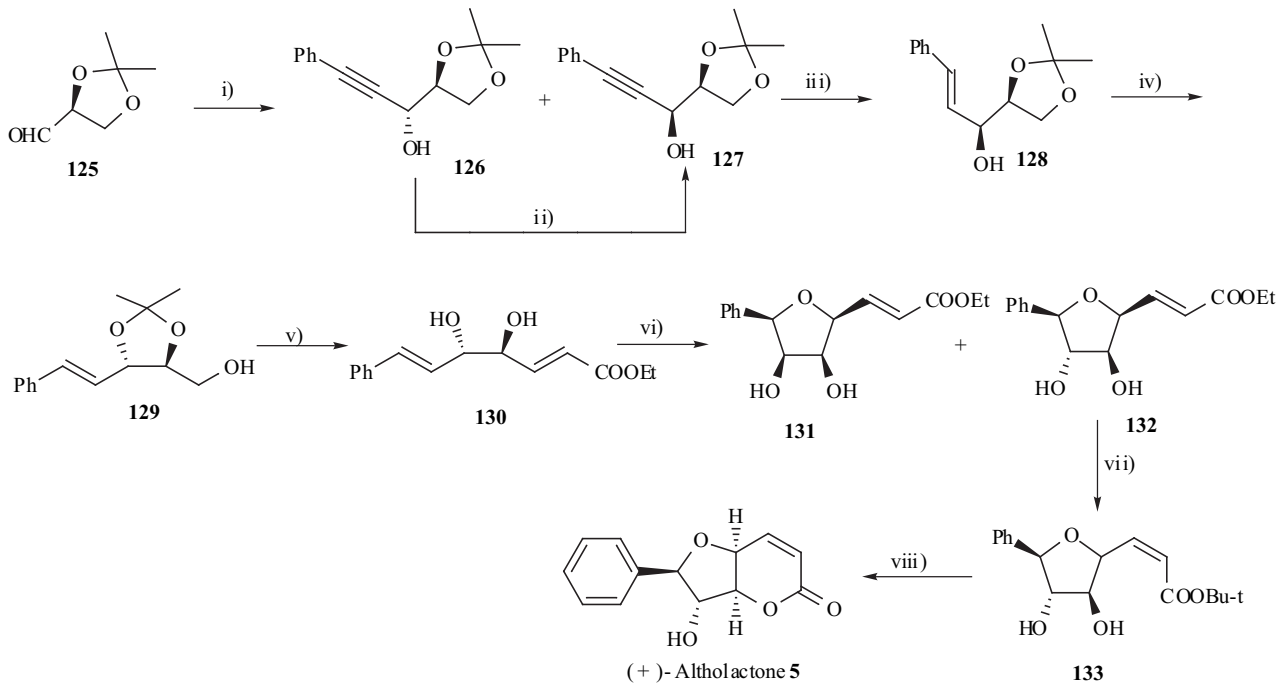


Scheme 22. Synthesis of (+)-Altholactone.

Reagents and conditions: i) PhMgBr, Et_2O, reflux, 77%, 40:41 = 16:1; ii) TsCl, pyridine, r.t., 24 h, 86%; iii) p-Toluenesulfonic acid, $HOCH_2CH_2OH$, PhH, 87%; iv) PhCOCl, pyridine, 98%; v) 1. Me_3SiI, CH_2Cl_2, -20°C, 53%; 2. PhCOCl, pyridine, 90%; 3. CF_3COOH/ H_2O (v/v = 80:20), 86%; vi) Ph_3P=$CHCOOCH_3$, Methanol, 69%; vii) 1N NaOH, then 1N H_2SO_4; viii) CF_3COOH, H_2O, 30 min, 55%.

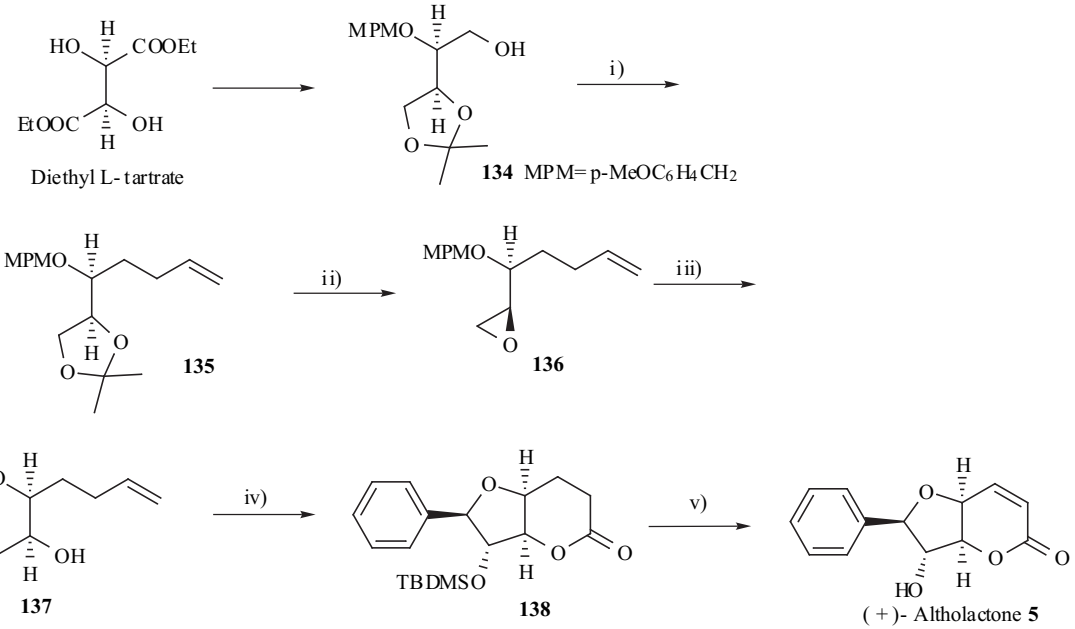
cis-ester **133**. Finally **133** was converted into the (+)-altholactone **5** (Scheme **23**).

In the same context, Somfai *et al.* has used the natural diethyl L- tartrate as starting material for the synthesis of



Scheme 23. Synthesis of (+)-Altholactone.

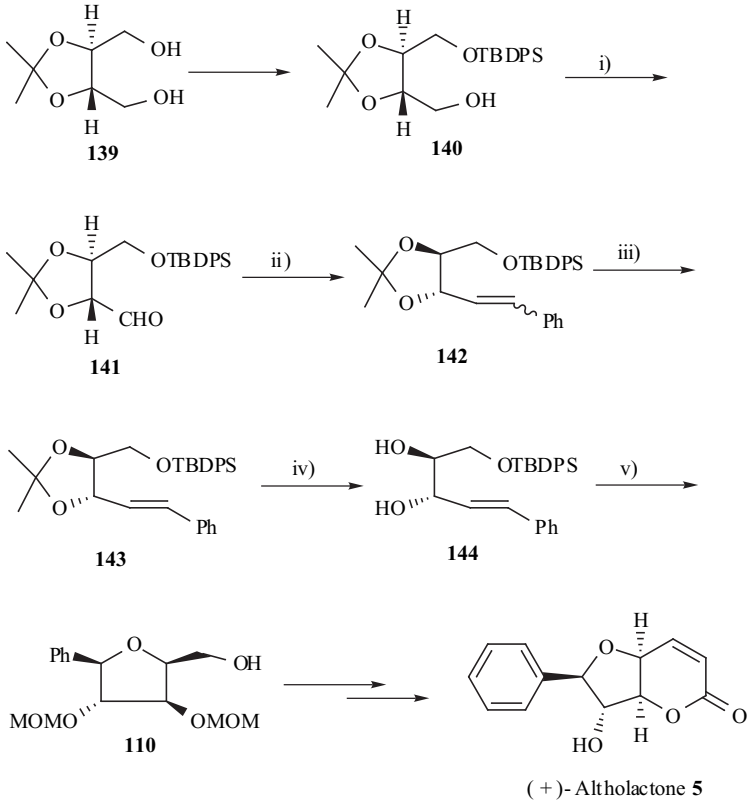
Reagents and conditions: i) n-BuLi, L-glyceraldehyde acetonide, -78°C- r.t.; ii) Ph_3P, PhCOOH, DEAD, THF; iii) LAH, THF, 0°C; iv) 1. Camphorsulfonic acid(cat.), acetone, r.t.; 2. $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78°C; v) 1. $(EtO)_2POCH_2COOEt$, *t*-BuOK, THF, -78°C- r.t.; 2. HOAc/ H_2O(v/v = 4:1); (vi) 1.MMPP (monoperoxyphthalate), acetone, r.t.; 2.Camphorsulfonic acid(cat.), CH_2Cl_2, r.t.; vii) 1. O_3, MeOH, -78°C, then Me_2S, -78°C- r.t.; 2. Ph_3P=CHCOOBu-t, MeOH, 0°C; viii) CF_3COOH, CH_2Cl_2, r.t.



Scheme 24. Synthesis of (+)-Altholactone.

Reagents and conditions: i) 1. TsCl, pyriding, 93%; 2. allylmagnesium, CuI, -30°C, THF, 84%; ii) 1. 2% aq. H_2SO_4, MeOH, 96%; 2. p-TsCl, prridine; 3. K_2CO_3, MeOH; iii) 1-lithio-1-phenylethylene, CuCN, THF, 87%; iv) 1. O_3, acetone, -78°C – 50°C, the Me_2S; 2. PCC, CH_2Cl_2; 3. BH_3·THF, THF, 0°C, then NaOH, H_2O_2, H_2SO_4; 4. TBDMSOTf, pyridine, CH_2Cl_2, 87%; v) 1.LDA, PhSeBr, THF, -78°C, then H_2O_2, $ClCH_2CH_2Cl$, 60°C; 2. Bu_4NF, THF, 91%.

(+)-altholactone **5** [36]. Tosylation of alcohol **134** followed by a copper catalysed addition of ally magnesium chloride affording alkene **135** in 78% yield. The **135** was converted into the epoxide **136**. The **136** was treated with 1-lithio-1-phenylethylene in the presence of CuCN to give the diene **137** in good yield. After conversion of diene **137** into dihydroaltholatone **138**, removal of silyl group in **138** then gave (+)-altholactone **5** (Scheme **24**).



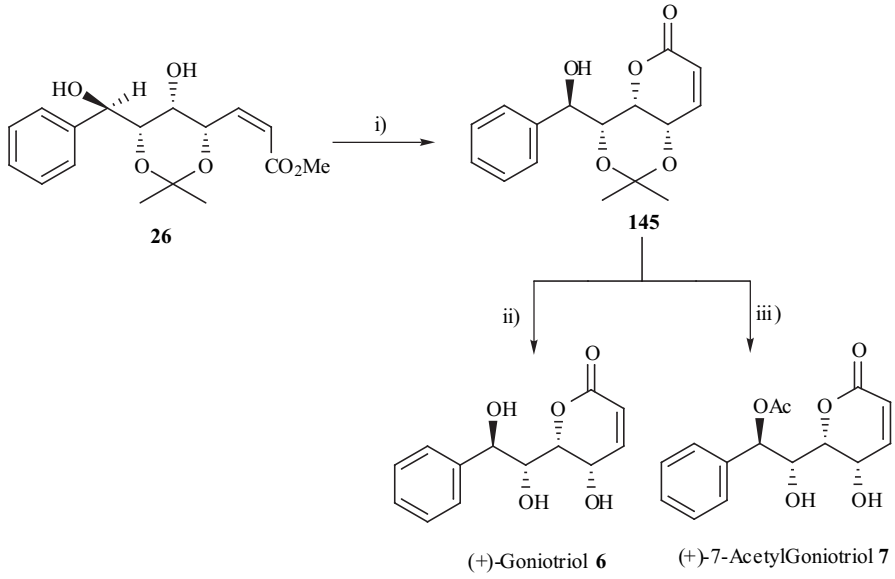
Scheme 25. Synthesis of (+)-Altholactone.

Reagents and conditions: i) NaH, TBDPSCl, THF; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C; iii) BuLi, $Ph_3P^+CH_2PhBr^-$, THF, -40°C; iv) PhSH, AIBN, benzene, reflux; v) 1. HOAc, H_2O, 60°C. ; 2. MMPP, acetone, r.t. 3. SiO_2, CH_2Cl_2, r.t. ; 4. MOMCl, Et_3N, THF, reflux; 5. TBAF, THF, r.t.

Recently, the formal synthesis of (+)-altholactone 5 has been achieved starting from L-tartaric acid using **110** as key intermediate. The key epoxy ring was introduced by monoperoxyphthalate in high stereoselectivity [37] (Scheme **25**).

D) SYNTHESIS OF (+)-GONIOTRIOL (6) AND (+)-7-ACETYLGONIOTRIOL (7)

Novel cytotoxic styrylpyrones, (+)-goniotriol 6 and (+)-7-acetylgoniotriol **7** were isolated from the stem bark of *Goniothalamus giganteus* Hook f., Thomas (Annonaceae),



Scheme 26. Synthesis of (+)-Goniotriol and (+)-7-AcetylGoniotriol.

Reagents and conditions: i) cat. DBU, THF; ii) AcOH, H_2O; iii) 1. Ac_2O, pyridine; 2. TFA, H_2O.

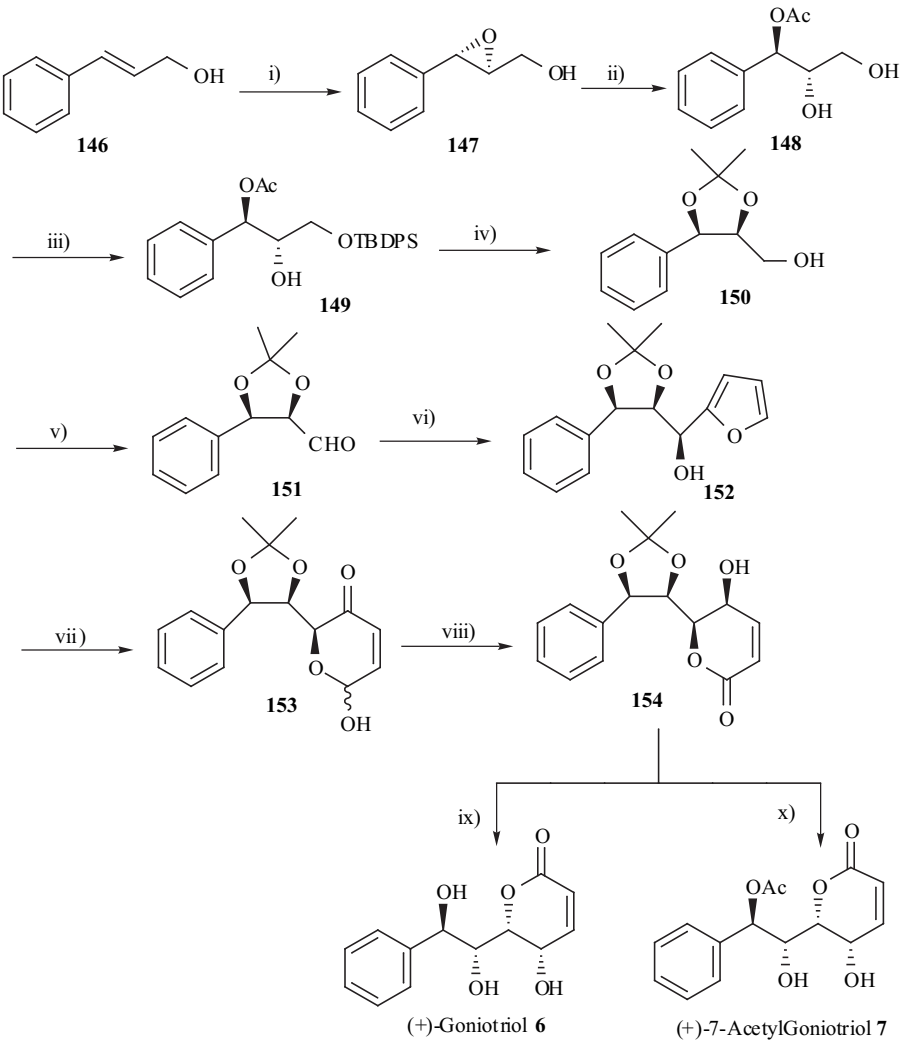
which were shown to be cytotoxic to human tumor cells. Their structure and configuration were confirmed by X-ray and syntheses. The absolute configurations of them had been established by Shing *et al. via* syntheses of their enantiomers from D-glycer-D-gulo-heptono-γ-lactone **10** [11]. (+)-goniotriol **6** and (+)-7-acetylgoniotriol **7** were easily synthesized from the common intermediate **26**. First, lactonisation of 1,3-dioxane **26** by DBU in THF gave the pyrone **145**, followed by hydrolysis of the isopropylidene group in **145** using aqueous acetic acid to provide the (+)-goniotriol 6 as colorless needs with m.p. = 178-180°C and $[\alpha]_D^{24}$ = + 118(*c* 0.9, MeOH){lit. [38], m.p. = 170°C and $[\alpha]_D^{30}$ = + 121(*c* 0.9, MeOH)}; for the synthesis of (+)-7-acetylgoniotriol **7** , acetylation of the pyrone **145** gave the 7-acetylpyrone , followed by hydrolysis of the isopropylidene group using TFA in CH_2Cl_2 to afford (+)-7-acetylgoniotriol **7** (Scheme **26**).

Zhou *et al.* published a different useful and versatile approach to the (+)-goniotriol **6** and (+)-7-acetylgoniotriol **7** from achiral starting material cinnamy alcohol *via* Sharpless asymmetric epoxidation and highly stereoselective 2-furyllium addition [39] (Scheme **27**).

Roberts *et al.* has also reported an efficient method for the total synthesis of the natural the (+)-goniotriol **6** (See Scheme **13**) and (+)-7-acetylgoniotriol **7** using Julia-Colonna asymmetric epoxidation of furyl styryl ketone as a key step [28]. The isomerisation of the acetonide **85** was converted into the **145**, then by the same steps as Shing group reported led to (+)-7-acetylgoniotriol **7** (See Scheme **26**).

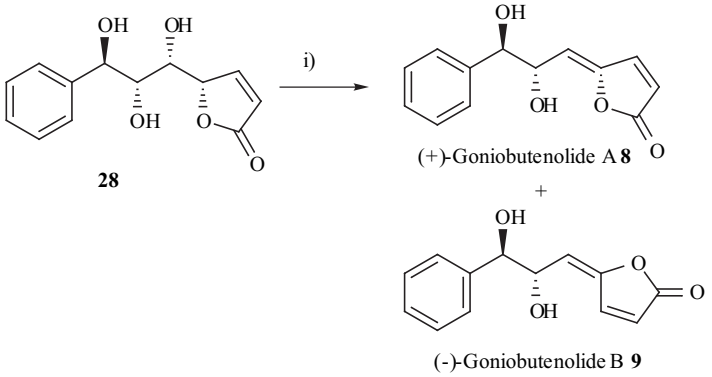
E) SYNTHESIS OF (+)-GONIOBUTENOLID A (8) AND (-)-GONIOBUTENOLID B (9)

In 1991, two new styryllactones, (+)-goniobutenolide A (**8**) and (-)-goniobutenolide B (**9**) were isolated from the stem bark of *Goniothalamus giganteus* Hook f., Thomas (Annonaceae), which were shown to be cytotoxic to human tumor cells [8]. Shing *et al.* had published a straightforward



Scheme 27. Synthesis of (+)-Goniotriol and (+)-7-AcetylGoniotriol.

Reagents and conditions: i) TBHP, *L*-(+)-DIPT, $Ti(O\text{-}iPr)_4$, CH_2Cl_2, -20°C – 0°C, 86% ; ii) $Ti(OAc)(O\text{-}iPr)_3$, $CHCl_3$, -20°C – 0°C, 3 h, 90%; iii) TBDPSCl, imidazole, THF, r.t., 24 h, 94%; iv) 1. K_2CO_3, MEOH, H_2O, r.t., 2 h, 85%; 2. $MeC(OMe)_2$, p-TsOH, CH_2Cl_2, r.t. 8 h, 91%; vi) 1.TBAF, THF, 2 h, 95%; 2. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C - 20°C; 3. 2-furyllithium, THF, -78°C – 0C; vii) TBHP, $VO(acac)_2$, CH_2Cl_2, 0°C, 12 h, 86%; viii) 1. CrO_3, HOAc, then $NaBH(OAc)_3$, *i*-PrOH, -5°C- 0°C; ix) TFA, THF, H_2O, r.t. 90%; x) 1. p-TsOH, acetone, r.t. 2 days, 80%; 2. Ac_2O, pyridine, DMAP, CH_2Cl_2, 87%; 3. HOAc/ H_2O(v/v = 3:1), 70°C- 80°C, 4 h, 85%.

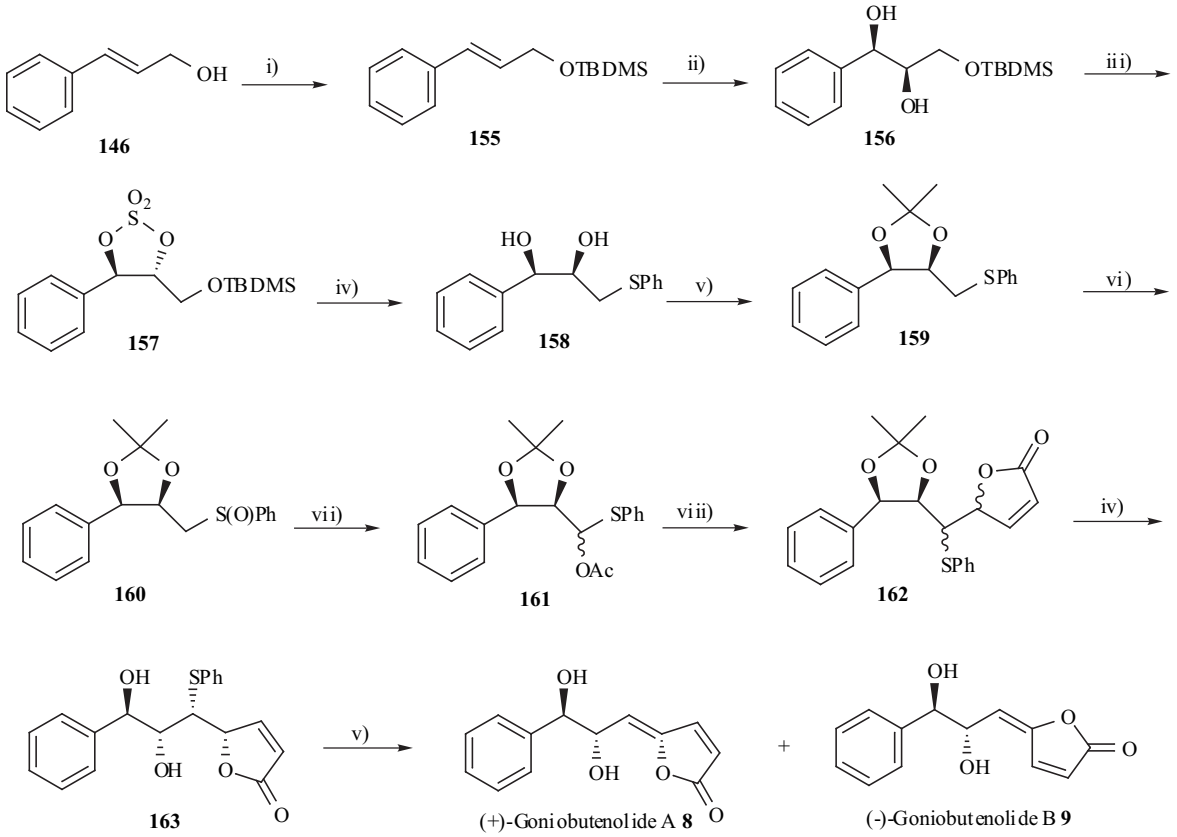


Scheme 28. Synthesis of (+) or (-)-Goniobutenolide.

Reagents and conditions:i) TFAA, Et_3N, CH_2Cl_2, r.t., then MeOH, 79%, **8:9** = 1:3.

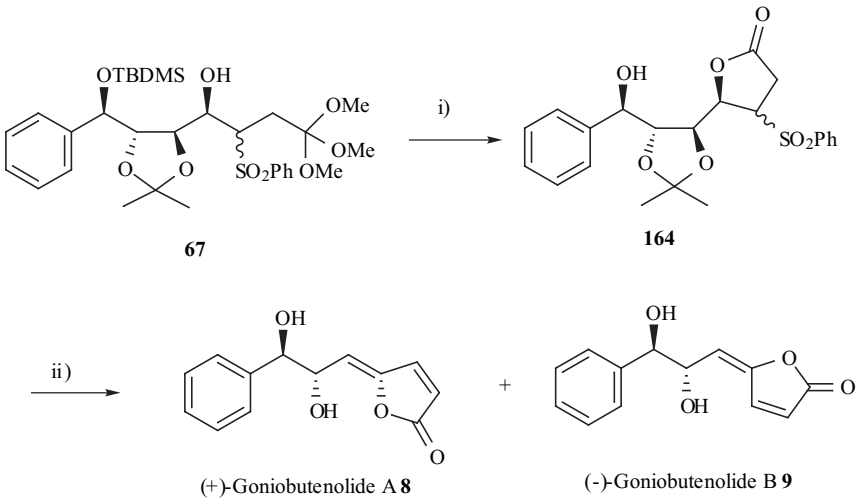
approach to enantiopure (+)-goniobutenolide A (**8**) and (-)-goniobutenolide B (**9**) in which the key step relied on a Wittig alkenation [11,40]. From the same starting material D-*glucoheptonic* γ-*lactone* **10**, the key intermediate **26** was prepared by subsequent steps. Protection of 26 with trifluoroacetic anhydride in the presence of Et_3N followed by hydrolysis to remove the eater to give the (+)-goniobutenolide A (**8**) and (-)-goniobutenolide B (**9**) Scheme **28**).

Ko *et al.* employed the asymmetric dihydroxylation (AD) as the key step to synthesize the (+)-goniobutenolide A (**8**) and (-)-goniobutenolide B (**9**) [42]. In this case, (*E*)-cinnamyl alcohol **146** was TBDMS- protected and the product **155** dihydroxylated using AD-mix-β to give **156**. The **156** was converted to the cyclic sulfated **157**. Then, the rearrangement –opening reaction was carried out by treating of **157** with TBAF followed by PhSNa and subsequent hydrolysis to afford the desired phenylthio *erythro*-diol **157**. The protection of the dihydroxyl group in **156** followed by oxidation of **159** to yield the sulfoxide **160**. Pummerer rearrangement of **160** produced **161**. **161** was treated with 2-trimethylsiloxyfuran in the presence of $SnCl_4$ to yield a



Scheme 29. Synthesis of (+) or (-)-Goniobutenolide.

Reagents and conditions: i) TBDMSCl, 100%; ii) AD-mix-β, 94%; iii) 1. $SOCl_2$, Et_3N; 2. $RuCl_3$, $NaIO_4$, 88%; iv) 1. TBAF; 2. PhSNa; 3. H_2SO_4, 79%; v) 2-methoxypropene, H^+; (vi) m-CPBA, 88%; vii) NaOAc, Ac_2O, 99%; viii)2-trimethylsiloxyfuran, $SnCl_4$, CH_2Cl_2, -70°C; ix) aq. 90% TFA, 84%; x) AgF, pyridine, 68%.



Scheme 30. Synthesis of (+) and (-)-Goniobutenolide.

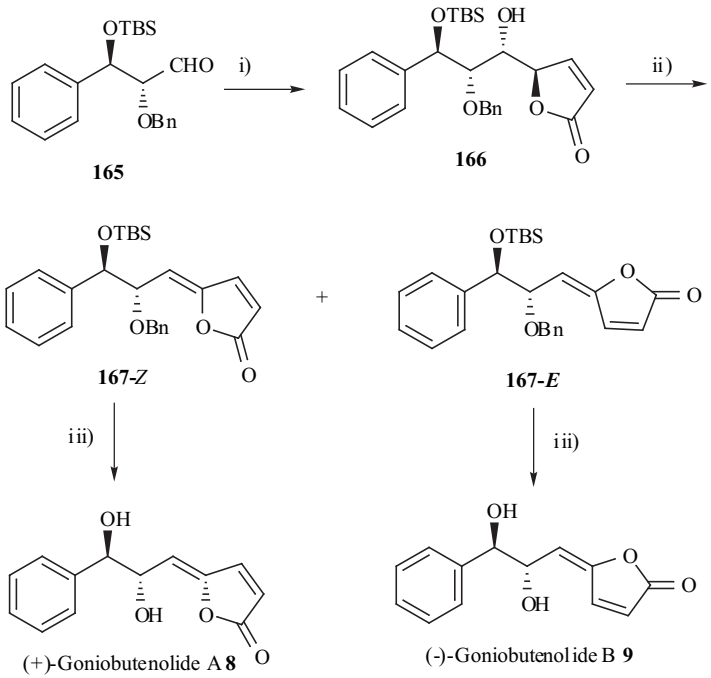
Reagents and conditions: i) cat. 10-camphorsulfonic acid, toluene, reflux, 1h, 94%; ii) 1. DBU, CH_2Cl_2, 0°C, 1 h, 85%; 2. HOAc, THF, H_2O, 60°C, 14 h, 75%.

mixture of products **162**, then, removal of acetonide in **163** accomplished with AgF/ pyridine to afford a 1.6: 1mixture of goniobuenolids A and B in 68% (Scheme **29**).

Vatèle [22] used the common advanced intermediate C_7 orthoester **67** with a catalytic amount of anhydrous 10-camphorsulfonic acid in toluene to give γ-butyrolactone. DBU-induced elimination of sulfonic acid followed by acid removal of TBDMS protecting group to afford a 3: 1 mixture of goniobuenolids A and B in 75% (Scheme **30**).

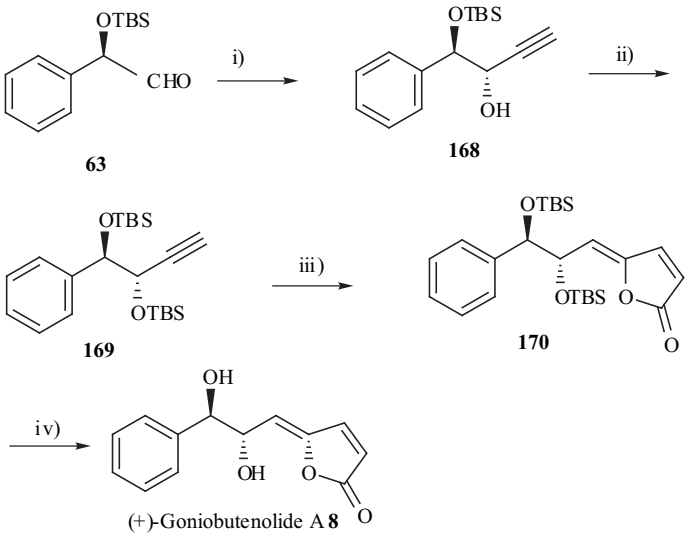
Hanaoka succeeded in a highly stereoselective aldol reaction of the aldehyde **165** derived from the chiral (+)-tricarbonyl (η^6-2-trimethylsilybenzaldehyde) chromium (0) complex **59** with 2-trimethylsilyloxyfuran afforded the lactone **166**. The lactone **167** was subsequently converted into the goniobuenolids A and B [20] (Scheme **31**).

One notable example has been described by Negishi *et al.* in their efficient synthesis of the goniobuenolids A from commercial D-mandelic acid *via* palladium-catalysed ene-yne cross- coupling lactonization cascade reaction [43] (Scheme **32**). This approach offers the most powerful way to prepare of the goniobuenolids A compared with the other methods as mentioned above.



Scheme 31. Synthesis of (+) and (-)-Goniobutenolide.

Reagents and conditions: i) $Ti(O\text{-}iPr)_2Cl_2$, CH_2Cl_2; ii) 1. MsCl, Et_3N, CH_2Cl_2, then $i\text{-}Pr_2NEt$, CH_2Cl_2, **167-*Z***: **167-*E*** = 94:6; 2. MsCl, Et_3N, CH_2Cl_2, then 10% K_2CO_3, **167-*Z***: **167-*E*** = 15:85; iii) TBAF, HF.



Scheme 32. Synthesis of (+) -Goniobutenolide.

Reagents and conditions: i) 4 eq. ethynylmagnesium chloride, THF, -78°C—22°C. (ii) TBSCl, imidazole, DMF, 22°C, 12 h. (iii) $Pd(Ph_3P)_2Cl_2$(0.05 eq.), (*Z*)-3-bromopropenoic acid(2 eq.), CuI, Et_3N, CH_3CN. (iv) THF, 3 N HCl, 22°C, 6 h.

CONCLUSION

As mentioned above the two ways to prepare styryl lactones are offered by chiral synthons using natural sources as starting materials and achiral materials using the asymmetric synthesis. In the past, most of the natural compounds of styryl lactones were reached by chiral synthons using natural sources, because they are rich and easy to use. On the other hand, it is without doubt that the asymmetric synthesis will continue to play more and more important role in the synthesis of natural products. The significant bioactivity and the unique structural features of these novel styryl lactones have prompted many research groups worldwide to develop new methods for the stereocontrolled synthesis of these compounds, showing in most cases excellent results. However, despite the variety of methods displayed, much effort remains to be done, dealing with the development of much more general and short routes.

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