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(±)-Diinsininone: made nature's way

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Abstract

We report the synthesis of diinsininone (**33**), the aglycone of (±)-diinsinin (**2**). Thereby, we complete the first construction of a proanthocyanidin (PA) type-A compound incorporating a [3.3.1]-bicyclic ketal as its characteristic core. Our strategy utilizes a coupling between a benzopyrylium salt and a flavanone that proves applicable to other PA type-A compounds. During this undertaking, treatment of naringenin (**9**) with 2-iodoxybenzoic acid (IBX) followed by reductive work-up affords eriodictyol (**10**). This reactivity mirrors that of catechol hydroxylase (F3H) found in the flavonoid pathway. Other interesting transformations include the formation of flavonoids through an *ortho*-quinone methide (*o*-QM) cycloaddition–oxidation sequence and regioselective β-glycosidations of several unprotected flavanones suggesting a likely synthesis of **2** from the aglycone **33**.

Keywords

Proanthocyanidin; [3.3.1]-Bicyclic ketal; Benzopyrylium; *o*-Quinone methide; Benzopyran; IBX; Catechol; Flavonoid

1. Introduction

Chemists should ponder probable biosynthetic pathways leading to their target, because few things are more humbling to one's best-laid plans than nature's simpler solution. Nature has been conducting and optimizing chemical experiments for millions of years; therefore, matching or exceeding nature's accumulated wisdom is a daunting challenge. However, the precise sequence used by nature to assemble its products is rarely known. In these instances, synthetic chemists are empowered with the ability to illuminate nature's hidden pathways by determining the reactivity inherent to its intermediates.

Consider the [3.3.1]-bicyclic compounds diinsininol (**1**) and diinsinin (**2**) shown in Figure 1. In nature's quest to build these compounds in an efficient manner, it might fashion a single flavan component using genomics, and then cause this entity to dimerize, forming bonds *i* and *ii*, whereupon oxidases and lipases would complete its creation. By mimicking this purported pathway, we hoped to reveal some of nature's more closely guarded secrets regarding chemoselectivity, diastereoselectivity and enantioselectivity during the assembly process leading to **1** and **2**.

In 1996, the compounds **1** and **2** were discovered in the rhizome of *Sarcophyte piriei* Hutch, a parasitic plant that grows on the roots of the *Acacia* species of tropical shrubs and trees.¹ A decoction of its tuber is used in Somalian folk medicine; an activity that led to their eventual isolation and evaluation.² Diinsininol (**1**) and diinsinin (**2**) inhibit prostaglandin synthesis (IC₅₀ values of 9.20 μM and 13.14 μM, respectively) and platelet activating factor-induced

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exocytosis (IC₅₀ values of 49 μM and 39 μM, respectively). These biological activities are common among drugs that inhibit cyclooxygenase-2 (COX-2) and protect cells from tumor growth; tumors with high COX-2 levels are usually larger and metastasize faster than those without.³

2. Biological relevance

The flavonoid carbon skeleton encompasses a range of structural and biological diversity and is widely distributed throughout the plant kingdom.⁴ Because of its abundance, it often proves useful as a starting material for synthesis. Its structural diversity on the other hand enables evaluation of an assortment of pharmacological targets. More than 5000 flavonoids have been isolated varying in the hydroxylation, methoxylation, glycosylation, and acylation patterns of the carbon backbone.⁵ This arsenal of structures evolved as a defense to oxidative stress and hungry herbivores.⁶

Flavonoids protect organisms from oxidative stress by destroying reactive oxygen species that would have otherwise caused cell damage. It has long been known that foods high in antioxidants lower the risk of many diseases, including cancer, cataract, heart disease, and rheumatoid arthritis.⁷ The so-called 'French Paradox' stems from the observation that French people consuming as much as 1200 mg of flavonoids per liter of red wine with structures similar to **1** and **2** display lower incidences of coronary disease despite a higher intake of saturated fat.⁸⁻¹²

In addition to these suppositious medical benefits, compounds **1** and **2** resemble antihyperglycemic components found within cinnamon, which have been studied for their ability to potentiate insulin, maintain normal blood sugar levels, and assist in fat metabolism.¹³ Currently insulin resistance, which is referred to as metabolic syndrome X, affects 50 million people. Syndrome X is linked to an unhealthy lifestyle, genetic factors, and the progression to type-II diabetes.¹⁴ In 2004, several powerful antihyperglycemic compounds were identified in cinnamon and determined to be trimer and tetramers of PA type-A compounds displaying the characteristic [3.3.1]-bicyclic ketal core.¹⁵

3. Relevance of the speculative biosynthetic pathways

The biosyntheses of **1** and **2** initially follows the flavonoid pathway, which proceeds from phenylalanine through *trans*-cinnamate, chalcones, flavanones, anthocyanidins, to flavans. It is among the best studied of biosynthetic pathways in nature.¹⁶⁻¹⁸ The optically active compounds **1** and **2** suggest a double union between two products emerging from the flavonoid pathway. It is reasonable to speculate that an organism would utilize an identical path for these structurally related natural products. Paths A and B have been proposed (Scheme 1). In our minds, these proposed routes are profoundly different and suggest different consequences for reactivity and stereochemistry leading to the [3.3.1]-bicyclic ketal. Path B, which has been shown to afford the singly linked type-B PA structures, was proposed by Nonaka to yield the [3.3.1]-bicyclic ketal structure found in type-A PA compounds by an oxidative cyclization. A catechin type-B dimer has been transformed into the corresponding type-A structure with picrylhydrazyl radical and hydrogen peroxide.¹⁹ Path B appears to entail the chemoselective addition of a flavanone or flavan nucleophile to an electrophile arising from the *para*-quinone methide or its corresponding cation. This initial coupling should be inherently diastereoselective. However, if a Path B-oxidation sequence does result in the biosyntheses of **1** and **2**, it is remarkable because the original stereocenters ultimately become compromised when carried to the optically active natural products. Path A, on the other hand, suggests that a benzopyrylium salt can undergo a net [3+3]-cycloaddition in an enantioselective fashion chaperoned by an unknown enzyme,²⁰ or perhaps proceeds in a diastereoselective fashion with the directing stereochemistry again compromised when forming the final natural products.

The oxidation state of the components at the time of coupling remains unclear as does the timing of the oxidation that distinguishes between the two natural products. Flavanone 3-hydroxylase (F3H) may catalyze hydroxylation of (2*S*)-flavanone to eriodictyol. A combination of di-hydroxylated and mono-hydroxylated materials leads to diinsininone (**33**), while a combination of di-hydroxylated systems provides diinsininolone (**34**). Alternatively, F3H or some derivative of this enzyme may establish divergence in oxidation states (catechol vs phenol) in the final or penultimate step of the biosynthesis. Similarly, glycosylation may occur as the final or penultimate step of the biosynthesis. Divergence among the pathways for similar components seems energetically wasteful for an organism.

4. Synthetic relevance

To the best of our knowledge, there are no previous synthetic endeavors addressing diinsininol (**1**), diinsinin (**2**), or similar type-A PA compounds in the literature. While there are numerous methods for the construction of chromans, the enantioselective construction of flavonoids is a surprisingly difficult task and it is difficult to improve upon their biosynthetic pathway.²¹ Recently, our group devised a strategy for the enantioselective assembly of non-natural flavonoids by a [4+2]-cycloaddition between an *o*-QM and a chiral enol ether. We utilized this process in the first total synthesis of the flavonoid (+)-mimosifoliol.²² We initially envisioned extending this strategy to the chroman functionality embedded within diinsininol (**1**) and diinsinin (**2**). The additional hydroxyl residue that distinguishes **1** from **2** could be introduced using our IBX oxidation–reduction sequence for the construction of *o*-quinols from phenols.²⁸

5. Related path A and B synthetic endeavors

Previous syntheses of the singly linked PA type-B structures have followed the putative biosynthetic route, Path B.^{23–26} However, unless other stereochemical substituents adjoin the site of reactivity and direct the process Path B couplings appear to result in a complex diastereomeric mixture of products. Moreover, regioselectivity and chemoselectivity prove problematic for most systems. Far less information is available regarding the likelihood of a successful Path A coupling. However, Jurd reports a simple benzopyrylium salt undergoes coupling with phloroglucinol to result in a similar [3.3.1]-bicyclic ketal in 25% yield.²⁷

6. Our synthetic studies

We began surveying these problems by constructing the flavans, flavanones, and dihydroxyflavanones, which might arise in the putative biosynthetic pathway, and then proceeded to investigate the inherent ability of these structures to form type-A and B PA adducts (Scheme 2). Recently, our group had shown that *o*-QMs generated from *o*-Boc salicyl-alcohols would undergo cycloadditions with electron-rich olefins forming chroman adducts that resemble compound **5**.²² However, our original two-pot process, involving reduction and coupling proved unfruitful with aldehyde **3**. This substrate mandates the use of an in situ reduction–cycloaddition protocol. The tris-*o*-Boc salicylaldehyde **3** (0.10 M diethyl ether, –78 °C), styrene **4** (40 equiv), and magnesium bromide dietherate (1.0 equiv) are subjected to lithium aluminum hydride (1.0 equiv) and thereby produce the flavan **5** in a 45% isolated yield.

C(4)-oxidation of flavan **5** (0.10 M methylene chloride) occurs with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2 equiv) in the presence of water (1.0 equiv) to afford the flavanone **8** in 88% yield. Cleavage of the *t*-butyl residues found in compounds **5** and **8** (0.01 M methylene chloride) is accomplished with zinc bromide (10 equiv) to afford the flavan **6** and the flavanone **9**, respectively. Per-methylation of **6** (0.10 M acetone) using methyl iodide (5.0 equiv) and potassium carbonate (4.0 equiv) affords tris-methylated flavan ether **7** and facilitates its structural identification.

Next, we used our one-pot two-step chemical process that mimics the enzyme F3H found in the flavan biosynthesis.²⁸ The unprotected flavanone **9** (0.03 M dimethyl sulfoxide) is subjected to 2-iodoxybenzoic acid (2.0 equiv) and forms a highly reactive *o*-quinone intermediate, which is reduced during work-up with sodium sulfite (3.0 equiv) to provide eriodictyol (**10**) in an isolated 80% yield. As previously observed, phenols bearing electron-withdrawing groups such as $-C(O)R$, $-CHO$, and $-NO_2$ fail to undergo oxidation with 2-iodoxybenzoic acid.²⁸ This reaction can be viewed as electrophilic aromatic substitution.²⁹ The $-C(O)R$ substituent of flavanone **9** deactivates the A-ring and effectively prevents its oxidation. With the phenol **9** and catechol **10** in hand, methods for their regioselective glycosidation were explored. The insolubility of substrates **9** and **10** severely limited the conditions that could be employed. After some experimentation, we found that phenol **9** and catechol **10** (0.10 M quinoline) undergo regioselective β -glycosidation with acetobromo- α -*D*-glucose **11** (1.50 equiv) and silver carbonate (1.50 equiv) to produce compounds **13** and **12** in good yield.³⁰ The following order of reactivity was observed for flavanone **9** and appears to follow the relative acidity of each phenol: C(5)-OH < c(4')-OH < c(7)-OH. Given this result, we expect the glycosidation of the aglycones of **1** and **2** to be fairly straightforward.

Next, we turned our attention to the formation of the C(4)-C(8) bond following a putative Path B biosynthesis. Given our experiences with diastereoselective additions to *o*-QMs, we decided to explore this reaction within the context of a flavanone (Scheme 3). The glycosidation reaction revealed that the hydroxyl residues of flavanones would also undergo regioselective alkylation. We decided to exploit this inherent reactivity for selective protection. Sequential treatment of flavanone **9** with methyl iodide, *tert*-butyldimethylsilyl triflate, and di-*tert*-butyl dicarbonate and the appropriate bases affords compound **15** in good yield (75%).

Reaction of the *o*-OBoc flavanone **15** (0.05 M tetrahydrofuran) with phenylmagnesium bromide (1.0 equiv) followed by lithium borohydride (1.0 equiv) results in flavan **16** formation in a 52% yield and a 3:2 ratio of diastereomers. We presume that the reaction proceeds through an *o*-QM intermediate. The lack of stereoselectivity was somewhat troubling and did not bode well for applying any of these Path B strategies to the syntheses of **1** and **2**. Therefore, we sought another method for carbon-carbon bond formation. The flavanone **9** was permethylated to afford compound **14**. Treatment of flavanone **14** (0.2 M tetrahydrofuran, -78°C) with the phloroglucinol lithium **17** (3.0 equiv) affords the chromene **18** by spontaneous elimination of the tertiary alcohol intermediate. Isomerization of the double bond within compound **18** (0.07 M benzene, 65°C) occurs upon treatment with ethoxymagnesium bromide (2.0 equiv) to form the enol ether **19**.³¹ We envisioned that debenylation of compound **19** and subsequent ketalization would afford the desired [3.3.1]-bicyclic system. However, treatment of the debenzylated adduct with strong acid results in loss of the phloroglucinol fragment from adduct **19**.

With compound (\pm)-**7** in hand, we considered other strategies mimicking Path B (Scheme 4).³² Treatment of the flavan (\pm)-**7** (0.10 M methylene chloride) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.5 equiv) affords a mixture of more than four stereoisomers of the dimer **22** in a combined 52% yield. Given this result, we expected optically pure **7** to give more than two diastereomers; there must be atropisomerism among the *trans* and/or *cis* adducts. To partially circumvent this stereochemical problem, we examined the oxidation of **7** (0.1 M methylene chloride) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.0 equiv) and in the presence of tribenzylated phloroglucinol (**20**) (3 equiv). The reaction proceeds in a 60% yield and affords the type-B PA structure **21** in a 3:2 ratio favoring the *trans* diastereomer. In addition to the stereochemistry issues raised by this strategy, there are numerous protecting group issues that would have to be resolved as well. Therefore, we began to investigate a Path A inspired synthesis.

A Path A strategy requires rapid and easy access to the corresponding benzopyrylium salts. We initially considered methods to construct these systems from **7**, **9**, and **10**. However, careful scrutiny of the literature reveals oxidative methods are plagued by low yields, crude mixtures.³³ Instead, we opted to explore a new protocol recently reported by Mas (Scheme 5).³⁴ 2,4,6-Triacetoxybenzaldehyde (**24**) undergoes condensation with hydroxyacetophenones **25** and **26** in a saturated hydrochloric acid solution in methanol to result in the benzopyrylium salts **27** and **28** in good yields.

We find that addition of an aqueous buffered solution of phloroglucinol **29** (3 equiv) to the respective benzopyryliums **27** and **28** (0.20 M methanol) affords the ketals **30** and **31**, respectively, in outstanding yields. Optimal conditions employ a Emrys microwave reactor with heating to 150 °C for 120 min. Isolation of non-ketalized products from reactions conducted at lower temperatures reveals that the carbon–carbon bond formation precedes the oxygen–carbon bond formation. While we entertained the possibility of desymmetrizing the *meso* compounds **30** and **31**, we first examined the addition of flavans and flavanones to the benzopyrylium salts **27** and **28**.

The benzopyrylium salt **27** (0.10 M methanol) combines with flavan **6** (6 equiv) using the previously described microwave equipment and results in the regioselective formation of the type-A PA compound **32** in 42% yield (Scheme 6). However, a 1:1 mixture of diastereomers is observed. Upon lowering the temperature to 120 °C and lengthening the reaction time to 20 h for the subsequent combination of the benzopyrylium **27** with the flavanone **9**, diinsininone (**33**) forms. To our delight, compound **33** emerges from this extended reaction as a single diastereomer. However, the similar conditions proved entirely unproductive for the combination of the benzopyrylium **27** with the hydroxylated flavanone **10**.

The formation of a single diastereomer of diinsininone (**33**) is explained by the equilibria shown in Scheme 7. It should be noted that we had originally imagined degrading naringin (**35**) to afford optically active (*S*)-C(2) flavanone **9**. However, in our hands, hydrolysis of the sugar results in formation of racemic **9** as determined by a Chiralcel OD-H column.³⁵

7. Conclusions

One day, a better understanding of the PA biosynthetic pathway may allow the genetic engineering of plants for the production of compounds coveted for their antioxidant and antihyperglycemic activities. Until that day arrives, chemical synthesis remains the best method for the construction of these compounds and enables the exploration of their biological activities. The preceding synthetic studies have illuminated inherent reactivity of several intermediates belonging to the flavonoid pathway. These studies suggest that compounds **1** and **2** most likely arise from an identical biosynthetic pathway proceeding through a Path A benzopyrylium coupling. Whether the oxidative divergence among these structures arise as the ultimate or penultimate step remains to be determined. Related natural products belonging to the Dragon's Blood family of flavanones, a name that derives from the red resin plant exudates, can also be accessed by appropriately adapting the above strategy (Fig. 2).^{32b}

8. Experimental

8.1. Aldehyde **3**

A flame-dried flask equipped with a stir-bar and a nitrogen line containing 2,4,6-trihydroxybenzaldehyde (2 g, dehydrated with P₂O₅, 0.05 M CH₂Cl₂), Hunig's Base (1.36 mL, 0.6 equiv), DMAP (four crystals), and Boc₂O (7.74 g, 3.2 equiv) was stirred overnight. The reaction was quenched with 1 M NH₄Cl and extracted twice with CH₂Cl₂. The organic layer was washed with water, brine, dried over MgSO₄, and concentrated in vacuo. The crude

mixture was then chromatographed on silica gel, eluting with petroleum ether/EtOAc (95:5) to afford the desired product in 75% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.24 (s, 1H), 6.88 (s, 2H), 1.46 (s, 18H), 1.42 (s, 9H).

8.2. Tris-protected flavan 5

A flame-dried flask equipped with stir-bar and nitrogen line, was charged with aldehyde **3** (50 mg, 0.1 M Et_2O), 1-*tert*-butoxy-4-vinylbenzene (0.19 mL, 40 equiv), and $\text{MgBr}_2\cdot\text{OEt}_2$ (28.4 mg, 1.00 equiv). The solution was cooled to -78°C and LiAlH_4 (4 mg, 1.00 equiv) was added. The reaction was warmed to rt over 3 h then quenched with 1 M NaHCO_3 and extracted with Et_2O . The ether layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (95:5) to afford the desired product in 45% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.08 (d, 2H, $J=9$ Hz), 6.70 (d, 2H, $J=9$ Hz), 6.39 (s, 1H), 6.34 (s, 1H), 5.20–4.90 (m, 1H), 2.60–2.20 (m, 4H), 1.45 (s, 9H), 1.40 (s, 18H).

8.3. Flavan 6

A flame-dried flask equipped with stir-bar and nitrogen line, was charged with flavan **5** (20.0 mg, 0.01 M CH_2Cl_2) and ZnBr_2 (87.5 mg, 10 equiv). The solution was stirred at rt for 6 h. The reaction was quenched with 1 M HCl and extracted twice with EtOAc. The ether layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (50:50) to afford the desired product in 75% yield. $^1\text{H NMR}$ (400 MHz, CD_6CO): δ 7.27 (d, 2H, $J=9$ Hz), 6.85 (d, 2H, $J=9$ Hz), 6.00 (s, 1H), 5.87 (s, 1H), 4.89–4.86 (m, 1H), 2.72–2.66 (m, 2H), 2.11–1.88 (m, 2H).

8.4. Tris-methylated chroman 7

A round-bottom flask equipped with a stir-bar was charged with flavan **6** (1.67 g, 0.2 M acetone), K_2CO_3 (340 mg, 4 equiv), and MeI (0.19 mL, 5 equiv). The reaction was stirred overnight and filtered. The reaction was diluted with H_2O and extracted twice with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (80:20) to afford the desired product in 90% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.36 (d, 2H, $J=9$ Hz), 6.93 (d, 2H, $J=9$ Hz), 6.13 (s, 1H), 6.09 (s, 1H), 4.93–4.92 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 2.80–2.60 (m, 4H), 2.20–1.97 (m, 4H).

8.5. Flavanone 8

Flavan **5** (30 mg, 1 equiv, 0.01 M CH_2Cl_2), H_2O (1 μL , 1 equiv), and DDQ (recrystallized from hot CHCl_3 , 26.5 mg, 2 equiv) were added to a round-bottom flask equipped with a stir-bar, a septum and stirred under N_2 (g) at rt overnight. The reaction was diluted with H_2O and extracted twice with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (70:30) to afford the desired product in 88% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.08 (d, 2H, $J=9$ Hz), 6.70 (d, 2H, $J=9$ Hz), 6.54 (s, 1H), 6.48 (s, 1H), 5.55–5.50 (m, 1H), 3.38–3.13 (m, 2H), 1.56 (s, 18H), 1.40 (s, 9H).

8.6. 4',5,7-Trihydroxyflavanone (9)

A flame-dried flask equipped with stir-bar and nitrogen line, was charged with flavanone **8** (20.0 mg, 0.01 M CH_2Cl_2) and ZnBr_2 (85.2 mg, 10 equiv). The solution was stirred at rt for 6 h. The reaction was quenched with 1 M HCl and extracted twice with EtOAc. The ether layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc

(50:50) to afford the desired product in 82% yield. ^1H NMR (400 MHz, CD_6CO): δ 12.19 (s, 1H), 9.59 (s, 1H), 8.55 (s, 1H), 7.39 (d, 2H, $J=9$ Hz), 6.90 (d, 2H, $J=9$ Hz), 5.95 (s, 1H), 5.94 (s, 1H), 5.48–5.44 (m, 1H), 3.22–3.15 (m, 2H), 2.75–2.70 (m, 2H); ^{13}C NMR (100 MHz, CD_6CO): δ 197.4, 167.3, 165.4, 164.5, 158.8, 130.9, 129.1, 116.3, 103.3, 96.8, 95.9, 80.0, 43.6, 30.5; HRMS (ESI-TOF) (M^+H^+) m/z calcd for $\text{C}_{15}\text{H}_{12}\text{O}_5$ 273.0685, found 273.0765.

8.7. Eriodictyol (10)²⁸

To a solution of flavanone **9** (1.011 g, 0.03 M DMSO) was added IBX³⁶ (2.135 g, 2 equiv) and stirred at rt for 5 h. As the reaction progressed, the color changed from a translucent yellow solution to an opaque brown solution. $\text{Na}_2\text{S}_2\text{O}_4$ (1.94 g, 3 equiv) was added to the reaction and stirred for an additional 4 h. The reaction was quenched with water (300 mL) and extracted with EtOAc (3 \times 100 mL). The combined organic extracts stirred with pH 8.5 buffer solution to remove *o*-iodobenzoic acid. The organic layer was washed with brine, dried with MgSO_4 , filtered, and concentrated. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (50:50) to afford the desired product in 80% yield. ^1H NMR (400 MHz, CD_6CO): δ 7.03 (s, 1H), 6.87 (s, 2H), 5.96–5.94 (m, 2H), 5.41–5.38 (m, 1H), 3.18 (m, 1H), 2.75 (m, 1H); ^{13}C NMR (100 MHz, CD_6CO): δ 167.7, 137.8, 135.7, 134.8, 116.8, 116.5, 102.0, 89.7, 86.5, 85.2, 73.6, 67.2, 66.3, 50.4, 14.0; HRMS (ESI-TOF) (M^+Na^+) m/z calcd for $\text{C}_{15}\text{H}_{12}\text{O}_6$ 311.0633, found 311.0525.

8.8. Acetobromo- α -D-glucose (11)

D-Glucose (2.05 g, 0.40 M pyridine) and Ac_2O (12 mL, 0.44 M) were stirred at rt overnight. The reaction was quenched with H_2O , extracted with CDCl_3 , washed with NaHCO_3 , dried with Na_2SO_4 , and afforded pentaacetyl-glucose. ^1H NMR (400 MHz, CDCl_3): δ 5.72–5.71 (m, 1H), 5.28–5.24 (m, 1H), 5.16–5.11 (m, 2H), 4.32–4.28 (m, 1H), 4.13–4.10 (m, 1H), 3.86 (m, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.8, 170.3, 169.6, 169.5, 169.2, 91.9, 73.0, 72.9, 70.4, 67.9, 61.6, 21.0, 20.9, 20.8, 20.7; HRMS (ESI-TOF) (M^+Na^+) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_{11}$ 413.1162, found 413.1057. When the pentaacetoglucose (2 g, 0.57 M acetic acid) was dissolved, HBr (0.64 mL, 48% in acetic acid) was added drop-wise. The reaction was stirred overnight, poured over an ice/ H_2O slurry, extracted with CHCl_3 , neutralized with NaHCO_3 , washed with H_2O , dried with Na_2SO_4 , and afforded acetobromo- α -D-glucose (**11**). ^1H NMR (400 MHz, CDCl_3): δ 6.62–6.61 (m, 1H), 5.59–5.55 (m, 1H), 5.19–5.15 (m, 1H), 4.86–4.83 (m, 1H), 4.36–4.30 (m, 2H), 4.15–4.12 (m, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.7, 170.1, 170.0, 169.7, 86.8, 72.3, 70.8, 70.4, 67.4, 61.1, 20.9, 20.9, 20.8, 20.7; HRMS (ESI-TOF) (M^+Na^+) m/z calcd for $\text{C}_{14}\text{H}_{19}\text{O}_9\text{Br}$ 433.0212, found 433.0126.

8.9. Naringenin glucoside 13³⁰

A solution of flavanone **9** (9.4 mg, 0.14 M quinoline), bromide **11** (21 mg, 1.50 equiv), and Ag_2CO_3 (13.8 mg, 1.5 equiv) was stirred for 6 h at rt. The reaction was poured into methanol, filtered through a short pad of Celite, and evaporated in vacuo. The residue was dissolved into EtOAc, washed with 1 N HCl, washed with brine, and dried over MgSO_4 . After evaporation, the resulting crude product was purified by flash chromatography eluting with hexane/EtOAc (1:1) to afford the desired product in 85% yield. The product was an inseparable mixture of diastereomers. ^1H NMR (400 MHz, DMSO): δ 12.03 (s, 1H), 9.65 (s, 1H), 7.31 (d, 2H, $J=9$ Hz), 6.79 (d, 2H, $J=9$ Hz), 6.16–6.09 (m, 2H), 5.67–5.63 (m, 1H), 5.53–5.50 (m, 1H), 5.37–5.34 (m, 1H), 5.06 (m, 2H), 4.30–4.26 (m, 1H), 4.15–4.05 (m, 2H), 3.40–3.33 (m, 1H), 2.76–2.70 (m, 1H), 2.00–1.95 (m, 12H); (ESI-TOF) (M^+Na) m/z calcd for $\text{C}_{29}\text{H}_{30}\text{O}_{14}$ 625.1636, found 625.1528.

8.10. Trimethylated naringenin 14

Naringenin (**9**, 1 g, 0.2 M acetone), K_2CO_3 (3.05 g, 6 equiv), and MeI (1.83 mL, 8 equiv) were stirred overnight. The reaction was filtered and concentrated in vacuo. The resulting crude product was purified by flash chromatography eluting with petroleum ether/EtOAc (70:30) to afford the desired product in 65% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 2H, $J=9$ Hz), 6.98 (d, 2H, 9 Hz), 6.18 (s, 1H), 6.16 (s, 1H), 5.45–5.40 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.03–2.85 (m, 2H), 2.64–2.58 (m, 2H).

8.11. Tris-protected naringenin 15

Naringenin (**9**, 162 mg, 0.1 M DMF), Na_2CO_3 (69 mg, 1.10 equiv), and MeI (0.4 mL, 1.10 equiv) were stirred at rt overnight. The reaction was quenched with H_2O and extracted with EtOAc. The organic layer was washed repeatedly with H_2O , washed with brine, and dried over $MgSO_4$. The resulting crude product was purified by flash chromatography (petroleum ether/EtOAc 50:50) to afford mono-protected naringenin. 1H NMR (400 MHz, CD_6CO): δ 12.15 (s, 1H), 8.57 (s, 1H), 7.40 (d, 2H, $J=8$ Hz), 6.89 (d, 2H, $J=8$ Hz), 6.04 (s, 1H), 6.03 (s, 1H), 5.39–5.35 (m, 1H), 3.82 (s, 3H), 3.10–3.03 (m, 2H), 2.78–2.70 (m, 2H). mono-Protected naringenin (66 mg, 0.1 M THF), 2,6-lutidine (0.028 mL, 1.05 equiv), and TBSOTf (0.056 mL, 1.05 equiv) were stirred at rt for 4 h. The reaction was quenched with H_2O , extracted with EtOAc, and dried with Na_2SO_4 . The resulting crude product was purified by flash chromatography (petroleum ether/EtOAc 80:20) to afford bis-protected naringenin. 1H NMR (400 MHz, CD_6CO): δ 12.15 (s, 1H), 7.47 (d, 2H, $J=8$ Hz), 6.96 (d, 2H, $J=8$ Hz), 6.07 (s, 1H), 6.05 (s, 1H), 5.55–5.51 (m, 1H), 3.86 (s, 3H), 3.27–3.19 (m, 2H), 2.81–2.77 (m, 2H), 1.00 (s, 9H), 0.33 (s, 6H). The bis-protected compound (0.1 M CH_2Cl_2), DMAP (one crystal), Hunig's Base (0.037 mL, 1.0 equiv), and Boc_2O (100 mg, 1.0 equiv) were stirred at rt for 1 h. The reaction was quenched with H_2O , extracted with EtOAc, and dried with Na_2SO_4 . The resulting crude product was purified by flash chromatography (petroleum ether/EtOAc 90:10) to afford tris-protected naringenin **15** in 75% yield. 1H NMR (400 MHz, CD_6CO): δ 7.50–7.48 (d, 2H, $J=8$ Hz), 6.98–6.95 (d, 2H, $J=8$ Hz), 6.50 (s, 1H), 6.37 (s, 1H), 5.52–5.49 (s, 1H), 3.90 (s, 3H), 3.08–3.05 (m, 2H), 2.85 (m, 2H), 1.54 (s, 9H), 1.01 (s, 9H), 0.25 (s, 6H).

8.12. Compound 16

A flame-dried flask equipped with stir-bar and nitrogen line, was charged with flavanone **15** (8.0 mg, 1 equiv, 0.05 M THF) and cooled to -78 °C. Phenylmagnesium bromide (8.0 μ L, 1.50 equiv, 3 M THF) was added drop-wise and stirred for 1 h. $LiBH_4$ (1.0 mg, 1.00 equiv) was added to the solution, warmed to rt, quenched with H_2O , and extracted with EtOAc. The ether layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (90:10) to afford the desired product in 52% yield.

8.13. Chromene 18

Bromotribenzylated phloroglucinol (65 mg, 0.3 M THF, 3 equiv) was cooled to -78 °C, n -BuLi (0.052 mL, 2.5 M THF, 3.00 equiv) was added drop-wise, and the reaction stirred until complete by TLC (eluting with petroleum ether/EtOAc 90:10). This solution was added drop-wise to a stirring solution of flavan **15** (13.7 mg, 0.2 M THF) at -78 °C. After 1 h, the reaction was quenched with H_2O , extracted EtOAc, washed with brine, and dried with $MgSO_4$. The reaction was purified by flash chromatographed with EtOAc/hexane (70:30) to afford the desired product in 72% yield. 1H NMR (400 MHz, $CDCl_3$): δ 7.53–7.22 (m, 17H), 6.61–6.59 (m, 2H), 6.35–6.30 (m, 2H), 6.14–6.12 (m, 1H), 5.92–5.91 (m, 1H), 4.91 (d, 1H, $J=5$ Hz), 4.76 (d, 1H, $J=5$ Hz), 5.05–4.96 (m, 6H), 3.73 (s, 3H), 3.72 (s, 3H), 3.30 (s, 3H); HRMS (ESI-TOF) ($M-H$)⁺ m/z calcd for $C_{45}H_{40}O_7$ 691.7900, found 691.2711.

8.14. Enol ether 19³¹

A flame-dried flask equipped with a stir-bar and a nitrogen line containing EtOH (2 equiv, 0.5 M THF) was cooled to 0 °C. Phenylmagnesium bromide (2 equiv) was added to the solution warmed to rt, then evaporated to dryness. The chromene **18** (1 equiv, 0.7 M benzene) was added to the EtOMgBr, equipped with a reflux condenser, stir-bar, nitrogen line, and refluxed for 6 h. The reaction was quenched with H₂O, extracted EtOAc, washed with brine, and dried with MgSO₄. The reaction was purified by flash chromatography eluting with EtOAc/hexane (70:30) to afford the desired product in 65% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.53–7.05 (m, 15H), 7.03 (d, 2H, *J*=8 Hz), 6.66 (d, 2H, *J*=8 Hz), 6.47 (s, 1H), 6.36 (d, 1H, *J*=10 Hz), 6.28–6.27 (m, 1H), 6.00 (s, 1H), 4.94 (s, 1H), 4.98 (s, 2H), 4.88–4.83 (m, 4H), 4.66 (d, 1H, *J*=10 Hz), 3.74 (s, 3H), 3.72 (s, 3H), 3.33 (s, 3H).

8.15. Chroman 21

To a flame-dried flask equipped with a stir-bar and a nitrogen line containing flavan **7** (20 mg, 0.10 M CH₂Cl₂) and tribenzylphloroglucinol (33.6 mg, 3 equiv) was added DDQ (recrystallized from hot CHCl₃, 15.8 mg, 1 equiv) at rt. The reaction was stirred for 3 h, quenched with H₂O, extracted with EtOAc, the organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (70:30) to afford the desired product in 60% yield.

8.16. Dimer 22

To a flame-dried flask equipped with a stir-bar and a nitrogen line containing flavan **7** (30 mg, 0.10 M CH₂Cl₂) stirring at rt was added DDQ (recrystallized from hot CHCl₃, 11.2 mg, 0.5 equiv). The reaction was stirred for 3 h, quenched with H₂O, extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/EtOAc (40:60) to afford the desired product in 52% yield.

8.17. 2,4,6-Triacetoxybenzaldehyde (24)

A flame-dried flask equipped with a stir-bar and a nitrogen line containing phenol **23**, dehydrated with P₂O₅, (2.58 g, 1 equiv, 0.15 M Et₂O), K₂CO₃ (8.41 g, 3.6 equiv), and Ac₂O (16.8 mL, 11 equiv) was stirred overnight. The reaction was filtered and concentrated to afford the desired product in 80% yield. ¹H NMR (400 MHz, CDCl₃): δ 10.13 (s, 1H), 6.97 (s, 2H), 2.38 (s, 6H), 2.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 185.6, 168.7, 167.9, 155.2, 1530.0, 118.3, 114.9, 21.4, 21.0; δ IR (CH₂Cl₂, ν_{max} cm⁻¹) 1778, 1697, 1616, 1580, 1433, 1370, 1298, 1180, 1122, 1051, 1022; HRMS (ESI-TOF) (M⁺+Na) *m/z* calcd for C₁₃H₁₂O₇ 303.2302, found 303.0484.

8.18. General method for benzopyrilium salt formation³⁴

A stream of anhydrous gaseous HCl was first passed through a solution of hydroxyacetophenone (1.6 g, 7 equiv, 0.12 M MeOH) at 0 °C, until the concentration of HCl rose to 15% by mass. A solution of aldehyde **24** (0.43 g, 1 equiv, 0.06 M MeOH) was then added drop-wise at 0 °C. At the end of the addition, the reaction mixture was kept for a few minutes at rt and evaporated to dryness. The resulting residue was vigorously stirred in Et₂O, which afforded the crude product after filtration and washing with the same solvent. The pure product was obtained by recrystallization in MeOH–HCl (95:5) in 65 and 70% yields for compounds **27** and **28**, respectively. *Luteolinidin Chloride* (**27**). ¹H NMR (400 MHz, CD₃OD–TFA 99:1): δ 8.95 (d, 1H, *J*=9 Hz), 7.94 (d, 1H, *J*=9 Hz), 7.78 (dd, 1H, *J*=9, 2 Hz), 7.65 (d, 1H, *J*=2 Hz), 6.98 (d, 1H, *J*=9 Hz), 6.87 (d, 1H, *J*=2 Hz), 6.63 (d, 1H, *J*=2 Hz); ¹³C NMR (100 MHz, CD₃OD–TFA 99:1): δ 172.4, 171.9, 160.2, 159.6, 156.1, 149.0, 148.0, 125.3, 121.6,

117.9, 115.9, 113.5, 110.6, 103.3, 96.1. *Apigeninidin Chloride (28)*. $^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD-TFA}$ 99:1): δ 9.06 (dd, 1H, $J=9$, 1 Hz), 8.27 (d, 2H, $J=9$ Hz), 8.01 (d, 1H, $J=9$ Hz), 7.06 (d, 2H, $J=9$ Hz), 6.92 (dd, 1H, $J=2$, 1 Hz), 6.64 (d, 1H, $J=2$ Hz); $^{13}\text{C NMR}$ (100 MHz, $\text{CD}_3\text{OD-TFA}$ 99:1): δ 172.7, 172.4, 167.3, 160.6, 160.0, 149.5, 133.1, 121.3, 118.4, 113.8, 110.3, 103.2, 96.1.

8.19. General method for the condensation of benzopyrilium salt with phloroglucinol²⁷

Benzopyrilium salt **27** (20 mg, 0.6 M MeOH/pH 5.8 buffer (1:1) and phloroglucinol (26.2 mg, 3 equiv) were heated at 150 °C for 2 h in an Emrys microwave reactor. The reaction was concentrated to dryness on silica gel and purified by flash chromatographed with EtOAc/hexane (80:20) to afford the desired product in 80% yield. *Compound 30*. $^1\text{H NMR}$ (400 MHz, CD_6CO): δ 7.19 (d, 1H, 2 Hz), 7.05 (dd, 1H, $J=2$, 8 Hz), 6.88 (d, 1H, $J=2$ Hz), 6.06 (s, 4H), 4.33 (t, 1H, $J=3$ Hz), 2.22 (d, 3H, $J=3$ Hz); $^{13}\text{C NMR}$ (100 MHz, CD_6CO): δ 158.1, 154.7, 154.3, 146.4, 145.6, 134.9, 118.4, 115.8, 114.2, 107.5, 99.4, 97.3, 96.7, 34.5, 21.4; HRMS (ESI-TOF) ($\text{M}^+\text{+Na}$) m/z calcd for $\text{C}_{21}\text{H}_{16}\text{O}_8$ 419.0843, found 419.0758. An alternative method for easier purification is as follows. The reaction is concentrated to dryness and submitted to pyridine (0.3 mL) and Ac_2O (0.5 mL) overnight. The reaction is quenched with 1 M HCl, repeatedly extracted with EtOAc, and dried with MgSO_4 . The reaction was purified with flash chromatography eluting with EtOAc/hexane (60:40) and the ketal and non-ketal compounds were isolated. *Acetylated compound 30*. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.56–7.27 (m, 3H), 6.74 (d, 2H, $J=2$ Hz), 6.54 (d, 2H, $J=2$ Hz), 4.28 (t, 1H, $J=3$ Hz), 2.42 (s, 6H), 2.33 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H, $J=3$ Hz), 2.26 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 169.2, 169.0, 168.3, 153.7, 150.2, 147.8, 142.9, 142.1, 139.0, 124.3, 123.7, 121.6, 115.7, 109.8, 108.5, 98.4, 33.0, 22.9, 21.7, 21.3, 20.9, 20.8; IR (CH_2Cl_2 , ν_{max} cm^{-1}) 1772, 1618, 1369, 1198, 1222, 1024; HRMS (ESI-TOF) ($\text{M}^+\text{+Na}$) m/z calcd for $\text{C}_{33}\text{H}_{28}\text{O}_{14}$ 671.1479, found 671.1378. *Enol ether 30*. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.53–7.22 (m, 3H), 6.90–6.82 (m, 4H), 5.32 (d, 1H, $J=4$ Hz), 4.90 (d, 1H, $J=4$ Hz), 2.48–2.25 (m, 21H); HRMS (ESI-TOF) ($\text{M}^+\text{+Na}$) m/z calcd for $\text{C}_{35}\text{H}_{30}\text{O}_{15}$ 713.1585, found 713.1511.

8.20. Acetylated compound of 31

Benzopyrilium salt **28** (30 mg, 0.6 M MeOH/pH 5.8 buffer (1:1) and phloroglucinol (39.0 mg, 3 equiv) were heated at 150 °C for 2 h in an Emrys microwave reactor. The reaction was concentrated to dryness and submitted to pyridine (0.3 mL) and Ac_2O (0.5 mL) overnight. The reaction is quenched with 1 M HCl, repeatedly extracted with EtOAc, and dried with MgSO_4 . The crude product was purified by flash chromatography with EtOAc/hexane (60:40) and the ketal and non-ketal product were isolated in 83% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.68 (d, 2H, $J=9$ Hz), 7.18 (d, 2H, $J=9$ Hz), 6.75 (d, 2H, $J=2$ Hz), 6.55 (d, 2H, $J=2$ Hz), 4.27 (t, 1H, $J=3$ Hz), 2.43 (s, 6H), 2.29 (d, 3H, $J=3$ Hz), 2.33 (s, 3H), 2.27 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 169.5, 169.2, 169.0, 153.8, 151.4, 150.2, 147.8, 137.8, 127.3, 121.8, 115.8, 109.7, 108.5, 98.9, 33.1, 23.0, 21.7, 21.4, 21.3; IR (CH_2Cl_2 , ν_{max} cm^{-1}) 1768, 1620, 1434, 1369, 1201, 1184, 1130, 1116, 1072, 1022, 904; HRMS (ESI-TOF) ($\text{M}^+\text{+Na}$) m/z calcd for $\text{C}_{31}\text{H}_{26}\text{O}_{12}$ 613.1424, found 613.1337. *Enol ether 31*. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.63 (d, 2H, $J=9$ Hz), 7.10 (d, 2H, $J=9$ Hz), 6.90–6.60 (m, 4H), 5.30 (d, 1H, $J=4$ Hz), 4.91 (d, 1H, $J=4$ Hz), 2.38–2.13 (m, 18H); HRMS (ESI-TOF) ($\text{M}^+\text{+Na}$) m/z calcd for $\text{C}_{33}\text{H}_{28}\text{O}_{13}$ 655.1530, found 655.1423.

8.21. Compound 32

Benzopyrilium salt **27** (8.5 mg, 0.6 M MeOH/pH 5.8 buffer (1:1) and flavan **6** (43 mg, 6 equiv) were heated at 150 °C for 2 h in an Emrys microwave reactor. The reaction was concentrated to dryness and submitted to pyridine and Ac_2O overnight. The reaction was quenched with 1 M HCl, repeatedly extracted with EtOAc, and dried with MgSO_4 . The desired product was

purified by gradient chromatography with EtOAc/hexane (60:40–80:20) and the desired product was isolated in 45% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.58–7.50 (m, 4H), 7.46–7.38 (m, 4H), 7.16–7.08 (m, 4H), 6.75–6.68 (m, 2H), 6.53–6.51 (m, 2H), 6.29–6.27 (m, 2H), 5.17–4.92 (m, 2H), 4.14 (br s, 2H), 2.97 (m, 8H), 2.44–2.31 (m, 40H); HRMS (ESI-TOF) (M⁺+Na) *m/z* calcd for C₄₂H₃₆O₁₅ 803.2054, found 803.1935.

8.22. Diinsininone (33)

Benzopyrilium salt **27** (8.9 mg, 0.6 M MeOH/pH 5.8 buffer (1:1) and flavanone **9** (47 mg, 6 equiv) were heated at 120 °C for 20 h in an Emrys microwave reactor. The reaction was concentrated to dryness and submitted to pyridine and Ac₂O overnight. The reaction was quenched with 1 M HCl, repeatedly extracted with EtOAc, and dried with MgSO₄. The desired product was purified by gradient chromatography with EtOAc/hexane (60:40–80:20) and the desired product was isolated in 32% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.57–7.48 (m, 8H), 7.24–7.19 (m, 6H), 6.74–6.72 (m, 2H), 6.51–6.50 (m, 4H), 5.60–5.51 (m, 2H), 4.47 (br s, 1H), 4.44 (br s, 1H), 3.09–3.00 (m, 2H), 2.78–2.27 (m, 2H), 2.39–2.27 (m, 40H); HRMS (ESI-TOF) (M⁺+Na) *m/z* calcd for C₄₂H₃₄O₁₆ 817.1847, found 817.1593.

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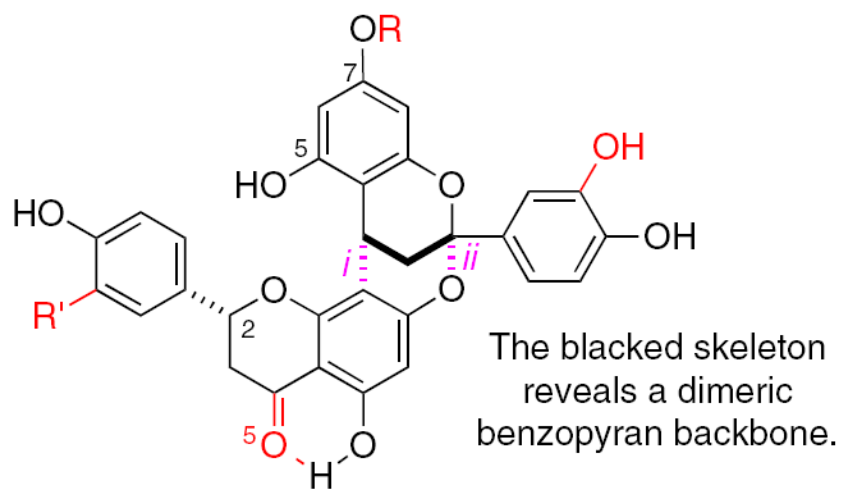
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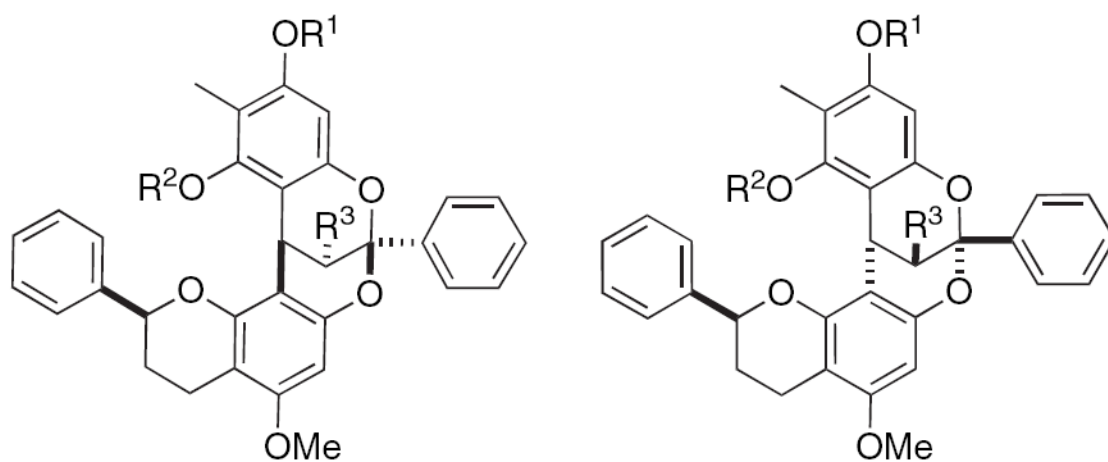
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diinsininol (**1**): R= β -glucose, R'=OH

diinsinin (**2**): R= β -glucose, R'=H

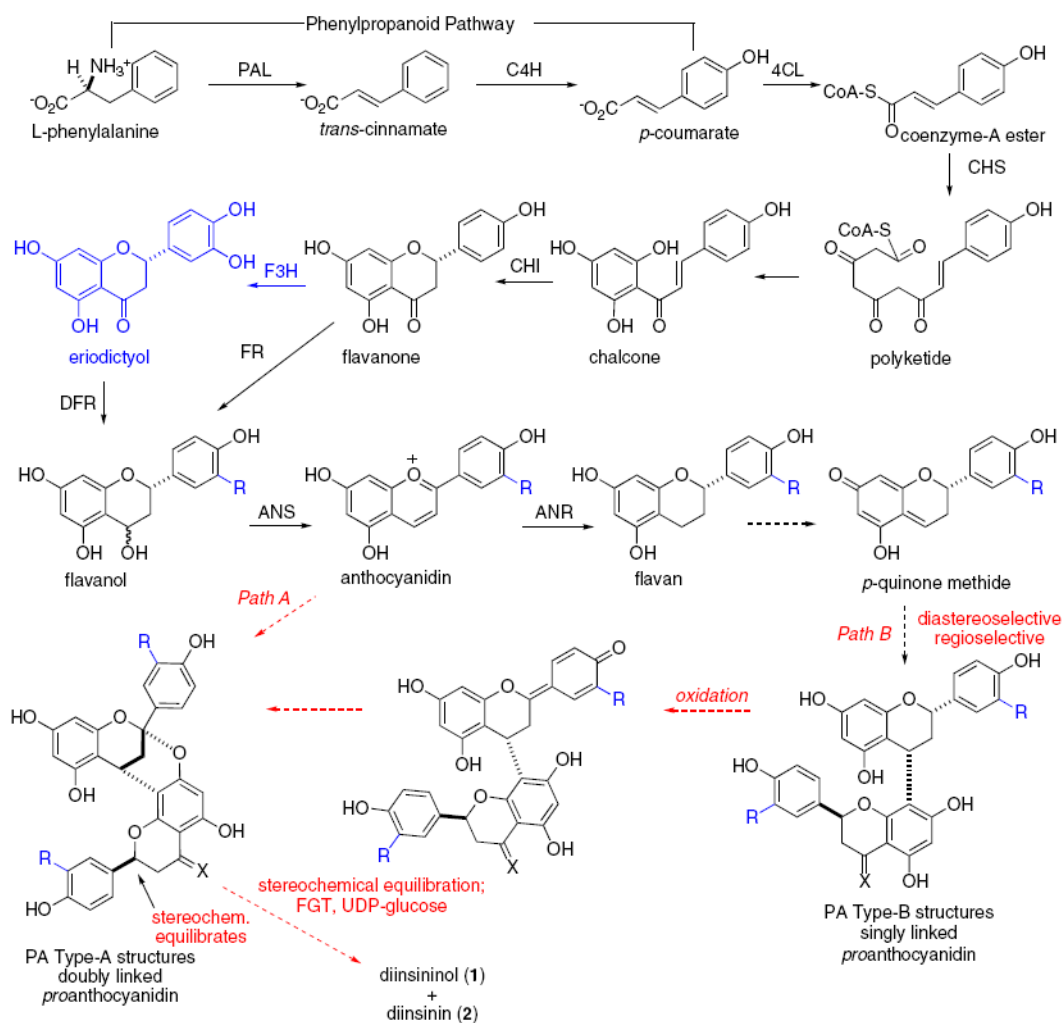
Figure 1.
PA type-A structures, diinsininol (**1**) and diinsinin (**2**).



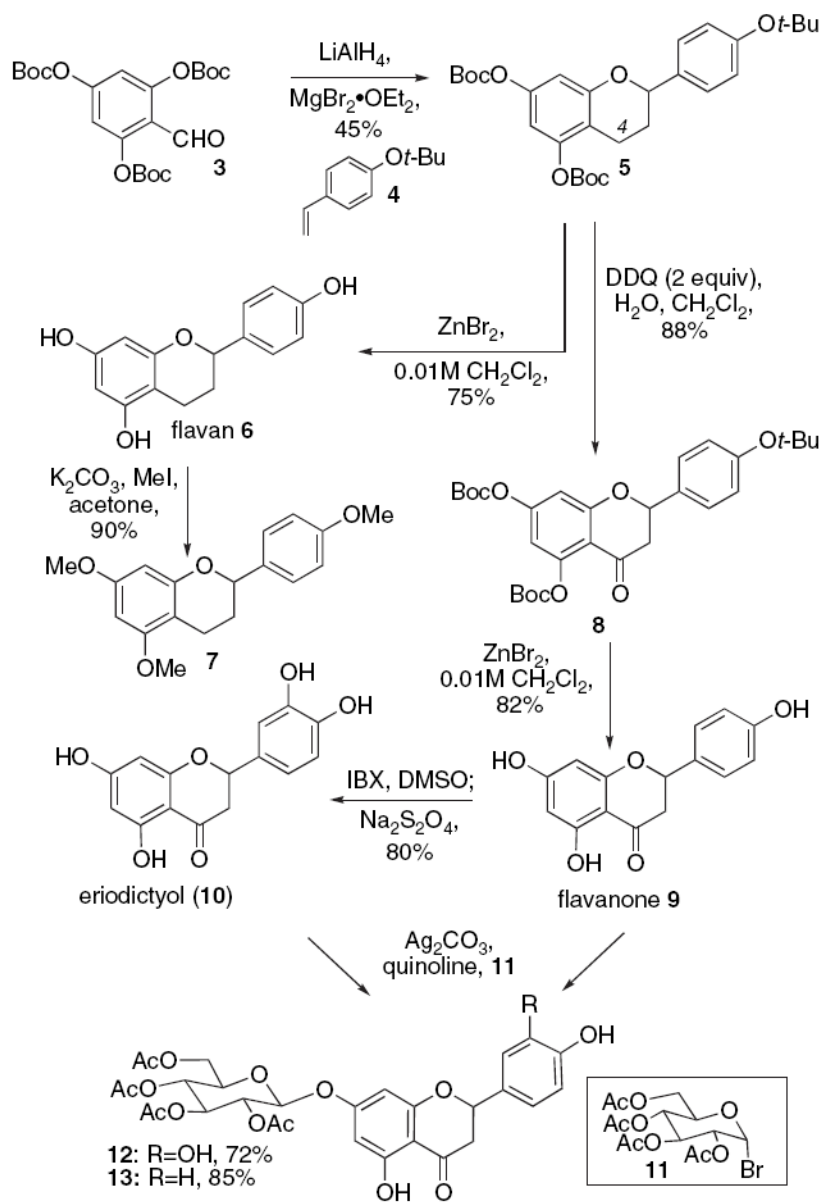
- 36:** $R^1=H; R^2=Me; R^3=OH$
37: $R^1=Me; R^2=Me; R^3=OH$
38: $R^1=Me; R^2=Me; R^3=OAc$
39: $R^1=H; R^2=Me; R^3=H$

- 40:** $R^1=Me; R^2=Me; R^3=H$
41: $R^1=Ac; R^2=Me; R^3=H$
42: $R^1=R^2=R^3=H$
43: $R^1=R^2=R^3=Me$

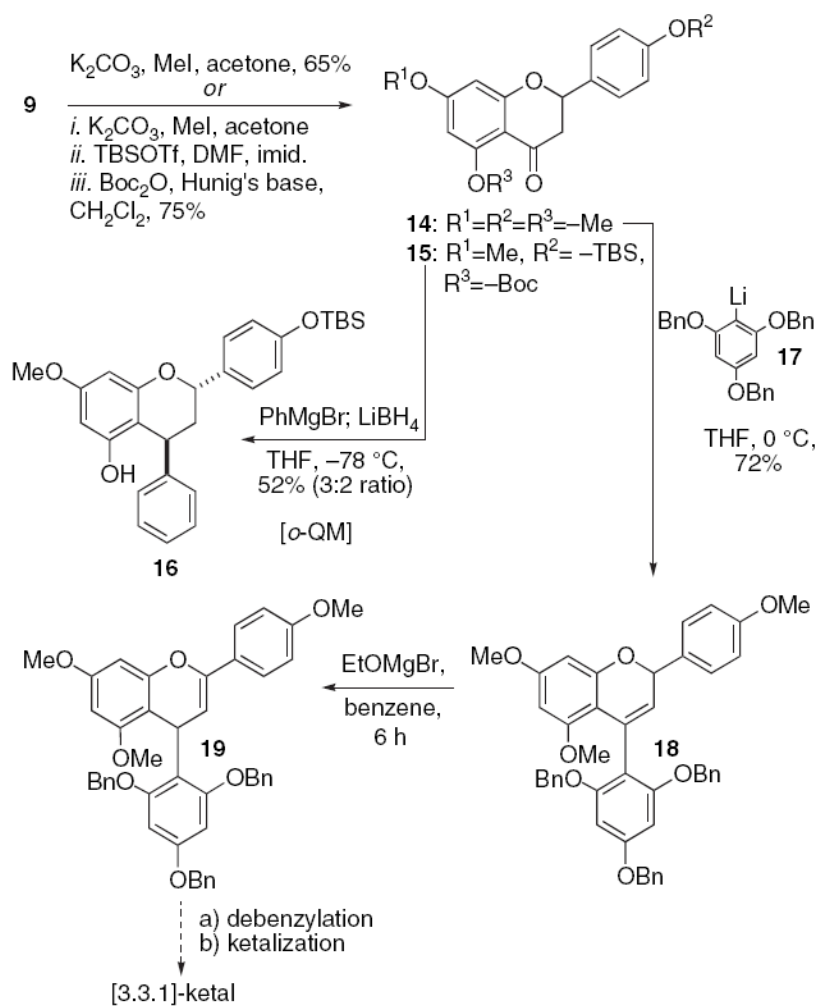
Figure 2.
 Natural products of the Dragon's Blood family.

**Scheme 1.**

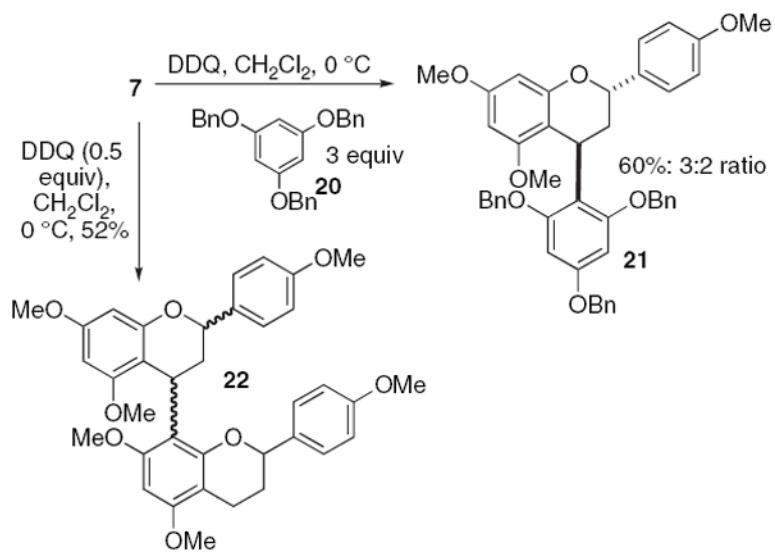
Known (solid arrows) and speculative (dashed arrows) biosynthetic pathways leading to **1** and **2**. PAL: phenylalanine ammonia lyase; C4H: cinnamate 4-hydroxylase; 4CL: 4-coumarate: CoA ligase; CHS: chalcone synthase; CHI: chalcone flavanone isomerase; F3H: flavanone 3-hydroxylase; FR: flavanone reductase; DFR: dihydroxyflavanone reductase; ANS: anthocyanidin synthase; ANR: anthocyanidin reductase.



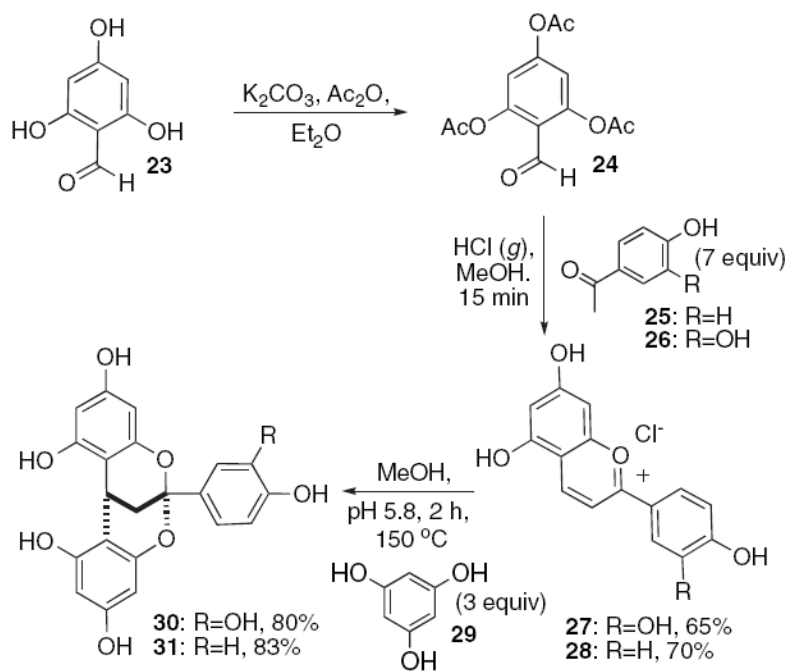
Scheme 2.
Synthesis of flavan, flavanone, and catechol.



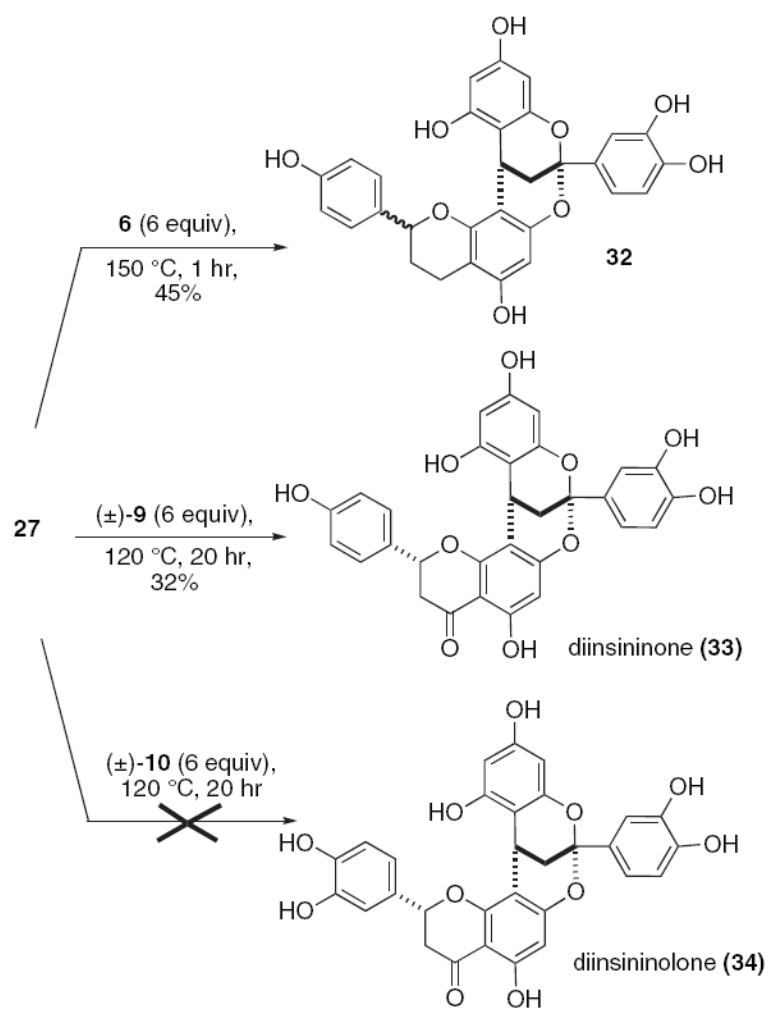
Scheme 3.
 α -QM reaction with flavanone backbone.



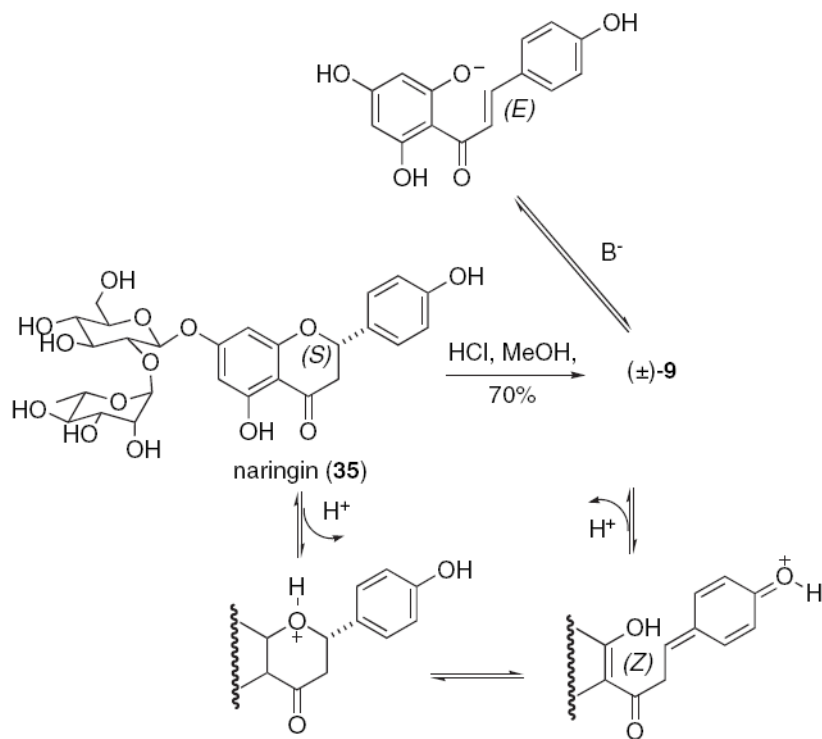
Scheme 4.
DDQ dimerization and coupling.

**Scheme 5.**

Mas's procedure provides benzopyrylium salts that readily undergo addition with phloroglucinol.



Scheme 6.
Reactions of the benzopyrilium salt **27** with flavan and flavanone.



Scheme 7.
Acid and base-catalyzed racemization of a C(2)-stereocenter.