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Studies toward the Unique Pederin Family Member Psymberin: Full Structure Elucidation, Two Alternative Total Syntheses, and Analogs

Yu Feng[†], **Xin Jiang**[†], and **Jef K. De Brabander**[†,‡,*]

[†]Department of Biochemistry, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038, United States

[‡]Harold C. Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038, United States

Abstract

Two synthetic approaches to psymberin have been accomplished. A highly convergent first generation synthesis led to the complete stereochemical assignment and demonstrated that psymberin and irciniastatin A are identical compounds. This synthesis featured a diastereoselective aldol coupling between the aryl fragment and a central tetrahydropyran core, and a novel one-pot procedure to convert an amide, via intermediacy of a sensitive methyl imidate, to the *N*-acyl aminal reminiscent of psymberin. The highlights of the second generation synthesis include an efficient iridium-catalyzed enantioselective bis-allylation of neopentyl glycol, and a stepwise Sonogashira coupling/cycloisomerization/reduction sequence to construct the dihydroisocoumarin unit. The two synthetic avenues were achieved in 17–18 steps (longest linear sequence, ~14–15 isolations) from 3 fragments prepared in 7–8 steps (1st generation) and 3–8 steps (2nd generation) each. This convergent approach allowed for the preparation of sufficient amounts of psymberin (~ 0.5 g) for follow-up biological studies. Meanwhile, our highly flexible strategy enabled the design and synthesis of multiple analogs, including a psymberin-pederin hybrid termed psympederin that proved crucial to a comprehensive understanding of the chemical biology of psymberin and related compounds that will be described in a subsequent manuscript.

INTRODUCTION

In 2004, Crews and Pettit independently reported the isolation of structurally novel, constitutionally identical cytotoxins. Psymberin (**1**) was obtained from the marine sponge *Psammocinia* sp.,[1] whereas irciniastatin A (**2**) was isolated from *Irciniaramosa* sp.[2] Multidimensional NMR studies substantiated the assigned relative configuration for psymberin as shown in **1**, save for the undefined configuration at C_4. The absolute configuration was assured through observation of a well-defined positive Cotton effect at the $n \rightarrow \Pi^*$ transition (280 nm) of the dihydroisocoumarin unit. The relative stereochemistry of irciniastatin A (**2**) was only resolved for the C^8–C^{13} aminal fragment. Given the differing relative configuration (C^8–C^9) and producing organisms, the structures formulated for irciniastatin and psymberin thus define two different natural products. The overall structural features of these natural products most closely resemble those of the pederin family of natural products including pederin (**3**),[3] and mycalamide A (**4**)[4] (Fig. 1).[5] However,

Corresponding Author Jef.Debrabander@UTSouthwestern.edu.

Supporting Information. Experimental procedures, characterization data, copies of NMR spectra, and X-Ray crystal structure data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org psymberin is uniquely extended with a dihydroisocoumarin unit not found in any of the other >36 members of the pederin family isolated to date, and lacks this family's signature acetal-containing pederate side chain.[5c]

Pederin, mycalamide and other members of the family are potent eukaryotic protein synthesis inhibitors and cytotoxic agents, which exhibit strong blistering activity upon contact with the skin.[5] An indication that psymberin might be endowed with an alternative mode of action came from the observation that psymberin, unlike pederin and mycalamide, displayed a highly differential cytotoxicity profile with >10,000-fold potency differences in the NCI 60 cell human tumor cell line panel.[1] In contrast, the material isolated by Pettit and coworkers did not exhibit this differential activity and uniformly inhibited the growth of a different selection of human cancer cell lines with single digit nanomolar potency. Irciniastatin also potently arrested the growth of human umbilical vein endothelial cells (HUVEC) with a GI_{50} of 0.5 nM with no evidence of tube formation, an indication it could be useful as an antivascular agent.[2]

Due to uncertainties regarding the structural relation between psymberin and irciniastatin, significant structural divergence from the pederin family of natural products, low natural abundance, and impressive biological activities, psymberin/irciniastatin has become an attractive target for synthetic pursuit. Through the total synthesis of several diastereoisomers consistent with partially assigned structures of **1** and **2**, our group concluded that psymberin and irciniastatin are actually identical compounds.[6] Several other total syntheses,[7] formal syntheses,[8] fragment syntheses,[9] as well as analog syntheses, [10] have appeared during recent years. A combined supply of natural psymberin and material prepared by our group enabled further in vivo evaluation by the NCI Developmental Therapeutics Program, which indicated encouraging therapeutic efficacy.[11] Additionally, our synthetic psymberin was explored as an antibody drug conjugate in collaboration with Seattle Genetics.[12] In a quest to discover the mode of action, and an interest in a more comprehensive preclinical evaluation of psymberin, we have continued our study of this fascinating natural product. In this paper, we describe a full account of the total synthesis, an improved second generation total synthesis, and the synthesis of strategically designed analogs of psymberin. In a subsequent article, we detail our biological investigations that led to the target identification of psymberin, and attributes that distinguish it from the pederin/mycalamide family of natural products.[13]

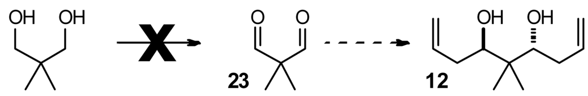
RESULTS AND DISCUSSION

First Generation Synthesis

Psymberin (**1**) is a complex polyketide comprising nine stereocenters, a geminal dimethyl, and a dihydroisocoumarin fragment. Its tetrahydropyranyl core is appended with a 2-hydroxy-3-methoxy-5-methyl-hex-5-enoic acid (psymberic acid) through an *N*-acylaminal linkage. As outlined in scheme 1, we anticipated to intercept an intermediate *N*-acyl-methoxyimidate **5** with a reducing agent to provide the C_8-*S* and C_8-*R* *N*-acyl aminals corresponding to the assigned structures of psymberin and irciniastatin, respectively. Given the unknown configuration at C_4, intermediate **5** would result from acylation of imidate **7**, to be prepared from the corresponding primary amide, with diastereomeric acid chlorides **6a** or **6b**. Both epimeric acid chlorides in turn will be accessible from a common intermediate to be derived from *D*-mannitol via a stereocontrolled methallylation. Our approach to **7** hinged on combing arylaldehyde **9**, to be derived from commercially available 2,4-dimethoxy-1-methylbenzene (**10**) and ethyl ketone **8** via a substrate-controlled aldol coupling to set the correct stereochemistry of the C_{15}-C_{17} stereotriad. Ethyl ketone **8** was envisioned to be derived from aldehyde **11**, in turn accessible through an oxidative cleavage of C_2-symmetric bis-homoallyl alcohol **12**.

Given the unknown configuration at C_4, we needed to prepare both diastereomers of the psymberic acid side chain (cf. **6a**/**6b**, Scheme 1). We initially approached this problem starting from known triol **13**, prepared in two steps from *D*-tartaric acid (Scheme 2, panel A).[14] Oxidative diol-cleavage of this material, [15] followed by treatment of the crude aldehyde **14** delivered an inseparable mixture of homoallylic alcohols. Selective protection of the primary alcohol and methylation of the secondary alcohol provided compounds **15a** and **15b**, which could be separated at this stage (ratio = ~1:1.4). Independent processing via desilylation and a two-step oxidation then provided protected psymberic acids **16a** and **16b**. In panel B, we delineate a stereoselective gram-scale synthesis of benzoyl-protected psymberic acids **20a** and **20b**. Starting from protected glyceraldehyde **17**, available via a one-step oxidation from *D*-mannitol,[16] asymmetric methallylation with a borane reagent derived from isobutenyllithium and (−)-Ipc_2BOMe,[17] followed by methylation delivered methyl ether **18** in 65% yield (2 steps) and 97:3 *dr*, a significant improvement over the 4:3 ratio obtained by Williams using the corresponding Grignard reagent.[9a] Acetonide hydrolysis, silylation of the primary and benzoylation of the secondary alcohol, followed by an acidic aqueous work-up provided 6.6 g of alcohol **19** over a three steps sequence from **18**. Finally, a two-step oxidation procedure yielded gram quantities of psymberic acid **20a** (7 steps from aldehyde **17**; 47% yield). The relative stereochemistry set during the methallylation step was ascertained through ^{1}H-NMR analysis of acetal **21**, obtained via ozonolysis of the terminal olefin **19**, followed by acetal formation (→ **21**). Diastereomeric acid **20b** was synthesized as outlined for acid **20a**, except that methallylation of aldehyde **17** exploited the antipodal borane reagent.

As we will detail later, our approach towards the central tetrahydropyranyl core of psymberin was inspired by the possibility to engage C_2-symmetrical bis-homoallyl alcohol **12** in an oxidative desymmetrization reaction. On paper, this compound should be available from an enantioselective bis-allylation of dialdehyde **23** (Eq. 1).[18] A practical problem arises when one considers that malondialdehydes are unstable, sensitive to hydrate formation, self-condensation and oligomerization. In fact, all attempts to generate pure dialdehyde **23** from neopentyl glycol met with failure. In light of this, we originally settled for a slightly longer approach starting from isobutyraldehyde (**24**, Scheme 3). According to a known literature procedure,[19] this material was converted in three steps to 3,3-dimethoxy-2,2-dimethylpropanal **25**, a mono-protected version of the corresponding malondialdehyde **23**. An enantioselective allylation of aldehyde **25** using Leighton's silane reagent **27** provided homoallyl alcohol **26** in 94% *ee*[20] Noteworthy, the dimethyl acetal was unmasked during the work-up conditions, enabling for a subsequent allylation under the same reaction conditions. The corresponding bishomoallyl alcohol **12** was thus obtained in 77% yield and >17:1 *dr*. Since our original route to this compound,[6] Krische and coworkers developed a creative two-directional carbonyl allylation from the alcohol oxidation level to circumvent the use of difficult to handle malondialdehydes.[21] As reported by Krische, treatment of diol **29** with allyl acetate employing a cyclometallated catalyst formed *in situ* from $[Ir(cod)Cl]_2$, (*R*)-Cl-MeO-BIPHEP **28**, 4-chloro-3-nitrobenzoic acid and Cs_2CO_3 in degassed dioxane, furnished diol **12** in 42% yield (99% *ee*, 20:1 *dr*) on a 4 gram scale. A mono-allylated intermediate was also isolated (not shown) in 24–30% yield. This material could be allylated under the same reaction conditions to obtain additional bis-allylated product **12** in 30% yield (51% combined yield from **29**).



(1)

At this point, we were hopeful that we could differentiate the termini of diene **12** via an oxidative cleavage of the terminal olefins, after which one of the resulting aldehydes would be trapped as a lactol. As shown in Scheme 4, this concept was best put to practice after mono-protection of diol **12** (silyl or benzyl) followed by ozonolytic cleavage of both double bonds to yield lactols **30a** (92%) and **30b** (76%), respectively. At this point, we needed to homologate the aldehyde to an ethyl ketone, and activate the lactol for introduction of the cyano group as a masked primary amide. In the event, acylation of the benzylated lactol **30b** provided acetate **11b** in 60% yield. Under the reaction conditions, dioxabicyclononane byproduct **31** was formed in 30% yield. Lewis acid-catalyzed acetate displacement with trimethylsilyl cyanide[22] yielded cyano acetal **32** wherein the aldehyde was trapped as a cyanohydrin (60% yield).[23] Hydrolysis of the cyanohydrin was more difficult than anticipated and provided aldehyde **33** in modest yields (31–36%). Treatment of this material with diethylzinc in the presence of a diaminocyclohexane-ligated titanium(IV) catalyst[24] was followed by Dess-Martin oxidation to [25] yield the corresponding ethyl ketone **8b** in 80% yield for this two-step procedure. In order to avoid cyanohydrin formation, we changed the order of events and first employed the diethylzinc addition to aldehyde **11b** yielding carbinol **34** in 87% yield. Unfortunately, cyanide displacement of acetate **34** was now accompanied by the formation of dioxabicyclononane byproduct **36**, resulting from intramolecular acetate displacement with the secondary alcohol. Preventing alcohol participation via oxidation of **34** to ethyl ketone **37**, obtained in 88% yield, now led to dehydrative dioxabicyclononane formation upon treatment with trimethylsilyl cyanide[22] and boron trifluoride etherate to yield bicycle **38** as the major product isolated in 47% yield, together with 14% of the desired ethyl ketone **8b**.

So far, we learned from the above synthetic exercises that activation of the anomeric acetate with boron trifluoride etherate not only enables cyanide introduction, but also leads to a facile formation of dioxabicyclononane and cyanohydrin byproducts in the presence of an aldehyde or ketone. Ultimately, we formulated a solution that started with the silylated lactol **30a** (Scheme 4, bottom). Acylation of this material was not accompanied by dioxabicyclononane ring formation (cfr. **31**), presumably because of the larger steric hindrance of the TBS protecting group. Ethyl ketone formation with diethylzinc using the Kobayashi[24] conditions also proceeded with higher yield, providing ethyl carbinol **39** in 68% yield (2 steps). To avoid formation of potential bicyclic ring products, we modified the conditions for introduction of the cyano group. In a one-pot procedure, trimethylsilyl cyanide[22] was added to alcohol **39** (neat) in the absence of Lewis acid to allow protection of the secondary alcohol as a silyl ether, followed by addition of a solution of zinc iodide in acetonitrile to initiate oxonium formation (**40**), followed by axial cyanide attack. After acidic aqueous workup, compound **41** was obtained in 91% yield and further oxidized to target ethyl ketone **8a** in 95% yield. Crystallographic analysis of crystals obtained from **8a** fully confirmed the assigned structure and relative stereochemistry. Using this optimized sequence, ethyl ketone **8a** was obtained in seven steps from bis-homoallylic alcohol **12** in 54% overall yield, versus ~7% overall yield (6–7 steps) for the synthesis of the corresponding benzylated ethyl ketone **8b**.

The synthesis of the aryl fragment **9** and coupling with ethyl ketone **8a** is shown in Scheme 5. Starting from the commercially available 2,4-dimethoxy-1-methylbenzene **10**, formylation, [26] oxidation to the corresponding carboxylic acid, and amidation afforded diethylamide **42** in 66% yield for the three-step sequence. *Ortho*-directed allylation[27] of this material was followed by deprotection of the phenolic methyl ethers with boron tribromide. Formation of the methyl ester **43** was best executed according to a protocol developed by Keck and coworkers,[28] i.e. treatment of the amide with trimethyloxonium tetrafluoroborate followed by aqueous hydrolysis of the incipient methylimidate. The overall yield for this three-step sequence was 45%. Subsequent protection of the phenols and a two-step oxidative cleavage of the double bond (dihydroxylation; diol-cleavage) delivered coupling partner aldehyde **9** in an eight-step sequence and 24% overall yield from commercially available starting material **10**.

Having accessed the psymberin fragments in high yield and enantiomerically pure form enabled us to explore their union via a convergent coupling strategy. First, we needed to accomplish a stereoselective aldol coupling between ethyl ketone **8a** and arylaldehyde **9**. Although initial explorations with titanium enolates ($TiCl_4$, $^{i}Pr_2NEt$)[29] only delivered mixtures of dia-stereoisomers (~1:1 ratio), we found that the *Z*-chlorophenylboryl enolate[30] **44** added to aldehyde **9** with high facial selectivity producing the *syn*-aldol product **45** in 88% yield and 12:1 *dr*.[31] The stereochemical outcome was predicted based on the inherent facial bias of enolate **44** when combined with aldehyde **9** (*Si*-face) through a chair-like transition state.[30] Stereoselective reduction of β-hydroxyketone **45** with catecholborane[32] provided lactone **47** after basic workup (99%). Quenching the reducing mixture with aqueous Na,K-tartrate permitted isolation of the 1,3-*syn*-diol for derivatization as acetonide **46**.[33] ^{1}H an ^{13}C NMR analysis of this derivative confirmed the 1,3-*syn* configuration.[34] Silylation of the secondary alcohol (→ **49**, 92%) set the stage for a mild nitrile hydrolysis exploiting a platinum(II)-catalyst (**50**) developed by Ghaffar and Parkins to deliver compound **51** in 99% yield.[35] Treatment of this compound with excess DDQ only removed the *ortho*-phenolic *p*-methoxybenzyl protecting group (99% yield). Fortunately, the second *p*-methoxybenzyl group could be removed via hydrogenolysis to deliver diol **53** (95%), which was transformed to mono-benzoate **54** in 91% yield.

The stage was now set to execute a reductive fragment coupling of dihydroisocoumarin **54** with the psymberic acid side chain. Our plan was to acylate imidate **55** with acid chloride **56** (from acid **16a**) and intercept the incipient acylimidate with a reducing agent (Scheme 6), a tactic employed for the synthesis of the structural relative pederin (**3**).[36] However, we were unable to prepare and handle imidate **55** using Me_3OBF_4 as reported.[36] Treatment of **54** with Me_3OBF_4 resulted in decomposition, methyl ester formation, and *N*-methylation. Reasoning that the acidity of Meerwein's salt and water are potential culprits, we screened for additives including Et_3N, $NaHCO_3$, proton sponge, molecular sieves, and pyridine to no avail. Extensive experimentation identified a uniquely beneficial effect of adding poly(4-vinylpyridine) (25% cross-linked) during the imidate formation with Me_3OBF_4 (CH_2Cl_2). After stirring at room temperature, the crude imidate reaction mixture was filtered and concentrated, followed by dissolving the crude imidate **55** in toluene, addition of Hunig's base and acid chloride **56**. The mixture was heated to 40 °C for 2 h, cooled to 0 °C and treated with an ethanolic sodium borohydride solution. After workup, the crude compounds were saponified to afford a separable mixture of **57a** and **57b** (~1:2 ratio)[37] in 57% yield from **54**. This saponification step was necessary because some acylation of the free phenol occurred during the acylation step with acid chloride **56**. Since bis-phenols **57a** and **57b** were unstable towards the oxidative conditions to remove the *p*-methoxybenzyl protecting group present in the psymberate side chain, and hydrogenolytic conditions resulted in saturation of the terminal 1,1-disubstituted olefin, these compounds were benzoylated to afford benzoates **58a** and **58b** respectively (70%). Oxidative removal of the *p*-methoxybenzyl protecting group now smoothly yielded alcohols **59a** and **59b**.

We anticipated an uneventful deprotection of both silyl ethers. Instead, treatment of **59a** and **59b** with tetrabutylammonium fluoride first removed the phenolic benzoate, followed by a slow but partial desilylation of one of the silyl ethers (crude NMR). Only a small amount of fully deprotected material was observed, even when a large excess of fluoride was added. We were unable to convert, nor purify, the crude mixture of compounds **60–62a** or **60–62b** to a globally deprotected material. However, thorough analysis of the crude ^{1}H-NMR spectra hinted that the mixture containing **62a** provided a spectral fingerprint congruent with that reported for psymberin.[1]

Although we had defined an endgame strategy toward psymberin, it was clear that protecting group issues were plaguing an efficient execution. From the above described initial forays toward psymberin, it became obvious that the *p*-methoxybenzyl protecting groups needed to be removed before installing the olefin-containing psymberic acid side chain, and that we needed more easily removable replacements for the silylether protecting groups. Toward this end, we processed diol **48**, obtained from silylether **47** via fluoride-mediated deprotection (TBAF, 99%, Scheme 5). As shown in Scheme 7, nitrile **48** was hydrolyzed with the Ghaffar-Parkins catalyst **50**,[35,38] followed by hydrogenolytic removal of the *p*-methoxybenzyl protecting groups and peracylation with acetic anhydride. The corresponding crystalline amide **63**, obtained in 88% yield (3 steps), permitted an unambiguous confirmation of the full stereochemistry as shown via crystallography. As before (Scheme 6), stirring a solution of amide **63** (CH_2Cl_2) with Me_3OBF_4 in the presence of poly(4-vinylpyridine) yielded a crude imidate mixture (→ **64**) that was filtered, concentrated, and resuspended in toluene. After addition of Hunig's base, acid chloride **6a** or **6b** was added, followed by heating to 40 °C for 2 h. The reaction mixture was then cooled to 0 °C and treated with an ethanolic sodium borohydride solution, providing after workup and saponification of the acetate protecting groups with a methanolic LiOH solution a separable mixture of **1** and **65** (71:29 ratio) in 56% yield from **6a** and an inseparable mixture of **66** and **67** (75:25 ratio) in 50% yield from **6b**.[37] As noted in the introduction, a constitutional identical natural product termed irciniastatin was isolated by the Pettit group.[2] Although the relative stereochemistry of irciniastatin was only partly resolved, the assignment dictated it to be a different compound than psymberin (structure **2** in Fig 1). Because the NMR spectra of psymberin and irciniastatin were recorded in different solvents, we recorded the spectra of psymberin/irciniastatin diastereoisomers **1**, **65–67** in both solvents reported for psymberin and irciniastatin respectively. Careful analysis of all the spectral data obtained for the four synthetic diastereoisomers indicated that **1** represents the true structure of natural psymberin as well as irciniastatin; i.e psymberin and irciniastatin are identical compounds.

Second Generation Synthesis

Although our first generation synthesis served us well in producing ~0.5 g of psymberin (**1**), introducing the dihydroisocoumarin fragment required an eight-step synthesis of aromatic aldehyde **9**, followed by a stereoselective aldol coupling and reductive lactonization. To facilitate future SAR studies around the aromatic fragment, we designed an alternative more flexible approach that would rely on a late-stage introduction of an aromatic electrophile such as triflate **69** via Sonogashira cross-coupling with an alkynyl partner such as **70** (see Scheme 8). The resulting alkyne-substituted benzoic acid derivative **68** would enable dihydroisocoumarin formation (**63**) via cycloisomerization followed by hydrogenation of the resulting isocoumarin. This approach has the advantage that many functionalized aromatic halides and triflates (from the phenol) are commercially available. For the synthesis of psymberin, aromatic triflate **69** is a known compound available in 3 steps from commercial trimethoxytoluene (**71**).[39] Alkynyl fragment **70** in turn would be accessible from lactol **30a** via a Marshall propargylation.[40]

As illustrated in Scheme 9, acylation of lactol **30a** delivered aldehyde **11a**, which was converted to *anti*-propargylic alcohol **72** via treatment with an *in situ* prepared allenylindium species derived from mesylate **71** according to Marshall and coworkers in good yield (70%) and excellent diastereoselectivity (*dr* >10:1, separable).[40, 41] The corresponding reaction with the allenylzinc species derived from **71** ($Pd(OAc)_2$, PPh_3, Et_2Zn in THF) led to decomposition.[40b] Acetate displacement with TMSCN[22] under conditions described for the corresponding reaction leading to **41** (Scheme 4), gave cyanotetrahydropyran **73** in 81% yield. Initial efforts to invert the stereochemistry of *anti*-alcohol **73** using contemporary Mitsunobu conditions (diethyl azodicarboxylate or diisopropyl azodicarboxylate, PPh_3, in THF) faied,[42] and led to elimination (enyne) or recovered starting material. However, exploiting condition developed by Tsunoda et al. (*N,N,N′,N′*-tetramethylazodicarboxamide, PBu_3, benzene) efficiently provided inverted *p*-nitrobenzoate **70** in 90% yield.[43] Initial model studies to construct the isocoumarin via a one-pot Pdcatalyzed heteroannulation between alkyne **70** and *o*-iodobenzoic acid indicated low conversion and significant amounts of phthalide formation.[44] Therefore, a stepwise construction of the isocoumarin was investigated.

Sonogashira coupling of alkyne **70** with penta-substituted aryl triflate **69** followed by saponification yielded benzoic acid-substituted alkyne **68** in 83% yield.[45]

As shown in Table 1, extensive experimentation was required to obtain the desired isocoumarin **74a**. Besides solving the issue of regioselectivity (5-*exo* to **74b** vs 6-*endo* to **74a**), the presence of the homopropargylic alcohol also could create issues with competing hydroalkoxylation and elimination to the enyne. Furthermore, the isocoumarin **74a** and isomeric alkylideneisobenzofuran-1(3*H*)-one **74b** were unstable to chromatography. Various cycloisomerization conditions[46] including Bronsted acid[47] (entries 1, 2), $InBr_3$[48] (entry 3), and $AuCl_3$(entry 4) gave complex mixtures from which no characterizable compounds could be observed by crude NMR. Silver(I)-mediated cycloisomerization proceeded more smoothly, but afforded an equimolar mixture of *5-exo* and *6-endo* products (entry 5, ~70% mass balance) similar to result reported in the literature.[49] Inspired by the cycloisomerization methodology developed by our group, we explored Zeise's dimer ($[Pt(CH_2CH_2)Cl_2]_2$).[50] Although 5 mol% of this catalyst now promoted the cycloisomerization at room temperature, the undesired 5-*exo* product dominated (3:7 ratio of **74a**:**74b**, ~50% mass balance, entry 6). Switching to JohnPhos-ligated AuCl[51] provided a slight improvement, but still favoring the undesired 5-*exo* product **74b** (entry 7).[52] In the end, we could overturn the regioselectivity favoring the desired 6-*endo* product when cationic Au(I) (PPh_3PAuCl, $AgSbF_6$) was engaged as the catalyst (2:1 ratio of **74a**:**74b**, ~60% mass balance, entry 8). The use of $(Ph_3P)AuNTf_2$[51] further improved the selectivity for the isocoumarin product **74a** (4:1 ratio, 75% mass balance, entry 9). Finally, dihydroisocoumarin **75** was obtained in 79% isolated yield and >95:5 regioselectivity by stirring a room temperature solution of alkyne **68** with 5 mol% of Xphosligated $AuNTf_2$[53] (entry 10, ~80% mass balance), followed by hydrogenation of **74a** with Crabtree's catalyst (>99%). Continuing with the psymberin synthesis, a two-step methyl (BBr_3) and silyl ether (HF/py) deprotection provided dihydroisocoumarin **76** in 73% yield for the two step sequence. Ghaffar-Parkins[35] nitrile hydrolysis followed by peracetylation provided a material (compound **63**) that was identical to that obtained via the route outlined in Scheme 5. Single crystal X-ray analysis of compound **63** obtained via this route further confirmed the stereochemistry as assigned. Overall, this synthetic approach towards psymberin entails an 18 steps longest linear sequence from three fragments each prepared in 3, 7, and 8 steps respectively. Although the overall yields using the two alternative synthetic approaches are similar, this 2nd generation approach offers an attractive late stage introduction of aromatic fragments for SAR around the dihydroisocoumarin structure.

Analog Synthesis

As noted in the introduction, psymberin is structurally distinct from other pederin family members in two important aspects: (1) it lacks the typical cyclic pederate side chain present in all other family members; and (2) psymberin is the only member containing a dihydroisocoumarin side chain. Here, we describe the synthesis of psymberin analogs that were useful for the structure-function and mode-of-action studies that will be detailed in a subsequent article.[13] The terminal olefin of **1** is distinct from the exocyclic double bond present in other pederin family members. In the subsequent article, we demonstrate that the homoallylic ether in pederin is responsible for the irritant/blistering activity associated with this class of compounds.[5] Although psymberin does not possess blistering activity,[13] hydrogenation of the terminal olefin of psymberin would allow for the preparation of a radio-labeled variant for biological studies. Thus, hydrogenation of psymberin (**1**) over platinum provides 95% of the corresponding dihydropsymberin **79** (Scheme 10). Alternatively, [C] phenolic methyl ether **78** or acetate **77** was prepared via methylation or acetylation of psymberin **1** (90–95% yield).

As mentioned above, to fully assess the importance of psymberin's unique dihydroisocoumarin moiety, we designed a truncated psymberin analog **85** (Scheme 11) that lacks this fragment, which is in essence also an analogue of pederin with the acyclic "psymberate" (C1–C6) side chain substituting for the cyclic "pederate" fragment reminiscent of the pederin/mycalamide natural products. The synthesis of this analog, which we term psympederin, commenced from the C*2*-symmetrical bis-homoallylic alcohol **12**, which was mono-acetylated via cyclic orthoacetate formation and hydrolysis under acidic conditions, followed by ozonolytic double bond cleavage to yield the desymmetrized lactol **30c** in 84% yield for the two-step process. Acylation of lactol **30c** then permitted olefination of the aldehyde, after which anomeric acetatenide[22] in the presence of ZnI_2 to yield a single axial nitrile **81** in 94% yield. The dihydroxylation of terminal olefin **81** required extensive experimentation to yield an acceptable diastereoselectivity. Dihydroxylation using the UpJohn process (cat. OsO_4, *N*-methylmorpholine) revealed an intrinsic facial bias slightly favoring the undesired diastereomer **82b**(**82a**:**82b** = 1:1.4), whereas Sharpless asymmetric dihydroxylation using the $(DHQ)_2$PYR or $(DHQ)_2$PHAL ligand was nonselective (1:1 ratio).[54] After some experimentation, we found that hydroxyquinine 9-phenanthryl ether (HQP ether) was the optimal ligand for the asymmetric dihydroxylation of **81**,[55] providing a ~3:1 mixture favoring the desired C_{15}-*S* configuration (**82a**). Kocienski and coworkers had previously screened various ligands for the asymmetric dihydroxylation of a closely related substrate (TBS-protected version of **81**) and found HQP ether also to be optimal, although selectivity for the desired diastereomer was lower (1.5:1) with their substrate.[56] This inseparable mixture of epimers was treated with Meerwein's salt and proton sponge to afford a separable mixture of methyl ethers **83a** and **83b**. The stereochemistry was determined by chemical correlation of acetate **83a** to the corresponding known TBS-ether.[56] Nitrile hydrolysis of the major methyl ether **83a** with use of the Ghaffar-Parkins catalyst[35] **80** (mixture of anomers) was treated with trimethylsilyl cya-provided acetylpedamide **84** in 95% yield.[57] The final introduction of the C_1–C_6 "psymberate" side chain was accomplished via the protocol outlined for the synthesis of psymberin (Scheme 7). Thus, acylation of the imidate derived from **84** with the acid chloride **6a** derived from carboxylic acid **20a** followed by reduction and saponification yielded a separable 1:4 mixture of psympederin **85** and *epi*-psympederin in 60% yield from acetylpedamide **84**.[58],[59] This result is in sharp contrast with the corresponding psymberin result where the natural methoxyaminal epimer dominated (3:1), and indicates that diastereoselectivity associated with the *N*-acylimidate reduction is highly dependent on the presence or absence of the dihydroisocoumarin fragment.

CONCLUSION

With its dihydroisocoumarin and acyclic *N*-acyl side chains, psymberin represents a structural and perhaps functional outlier of the pederin/mycalamide family of natural products. In this manuscript, we have described a detailed synthetic study of psymberin, including two alternative total syntheses and the design of analogs and probe reagents for biological studies. We also assigned the full stereostructure of psymberin and demonstrated that psymberin and irciniastatin are actually identical compounds. Our total syntheses are based on a convergent, flexible strategy that delivered ~ 0.5 g of psymberin in 17–18 steps (longest liner sequence) from three fragments prepared in 7–8 steps (1st generation) or 3–8 steps (2nd generation) each. The synthesis of the central tetrahydropyranyl fragment via a double dehydrogenative allylation developed by Krische, followed by an oxidative desymmetrization was crucial to the successful implementation of an efficient total synthesis. Other highlights include: (1) a cyanide displacement avoiding dioxabicycloalkane ring formation, (2) a stereoselective aldol coupling/one-pot reduction-dihydroisocoumarin formation, (3) exploitation of the Ghaffar-Parkins Pt(II) catalyst for nitrile hydrolysis in complex molecular settings, (4) an optimized procedure for the reductive *N*-acyl aminal fragment coupling showing a uniquely beneficial effect of polyvinylpyridine during methylimidate formation with Me_3OBF_4, and (5) a regioselective gold(I)-catalyzed isocoumarin formation from *ortho*-alkynyl benzoic acids. Founded on this synthetic footing, we were able to study the biology and identify the molecular target of psymberin, which will be detailed in a subsequent manuscript.[13]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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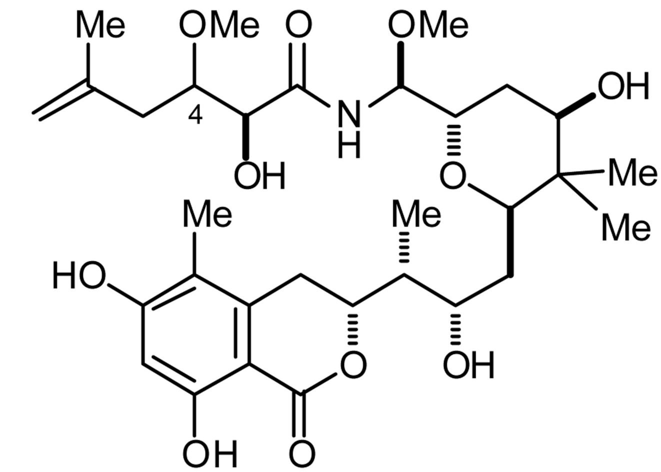
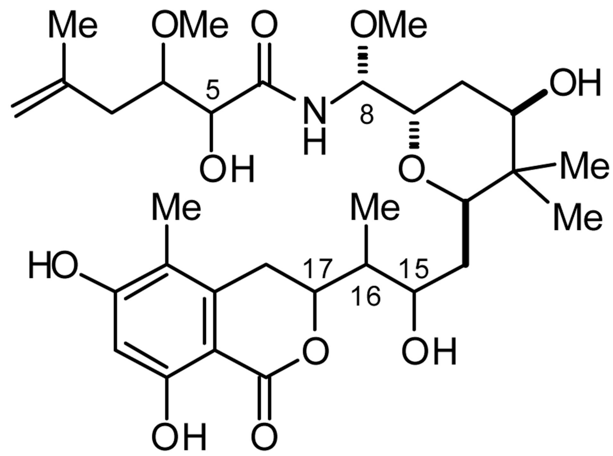
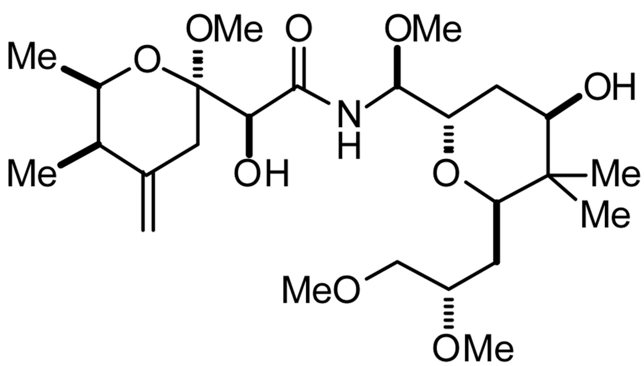
57. Our synthesis of acetylpedamide, accomplished in 8 steps from neopentylglycol **29**, compares favorable to Nakata's and Kocienski's [55] 15-step syntheses of benzoylpedamide (from *S*-malic acid) and *tert*-butyldimethylsilylpedamide (from ethyl isobutyrate), respectively.
58. A similar coupling between benzoylpedamide and the pederin "pederate" fragment in Nakata's[36] pederin total synthesis also yielded a 1:3 mixture of pederin and *epi*-pederin (38% yield).
59. The natural C_8-*S*configuration of **85** was assigned based upon a detailed analysis of ^{1}H-^{1}H coupling constants and 1D- and 2D-NOE correlations, see ref. 10a for details.



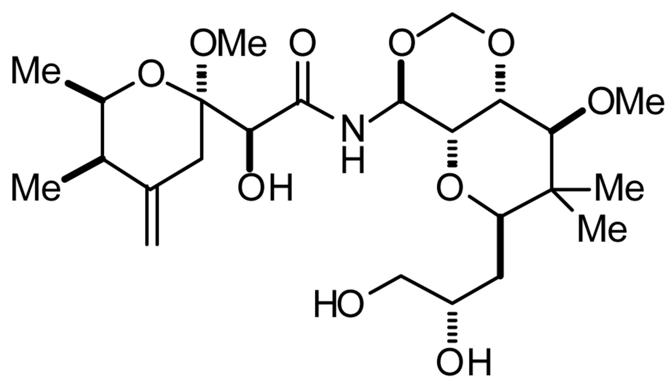
psymberin, **1**
from the sponge Psammocinia sp.



irciniastatin A, **2**
from the sponge ircinia ramosa sp.

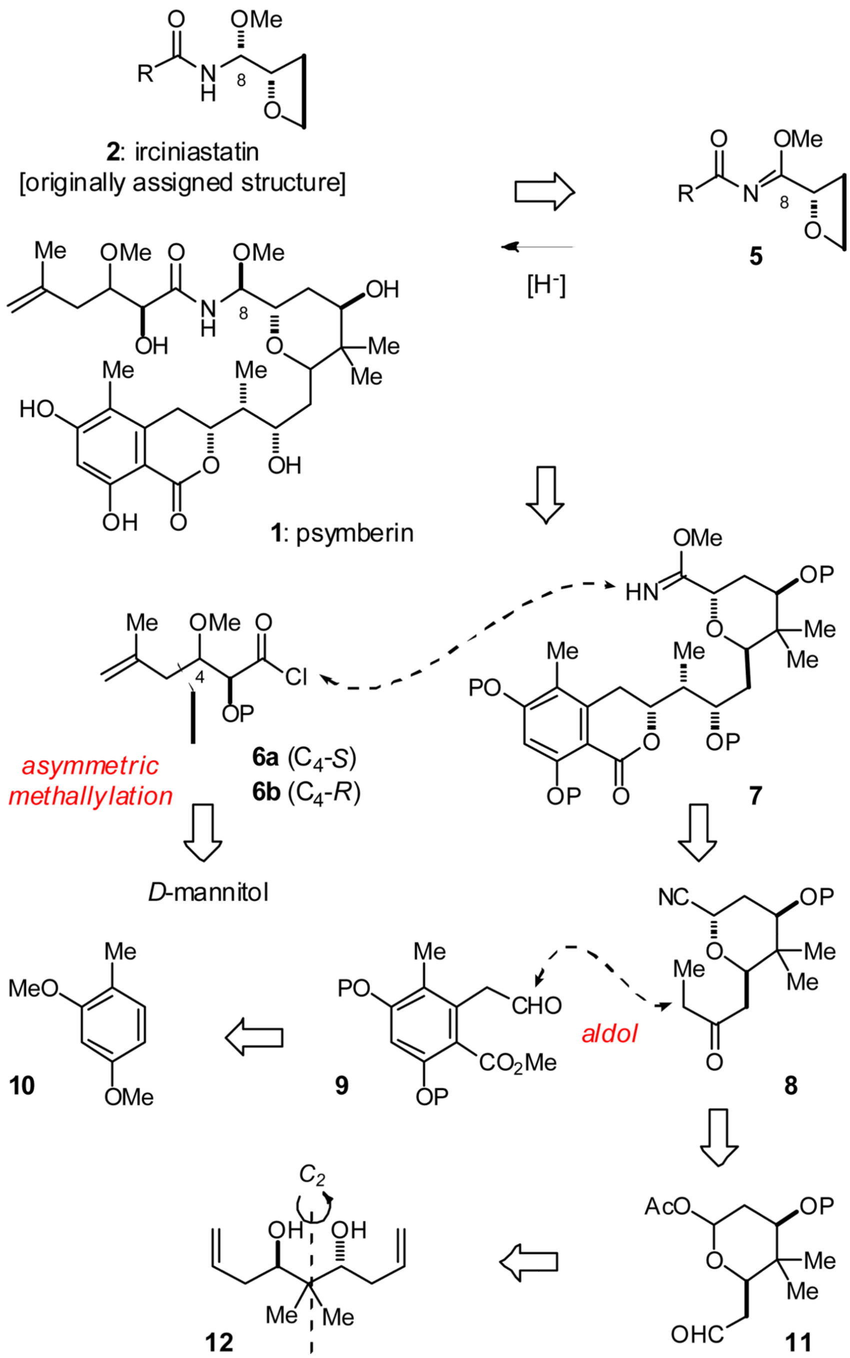


pederin, **3**
from the beetle P. fuscipes

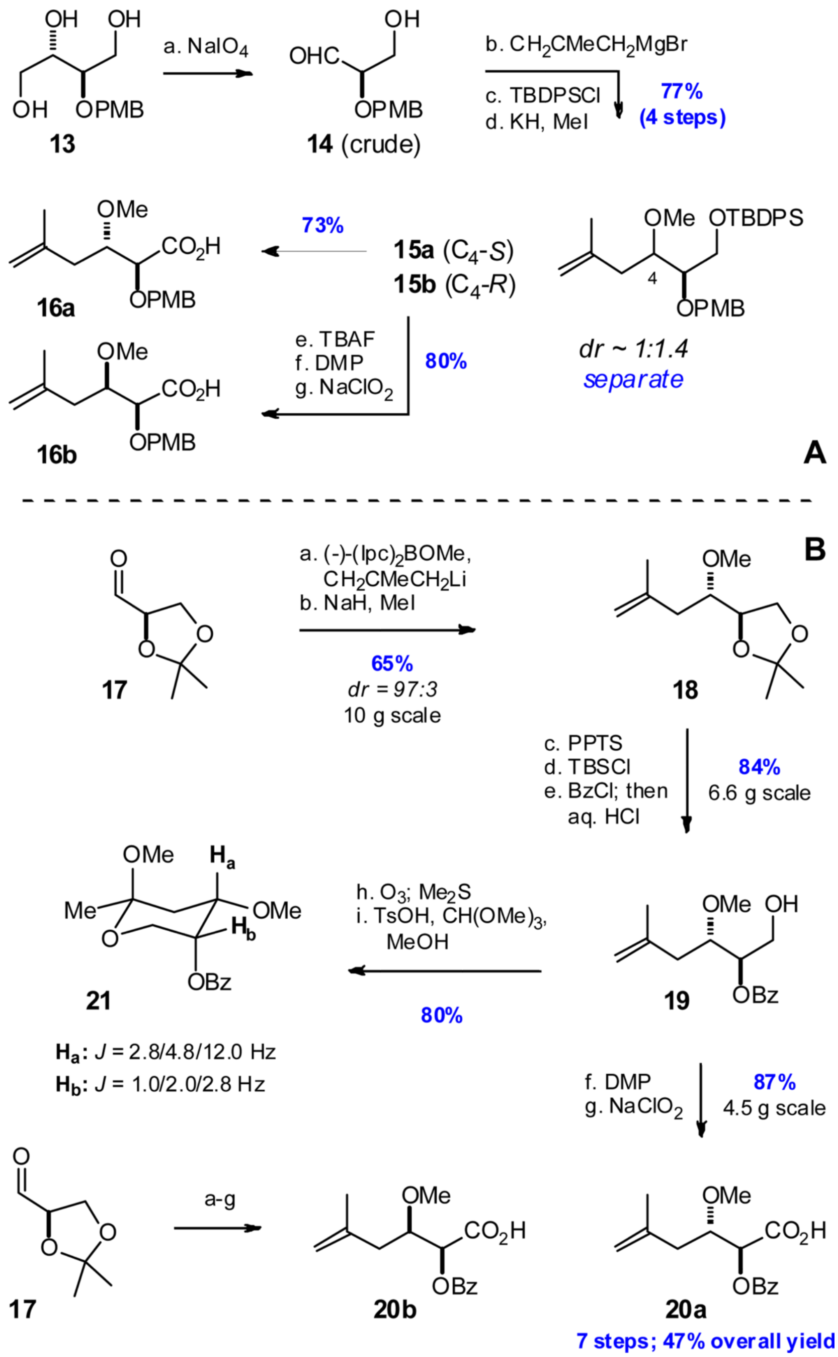


mycalamide A, **4**
from the sponge Mycale sp.

Figure 1.
Psymberin and other representative natural products of the pederin family.



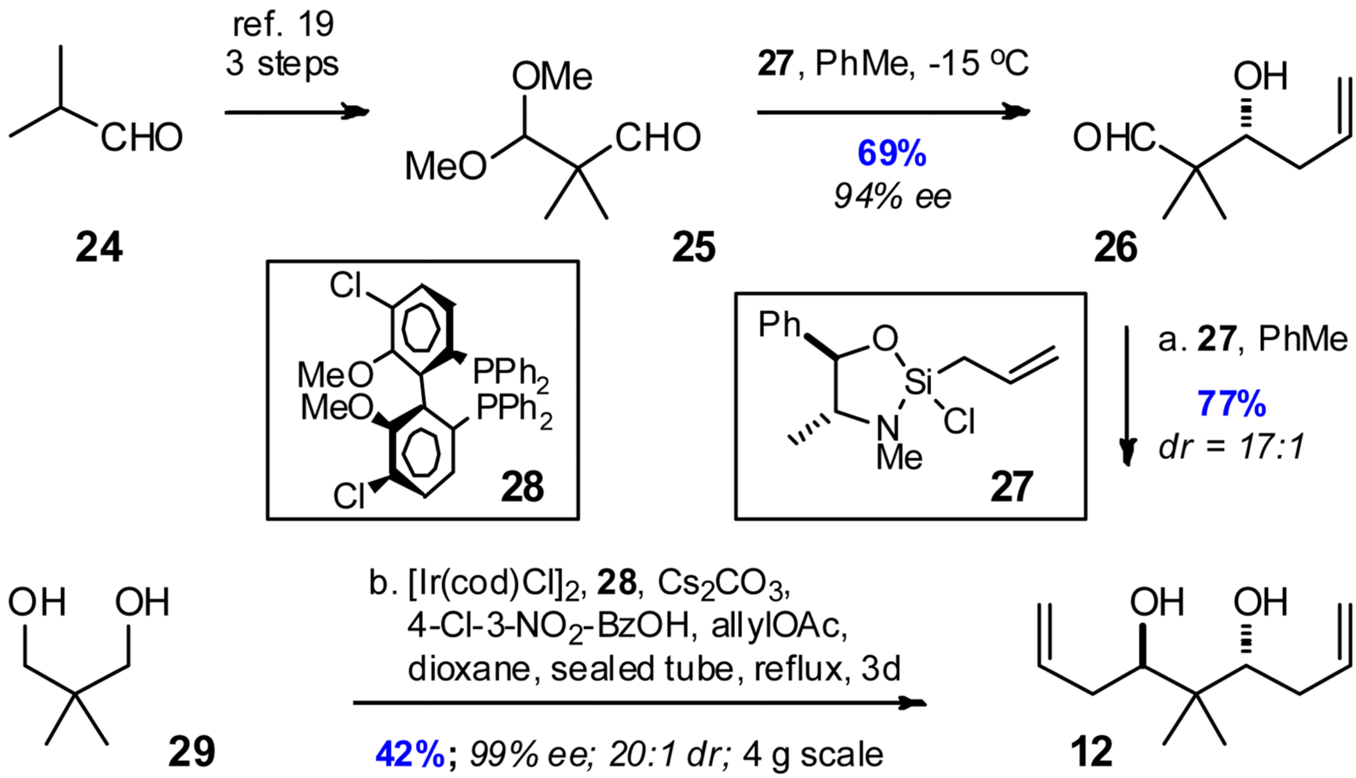
Scheme 1.
Synthetic Plan.



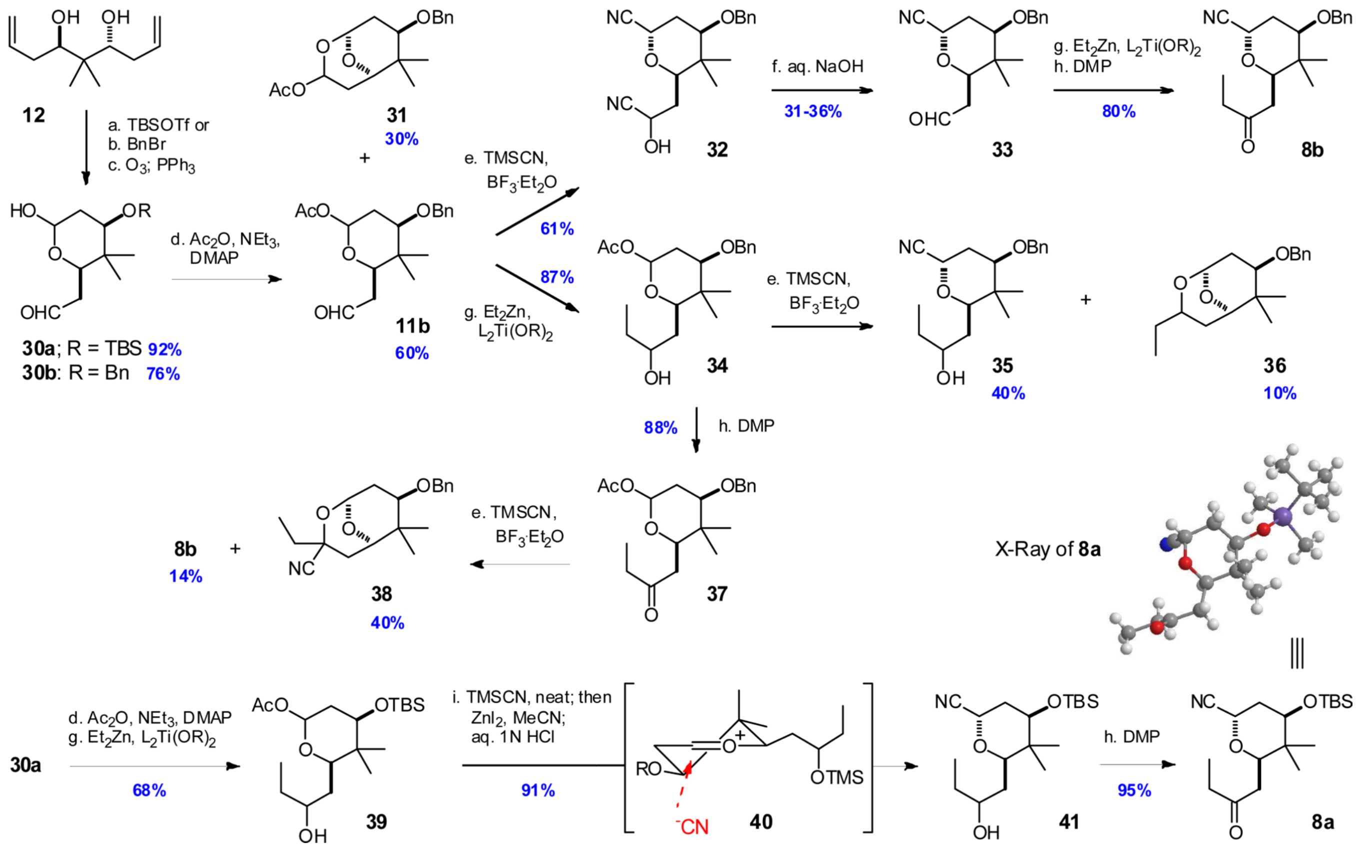
Scheme 2. Synthesis of Psymberic Acids[a]

[a] Reagents and conditions: Panel **A**: (a) $NaIO_4$, CH_2Cl_2, aq. $NaHCO_3$; (b) $CH_2CCH_3CH_2MgBr$, THF, −78 °C; (c) TBDPSCl, imidazole, DMF; (d) KH, MeI, THF, 77% (4 steps); (e) TBAF, THF, 85%; (f) DMP, CH_2Cl_2, 95%; (g) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, t-BuOH/H_2O, 99%. Panel **B**: (a) (−)-$(Ipc)_2BOMe$ ((+)-$(Ipc)_2BOMe$ for **20b**), CH_2CMeCH_2Li, Et_2O, −78 °C, 69%; (b) NaH, MeI, THF, 95%; (c) PPTS, MeOH/H_2O, 50 °C, 93%; (d) TBSCl, imidazole, CH_2Cl_2, 95%; (e) BzCl, py; then aq. 3 N HCl, 95%; (f) DMP, CH_2Cl_2; (g) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, ^{t}BuOH/H_2O, 87% over

two steps; (h) O_3, CH_2Cl_2; Me_2S; (i) TsOH, $CH(OMe)_3$, MeOH, 80% over two steps. Abbreviations: DMP, Dess-Martin Periodinane; Ipc, isopinocampheyl.

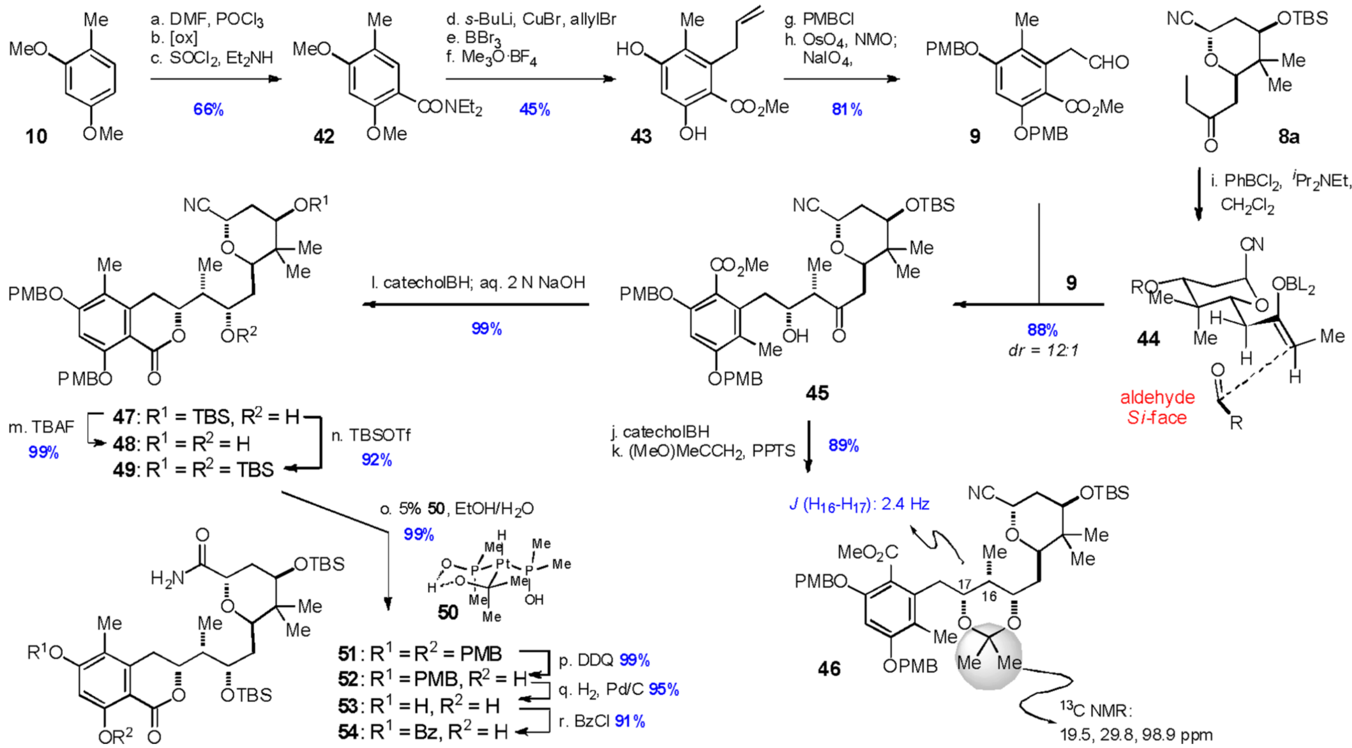


Scheme 3.
Synthesis of Bis-Homoallyl Alcohol **12**.



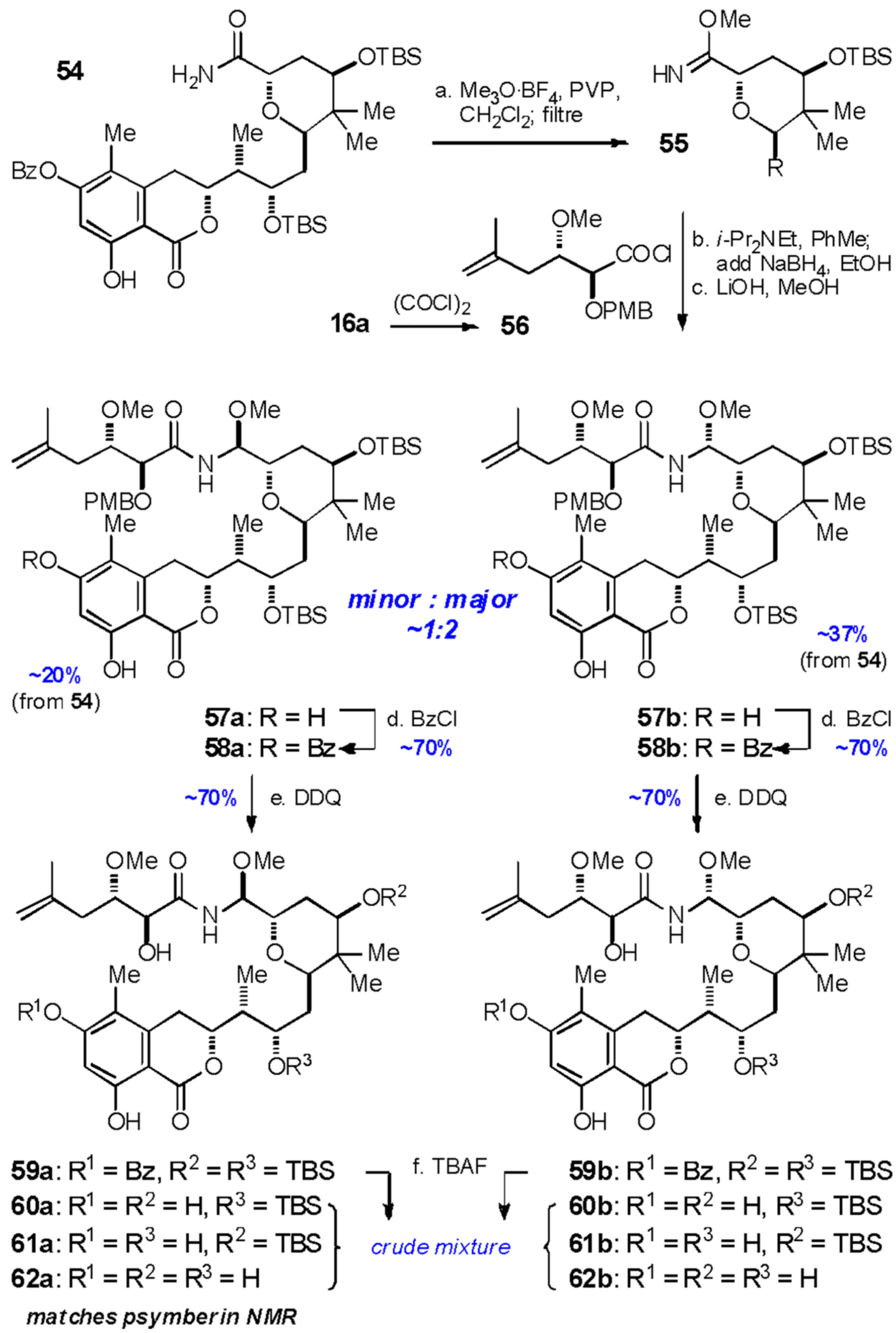
Scheme 4. Synthesis of Ethyl Ketone 8 Through Desymmetrization of Bis-homoallylic Alcohol 12.[a]

[a] Reagents and Conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2; (b) BnBr, NaH, THF; (c) O_3, CH_2Cl_2; PPh_3; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (e) TMSCN, $BF_3{\cdot}Et_2O$, MeCN; (f) aq. NaOH, Et_2O; (g) $Ti(O^iPr)_4$, *N,N'*-(1*R*,2*R*-cyclohexane-1,2-diyl)bis(trifluoromethanesulfonamide), Et_2Zn, PhMe; (h) DMP, CH_2Cl_2; (i) TMSCN, RT; then ZnI_2, MeCN; then aq. 1 N HCl.



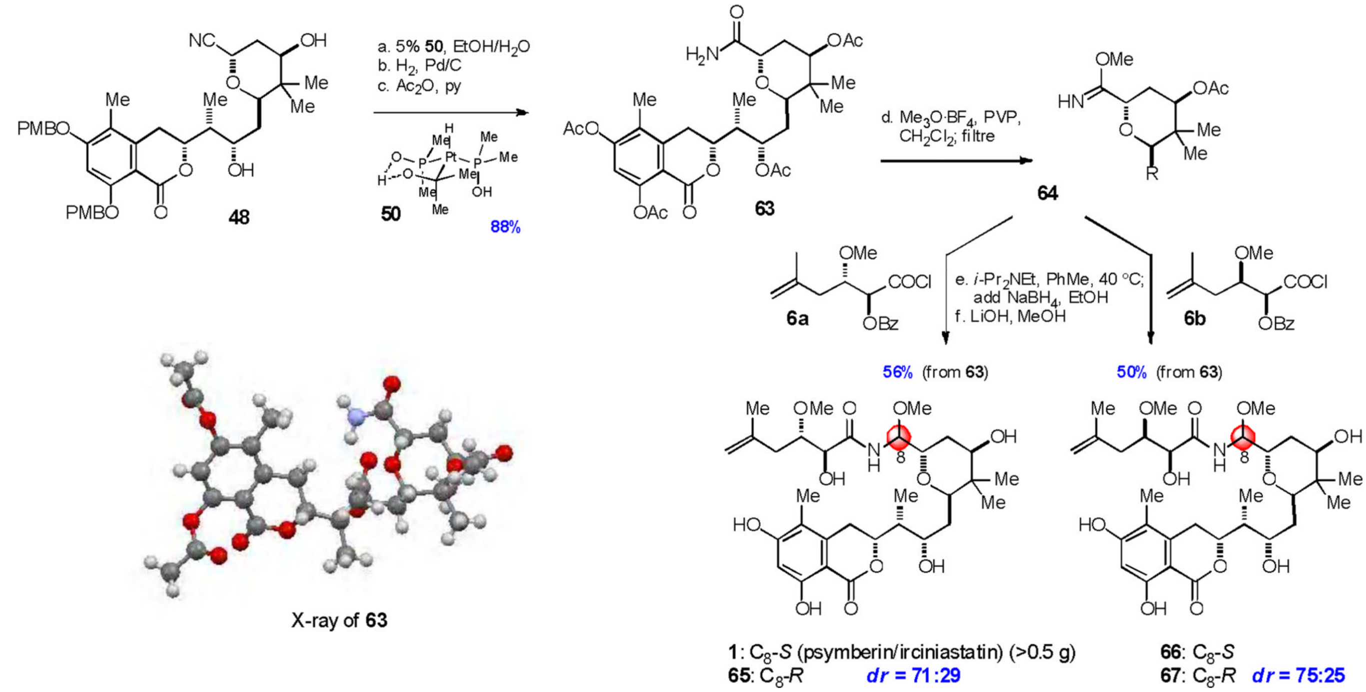
Scheme 5. Synthesis of Dihydroisocoumarin Fragments.[a]

[a] Reagents and Conditions: (a) DMF, $POCl_3$, 80%; (b) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH/H_2O, 85%; (c) $SOCl_2$, benzene; Et_2NH, 97%; (d) *sec*-BuLi, $CuBrSMe_2$, allylBr, THF, −78 °C, 76%; (e) BBr_3, CH_2Cl_2, −78 to 25 °C, 81%; (f) Me_3OBF_4, CH_2Cl_2; Na_2CO_3, MeOH, 73%; (g) PMBCl, Bu_4NI, K_2CO_3, DMF, 80 °C, 92%; (h) cat. OsO_4, NMO, THF/H_2O; $NaIO_4$, aq MeOH, 81%; (i) $PhBCl_2$, ${}^{i}Pr_2NEt$, CH_2Cl_2, −78 °C, 88%, 12:1 *dr*; (j) catecholborane, THF, 0 °C; (k) (MeO)$MeCCH_2$, PPTS, 89% over two steps; (l) catecholborane, THF, 0 °C; aq 2 N NaOH, 99%; (m) TBAF, THF, 99%; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 92%; (o) cat. [PtH(PMe_2OH)(PMe_2O)^{2}H] (**50**), EtOH/H_2O, 80 °C, 99%; (p) DDQ, CH_2Cl_2/H_2O, 99%, (q) H_2, Pd/C, EtOH, 95%, (r) BzCl, ${}^{i}Pr_2NEt$, PhMe, 91%.



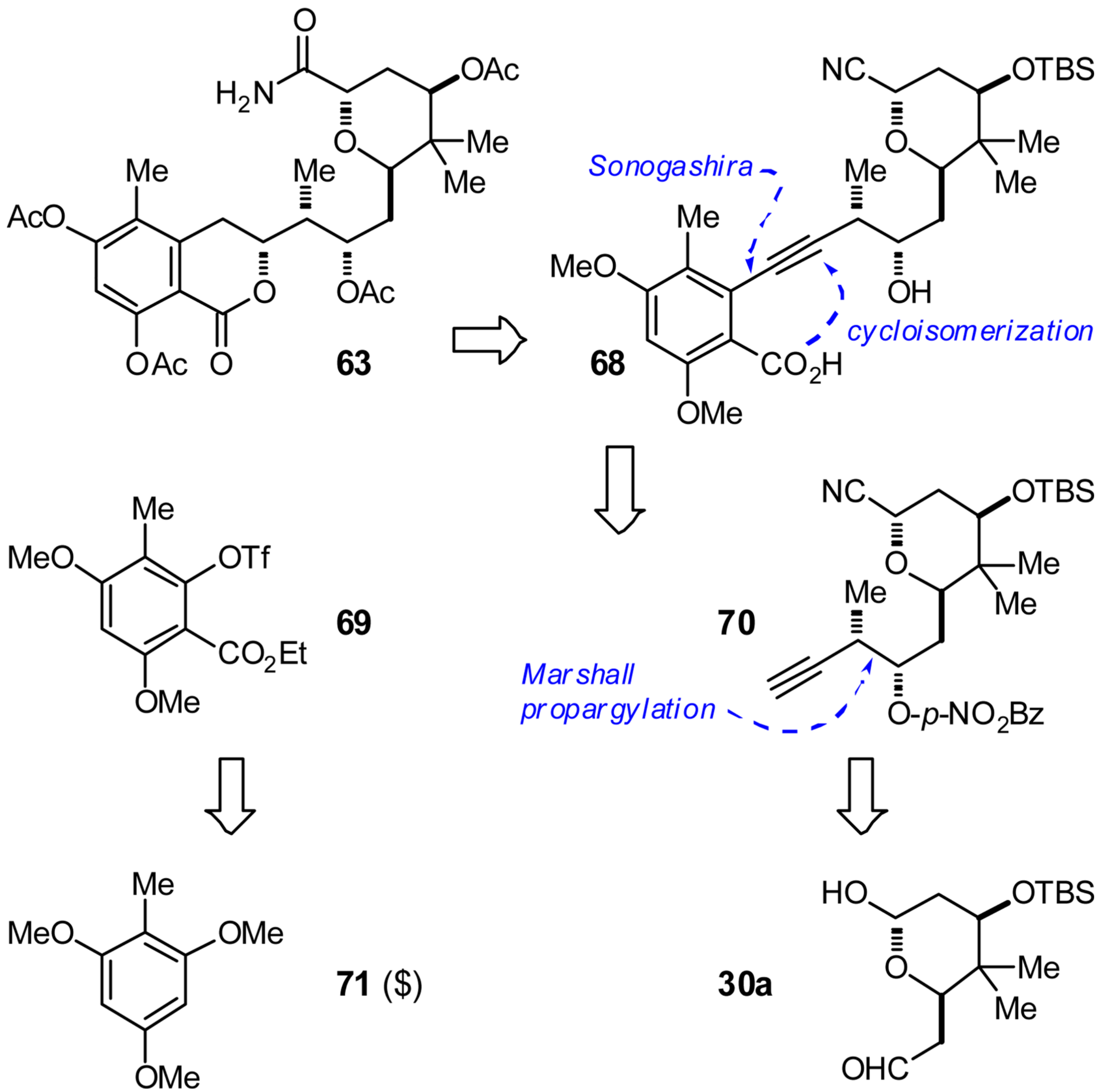
Scheme 6. Initial Attempts Toward Psymberin.[a]

[a] Reagents and conditions: (a) Me_3OBF_4, CH_2Cl_2, PVP, rt; filter, concentrate; (b) PhMe, $^{i}Pr_2NEt$, **56**, 40 °C, 2 h, cool to 0 °C; then add $NaBH_4$in EtOH; (c) LiOH, MeOH, rt; (d) BzCl, $^{i}Pr_2NEt$, PhMe, 70%; (e) DDQ, CH_2Cl_2/H_2O, 70%; (f) TBAF, THF. Abbreviations: PVP, poly(4-vinylpyridine) (25% cross-linked).

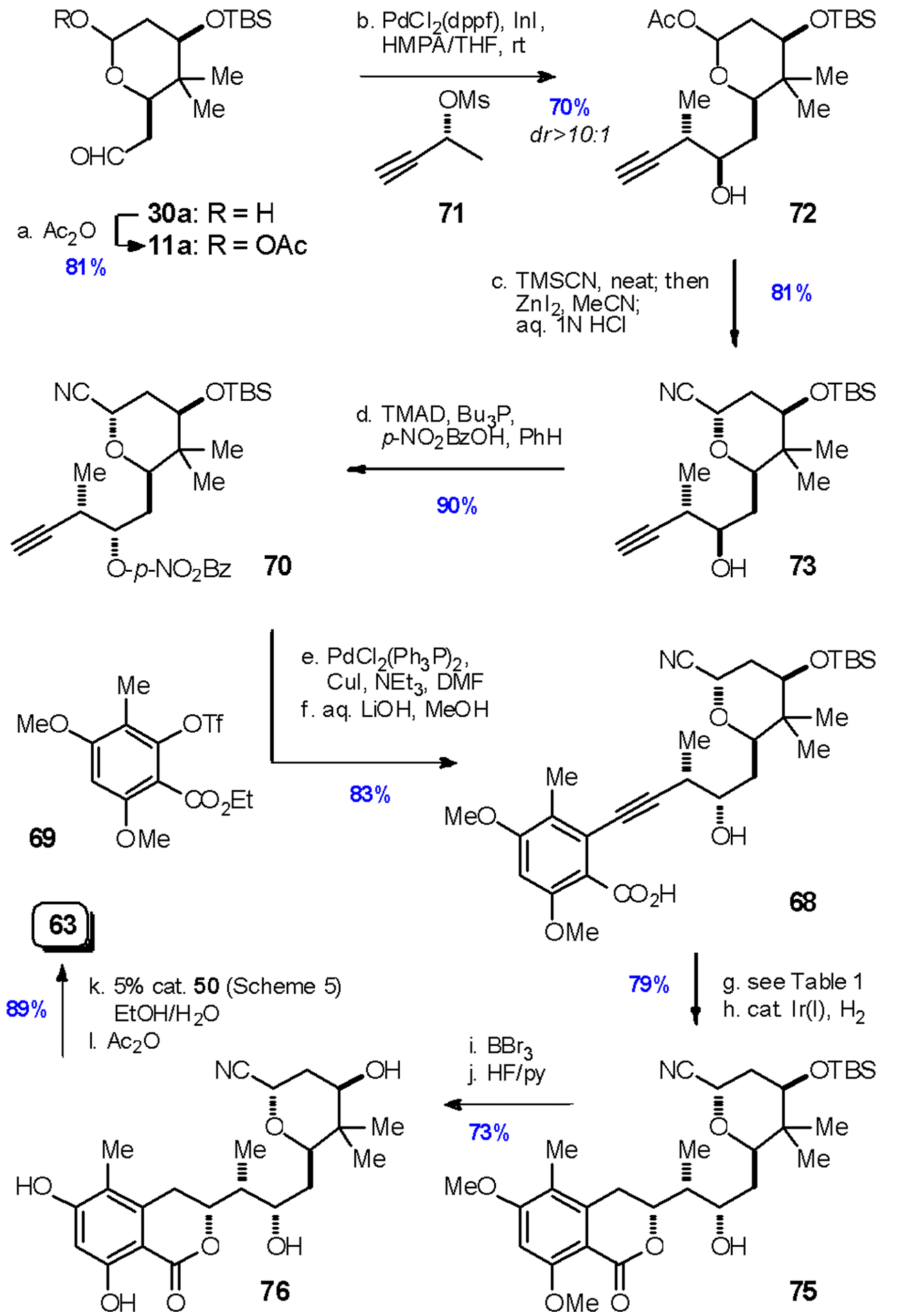


Scheme 7. Synthesis of Psymberin and Diastereomers. [a]

[a] Reagents and Conditions: (a) cat. [PtH(PMe$_2$OH)(PMe$_2$O)$_2$)H] (**50**), EtOH/H$_2$O, 80 °C, 97%; (b) 10% Pd/C, H$_2$, EtOH, 99%; (c) Ac$_2$O, pyridine, 92%; (d) **63**, Me$_3$OBF$_4$, CH$_2$Cl$_2$, PVP, rt; filter, concentrate; (e) crude **64**, PhMe, ^{i}Pr$_2$NEt, **6a** or **6b**, 40 °C, 2 h, cool to 0 °C; then add NaBH$_4$ in EtOH; (f) LiOH, MeOH.

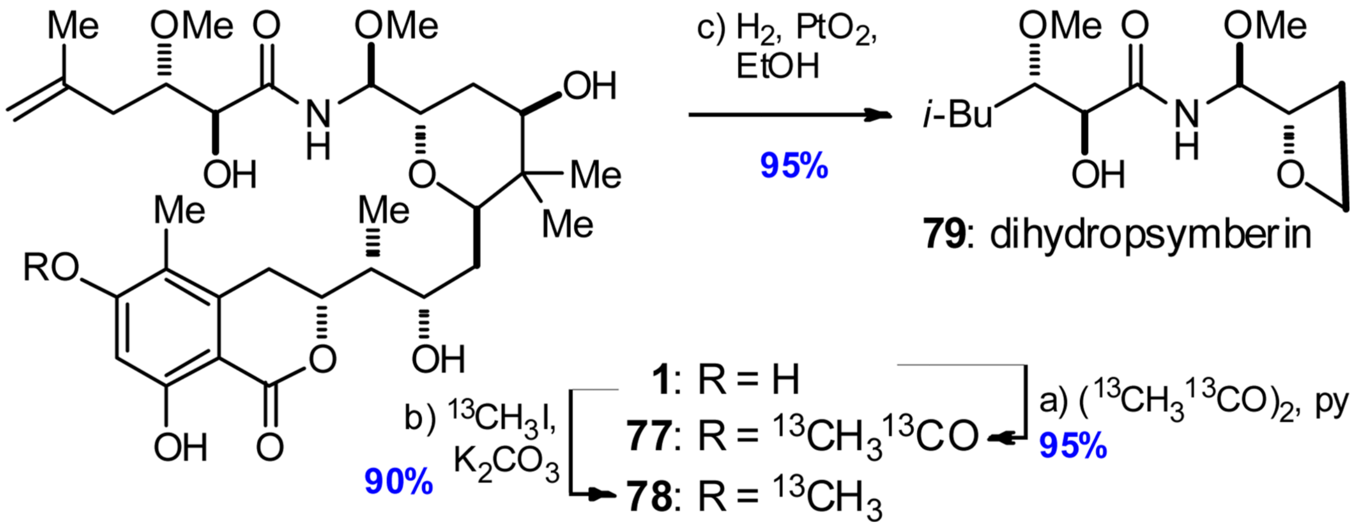


Scheme 8.
Alternative Synthetic Strategy.



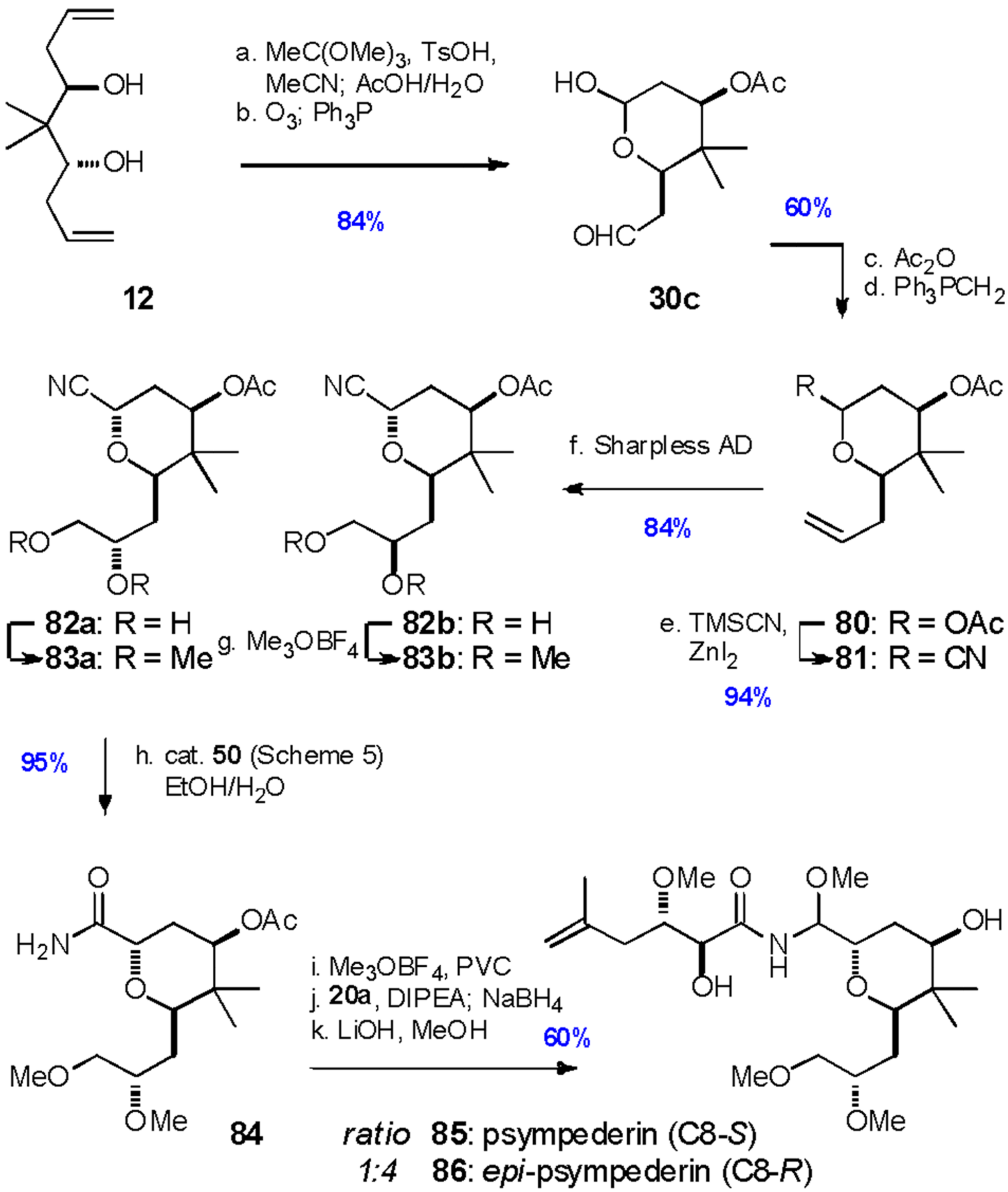
Scheme 9. Alternative Synthesis of Dihydroisocoumarin 63.[a]

[a] Reagents and Conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 81%; (b) **55**, $PdCl_2(dppf)_2$, InI, HMPA, THF, rt, 70%, *dr* > 10:1; (c) TMSCN (neat); ZnI_2, MeCN; aq. 1N HCl, 81%; (d) TMAD, Bu_3P, p-NO_4BzOH, benzene, 90%; (e) **51**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 40 °C, 83%; (f) aq. 1N LiOH, MeOH, 0 °C, 99%; (g) $AuNTf_2$(Xphos) (5 mol%), CH_2Cl_2, rt; (h) H_2 (1 atm), cat. [Ir(cod)(PCy_3)(py)]PF_6 (2 mol%), CH_2Cl_2, rt, 79% over two steps; (i) BBr_3, CH_2Cl_2, −78 to 25 °C, 77%; (j) HF/Pyridine, THF, 95%; (k) cat. [PtH(PMe_2OH)(PMe_2O)$_2$H] (**50**), EtOH/H_2O, 80 °C, 97%; (l) Ac_2O, pyridine, 92%. Abbreviations: TMAD, *N,N,N′,N′*-tetramethylazodicarboxamide.



Scheme 10.

Synthesis of Methyl-, Acetyl-, and Dihydro-Psymberin.

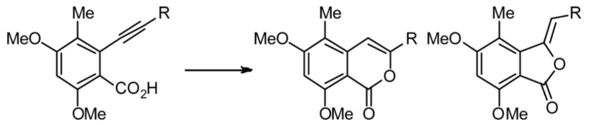


Scheme 11. Synthesis of a Psymberin-Pederin Hybrid, Psympederin[a]

[a] Reagents and Conditions: (a) $MeC(OMe)_3$, *p*-TsOH, MeCN; $AcOH/H_2O$, 88%; (b) O_3, CH_2Cl_2; PPh_3, 95%; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (d) Ph_3PCH_2, CH_2Cl_2, 60% (2 steps); (e) TMSCN, ZnI_2, MeCN, 94%; (f) hydroxyquinine 9-phenanthryl ether, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C; OsO_4, 92%; (g) Me_3OBF_4, CH_2Cl_2, 2,6-lutidine, 93%; (h) cat. $[PtH(PMe_2OH)(PMe_2O)_2H]$ (**50**), EtOH/H_2O, 80 °C, 95%; (i) Me_3OBF_4, CH_2Cl_2, PVP; filter, concentrate; (j) PhMe, $^iPr_2NEt$, **6a**, 40 °C, 2 h, cool to 0 °C; then add $NaBH_4$ in EtOH; (k) LiOH, MeOH, 60% (3 steps).

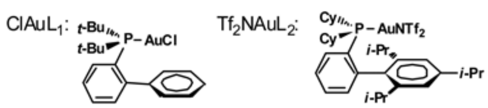
Table 1

Cycloisomerization of Alkynyl Benzoic Acid **68**.[a]



68 **74a** (*6-endo*) **74b** (*5-exo*)

Entry	Reagent	Solvent	Time(h)	Temp	74a:b
1	*p*TsOH[b]	EtOH	0.1	100 °C	-
2	TFA[b]	THF	3	Δ	-
3	$InBr_3$[b]	THF	1	Δ	-
4	$AuCl_3$[c]	aq. ACN	2	50°C	-
5	$AgSbF_6$[c]	DMF	4	60°C	1:1
6	$Pt(C_2H_4)Cl_2]_2$[c]	DMF	0.5	rt	3:7
7	$ClAuL_1$[c]	CH_2Cl_2	1	rt	2:5
8	$Ph_3PAuCl/AgSbF_6$[c]	CH_2Cl_2	1	rt	2:1
9	$Ph_3PAuNTf_2$[c]	CH_2Cl_2	1	rt	4:1
10	**Tf_2NAuL_2[c]**	**CH_2Cl_2**	**1**	**rt**	**>95:5**



[a]All reactions were performed with 50 μmol **68**.

(b)20 mol%.

(c)5 mol%.

(d)Ratios were determined by 1H-NMR.