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Progress in the Synthesis of Iridoids and Related Natural Products

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1. INTRODUCTION

A number of iridoids and secoiridoids which possess a wide range of biological activity have been isolated from plants and insects. For example, dihydronpetalactone, isodihydronepetalactone, iridomyrmecin, isoiridomyrmecin, neonepetalactone, nepetalactone, actinidine (iridoid alkaloid) and dihydroactinidiolide (carotenoid metabolite), the mixture being a potent attractant for cat, have been isolated from Actinidia polygama Miq. (Fig. 1). Similarly neomatatabiol, isoneomatatabiol, dehydroiridodiol, iridodiol and matatabiol have been isolated from the same plant and the mixture serves as a potent attractant for lacewing (Fig. 2) (1-3).

![Figure 1](attachment:image.png)
From a synthetic and biosynthetic point of view, dehydroiridodial, chrysomelidial and iridodial are considered to be the central intermediates for the biosynthesis of other iridoids from *Actinidia polygama* Miq.. The chemical interconversion of these iridoids has been demonstrated as shown in Scheme 1.

The broad diversity of both structure and biological activity exhibited by iridoids and seco-iridoids has generated much interest in their general synthesis starting from a common intermediate. We have developed two general methodologies for the synthesis of polyfunctional iridoids and related natural products. One approach involves the effective utilization of tricyclo[3,3,0,0^2,8]octanone derivative as a building block. This methodology enabled the efficient synthesis of loganin, chrysomelidial, forthyside aglycone and other cyclopentanoid natural products. The same methodology was independently developed by Demuth *et al.* (4) and widely utilized for the synthesis of iridoids and polyquinanes. Similar methodology utilizing [3,3,0]-octane derivatives has been known and successfully applied for the synthesis of iridoids (5). The second approach is the effective utilization of (+)-genipin as a chiral building block whose functionality is quite fit for the
synthesis of polyfunctional iridoids and related natural products. Furthermore, (+)-genipin is easily obtained by the enzymatic hydrolysis of geniposide with Cellulosin AC-40 and it can be supplied from industry in Kg scale. The alternative non-enzymatic efficient method which we developed is the hydrolysis of geniposide using hydroxymercuration followed by treatment with SnCl₂ or sodium 3-mercaptopropionate. The second methodology enabled the efficient synthesis of loganin, penstemide, didrovaltrate, plumericin, allamandicin, plumeride, gardenoside, garjasmin, asperuloside, cernibial, baldrical, secologanin, sweroside, gentiopicroside, kingiside, morronoside, sarracenin, petiodial and udoteatrial in optically active form.

\[ \text{geniposide} \xrightarrow{1) \text{Hg(OAc)}_2 \text{acetone-water}} \text{genipin} \xrightarrow{2) \text{SnCl}_2 \text{or HSC}_2\text{H}_4\text{CO}_2\text{Na}} \]

2. CHRYSMELIDIAL, LOGANIN AND FORSYTHEIDE

The increasing number of cyclopentanoid natural products and their interesting biological activity has stirred considerable interest into synthesis of such compounds. We have embarked upon the synthesis of polyfunctional iridoids via the same intermediate which may be easily obtained from an ordinary starting material. We selected tricyclo[3,3,0,0²₈]octanone as the versatile intermediate. Tricyclo[3,3,0,0²₈]octanone, obtained from photolysis of bicyclo[2,2,2]octenone or decomposition of 2-cyclopenten-1-yl diazomethylketone with cupric sulfate, was transformed with formic acid or p-toluensulfonic acid into functionalized bicyclo[3,3,0]octanone, which has a distinguishable functional group in the each five membered ring and can be led into cyclopentanoid natural products via the selective conversion of the functional group. We have applied this versatile intermediate, tricyclo[3,3,0,0²₈]octanone towards the synthesis of polyfunctional iridoids, chrysomelidial, loganin and forsythide.

2.1 Synthesis of Chrysomelidial(6) (Scheme 2)

Recently a new monoterpen dial, dehydroiridodial, was isolated as a pungent principle of *Actinidia polygama* Miq., and it was synthesized by K. Yoshihara et al. (7). On the other hand, chrysomelidial (1), the stereoisomer of dehydroiridodial, was isolated from the larval defensive secretion of a chrysomelide beetle (*Plagiodera versicolora*) in 1977, and it was synthesized in 1978 by J. Meinwald et al. (8). Both syntheses were non-stereospecific involving tedious separation steps.

We first attempted the stereocontrolled synthesis of chrysomelidial from 4-methyltricyclo[3,3,0,0²₈]octan-3-one (2) which was prepared from diethyl 2-cyclopentene-1-ylmalonate by the general method of Doering. Methylation of diethyl 2-cyclopentene-1-ylmalonate with methyl iodide followed by hydrolysis and decarboxylation afforded 2-(2-cyclopentene-1-yl)propionic acid in
79% yield. Conversion of this acid into its acid chloride followed by treatment with ethereal diazomethane furnished the diazo ketone 3 and the decomposition of the latter with cupric sulfate in refluxing cyclohexane yielded 4-methyl-tricyclo[3,3,0,0²,8]octan-3-one (2) in 83% overall yield.

![Chemical structures and reactions](image)

Scheme 2

Ring cleavage of 2 with 99% formic acid at 70-80 °C for 30 min followed by methanolysis and ketalization in the usual manner gave in 87% yield a mixture of the desired ketal (C₂-8 bond cleavage) and its structural isomer (C₁₂ bond cleavage) in a ratio of 4:1 by ¹H-NMR. The two isomers were easily separated by column chromatography. This desired ketal was oxidized with chromium trioxide-pyridine complex in methylene chloride to give the corresponding ketone 4 which, upon alkylation with methyl lithium in ether at -78 °C followed by treatment with p-toluenesulfonic acid in aqueous THF, afforded the ketoalcohol 5 in 81% yield. Refluxing of 5 with p-toluenesulfonyl hydrazine in methanol for 30 min produced the corresponding hydrazone in 93% yield. Treatment of this resulting hydrazone with excess n-butyl lithium in THF, followed by oxidation with osmium tetroxide in ether, and acetylation gave in 75% yield the stereoisomeric mixture of diacetates and
triacetate in a ratio of 83:14:3. Diacetates were treated with phosphoryl chloride in pyridine at 50 °C for 3 h to form in 97% yield a mixture of the desired tetra-substituted olefin and tri-substituted olefin in a ratio of ca. 15:85 by ^1H-NMR. Reduction of the tetrasubstituted olefin mixture with lithium aluminium hydride in ether followed by oxidation with sodium periodate in ether-water (1:1) at 4 °C for 24 h afforded chrysomelidial in excellent yields. The same oxidation of the trisubstituted olefin produced the hydrate 6, which was transformed into chrysomelidial by refluxing in 50% aqueous acetic acid in 99% yield. The diacetate was also converted to chrysomelidial by the same procedure.

2.2 Synthesis of Loganin Aglycone Silylether (Scheme 3)

Loganin was first isolated from Strychnos nux vomica and it is a widely distributed secondary plant metabolite (9). It has proven to be an important monoterpene in plant biochemistry due to the role in the biosynthesis of indole alkaloids and other natural products (10). We have employed the versatile intermediate 3 in the synthesis of loganin (11-12).

Reactions:
- a) HCO₂H; NaOMe
- b) ethylene glycol, p-TsOH; CrO₃, Pyr.
- c) TsNH₂; 89% from 2
- d) n-BuLi; CICO₂Me, 32%
- e) LDA; H⁺, 96%
- f) OsO₄; H⁺, 89%
- g) NaIO₄, 90%
- h) MeOH, cation exchange resin, 85%

Scheme 3

Reaction of 3 with p-toluenesulfonylhydrazine and molecular sieves (3A) in CH₃OH under reflux for 45 min gave the tosylhydrazone 7. Treatment of 7 with butyl lithium in N,N,N',N'-
tetramethylethylenediamine, followed by trapping of the produced vinyl anion with DMF gave the α,β-unsaturated aldehyde in 36% yield. Oxidation of the aldehyde with active MnO₂ in the presence of HCN in CH₃OH at room temperature for 18 h afforded the α,β-unsaturated ester 8 in 82% yield. On the other hand, direct conversion of 7 to 8 was also accomplished in 32% overall yield by treatment of 7 with BuLi and then trapping of the produced vinyl anion with methyl chloroformate instead of DMF. Deprotonation of 8 with lithium diisopropylamide in THF at -78 °C produced the lithium enolate of 8 in situ, which was kinetically protonated by exposure to aqueous acetic acid at 0 °C to give the β,γ-unstaurated ester 9 in 96% yield. Oxidation of 9 with OsO₄ in ether at 25 °C for 48 h, followed by decomposition with NaHSO₃, and deprotection of ethylene acetal with p-toluene sulfonic acid in aqueous THF at 30 °C for 24 h gave the dihydroxy-keto derivative, which was oxidized with sodium periodate in ether/water 1:1 at 4 °C for 24 h to afford dehydrologanin aglycone 10 in 81% yield. Dehydrologanin aglycone (10) was transformed into the corresponding 1-O-methyl derivative (11) in 85% yield by treatment with cation exchange resin in CH₃OH at 25 °C for 48 h. The ¹H-NMR and IR spectrum of the synthetic methyl ester 11 were consistent with those of the reported methyl ether; this methyl ester 11 has already been converted into (+)-loganin by Büchi et al. (12a). Thus, a new synthetic route to loganin was established.

2.3 Synthesis of Forsythide Aglycone Dimethyl Ester (Scheme 4)

We have now demonstrated the potential utility of 4-methyl-tricyclo[3,3,0,0²⁸]octan-3-one 4 as a versatile intermediate in the synthesis of chrysomelidal (6) and loganin. We next describe the stereocancrolled synthesis of (+)-forsythide aglycone dimethyl ester (12), starting from another versatile synthon, 4-methoxycarbonyl-tricyclo[3,3,0,0²⁸]octan-3-one (14). Forsythide (13) is a naturally occurring iridoid glucoside isolated from the fresh leaves of Forsythia viridissima Lindl. The key intermediate 14 was prepared from tricyclo[3,3,0,0²⁸]octan-3-one (13) by methoxycarbonylation with dimethyl carbonate and sodium hydride in dimethoxyethane at reflux temperature in 84% yield (Scheme 4). Although the cyclopropane ring of 2 or 13 could be cleaved with 99% formic acid at 70-80 °C to afforded the corresponding formate (C₂-8 bond cleavage) and its isomer (C₁-2 bond cleavage), in the case of 14 with a methoxycarbonyl group at C₄ position, only the C₂-8 bond was selectively cleaved with 99% formic acid in the presence of conc. sulfuric acid at room temperature to afford the desired formate. Subsequent treatment with sodium methoxide afforded the hydroxyl keto ester in 88% yield from 14. Deoxygenation of the ketone at the C₃ position was achieved by the thiketalization followed by reduction with Raney Ni (W-2). Thus, the hydroxyl keto ester gave the hydroxy ester 15 in 80% yield. Compound 15 was oxidized with Jones reagent to give the keto ester which was converted into the corresponding cyanohydrin by treatment with KCN and AcOH in EtOH at 30 °C in good yield. This was dehydrated with phosphoryl chloride in pyridine to give the α,β-unsaturated nitrile 16 in 84% yield. Compound 16 was hydrolyzed with potassium hydroxide in ethylene glycol at 160-180 °C to its dicarboxylic acid which was treated with diazomethane to give the corresponding diester in 79% yield. The diester was deprotonated with lithium diisopropyl amide-hexamethyl-phosphoramide complex in THF at -78 °C.
to produce the lithium enolate of the diester in situ, which was quenched with acetic acid to give the β,γ-unsaturated ester 17 in 84% yield (ratio: α/β/γ = 1.0/10.4 by 1H-NMR).

\[
\begin{array}{ccc}
13 & \xrightarrow{a} & 14 \\
\xrightarrow{b,c,d} & & \xrightarrow{e,f} \\
\end{array}
\]

\[
\begin{array}{ccc}
16 & \xrightarrow{g} & 17 \\
\xrightarrow{h} & & \\
\end{array}
\]

Ozonolysis of the mixture of 17 followed by reductive workup with Zn/AcOH directly led to (+)-forsythide aglycone dimethyl ester 12 after purification by preparative TLC as an oil. This was an epimeric mixture at the C1 position and was obtained in 66% yield (ratio: α-OH/β-OH = 3.5/1.0 by 1H-NMR). The stereocontrolled and facile synthesis of (+)-forsythide aglycone dimethyl ester 12 was thus achieved starting from the versatile synthon 14.

3. PENSTEMIDE AND DIDROVALTRATE

Penstemide was isolated from the methanol extracts of Penstemon deuts Dongl. ex Lindl. (Scrophulariaceae) by J. R. Cole et al. (14) in 1976 and its structure was revised to the present structure in 1979 (15). On the other hand, didrovaltrate was isolated from the Valeriana Wallichii D. C. in 1968 (16) and its correct stereochemistry including absolute configuration was established in 1973 by Thies et al. (17). Penstemide was found to exhibit activity against the P-388 lymphocytic leukemia test system and didrovaltrate is a very potent cytotoxic agent for the rat hepatoma cells and induces high percent definitive remissions of the Krebs II ascitic tumors (18).

3.1 The Synthesis of Penstemide Aglycone (Scheme 5)

Selective protection of hydroxyl groups of genipin with different protective groups followed by reduction of the methoxycarbonyl group with DIBAL and oxidation of resulting alcohol with BaMnO₄ yielded the aldehyde 18. Selective deprotection of the hemiacetal protective group followed by acylation with isovaleric acid in the presence of carbonyl diimidazole and DBU and reduction with
NaBH₄ furnished penstemide aglycone silylether 19 in very high yield. Glucosidation of the primary alcohol 19 followed by deprotection would lead to the synthesis of penstemide.

![Diagram of the synthesis of penstemide aglycone](image)

**Scheme 5**

### 3.2 The Synthesis of Didrovaltrate (Scheme 6)

Selective protection of the hydroxyl group of the hemiacetal of genipin followed by treatment with diphenyl disulfide in the presence of tri-n-butylphosphine yielded the phenyl thioether 20. To avoid the elimination of the more reactive primary hydroxyl group at the stage of acylation, two isovaleryl groups were introduced by the following sequence. The hydroxyl group of the hemiacetal was acylated first by the same procedure used as that in the synthesis of penstemide aglycone, and then the primary alcohol was acylated to yield diisovalerate 22. Oxidation of phenylsulfide to phenyl sulfoxide 23 followed by Evans' rearrangement and oxidation of the resulting allylic alcohol gave the exomethylene ketone 24 in high yield. Reduction of the ketone 24 to the β-hydroxy olefin 25 followed by Sharpless oxidation afforded the β-epoxy alcohol 26. Inversion of the β-hydroxyl group to α-acetoxyl group was successfully carried out by a SN2 reaction of triflate with acetate anion in the presence of 18-Crown-6 to accomplish the synthesis of didrovaltrate.
genipin  a, b, c  PhS-OTBDMS  d, e  R=OTBDMS  R=CH₃OH  f, g  R=OH  R=CHO

20: R=SPh

R=CHO  21: R=CH₂OH

22: R=PhS  23: R=PhSO

α-OH:β-OH=1:11

a) t-BuMe₂SiCl, AgNO₃  b) PPTS, 98% from genipin  c) (PhS)₂, n-Bu₃P, 94%  d) DIBAL, quant.  e) BaMnO₄, quant.  f) n-Bu₄NF, 94%  g) (Me)₂CHCH₂CO₂H, Im₂CO, DBU, 98% for 21 and 78% for 22  h) NaBH₄, CeCl₃, 90%  i) OXONE, 89%  j) (MeO)₃P, 87%  k) BaMnO₄, quant.  l) NaBH₄, CeCl₃, 95%  m) TBHP, VO(acac)₂, 89%  n) (CF₃SO₂)₂O, DMAP, CH₂Cl₂, -40 °C to -20 °C  o) AcOH, AcOK, 18-Crown-6, CH₂Cl₂-acetone, -20 °C to rt, 78%

Scheme 6
The fruits of *Gardenia jasminoides* Ellis are a Chinese traditional medicine used for treatment of hepatitis and hemafecia. During a screening test on antifertility agents from the flowers of this plant, J-P. Gu and R-S. Xu (19) isolated garjasmin and garjasmidin. Gardenoside (20) was isolated from *Gardenia jasminoides* f. grandiflora and other plants. Asperuloside (21) was isolated from *Asperua odorata* L.

\[
\begin{align*}
\text{gardenoside aglycone silyl ether} & \\
\text{asperuloside aglycone silyl ether} & \\
\end{align*}
\]

a) cat. OsO₄, NMO, t-BuOH:acetone:H₂O=10:3:1, 85%  b) 1.5 eq. Tf₂O, DMAP, CH₂Cl₂; DBU, 76%  c) PPTS, acetone-H₂O  d) 5 eq. n-Bu₄NF; p-TsOH, 53%  e) PPTS, acetone-H₂O, reflux, 50%  f) TBDMSO, Im, DMF, 93% from 28  g) 1 eq. KH, THF, 0 °C  h) DCC, DMAP, CH₂Cl₂, 85% from 30  i) PPTS, acetone:H₂O=3:1, reflux  j) Ac₂O, Pyr., DMAP, 54% from 31

Scheme 7
Garjasmin and asperuloside aglycone silyl ether were synthesized from genipin via gardenoside aglycone silyl ether (Scheme 7). Dihydroxylation of genipin disilyl ether \(27\) with osmium tetroxide followed by the selective elimination of the secondary alcohol via triflate gave disilyl ether of gardenoside aglycone \(28\) in good yield. Upon treatment of \(28\) with PPTS in aqueous acetone, the silyl group attached to the primary alcohol was first hydrolyzed to give gardenoside aglycone silyl ether. The prolonged reaction time, however, caused transposition of the tertiary hydroxy group to yield the desired C6 hydroxylated compounds as a mixture of stereoisomers \(29\) in about 3.6 to 1 ratio. This observed hydroxy transposition was significant in that the transposition of hydroxyl group in the proposed biosynthetic pathway (22) of gardenoside from geniposide proceeded in the opposite direction. The major isomer (\(\beta\)-hydroxy) was converted into asperuloside aglycone silyl ether as shown in Scheme 7. Treatment of the alcohol \(30\), obtained by silylation of the primary alcohol in \(29\), with potassium hydride in THF cleanly afforded the hydroxy acid, which was then lactonized with DCC to give the desired lactone \(31\). Finally hydrolysis of the silyl group to the primary alcohol followed by acetylation of the resulting alcohol completed the synthesis of asperuloside aglycone silyl ether. Garjasmin was synthesized from \(28\) by treatment with a large excess amount of TBAF (5 equiv.) followed by acidification with p-toluenesulfonic acid (p-TsOH) in 53% yield.

5. ALLAMANDICIN, PLUMERICIN AND PLUMIERIDE

In the course of a search for tumor inhibitors of plant origin, Kupchan et al. (23) isolated several iridoids from *Allamanda catharica* Linn (Apocyanaceae). These are allamandin, allamandicin, allamdin, plumericin and isoplumericin. Members of this class exhibit cytotoxic, antileukemic, antifungal and antimicrobial activities.

![Chemical structures](image)

**allamandicin**  **plumericin**  **plumieride**

**Synthesis of Allamandicin, Plumericin (Scheme 8), and Plumieride (Scheme 9)**

In 1983, Trost et al. (25) reported the synthesis of plumericin and allamandin by using the concept of substitutive spiroannulation and new carbomethoxylation of an enol ether starting from bicyclo[3,3,0]-octenone derivative. Allamcin (26), isolated from *Allamanda* sp. was synthesized by Pattenden et al. (27) in 1986 also starting from bicyclo[3,3,0]-octenon derivative. On the other hand,
a) Ac₂O, Pyr., CH₂Cl₂, 92%  b) Pd(PPh₃)₄, Ph₃P, THF; MeCOCH₂CO₂Me, NaH,THF, quant.  c) 2,2-Dimethyl-1,3-propanediol, p-TsOH, C₆H₆, 86%  d) cat. OsO₄, NMO, t-BuOH-acetone-H₂O, ~50%  e) NaOMe, MeOH, 94%  f) (CF₃SO₂)₂O/DMAP/CH₂Cl₂; DBU, 90%  g) Ph₃CBF₄, CH₂Cl₂, 78%  h) PhSeBr or PhSeCl, DMAP, CH₂Cl₂  i) H₂O₂, CH₂Cl₂, 80% from 35  j) n-Bu₄NF, 2 eq. AcOH, THF, quant.  k) Et₃SiH, TFA, 0 °C, 18 h, 40%  l) Et₃SiH, TFA, rt, 20 h

Scheme 8
Inoue et al. (28) succeeded in the synthesis of plumieride (24) from 10-dehydrogardenoside tetraacetate and ethylacetoacetate by a biomimetic route in 1979. In our synthesis of plumericin and allamandin, plumieride which was thought to be a biogenetic precursor (29) was selected as the key intermediate. We first attempted the coupling of genipin with methyl acetoacetate. Selective protection of the hydroxyl group of genipin hemiacetal followed by acetylation produced allyl acetate 32. Palladium π allyl complex mediated coupling reaction (30) of allylacete with sodium salt of methylacetoacetate produced the coupling product 33 in quantitative yield. Protection of the ketone as an acetal followed by reaction with osmium tetroxide yielded the dihydroxy compound 34. Both lactonization and dehydration proceeded in high yield by the treatment of 34 with sodium methoxide followed by treatment with trifluoromethanesulfonic anhydride, 4-dimethylaminopyridine and DBU. It is noteworthy that the use of trifluoromethane sulfonyl chloride gave the chloride by substitution.

Difficulty in a similar dehydration was reported in the synthesis of plumericin by Trost (31). Deprotection of the acetal protecting group proceeded well on treatment with tritylfluoroborate. The introduction of phenylselenyl group and selenoxide elimination also proceeded nicely to give an unsaturated keto lactone 36 (32). Reduction of the keto lactone 36 with triethylsilane in trifluoroacetic acid (33) furnished a mixture of plumieride aglycone silyl ether (41) and its epimer 42 (60:40) in 78% yield (Scheme 9). Desilylation of 36 with tetrabutylammonium fluoride (TBAF) in the presence of 2 equiv. of acetic acid followed by Michael addition of the alcohol produced the tetracyclic ether 37 in quantitative yield. The final step is the stereoselective reduction of the keto group to give allamandin. After many fruitless attempts, it was found that this reaction was best performed by the reduction with triethylsilane in CF₃CO₂H at 0 °C to accomplish the synthesis of (+)-allamandin. In this case (+)-epi-allamandin (38) and (+)-iso-allamandin (39) were also obtained. Any reductions in basic conditions gave fruitless results. When this reduction was carried out at room temperature, a mixture of (+)-plumericin and (+)-iso-plumericin (40) (75:25) were obtained in 50% yield. Dehydration of a mixture of allamandin and epi-allamandin (38) (75:25) with phosphoryl chloride afforded a mixture of (+)-plumericin and (+)-iso-plumericin (40) (75:25) in 83% yield.

![Scheme 9](image-url)
6. CERBINAL AND BALDRINAL

Cerbinal (43) (34), a yellow pigment, was isolated from the bark of Cerbera manghas L. in 1977. It was later isolated from Gardenia jasminoides Ellis again in 1986 (35). Cerbinal was reported to show antifugal activity against Bipolaris sorokiniana, Helminthosporium, Pyricularia, Colletotrichum lagenarium and Puccinia species. At concentrations of 0.75-4 µg/ml, 43 caused 100% inhibition of germination of spores of Puccinia species on oat, wheat, Welsh onion and white clover. The interesting thing is that both plants are used as traditional medicinal herbs. Cerbinal has been recognized by its characteristic Δ3,5,7,9-tetraene 10π aromatic system (a unique cyclopentadieno[c]pyran ring system). This unusual iridoid structure can also be found in baldrinal (44) (36), viburtinal (45) (37) and halitunal (46) (38). Baldrinal (44) was isolated from the roots of Valeriana wallichii D.C., which was recently found to exhibit potent cytotoxicity in vitro against HTC hepatoma cells and anti-tumor activities in vivo against KREBS II ascitic tumor, while viburtinal was isolated from the leaves of Viburnum tinus and Viburnum opulus (Carpirifoliaceae). Its dried leaves have been traditionally used as a spasmolytic, in indigenous medicine. Halitunal (46), a novel diterpene aldehyde also possessing a unique cyclopentadieno[c]pyran ring system was also isolated from the marine alga Halimeda tuna. Halitunal was reported to show antiviral activity against murine coronavirus A59 in vitro.

\[
\begin{align*}
\text{cerbinal (43)} & \quad \text{baldrinal (44)} & \quad \text{viburtinal (45)} \\
\includegraphics[width=0.3\textwidth]{cerbinal.png} & \includegraphics[width=0.3\textwidth]{baldrinal.png} & \includegraphics[width=0.3\textwidth]{viburtinal.png}
\end{align*}
\]

halitunal (46)

In this section we would like to describe an efficient synthesis of 43 and 44 from (+)-genipin. It is anticipated that the introduction of the double bond at the C1-C9 position would make the dehydrogenation of C5-H and C6-H feasible to result in the formation of the desired aromatic system. We have been reported (39) the first synthesis of 43 from genipin. To approach the synthesis of other compounds involving the same aromatic system with different side chains, we needed to obtain 43 more conveniently and efficiently. We therefore tried to find a more efficient synthetic route to get this key compound.
The silylation of genipin with t-butyldimethylsilyl chloride in the presence of imidazole gave the monosilyl ether 47 quantitatively (Scheme 10). For the subsequent dehydration, we then tried to convert the hydroxy group of 47 into several leaving groups. However it was difficult to get compounds with leaving groups on the hemiacetal carbon, because of the instability of intermediates. We found that the thioimidazolide (40) underwent thermal decomposition smoothly to give the eliminated compound. Thus, treatment of 47 with 1,1'-thiocarbonyldiimidazole in benzene afforded the thioimidazolide. Since the product was too unstable for isolation, it was then heated up in refluxing benzene giving rise to the key intermediate 48. Upon treatment of 48 with DDQ in benzene, the expected dehydrogenation between C5-C6 and oxidation of the allylic carbon occurred to give 43 as yellow needle crystals in 37% overall yield. All the experimental procedures could be carried out in a one-pot procedure and under mild conditions. Considering this successful synthetic route, the synthesis of cerbinal 43 would be hope to up to an industry scale.

![Scheme 10](image)

a) t-butyldimethylsilyl chloride, imidazole, CH₂Cl₂, 100% b) 1,1'-thiocarbonyldiimidazole, benzene, rt, overnight c) AIBN, benzene, reflux, 3 h d) 1.5 eq. DDQ, benzene, rt, 1 h, 37% from genipin e) 2, 2-dimethyl-1, 3-propanediol, cat. PPTS, benzene, reflux, 2 h, 88% f) DIBAL, THF, -78 °C, 42%, recovery 23% g) Ac₂O, Pyr., 86% h) cat. PPTS, THF-H₂O, rt, 2 h, 66%

Protection of the aldehyde moiety in 43 with 2,2-dimethyl-1,3-propanediol in the presence of a catalytic amount of a weaker acid PPTS was achieved to afford 49. Treatment of 49 with DIBAL/THF at -78 °C successfully afforded the key intermediate 50 in 42% yield. Although four
equivalents of DIBAL were used, the activity of DIBAL decreased because of the use of THF as a solvent, and it led to the recovery of 49 in 23% yield. Subsequent acetylation of 50 gave 51 in good yield. Deprotection of 51 with catalytic amount of PPTS successfully afforded baldrinal in 66% yield. It seemed that this cyclopentadieno[c]pyran ring system was very unstable in the presence of nucleophiles under acidic or basic conditions. We found that in the presence of a primary amine such as benzylamine, 43 quickly reacted with 2 equivalents of amine to give unknown derivatives. However in the case of over 5 equivalents of benzylamine, an O/N exchange very quickly occurred to give a cyclopenta[c]pyridine derivative (52) (Scheme 11). This result was also found in baldrinal.

(41) To our surprise, cerbinal did not show any cytotoxicity against several human carcinomas.

![Scheme 11](image.png)

As described above we have developed a general method for the efficient synthesis of cerbinal involving a cyclopentadieno[c]pyran ring system. Using cerbinal as a building block, we have successfully achieved the synthesis of baldrinal. This synthetic scheme helped us to gain a lot of information about the chemical properties and biological activities of this unique aromatic system. This synthetic scheme may be applied to the synthesis of 45 and 46 as well as an unnatural 10 π iridoids to investigate their structure-activity relationship in their biological activities, especially their antitumor activity.

7. SECOIRIDOIDS

7.1 Secologanin, Sweroside and Gentiopicroside (Scheme 12)

Secologanin was isolated from *Lonicera morrowii* A. Gray (kingimboku) by Mitsuhashi *et al.* in 1970 (42) and has considerable biosynthetic significance, because it is the common non-nitrogenous precursor to a vast and diverse array of indole alkaloids (43). Secologanin is biosynthesized via loganin by C7,8 cleavage of the five membered ring.

The biomimetic fragmentation approach to the synthesis of secologanin has been employed by L. F. Tietze (44) and J. J. Partridge (45). We have applied the oxidative fragmentation of γ-hydroxy alkylstannane with lead tetraacetate, which was previously developed in our laboratory, (46) to the synthesis of brefeldin A.
The monosilyl ether 53 was obtained from genipin by disilylation of the primary hydroxyl group and the hemiacetal, followed by selective desilylation of the primary hydroxyl group with PPTS in 98% yield. This simple procedure was very useful for both regioselective and stereoselective protection of the hydroxy group of the hemiacetal in genipin. Allylic rearrangement of the free hydroxyl group of 55 was achieved by Evans rearrangement. Thus 53 was converted to a thioether, which was oxidized to give the sulfoxide. Thermal rearrangement of the resulting sulfoxide proceeded smoothly to give the alcohol 54, which was subjected to oxidation, yielding the exomethylene ketone 55.

It is well known that trialkylstannyl lithium normally adds to α,β-unsaturated ketone to give the formal 1,4-adduct in excellent yield (48). However, treatment of 55 with tributylstannyl lithium gave the desired 1,4-adduct in only 23% yield along with the dimeric product. The dimer might be formed by 1,4-addition of the α-anion of 55 to the starting exomethylene ketone. Presumably tributylstannyl lithium acted as base. When triphenylstannyl lithium was allowed to react with the exomethylene ketone 55, however, the normal 1,4-adduct 56 was obtained in 70% yield. After reduction of 56, treatment of the resulting alcohol with lead tetraacetate did not afford any secologanin aglycone-O-methyl ether. Presumably, electron withdrawing phenyl groups decrease the electron density on the tin atom causing destabilization of the β-carbonium ion or radical intermediate. Hypercovalent bond formation of tin with γ-hydroxy group may also retard the fragmentation reaction.

Thus, it was necessary to find an effective reagent which gives the 1,4-adduct of tributyltin to the cisoid enone such as 55. Attempts to use ate complexes, (PhSCuSnBu3)Li+ and n-Bu3SnCu+Me2S-LiBr (49) also gave the desired ketone in low yield. The dimeric product was formed as a by-product. Fortunately, it was found that (trimethylsilyl)tributylstannane was an excellent reagent for 1,4-addition of tributyltin group to cisoid enone (50). Thus, the exomethylene ketone 55 reacted cleanly with the above reagent in the presence of both a catalytic amount of KCN and 18-crown-6 to afford the desired silyl enol ether which was subjected to selective removal of trimethylsilyl group with t-Bu4NF in the presence of acetic acid. The keto stannane 56 was obtained in high yield from 55. Finally, the synthesis of secologanin aglycone-O-silyl ether (58) was achieved by reduction of 56 followed by oxidative fragmentation with lead tetraacetate. It should be noted that in contrast to Grob type fragmentation (44) this oxidative fragmentation proceeded from both cis and trans isomers in respect of the hydroxyl and tributylstannylmethyl groups of 57. Sweroside aglycone-O-silyl ether (59) was obtained by the reduction of secologanin aglycone silylether (58) with sodium borohydride quantitatively.
Scheme 12

a) mCPBA, CH₂Cl₂, -78 °C, 89%  
b) (MeO)₃P, MeOH, reflux, 98%  
c) BaMnO₄, CH₂Cl₂, rt, 94%  
d) TMS-SnBu₃, KCN, 18-crown-6, THF, -20 °C  
e) Bu₄NF·3H₂O, 2 eq. AcOH, THF, 0 °C, 80% from 55  
f) NaBH₄, MeOH, rt, 96.5%  
g) Pb(OAc)₄, CaCO₃, benzene, reflux, 80%  
h) NaBH₄, MeOH, rt, ~99%  
i) piperidine, benzene, reflux; PhSeBr, THF, -78 °C, 91%  
j) aq. MeOH, NaIO₄, rt, 72%  
k) NaBH₄, MeOH, rt  
l) cat. NaOMe, hv, sens., 74%
Gentiopicroside, which is the principal bitter glucoside of common gentians, was isolated in 1862 (51) and has been widely used as stomachic or antidote from ancient times. The instability of the gentiopicroside made its structure elucidation extremely difficult (52). Inoue suggested that gentiopicroside could be biosynthesized via sweroside and swertiamarin (53). Secologanin aglycone silyl ether (58) was converted to its enamine with piperidine and phenyl selenyl group was introduced into the α position of the aldehyde to give 60 in 91% overall yield. Oxidation of 60 with NaI04 gave the α,β-unsaturated aldehyde 61 in 72% yield. Treatment of 61 with NaBH4 in methanol resulted in the formation of gentiopicroside aglycone-α-silyl ether (63) (20%) contaminated with the allyl alcohol 62 (38%). We attempted the conversion of the allyl alcohol 62 into gentiopicroside aglycone silyl ether (63) by the photosensitized isomerization of the double bond in the presence of a catalytic amount of base (54). Irradiation of 62 in the presence of both catalytic amount of NaOMe as base and 2-acetonaphthone as sensitizer at 0 °C resulted in the formation of the desired gentiopicroside aglycone silyl ether (63) in good yields. Similar irreversible photoisomerization was carried out in the synthesis of manoalide as shown below (55).

\[ \text{seco-manooolide} \xrightarrow{hv\text{ quant.}} \text{manoalide} \]

### 7.2 Kingiside, Morronoside and Sarracenin (Scheme 13)

Secologanin, kingiside, morronoside and sweroside have been isolated from Lonicera morrowii A. Gray by Souzu and Mitsuhashi (42, 56). Considering the fact that these four glucosides coexist in the same plant, these compounds are supposed to be biogenetically close congeners as suggested by Inoue (22). Since kingiside is biosynthesized via secologanin, we therefore attempted first to synthesize kingiside aglycone-α-silyl ether (64) from secologanin aglycone silyl ether (58). Secologanin aglycone silyl ether (58) was oxidized to give the corresponding carboxylic acid. PhSeBr was found to be an excellent reagent for lactonization. Deselenylation of the selenolactone with triphenylstannane gave a lactone, which was assigned as epi-kingiside aglycone silyl ether (69). Selenolactonization under equilibrium conditions ensured the formation of the thermodynamically more stable selenolactone (57). In order to control C8 stereochemistry, we tried an alternative route. The exomethylene ketone 55, which was also a key intermediate in the synthesis of the secologanin aglycone (58), was hydrogenated to give the cyclopentanone 65. The stereochemistry was completely controlled by the approach of the catalyst from the convex face of 55. The Baeyer-Villiger oxidation of the labile cyclopentanone 65 gave the kingiside aglycone-α-silyl ether (64). Morronoside aglycone-α-silyl ether (67) was obtained by chemoselective reduction of kingiside aglycone-α-silyl ether (64) with excess diborane. Reduction of 64 with 1 eq. DIBAL at -78 °C, however, afforded a mixture of the starting material and the diol. Desilylation of 67 followed by cyclization under acidic condition furnished (-)-sarracenin. 8-Epi-sarracenin was also synthesized.
from 8-epi-kingside aglycone silylether via 8-epi-morronoside silylether by the same procedure. Isomerization of 65 with DBU gave dehydrologanin aglycone silylether (66), which was also transformed to 8-epi-kingside aglycone silyl ether (69), 8-epi-morronoside aglycone silylether (70) and 8-epi-sarracenin (71) by the same procedure.

\[
\begin{align*}
55 & \xrightarrow{a} 65 & \xrightarrow{b} 64 \\
& \xrightarrow{c} 66 & \xrightarrow{d} 67 & \xrightarrow{e,f} 68 \\
& \xrightarrow{b} 69 & \xrightarrow{d} 70 & \xrightarrow{e,f} 71
\end{align*}
\]

\[\begin{array}{c}
\text{OTBDMS} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{OTBDMS} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{OTBDMS} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{OTBDMS} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{OTBDMS} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{OTBDMS} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{OTBDMS} \\
\text{H} \\
\text{CO}_2\text{Me}
\end{array}\]

\[
\begin{array}{c}
\text{dehydrologanin aglycone silylether} \\
\text{morronoside aglycone silylether} \\
\text{sarracenin} \\
\text{8-epi-kingside aglycone silylether} \\
\text{8-epi-morronoside aglycone silylether} \\
\text{8-epi-sarracenin}
\end{array}\]

a) H\textsubscript{2}, cat. Pd-C, EtOH, rt  b) mCPBA, Na\textsubscript{2}HPO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, rt, 56% from 55  c) DBU, CH\textsubscript{2}Cl\textsubscript{2}, 90%  d) BH\textsubscript{3}, THF, rt, 56%  e) Bu\textsubscript{4}NF, THF  f) TsOH, CH\textsubscript{2}Cl\textsubscript{2}, 79% from 67

Scheme 13
Udoteal, a marine linear diterpene, is considered to be a key intermediate for the biosynthesis of petiodial, udoteatrial, halimedatrial, halimedalactone and halitunal having an iridoid framework. On the other hand, seco-manoalide, a sesterterpene having a γ-hydroxy butenolide ring, is considered to be formed from a linear sesterterpene whose functionality is very similar to udoteal. It may be possible to think that synthetic seco-manoalide analogue, which is a remarkable phospholipase A2 inhibitor, will be isolated in the future.
8.1 Petiodial (Scheme 14)

(-)-Petiodial was isolated from the marine algae, *Udotea petiolata*, collected in Naples (58) and from *Udotea Flabellum* (59) in Carribean independently. This monocyclic diterpenoid dialdehyde shows significant biological activities against several marine bacteria, inhibits of cell division in fertilized sea urchin eggs, and is toxic to herbivorous damselfish causing death within one hour. Besides petiodial, the diterpenoids udoteatrial (60) and halimedatrial (61) have been reported possessing similar structures. The absolute configuration of these compounds has not been determined, and in the case of petiodial the relative stereochemistry has also not been reported yet. In the biosynthesis of these diterpenoids, the corresponding linear diterpene udoteal, isolated from the algae, was suggested to be the biogenetic precursors (61). In this section the first efficient synthesis (62) of optically active petiodial and determination of its absolute structure (65, 7R) has been described.

For the efficient synthesis of optically active petiodial, we started from the easily obtainable (+)-genipin. Silylation of genipin gave disilyl ether 27 which was subjected to reduction with DIBAL to give the alcohol 72 in 92% yield from genipin. Alkylation of the mesylate prepared in situ from 72 was successful at low temperature as follows. Alcohol 72 was treated with n-BuLi in THF at -78 °C followed by addition of mesyl chloride, and the lithium anion of geranyl tolyl sulfone (63) was reacted with the mesylate 73 prepared as above to give desired alkylated compound 74 in 80% yield. Attempts to detect the intermediary mesylate by thin layer chromatography was unsuccessful because of its instability at room temperature, as encountered in the corresponding chloride, and trichloroacetate. This result suggests that these type of iridoids having a good leaving group at C11 decompose readily at room temperature. Selective desilylation of 74 with PPTS in ethanol gave the monosilyl ether (75), which was subjected to reduction to afford the alcohol 76 in 64% yield. Acetylation of 76 followed by rapid treatment with n-Bu4NF afforded the hemiacetal 77 in 93% yield. This compound was a positional isomer of the double bond in petiodial. Isomerization of the double bond in the five membered ring of 77 proved to be unexpectedly difficult and highly critical conditions were required for this isomerization. Refluxing an anhydrous benzene solution (0.05 M in substrate) of the hemiacetal 77 containing 0.5 equivalent of diazabicycloundecene (DBU) afforded the dial 78 and its stereoisomer 79 in 80% yield. More vigorous conditions or use of THF as solvent gave the desired compounds in lower yield. Treatment with other bases such as sodium hydride or sodium hydroxide under various reaction conditions gave only trace amounts of the desired compounds. From the mixture obtained above, each stereoisomer, 78 and 79 was isolated by thin layer chromatography respectively with a ratio of 3:2. 1H- and 13C-NMR spectra of the major component 78 were identical with those of the natural petiodial. The sign of optical rotations of the synthesized petiodial 78 ([α]D25 = 32.9° (c=1.2, CHCl3)) was opposite to that of the natural compound ([α]D25 =-28° (c=1.5, CHCl3)), our synthetic petiodial 78 was therefore the antipode of natural one. Thus, the first synthesis of the enantiomer of natural petiodial was achieved efficiently, and the absolute stereochemistry of the stereogenic center at C6 in natural petiodial was determined as S configuration.
Scheme 14

a) DIBAL, CH₂Cl₂, -78 °C, ~99%  b) BuLi, -78 °C, THF, then MsCl  c) geranyl sulfone, BuLi, THF, -78 °C, 30 min.; then 73, 63% from 72  d) PPTS, EtOH, 25 °C, 20 h, 80%  e) Li, EtNH₂, -78 °C, 79%  f) Ac₂O, DMAP, Et₃N, rt, 95%  g) Bu₂NF-3H₂O, 0 °C, 8 min, 98%  h) 0.5 eq. DBU, benzene, reflux, 2 h, 80%  i) LiAlH₄-BuOH, THF, -78 °C, 71%  j) Swern oxid., 80%  k) BaMnO₄, >70%
Next the absolute stereochemistry of another asymmetric center at C7 of 78 was determined as follows. Reduction of the mixture of (+)-petiodial (78) and its diastereoisomer 79 obtained above with LiAlH(t-BuO)3 (64) afforded the corresponding diols which were isolated respectively in a ratio of 3:2. The major alcohol 80 was reconverted into (+)-petiodial (78) by Swern oxidation. Each diastereoisomer of the diol 80 and 81 was subjected to oxidation with BaMnO4 (65) to give the lactone 82 and its isomer 83, respectively. The stereochemistry of 82 and 83 was elucidated respectively by comparing their 1H-NMR spectra with those of neonepetalactone and iso-neonepetalactone (66). Thus the methylene protons in the lactone ring of 82 were observed at δ 4.35 and 4.24 ppm as a part of an ABX pattern (J_{AB}=11.5 Hz, J_{AX}=3.0 Hz, J_{BX}=2.0 Hz), while those of 83 were at δ 4.39 and 3.94 ppm, (J_{AB}=11.0 Hz, J_{AX}=4.0 Hz, J_{BX}=11.0 Hz). The above features of the 1H-NMR spectra of both lactones 82 and 83 were in good agreement with those of the corresponding methylene protons of neonepetalactone (δ 4.34 and 4.19, dd, J_{AB}=11.0 Hz, J_{AX}=3.0 Hz, J_{BX}=3.0 Hz) and iso-neonepetalactone (δ 4.24 and 3.89, dd, J_{AB}=11.0 Hz, J_{AX}=5.0 Hz, J_{BX}=11.0 Hz), whose stereochemistry has been established. We could therefore assign the relative stereochemistry between C6 and C7 in (+)-petiodial 78 as (6R, 7S). The absolute structure of natural (-)-petiodial was then determined as (6S, 7R).

This synthesis also confirmed that the biogenetic precursor of petiodial is not an iridoid, but it could be a linear diterpene udoteal. The synthetic method employed here could be expanded to get various analogues involving different side chain. These compounds might show much better biological activities than those of petiodial. From this successful synthesis we can expand our research fields into more complicated diterpenes involving a cyclopentene ring system.

### 8.2 Udoteatrial Hydrate

The unique monocyclic diterpenoid trialdehyde udoteatral (84) (60) isolated from marine algae *Udotea flabellum*, was reported to show antimicrobial activity against *Staphylococcus aureus* and *Candida albicans*. Since all three substituents on the cyclopentane ring are in cis relationship, udoteatral is known to exist as a form of the mono-hydrate. Although the relative stereostructure of natural udoteatral hydrate (85) was confirmed as (25*, 3R*, 6S*) by synthesis of the racemic form (67), its absolute configuration has remained uncertain.

Since udoteatral hydrate (85) could be considered to consist of the iridoid carbon framework and geranyl side chain, we decided to investigate the synthesis of 85 starting from genipin to demonstrate the usefulness of genipin as a chiral building block as well as to confirm the absolute configuration of 85. In this section, the synthesis (68) of the optically active 85 and the absolute configuration of natural udoteatral hydrate is described.

To introduce the geranyl side chain into the iridoid carbon framework, the tricyclic exo-methylene lactone 86 was designated to be the key intermediate. The problem upon
introduction of the geranyl side chain was the stereocontrol of the newly formed stereogenic center at C7. Since it seemed, however, that the side chain in 85 occupied the thermodynamically stable α-configuration, it was considered that base catalyzed isomerization could control the stereochemistry at C7 after introduction of the side chain into 86. To support this assumption, semiempirical calculations (PM3) (69) of simplified analogues derived from 86 did show that the α-isomer were more stable than the β-isomer.

Oxidation of genipin with barium manganate followed by hydrogenation with Rh/Al2O3 afforded stereoselectively the tricyclic hemiacetal 87, which was then converted into the methylacetal 88. Reduction of 88 followed by acetylation gave the acetate 89 in good yield. Bromohydrin formation with NBS-H2O followed by Swern oxidation afforded the corresponding bromoacetate 90, which was successively treated with zinc in acetic acid (70) to give the key intermediate 86. With 86 in hand, the stereochemistry at C7 was then considered carefully, and the stereochemistry at C7 was confirmed by single crystal X-ray analysis of model compounds.

Thus, treatment of the lithium salt of geranyl sulfone with 86 afforded the 1,4-addition product 91. Since the removal of the sulfone group from 91 was unsuccessful, the lactone carbonyl in 91 was temporarily reduced and protected with TBDMS to give the acetal 92. Birch reduction (71) of the sulfone moiety in 92 afforded the compound 93, which was deprotected and oxidized with PCC to afford homogeranyl lactone (94 and 95) as a mixture of diastereoisomers, of which the ratio was found to be 3:1 by 1H-NMR spectroscopy. This mixture was separated by HPLC and the major isomer 94 could be isomerized into a 1:1 mixture of 94 and 95 under the influence of DBU in refluxing toluene. Reduction of the α-homogeranyl lactone 94 with DIBAL followed by acid hydrolysis of the resulting hemiacetal accomplished the synthesis of 85. In order to determine the absolute configuration of natural udoteatrial hydrate, 85 was converted to the diacetate 97 and 98, the spectral data of which were in good agreement with those reported previously. The signs of optical rotations of our synthetic diacetates, however, were opposite to those of natural diacetates which confirms the absolute configuration of natural udoteatrial hydrate as (2R, 3S, 6S, 7S) as shown in Scheme 15.
genipin → a → \[
\begin{align*}
\text{MeO} & , \\
\text{O f,g} & , \\
\text{CO}_2\text{Me} & , \\
\end{align*}
\]
\[87: R=H, R'=\text{CO}_2\text{Me}\]
\[88: R=\text{Me}, R'=\text{CO}_2\text{Me}\]
\[89: R=\text{Me}, R'=\text{CH}_2\text{OAc}\]

\[\text{MeO} , \]
\[\text{86} \]

\[\text{MeO} , \]
\[\text{87: X=H, Y=O, R=S_2\text{Tol}}\]
\[\text{88: X=H, Y=O, R=H}}\]
\[\text{89: X=H, Y=O, R=H}}\]

\[\text{91: X, Y=O, R=SO}_2\text{Tol}}\]
\[\text{92: X=H, Y=OTBDMS, R=SO}_2\text{Tol}}\]
\[\text{93: X=H, Y=OTBDMS, R=H}}\]

\[94: \alpha\text{-homogeneranyl}}\]
\[95: \beta\text{-homogeneranyl}}\]

\[\text{94} \rightarrow \text{p, q} \rightarrow \text{85} \rightarrow \text{ent-udoteatrial hydrate}}\]

\[r \rightarrow \text{99} \rightarrow \text{7-epi-ent-udoteatrial hydrate}}\]

\[\text{97} \rightarrow \text{98} \rightarrow \text{99} \rightarrow \text{95} \rightarrow \text{88} \rightarrow \text{87} \rightarrow \text{86} \rightarrow \text{genipin}}\]

a) \text{BaMnO}_4, \text{CH}_2\text{Cl}_2, \text{rt, 71%} \ b) \text{cat. Rh-AI}_2\text{O}_3, \text{H}_2, \text{AcOEt, rt, 56%} \ c) \text{BF}_3\text{Et}_2\text{O}, \text{MeOH, 0 °C, 95%} \ d) \text{DIBAL, CH}_2\text{Cl}_2, -78 °C, 90%} \ e) \text{Ac}_2\text{O, Et}_3\text{N, DMAP, rt, 94%} \ f) \text{NBS, H}_2\text{O, DMSO, rt}}\]

\[\text{g) Swern oxid}}\]
\[\text{h) Zn, AcOH, ether, rt, 63% from 89}}\]
\[\text{i) geranyl p-tolyl sulphone, LDA, THF, -78 °C, then 86, 82%} \ j) \text{DIBAL, CH}_2\text{Cl}_2, -78 °C, 93%} \ k) \text{TBDMSOTf, 2,6-lutidine, CH}_2\text{Cl}_2, -78 °C, 90%} \ l) \text{Li/EtNH}_2, \text{THF, -78 °C, 76%} \ m) \text{TBAF, THF, 0 °C, 90%} \ n) \text{PCC, CH}_2\text{Cl}_2, \text{rt, 80%} \ o) \text{DBU, toluene, reflux, 12 h, 70%} \ p) \text{DIBALH, CH}_2\text{Cl}_2, -78 °C, 99%} \ q) \text{(0.1M) p-TsOH, THF:H}_2\text{O:acetone = 4:2:1, rt, 69%} \ r) \text{Ac}_2\text{O, Pr}_y, \text{rt, 66% for 97 and 98, 52% for 96}}\]

\[\text{Scheme 15}\]
Our synthesis, employing the tricyclic exomethylene lactone 86 as the key intermediate, was designed to obtain analogues involving a variety of side chains instead of geranyl group. Next, preliminary investigations of the structure and activity relationships of the synthetic analogues of ent-udoteatrial hydrate was examined. The homogeranyl lactone 95 was reduced with DIBAL followed by acid hydrolysis of the resulting hemiacetal to afford the ent-7-epi-udoteatrial hydrate (96). Acetylation of 96 was found to give the acetate 99 as the sole product.

To examine the effect of the side chain on the biological activities, we chose the compound bearing the methyl group as a simple side chain to compare with those involving the homogeranyl group. Thus, hydrogenation of 86 with Rh/Al₂O₃ stereoselectively afforded the β-methyl derivative 100 (Scheme 16). The α-methyl isomer 101 could be obtained by base catalyzed isomerization of 100. Compounds 100 and 101 were converted into the diacetates 102, 103 and 104, respectively, by the same reaction sequence as that described for the preparation of 97, 98 and 99 from 94 and 95.

Scheme 16

Since the monohydrate form of the trialdehyde was not stable enough for biological tests, their diacetates were used instead. The biological properties of these analogues (97, 98, 99, 102, 103 and 104) were then examined. Although the natural udoteatrial hydrate was
reported to show antimicrobial activities against *Staphylococcus aureus* and *Candida albicans*, none of these analogues was active against various microorganisms. At this moment it was not clear whether protection of the two hemiacetal portions of 85 as acetate would decrease the activities of the natural product.

On the other hand, assay of *in vitro* cytotoxicity of these analogues afforded significant results. Thus, the compounds possessing the homogeranyl side chain (97, 98 and 99) were found to be cytotoxic against KB human oral epidermoid carcinoma and human lung carcinoma A-549 as summarized in the Table (72). Compound 97 was the most toxic among the analogues examined at concentration of $4 \times 10^{-1}$ μg/ml. The effect of side chain was apparent from the fact that the methyl derivatives were much less toxic relative to compounds 97, 98 and 99 (73). Furthermore, 97 having the acetate in an axial orientation at C19 exhibited at least 4 fold enhanced cytotoxicity than those having equatorial acetates. From the stereoelectronic point of view, it was suggested that compounds with the better leaving ability of the acetoxy group showed stronger cytotoxicity, although the mechanism of the inhibition of cell growth of these compounds was not understood at all. This observation suggested that the generation of oxonium species by elimination of the acetoxy group might be relevant for the exhibition of cytotoxicity of these compounds. Such oxonium species may act as alkylating agents as is well known in the case of iminium species generated in the naphthyridinomycin/saframycin class of antitumor antibiotics.

| Compound No. | IC$_{50}$ (μg/ml) | Human KB Cells | Human A-549 |
|--------------|-----------------|----------------|-------------|
| 97           | 0.4             | 0.5            |             |
| 98           | 1.6             | 1.9            |             |
| 99           | 3.4             | 3.9            |             |
| 102 and 103  | >25.0           | >25.0          |             |
| 104          | >25.0           | >25.0          |             |

In conclusion, we have found that the analogues of *ent*-udoteatrial hydrate were cytotoxic against human carcinoma *in vitro*. For the exhibition of cytotoxicity the presence of the homogeranyl side chain as well as the stereochemistry of the acetoxy group at C19 seemed to be important factors. Our findings reported here may be valuable for the evaluation of new lead-compounds for cancer chemotherapy. The question we are facing is whether the diacetates of natural udoteatrial hydrate would show comparable cytotoxicity.
9 CONCLUSION

All iridoids and related natural products which are described in Figure 4 and Figure 5 have two or three aldehydes or equivalent functionalities such as enol ether or hemiacetal groups. These functionalities may play a major role for the display of biological and pharmacological activities. We have synthesized the silyl ether of iridoid aglycones in those cases where the natural products are glucosides, because the real biological activity should be revealed by the aglycone having the aldehyde functionality, which is prepared by desilylation in nearly neutral conditions. The iridoid molecules are reminiscent of a large number of known biologically active dialdehydes such as polygodial, warburganal and manoalide.

Figure 4
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