ASYMMETRIC TOTAL SYNTHESIS OF ANTITUMOR STYRYL LACTONES AND RELATED NATURAL PRODUCTS

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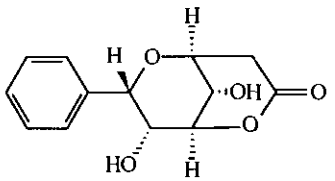
Abstract - Total synthesis of antitumor styryl lactones based on Sharpless asymmetric dihydroxylation and asymmetric epoxidation starting from methyl cinnamate and cinnamyl alcohol, respectively, was described. Synthesis of the natural asperlin and its related compound by peculiar kinetic resolution was also described.

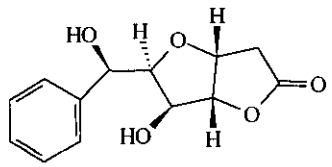
CONTENTS

1. INTRODUCTION

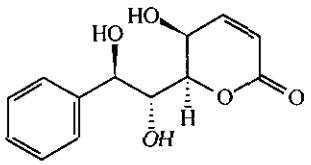
Styryl lactones are some new natural heterocyclic compounds isolated from *goniothalamus giganteus* (*Annonaceae*) and other plants, which have shown to have antitumor activity to several human tumor cells. Up to now, more than twenty styryl lactones have been isolated from plants, e. g.



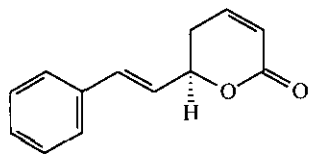
(+)-Goniopypyrone



(+)-Goniofufurone



(+)-Goniotriol



(+)-Goniothalamin

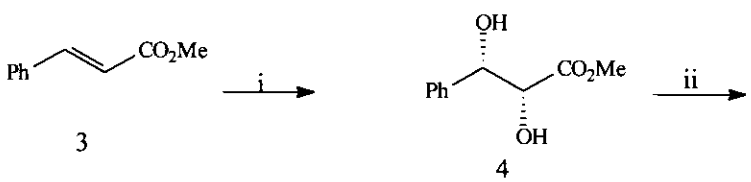
Figure 1

In these compounds, there are almost the same structure characteristics, that are: (a) with the part of styryl or styryl with functional groups; (b) with the part of α -pyranone or α -furanone (**Figure 1**).
Due to their excellent bioactivities and interesting heterocyclic structures, synthesis of these compounds soon become one of the hot research fields in the world. The synthetic strategies in the literatures are almost starting from chiral material, such as sugars, tartaric acid and 2,3-*O*-isopropylidene-D-glyceraldehyde.
In this review, we describe the asymmetric total synthesis of these natural products employing the Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation starting from methyl cinnamate and cinnamyl alcohol, respectively. A highly efficient peculiar kinetic resolution of unsymmetrical divinyl methanols by asymmetric epoxidation utilizing modified Sharpless epoxidation method have been discovered by us. This kinetic resolution produced two oxidation products with high ee value. A short synthesis of the natural asperlin and its related compounds by this kinetic resolution was also described.

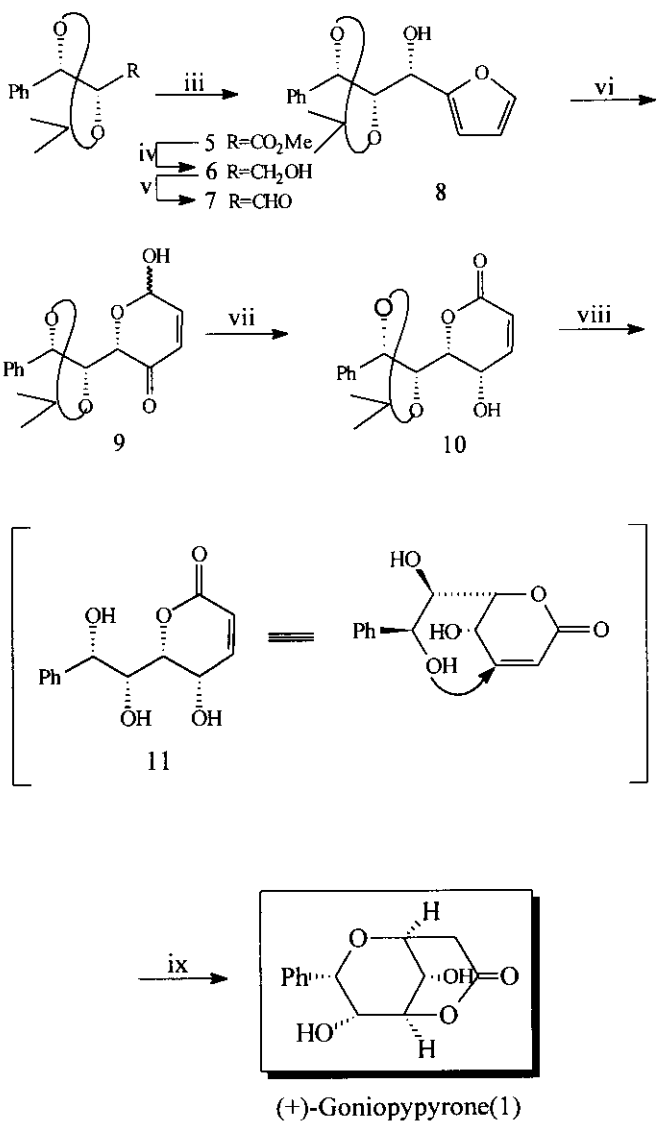
2. Synthesis based on Sharpless asymmetric dihydroxylation

2.1. Synthesis of (+)-goniopypyrone (**1**)[1] *and (+)-9-deoxygoniopypyrone* (**2**)[2]

The styryl lactones, (+)-goniopypyrone (**1**)[3] and 9-deoxygoniopypyrone (**2**),[4] were recently isolated from the stem bark of *goniothalamus giganteus* and shown to have significant cytotoxic activity.[4,5] Several groups have paid attention to synthesis of these two styryl lactones.[6-8] The synthetic methods, however, were almost all from carbohydrates[6] or 2,3-*O*-isopropylidene-D-glyceraldehyde[7,8] as the chiral materials. We planned to asymmetric total synthesis of **1** and **2** involving the asymmetric dihydroxylation of the inexpensive methyl cinnamate (**3**).
The synthetic route to **1** is depicted in the **Scheme 1**. Swern oxidation of **6** followed by immediate addition of 2-furylcopper,[9] prepared from furyl Grignard reagent and CuBr, to the liberated aldehyde (**7**) gave the *syn* adduct (**8**) (the ratio of *syn* to *anti* adduct was determined to be 98.7 : 1.3 by GC), whereas reaction of **7** with 2-furyllithium only gave 2.5 : 1 *syn* selectivity. Oxidation of the anomeric mixture of **9** with CrO_3-AcOH followed by stereoselective reduction of α,β-unsaturated lactone with $NaBH(OAc)_3$ in 1:1 mixture of isopropyl alcohol and acetic acid[7] at -10°C gave an unseparable mixture of hydropyanone (**10**), the ratio of the two isomers (α-OH and β-OH) was determined to be 9:1 based on the ^1H nmr analysis. Intramolecular Michael reaction of **11** was mediated by a catalytic amount of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) in THF to give **1**[3] in eight steps with an overall yield of 20%.



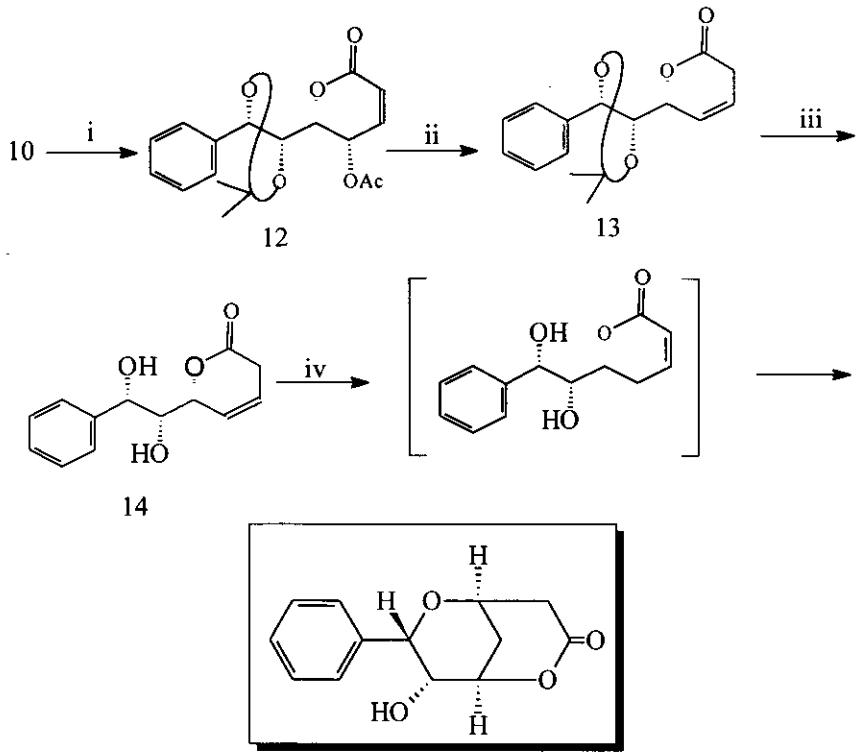
3 4



Scheme 1

Reagents and Conditions : i, OsO_4, DHQ-CLB, 92%; ii, $Me_2C(OMe)_2$, *p*-TsOH, 99%; iii, CuBr, $(C_4H_3O)MgBr$, 54% from **6**; iv, $LiAlH_4$; v, DMSO, $(COCl)_2$, Et_3N; vi, TBHP, $VO(acac)_2$, 87%; vii, 1. CrO_3, AcOH; 2. $NaBH(OAc)_3$, 65%; viii, AcOH, 90%; ix, 0.05%(v/v) DBU in THF, rt, 1 day, 85%.

To synthesize the (+)-9-deoxygoniopypyrone (**2**), the same intermediate (**10**) was used as starting material (**Scheme 2**). Acetylation of **10** with acetic anhydride followed by reductive deacetoxylation with zinc amalgam in etheral hydrogen chloride[10] furnished olefin (**13**) in 80% overall yield from **10**. Acid hydrolysis of the acetonide (**13**) with trifluoroacetic acid and water produced diol (**14**) in yield of 93%. Treatment of **14** with DBU in benzene directly provided title compound (**2**) by intramolecular Michael addition in yield of 67%.



Scheme 2

Reagents and Conditions : i, Ac_2O, Py-DMAP, CH_2Cl_2, rt, 1 h, 87%; ii, Zn-Hg, HCl in Et_2O, 0°C, 2 h, 92%; iii, CF_3CO_2H, THF, H_2O, rt, 93%; iv, DBU, C_6H_6, 80°C, 2 h, 67%.

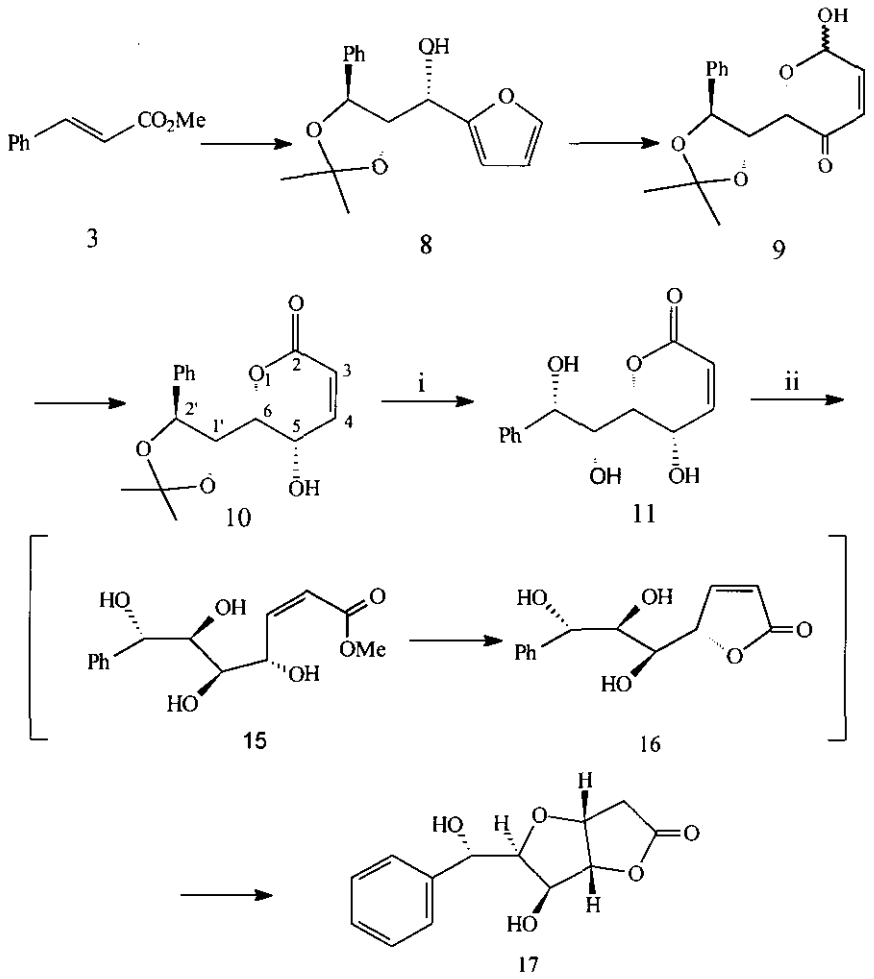
2.2 *Synthesis of (+)-8-epi-goniofufurone* (**17**)[11]

Recently, one of styryl lactones, (+)-8-*epi*-goniofufurone (**17**), was isolated from the stem bark of *goniothalamus giganteus* (*Annonaceae*)[4] and shown to have cytotoxic activity. The structure of (+)-8-*epi*-goniofufurone (**17**) has been established by both spectroscopy and X-ray crystallography,[4] and its absolute configuration has been determined to be that shown, based on the synthesis of its enantiomer, (-)-8-*epi*-goniofufurone, starting from sugars.[12,13] Herein, we present a convenient synthesis of (+)-8-*epi*-goniofufurone (**17**) from methyl cinnamate employing an intramolecular double cyclisation as the key step.

Our previous work has shown that methyl cinnamate (**3**) could be converted into highly *syn*-selective adduct (**8**), the anomeric mixture of **9** and the allyl alcohol (**10**).[1] The configuration of 5-OH in compound (**10**) was confirmed after deprotection with trifluoroacetic acid (THF-water) provided the known triol (**11**).[6] (**Scheme 3**)

In order to transform six-membered ring lactone (**11**) into five-membered ring lactone (**16**), we first tried acidic hydrolysis of **11** with HCl in THF, but no reaction occurred. Basic hydrolysis of compound (**11**) with 0.5 M NaOH followed by acidification of the resulting carboxylate with 1 M HCl unfortunately afforded the recovered lactone (**11**) as the major component. Finally, hydrolysis of the lactone (**11**) with 0.5 M NaOH followed by treatment with 1 M HCl and CH_2N_2 gave neither the expected ester (**15**) nor the lactone (**16**), but instead the (+)-8-*epi*-goniofufurone (**17**) directly, mp 194-195°C, $[\alpha]^{20}_D$ 103° (c 0.3 in EtOH) {lit.,[4] mp 190-192°C, $[\alpha]^{20}_D$ 108° (c 0.2 in EtOH)}. On a six -

membered α,β-unsaturated lactone, the intramolecular Michael reaction (forming the second six-membered ring) have to be initiated by a catalytic amount of DBU in THF.[1,7] However, this double cyclization (lactonisation and intramolecular Michael addition) that could be performed in one pot, may be due to the easy formation of the five-membered ring. We have stereoselectively synthesized (+)-8-*epi*-goniofufurone (**17**) from methyl cinnamate (**3**) in nine steps with an overall yield of 14%.



Scheme 3

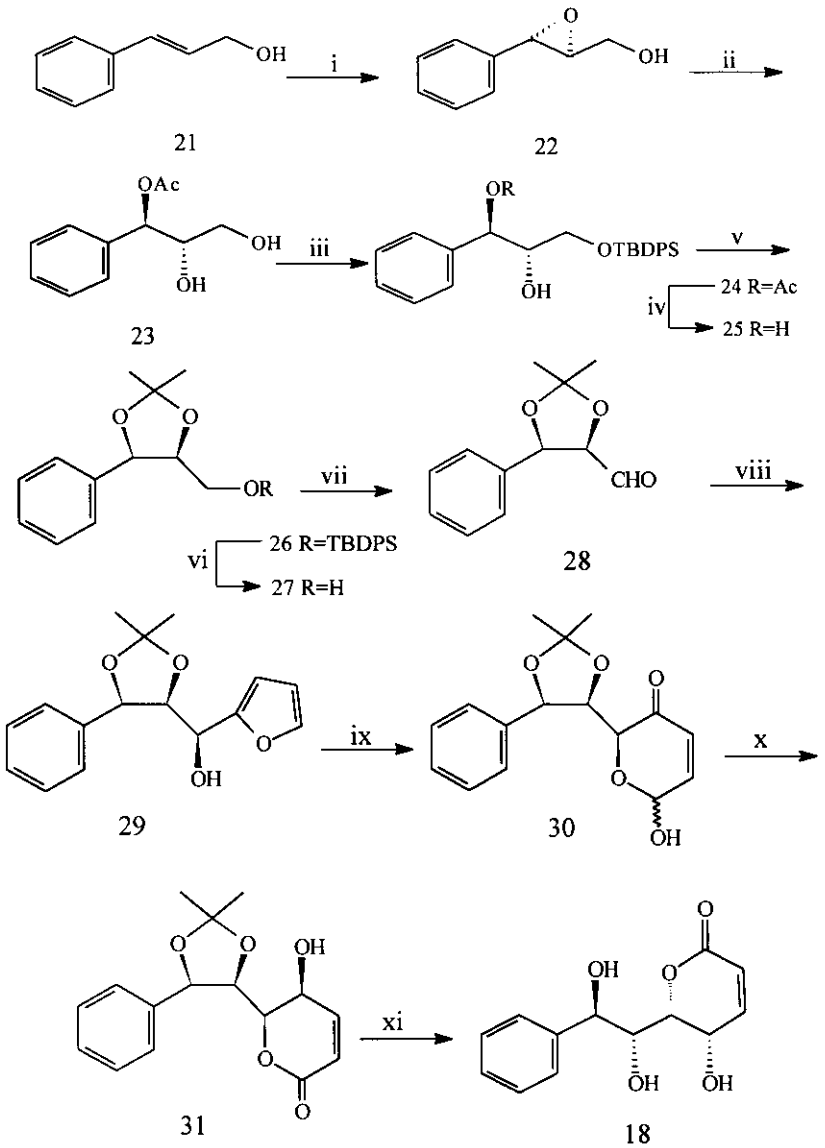
Reagents and Conditions : i, CF_3CO_2H, THF, H_2O, rt, 90%; ii, 0.5 M NaOH, rt, 20 min; then 1 M HCl, CH_2N_2, 60%.

3. Synthesis based on Sharpless asymmetric epoxidation

3.1. Synthesis of (+)-goniotriol (**18**),[14] *(+)-goniofufurone* (**19**)[14] *and (+)-8-acetylgoniotriol* (**20**)[15]

(+)-Goniotriol (**18**) was isolated from the leaves and twigs of *Goniothalamus sesquipedalis* (*Annoaceae*)[16] and from the stem bark of *Goniothalamus giganteus* (*Annonaceae*),[5] whereas (+)-goniofufurone (**19**) has been extracted from the stem bark of *Goniothalamus giganteus*.[3] Both of them were shown to have significant cytotoxic activities toward human tumor cells.[3,5] Because of their

cytotoxicity as well as the interesting heterocyclic skeletons, several groups have paid attention to the synthesis of these two styryl lactones.[8,17-19] We provided the enantioselective synthesis of goniotriol (**18**), goniofufurone (**19**) and (+)-acetylgoniotriol (**20**) from cinnamyl alcohol via asymmetric epoxidation and highly stereoselective 2- furyllithium addition.



Scheme 4

Reagents and Conditions: i, TBHP, L-(+)-DIPT, $Ti(OiPr)_4$, CH_2Cl_2, -20°C to 0°C, 86%; ii, $Ti(OAc)(OiPr)_3$, $CHCl_3$, -20°C to 0°C, 3 h, 90%; iii, TBDPSCl, imidazole, THF, rt, 24 h, 94%; iv, K_2CO_3, MeOH, H_2O, rt, 2 h, 85%; v, $MeC(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt, 8 h, 91%; vi, *n*-Bu_4NF, THF, rt, 2 h, 95%; vii, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C to -20°C; viii, 2-furyllithium, THF, -78°C to 0°C, 74% from **27**; ix, TBHP, $VO(acac)_2$, CH_2Cl_2, 0°C, 12 h, 86%; x, CrO_3, HOAc, 25°C to 30°C, 15 min; then, *i*PrOH, $NaBH(OAc)_3$, -5°C to 0°C, 69%; xi, TFA, THF, H_2O, rt, 90%.

The route to goniotriol (**18**) is illustrated in **Scheme 4**. The asymmetric epoxidation of cinnamyl alcohol (**21**) using Sharpless reagent[20] yielded 2,3-epoxy alcohol (**22**) in 86% yield. Highly regioselective cleavage of oxirane ring of **22** with tri(isopropoxy)titanium acetate[21] successfully afforded acetate (**23**) in 90% yield. Swern oxidation afforded aldehyde (**28**), which, due to its instability, was immediately treated with 2-furyllithium[22] to give the *syn*-adduct (**29**) as colorless prisms in 74% yield, together with the *anti*-adduct as an oil in 2.4% yield. The ratio of *syn* to *anti* adduct was *ca.* 30:1. The highly *syn*-selective addition of 2-furyllithium to **28** was due to the space obstruction of the phenyl ring, so that the 2-furyllithium could attack the carbonyl group from the back face of **28** (**Figure 2**).

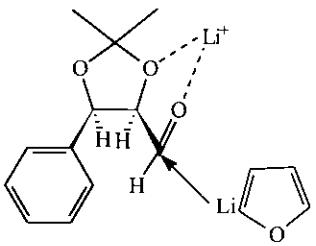
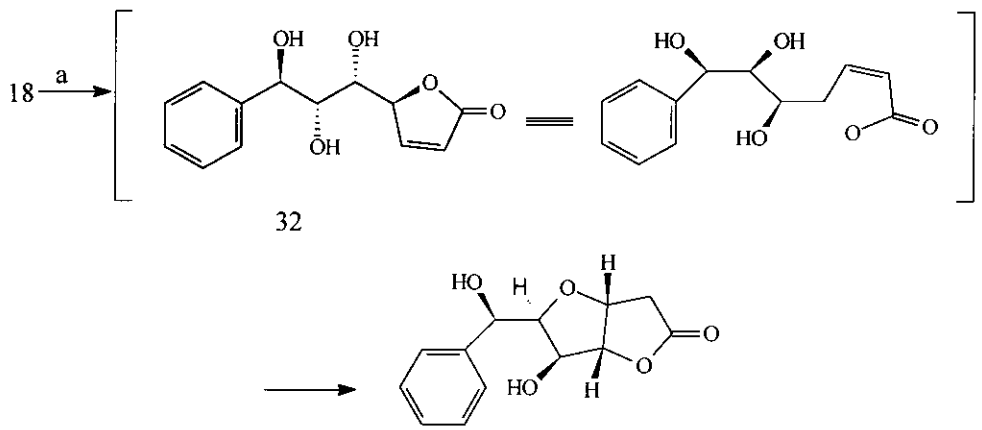


Figure 2

Finally, deprotection of **31** with trifluoroacetic acid smoothly provided the desired **18** (90% yield). Treatment of **18** with a catalytic amount of DBU in THF brought about the ring transformation to provide (+)-goniofufurone (**19**) directly.[8] The cyclization pathway probably involved a two-step sequence in which the six membered lactone was converted into the five-membered lactone (**32**) and then **32** was cyclized to form the bicyclic skeleton through an intramolecular Michael addition (**Scheme 5**).

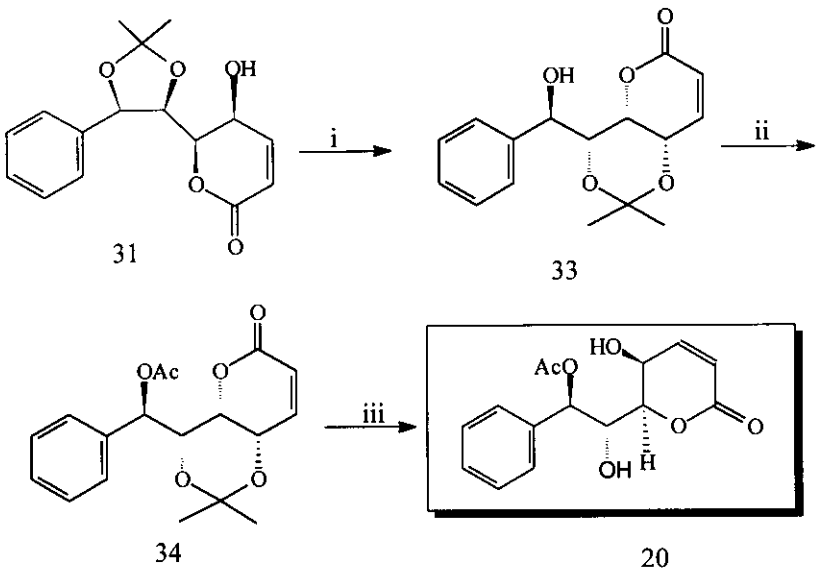


Scheme 5

Reagents and Conditions: a, DBU, THF, rt, 4 days, 56%.

The enantioselective synthesis of two styryl lactones, (+)-goniotriol and (+)-goniofufurone has been completed starting from cinnamyl alcohol in ten and eleven steps with an overall yield of 21% and 12%, respectively.

(+)-8-Acetylgoniotriol (**20**) was isolated from the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (*Annonaceae*),[3] which was shown to be cytotoxic to human tumor cells.[3] The absolute configuration of **20** has been confirmed by synthesis of **20** and its enontiomer from chiral starting material.[8,23] A stereoselective synthesis of this natural styryl lactone (**20**) from the same important intermediate (**31**). Treatment of **31** with *p*-toluenesulfonic acid in acetone gave the acetone group migrated product (**33**) in 80% yield. Acetylation of **33** with acetic anhydride produced the acetate (**34**) in 87% yield. Finally, acid hydrolysis of **34** yielded the (+)-8-acetylgoniotriol (**20**) in 85% yield (**Scheme 6**).

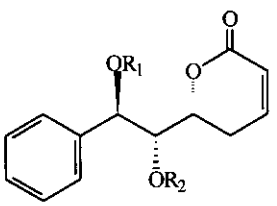


Scheme 6

Reagents and Conditions : i, *p*-TsOH, Me_2CO, rt, 2 days, 80%; ii, Ac_2O, Py, DMAP, CH_2Cl_2, rt, 2 h, 87%; iii, HOAc-H_2O (3:1), 70°C to 80°C, 4 h , 85%.

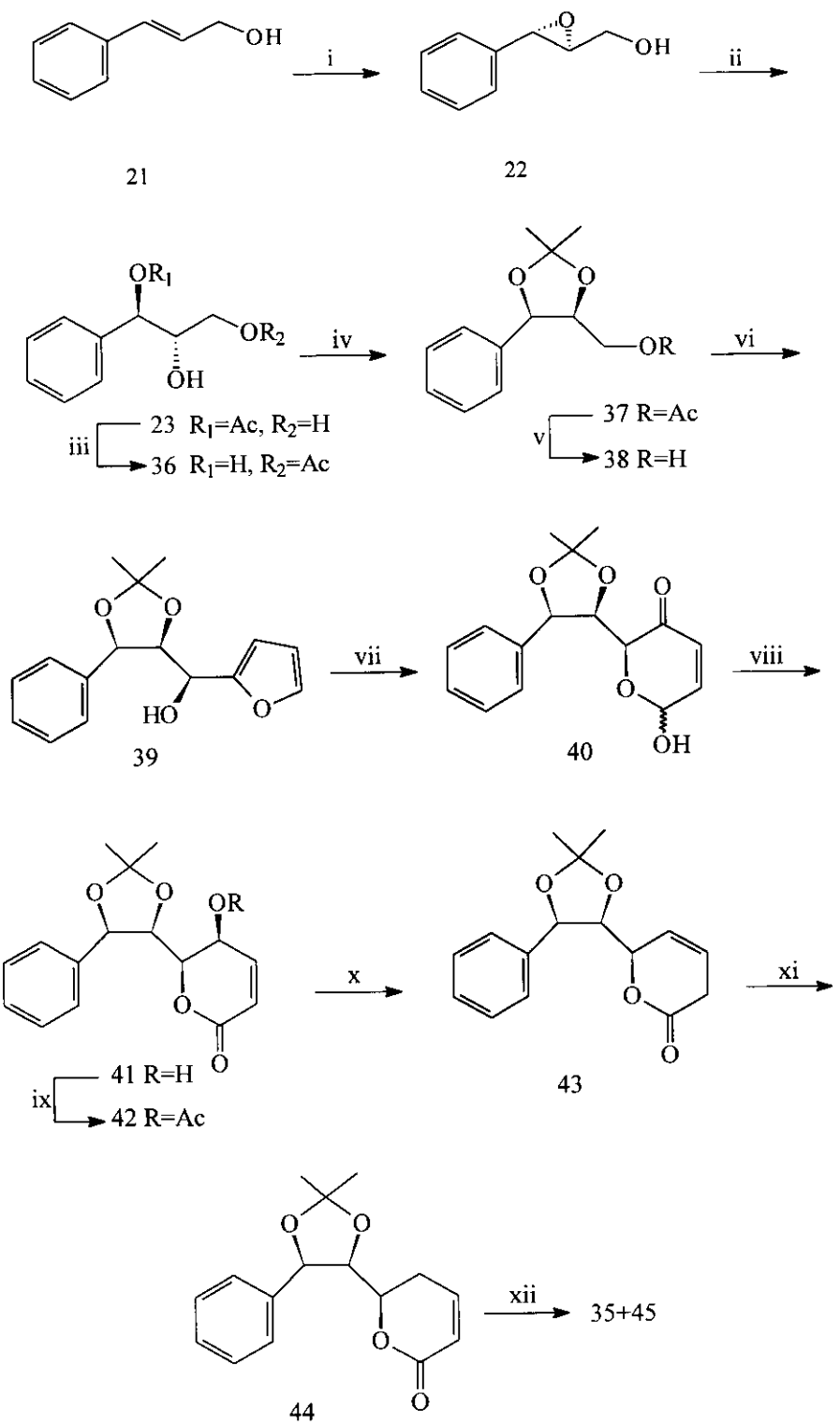
3.2. Synthesis of (+)-goniodiol-8-monoacetate (**35**)[24]

In 1992, a novel bioactive styryl lactone, goniodiol-8-monoacetate (**35**), was isolated from the leaves of *Goniothalamus amuyon*,[25] and shown to have significant cytotoxic activities toward several human tumour cells. The structure and relative configuration of **35** have been determined by spectroscopic studies.[25] As a part of our work on styryl lactones, we report herein the first asymmetric total synthesis of **35** (**Scheme 7**).



35 R_1=Ac, R_2=H

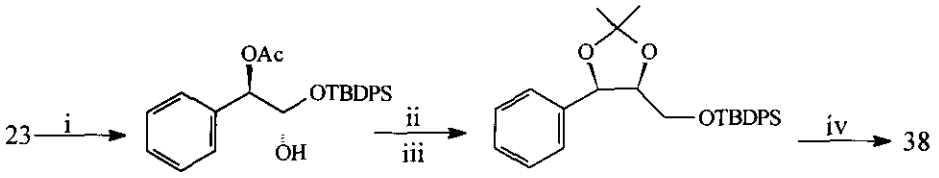
45 R_1=Ac, R_2=Ac


OH
i
O
OH
ii
21
22
OR1
OR2
OH
iv
O
O
OR
vi
iii
23 R1=Ac, R2=H
36 R1=H, R2=Ac
v
37 R=Ac
38 R=H
HO
O
vii
O
O
O
viii
OH
39
40
OR
x
xi
41 R=H
ix
42 R=Ac
43
xii
35+45
44

Scheme 7

Reagents and Conditions : i, TBHP, $Ti(OiPr)_4$, L-(+)-DIPT, 4 Å molecular sieves, CH_2Cl_2, -20°C, 86%; ii, $Ti(OAc)(OiPr)_3$, $CHCl_3$, -20°C to 0°C, 90%; iii, 1 M HCl, silica gel, THF, rt, 84%; iv, $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt, 8 h; v, 15% NaOH, THF, H_2O, rt, 90% from **36**; vi, Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C to -20°C then 2-lithiumfuran, THF, -78°C to -30°C, 74%; vii, TBHP, $VO(acac)_2$, CH_2Cl_2, 0°C, 84%; viii, CrO_3, HOAc, 25°C-30°C, 15 min; then $NaBH(OAc)_3$, *i*PrOH-HOAc (1:1), -10°C to rt, 60%; ix, Ac_2O, Py, DMAP, CH_2Cl_2, rt, 4 h, 98%; x, Zn-Hg, HCl, Et_2O, rt, 4 h, 87%; xi, DBU, C_6H_6, 80°C, 2 h , 85%; xii, TFA, H_2O, rt, 4 h, then Ac_2O, Py, DMAP, CH_2Cl_2, 0°C to rt, 44% .

Acid treatment of **23** which obtained from the same epoxide (**22**), with silica gel and HCl in THF caused the migration of the acetoxy group from the secondary to the primary hydroxy group to provide acetate (**36**) in 84% yield. Protection of the diol (**36**) with 2,2-dimethoxypropane followed by deacetylation with 15% aq. NaOH in THF afforded the alcohol (**38**) in 90% overall yield from **36,** 98% ee. The conversion of **23** into **38** by the route in **Scheme 8** gave a product with an identical $[\alpha]^{20}_D$. The optical purity of **38** was determined by GC (98% enantiomeric excess) on a chiral column (Cydex-B).



Scheme 8

Reagents and Conditions : i, TBDPSCl, imidazole, THF, rt, 84%; ii, 15% NaOH, THF, H_2O, rt; iii, $Me_2C(OMe)_2$, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2, rt; iv, *n*-Bu_4NF, THF, 0°C, 90% overall yield in two steps.

Swern oxidation afforded a unstable aldehyde, which was immediately treated with 2-furyllithium[22] to give the *syn*-adduct (**39**) as colourless prism in 74% yield, together with the *anti*-adduct as an oil in 2.4% yield. The *syn*-configuration in compound (**39**) was confirmed by X-ray diffraction analysis (**Figure 3**).

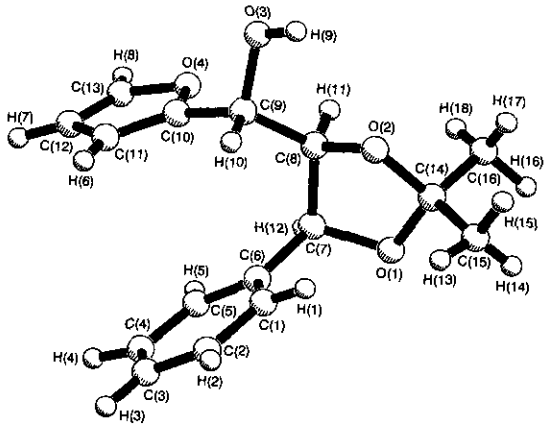


Figure 3 Molecular structure of **39**

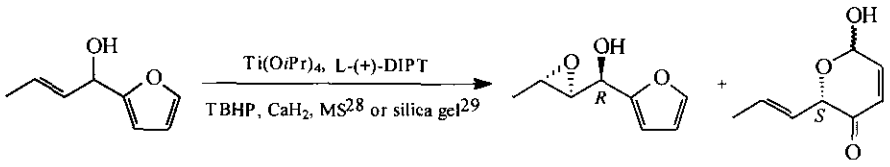
Oxidation of furylmethanol (**39**) with tert-butylhydroperoxide in the presence of $VO(acac)_2$ gave compound (**40**) as a mixture of α- and β-anomers. Oxidation of **40** with chromium (VI) oxide in acetic acid followed by immediate reduction with sodium triacetoxyborohydride[7] in one pot furnished the allyl alcohol (**41**) in 60% yield. Acetylation of **41** with acetic anhydride furnished the acetate (**42**) in 98% yield. Reductive deacetoxylation of acetate (**42**) with zinc amalgam in ethereal hydrogen chloride[10] gave the olefin (**43**) in 87% yield. Reconjugation of **43** with DBU produced the lactone (**44**) in 85% yield (reconjugation of **43** with triethylamine only gave poor yield), mp 133-134°C, $[\alpha]^{20}_D$ -100° (c 0.9 in EtOH). Hydrolysis of ketal (**44**) with trifluoroacetic acid and water (3:1) followed by acetylation of **44** with acetic anhydride afforded **35** in 44% overall yield in two steps, mp 110-111°C, $[\alpha]^{20}_D$ +44° (c 0.3 in $CHCl_3$), {lit.,[25] mp 111-113°C , $[\alpha]^{20}_D$ +43° (c 0.1 in $CHCl_3$)}, and another natural styryl lactone, goniodiol diacetate (**45**)[16] in 38% overall yield, mp 150-151°C, $[\alpha]^{20}_D$ +82 (c 0.5 in $CHCl_3$) {lit.,[25] mp 150 °C, $[\alpha]^{20}_D$ +84.5° ($CHCl_3$)}.

Since the spectroscopic data of the synthetic **35** are in accord with the data for natural **35**[25] and the X-ray diffraction analysis of **39** is determined, the absolute configuration of the goniodiol-8-monoacetate is confirmed as **35**.

4. Synthesis based on the peculiar kinetic resolution

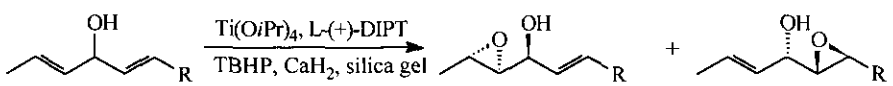
4.1. Peculiar kinetic resolution of the unsymmetric divinylmethanols[26]

After the asymmetric epoxidation of symmetric divinylmethanols has been described by several groups,[27] a peculiar kinetic resolution of racemic 2-furylmethanols was independently discovered by Honda[28] and us[29] *to produce two oxidation products* (**eq. 1**). We further did the systematic studies on kinetic resolution of unsymmetric divinylmethanols.[30]

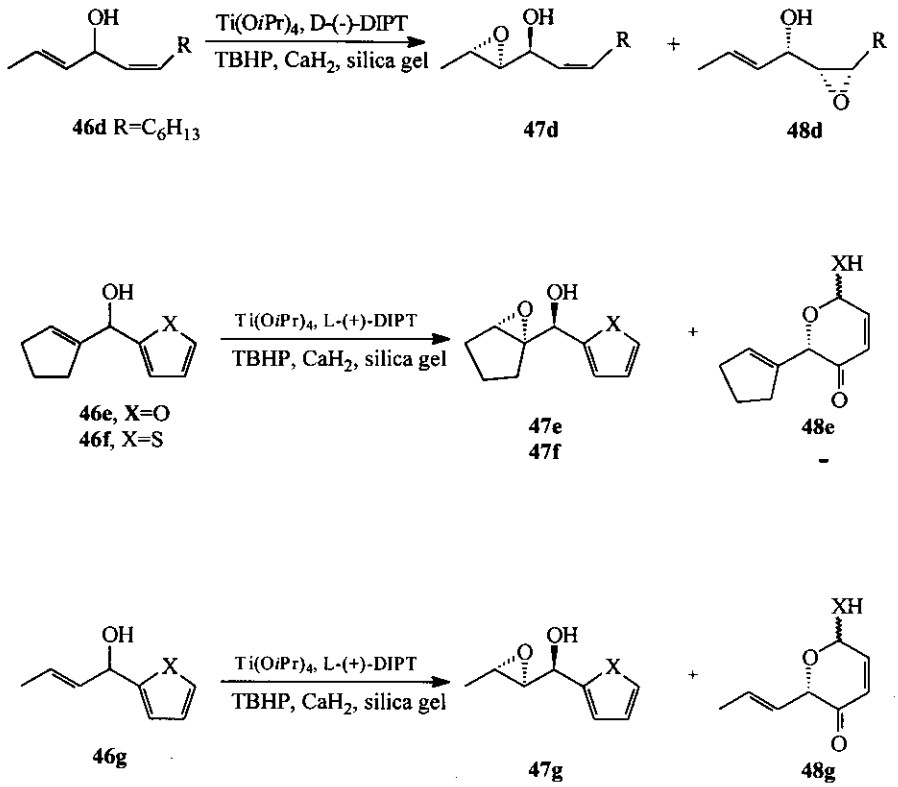


eq. 1

The kinetic resolution of **46a, b, c** under 0.5 eq. of tert-butylhydroperoxide (TBHP) in the presence of $Ti(OiPr)_4$ and L-(+)- or D-(-)-diisopropyl tartrate (DIPT) (**Scheme 9**) gave products (**47a, b, c** and **48a, b, c**) with both good yields and high ee values (Table 1). However, for **46d** the reaction produced **47d** with both high yield and high ee value, and only a trace amount of oxidation product (**48d**) was obtained, in which a *cis*-double bond was oxidized (Table 1). It may be due to the lower reaction activity of *cis*-double bond than that of *trans*- double bond. In experiment, we also found the double bond in five-membered ring in **46e** and **46f** was easy to be oxidized with good yields, but only low ee values were obtained (Table 1). The slow-reacting enantiomers became a complex mixture during work-up in kinetic resolutions. It can also be seen from the kinetic resolution of **46g** that the furyl ring is easier to be oxidized than normal double bond.[31]



46a, R=*n*-Hex **47a** **48a**
46b, R=*n*-Bu **47b** **48b**
46c, R=Ph **47c** **48c**



Scheme 9

Table 1. Kinetic resolution of **46a-f** (0.5 eq. of TBHP was used)[a]

substrate	DIPT	time	47			48		
			yield	ee[b]	conf.[c]	yield	ee[b]	conf.[c]
46a	L-(+)-	6 h	24.4%	> 95%	S	22.1%	> 95%	S
46b	L-(+)-	6 h	24%	> 95%	S	21%	> 95%	S
46c	D-(-)-	6 h	27.9%	> 95%	R	19.1%	> 95%	R
46d	L-(+)-	48 h	42.5%	> 95%	S	2.5%	82%	S
46e	D-(-)-	6 h	21.4%	65%	-	24%	-	-
46f	D-(-)-	6 h	35%	50%	-	-	-	-
46g	L-(+)-	6 h	4.5%	> 95%	R	33%	> 95%	S
46g	D-(-)-	6 h	4%	> 95%	S	32%	> 95%	R

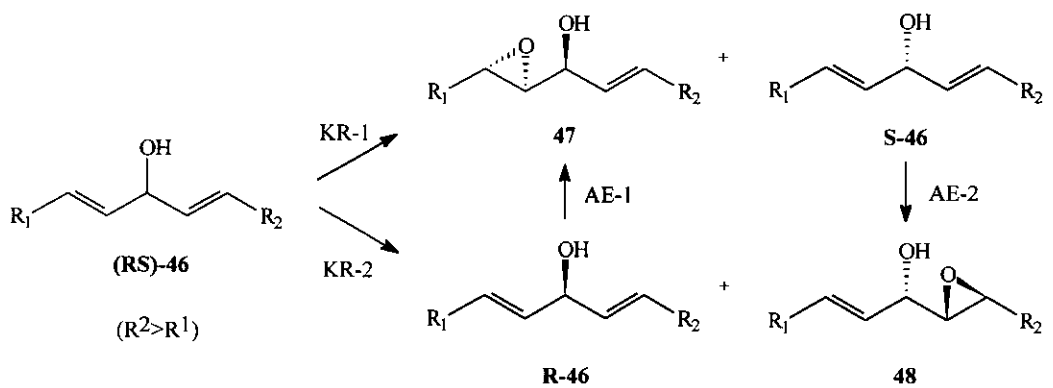
a. All reactions were carried out with 1.0 eq. of $Ti(OiPr)_4$, 1.2 eq. of DIPT in the presence of CaH_2 and silica gel at -25 °C. b. The ee values were determined by Mosher ester based on ^1H NMR (300 MHz) analyses. c. Determined by ^1H NMR (300 MHz) analyses of (R)- and (S)- Mosher ester.

When 1.0 eq. of TBHP was used, the reaction gave higher yield than that of 0.5 eq. of TBHP used, especially for those oxidation of the substrates with relative low active double bond, such as **48d** and **47g** (Table 2). It was noteworthy that the ee values were almost unchanged (Table 2).

Table 2. Kinetic resolution of **46a-f** (1.0 eq. of TBHP was used)[a]

substrate	DIPT	time	47			48		
			yield	ee[b]	$[\alpha]_D^{20}$ [c]	yield	ee[b]	$[\alpha]_D^{20}$ [c]
46a	L-(+)-	6 h	41.2%	> 95%	-20.4	41%	> 95%	-25.2
	D-(-)-	6 h	40.9%	> 95%	+21	40%	> 95%	+24.7
46b	L-(+)-	6 h	42%	> 95%	-24.8	40%	> 95%	-25.3
	D-(-)-	6 h	46.2%	> 95%	+25.7	44.1%	> 95%	+24.5
46c	L-(+)-	6 h	41.6%	> 95%	-46.5	32.2%	> 95%	-29.7
	D-(-)-	6 h	39.7%	> 95%	+46.4	30.4%	> 95%	+27.4
46d	D-(-)-	48 h	45.5%	> 95%	-20.9	23.5%	80%	+10.6
46e	L-(+)-	6 h	46%	50%	+5.1	42%	-	-
46f	L-(+)-	6 h	55%	46%	-2.4	-	-	-
46g	L-(+)-	6 h	30.3%	> 95%	-11	36.4%	> 95%	-
	D-(-)-	6 h	34%	> 95%	+11	33%	> 95%	-

a. All reactions were carried out with 1.0 eq. of $Ti(OiPr)_4$, 1.2 eq. of DIPT in the presence of CaH_2 and silica gel at -25 °C. b. The ee values were determined by Mosher ester based on ^1H NMR (300 MHz) analyses. c. All optical rotations were measured in ethanol (c = 1.0~2.0).



Scheme 10

Since there are two oxidized moieties in the racemic substrate (**46**), a double kinetic resolution (*KR*-1 and *KR*-2) was occurred (**Scheme 10**). When L-(+)-DIPT is used, the left double bond in substrate (**46**) could be oxidized by the chiral complex of $Ti(OiPr)_4$ and L-(+)-DIPT to provide the epoxy alcohol (**47**) and a slow-reacting enantiomer (**S-46**) (*KR*-1). Similarly, the right double bond in **46** could also be oxidized by the reagents to give the oxidation product (**48**) and another slow-reacting enantiomer (**R-46**) (*KR*-2). The

reaction rates of *KR*-1 and *KR*-2 depend on the reaction activities of the two double bonds. After the kinetic resolutions, further asymmetric epoxidations may also occur to convert **R-46** into **47** (*AE*-1) in which oxidation of the left double bond is matched with the chiral complex, while that of the right double bond is mismatched. In the same way, **S-46** may also be transformed into **48** (*AE*-2).
The absolute configurations of α-carbon of secondary alcohols were determined by ^{1}H nmr (300 MHz) analyses of (*R*)- and (*S*)-Mosher esters (**Figure 4**).[32]

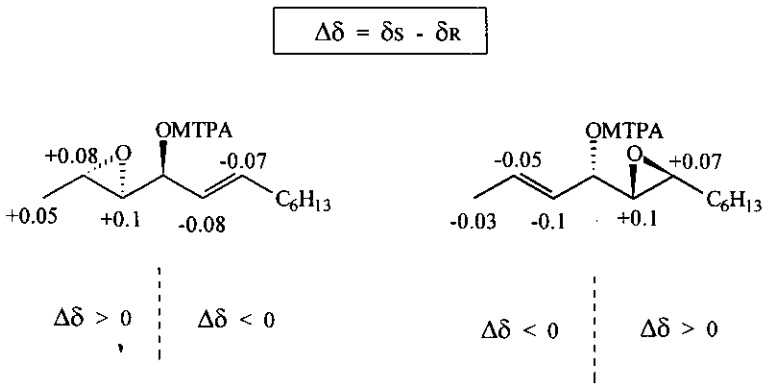
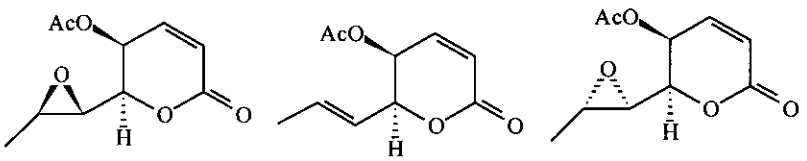


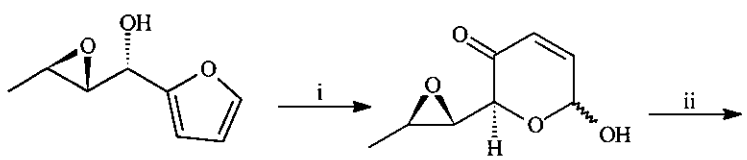
Figure 4

4.2. Synthesis of (+)-asperlin, (+)-acetylphomalactone and (5S,6S,7R,8S)-asperlin[29]
Based on this strategy, we next describe two short synthetic routes to natural asperlin (**49**) from (+)-**47g** and acetylphomalactone (**50**) and (5*S*, 6*S*, 7*R*, 8*S*)-asperlin (**51**) from (+)-**48g** (**Scheme11**).

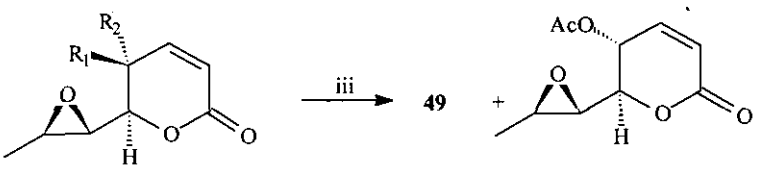


49 **50** **51**

(+)-Asperlin (**49**), as a crystalline metabolite isolated from *Aspergillus nidulans*[33] and *Aspergillus caespitosus*,[34] has shown to exhibit antitumor and antibacterial activity, while (+)-acetylphomalactone (**50**) and (+)-(5S,6S,7R,8S)-asperlin (**51**), which have shown anti-microbial activity, were also isolated from *Aspergillus caespitosus* together with (+)-asperlin (**49**).[34] Owing to the interesting bioactivities of these compounds, they have been synthesized by several groups.[35] Recently, a convenient synthesis of natural asperlin (**49**) starting from 2-furylmethanol (divinylmethanol) has been reported by Honda[28] and us,[29] independently. Now, we would like to further report the enantio-selective syntheses of (+)-asperlin (**49**) with related compounds, (+)-acetylphomalactone (**50**) and (+)-(5S,6S,7R,8S)-asperlin (**51**) based on this kinetic resolution of racemic unsymmetric divinylmethanols employing modified Sharpless reagents.[20]



(+)-47g **52**



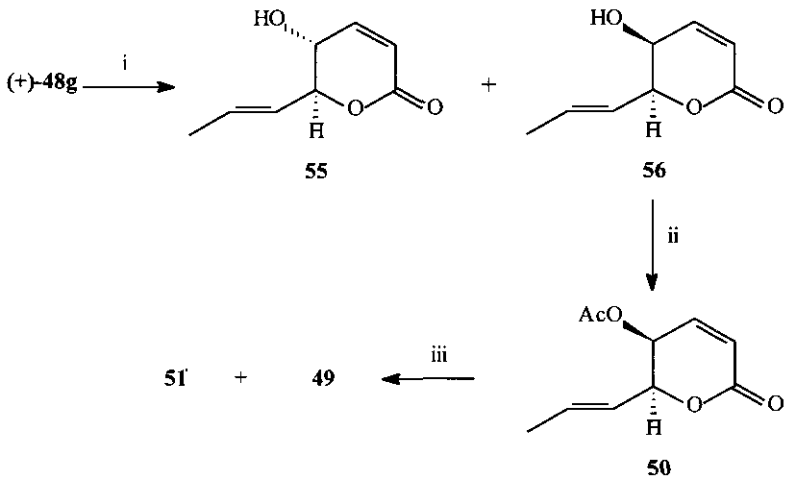
53a , R_1=OH, R_2=H
53b, R_1=H, R_2=OH

54

Scheme 11

Reagents and Conditions: i. TBHP, $VO(acac)_2$, CH_2Cl_2, 0°C, 74.5%; ii. CrO_3, HOAc, 25°C, 15 min; then $NaBH(OAc)_3$, HOAc, *i*PrOH, -5°C, 1 h; iii. Ac_2O, Py, DMAP, rt, 21% overall yield from **52** to **49** and 19% overall yield from **52** to **54**, respectively.

Oxidation of (+)-**47g** with TBHP in the presence of a catalytic amount of $VO(acac)_2$ afforded pyranone (**52**) in 74.5% yield as a mixture of α- and β-anomers, which was oxidized with chromium (VI) oxide, followed by immediate reduction with sodium triacetoxyborohydride in one pot to provide the alcohol (**53a** and **53b**) (**53a** : **53b** ≈ 1:1). Finally, acetylation of **53a** and **53b** with acetic anhydride gave (+)-asperlin (**49**) in 21% yield (from **52**), mp 70-71°C, $[\alpha]_D^{20}$ +330° (c 0.3 in EtOH) {lit.,[35d,34] mp 71°C, $[\alpha]_D^{20}$ +332° (EtOH)}, together with the 5-*epi*-asperlin (**54**) in 19% yield (from **52**), mp 80-81°C, $[\alpha]_D^{20}$ -186° (c 0.5 in EtOH) {lit.,[35d] mp 81-81.5°C, $[\alpha]_D^{20}$ -185° (c 0.5 in EtOH)}.
Another synthetic route to natural **50** and **51** from (+)-**48g** is shown in **Scheme 12**. Oxidation of pyranone [(+)-**48g**] by chromium (VI) oxide afforded **55** in 29% yield, together with **56** in 32% yield. Acetylation of **56** with acetic anhydride provided natural **50** in 75% yield. Finally, oxidation of **50** with *m*-CPBA yielded **49** (35 %) and **51** (19 %).



Scheme 12

Reagents and Conditions: i. CrO_3, HOAc, 25 °C, 15 min; then $NaBH(OAc)_3$, HOAc, *i*PrOH, -5 °C, 1 h, **55** in 29% yield and **56** in 32% yield, respectively; ii. Ac_2O, Py, DMAP, rt, 75%; iii. *m*-CPBA, CH_2Cl_2, rt, 48 h, **49** in 35% yield and **51** in 19% yield, respectively.

In summary, a highly efficient double kinetic resolution of unsymmetric divinylmethanols has been developed utilizing modified Sharpless reagent. This resolution can be used as a general method to provide two epoxy alcohols with three chiral centers and the utilizing of both of them as good chiral building blocks for syntheses of natural products was illustrated by the convenient syntheses of (+)-asperlin (**49**), (+)-acetylphomalactone (**50**) and (5*S*,6*S*,7*R*,8*S*)-asperlin (**51**).

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