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Momilactone and Related Diterpenoids as Potential Agricultural Chemicals

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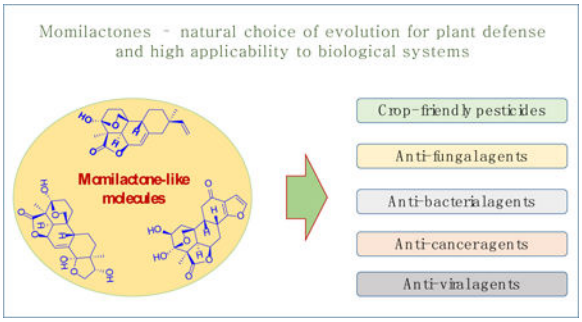
Abstract

Momilactones are allelochemicals in rice and moss defense. Momilactone-like compounds are therefore considered important secondary metabolites for plant defense. They may serve as promising lead compounds for crop-friendly herbicides, as well as anti-fungal and anti-bacterial agents. Many of these substances possess potent cytotoxicity property against cancer cell lines as well. The present paper is the first review on these versatile molecules, focusing on the structure, biological activity, chemical synthesis, and biosynthesis of the naturally occurring momilactone-like molecules reported from 1973 to 2017.

Graphical Abstract



Keywords

momilactone; (9β-H)-pimarane; allelochemical; phytoalexin; germination inhibitor

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Conflict of Interest

The authors declare no competing financial interest.

1. Introduction

Momilactones belong to a small family of naturally occurring diterpenes known as (9β-H)-pimaranes, which is characterized by a β-orientation of the proton on carbon-9 of the pimarane skeleton. Momilactones A (**1**) and B (**2**) were first isolated from the seed husks of rice (*Oryza sativa* L., cv. Koshihikari),[1,2] bearing a 19,6β-lactone structure. The name "momi" refers to the origin of these compounds, the rice husk, as known in the Japanese language, thus "momilactone". These compounds were soon found to exhibit germination-inhibitory,[3] seedling growth-inhibitory,[3] and phytoalexin[2, 4, 5] activities. Later, the allelochemical property of these compounds were also established.[6–14] Momilactone B exhibited potent antifungal activity against the rice blast pathogen *Piricularia oryzae*, which caused the devastating disease leading to 10–30% loss of the total rice harvest, as well as production loss of wheat, barley, and millet crops.[2, 4] Momilactones were also found to be allelochemicals in the defense responses of the moss *Hypnum plumaeforme*.[15–18]

The roles of momilactones in rice defense and their biological significance are evident. Up till now, several momilactone-like compounds have been identified from rice plants and mosses.[19–23] It is likely that they are stress-induced secondary metabolites with limited structural diversity. However, literature search revealed that a few plants in the *Casimirella* and *Icacina* genera (Icacinaceae) are also producers of (9β-H)-pimarane-19,6β-lactones and related metabolites. This review focuses on the structures, biological activities, chemical synthesis, and biosynthesis of naturally occurring momilactone-like molecules reported since 1973. A comprehensive overview is provided with the aim of inspiring researchers on these unique metabolites as potential agricultural tools.

2. Natural Distribution and Chemical Classification of (9β-H)-Pimaranes

Momilactone-like molecules have been reported from the bryophytes (*Hypnum plumaeforme* and *Pseudoleskeella papillosa*) and flowering plants, including monocots (*Oryza sativa*) and dicots (*Icacina*, *Casimirella* and *Annona* spp.).

These (9β-H)-pimaranes and derivatives can be classified into the following structural types (Figure 1 and Table 1):

- (9β-H)-pimarane (**1**−**3**, **7**, **8**, **16**−**22**, **24**, **25**, **39**),
- 19-*nor*-(9β-H)-pimarane (**6**),
- 15,16,17-tri-*nor*-(9β-H)-pimarane (**9**, **10**, **13**−**15**),
- 17-*nor*-(9β-H)-pimarane (**11**, **12**, **26**, **27**, **36**−**38**, **40**),
- 16-*nor*-(9β-H)-pimarane (**23**),
- 17-*nor*-pimarane (**28**−**35**, **42**),
- 16,17-di-*nor*-pimarane (**41**),
- 17,19-di-*nor*-pimarane (**43**),
- rearranged 17-*nor*-pimarane (**44**),

- (9β-H)-pimarane alkaloid (**45**−**47**), and
- other derivatives of (9β-H)-pimarane (**4**, **5**).

Compounds **4**, **5**, **28**−**35**, **41**−**47** were proposed to be biogenetically derived from (9β-H)-pimaranes in the related plant resources (Figures 1 and 2, and Table 1).

(9β-H)-Pimaranes from rice and moss. During the investigation of growth regulating substances in higher plants, two active components momilactones A (**1**) and B (**2**) were isolated from the seed husks of *Oryza sativa* cv. Koshihikari in 1973.[1] The (9β-H)-configuration of **1** and **2** was initially erroneously assigned but later revised through X-ray single crystal diffraction analysis, when momilactone C (**3**) was identified from the same source.[19] Momilactones A−C possess a 9β-H in the structure in contrast to the 9α-H in normal pimaranes. Subsequently, momilactones D (**5**) and E (**6**) were identified from the roots of *O. sativa*.[23] Strictly speaking, momilactone E (**6**), which is a 19-*nor*-(9β-H)-pimarane, should have not been called ‘momilactone’ because it does not contain a lactone structure in the molecule. Two other non-lactone derivatives, 6,19β-epoxy-3β-hydroxy-5α,9β-pimara-7,15-diene (**7**)[21] and (9β-H)-pimara-7,15-diene-3β,6β,19-triol (**8**),[22] were subsequently isolated from the rice husks and from rice leaves after UV-irradiation, respectively.

Besides rice plants, momilactones A (**1**) and B (**2**), and 3-oxo-pimara-7,9-dien-19,6β-olide (**4**) (which was arbitrarily called momilactone C in a paper published in 2012,[20] albeit the same trivial name had already been assigned to structure **3** in 1976)[19] are present in two species of moss (*Hypnum plumaeforme* and *Pseudoleskeella papillosa*).[15–17, 20]

(9β-H)-Pimaranes from *Casimirella* and *Icacina* Plants (Icacinaceae). According to Howard, the genus name of *Humirianthera* is a synonym of *Casimirella*.[24] The name *Casimirella* is therefore used in this review. In Amazon, the tubers of *Casimirella rupestris* are used to make into a kind of flour as a food ingredient by the natives;[25] while those of *C. ampla* are used for the treatment of snakebites.[26] Phytochemical investigation on the tubers of *C. rupestris* led to the identification of six degraded diterpenes, humirianthenolides A−F (**9**−**11**, **13**−**15**).[25] Among them, humirianthenolide C (**11**) is a 17-*nor*-(9β-H)-pimarane, while the others are 15,16,17-tri-*nor*-(9β-H)-pimaranes. On the other hand, humirianthol (**16**) and acrenol (**19**) were isolated from the tubers of *C. ampla*.[27] The absolute configuration of humirianthol (**16**) was established later by X-ray analysis of its 15-*O*-aectate derivative based on the assumption of (15*S*)-configuration as suggested by the Horeau method,[28] and further confirmed by single-crystal X-ray diffraction using CuK_α X-ray source.[29] The C-15 configuration of **19** remains undefined. In another study, bioassay-guided isolation of two *Casimirella spp.* led to the identification of 15(*R*)-humirianthol (**17**), humirianthone (**20**), 1β-hydroxyhumirianthone (**21**), and an oxidized derivative of annonalide (**23**). Compound **23** is a 16-*nor*-(9β-H)-pimarane previously reported as an oxidation product of annonalide (**22**).[26] Interestingly, annonalide is a (9β-H)-pimarane first found in the bulbs of *Annona coriacea*,[30–32] and later isolated from *C. amper* and other unidentified *C.* species.[26, 27] The configurations of C-9 and C-13 were initially erroneously assigned[30, 31] but later revised based on single-crystal X-ray diffraction data.[32]

Icacinol (**24**) was first isolated from *Icacina claessensis*,[33] and its absolute configuration was established by single-crystal X-ray diffraction.[29] From the root of *I. mannii*, a shrub endemic to tropical Africa as a popular folkloric medicine for the treatment of tumors, a 17-*nor*-(9β-H)-pimarane, icacenone (**26**), was identified by NMR and X-ray analyses.[34] On the other hand, *I. trichantha* is a traditional herbal medicine in Nigeria and neighboring countries, whose tuber is often prescribed by the herbalists for the treatment of food poisoning, constipation, and malaria.[35] Phytochemical investigations of this plant in our laboratories have resulted in the isolation of twenty-five (9β-H)-pimaranes and derivatives, including humirianthenolide C (**11**), 2β-hydroxyhumirianthenolide C (**12**), humirianthol (**16**), 14α-methoxyhumirianthol (**18**), icacinol (**24**), 17-hydroxyicacinol (**25**), icacenone (**26**), 7α-hydroxyicacenone (**27**), icacinlactones A−L (**28**, **30**, **31**, **34**−**42**), 12-hydroxyicacinlactone A (**29**), 7α-hydroxyicacinlactone B (**32**), 7β-hydroxyicacinlactone B (**33**), icacintrichanone (**43**), and icacintrichantholide (**44**).[29, 36–39] The absolute configurations of **18**, **27**, **30**, **31**, **40**, and **41** were established as (3*S*,4*R*,5*R*,6*S*,9*S*,10*S*,13*S*,14*S*,15*S*) (**18**), (2*S*,3*R*,4*R*,5*R*,6*S*,7*S*,8*S*,9*R*) (**27**), (3*S*,4*R*,5*R*,6*R*,10*R*) (**30**), (2*S*,3*R*,4*R*,5*R*,6*R*,10*R*) (**31**), and (3*S*,4*R*,5*R*,6*R*,8*R*,9*R*,10*S*) (**40**), (3*S*,4*R*,5*R*,6*R*,10*R*) (**41**), and (3*S*,4*R*,5*R*,6*R*,10*R*) (**44**), respectively, by the single-crystal X-ray diffraction data. Compounds **28**−**35**, and **41**−**44** are proposed to be biosynthesized via a (9β-H)-pimarane pathway. In addition, three diterpene alkaloids, icacine (**45**), icaceine (**46**), and de-*N*-methylicaceine (**47**), have been reported from the leaves and roots of *I. guesfeldtii*, whose root decoction is used as an anticonvulsant in traditional medicine in tropical Africa. The structure of **45** was confirmed by single-crystal X-ray diffraction,[40] while the configurations of **46** and **47** were not fully assigned though they were thought to be structurally related to **45**.[41]

3. Biological Activities

3.1. Seeds Germination Inhibition

Momilactones A (**1**) and B (**2**) inhibited the germination of *Arabidopsis* at concentrations above 30 μM and 10 μM, with IC_{50} values of 742 μM and 48.4 μM, respectively.[42] Momilactone B (**2**) could also completely inhibit the germination of *Leptochloa chinenesis* (at 4 ppm), *Amaranthus retroflexus* (at 20 ppm), and *Cyperus difformis* (at 20 ppm).[43]

Our recent study revealed that icacinol (**24**) was able to reduce the germination of *Arabidopsis* seeds at 5.3 μM by 20%. Dose-dependent responses were observed at 26.5 μM (66%), 53 μM (36%), and 265 μM (<1%).[44]

3.2. Plant Growth Inhibition on Rice Field Weeds and Other Plants

Barnyard grass (*Echinochloa crus-galli*) is a major noxious weed associated with rice especially in southern China. Momilactone B (**2**) inhibited the growth of shoots and roots of barnyard grass at concentrations greater than 1 μM, displaying 59−82% inhibition,[11] with an IC_{50} values of ca. 6.5 μM.[45] The compound also inhibited the growth of the shoots and roots of other monocots and dicots in a concentration-dependent manner, including cress (*Lepidium sativum*), lettuce (*Lactusa sativa* cv. Santanasu), alfafa (*Medicago sativa*), ryegrass (*Lodium multiflorum*), timothy (*Phleum pretense*), *Echinochloa colonum*, crabgrass (*Digitaria sanguinalis*), Chinese cabbage (*Brassica rapa* cv. Harumaki-ichigou), and

Arabidopsis thaliana.[45, 46] On the other hand, the potency of momilactone A (**1**) was far less than that of **2**.

The plant growth inhibitory mechanism for momilactones in barnyard grass has been associated with the altered expressions of miRNA relevant to plant hormone signal transduction, nucleotide excision repair, peroxisome proliferator-activated receptor pathway (PPAR pathway), and the p53 signaling pathway.[47] When *Arabidopsis* was treated with momilactone A (**1**) or B (**2**), protein expressions of cruciferin 2, cruciferin 3 and cruciferina were up-regulated. These proteins are storage proteins playing an important role as source of nitrogen for seed germination. Momilactones may therefore inhibit the germination of *Arabidopsis* seeds through a process of inhibition of the degradation process of cruciferins and cruciferina.[42] Momilactone B was also found to inhibit the growth of *Arabidopsis* seedlings by the accumulation of subtilisin-like serine protease, amyrin synthase LUP2, β-glucosidase and malate synthase.[48] These proteins are involved in the metabolic turnover and the production of intermediates needed for cell structures during plant growth and development. In addition, momilactone B induced proteins associated with plant defense responses, such as glutathione S-transferase and 1-cysteine peroxiredoxin 1.

The inhibitory effects of momilactones A (**1**) and B (**2**) on the root and shoot growth of rice seedlings have been shown to be minimal; they displayed positive results only at concentrations greater than 100 and 300 μM, respectively.[45] At concentration levels cytotoxic to the weeds, **1** and **2** exerted no visible damage to rice seedlings.[49]

Apart from the momilactones, icacinol (**24**) caused significant damages to *Arabidopsis* leaf expansion.[44] *Arabidopsis* plant treated with **24** also showed indications of stress, where anthocyanins increased and chlorophyll was reduced. Such findings reinforce the hypothesis that (9β-H)-pimarane lactones may serve as a potential source of agrichemicals.

3.3. Antifungal and Antibacterial Activities

Rice blast, mainly caused by infection from *Magnaporthe oryzae* (*syn. Magnaporthe grisea*, *Pyricularia grisea /oryzae*), is the most devastating disease of rice crop all over the world. Momilactones A (**1**) and B (**2**) were reported to display anti-*M. oryzae* activity in 1977,[4] and subsequently, many other components from the resistant strains of rice were tested against *M. oryzae* (Table 2). Among them, momilactone B (**2**) showed highest potency against both spore germination and germ tube growth of the fungus. Humirianthone (**20**) exhibited weak anti-fungal activity as well (IC_{50} > 69 μM).[26]

Other anti-fungal assays demonstrated that momilactone B (**2**) possessed more potent antifungal activity than momilactone A (**1**), in test species such as *Botrytis cinerea*, *Fusarium solani*, and *Colletrotrichum gloeosporioides*.[50] At the same time, humirianthone (**17**) displayed potent anti-fungal activity against *Phytophthora infestans* with an IC_{50} value of 1.1 μM.[26]

Momilactones A (**1**) and B (**2**) exhibited antibacterial activity against *Pseudomonus ovalis*, *Bacillus cereus*, *Bacillus pumilus*, and *Escherichia coli*.[50] Momilactone A showed high selectivity toward *E. coli* with a minimal inhibitory concentration value of 5 μM.

3.4. Cytotoxicity against Cancer Cell Lines

Momilactones A (**1**) and B (**2**) exhibited cytotoxic activity against P388 murine leukemia cells with IC_{50} values of 2.71 μM and 0.21 μM, respectively.[51] In addition, momilactone B (**2**) decreased viability of blood cancer cells, i.e. HL-60 (human myeloblastic leukemia cells), Jurkart (human leukemic T cells), RBL-2H3 (a basophilic leukemia cell line), and p815 (mouse mastocytoma cells), at concentrations below 6 μM. The cytotoxic activity on Jurkart cells was associated with an induction of apoptosis via caspase and mitochondria.[52] Momilactone B (**2**) was also cytotoxic against human colon cancer cells lines HT-29 and SW620 (IC_{50} values < 1 μM),[53] and the T47D breast cancer cell line. The effect was accompanied by a regulation of the expression of apoptosis-related genes and an induction of apoptosis through STAT5b and a caspase-3 dependent pathway.[54] In human leukemia U937 cells, **2** caused G1 cell cycle arrest and apoptosis through the induction of p21 expression, inhibition of Cdk/cyclin-associated kinase activities, and a down-regulation of phosphorylation of pRB.[55]

Several other cytotoxic momilactone-like compounds are summarized in Table 3. Among them, humirianthenolide C (**11**) displayed the highest potencies.[26, 29, 36–38]

4. Biogenesis of Momilactone-Like Molecules

In plants, the C5 unit of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) are biosynthesized through the mevalonate (MVA) and/or methylerythritol 4-phosphate (MEP) pathways.[56] During the process, *E,E,E*-geranylgeranyl pyrophosphate (GGPP) is formed in the plastids,[57, 58] and subsequent enzyme-catalyzed *E,E,E*-GGPP cyclization reactions lead to the formation of a diversity of diterpene skeletons.

For (9β-H)-pimaranes, *syn*-copalyl diphosphate (*syn*-CPP) serves as a key intermediate during their biosynthesis (Scheme 1). Thus, initiated by protonation at the terminal double bond, the chair-boat conformational *E,E,E*-GGPP gives rise to *syn*-CPP via the 8-carbonium ion. The *syn*-CPP is then cyclized to (9β-H)-pimarane-7,15-diene by a *si*-face attack of C-17. Type A and type B cyclases are involved in the process.[59] In rice, type B cyclase *OsCPS4* takes part in the formation of *syn*-CPP, and type A cyclase *OsKSL4* functions as (9β-H)-pimarane-7,15-diene synthase, which could be induced in rice leaves by UV-irradiation.[60] The microsomal cytochrome P450 monooxygenases (P450s) are also involved in the downstream oxidation of the (9β-H)-pimarane-7,15-diene leading to diverse structures of momilactone-like molecules.

The genes for momilactone biosynthesis in rice have been identified in a 168-kb region on chromosome-4, on which both *OsKSL4* and *OsCPS4* genes are located. The *OsKSL4* gene also locates in the proximity of P450 *CYP99A2* and *CYP99A3* genes, as well as a putative dehydrogenase gene (*AK103462*), which are chitin- and UV-inducible.[61, 62] The involvements of *CYP99A2* and *CYP99A3* in momilactone biosynthesis have been confirmed by gene-knockdown experiments.[62] *CYP99A3* was found to catalyze consecutive oxidations of the C_{19} methyl group of the momilactone precursor, (9β-H)-pimara-7,15-diene, to form, sequentially, (9β-H)-pimara-7,15-dien-19-ol, (9β-H)-pimara-7,15-dien-19-al,

and (9β-H)-pimara-7,15-dien-19-oic acid.[63] On the other hand, *CYP99A2* is involved to a much lesser extent.

The (9β-H)-pimara-7,15-dien-19-oic acid is presumed to give rise to the (9β-H)-pimara-7,15-dien-19,6β-olide via 3β- and 6β-hydroxylation through the participation of P450 genes *CYP701A8*[64] and *CYP76M8*[65], respectively. The 3β-hydroxy-(9β-H)-pimara-7,15-dien-19,6β-olide is then converted to momilactone A (**1**) by *AK103462* (*OsMAS*). The same reaction has also been observed in UV-irradiated rice leaves, in which the conversion was accomplished by a soluble protein fraction in the presence of NAD^+.[66]

Momilactone B (**2**) was proposed to form from **1** through C_{20}-hydroxylation and hemi-ketal ring closure. The possible biosynthesis of momilactone C (**3**), momilactones D and E (**5** and **6**), 6,19β-epoxy-3β-hydroxy-5α,9β-pimara-7,15-diene (**7**), and (9β-H)-pimara-7,15-diene-3β,6β,19-triol (**8**) in rice have also been proposed as shown in Scheme 1.

The OsTGAP1 is an elicitor-inducible rice basic leucine zipper (bZIP) transcription factor, which is essential for momilactone biosynthesis and play an essential role on the expression of all five genes in the gene cluster (*OsCPS4*, *OsKSL4*, *CYP99A2*, *CYP99A3*, and *OsMAS*). OsTGAP1 is also involved in the transcriptional regulation of *OsDXS3* in the MEP pathway. It serves as a crucial master regulator that controls the inducible expression of biosynthetic genes and upstream pathway genes required for diterpenoid phytoalexin production as part of the rice defensive response.[67] In addition, a rice transcription factor named diterpenoid phytoalexin factor (DPF), a basic helix-loop-helix transcription factor, was also reported.[68] DPF plays a central and positive role in the biosynthesis of diterpenoid phytoalexin in rice, and it activates the promoters of *CPS2* (copalyl diphosphate synthase 2) and *CYP99A2*, whose products are implicated in the biosynthesis of momilactones. The gene encoding DPF is expressed mainly in roots and panicles, and inducible in leaves by blast infection, copper chloride, or UV light.

For the biosynthesis of momilactone-like molecules in *Icacina* and *Casimirella*, little information is available up till now. (9β-H)-Pimara-7,15-diene was proposed to be the common precursor for most of these molecules.

5. Synthetic Studies toward Momilactone-Like Molecules

5.1. Synthesis of model compound (±)-4,4-dinor-(9β-H)-pimara-7,15-diene (48)

The unusual *trans-syn* tricyclic skeleton of momilactones, as well as the high functionalization of rings A and B, makes the chemical synthesis of this family of diterpenes challenging. Early efforts towards the total synthesis of momilactones focused on the construction of the *trans-syn* tricyclic skeleton, exemplified by the model compound (±)-4,4-dinor-(9βH)-pimara-7,15-diene (**48**, Scheme 2). Compound **48** possesses all main features of the BC-ring system of momilactones, including the *trans-syn* ring arrangement, the $\Delta^{7,8}$-double bond, and the α-methyl and β-vinyl substitutions at C-13.

As shown in Scheme 2, the syntheses of compound **48** through three different approaches were reported by de Groot's group.[69, 70] Starting from alkene **49**, Diels-Alder annulation

using 2-*t*-butyldimethylsilyloxybutadiene (**50**) catalyzed by dry $ZnCl_2$ provides the *trans-syn-cis* adduct **51** in high yield. Deformylation of **51** followed by hydride reduction affords the alcohol **52**. The conversion of **52** to the desired product **48** was accomplished through two different approaches. In the first route, the dehydration of **52** using $POCl_3$/pyridine produced enolate **53**. Then an electrophilic attacked by 2-ethoxy-1,3-dithiolane provides intermediate **54**, which could be reduced and deprotected to give an aldehyde **55**. The aldehyde group of **55** was then converted to the 13-vinyl substitution through a Wittig reaction with methylenetriphenylphosphorane. Interestingly, considerable epimerization at C-12 and C-13 occured in the Wittig conditions and only a very small amount of α-vinyl product was obtained. Oxidation of the racemic alcohol followed by Wolff-Kishner reduction afforded compound **48** as optically pure product.

The second approach started by protecting the alcohol group of **52** as an acetyl ester **57**.[69] The α-ester group was used as a directing group for the introduction of 2-ethoxy-1,3-dithiolane to give **58**. The ester was then hydrolyzed and dehydrated to intermediate **59**, followed by the reduction of the ketone to make **60**. Similarly, the Wittig reaction of **60** led to the epimerization of the C-12 alcohol, but no *α*-vinyl product could be detected, and the intermediate **56** was converted to **48** using the same conditions as described for the first route.

The third synthetic route of **48** was initiated by first deformylating intermediate **51**, followed by reduction and dehydration to provide enolate **62**.[70] Electrophilic attack of **62** by 2-ethoxy-1,3-dithiolane, followed by reduction with $NaBH_4$, afforded intermediate **55**, which could be converted to **48** using the same procedures as described for the previous two routes.

Taken together, the key step for the above synthetic routes is the Diels-Alder annulation, which provides the *trans-syn-cis* skeleton of the diterpene. Subsequent conversion of this skeleton to the desired product could thus be accomplished through different functionalization methods.

5.2. Synthesis of model compound (9*β*-H)-pimara-7,15-diene (72) and 3*β*-hydroxy-(9*β*-H)-pimara-7,15-diene (86)

The Diels-Alder annulation approach was used by de Groot's group for the synthesis of (9*β*-H)-pimara-7,15-diene (**72**),[71] another model compound which differs from **48** by a dimethyl substitution on C-14. As shown in Scheme 3, the dimethyl Diels-Alder substrate **65** was prepared from compound **64**, and the annulation of **65** with 2-*t*-butyldimethylsilyloxybutadiene afforded compound **66**, which was the counterpart of **51** in the above routes. A sequential conversion including deformylation, reduction, and acetylation provides the enolate **68**, which was substituted with [(1-chloroethyl)thio]benzene to give intermediate **69**. The 1*β*-phenylethylsulfane group was introduced as a vinyl precursor, which was subjected to an oxidative de-sulfur reaction to afford compound **70**. The ketone group was reduced with Wolff-Kishner conditions and the $\Delta^{7,8}$-double bond was introduced by the dehydration of C-8 hydroxyl, affording the target product **72**.[71]

Another synthesis of compound **72** was reported by Chu and Coates.[72] To introduce the 9*β*-H, a methodology employing catecholborane reduction of tosylhydrazones was used to

construct the trans-syn tricyclic system. As shown in Scheme 4, the isolated natural product **73** was treated with HCl to afford its Δ^8 isomer, followed by a regioselective allylic oxidation at C-7 with CrO_3•2pyr to afford intermediate **75**. Condensation of this intermediate with *p*-tosylhydrazine provides the isopimaradienone tosylhydrazone **76**. Reaction of **76** with catecholborane in $CHC1_3$ followed by allylic diazene rearrangement[73, 74] promoted by sodium acetate leads to compound **79** in 52% yield (along with the 15, l6-dihydro byproduct). The stereochemistry of the tosylhydrazone reductions was rationalized assuming initial ψ-axial (7α) delivery of hydride from catecholborane to the C=N group, followed by boro sulfinate elimination and β-facial transfer of hydrogen to C-9. Conformational inversion of ring B to a half-boat form (intermediate **77** to **78**) was presumably necessary for a concerted fragmentation to occur. The 4α ester substitution is then converted to a methyl group through a sequence of reduction, mesylation, sulfur substitution, and reductive de-sulfur reactions, affording the desired product **72**.

The aforementioned methodology has been applied in the synthesis of 3*β*-hydroxy-(9*β*-H)-pimara-7,15-diene (**86**) by Yajima et al,[75] as depicted in Scheme 5. The starting material **82** was first converted to C-13 substituted intermediate **83**, the allylic oxidation of which afforded ketone **84**. Condensation of this ketone with *p*-tosylhydrazine provided the tosylhydrazone precursor **85**, which was then subjected to catecholborane reduction and allylic diazene rearrangement to afford the desired product **86**. This compound was proposed to be a possible biosynthetic precursor of momilactone A, through compound **87** as a possible intermediate.[75]

5.3. Total synthesis of (±)-momilactone A (1)

In 2002, Germain and Deslongchamps reported the total synthesis of (±)-momilactone A in more than 20 steps.[76] A diastereoselective transannular Diels-Alder reaction on a trans-trans-cis macrocyclic triene, which had been developed by the same group,[77, 78] was used as the key step. As shown in Scheme 6, an Aldol reaction between compounds **89** and **90** affords diastereomers **91a** and **91b** in 88% yield. The hydroxyl group was protected as MOM ether, and selective desilylation of the primary hydroxyl ether yielded compounds **93a** and **93b**. The terminal hydroxy was then converted to a chlorine using hexachloroacetone/Ph_3P. The key step of the synthesis could be accomplished by the slow addition of these allylic chlorides into a suspension of cesium carbonate in refluxing acetonitrile under high dilution. The macrocyclization-cycloaddition took place in a single step to afford the trans-syn-trans tricycles **95a** and **95b** in 40% and 60% yields, respectively. A sterically favored endo transition state having a chair-boat-chair conformation was proposed to explain the specific formation of the trans-syn-trans tricycle. Furthermore, the isomerization of **95a** to **95b** was accomplished by a series of reactions including MOM removal (**96**), oxidation (**97**), reduction (**98**), and the re-protection of the hydroxyl group with MOMCl, through similar chair-boat-chair conformations of the intermediates.

Starting from intermediate **95b**, a linear sequence of conversions was accomplished (Scheme 7).[76] Thus, partial hydrolysis of the malonate **95b** produced the equatorial *β* monoacid **99**, which was then reduced to an alcohol and protected as an ethoxyethyl ether **101**. Then the axial ester was reduced with $LiAlH_4$ to give alcohol **102**, which was converted to tosylate

103. The equatorial ether was de-protected, followed by the reduction of the axial tosylate to a methyl (**105**). Then the MOM ether on ring A was cleaved (**106**), and treatment of **106** with *N*-bromoacetamide (NBA) and silver acetate in acetic acid gave rise to bromoacetate **107** with excellent stereoselectivity. Simultaneous oxidation of both hydroxy groups using Dess-Martin periodinane yielded the corresponding keto aldehyde **108**, and **108** was treated with Wittig conditions to convert the equatorial aldehyde to a terminal olefin (**109**). Subsequent displacement of the bromide was realized using AcOH-H_2O followed by methanolysis of the acetate to yield the lactone **110.** It was proposed that under basic conditions, epimerization at C-4 must have occurred and the axial ester is trapped by the C6-alcohol to form the γ-lactone. Treatment of **110** with Cs_2CO_3 and methyl iodide in acetonitrile afforded **111** in good yield. The final step of the synthesis was achieved using Burgess reagent in toluene at reflux,[79] and momilactone A was obtained in a moderate yield. Interestingly, the Burgess reagent is normally used for *syn*-elimination, thus the success of it in this reaction is probably due to the formation of the highly reactive sulfamate ester intermediate (by addition of the Burgess reagent to the secondary alcohol) that decomposes at high temperature to give the alkene. Normal dehydration conditions ($SOCl_2$, $POCl_3$, Mitsunobu conditions, etc.) do not work in this case, likely due to the steric hindrance of the secondary alcohol.

6. Further Prospects

Momilactones, exemplified by the versatile momilactone B, are thought to be the natural choice of evolution for rice and moss defense. Momilactone-like molecules are therefore believed to be of high applicability to the biological systems and potential sources for promising lead compounds for crop-friendly pesticides to support the development of green agriculture. Indeed, momilactones A and B have been patented as herbicides and anticancer agents as well.[80–82] However, the commercial supply is always a challenge for practical utilization of momilactones. Total synthesis remains a possible solution, but likely economically impractical and also not environment-friendly, despite the total synthesis of momilactone A has been reported many years ago.[83] The attempt on bioengineering is another possible approach, but limited investigation has been reported so far.[84–86] Natural supplies of momilactone-like molecules is another option, for which *Icacina*, *Casimirella* and their affinitive genera may be worthy to be further investigated. Unlike rice and moss in which these compounds are formed as stress-induced metabolites with limited quantities, momilactone-like molecules in *Icacina* and *Casimirella* display high structural diversity and high contents, providing opportunities for the discovery of promising lead compounds as well as precursors for semi-synthesis. Furthermore, in addition to their potentials for development into crop-friendly herbicides, antifungal, antibacterial, and antitumor agents, momilactone-like molecules are believed to possess other properties. Our group has demonstrated *in vitro* anti-herpes activity in some members of (9β-H)-pimarane lactones (unpublished), revealing their antiviral potential. It is our wish that this comprehensive overview will inspire further research interests on these unique molecules.

References

1. Kato T; Kabuto C; Sasaki N; Tsunagawa M; Aizawa H; Fujita K; Kato Y; Kitahara Y, Momilactones, growth inhibitors from rice, *Oryza sativa* L. Tetrahedron Lett. 1973, 39, 3861–3864.
2. Cartwright DW; langcake P; Pryce RJ; Leworthy DP; Ride JP, Isolation and characterization of two phytoalexins from rice as momilactiones A and B. Phytochemistry 1981, 20, 535–537.
3. Takahashi N; Kato T; Tsunagawa M; Sasaki N; Kitahara Y, Mechanisms of dormancy in rice seeds. II. New growth inhibitors, momilactone-A and -B isolated from the hulls of rice seeds. Japan J. Breed 1976, 26, 91–98.
4. Cartwright D; Langcake P; Pryce RJ; Leworthy DP, Chemical activation of host defence mechanisms as a basis for crop protection. Nature 1977, 267, 511–513.
5. Langcake P; Cartwright D; Leworthy DP; Pryce RJ; Ride JP, The dichlorocyclopropanes, fungicides with an indirect mode of action? Neth. J. Pl. Path 1978, 83 (Suppl. 1), 153–155.
6. Kato-Noguchi H; Ino T; Sata N; Yamamura S, Isolation and identification of a potent allelopathic substance in rice rot exudates. Physiol. Plantarum 2002, 115, 401–405.
7. Kato-Noguchi H, Isolation of allelopathic substances in rice seedlings. Plant Prod. Sci 2002, 5, 8–10.
8. Kato-Noguchi H; Ino T, Rice seedlings release momilactone B into the environment. Phytochemistry 2003, 63, 551–554. [PubMed: 12809715]
9. Kato-Noguchi H, Allelopathic substance in rice root exudates: Rediscovery of momilactone B as an allelochemical. J. Plant Physiol. 2004, 161, 271–276. [PubMed: 15077625]
10. Kato-Noguchi H; Ino T, Possible involvement of momilactone B in rice allelopathy. J. Plant Physiol. 2005, 162, 718–721. [PubMed: 16008095]
11. Kato-Noguchi H; Hasegawa M; Ino T; Ota K; Kujime H, Contribution of momilactone A and B to rice allelopathy. J. Plant Physiol. 2010, 167, 787–791. [PubMed: 20170980]
12. Kato-Noguchi H, Barnyard grass-induced rice allelopathy and momilactone B. J. Plant Physiol. 2011, 168, 1016–1020. [PubMed: 21392842]
13. Kato-Noguchi H, Rice allelopathy and momilactone. Pak. J. Weed Sci. Res 2012, 18, 289–296.
14. Kato-Noguchi H; Peters RJ, The role of momilactones in rice allelopathy. J. Chem. Ecol 2013, 39, 175–185. [PubMed: 23385366]
15. Nozaki H; Hayashi K; Nishimura N; Kawaide H; Matsuo A; Takaoka D, Momilactone A and B as allelochemicals from Moss *Hypnum plumaeforme*: First occurrence in Bryophytes. Biosci. Biotechnol. Biochem 2007, 71, 3127–3130. [PubMed: 18071239]
16. Kato-Noguchi H; Kobayashi K, Jasmonic acid, protein phosphatase inhibitor, metals and UV-irradiation increased momilactone A and B concentrations in the moss *Hypnum plumaeforme*. J. Plant Physiol. 2009, 166, 1118–1122. [PubMed: 19232772]
17. Kato-Noguchi H, Secretion of momilactone A and B by the moss Hypnum plumaeforme. Plant Signal. Behav. 2009, 4, 737–739. [PubMed: 19820317]
18. Kato-Noguchi H; Kobayashi K; Shigemori H, Allelopathy of the moss Hypnum plumaeforme by the production of momilactone A and B. Weed Res. 2009, 49, 621–627.
19. Tsunakawa M; Ohba A; Sasaki N; Kabuto C; Kato T; Kitahara Y; Takahashi N, Momilactone-C, a minor constituent of growth inhibitors in rice husk. Chem. Lett 1976, 1157–1158.
20. Liu N; Wang S; Lou H, A new pimarane-type diterpenoid from moss Pseudoleskeella papillosa (Lindb.) Kindb. Acta Pharm. Sin. B 2012, 2, 256–259.
21. Li G; Xu Q-L; He C-M; Zeng L; Wang H-F, Two new anti-fungal diterpenoids from the husks of Oryza sativa. Phytochem. Lett 2014, 10, 309–312.
22. Horie K; Inoue Y; Sakai M; Yao Q; Tanimoto Y; Koga J; Toshima H; Hasegawa M, Identification of UV-induced diterpenes including a new diterpene phytoalexin, phytocassane F, from rice leaves by complementary GC/MS and LC/MS approaches. J. Agric. Food Chem. 2015, 63, 4050–4059. [PubMed: 25865436]
23. Cho J-G; Cha B-J; Lee SM; Shrestha S; Jeong R-H; Lee DS; Kim Y-C; Lee D-G; Kang H-C; Kim J; Baek N-I, Diterpenes from the roots of Oryza sativa L. and their inhibition activity on NO

production in LPS-stimulated RAW264.7 macrophages. Chem. Biodivers 2015, 12, 1356–1364. [PubMed: 26363880]

24. Howard RA, A revision of Casimirella, including Humirianthera (Icacinaceae). Brittonia 1992, 44, 166–172.
25. Zoghbi MDGB; Roque NF; Gottlieb HE, Humirianthenolides, new degraded diterpenoids from *Humirianthera rupestri*. Phytochemistry 1981, 20, 1669–1673.
26. Adou E; Williams RB; Schilling JK; Malone S; Meyer J; Wisse JH; Frederik D; Koese D; Werkhoven MCM; Snipes CE; Werk TL; Kingston DGI, Cytotoxic diterpenoids from two lianas from the Suriname rainforest. Bioorg. Med. Chem 2005, 13, 6009–6014. [PubMed: 16125394]
27. Graebner IB; Mostardeiro MA; Ethur EM; Burrow RA; Dessoy ECS; Morel AF, Diterpenoids from *Humirianthera ampla*. Phytochemistry 2000, 53, 955–959. [PubMed: 10820811]
28. Burrow RA; Morel AF; Graebner IB; Farrar DH; Lough AJ, The acetyl derivative of humirianthol. Acta Crystallogr., Sect. E Struct. Rep. Online 2003, 59, o347–o349.
29. Monday Onakpa M.; Zhao M; Goedecke T; Chen W-L; Che C-T; Santarsiero BD; Swanson SM; Uzoma Asuzu I., Cytotoxic (9βH)-pimarane and (9βH)-17-norpimarane diterpenes from the tuber of Icacina trichantha. Chem. Biodivers 2014, 11, 1914–1922. [PubMed: 25491335]
30. Mussini P; Orsini F; Pelizzoni F; Ferrari G, Constituents of *Annona coriacea*. Structure of a new diterpenoid. J. Chem. Soc., Perkin Trans. 1 1973, 2551–2557.
31. Mussini P; Orsini F; Pelizzoni F; Buckwalter BL; Wenkert E, Carbon-13 nuclear magnetic resonance spectroscopy of naturally occurring substances.. XXII. Carbon-13 configuration of annonalide. Tetrahedron Lett. 1973, 14, 4849–4851.
32. Orsini F; Pellizoni F; McPhail AT; Onan KD; Wenkert E, The structure of annonalide. Tetrahedron Lett. 1977, 18, 1085–1088.
33. On'okoko P; Vanhaelen M; Vanhaelen-Fastre R; Declercq JP; Van Meerssche M, The constitution of icacinol, a new diterpene with a pimarane skeleton from *Icacina claessensis*. Tetrahedron 1985, 41, 745–748.
34. On'Okoko P; Vanhaelen M; Vanhaelen-Fastre R; Declercq JP; Van Meerssche M, Icacenone, a furanoditerpene with a pimarane skeleton from *Icacina mannii*. Phytochemistry 1985, 24, 2452–2453.
35. Asuzu IU; Abubakar II, The effects of Icacina trichantha tuber extract on the nervous system. Phytother. Res 1995, 9, 21–25.
36. Zhao M; Onakpa MM; Santarsiero BD; Chen W-L; Szymulanska-Ramamurthy KM; Swanson SM; Burdette JE; Che C-T, (9βH)-Pimaranes and derivatives from the tuber of *Icacina trichantha*. J. Nat. Prod 2015, 78, 2731–2737. [PubMed: 26523419]
37. Zhao M; Onakpa MM; Chen W-L; Santarsiero BD; Swanson SM; Burdette JE; Asuzu IU; Che C-T, 17-Norpimaranes and (9βH)-17-norpimaranes from the tuber of Icacina trichantha. J. Nat. Prod 2015, 78, 789–796. [PubMed: 25782063]
38. Zhao M; Onakpa MM; Santarsiero BD; Huang X-J; Zhang X-Q; Chen J; Cheng J-J; Longnecker R; Che C-T, Icacinlactone H and icacintrichantholide from the tuber of *Icacina trichantha*. Org. Lett 2015, 17, 3834–3837. [PubMed: 26183449]
39. Guo B; Onakpa MM; Huang X-J; Santarsiero BD; Chen W-L; Zhao M; Zhang X-Q; Swanson SM; Burdette JE; Che C-T, Di-nor- and 17-nor-pimaranes from *Icacina trichantha*. J. Nat. Prod 2016, 79, 1815–1821. [PubMed: 27340832]
40. On'Okoko P; Hans M; Colau B; Hootele C; Declercq JP; Germain G; Van Meerssche M, Icacine, a new diterpene alkaloid from *Icacina guessfeldtii*. Bull. Soc. Chim. Belg 1977, 86, 655–661.
41. On'okoto P; Vanhaelen M, Two new diterpene-based alkaloids from *Icacina guesfeldtii*. Phytochemistry 1980, 19, 303–305.
42. Kato-Noguchi H; Ota K; Kujime H; Ogawa M, Effects of momilactone on the protein expression in Arabidopsis germination. Weed Biol. Manag 2013, 13, 19–23.
43. Chung I-M; Hahn S-J; Ahmad A, Confirmation of potential herbicidal agents in hulls of rice, *Oryza sativa*. J. Chem. Ecol 2005, 31, 1339–1352. [PubMed: 16222775]
44. Zhao M; Guo B; Onakpa MM; Wong T; Wakasa K; Che CT; Warpeha KM, Activity of icacinol from Icacina trichantha on seedling growth of Oryza sativa and *Arabidopsis thaliana*. J. Nat. Prod 2017, 80, 3314–3318. [PubMed: 29227099]

45. Kato-Noguchi H; Ota K, Biological activities of rice allelochemicals momilactone A and B. J. Rice Res. 2013, 1, 108.
46. Kato-Noguchi H; Ota K; Kujime H, Absorption of momilactone A and B by *Arabidopsis thaliana* L. and the growth inhibitory effects. J. Plant Physiol. 2012, 169, 1471–1476. [PubMed: 22818889]
47. Fang C; Li Y; Li C; Li B; Ren Y; Zheng H; Zeng X; Shen L; Lin W, Identification and comparative analysis of microRNAs in barnyardgrass (Echinochloa crus-galli) in response to rice allelopathy. Plant Cell Environ. 2015, 38, 1368–1381. [PubMed: 25438645]
48. Kato-Noguchi H; Kitajima S, Momilactone sensitive proteins in *Arabidopsis thaliana*. Nat. Prod. Commun 2015, 10, 729–732. [PubMed: 26058145]
49. Kato-Noguchi H; Ota K; Ino T, Release of momilactone A and B from rice plants into the rhizosphere and its bioactivities. Allelopathy J. 2008, 22, 321–328.
50. Fukuta M; Xuan TD; Deba F; Tawata S; Khanh TD; Chung IM, Comparative efficacies in vitro of antibacterial, fungicidal, antioxidant, and herbicidal activities of momilatones A and B. J. Plant Interact. 2007, 2, 245–251.
51. Chung IM; Ali M; Hahn SJ; Siddiqui NA; Lim YH; Ahmad A, Chemical constituents from the hulls of *Oryza sativa* with cytotoxic activity. Chem. Nat. Compd 2005, 41, 182–189.
52. Lee SC; Chung I-M; Jin YJ; Song YS; Seo SY; Park BS; Cho KH; Yoo KS; Kim T-H; Yee S-B; Bae Y-S; Yoo YH, Momilactone B, an allelochemical of rice hulls, induces apoptosis on human lymphoma cells (Jurkat) in a micromolar concentration. Nutr. Cancer 2008, 60, 542–551. [PubMed: 18584489]
53. Kim S-J; Park H-R; Park E; Lee S-C, Cytotoxic and antitumor activity of momilactone B from rice hulls. J. Agric. Food Chem. 2007, 55, 1702–1706. [PubMed: 17326606]
54. Joung Y-H; Lim E-J; Kim M-S; Lim SD; Yoon S-Y; Lim YC; Yoo YB; Ye S-K; Park T; Chung I-M; Bae K-Y; Yang YM, Enhancement of hypoxia-induced apoptosis of human breast cancer cells via STAT5b by momilactone B. Int. J. Oncol 2008, 33, 477–484. [PubMed: 18695876]
55. Park C; Jeong NY; Kim G-Y; Han MH; Chung I-M; Kim W-J; Yoo YH; Choi YH, Momilactone B induces apoptosis and G1 arrest of the cell cycle in human monocytic leukemia U937 cells through downregulation of pRB phosphorylation and induction of the cyclin-dependent kinase inhibitor p21Waf1/Cip1. Oncol. Rep 2014, 31, 1653–1660. [PubMed: 24503697]
56. Lichtenthaler HK; Schwender J; Disch A; Rohmer M, Biosynthesis of isoprenoids in higher plant chloroplasts proceeds via a mevalonate-independent pathway. FEBS Lett. 1997, 400, 271–274. [PubMed: 9009212]
57. Lichtenthaler HK, The 1-deoxy-D-xylulose-5-phosphate pathway of isoprenoid biosynthesis in plants. Annu. Rev. Plant Physiol. Plant Mol. Biol 1999, 50, 47–65. [PubMed: 15012203]
58. Rohmer M, The discovery of a mevalonate-independent pathway for isoprenoid biosynthesis in bacteria, algae and higher plants. Nat. Prod. Rep 1999, 16, 565–574. [PubMed: 10584331]
59. MacMillan J; Beale MH, Diterpene biosynthesis. In Comprehensive Natural Products Chemistry, Cane DE, Ed. Pergamon Press.: Oxford, 2000; Vol. 2, 217–241.
60. Yamane H, Biosynthesis of phytoalexins and regulatory mechanisms of it in rice. Biosci. Biotechnol. Biochem 2013, 77, 1141–1148. [PubMed: 23748776]
61. Otomo K; Kanno Y; Motegi A; Kenmoku H; Yamane H; Mitsuhashi W; Oikawa H; Toshima H; Itoh H; Matsuoka M; Sassa T; Toyomasu T, Diterpene cyclases responsible for the biosynthesis of phytoalexins, momilactones A, B, and oryzalexins A-F in rice. Biosci. Biotechnol. Biochem 2004, 68, 2001–2006. [PubMed: 15388982]
62. Shimura K; Okada A; Okada K; Jikumaru Y; Ko K-W; Toyomasu T; Sassa T; Hasegawa M; Kodama O; Shibuya N; Koga J; Nojiri H; Yamane H, Identification of a biosynthetic gene cluster in rice for momilactones. J. Biol. Chem 2007, 282, 34013–34018. [PubMed: 17872948]
63. Wang Q; Hillwig ML; Peters RJ, CYP99A3: functional identification of a diterpene oxidase from the momilactone biosynthetic gene cluster in rice. Plant J. 2011, 65, 87–95. [PubMed: 21175892]
64. Kitaoka N; Wu Y; Xu M; Peters RJ, Optimization of recombinant expression enables discovery of novel cytochrome P450 activity in rice diterpenoid biosynthesis. Appl. Microbiol. Biotechnol 2015, 99, 7549–7558. [PubMed: 25758958]

65. Wang Q; Hillwig ML; Okada K; Yamazaki K; Wu Y; Swaminathan S; Yamane H; Peters RJ, Characterization of CYP76M5–8 indicates metabolic plasticity within a plant biosynthetic gene cluster. J. Biol. Chem 2012, 287, 6159–6168. [PubMed: 22215681]
66. Atawong A; Hasegawa M; Kodama O, Biosynthesis of rice phytoalexin: enzymatic conversion of 3β-hydroxy-9β-pimara-7,15-dien-19,6β-olide to momilactone A. Biosci. Biotechnol. Biochem 2002, 66, 566–570. [PubMed: 12005050]
67. Okada A; Okada K; Miyamoto K; Koga J; Shibuya N; Nojiri H; Yamane H, OsTGAP1, a bZIP transcription factor, coordinately regulates the inductive production of diterpenoid phytoalexins in Rice. J. Biol. Chem 2009, 284, 26510–26518. [PubMed: 19635799]
68. Yamamura C; Mizutani E; Okada K; Nakagawa H; Fukushima S; Tanaka A; Maeda S; Kamakura T; Yamane H; Takatsuji H; Mori M, Diterpenoid phytoalexin factor, a bHLH transcription factor, plays a central role in the biosynthesis of diterpenoid phytoalexins in rice. Plant J. 2015, 84, 1100–1113. [PubMed: 26506081]
69. Sichererroetman A; Jansen BJM; de Groot A, Stereospecific preparation of (+/−)-4,4-dinor-9-beta-H-pimara-7,15-diene, a model for the total synthesis of momilactone type diterpenes. Tetrahedron Lett. 1984, 25, 2593–2596.
70. Sicherer-Roetman A; Jansen BJM; de Groot A, Investigation into the total synthesis of momilactones. Stereoselective preparation of (±)-4,4-dinor-9βH-pimara-7,19-diene. Recl. Trav. Chim. Pays-B. 1985, 104, 193–202.
71. Jansen BJM; Schepers GC; de Groot A, The stereoselective synthesis of (±)-9βH-pimara-7,19-diene. Tetrahedron Lett. 1989, 45, 2773–2776.
72. Chu M; Coates RM, Partial synthesis of 9,10-syn diterpenes via tosylhydrazone reduction - (−)-(9-beta)-primara-7,15-diene and (−)-(9-beta)-isopimaradiene. J. Org. Chem 1992, 57, 4590–4597.
73. Kabalka GW; Yang DTC; Baker JD, Deoxygenation of alpha,beta-unsaturated aldehydes and ketones via catecholborane reduction of corresponding tosylhydrazones. J. Org. Chem 1976, 41, 574–575.
74. Wood JL; Porco JA; Taunton J; Lee AY; Clardy J; Schreiber SL, Application of the Allylic Diazene Rearrangement - Synthesis of the enediyne-bridged tricyclic core of dynemicin-A. J. Am. Chem. Soc 1992, 114, 5898–5900.
75. Yajima A; Toda K; Okada K; Yamane H; Yamamoto M; Hasegawa M; Katsuta R; Nukada T, Stereocontrolled total synthesis of (+/−)-3 beta-hydroxy-9 beta-pimara-7,15-diene, a putative biosynthetic intermediate of momilactones. Tetrahedron Lett. 2011, 52, 3212–3215.
76. Germain J; Deslongchamps P, Total synthesis of (+/−)-momilactone A. J. Org. Chem 2002, 67, 5269–5278. [PubMed: 12126415]
77. Marsault E; Toro A; Nowak P; Deslongchamps P, The transannular Diels-Alder strategy: applications to total synthesis. Tetrahedron 2001, 57, 4243–4260.
78. Germain J; Deslongchamps P, Transannular Diels-Alder approach to the synthesis of momilactone A. Tetrahedron Lett. 1999, 40, 4051–4054.
79. Burgess EM; Penton HR; Taylor EA, Thermal reactions of alkyl N-carbomethoxysulfamate esters. J. Org. Chem 1973, 38, 26–31.
80. Chung IM; Ateeque A; Kim JS Momilactones A and B from rice hulls as herbicides. 2005–12810220060160701, 20050512, 2006.
81. Yang YM; Jung IM; Jung YH; Bae GY Momilactone B for preventing and treating solid neoplasm. 2007–1018552009036688, 20071010, 2009.
82. You YH; Chung IM Pharmaceutical composition comprising momilactone B as major component for treating leukemia, preferably acute lymphocytic leukemia, and drug thereof. 2005–305632006108373, 20050413, 2006.
83. Germain J; Deslongchamps P, Total synthesis of (±)-momilactone A. J. Org. Chem 2002, 67, 5269–5278. [PubMed: 12126415]
84. Mohan RS; Yee NKN; Coates RM; Ren Y-Y; Stamenkovic P; Mendez I; West CA, Biosynthesis of cyclic diterpene hydrocarbons in rice cell suspensions: conversion of 9,10-syn-labda-8(17), 13-dienyl diphosphate to 9β-pimara-7,15-diene and stemar-13-ene. Arch. Biochem. Biophys 1996, 330, 33–47. [PubMed: 8651702]

85. Nojiri H; Sugimori M; Yamane H; Nishimura Y; Yamada A; Shibuya N; Kodama O; Murofushi N; Omori T, Involvement of jasmonic acid in elicitor-induced phytoalexin production in suspension-cultured rice cells. Plant Physiol. 1996, 110, 387–92. [PubMed: 12226190]

86. Shimizu T; Jikumaru Y; Okada A; Okada K; Koga J; Umemura K; Minami E; Shibuya N; Hasegawa M; Kodama O; Nojiri H; Yamane H, Effects of a bile acid elicitor, cholic acid, on the biosynthesis of diterpenoid phytoalexins in suspension-cultured rice cells. Phytochemistry 2008, 69, 973–981. [PubMed: 18045629]

87. Chung I-M; Ali M; Ahmad A, Oryzasesterpenolide from the hulls of *Oryza sativa* and complete NMR assignments of momilactones A, B and tricin. Asian J. Chem 2005, 17, 2467–2478.

88. Koga J, Structure, function, and biological activity of rice phytoalexins and elicitors In Plant-derived antimycotics: Current trends and future prospects, Rai M; Mares D, Eds. Haworth Press: New York, 2003; pp 497–524.

89. Toyomasu T; Kagahara T; Okada K; Koga J; Hasegawa M; Mitsuhashi W; Sassa T; Yamane H, Diterpene phytoalexins are biosynthesized in and exuded from the roots of rice seedlings. Biosci. Biotechnol. Biochem 2008, 72, 562–567. [PubMed: 18256463]

90. Koga J, Structure, function, and biological activity of rice phytoalexins and elicitors In Plant-Derived Antimycotics:Trends Current and Prospects Future, Rai M; D. M, Eds. Haworth Press: New York, 2003; 497–524.

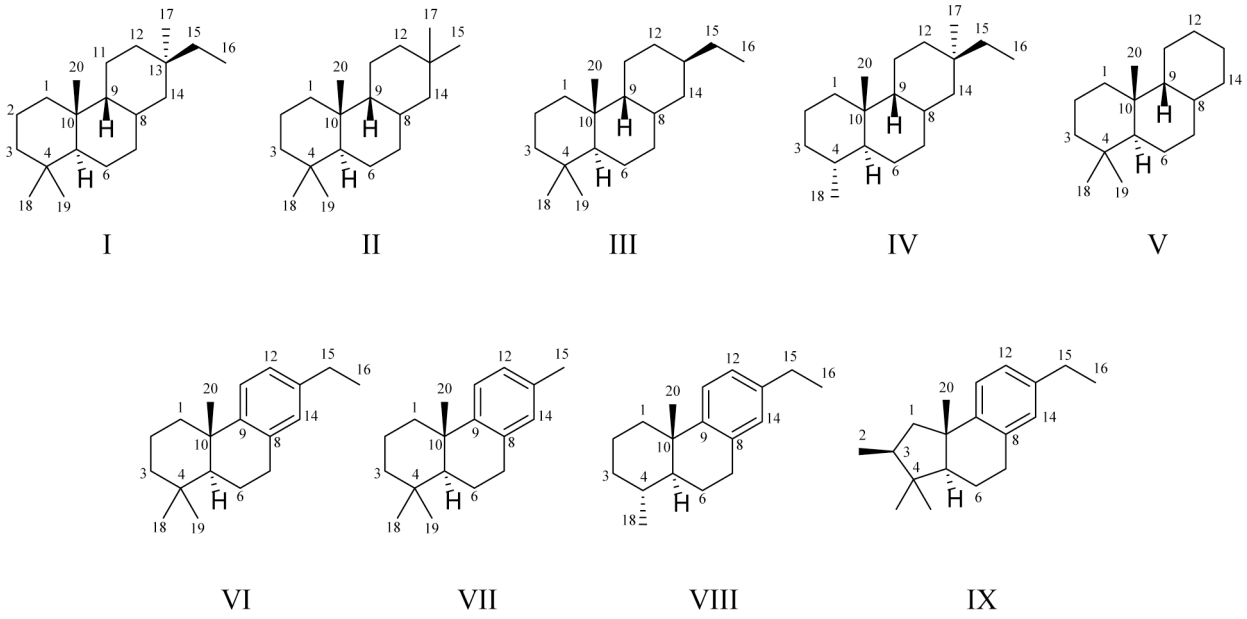
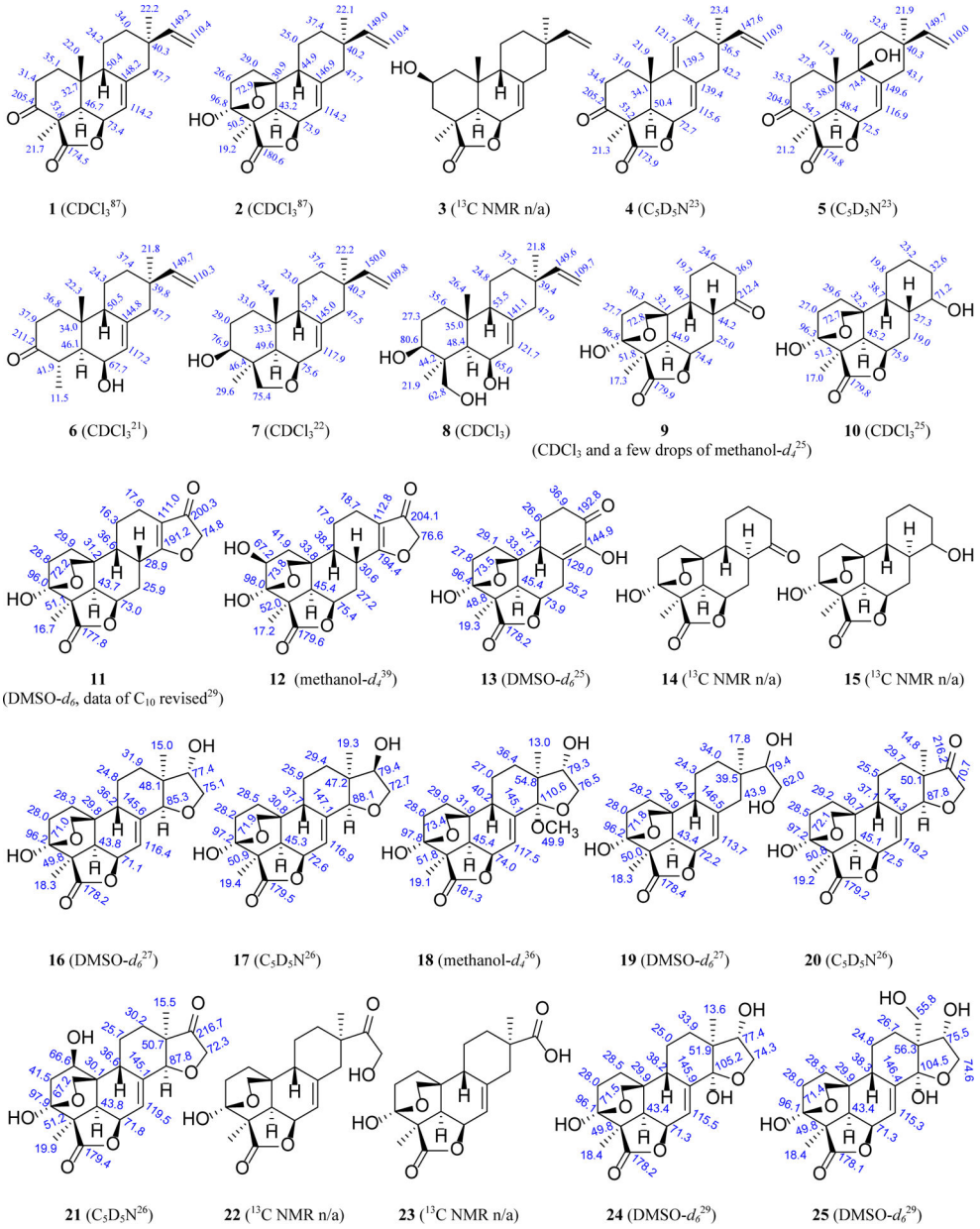


Figure 1.

Key structural skeletons of momilactone and related diterpenoids. (I) (9β-H)-pimarane; (II) 16-*nor*-(9β-H)-pimarane; (III) 17-*nor*-(9β-H)-pimarane; (IV) 19-*nor*-(9β-H)-pimarane; (V) 15,16,17-tri-*nor*-(9β-H)-pimarane; (VI) 17-*nor*-pimarane; (VII) 16,17-di-*nor*-pimarane; (VIII) 17,19-di-*nor*-pimarane; (IX) rearranged 17-*nor*-pimarane



1 ($CDCl_3$[87]) **2** ($CDCl_3$[87]) **3** (^{13}C NMR n/a) **4** (C_5D_5N[23]) **5** (C_5D_5N[23])

6 ($CDCl_3$[21]) **7** ($CDCl_3$[22]) **8** ($CDCl_3$) **9** ($CDCl_3$ and a few drops of methanol-d_4[25]) **10** ($CDCl_3$[25])

11 (DMSO-d_6, data of C_{10} revised[29]) **12** (methanol-d_4[39]) **13** (DMSO-d_6[25]) **14** (^{13}C NMR n/a) **15** (^{13}C NMR n/a)

16 (DMSO-d_6[27]) **17** (C_5D_5N[26]) **18** (methanol-d_4[36]) **19** (DMSO-d_6[27]) **20** (C_5D_5N[26])

21 (C_5D_5N[26]) **22** (^{13}C NMR n/a) **23** (^{13}C NMR n/a) **24** (DMSO-d_6[29]) **25** (DMSO-d_6[29])

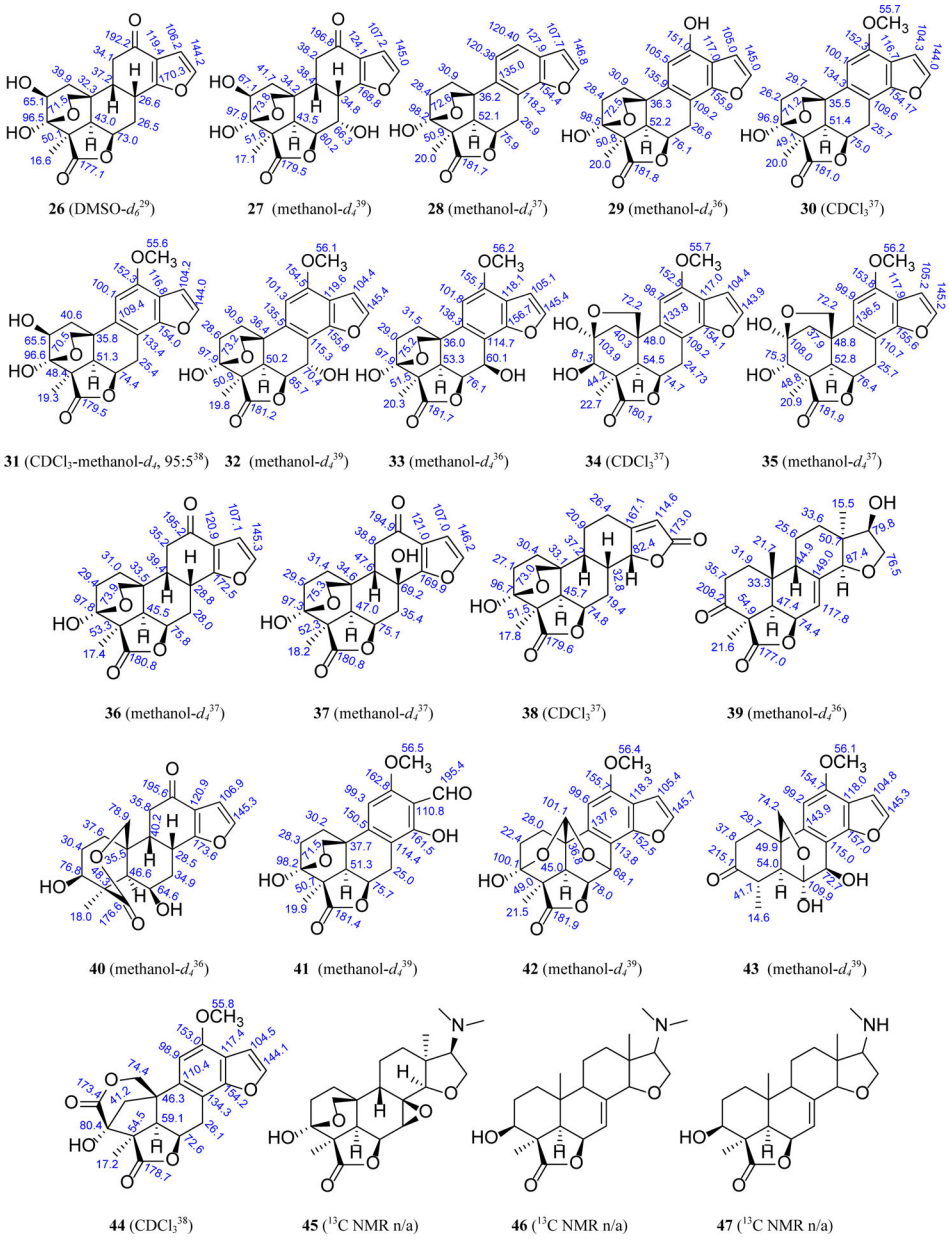
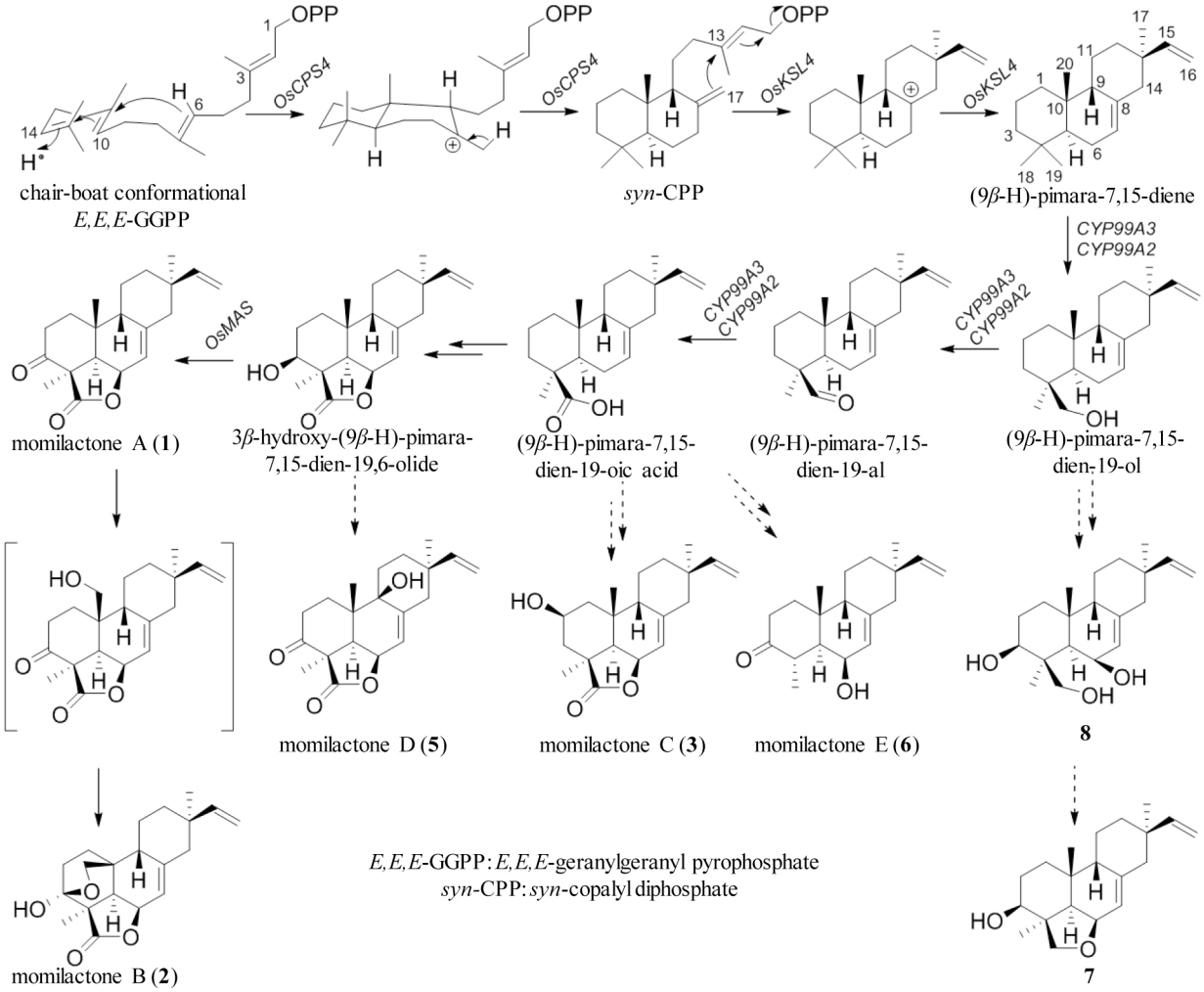


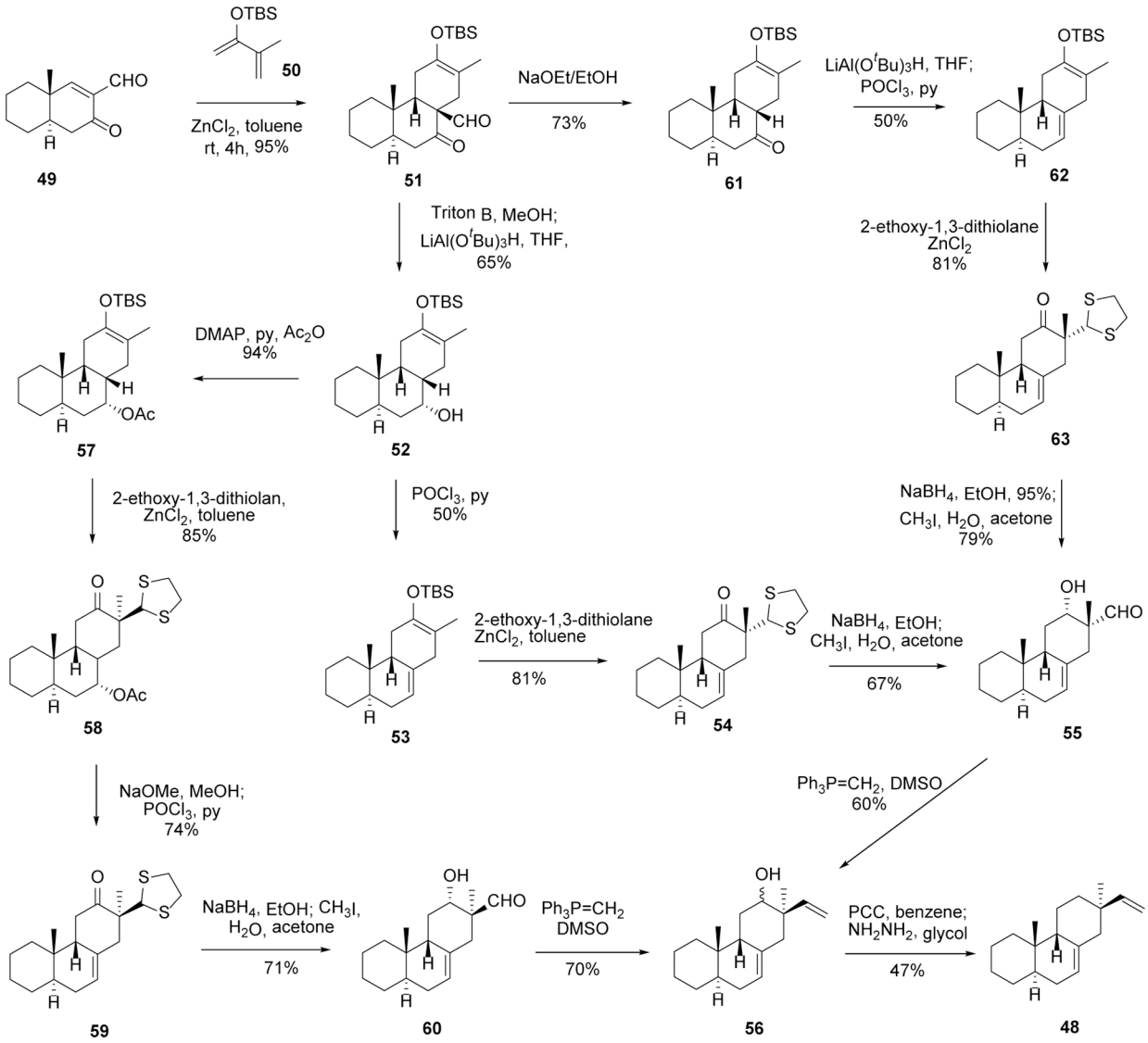
Figure 2.

Structures of naturally occurring momilactone and related diterpenoids (showing ^{13}C NMR spectroscopic data, solvents and references)



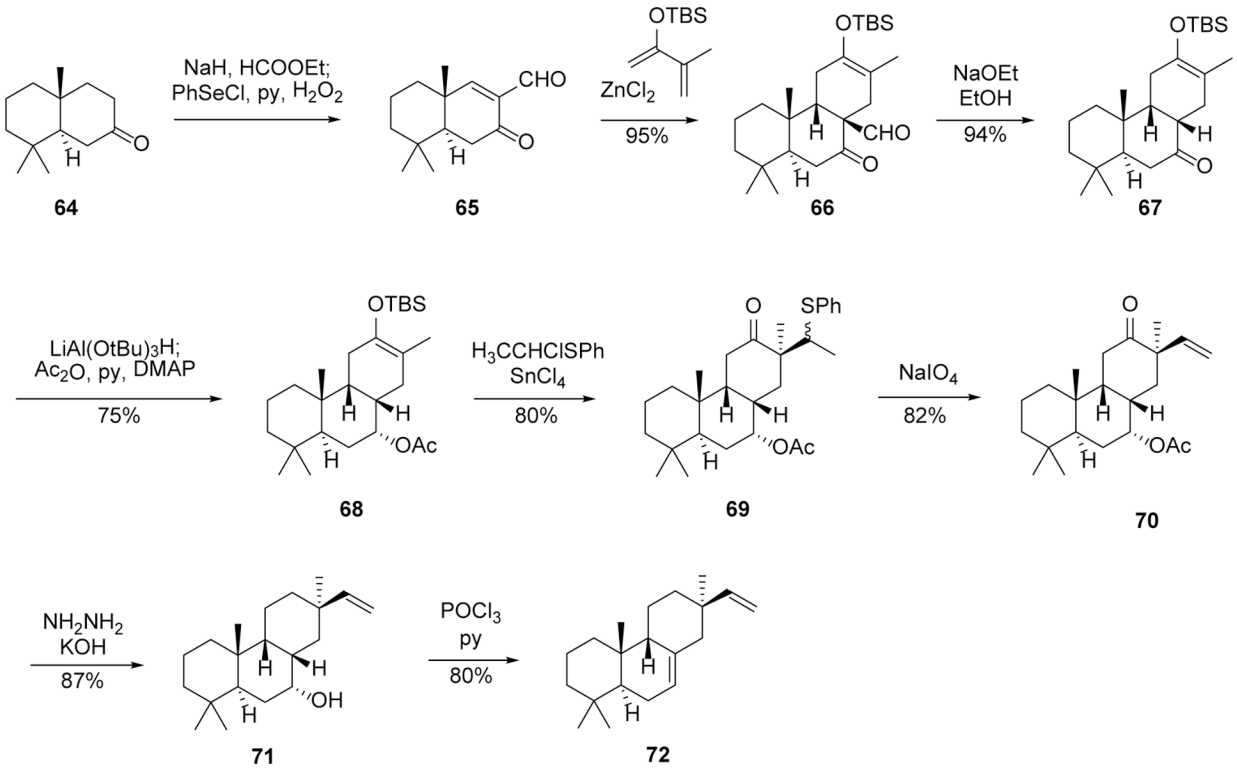
Scheme 1.

Biogenetic pathway for momilactone and related diterpenoids in rice plant



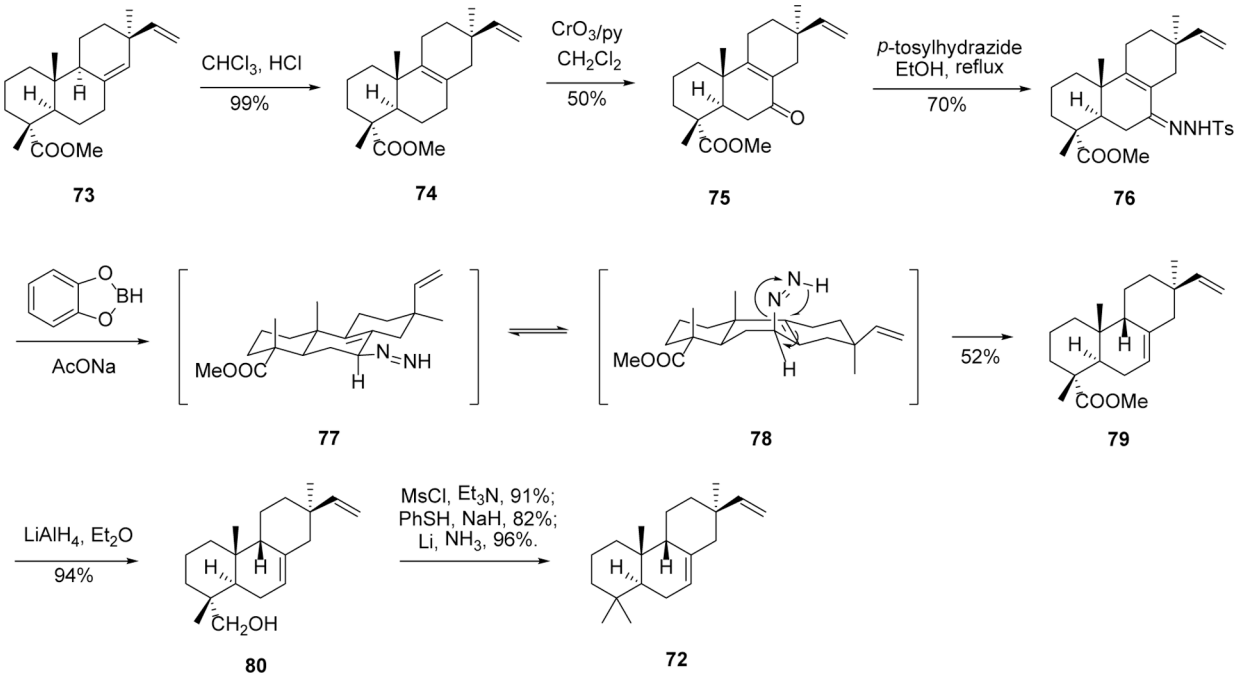
Scheme 2.

Synthesis of model compound (±)-4,4-dinor-(9β-H)-pimara-7,15-diene (**48**).



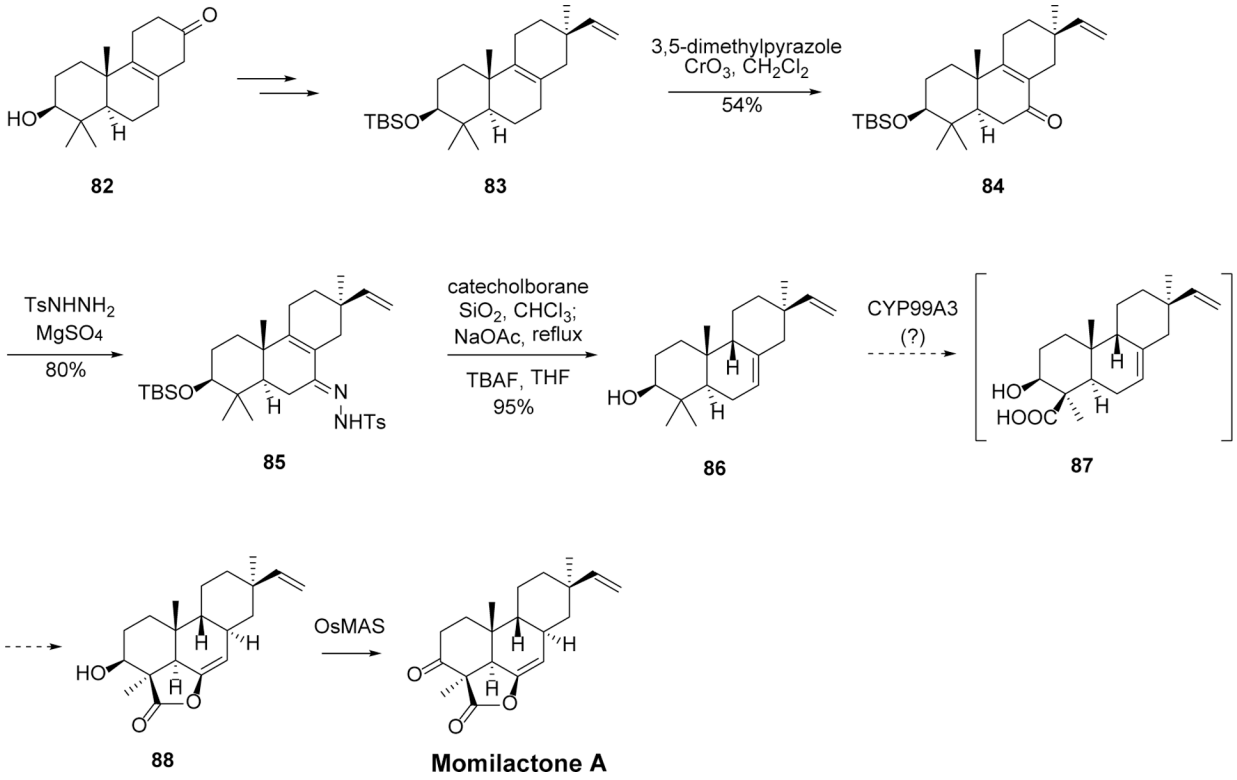
Scheme 3.

Synthesis of (9β-H)-pimara-7,15-diene (**72**).



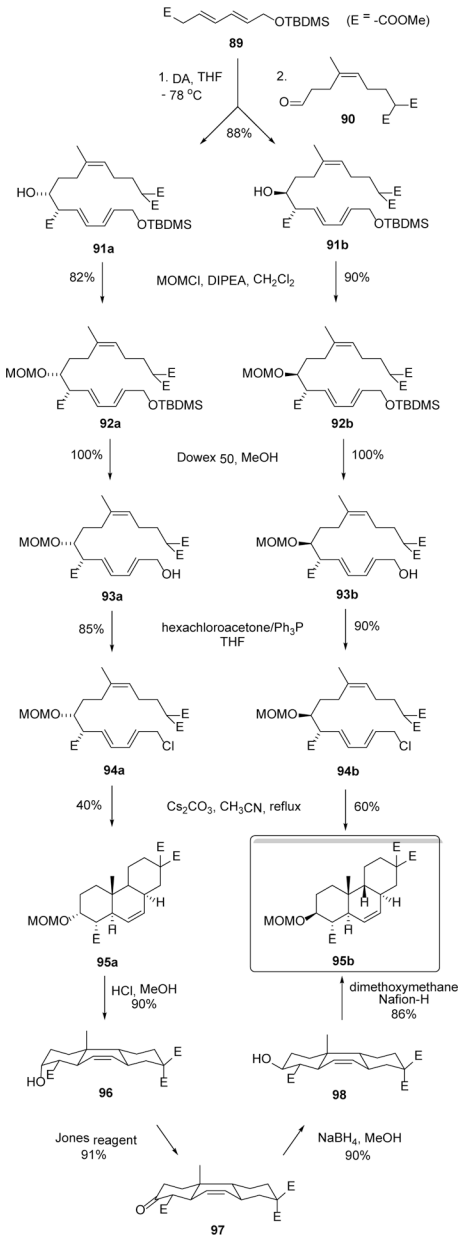
Scheme 4.

Another synthesis of (9β-H)-pimara-7,15-diene (**72**).

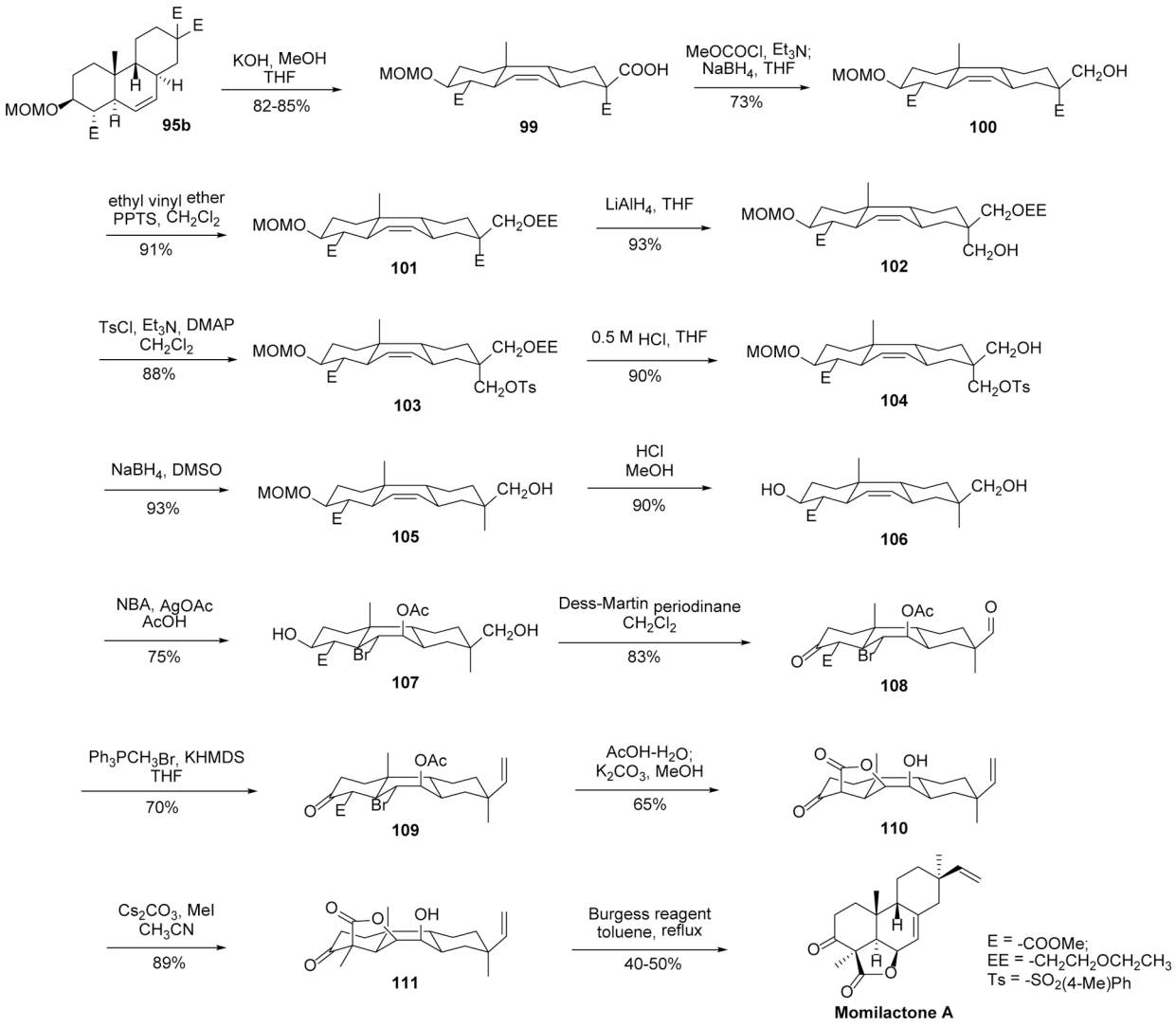


Scheme 5.

Synthesis of 3β-hydroxy-(9β-H)-pimara-7,15-diene (**86**) as a possible intermediate for the biosynthesis of momilactone A.



Scheme 6.
Synthesis of intermediate **95b**.



Scheme 7.

Total synthesis of (±)-momilactone A from intermediate **95b**.

Table 1.

Naturally occurring momilactone and related diterpenoids

Name	Structural Type	Source
Momilactone A (**1**)	(9β-H)-pimarane	*Oryza sativa*;[1, 2] *Hypnum plumaeforme*;[15] *Pseudoleskeella papillosa*[20]
Momilactone B (**2**)	(9β-H)-pimarane	*O. sativa*;[1, 2] *H. plumaeforme*[15]
Momilactone C (**3**)[a]	(9β-H)-pimarane	*O. sativa*[19]
Momilactone C (3-Oxo-pimara-7,9-dien-19,6β-olide, **4**)[a]	(9β-H)-pimarane derivative	*P. papillosa*[20]
Momilactone D (**5**)	(9β-OH)-pimarane	*O. sativa*[23]
Momilactone E (**6**)	19-*nor*-(9β-H)-pimarane	*O. sativa*[23]
6,19β-Epoxy-3β-hydroxy-5α,9β-pimara-7,15-diene (**7**)	(9β-H)-pimarane	*O. sativa*[21]
(9βH)-Pimara-7,15-diene-3β,6β,19-triol (**8**)	(9β-H)-pimarane	*O. sativa*[22]
Humirianthenolide A (**9**)	15,16,17-tri-*nor*-(9β-H)-pimarane	*Casimirella rupestris*[25]
Humirianthenolide B (**10**)	15,16,17-tri-*nor*-(9β-H)-pimarane	*C. rupestris*[25]
Humirianthenolide C (**11**)	17-*nor*-(9β-H)-pimarane	*C. rupestris*;[25] *Icacina trichantha*[29]
2β-Hydroxyhumiriantholide C (**12**)	17-*nor*-(9β-H)-pimarane	*I. trichantha*[39]
Humirianthenolide D (**13**)	15,16,17-tri-*nor*-(9β-H)-pimarane	*C. rupestris*[25]
Humirianthenolide E (**14**)	15,16,17-tri-*nor*-(9β-H)-pimarane	*C. rupestris*[25]
Humirianthenolide F (**15**)	15,16,17-tri-*nor*-(9β-H)-pimarane	*C. rupestris*[25]
Humirianthol (**16**)	(9β-H)-pimarane	*C. spp.*;[26] *C. ampla*;[27] *I. trichantha*[29]
15*R*-Humirianthol (**17**)	(9β-H)-pimarane	*C. spp*[26]
14α-Methoxyhumirianthol (**18**)	(9β-H)-pimarane	*I. trichantha*[36]
Acrenol (**19**)	(9β-H)-pimarane	*C. ampla*[27]
Humirianthone (**20**)	(9β-H)-pimarane	*C. spp.*[26]
1β-Hydroxyhumirianthone (**21**)	(9β-H)-pimarane	*C. spp.*[26]
Annonalide (**22**)	(9β-H)-pimarane	*C. spp.*;[26, 28] *Annona coriacea*[30–32]
Oxidized annonalide (**23**)	16-*nor*-(9β-H)-pimarane	*C. spp.*[26]
Icacinol (**24**)	(9β-H)-pimarane	*C. spp.*;[26] *I. claessensis*;[33] *I. trichantha*[29]
17-Hydroxyicacinol (**25**)	(9β-H)-pimarane	*I. trichantha*[29]
Icacenone (**26**)	17-*nor*-(9β-H)-pimarane	*I. mannii*;[34] *I. trichantha*[29]
7α-Hydroxyicacenone (**27**)	17-*nor*-(9β-H)-pimarane	*I. trichantha*[39]
Icacinlactone A (**28**)	17-*nor*-pimarane	*I. trichantha*[37]
12-Hydroxyicacinlactone A (**29**)	17-*nor*-pimarane	*I. trichantha*[36]
Icacinlactone B (**30**)	17-*nor*-pimarane	*I. trichantha*[37]
2β-Hydroxyicacinlactone B (Icacinlactone H, **31**)	17-*nor*-pimarane	*I. trichantha*[38]
7α-Hydroxyicacinlactone B (**32**)	17-*nor*-pimarane	*I. trichantha*[39]
7β-Hydroxyicacinlactone B (**33**)	17-*nor*-pimarane	*I. trichantha*[36]
Icacinlactone C (**34**)	17-*nor*-pimarane	*I. trichantha*[37]
Icacinlactone D (**35**)	17-*nor*-pimarane	*I. trichantha*[37]
Icacinlactone E	17-*nor*-(9β-H)-pimarane	*I. trichantha*[37]

Name	Structural Type	Source
(2-Dehydroxyicacenone, **36**)		
Icacinlactone F (8β-Hydroxyicacinlactone E, **37**)	17-*nor*-(9β-H)-pimarane	*I. trichantha*[37]
Icacinlactone G (**38**)	17-*nor*-(9β-H)-pimarane	*I. trichantha*[37]
Icacinlactone I (**39**)	(9β-H)-pimarane	*I. trichantha*[36]
Icacinlactone J (**40**)	17-*nor*-(9β-H)-pimarane	*I. trichantha*[37]
Icacinlactone K (**41**)	16,17-di-*nor*-pimarane	*I. trichantha*[39]
Icacinlactone L (**42**)	17-*nor*-pimarane	*I. trichantha*[39]
Icacintrichanone (**43**)	17,19-di-*nor*-pimarane	*I. trichantha*[39]
Icacintrichantholide (**44**)	rearranged 17-*nor*-pimarane	*I. trichantha*[38]
Icacine (**45**)	(9β-H)-pimarane alkaloid	*I. guesfeldtii*[40]
Icaceine (**46**)	(9β-H)-pimarane alkaloid	*I. guesfeldtii*[41]
De-*N*-methylicaceine (**47**)	(9β-H)-pimarane alkaloid	*I. guesfeldtii*[41]

[a] In the literature, two structurally distinct compounds have been named momilactone C.

Table 2.

Inhibitory activities against *Magnaporthe oryzae* of rice components (IC_{50}, μM)

	Compound Class	Spore Germination[88]	Germ Tube Growth
Momilactone A (**1**)	(9β-H)-pimarane	47.8	74[22], 15.9[88]
Momilactone B (**2**)	(9β-H)-pimarane	9.1	3.0[4]
Oryzalexin A	*ent*-sandaracopimarane	384.1	-
Oryzalexin B	*ent*-sandaracopimarane	245.0	-
Oryzalexin C	*ent*-sandaracopimarane	453.3	-
Oryzalexin D	*ent*-sandaracopimarane	75.7	-
Oryzalexin E	*ent*-sandaracopimarane	205.6	-
Oryzalexin F	*ent*-sandaracopimarane	338.8	-
Oryzalexin S	stemarane	65.8	122[22]
Phytocassane A	*ent*-cassane	63.3	15.8[89]
Phytocassane B	*ent*-cassane	12.0	4.5[89]
Phytocassane C	*ent*-cassane	22.0	9.4[89]
Phytocassane D	*ent*-cassane	79.1[90]	31.6[89]
Phytocassane E	*ent*-cassane	19.0[90]	6.3[89]
Phytocassane F	*ent*-cassane	*[22]	16[22]
Sakuranetin	flavanone	52.4[90]	37[22]

*Completely inhibited at 300 μM

Table 3.

Cytotoxic activities of momilactone-like molecules (IC50, μM)*

Compound	MDA-MB-435	HT-29	MDA-MB-231	OVCAR3	A2780
Humirianthenolide C (**11**)	0.66	3.00	0.67	1.05	-
2β-Humirianthenolide C (**12**)	1.48	-	2.85	3.23	-
Humirianthol (**16**)	1.65	4.94	3.74	4.12	3.0
15*R*-Humirianthol (**17**)	-	-	-	-	2.2
14α-Methoxyhumirianthol (**18**)	7.04	-	16.91	15.23	-
Acrenol (**19**)	-	-	-	-	1.8
Humirianthone (**20**)	-	-	-	-	6.1
Annonalide (**22**)	-	-	-	-	3.9
Icacinol (**24**)	1.25	4.23	7.30	7.55	1.7
17-Hydroxyicacinol (**25**)	5.61	18.27	-	-	-
Icacenone (**26**)	6.44	13.25	10.85	18.71	-
7α-Hydroxyicacenone (**27**)	2.91	-	7.60	7.53	-
Icacinlactone F (**37**)	6.16	-	8.94	10.5	-

*MDA-MB-435: Human melanoma cell line; HT-29: Human colorectal adenocarcinoma epithelial cell line; MDA-MB-231: Human breast adenocarcinoma epithelial cell line; OVCAR3: Human ovarian adenocarcinoma epithelial cell line; A2780: Human ovarian cancer epithelial cell line. Compounds **25**–**29**, **31**–**37** were inactive against MDA-MB-231, MDA-MB-435, and OVCAR3 (IC_{50} > 20 μM);