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# Total Synthesis of the Proposed Structure of Ardimerin, and Proposal for its Structural Revision

Ryota Nakayama, Eva-Maria Tanzer, Takenori Kusumi, Ken Ohmori*, and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551, Japan (e-mail: kohmori@chem.titech.ac.jp, ksuzuki@chem.titech.ac.jp)

Dedicated to Prof. Dr. Dieter Seebach on the occasion of his 79th birthday

We report the first total synthesis of the proposed structure of ardimerin, which was achieved in 14 steps starting from 2,3,4-trimethoxybenzoic acid. The key steps include the β-selective formation of the crucial *C*-glycoside linkage and stepwise construction of the strained 8-membered salicylide core. The synthesis revealed that the proposed structure **1** does not match the natural product. A proposal is made for reassigning the isolated natural product to the already known structure of bergenin. Interesting properties of the synthetic 8-membered salicylides are documented, including their susceptibility toward nucleophilic ring opening and the bowl chirality.

**Keywords**: Ardimerin・Structure Revision・Bergenin・*C*-Glycosides・Lactones

## Introduction

The subtropical plant *Ardisia japonica* is commonly used in traditional Chinese medicine as an antitussive or diuretic agent as well as for stopping uterine bleeding.[1] Phytochemical tests of *Ardisia* have led to the discovery of numerous constituents with a variety of biological acitvities.[2] In 2002, *Jung et al.* isolated a compound from the plant with a potent DPPH radical scavenging activity, and named it "ardimerin". The structure was proposed to be **1**, an unusual cyclic dimer of a *C*-glycosyl salicylic acid derivative (Figure 1a). Moreover, the corresponding digallate **2** was reported in 2007, as an inhibitor against HIV-1 and HIV-2 RNase H.[4]

Considerable attention has been paid to these compounds,[1][2c][5] not only because they hold great potential as therapeutic leads, but also due to their unusual structural features, including the presence of a rare 8-membered salicylide[6] that appeared to be unstable. While the *s-trans* ester linkage is stereoelectronically preferred by the n–σ□ conjugation (Figure 1b), the medium-sized ring imposes the unfavorable *s-cis* conformation.[7] Thus, construction of such 8-membered salicylides is challenging, and reported approaches have been limited, *e.g.*, condensation of salicylic acid derivative[8] and the Baeyer–Villiger oxidation of cyclohexanedione.[7a] Indeed, *Minehan et al.* reported the synthesis of the dimethyl-protected derivative of **1**, although the deprotection failed presumably due to the instability of the 8-membered salicylide core.[5]

In view of our long-standing synthetic interest in aryl *C*-glycoside natural products,[9] we were intrigued by the synthesis of **1** possessing unusual *C*-glycoside structure attached to the 8-membered salicylide. In addition, during the synthetic planning process, we noted another anomaly in **1** in that the oxygenation pattern of the aromatic part, 2, 3, 4-trihydroxybenzoic acid, is rare in nature. This is in contrast to the commonly-seen 3, 4, 5-oxygenation pattern of gallic acid (Figure 1c).

Our presentiments surrounding the sensitive salicylide structure as well as the unusual aromatic substitution pattern proved true. In this paper, we wish to report the first total synthesis of the proposed structure **1**, which was found to not represent the natural product.

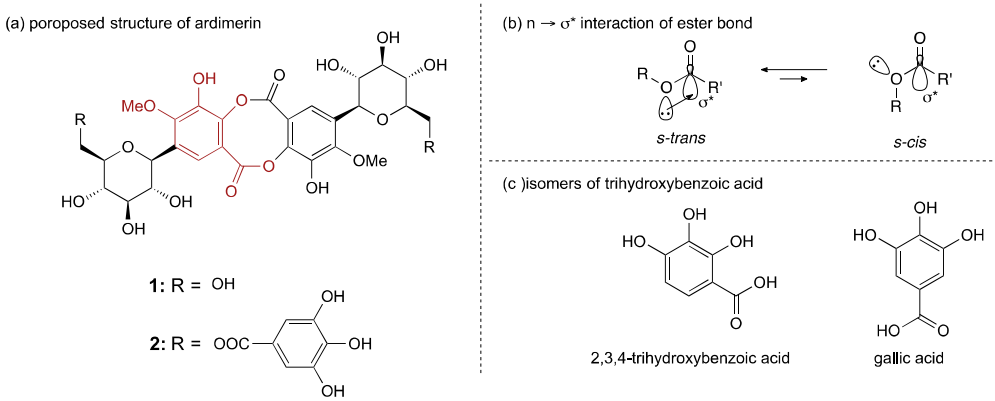


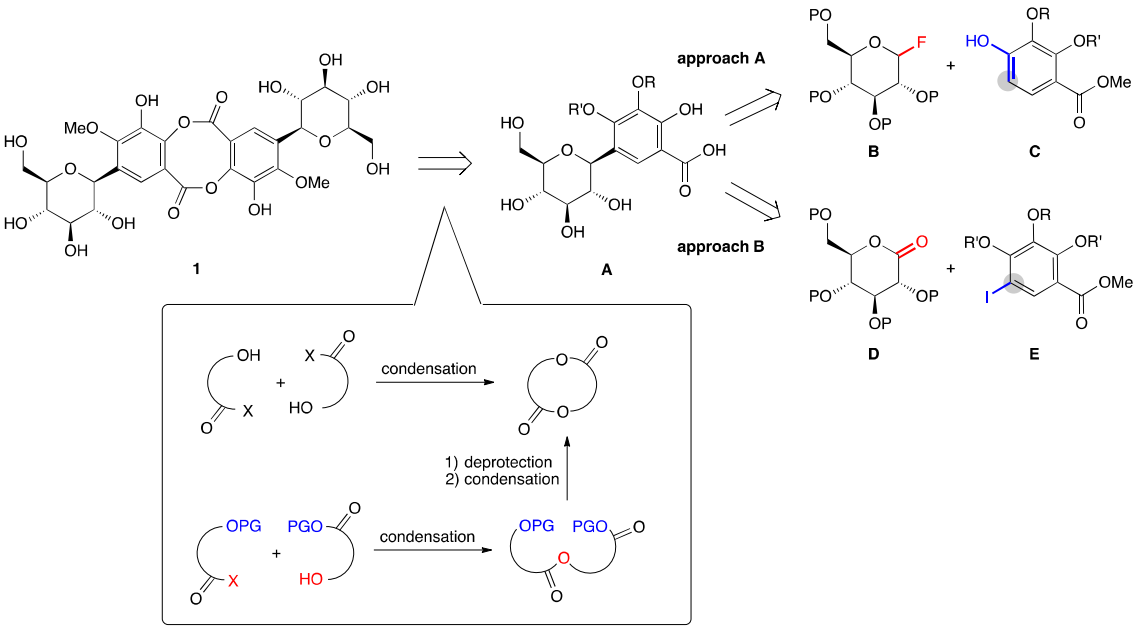

**Figure 1.** Structural features of **1**

## Results and Discussion

### 1. Retrosynthetic Analysis

Scheme 1 depicts the retrosynthetic analysis of **1**. The foreseen challenges included: (1) the selective formation of the 8-membered salicylide that would have sizable strain, and (2) the regio- and stereoselective construction of the aryl *C*-glycoside linkage.

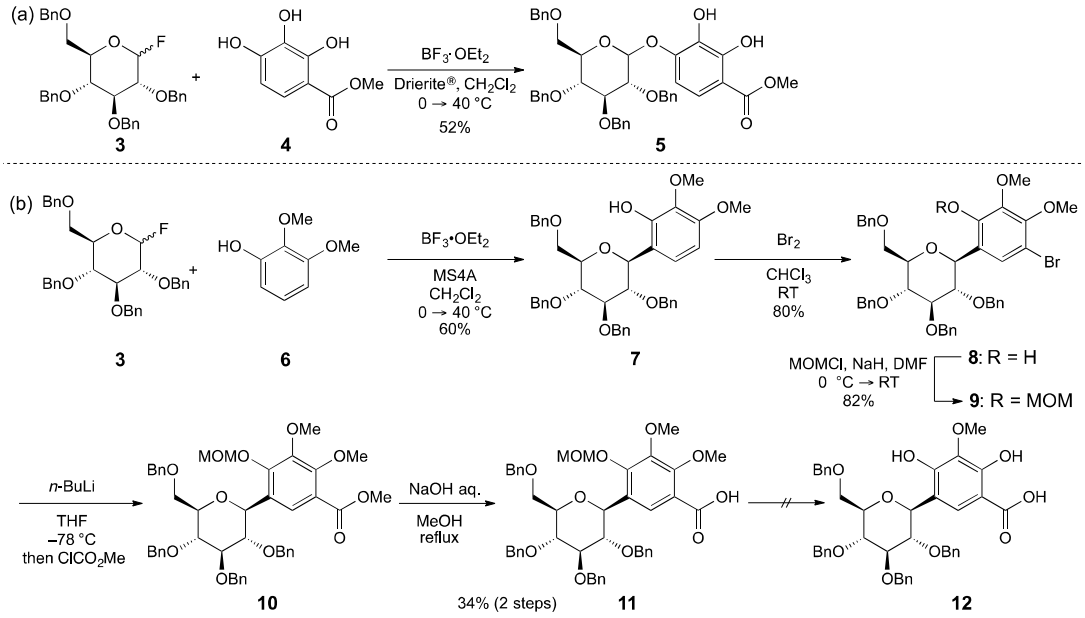
We envisioned that the key salicylide core could be constructed by dimerization of the monomeric *C*-glycoside **A**. Two routes were examined: (1) direct dimerization, and (2) stepwise approach. The β-linked glucoside in **A** would be constructed via two possible approaches. Approach A is based on the *O*→*C* glycoside rearrangement previously developed in our laboratory,[9] and approach B relies on the nucleophilic addition of organometallics followed by hydride reduction.[10]




**Scheme 1.** Synthetic plan

### 2. *C*-Glycoside formation

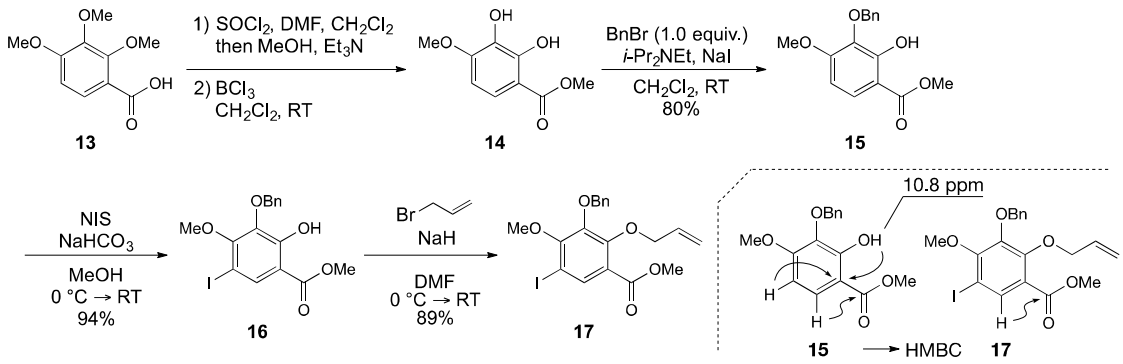
**2.1 Approach A** Using the *O*→*C* glycoside rearrangement procedure, we examined the formation of the *C*-glycoside bond (Scheme 2). An initial trial was conducted using fluoro sugar **3**, phenol **4**, and $BF_3 \cdot OEt_2$ as the Lewis acid of choice (Drierite®, $CH_2Cl_2$, 0 → 40 °C). However, this phenol displayed low reactivity, resulting in the isolation of *O*-glycoside **5** in 52% yield (Scheme 2a). To improve the reactivity of the




**Scheme 2.** Attempted *O*→*C* glycoside rearrangement (**approach A**)

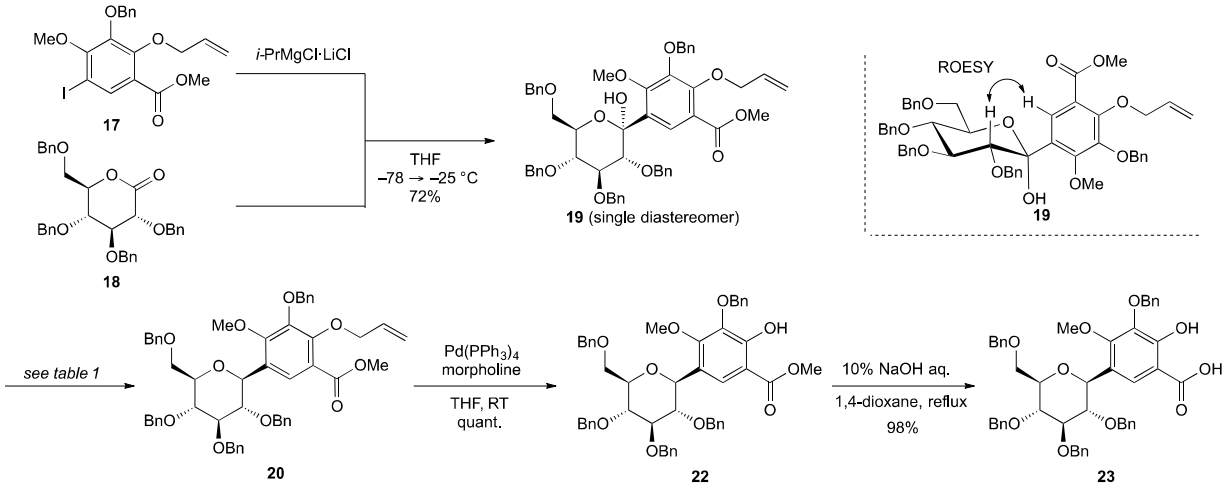
phenolic partner, other starting materials were employed (Scheme 2b). Indeed, phenol **6** underwent the *O*→*C* glycoside rearrangement with fluoro sugar **3** in the presence of $BF_3 \cdot OEt_2$ (MS 4Å, $CH_2Cl_2$, 0 ° C → RT), giving the desired *C*-glycoside **7** in 60% yield. Treatment of **7** with bromine afforded bromide **8**, which was protected (methoxymethyl chloride, NaH, DMF, 0 ° C → RT) to give methoxymethyl ether **9**. Bromide **9** was treated with *n*-BuLi (THF, –78 °C, 30 min), and the resulting aryl anion was allowed to react with $ClCO_2Me$ (–78 °C → RT), affording methyl ester **10**. The crude ester **10** was subjected to saponification, yielding acid **11** in 34% yield in 2 steps. Finally, selective removal of the methyl group, *ortho* to the carbonyl moiety, was examined using a combination of $CeCl_3 \cdot 7H_2O$ and NaI, which, however, resulted in failure, giving only decarboxylaed product of the starting material **11**.

**2.2 Approach B** Faced with the difficulty in the *O*→*C* glycoside rearrangement, we decided to change the synthetic approach to nucleophilic addition of organometallic reagent to the protected gluconolactone. Scheme 3 shows the synthesis of iodide **17**. Following the known protocol, 2,3,4-trimethoxybenzoic acid (**13**) was converted to catechol **14** in two steps.[11] Initial attempts at the selective mono-benzylation of catechol **14** (BnBr, $Cs_2CO_3$, acetone, 80 °C) gave poor results, affording the dibenzylated product. However, the projected mono-benzylation became possible by employing *i*-$Pr_2NEt$[12] (BnBr, cat. NaI, $CH_2Cl_2$, RT), giving mono-benzyl ether **15** in 80% yield. The structure of **15** was assigned by HMBC correlations as shown in Scheme 3. Iodination of **15** with *N*-iodosuccinimide (NIS) in the presence of $NaHCO_3$ gave iodide **16**, which was treated with allyl bromide and NaH (DMF, 0 °C → RT) to give allyl ether **17**. The structure of **17** was verified by the diagnostic HMBC cross peak (see Scheme 3).




**Scheme 3.** Synthesis of iodide **17**.

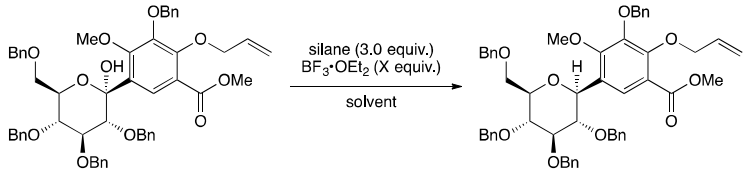
Aryl iodide **17** was subjected to halogen–metal exchange reaction, and subsequently allowed to react with D-gluconolactone **18** (Scheme 4). The concern at this stage was the compatibility of the methoxycarbonyl group. Indeed, use of *n*-BuLi gave lactol **19** in 24% yield with many unidentified side products. Pleasingly, screening identified *i*-PrMgCl·LiCl[13] as the reagent of choice: Treatment of iodide **17** with *i*-PrMgCl·LiCl (THF, –78 °C, 20 min) followed by the addition of lactone **18** (–25 °C, 4.5 h) afforded lactol **19** in 72% yield as a sole *C*-β isomer, which was confirmed by the ROESY correlation (see Scheme 4).




**Scheme 4.** Synthesis of hydroxy acid **23**

The next stage was the Lewis acid-mediated silane reduction of lactol **19** (Table 1). Treatment of lactol **19** with $Et_3SiH$ in the presence of 3.0 equivalents of $BF_3 \cdot OEt_2$ ($CH_2Cl_2$, –78 → 0 °C) gave *C*-glycoside **20** in 71% yield as a mixture of β/α anomers (90:10) (entry 1). The configurations were verified by the NOE studies on the separated anomers (Figure 2a). Use of *i*-$Pr_3SiH$ [$BF_3 \cdot OEt_2$ (3.0 equiv.), $CH_2Cl_2$, –40→0 °C][14] reinforced the β-stereoselectivity to give **20** in 52% yield. Byproduct **21** (Figure 2b) was obtained in 22% yield, arising from the debenzylation of the phenol protecting group (entry 2). To moderate the Lewis acidity to suppress the undesired debenzylation, a mixed solvent system (MeCN and $CH_2Cl_2$ = 3/1) was employed, which allowed in a slight increase of the yield of **20** (69%), and the formation of **21** was almost suppressed (8%) (entry 3). An optimal set of conditions, *i.e.*, use of *i*-$Pr_3SiH$ in the presence of 1.5 equivalents of $BF_3 \cdot OEt_2$ (MeCN, –40→0 °C), afforded β-*C*-glycoside **20** in high yield without producing **21** (entry 4). The conditions were scalable to the level employing 8.0 g of **19** as the starting material (entry 5).

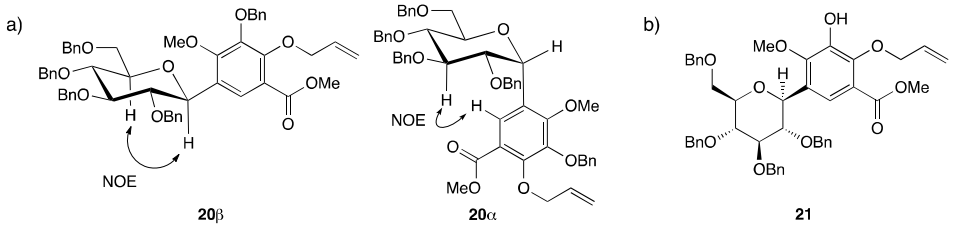
**Table 1.** Reduction of lactol **19**




**19** **20**

| Entry | Silane[a] | X [equiv.] | Solvent | Temp. [°C] | Time [h] | **20** [%][b] | Ratio (β:α) | **21** [%][b] |
|---|---|---|---|---|---|---|---|---|
| 1 | $Et_3SiH$ | 3.0 | $CH_2Cl_2$ | –78 → 0 | 1.2 | 71 | 90:10 | ND |
| 2 | *i*-$Pr_3SiH$ | 3.0 | $CH_2Cl_2$ | –40 → 0 | 3.5 | 52 | >99:<1 | 22 |
| 3 | *i*-$Pr_3SiH$ | 3.0 | $CH_3CN/CH_2Cl_2$[c] | –40 → 0 | 2.0 | 69 | >99:<1 | 8 |
| 4 | *i*-$Pr_3SiH$ | 1.5 | $CH_3CN$ | –40 → 0 | 2.0 | 81 | >99:<1 | 7 |
| 5[d] | *i*-$Pr_3SiH$ | 1.5 | $CH_3CN$ | –40 → 0 | 2.0 | 82 | >99:<1 | ND |

[a] Three equivalents of silane were used. [b] Yield after purification by preparative TLC. [c] $CH_3CN/CH_2Cl_2$ = 3/1. [d] 8.0 g scale.




**20**β **20**α **21**

**Figure 2.** NOE correlations of *C*-glycoside **20** and phenol byproduct **21**

*C*-Glycoside **20** was treated with a catalytic amount of $Pd(PPh_3)_4$ in the presence of morpholine (THF, RT) to give deallylated product **22**, which was hydrolyzed to give hydroxy acid **23** in 98% yield over 2 steps (Scheme 4). In the $^1$H-NMR spectra of **22** (300 K, 600 MHz), H(1) of the glucosyl moiety was observed as a broad singlet at δ 4.58. The broadening suggested the slow rotation of the aryl *C*-glycoside bond (Figure 3). At 323 K (400 MHz), this signal was observed as a doublet ($^3J_{HH}$ = 9.6 Hz), confirming the β-configuration.

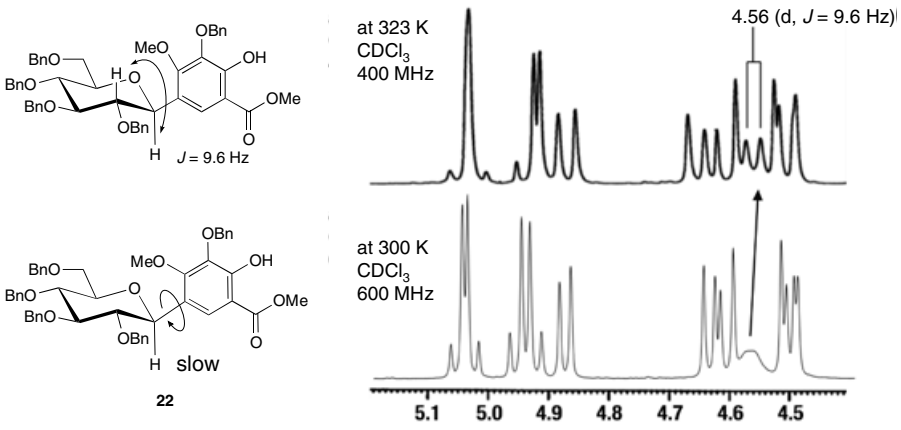
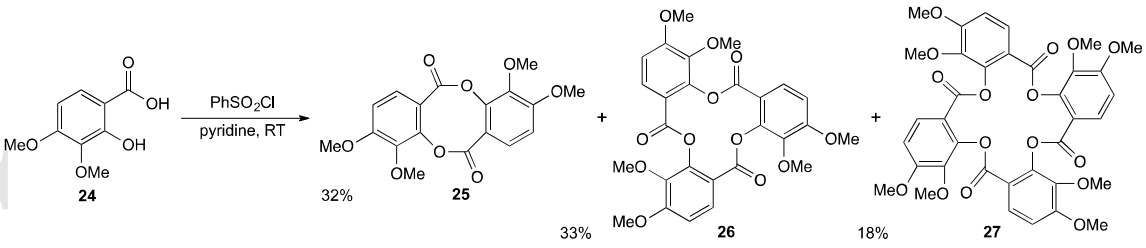



**Figure 3.** Variable-temperature $^1$H-NMR of compound **22**

### 3. Salicylide formation

**3.1 Model study** In order to test the feasibility of a direct dimerization, a model study was carried out using model compound **24** (Scheme 5). After screening many different condensing agents, we identified benzenesulfonyl chloride as an effective reagent, giving the desired salicylide **25** in 32% yield along with the undesired trimer **26** (33%) and tetramer **27** (18%). In the IR spectrum of salicylide **25**, the C=O stretching band was observed at 1758 $cm^{-1}$. Compared to compound **26** (1737 $cm^{-1}$), the band clearly shifted to higher frequency, suggesting that the ester linkage of the salicylide core adopts *s-cis* conformation. These results are consistent with the pioneering study by *Seebach* and coworkers.[7a]

Furthermore, we obtained single crystals of dimer **25** and trimer **26** suitable for X-ray analysises. It turned out that the ester linkages of salicylide **25** adopt *s-cis* conformation, and those of trimer **26** *s-trans* conformation, respectively (Figure 4). Interestingly, dimer **25** is strongly distorted from planarity, while trimer **26** was almost planar.[6][7]




**Scheme 5.** Direct dimerization of model compound **24**

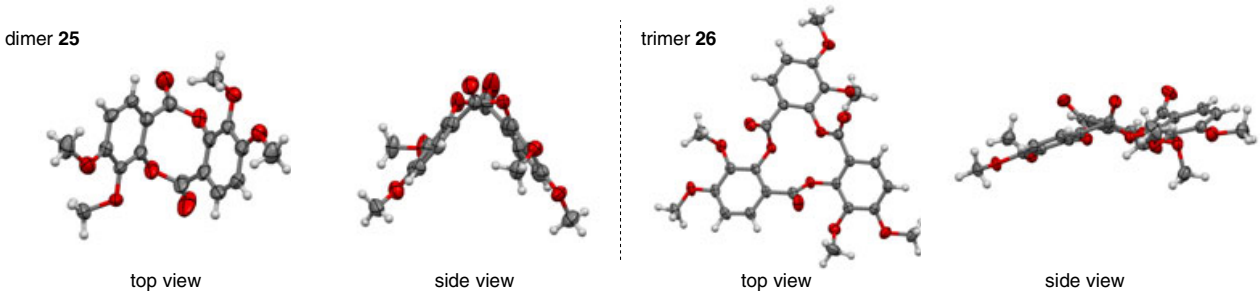



**Figure 4.** X-Ray structures of dimer **25** and trimer **26**

Another interesting observation was the *bowl chirality* in the related dimer **28** (Figure 5). Note that the protections for C(3) and C(3')-phenols in **28** are benzyl- rather than methyl-groups. In the $^1$H NMR spectra of **28** (DMSO-$d_6$, 400MHz), the geminal coupling between two benzyl protons was observed, suggesting the 8-membered salicylide core possesses bowl chirality.[7] To observe the dynamic behavior, variable-temperature $^1$H NMR experiments were performed. During raising the temperature, the peaks became broadened and coalesced at 355 K, and further heating sharpened the peak. The estimated barrier for flipping was $\Delta G^{\ddagger}$ = 18 kcal mol$^{-1}$.[7c]

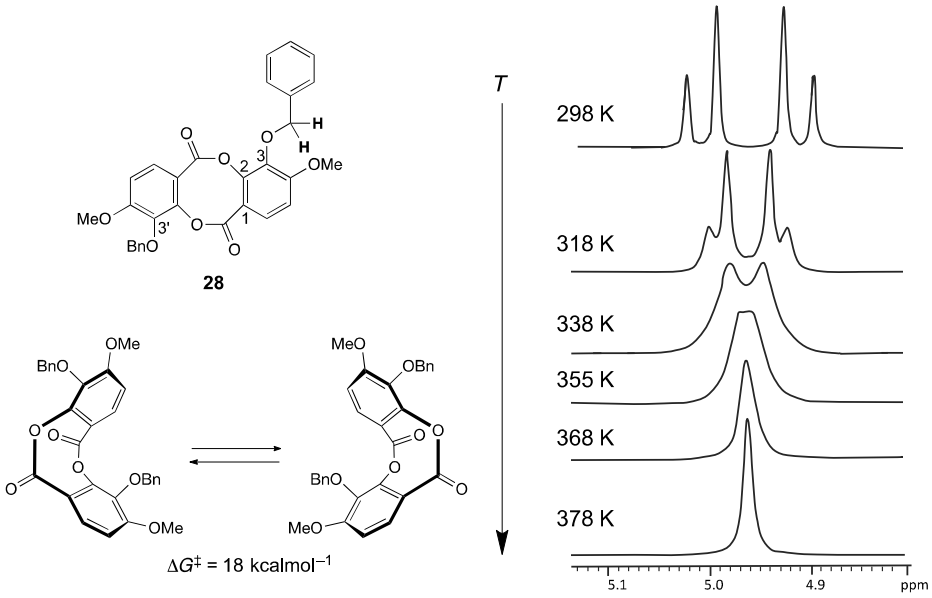
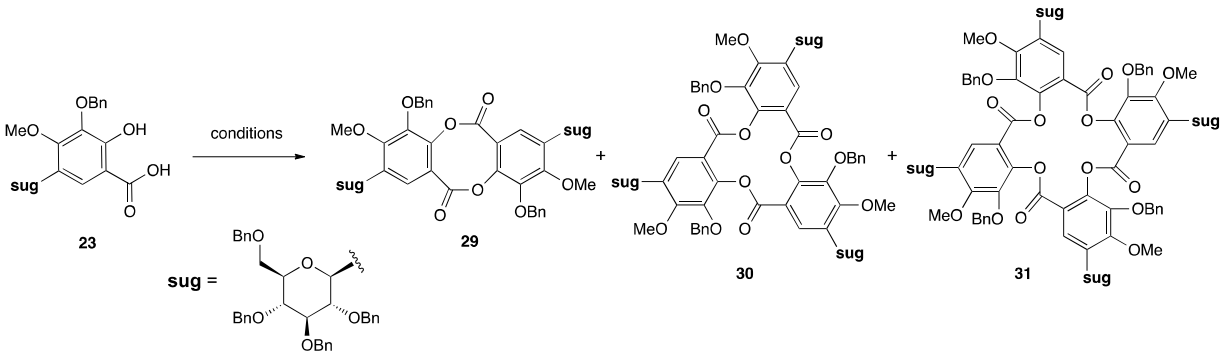



**Figure 5.** Dynamic NMR experiment (DMSO-$d_6$, 400 MHz)

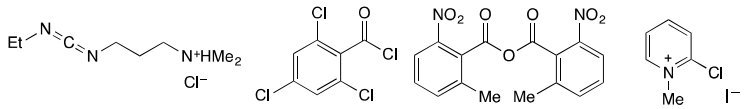
**3.2 Direct dimerization** We proceeded to explore the optimal conditions for the direct dimerization of *C*-glycosidic salicylic acid **23** (Table 2). It turned out that EDCI (**A**), trichlorobenzoyl chloride (**B**), and MNBA (**C**) were not effective for this transformation, giving salicylide **28** in low yields with many unidentified products (entries 1–3). On the other hand, treatment of **23** with $SOCl_2$ followed by the addition of $Et_3N$ and DMAP in toluene afforded trimer **30** in 40% yield (entry 4). Under the Mukaiyama conditions using 2-chloro-*N*-methylpyridinium salt, the formation of salicylide **29** was improved (19%), although sizable amounts of trimer **30** and tetramer **31** were produced (entry 5). Use of $PhSO_2Cl$ led to a slight increase in the yield of **29** (20%), although formation of trimer **30** and tetramer **31** still persisted (entry 6). Preferential formation of the trimer and the tetramer rather than the desired dimer could be attributed to the low population of the *s-cis* conformer of the acyclic dimer **32**, required for the desired cyclodimerization to give salicylide **29** (Figure 6). In the IR spectrum of salicylide **29**, the C=O stretching band was observed again at 1763 cm$^{-1}$, suggesting that the ester linkage of the salicylide core adopts *s-cis* conformation.

**Table 2.** Direct salicylide formation



| Entry | Reagents | Solvent | Temp | Time [h] | **29**[a] [%] | **30**[a] [%] | **31**[a] [%] |
|---|---|---|---|---|---|---|---|
| 1 | **A**, DMAP | $CH_2Cl_2$ | RT | 6.0 | 9 | 18 | ND |
| 2 | **B**, $Et_3N$, DMAP | $CH_2Cl_2$ | RT | 6.0 | 11 | ND | trace |
| 3 | **C**, $Et_3N$ | $CH_3CN$ | RT | 8.5 | | decomposed | |
| 4 | $SOCl_2$, $BnEt_3NCl$[b] then $Et_3N$, DMAP | $Cl(CH_2)_2Cl$ then toluene | RT | 4.0 | 11 | 40 | ND |
| 5 | **D**, $Et_3N$, DMAP | toluene | 90 °C | 5.0 | 19 | 23 | 9 |
| 6 | $PhSO_2Cl$ | pyridine | RT | 4.0 | 20 | 37 | 12 |

[a] Yields after purification by preparative TLC. [b] Acid **23** was treated with thionyl chloride and $BnEt_3NCl$ for 1.5 h followed by removal of the solvent. The residue was added to the toluene solution of $Et_3N$ and DMAP, and stirred for 2.5 h.




**A** **B** **C** **D**

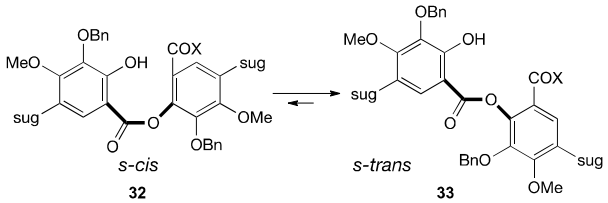
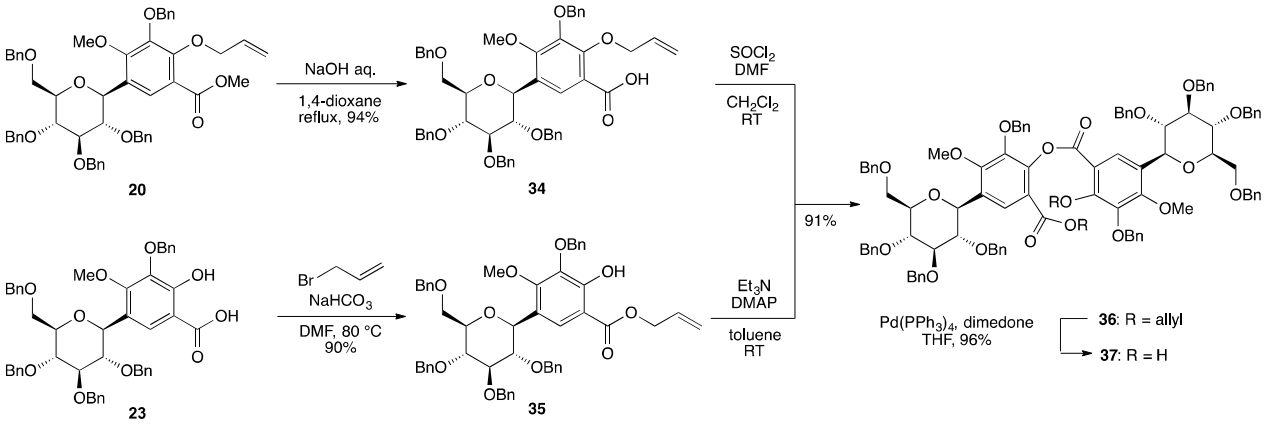



**Figure 6.** *s-Cis* and *s-trans* conformers of the reaction intermediate

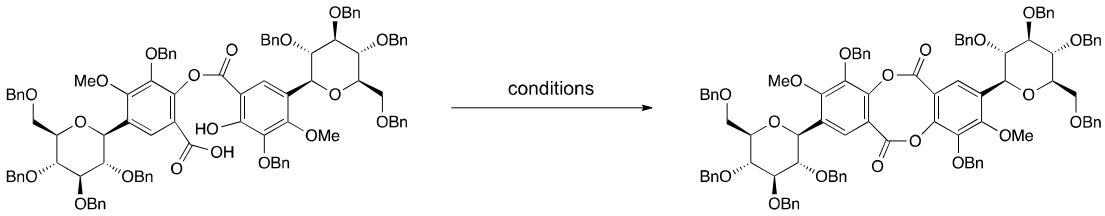
**3.3 Stepwise dimerization** Faced with the difficulty in the direct dimerization, we opted for a stepwise approach, that is, to form the two ester linkages as separate steps. For this purpose, we prepared benzoic acid **34** and phenol **35** as the differentially-protected monomer units (Scheme 6). Saponification of **20** (10% NaOH aq., 1,4-dioxane, reflux) gave benzoic acid **34** in 94% yield, while carboxylic acid **23** was converted to allyl ester **35** in 90% yield. Acid **34** was converted to the corresponding acid chloride by treatment with thionyl chloride in the presence of a catalytic amount of DMF ($CH_2Cl_2$, RT). After removal of the solvents, to the residue was added a toluene solution of phenol **35** followed by $Et_3N$ and DMAP to give ester **36** in 91% yield. Simultaneous removal of two allyl groups in **36** gave seco acid **37**, which was ready for the lactonization step.




**Scheme 6.** Synthesis of *seco* acid **37**

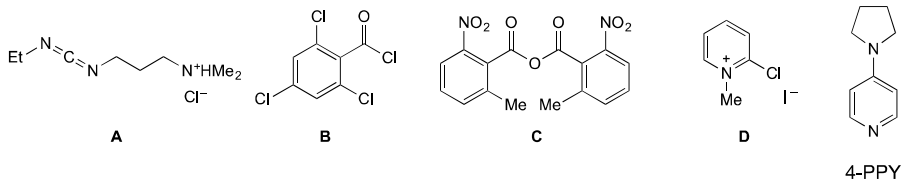
Table 3 summarizes the results of the salicylide formation. Treatment of **37** with EDCI (**A**) and DMAP ($CH_2Cl_2$, RT) caused only decomposition (entry 1). Use of MNBA (**C**)[15] or 2-chloro-*N*-methylpyridinium iodide (**D**)[16] as a condensing agent gave the desired salicylide **29** in moderate yields (entries 2 and 3). By contrast, an excellent result was obtained by the Yamaguchi lactonization.[17] The initial trial using the standard conditions, such that treatment of acid **37** with 2,4,6-trichlorobenzoyl chloride (**B**) ($Et_3N$, toluene, RT), failed to convert **37** to the mixed anhydride. The attempted lactonization under the Yonemitsu conditions [the seco acid **37** was added to a toluene solution of 2,4,6-trichlorobenzoyl chloride, $Et_3N$, and 2.0 equivalents of DMAP (5.0 mM, RT)] gave rise to decomposed products, resulting from the DMAP-induced cleavage of the ester linkage (entry 4).[18] However, reducing the amount of DMAP to 0.2 equivalents gave salicylide **29** in high yield (entry 5). Use of 4-pyrrolidinopyridine (4-PPY) led to a slight increase of the yield (entry 6).

**Table 3.** Salicylide formation



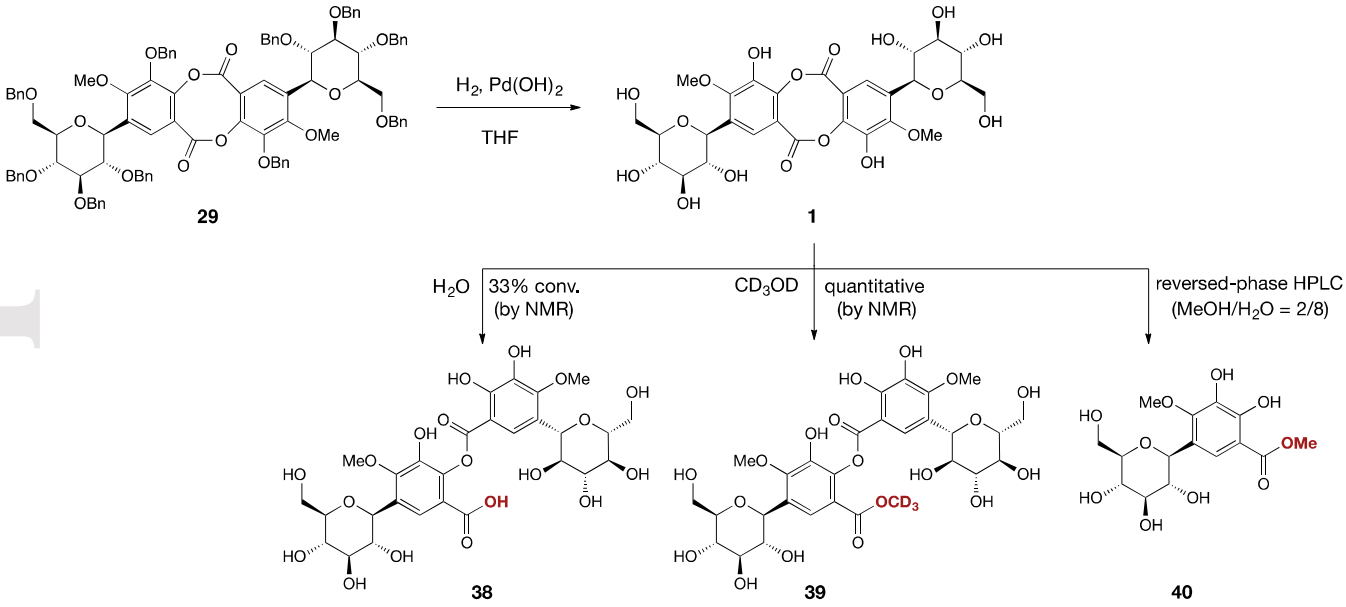

| Entry | Reagents | Solvent | Temp. | **29** |
|---|---|---|---|---|
| 1 | **A**, DMAP (1.2) | $CH_2Cl_2$ | RT | ND |
| 2 | **C**, $Et_3N$ (2.2), DMAP (0.2) | toluene | RT | 65 |
| 3 | **D**, $Et_3N$ (8.0) | $CH_3CN$ | 90 °C | 69 |
| 4 | **B**, $Et_3N$ (1.2), DMAP (2.0) | toluene | RT | ND |
| 5 | **B**, $Et_3N$ (2.2), DMAP (0.2) | toluene | RT | 85 |

| | | | | |
|---|---|---|---|---|
| 6 | **B**, $Et_3N$ (2.2), 4-PPY (0.2) | toluene | RT | 88 |




## 4. Structure elucidation

Finally, global deprotection of **29** [$H_2$, $Pd(OH)_2$, THF, room temperature] afforded the targeted structure **1** (Scheme 7). To our surprise, the product turned out to be extremely unstable, easily prone to solvolytic ring opening. For example, when the crude material was suspended in water, partial cleavage of the salicylide occurred, giving hydroxy acid **38**. When dissolved in $CD_3OD$, the salicylide was immediately solvolyzed, giving $d_3$-methyl ester **39**. Attempted isolation of **1** by the reported protocol (reversed-phase HPLC, MeOH:$H_2O$ = 2:8)[3] also caused decomposition, giving a trace amount of monomeric methyl ester **40**. The crude material of **1** was obtained by careful filtration under an argon atmosphere through a membrane filter (THF), and then concentrated in *vacuo*. Using this crude material, the structure of compound **1** was unambiguously confirmed by $^1H$ and $^{13}C$ NMR spectroscopy and high-resolution mass spectroscopy (HRMS). The HRMS (ESI, negative) of the synthetic material **1** indicated the molecular formula of $C_{28}H_{31}O_{18}$ ($[M–H]^-$ *m/z* 655.1510). Thanks to the generous donation of the NMR spectra measured in DMSO-$d_6$ from Prof. Jung, we compared the $^{13}C$-NMR spectra of the synthetic **1** with that of the natural product. The data did not match, suggesting the structure incongruity (Table 4).




**Scheme 7.** Synthesis of **1** and its instability to $H_2O$ and MeOH

**Table 4.** Comparison of $^{13}$C-NMR reported for the natural product and the synthetic material **1**[a]

| Reported [b] | Synthetic [c] | Reported [b] | Synthetic [c] |
|---|---|---|---|
| $\delta_C$ | $\delta_C$ **major** (minor) | $\delta_C$ | $\delta_C$ **major** (minor) |
| 163.5 | **164.5** | 81.9 | **81.9** (81.7) |
| 151.2 | **151.4** (152.0) | 79.9 | **78.3** (78.5) |
| 148.2 | **142.4** (142.7) | 73.8 | **74.6** |
| 140.7 | **137.7** (1137.9) | 72.3 | **73.7** (72.7) |
| 118.2 | **133.4** (133.1) | 70.8 | **70.3** |
| 116.0 | **119.1** (118.8) | 61.2 | **61.4** (61.3) |
| 109.6 | **117.7** (118.3) | 59.9 | **61.21** (61.24) |

[a] Measured in DMSO-$d_6$. [b] 400 MHz. [c] 600 MHz.

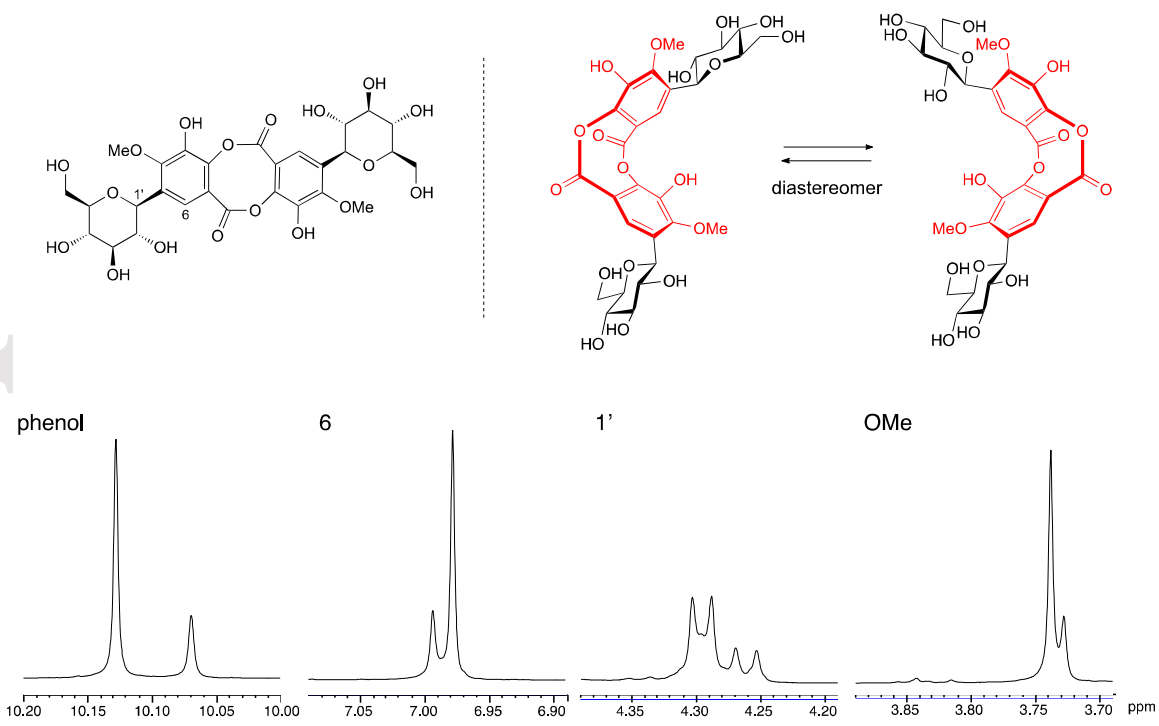



**Figure 7.** Partial $^1$H NMR spectrum of compound **1** (600 MHz, DMSO-$d_6$)

Interestingly, the NMR spectrum of the synthetic sample suggested the presence of two diastereomers that is due to the bowl chirality relative to the glycoside chirality (Figure 7).

At this stage, we asked ourselves what the real structure of the natural product was. We found a clue: the differences in the $^{13}C$ NMR spectra between the synthetic material and the reported data mostly centered on the aromatic peaks, strongly suggesting the incongruity of the aromatic substitution pattern. A notion came to us that the 2,3,4-trihydroxybenzoic acid derivatives are relatively rare compared to the 3,4,5-trihydroxycounterpart (gallic acid). A literature search indicated the ratio of roughly 1:15.

The original report mentioned "*the $^{1}H$ and $^{13}C$ NMR spectra of the natural product were reminiscent of bergenin* (**41**)",[3] which led us to a naive assumption that the bergenin dimers might be the true natural product (Figure 8). In order to prepare the assumed dimers, we purchased a sample of **41** (Tokyo Chemical Industry Co., Inc.) and were surprised to notice that the $^{1}H$ and $^{13}C$ NMR coincided with the reported data for "ardimerin",[1] which was also the case with the per-acetyl derivative ($Ac_2O$, pyridine, RT). In view of the fact, we had a strong suspicion that "ardimerin" is identical to bergenin itself.

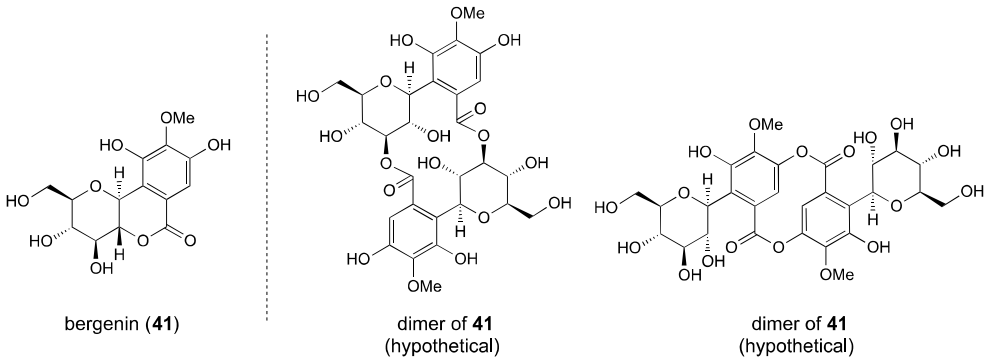



**Figure 8.** Structures of bergenin (**41**) and its hypothetical dimers

The question was why the misassignment had occurred. The basis of the original assignment of the dimeric structure came from the high-resolution FAB-MS data (*m/z* 657.4563, $C_{28}H_{32}O_6$). Surprisingly, the FAB-MS spectra by our measurement of bergenin (**41**) showed the cluster ion peak observed at *m/z* 657 as $[2M+H]^+$ rather than the parent peak *m/z* 329 $[M+H]^+$ (Figure 9).[2, 20]

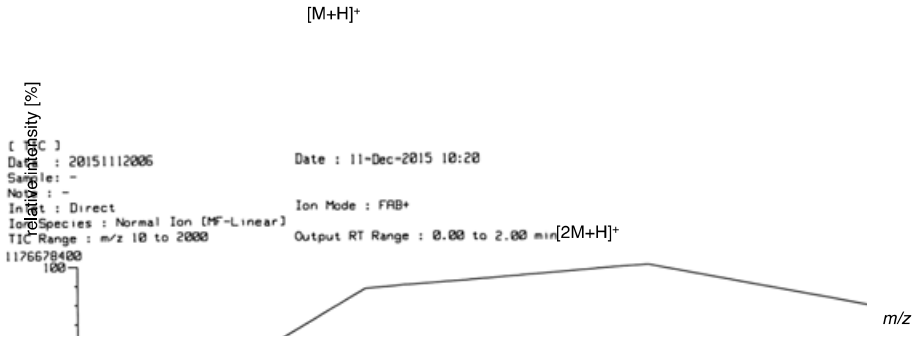



**Figure 9.** FAB-MS spectra of bergenin

We identified another pitfall leading to the misassignment in the NMR interpretation (Figure 10). In the HMBC spectrum of bergenin (**41**), the $^{4}J_{HC}$ correlation between the aryl proton and C(1') of the glucosyl moiety was clearly observed (red arrow, Figure 10a). In the original paper,[1] this HMBC correlation was erroneously assigned as $^{3}J_{HC}$ between the aryl proton and C(1')

[1] Further supporting fact is that bergenin was previously isolated from *Ardisia japonica*.[19] Strangely, however, the specific optical rotation of ardimerin (+48.2°) was opposite of the sign for the reported data of bergenin (–38.9°).

[2] The cluster ion peak was more clearly observed in the ESI-MS spectra (see *Supporting Information*).

as shown by the red arrow in Figure 10b, which led them to conclude the vicinal relationship of the aryl proton and the *C*-glycoside linkage. Moreover, unfortunately, bergenin showed no $^{3}J_{HC}$ correlation between H(2') and the carbonyl carbon, which gave a further support to the misassignment.

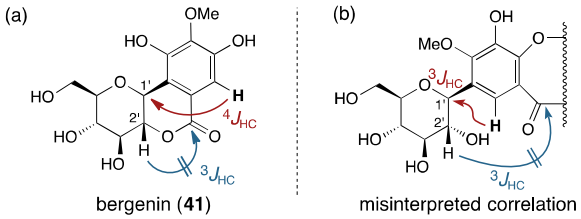



**Figure 10.** HMBC correlation of bergenin and the original misassignment

## Conclusions

In conclusion, the first total synthesis of **1**, the proposed structure of ardimerin, was accomplished via a stepwise dimerization of the *C*-glycoside. The analytical study revealed that the natural product isolated by *Jung et al.* and named as "ardimerin" does not correspond to compound **1**. We propose that the identity is bergenin.

## Experimental Section

### *General*

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry argon. The authentic sample of bergenin was obtained from Tokyo Chemical Industry Co., Inc. Ethereal solvents (anhydrous; Kanto Chemical Co., Inc.) were used as received. DMF and acetonitrile were distilled over $CaH_2$, hexane was distilled from Na, and stored over 4Å molecular sieves. Other reagents were used without further purification as received from commercial suppliers. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (TLC silica gel 60 $F_{254}$, Art 5715, 0.25 mm) were used. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Silica gel 60 $PF_{254}$ (Art7747). For flash column chromatography, silica gel 60N (Spherical, neutral, 63-210 □m) from Kanto Chemical was used. Higher-accuracy purifications were performed by Smart Flash EPCLC W-Prep 2XY system (YAMAZEN SCIENCE, inc.). Melting point (mp) determinations were performed by using a Yanaco MP-500 instrument or a METTLER TOLEDO MP70 melting point system, and are uncorrected. $^{1}$H- and $^{13}$C-NMR were measured on a JEOL JNM Lamda-400 (400 MHz), JEOL JNM ECX-500 (500 MHz), or Bruker AV-600 (600 MHz) spectrometer in the solvent indicated; Chemical shifts (δ) are expressed in parts per million downfield from internal standard (tetramethylsilane), and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR spectrometer. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded by using a Perkin-Elmer 100 FTIR spectrometer equipped with a universal ATR sampling accessory. High-resolution mass spectra (HR-MS) were obtained with Bruker Daltonics micrOTOF-Q II. X-Ray crystallographic data were recorded with a Rigaku RAXIS-RAPID diffractometer.

*Methyl 3-benzyl-2-hydroxy-4-methoxybenzoate (**15**).*

To a solution of **14** (101 mg, 511 μmol), DIPEA (180 μL, 1.03 mmol) and NaI (15.3 mg, 102 μmol) in $CH_2Cl_2$ (2.0 mL) was added BnBr (61.0 μL, 512 μmol) at room temperature. After stirring for 20 h, the reaction was stopped by adding saturated aqueous $NH_4Cl$, and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/$Et_2O$ = 2/1) to afford **15** (118 mg, 80%) as a white solid. $R_f$ 0.54 (hexane/$Et_2O$ 2:1); $^1$H-NMR (600 MHz, $CDCl_3$) 3.88 (*s*, Me); 3.95 (*s*, Me); 5.11 (*s*, $CH_2$); 6.48 (*d*, $^3J$(H,H) = 9.0, H–C); 7.32 (*t*, $^3J$(H,H) = 7.4, H–C); 7.38 (*t* $^3J$(H,H) = 7.4, H–C(2)); 7.55 (*d*, $^3J$(H,H) = 7.4, H–C(2)); 7.63 (*d*, $^3J$(H,H) = 9.0, H–C); 10.96 (*s*, OH). Anal. calc. for $C_{16}H_{16}O_5$ (288.30): C 66.66, H 5.59; found: C 66.78, H 5.45. Spectral data matched the reported data.[21]

*Methyl 3-benzyloxy-2-hydroxy-5-iodo-4-methoxybenzoate (**16**).*

To a suspension of **15** (751 mg, 2.60 mmol), $NaHCO_3$ (2.21 g, 26.3 mmol) in MeOH (26 mL) was added NIS (884 mg, 3.93 mmol) at 0 °C. After stirring for 1 h at room temperature, the resulting mixture was diluted with $CH_2Cl_2$ and $H_2O$ was added. The aqueous phase was separated and extracted with $CH_2Cl_2$ (×3). The combined organic extracts were washed with 15% aqueous $Na_2S_2O_3$ and water, dried over anhydrous $Na_2SO_4$, filtered and then concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 95/5) to afford **16** (1.01 g, 94%) as a white solid. $R_f$ = 0.60 (hexane/EtOAc 4:1). M.p. 88–90 °C. $^1$H-NMR (600 MHz, $CDCl_3$): 3.95 (*s*, Me); 3.96 (*s*, Me); 5.07 (*s*, $CH_2$); 7.33–7.39 (*m*, H–C(3)), 7.51 (*d*, $^3J$(H,H) = 7.4, H–C(2)); 8.03 (*s*, H–C), 10.97 (*s*, 1H, OH). $^{13}$C-NMR (150 MHz, $CDCl_3$): 52.5; 61.3; 75.3; 78.7; 111.1; 128.2; 128.39 (2C); 128.44 (2C); 134.0; 136.9; 139.9; 157.4; 158.0; 169.3. IR (ATR): 3204, 3029, 2951, 1683 (C=O), 1598, 1439, 1418, 1319, 1255, 1201, 1019, 956, 739, 694. HR-ESI-MS: 436.9845 ([*M*+Na]$^+$, $C_{16}H_{15}INaO_5^+$; calc. 436.9856).

*Methyl 2-allyloxy-3-benzyloxy-5-iodo-4-methoxybenzoate (**17**).*

To a suspension of NaH (63% dispersion in mineral oil, 316 mg, 8.30 mmol) in DMF (20 mL) was added **16** (2.85 g, 6.88 mmol) in DMF (50 mL) followed by allyl bromide (1.15 mL, 13.5 mmol) at 0 °C. After stirring for 13 h at room temperature, the reaction was quenched by adding saturated aqueous $NH_4Cl$. The resulting mixture was extracted with $Et_2O$ (×3). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/$Et_2O$ = 90/10) to afford **17** (2.81 g, 89%) as a white solid. $R_f$ = 0.48 (hexane/EtOAc 4:1). M.p. 47–49 °C. $^1$H-NMR (600 MHz, $CDCl_3$): 3.89 (*s*, Me); 3.93 (*s*, Me); 4.60 (*d*, $^3J$(H,H) = 5.9, $CH_2$); 5.02 (*s*, $CH_2$); 5.24 (*dd*, $^3J$(H,H) = 10.4, $^2J$(H,H) = 1.1, H–C); 5.35 (*dd*, $^3J$(H,H) = 17.1, $^2J$(H,H) = 1.1, H–C); 6.89 (*ddt*, $^3J$(H,H) = 17.1, 10.4, 5.9, H–C); 7.34–7.41 (m, H–C(3)); 7.48 (*d*, $^3J$(H,H)= 7.14, H–C(3)); 8.02 (*s*, H–C). $^{13}$C-NMR (150 MHz, $CDCl_3$): 52.2; 61.2; 75.5; 75.9; 85.1; 118.3; 123.2; 128.3; 128.4 (2C); 128.9 (2C); 133.5; 135.3; 136.7; 133.5; 135.3; 136.7; 146.3; 154.3; 157.3; 164.7. IR (ATR): 3069, 3031, 2979, 2944, 2894, 1731 (C=O), 1574, 1415, 1280, 1190, 1068, 1017, 967, 926, 692. HR-ESI-MS: 499.0172 ([*M*+Na]$^+$, $C_{19}H_{19}INaO_5^+$; calc. 499.0169).

*Lactol **19**.*

Iodide **17** (2.98 g, 6.56 mmol) was azeotropically dried with toluene (5 mL × 3) and dissolved in THF (70 mL), to which was added *i*-PrMgCl·LiCl (10.8 mL, 0.95 M THF soln.) at –78 °C. After stirring for 10 min at this temperature, gluconolactone **18** [azeotropically dried with toluene (5mL × 3), 1.3 M in THF, 5.0 mL, 6.57 mmol] was added at –78 °C, and the reaction temperature was immediately raised to –25 °C. After stirring for 4 h at this temperature, the reaction was quenched by adding AcOH (1.2 M solution in THF, 10.0 mL, 12.0 mmol) dropwise at –78 °C. After stirring for 30 min at this temperature, the mixture was warmed to room temperature. To it was added saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with

EtOAc (× 3). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 90/10 69/31) to afford lactol **19** (4.11 g, 72%) as a colorless oil. $R_f$ = 0.27 (toluene/$Et_2O$ 85:15). $[\alpha]_{365}^{20}$ = –44.4 (*c* = 0.289, $CHCl_3$) $^1$H-NMR (600 MHz, $CDCl_3$): 3.71 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 3.81–3.87 (*m*, $CH_2$(1), Me (6)); 3.89–3.95 (*m*, H–C, $CH_2$(1)); 4.02 (*dd*, $^3J$(H,H) = 9.1, 9.1, H–C); 4.12 (*brt*, H–C(2)); 4.48 (*d*, $^2J$(H,H) = 11.5, $CH_2$(1)); 4.49 (*d*, $^2J$(H,H) = 9.1, $CH_2$(1)); 5.54 (*d*, $^2J$(H,H) = 11.9, $CH_2$(1)); 4.59 (*dd*, $^2J$(H,H) = 11.6, $^3J$(H,H) = 5.7, $CH_2$(1)); 4.67 (*dd*, $^2J$(H,H) = 11.6, $^3J$(H,H) = 5.7, $CH_2$(1)); 4.69 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)); 4.89–4.93 (*m*, $CH_2$(4)); 4.98 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 5.24 (*d*, $^3J$(H,H) = 10.3, $CH_2$(1)); 5.37 (*d*, $^3J$(H,H) = 17.1, $CH_2$(1)); 6.14 (*ddt*, $^3J$(H,H) = 17.1, 10.3, 5.7, H–C); 6.93 (*d*, $^3J$(H,H) = 7.2, H–C(2)); 7.16 (*dd*, $^3J$(H,H) = 14.3, H–C(3)); 7.24–7.33 (*m*, H–C(19)); 7.44 (*d*, $^3J$(H,H) = 7.2, H–C(2)); 7.93 (*s*, H–C). $^{13}$C-NMR (150 MHz, $CDCl_3$, several signals overlapped): 29.7; 52.0; 62.4; 68.9; 72.1; 73.2; 75.0; 75.1; 75.4; 75.7; 78.0; 83.2; 83.7; 97.8; 118.2; 120.8; 125.3; 127.5; 127.66; 127.69; 127.76; 127.78; 127.8; 128.2; 128.3; 128.4; 128.5; 130.7; 130.7; 133.8; 136.9; 137.4; 138.2; 138.4; 138.6; 146.8; 154.2; 156.1; 165.6. IR (neat) 3441, 3063, 3030, 2947, 2867, 1728 (C=O), 1598, 1454, 1310, 1212, 1086, 1013, 736, 697. HR-ESI-MS: 889.3525 ([*M*+Na]$^+$, $C_{53}H_{54}NaO_{11}^+$; calc. 889.3558).

*C-Glucoside **20**.*

Lactol **19** (7.90 g, 9.11 mmol) was azeotropically dried with toluene (5 mL × 3) and dissolved in $CH_3CN$ (80 mL), to which was added *i*-$Pr_3SiH$ (5.59 mL, 27.2 mmol) and $BF_3{\cdot}OEt_2$ (1.70 mL, 13.4 mmol) at –40 °C. After stirring for 15 min at this temperature, the reaction mixture was warmed to 0 °C. After stirring for 65 min, the reaction was quenched by adding saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous phase was back-extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 80/20) to afford *C*-glycoside **20** (6.35 g, 82%) as a colorless oil. $R_f$ = 0.28 (hexane/EtOAc 4:1). $[\alpha]_{365}^{23}$ = –24.1 (*c* = 1.10, $CHCl_3$). $^1$H-NMR (600 MHz, $CDCl_3$): 3.58–3.64 (*br*, H–C); 3.77–3.85 (*m*, H–C(3), $CH_2$); 3.87 (*s*, Me); 3.88 (*s*, Me); 4.02 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.52 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.54 (*d*, $^2J$(H,H) = 12.2, $CH_2$(1)); 4.61 (*d*, $^2J$(H,H) = 12.2, $CH_2$(1)); 4.62–4.64 (*m*, H–C, $CH_2$(3)); 4.87 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.91–5.00 (*m*, $CH_2$(4)); 5.24 (*d*, $^2J$(H,H) = 10.4, $CH_2$(1)); 5.37 (*dd*, $^3J$(H,H) = 17.2, $^2J$(H,H) = 1.2, $CH_2$(1)); 6.14 (*ddt*, $^3J$(H,H) = 17.2, 10.4, 5.9, H–C); 6.89 (*d*, $^3J$(H,H) = 6.1, H–C(2)); 7.12 (*m*, H–C(3)); 7.20 (*m*, H–C(2)); 7.25–7.40 (*m*, H–C(16)); 7.48 (*d*, $^3J$(H,H) = 7.3, H–C(2)); 7.73 (*s*, H–C). $^{13}$C-NMR (150 MHz, $CDCl_3$, several signals overlapped): 52.0; 61.9; 69.1; 73.3; 75.0; 75.1; 75.45; 75.50; 75.53; 78.4; 79.4; 83.0; 87.0; 118.1; 121.2; 127.51; 127.52; 127.6; 127.67; 127.72; 128.0; 128.07; 128.10; 128.2; 128.3; 128.4; 128.5; 128.6; 133.9; 137.1; 137.6; 138.19; 138.24; 138.71; 153.6; 156.5; 165.6. IR (neat) 3064, 3031, 2941, 2903, 2868, 1728 (C=O), 1599, 1454, 1322, 1209, 1070, 1028, 994, 736, 697. HR-ESI-MS: 873.3596 ([*M*+Na]$^+$, $C_{53}H_{54}NaO_{10}^+$; calc. 873.3609).

*C-Glycoside **22**.*

To a solution of **20** (3.17 g, 3.73 mmol) in THF (35 mL) was added $Pd(PPh_3)_4$ (435 mg, 0.376 mmol) and morpholine (3.08 ml, 35.3 mmol) at room temperature. After stirring for 2 h, the reaction was quenched by adding saturated aqueous $NH_4Cl$, and the resulting mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 90/10 80/20) to afford **22** (3.03 g, quant.) as a colorless oil. $R_f$ = 0.35 (hexane/$Et_2O$ 6:4). $[\alpha]_{365}^{20}$ = –125 (*c* = 1.10, $CHCl_3$). $^1$H-NMR (600 MHz, $CDCl_3$): 3.57–3.62 (*brd*, H–C); 3.69 (*brs*, H–C); 3.73 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)); 3.75–3.85 (*m*, $CH_2$(1), H–C(2)); 3.91 (*s*, Me); 3.92 (*s*, Me); 4.09 (*d*, $^2J$(H,H) = 10.8, $CH_2$(1)); 4.51 (*d*, $^2J$(H,H) = 10.8, $CH_2$(1)); 4.52 (*d*, $^2J$(H,H) = 12.2, $CH_2$(1)); 4.58 (*br*, 1H); 4.62 (*d*, $^2J$(H,H) = 12.2, $CH_2$(1)); 4.65 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.87 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.92 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)); 4.95 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)); 5.02 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)); 5.05 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)); 6.89 (*d*, $^3J$(H,H) = 7.0, H–C(2)); 7.08–7.15 (*m*, H–C(3)); 7.20 (*d*, $^3J$(H,H) = 7.0, H–C(2)); 7.25–7.39 (*m*, H–C(16)); 7.52 (*d*, $^3J$(H,H) = 7.4, H–C(2)); 7.61 (*s*, H–C); 10.99 (*s*, OH). $^{13}$C-NMR (150 MHz, $CDCl_3$, several signals overlapped): 61.8; 69.1; □73.4; 74.8; 74.0; 75.1; 75.5; 78.4; 79.3; 82.8; 87.1; 109.0; 124.0; 127.4; 127.52; 127.55; 127.62; 127.65; 128.0; 128.1; 128.2; 128.29; 128.33; 128.4; 137.3; 137.6; 138.2; 138.3; 138.7; 139.6; 156.5; 157.5; 170.3. IR (neat) 3030, 2923, 2855, 1673 (C=O), 1435, 1342, 1211, 1070, 736, 697. HR-ESI-MS: 833.3329. ([*M*+Na]$^+$, $C_{50}H_{50}NaO_{10}^+$; calc. 833.3296).

*C-Glycoside **23**.*

To a solution of **22** (4.94 g, 3.69 mmol) in 1,4-dioxane (30 mL) was added 10% aqueous NaOH (20 mL) at room temperature. The reaction mixture was refluxed for 1.5 h. After cooling to room temperature, the reaction was quenched by adding 3M HCl (20 mL), and the mixture was extracted with EtOAc (×3). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 60/40 + TFA 1%) to afford **23** (2.88 g, 98%) as a purple amorphous solid. $R_f$ = 0.34 (MeOH/$CHCl_3$ 1:9). $[\alpha]_{365}^{20}$ = –118 (*c* = 0.923, $CHCl_3$); $^1$H-NMR (600 MHz, $CDCl_3$): 3.62–3.71 (*br*, H–C(2)); 3.73–3.79 (*m*, H–C, $CH_2$(1)); 3.79–3.87 (*m*, H–C, $CH_2$(1)); 3.94 (*s*, Me); 4.05 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.49 (*d*, 1H, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.55 (*d*, $^2J$(H,H) = 12.2, $CH_2$(1)); 4.58(*d*, $^2J$(H,H) = 10.8, $CH_2$(1)); 4.65 (*brd* $^2J$(H,H) = 12.2, H–C, $CH_2$(1)); 4.87 (*d*, $^2J$(H,H) = 10.8 Hz); 4.91 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)); 4.96 (*d*, $^2J$(H,H) = 11.0 $CH_2$(1)); 5.03 (*s*, $CH_2$); 6.88 (*d*, $^3J$(H,H) = 8.0, H–C(2)); 7.09–7.12 (*m*, H–C(3)); 7.17 (*d*, $^3J$(H,H) = 5.8, H–C(2)); 7.22–7.37 (*m*, H–C(16)); 7.49 (*d*, $^3J$(H,H) = 7.4, H–C(2)); 7.65 (*s*, H–C); 10.91 (*s*, OH). $^{13}$C-NMR (150 MHz, $CDCl_3$, several signals overlapped): 61.8; 68.9; 73.2; 74.95; 74.98; 75.1; 75.6; 78.4; 78.6; 83.1; 87.1; 108.2; 123.5; 125.3; 127.6; 127.7; 127.8; 127.98; 128.03; 128.14; 128.16; 128.28; 128.39; 128.43; 128.45; 137.3; 137.46; 137.51; 138.1; 138.7; 139.5; 156.9; 157.8; 172.0. IR (neat) 3064, 2924, 2859, 1673 (C=O), 1615, 1497, 1454, 1442, 1343, 1211, 1070, 1028, 798, 736, 697. HR-ESI-MS: 819.3110 ([*M*+Na]$^+$, $C_{49}H_{48}NaO_{10}^+$; calc. 819.3140). Anal. calc. for $C_{49}H_{48}O_{10}$ (796.91): C 73.85, H 6.07; found: C 73.64, H 5.89.

*C-Glycoside **34**.*

To a solution of **20** (1.09 g, 1.28 mmol) in 1,4-dioxane (10 mL) was added 10% aqueous NaOH (6.0 mL) at room temperature. The reaction mixture was refluxed for 1.5 h. After cooling to room temperature, the reaction was quenched by adding 3 M HCl (7 mL), and the mixture was extracted with EtOAc (× 3).The combined organic extracts dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 70/30 + TFA 1%) to afford **34** (1.01 mg, 94%) as a white amorphous solid. $R_f$ 0.67 ($CHCl_3$/MeOH 9:1). $[\alpha]_{365}^{20}$ = –63.8 (*c* = 1.03, $CHCl_3$). $^1$H-NMR (600 MHz, $CDCl_3$): 3.61–3.65 (*br*, H–C); 3.68–3.77 (*m*, H–C(2), $CH_2$); 3.83 (*t*, $^3J$(H,H) = 8.9, H–C); 3.89 (*s*, Me); 4.09 (*d*, $^2J$(H,H) = 11.2, $CH_2$(1)); 4.53 (*d*, $^2J$(H,H) = 12.2, $CH_2$(1)); 4.54–4.59 (*m*, $CH_2$); 4.61 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.65 (*brd*, H–C); 4.82 (*d*, $^2J$(H,H) = 6.4, $CH_2$); 4.86 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)); 4.90–4.97 (*m*, $CH_2$(4)); 5.35 (*d*, $^2J$(H,H) = 11.7, $CH_2$(1)); 5.39 (*d*, $^2J$(H,H) = 17.0, $CH_2$(1)); 6.03 (*ddt*, $^3J$(H,H) = 17.0, 11.7, 6.4, H–C); 6.89 (*d*, $^3J$(H,H) = 7.3, H–C(2)); 7.10–7.15 (*m*, H–C(3)); 7.18–7.19 (*m*, H–C(2)); 7.24–7.46 (*m*, 18H); 8.01 (*s*, H–C); 10.88 (*br*, OH). $^{13}$C-NMR (150 MHz, $CDCl_3$, several signals are overlapped): 61.9; 69.2; 73.4; 75.0; 75.2; 75.5; 75.9; 76.4; 78.5; 79.5; 82.8; 87.1; 118.0; 121.5; 127.8; 127.96; 128.03; 128.14; 128.37; 128.42; 128.56; 128.66; 130.3; 131.5; 136.4; 137.7; 138.12; 138.16; 138.7; 144.3; 151.6; 157.5; 167.7. IR (neat) 3202, 3031, 2917, 2868, 1741, 1745, 1693 (C=O), 1454, 1361, 1312, 1070, 1028, 992, 737, 697. HR-ESI-MS: 859.3429 ([*M*+Na]$^+$, $C_{52}H_{52}NaO_{10}^+$; calc. 859.3453).

*C-Glycoside **35**.*

To a solution of **23** (989 mg, 1.24 mmol), and $NaHCO_3$ (161 mg, 1.92 mmol) in DMF (13 mL) was added 1-bromo-2-propene (0.160 mL, 1.89 mmol) at room temperature. The resulting reaction mixture was refluxed for 2.5 h. After cooling to room temperature, the reaction was quenched by addition of water. The mixture was extracted with $Et_2O$ (× 3). The combined extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 90/10 69/31) to afford **35** (939 mg, 90%) as a purple amorphous solid. $R_f$ 0.54 (hexane/EtOAc 4:1). $[\alpha]_{365}^{20}$ = –128 (*c* = 1.06, $CHCl_3$). $^1$H-NMR (600 MHz, $CDCl_3$): 3.59 (*brd*, H–C), 3.72–3.77 (*m*, H–C, $CH_2$(1)), 3.78–3.86 (*m*, H–C(2), $CH_2$(1)), 3.92 (*s*, Me), 4.08 (*brd*, $^2J$(H,H) = 10.1, $CH_2$(1)), 4.50–4.52 (*m*, $CH_2$(2)), 4.56 (*br*, H–C), 4.62 (*d*, $^2J$(H,H) = 12.2, $CH_2$(1)), 4.65 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)), 4.81 (*d*, $^2J$(H,H) = 5.7, $CH_2$), 4.88 (*d*, $^2J$(H,H) = 10.7, $CH_2$(1)), 4.92 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)), 4.95 (*d*, $^2J$(H,H) = 11.0, $CH_2$(1)), 5.02 (*d*, $^2J$(H,H) = 10.6, $CH_2$(1)), 5.05 (*d*, $^2J$(H,H) = 10.6, $CH_2$(1)), 5.29 (*d*, $^2J$(H,H) = 10.5, $CH_2$(1)), 5.39 (*d*, $^2J$(H,H) = 17.1, $CH_2$(1)), 5.99 (*ddt*, $^3J$(H,H) = 17.1, 10.5, 5.7, H–C), 6.89 (*d*, $^3J$(H,H) = 6.8, H–C(2)), 7.09–7.14 (*m*, H–C(3)), 7.21 (*d*, $^3J$(H,H) = 6.7, H–C(2)), 7.25–7.38 (*m*, H–C(16)), 7.52 (*d*, $^3J$(H,H) = 7.4, H–C(2)), 7.64 (*s*, H–C), 11.00 (*s*, OH). $^{13}$C-NMR (150 MHz, $CDCl_3$) 61.9; 65.9; 69.1; 73.4; 74.8; 75.1; 75.6; 78.4; 79.4; 81.4; 82.7; 108.9; 119.1; 123.9; 124.6; 127.48; 127.59; 127.62; 127.69, 127.73, 137.73, 127.93, 128.06, 128.10, 128.14, 128.28; 128.34; 128.39; 128.41; 131.5; 137.3; 137.3; 137.7; 138.2; 138.3; 138.7; 156.7; 157.6; 169.6. IR (neat) 3064, 3030, 2867, 1671

(C=O), 1613, 1454, 1363, 1330, 1207, 1069, 1028, 991, 736, 697. HR-ESI-MS: 859.3431 ([*M*+Na]$^+$, $C_{52}H_{52}NaO_{10}^+$; calc. 859.3453).

*Ester **36**.*

To a solution of **34** (615 mg, 735 μmol) in $CH_2Cl_2$ (7.0 mL) was added DMF (11.5 μ□, 149 μmol) and $SOCl_2$ (105 μL, 1.47 mmol) at room temperature. After stirring for 1.5 h at this temperature, the solution was concentrated in vacuo and the volatile materials were removed by co-evaporation with toluene (5 mL ×1). The residue was taken up in toluene (2.5 mL) and **35** (0.1 M in toluene, 7.45 mL, 745 μmol) followed by $Et_3N$ (115 μL, 829 μmol), and DMAP (22.0 mg, 180 μmol) were added. After stirring for 1.5 h at room temperature, the reaction was stopped by adding saturated aqueous $NH_4Cl$. The mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 80/20) to afford **36** (1.11 g, 91%) as a colorless oil. Unreacted phenol **35** (33.2 mg, 5%) was recovered as a colorless oil. $R_f$ 0.31 (hexane/EtOAc 4:1). $[\alpha]_{365}^{20}$ = –98.1 (*c* = 0.435, $CHCl_3$). $^1$H-NMR (600 MHz, $CDCl_3$): 3.64 (*brt*, H–C(2)); 3.70–3.88 (*m*, H–C(6); $CH_2$(4), Me); 3.89 (*s*, Me); 4.01 (*d*, $^2J$(H,H) = 10.4, $CH_2$(1)); 4.10 (*d*, $^2J$(H,H) = 10.6, $CH_2$(1)); 4.47–452 (*m*, $CH_2$(2)); 4.56 (*d*, $^2J$(H,H) = 11.4, $CH_2$(2)); 4.60–4.67 (*m*, H–C, $CH_2$(8)); 4.72 (*brs*, H–C); 4.85–5.02 (*m*, $CH_2$(11)); 5.05 (*d*, $^2J$(H,H) = 10.5, $CH_2$(1)); 5.08 (*d*, $^2J$(H,H) = 10.3, $CH_2$(1)); 5.19 (*d*, $^2J$(H,H) = 17.1, $CH_2$(1)); 5.26 (*d*, $^2J$(H,H) = 17.2, $CH_2$(1)); 5.80 (*ddt*, $^3J$(H,H) = 17.1, 10.5, 5.7, H–C); 6.07 (*ddt*, $^3J$(H,H) = 17.2, 10.3, 5.9, H–C); 6.91–6.96 (*m*, H–C(4)); 7.08–7.39 (*m*, H–C(44)); 7.49 (*d*, $^3J$(H,H) = 7.2, H–C(2)); 7.95 (*s*, H–C); 8.11 (*brs*, H–C). $^{13}$C-NMR (150 MHz, $CDCl_3$, several peaks are overlapped): 61.8; 62.0; 65.6; 69.0; 69.1; 73.3; 73.4; 75.1; 75.16; 75.25; 75.30; 75.5; 75.6; 78.35; 78.40; 79.4; 79.5; 86.9; 87.0; 117.8; 118.4; 119.9; 120.1; 127.48; 127.51; 127.57; 127.65; 127.66; 127.70; 127.75; 127.79; 127.9; 128.0; 128.1, 128.2; 128.30; 128.33; 128.38; 128.40; 128.44; 128.46; 128.48; 128.7; 130.9; 132.0; 134.0; 136.8; 137.1; 137.4; 137.7; 138.1; 138.2; 138.6; 138.7; 145.1; 145.6; 154.7; 156.5; 157.2; 162.6; 163.5. IR (neat) 3030, 2867, 1752 (C=O), 1723 (C=O), 1453, 1360, 1320, 1205, 1154, 1067, 990, 736, 697. HR-ESI-MS: 1677.6898 ([*M*+Na]$^+$, $C_{104}H_{102}NaO_{19}^+$; calc. 1677.69075).

*Seco acid **37**.*

To a solution of ester **36** (104 mg, 62.9 μmol) in THF (3.0 mL) was added $Pd(PPh_3)_4$ (7.0 mg, 6.1 μmol) and dimedone (43.0 mg, 307 μmol) at room temperature. After stirring for 2.0 h, the reaction was quenched upon addition of saturated aqueous $NH_4Cl$, and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo The residue was purified by preparative TLC (silica gel, hexane/EtOAc = 50/50) to afford **37** (96.6 mg, 96%) as a white amorphous solid. $R_f$ = 0.19 (hexane/EtOAc 7:3). $[\alpha]_{365}^{20}$ = –160 (*c* = 1.79, $CHCl_3$). $^1$H-NMR (600 MHz, $CDCl_3$): 3.60 (*br*, H–C); 3.64 (*brd*, $^3J$(H,H) = 9.6, H–C); 3.71–3.84 (*m*, H–C(6), $CH_2$(4)); 3.86 (*s*, Me); 3.93 (*s*, Me); 4.02 (*d*, $^2J$(H,H) = 10.8, $CH_2$(1)); 4.08 (*d*, $^2J$(H,H) = 10.8, $CH_2$(1)); 4.47 (*m*, $CH_2$(2)); 4.53 (*d*, $^2J$(H,H) = 12.0, $CH_2$(1)); 4.56–4.62 (*m*, $CH_2$(5), H–C(1)); 4.69 (*brs*, H–C); 4.84 (*d*, $^2J$(H,H) = 4.2, $CH_2$(1)); 4.86 (*d*, $^2J$(H,H) = 4.2, $CH_2$(1)); 4.88–4.96 (*m*, $CH_2$(6)); 4.99 (*d*, $^2J$(H,H) = 11.4, $CH_2$(1)); 5.04 (*d*, $^2J$(H,H) = 11.4, $CH_2$(1)); 6.93 (*m*, H–C(4)); 7.08–7.18 (*m*, H–C(16)); 7.21–7.36 (*m*, H–C(28)); 7.51 (*d*, $^3J$(H,H) = 7.8, H–C(2)); 7.95 (*s*, H–C); 8.00 (*brs*, H–C(1)); 10.50 (*s*, OH). $^{13}$C-NMR (150 MHz, $CDCl_3$, several peaks are overlapped): 61.7; 61.9; 69.0; 69.1; 73.38; 73.40; 75.01; 75.07; 75.12; 75.21; 75.4; 75.5; 75.6; 78.4; 78.5; 79.3; 79.5; 82.9; 86.9; 87.1; 108.4; 118.9; 124.4; 127.57; 127.63; 127.66; 127.71; 127.77; 127.96; 127.99; 128.05; 128.09; 128.16; 128.19; 128.23; 128.26; 128.28; 128.33; 128.32; 128.39; 128.42; 128.44; 131.7; 136.4; 137.3; 137.4; 137.9; 138.08; 138.12; 138.14; 138.21; 137.70; 137.72; 139.8; 144.6; 144.9; 156.95; 157.05; 158.2; 165.4; 167.6. IR (neat): 3183, 3030, 2869, 1720 (C=O), 1691 (C=O), 1604, 1454, 1339, 1067, 1028, 736, 697. HR-ESI-MS: 1597.6265 ([*M*+Na]$^+$, $C_{98}H_{94}NaO_{19}^+$; calc. 1597.6282).

*Salicylide **29**.*

To a solution of hydroxy acid **37** (156 mg, 99.0 μmol), $Et_3N$ (30.5 μL, 220 μmol), and 2,3,4-trichlorobenzoyl chloride (19.0 μL, 122 μmol) in toluene (6.0 mL) was added 4-pyrrolidinopyridine (2.3 mg 15.5 μmol) at room temperature. After stirring for 1.0 h, the reaction was quenched by adding saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo The

residue was purified by preparative TLC (silica gel, hexane/EtOAc = 90/10 69/31) to afford **29** (137 mg, 88%) as a white amorphous solid. $R_f$ (hexane/EtOAc 4:1). $[\alpha]_D^{20}$ = +15.0 (*c* = 0.953, $CHCl_3$). $^1$H-NMR (600 MHz, $CDCl_3$, signals from the minor diastereomer are marked with an asterisk): 3.25–3.40* (*br*); 3.35–3.64 (*m*); 3.72 (*s*, Me); 3.80 (*t*, $^3J$(H,H) = 8.6, H–C); 4.13 (*d*, $^2J$(H,H) = 11.1, $CH_2$(1)); 4.19–4.16* (*br*); 4.33 (*d*, $^2J$(H,H) = 12.3, $CH_2$(1)); 4.39 (*d*, $^2J$(H,H) = 12.3, $CH_2$(1)); 4.56 (*m*, $CH_2$(2)); 4.62 (*d*, $^3J$(H,H) = 9.6, H–C); 4.69 (*d*, $^2J$(H,H) = 10.0, $CH_2$(1)); 4.88–4.94 (*m*, $CH_2$(3)); 5.03–5.09 (*m*, $CH_2$); 6.60–6.75* (*br*); 6.93 (*d*, $^3J$(H,H) = 5.9, H–C); 7.05–7.46 (*m*, H–C(29)); 7.47–7.59 (*m*, H–C(2)). $^{13}$C-NMR (150 MHz, $CDCl_3$, signals from the minor diastereomer are marked with an asterisk*): 61.8; 68.7*; 69.0; 73.3; 73.9*; 75.05; 75.47; 75.8; 77.9*; 78.4; 78.9*; 79.6; 83.1; 86.8*; 87.0; 118.9*; 119.1; 123.9; 127.5–128.9 (Bn); 128.9; 133.1; 136.1; 137.17*; 137.4; 137.9; 138.0; 138.6; 144.1; 144.5; 156.5; 163.1*; 163.4. IR (neat) 3063, 3030, 2867, 1763 (C=O), 1600, 1454, 1325, 1160, 1093, 1067. HR-ESI-MS: 1579.6195 ([*M*+Na]$^+$, $C_{98}H_{92}NaO_{18}^+$; calc. 1579.6176).

*Compound **1**.*

A two-necked flask, thoroughly purged with argon, was charged with $Pd(OH)_2$ (17.9 mg), to which was added a solution of **29** (199 mg, 127 μmol) in THF (6.0 mL). The atmosphere was changed from argon to $H_2$ (1 atm), and the mixture was stirred for 7 h at room temperature. After changing the atmosphere from $H_2$ back to argon, the mixture was filtered through a membrane filter (HLC-DISK 13, 0.45 μm, Kanto Chemical Co., Inc.). The filtrate was concentrated in vacuo to afford the crude material of **1** (98.5 mg) as a white solid.

$^1$H-NMR (600 MHz, $CDCl_3$, signals from the minor diastereomer are marked with an asterisk*): 3.14–3.16 (*m*, H–C(2)); 3.24–3.26 (*m*, H–C(2)); 3.38 (*m*, $CH_2$(1)); 3.63 (*m*, $CH_2$(1); 3.72* (*s*, Me(0.6)); 3.74 (*s*, Me(2.4); 4.26* (*d*, $^3J$(H,H) = 9.7, H–C(0.2)); 4.29 (*d*, $^3J$(H,H) = 8.6, H–C(0.8)); 4.38–4.60 (*br*, OH); 4.35–5.10 (*br*, OH(3)); 6.98 (*s*, H–C(0.8)); 6.99* (*s*, H–C(0.2)); 10.06* (*s*, OH(0.2)); 10.12 (*s*, OH(0.8)). $^{13}$C-NMR (150 MHz, $CDCl_3$, signals from the minor diastereomer are marked with an asterisk*): 61.21; 61.24*; 61.30*; 61.41; 70.3; 72.7*; 73.7; 74.6; 78.3; 78.5*; 81.7*; 81.9; 117.7; 118.3*; 118.8*; 119.1; 133.1*; 133.4; 137.7; 137.9*; 142.4; 142.7*; 151.4; 152.0*; 164.5. HR-ESI-MS: 655.1510 ([*M*–H]$^-$, $C_{28}H_{31}O_{18}^-$; calc. 655.1516).

## Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/xxxxxx.

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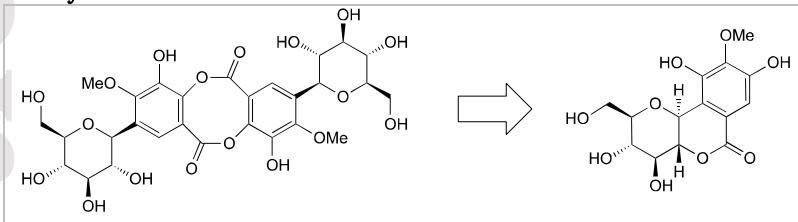
**Entry for the Table of Contents**




originally proposed structure of ardimerin

(*synthetic material does not match reported data for natural product*)

bergenin