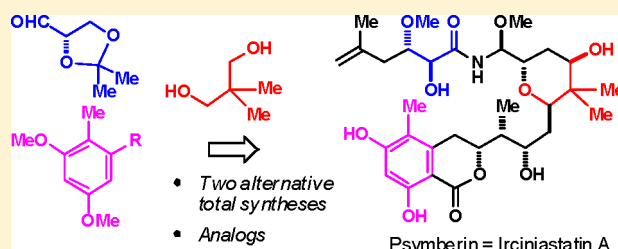


## Studies toward the Unique Pederin Family Member Psymberin: Full Structure Elucidation, Two Alternative Total Syntheses, and Analogs

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## S Supporting Information

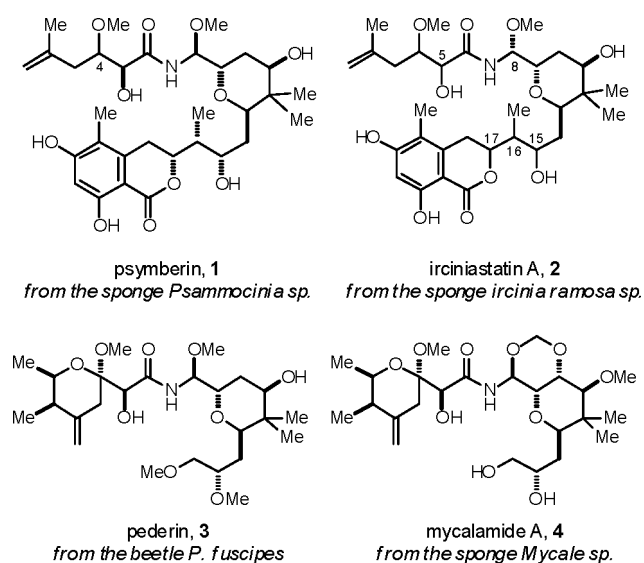
**ABSTRACT:** Two synthetic approaches to psymberin have been accomplished. A highly convergent first generation synthesis led to the complete stereochemical assignment and demonstrated that psymberin and irciniastatin A are identical compounds. This synthesis featured a diastereoselective aldol coupling 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 bisallylation 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 (first generation) and 3–8 (second generation) steps 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.



## 1. 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.,<sup>1</sup> whereas irciniastatin A (**2**) was isolated from the *Ircinia ramosa* sp.<sup>2</sup> Multidimensional NMR studies substantiated the assigned relative configuration for psymberin as shown in **1**, save for the undefined configuration at C<sub>4</sub>. 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<sub>8</sub>–C<sub>13</sub> aminal fragment. Given the differing relative configuration (C<sub>8</sub>–C<sub>9</sub>) 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**)<sup>3</sup> and mycalamide A (**4**)<sup>4</sup> (Figure 1).<sup>5</sup> However, 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.<sup>5c</sup>

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.<sup>5</sup> An indication that psymberin might be endowed with an alternative mode of action came from the observation



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

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.<sup>1</sup> In

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contrast, the material isolated by Pettit and co-workers 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 antivasular agent.<sup>2</sup>

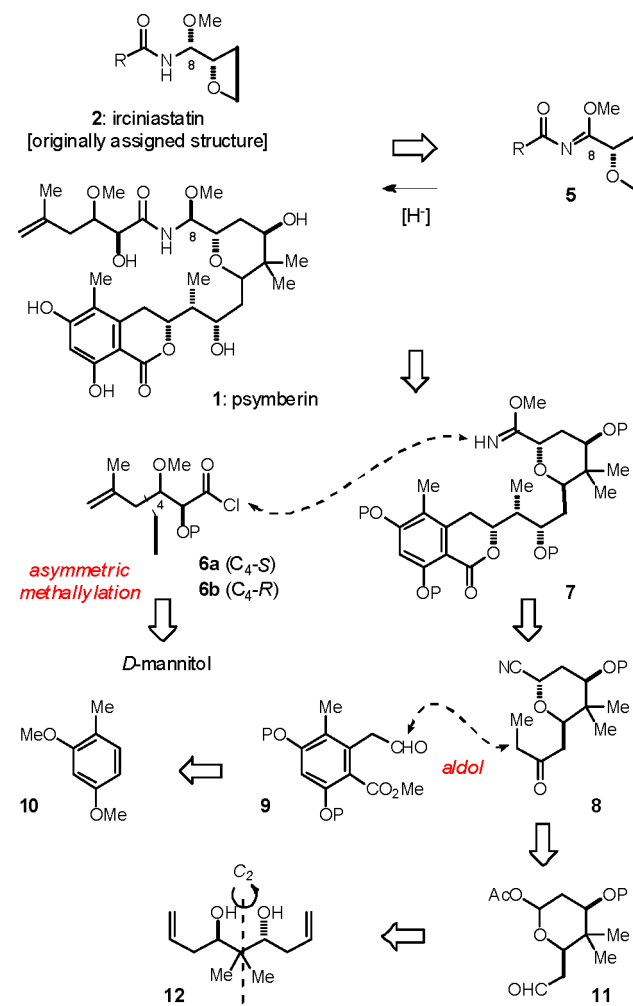
Due to uncertainties regarding the structural relation between psymberin and irciniastatin, significant structural divergence from the pederin family of natural products, low natural abundance, and impressive biological activities, psymberin/irciniastatin has become an attractive target for synthetic 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.<sup>6</sup> Several other total,<sup>7</sup> formal,<sup>8</sup> fragment<sup>9</sup> as well as analog syntheses<sup>10</sup> 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.<sup>11</sup> Additionally, our synthetic psymberin was explored as an antibody drug conjugate in collaboration with Seattle Genetics.<sup>12</sup> 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.<sup>13</sup>

## 2. RESULTS AND DISCUSSION

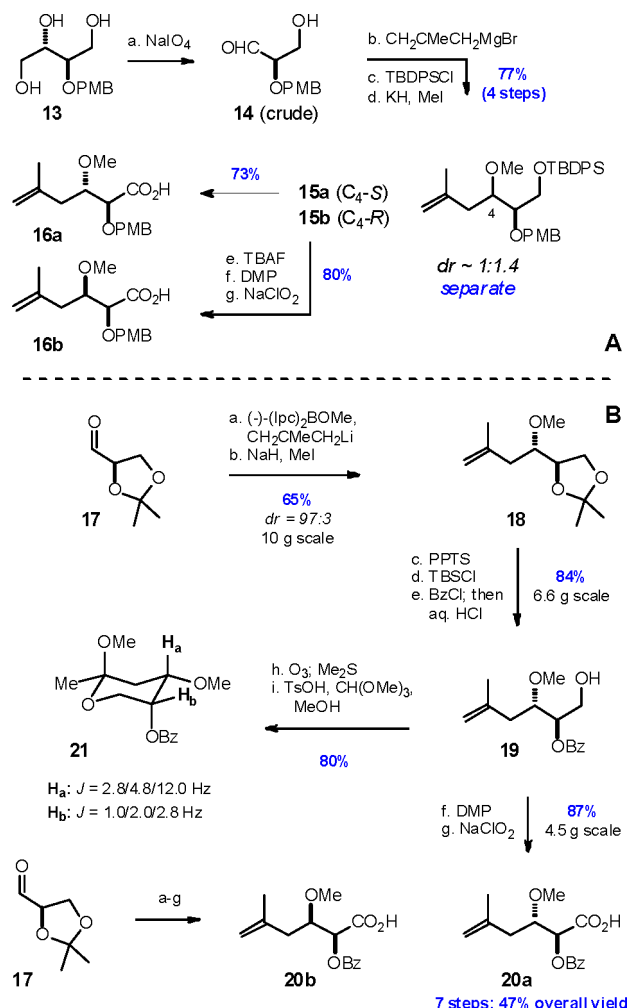
**2.1. First Generation Synthesis.** Psymberin (**1**) is a complex polyketide comprising nine stereocenters, a geminal dimethyl, and a dihydroisocoumarin fragment. Its tetrahydropyran core is appended with a 2-hydroxy-3-methoxy-5-methylhex-5-enoic acid (psymberic acid) through an *N*-acylaminal linkage. As outlined in Scheme 1, we anticipated to intercept an intermediate *N*-acyl-methoxyimide **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 imide **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 combining 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 bishomoallyl 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*-

Scheme 1. Synthetic Plan



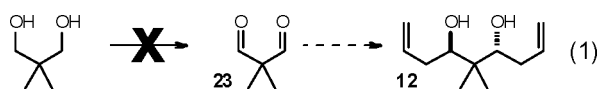
tartaric acid (Scheme 2A).<sup>14</sup> Oxidative diol-cleavage of this material,<sup>15</sup> followed by treatment of the crude aldehyde **14**, delivered an inseparable mixture of homoallylic alcohols. Selective protection of the primary alcohol and methylation of the secondary alcohol provided compounds **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 Scheme 2B, 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,<sup>16</sup> asymmetric methallylation with a borane reagent derived from isobutenyllithium and (–)-Ipc<sub>2</sub>BOME,<sup>17</sup> 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.<sup>9a</sup> Acetonide hydrolysis, silylation of the primary and benzoylation of the secondary alcohol, followed by an acidic aqueous workup provided 6.6 g of alcohol **19** over a three-step sequence from **18**. Finally, a two-step oxidation procedure yielded gram quantities of psymberic acid **20a** (seven steps from aldehyde **17**; 47% yield). The relative stereochemistry set during the methallylation step was ascertained through <sup>1</sup>H NMR analysis of acetal **21**, obtained via ozonolysis of the terminal olefin **19**, followed by acetal formation (→**21**). Diastereomeric alcohol **20b** was

Scheme 2. Synthesis of Psymberic Acids<sup>a</sup>

<sup>a</sup>Reagents and conditions: (A): (a) NaIO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, aq NaHCO<sub>3</sub>; (b) CH<sub>2</sub>CCH<sub>3</sub>CH<sub>2</sub>MgBr, THF, -78 °C; (c) TBDPSCI, imidazole, DMF; (d) KH, MeI, THF, 77% (4 steps); (e) TBAF, THF, 85%; (f) DMP, CH<sub>2</sub>Cl<sub>2</sub>, 95%; (g) NaH<sub>2</sub>PO<sub>4</sub>, NaClO<sub>2</sub>, 2-methyl-2-butene, <sup>t</sup>BuOH/H<sub>2</sub>O, 99%. (B): (a) (-)-(Ipc)<sub>2</sub>BOMe [(+)-(Ipc)<sub>2</sub>BOMe for 20b], CH<sub>2</sub>CMeCH<sub>2</sub>Li, Et<sub>2</sub>O, -78 °C, 69%; (b) NaH, MeI, THF, 95%; (c) PPTS, MeOH/H<sub>2</sub>O, 50 °C, 93%; (d) TBSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, 95%; (e) BzCl, py; then aq 3 N HCl, 95%; (f) DMP, CH<sub>2</sub>Cl<sub>2</sub>; (g) NaH<sub>2</sub>PO<sub>4</sub>, NaClO<sub>2</sub>, 2-methyl-2-butene, <sup>t</sup>BuOH/H<sub>2</sub>O, 87% over two steps; (h) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; Me<sub>2</sub>S; (i) TsOH, CH(OMe)<sub>3</sub>, MeOH, 80% over two steps. Abbreviations: DMP, Dess–Martin periodinane; Ipc, isopinocampheyl.

synthesized as outlined for acid 20a, except that methallation of aldehyde 17 exploited the antipodal borane reagent.

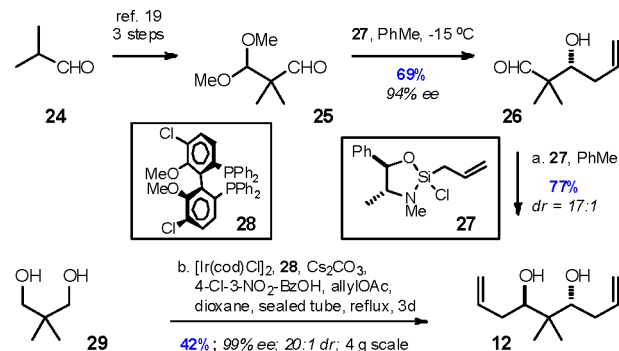
As we will detail later, our approach toward the central tetrahydropyranyl core of psymberin was inspired by the possibility to engage C<sub>2</sub>-symmetrical bishomoallyl alcohol 12 in an oxidative desymmetrization reaction. On paper, this compound should be available from an enantioselective bisallylation of dialdehyde 23 (eq 1).<sup>18</sup> A practical problem



arises when one considers that malondialdehydes are unstable and sensitive to hydrate formation, self-condensation, and

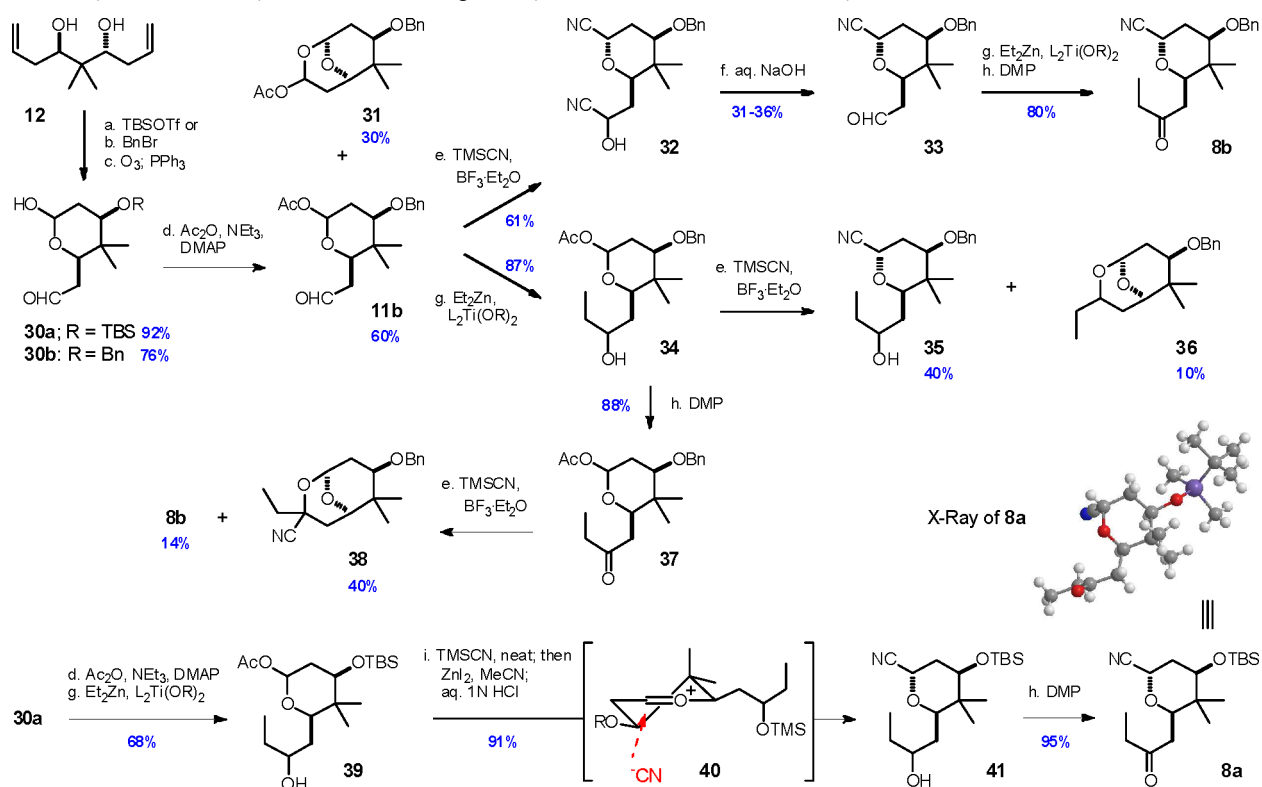
oligomerization. In fact, all attempts to generate pure dialdehyde 23 from neopentyl glycol met with failure. In light of this, we originally settled for a slightly longer approach starting from isobutyraldehyde (24, Scheme 3). According to a

## Scheme 3. Synthesis of Bishomoallyl Alcohol 12



known literature procedure,<sup>19</sup> this material was converted in three steps to 3,3-dimethoxy-2,2-dimethylpropanal 25, a monoprotected 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.<sup>20</sup> Noteworthy, the dimethyl acetal was unmasked during the workup 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,<sup>6</sup> Krische and co-workers developed a creative two-directional carbonyl allylation from the alcohol oxidation level to circumvent the use of difficult to handle malondialdehydes.<sup>21</sup> As reported by Krische, treatment of diol 29 with allyl acetate employing a cyclometalated catalyst, formed *in situ* from [Ir(cod)Cl]<sub>2</sub>, (R)-Cl–MeO–BIPHEP 28, 4-chloro-3-nitrobenzoic acid, and Cs<sub>2</sub>CO<sub>3</sub> in degassed dioxane, furnished diol 12 in 42% yield (99% ee, 20:1 dr) on a 4 g scale. A monoallylated intermediate was also isolated (not shown) in 24–30% yield. This material could be allylated under the same reaction conditions to obtain additional bisallylated product 12 in 30% yield (51% combined yield from 29).

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 monoprotection 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<sup>22</sup> yielded cyano acetal 32, wherein the aldehyde was trapped as a cyanohydrin (60% yield).<sup>23</sup> 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<sup>24</sup> was followed by Dess–Martin oxidation<sup>25</sup> yield the corresponding ethyl ketone 8b in 80% yield for this two-step

Scheme 4. Synthesis of Ethyl Ketone 8 Through Desymmetrization of Bishomoallylic Alcohol 12<sup>a</sup>

<sup>a</sup>Reagents and Conditions: (a) TBSOTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ; (b) BnBr, NaH, THF; (c)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ;  $\text{PPh}_3$ ; (d)  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ; (e) TMSCN,  $\text{BF}_3\cdot\text{Et}_2\text{O}$ , MeCN; (f) aq. NaOH,  $\text{Et}_2\text{O}$ ; (g)  $\text{Ti}(\text{O}^i\text{Pr})_4$ ,  $N,N'$ -(1*R*,2*R*-cyclohexane-1,2-diyl)bis(trifluoromethanesulfonamide),  $\text{Et}_2\text{Zn}$ , PhMe; (h) DMP,  $\text{CH}_2\text{Cl}_2$ ; (i) TMSCN, RT; then  $\text{ZnI}_2$ , MeCN; then aq. 1 N HCl.

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 by-product 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<sup>22</sup> 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<sup>24</sup> conditions also proceeded with higher yield, providing ethyl carbinol 39 in 68% yield (two 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<sup>22</sup> 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

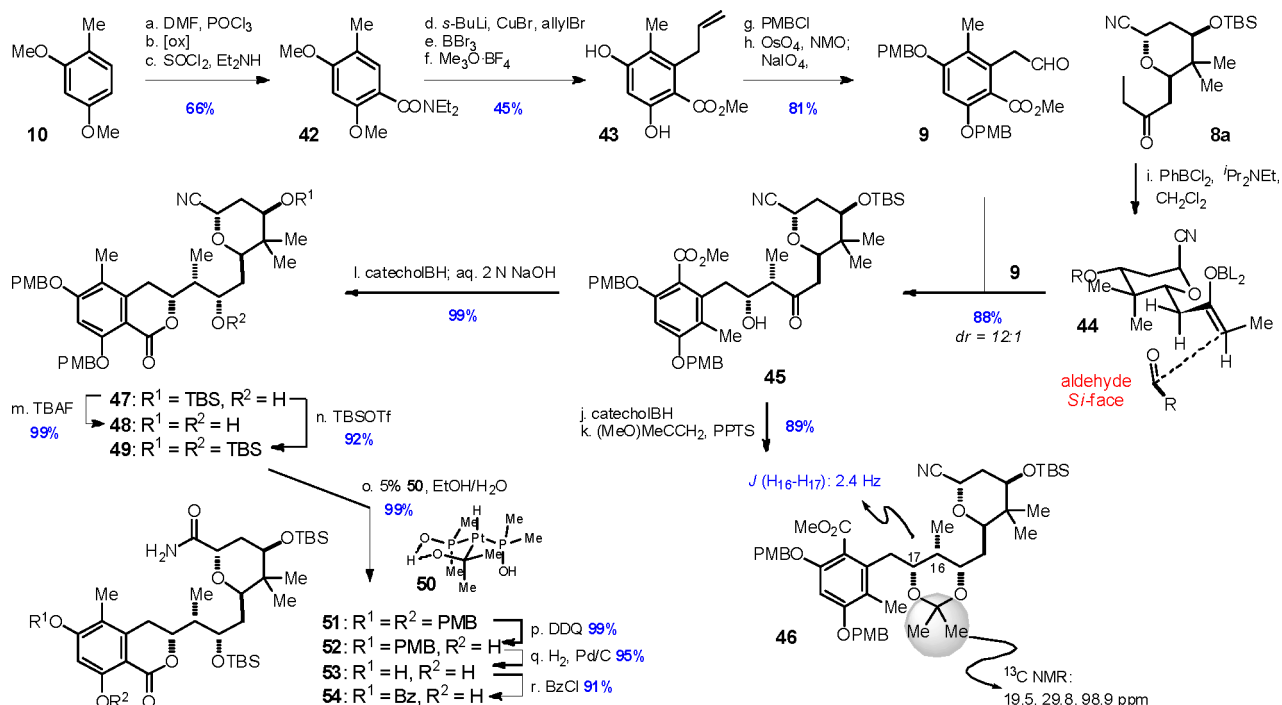
acetonitrile to initiate oxonium formation (40), followed by axial cyanide attack. After acidic aqueous workup, compound 41 was obtained in 91% yield and further oxidized to target ethyl ketone 8a in 95% yield. Crystallographic analysis of crystals obtained from 8a fully confirmed the assigned structure and relative stereochemistry. Using this optimized sequence, ethyl ketone 8a was obtained in seven steps from bishomoallylic 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 the coupling with ethyl ketone 8a are shown in Scheme 5. Starting from the commercially available 2,4-dimethoxy-1-methylbenzene 10, formylation,<sup>26</sup> oxidation to the corresponding carboxylic acid, and amidation afforded diethylamide 42 in 66% yield for the three-step sequence. *Ortho*-directed allylation<sup>27</sup> 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 co-workers,<sup>28</sup> 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



**Scheme 5. Synthesis of Dihydroisocoumarin Fragments<sup>a</sup>**



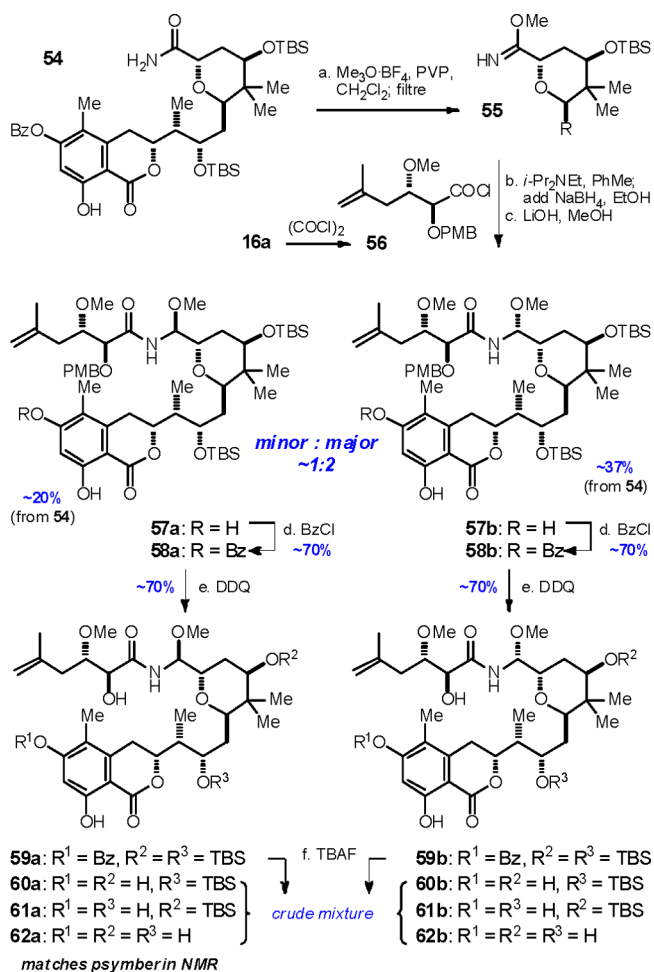
<sup>a</sup>Reagents and Conditions: (a) DMF, POCl<sub>3</sub>, 80%; (b) NaH<sub>2</sub>PO<sub>4</sub>, NaClO<sub>2</sub>, 2-methyl-2-butene, <sup>t</sup>BuOH/H<sub>2</sub>O, 85%; (c) SOCl<sub>2</sub>, benzene; Et<sub>3</sub>NH, 97%; (d) *sec*-BuLi, CuBr·SMe<sub>2</sub>, allylBr, THF, −78 °C, 76%; (e) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, −78 to 25 °C, 81%; (f) Me<sub>3</sub>OBf<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; Na<sub>2</sub>CO<sub>3</sub>, MeOH, 73%; (g) PMBCl, Bu<sub>4</sub>Nl, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 92%; (h) cat. OsO<sub>4</sub>, NMO, THF/H<sub>2</sub>O; NaIO<sub>4</sub>, aq MeOH, 81%; (i) PhBCl<sub>2</sub>, <sup>t</sup>Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, −78 °C, 88%, 12:1 dr; (j) catecholborane, THF, 0 °C; (k) (MeO)MeCCCH<sub>2</sub>, PPTS, 89% over two steps; (l) catecholborane, THF, 0 °C; aq 2 N NaOH, 99%; (m) TBAF, THF, 99%; (n) TBSTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 92%; (o) cat. [PtH(PMe<sub>2</sub>OH)(PMe<sub>2</sub>O)<sub>2</sub>H] (**50**), EtOH/H<sub>2</sub>O, 80 °C, 99%; (p) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O, 99%; (q) H<sub>2</sub>, Pd/C, EtOH, 95%, (r) BzCl, <sup>t</sup>Pr<sub>2</sub>NEt, PhMe, 91%.

accomplish a stereoselective aldol coupling between ethyl ketone **8a** and arylaldehyde **9**. Although initial explorations with titanium enolates ( $\text{TiCl}_4$ ,  $^i\text{Pr}_2\text{NEt}$ )<sup>29</sup> only delivered mixtures of diastereoisomers ( $\sim 1:1$  ratio), we found that the *Z*-chlorophenylboryl enolate<sup>30</sup> **44** added to aldehyde **9** with high facial selectivity producing the *syn*-aldol product **45** in 88% yield and 12:1 dr.<sup>31</sup> 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.<sup>30</sup> Stereoselective reduction of  $\beta$ -hydroxyketone **45** with catecholborane<sup>32</sup> 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 acetone **46**.<sup>33</sup>  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis of this derivative confirmed the 1,3-*syn* configuration.<sup>34</sup> Silylation of the secondary alcohol ( $\rightarrow$ **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.<sup>35</sup> 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 monobenzoate **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 imide **55** with acid chloride **56** (from acid **16a**) and intercept the incipient acylimide with a reducing agent (Scheme 6), a tactic employed for the synthesis of the structural relative pederin (**3**).<sup>36</sup> However, we were unable to prepare and handle imide

**55** using  $\text{Me}_3\text{OBF}_4$  as reported.<sup>36</sup> Treatment of **54** with  $\text{Me}_3\text{OBF}_4$  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  $\text{Et}_3\text{N}$ ,  $\text{NaHCO}_3$ , 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 imide formation with  $\text{Me}_3\text{OBF}_4$  ( $\text{CH}_2\text{Cl}_2$ ). After stirring at room temperature, the crude imide reaction mixture was filtered and concentrated, followed by dissolving the crude imide **55** in toluene, and 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)<sup>37</sup> 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 bisphenols **57a** and **57b** were unstable toward 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

Scheme 6. Initial Attempts Toward Psymberin<sup>a</sup>

<sup>a</sup>Reagents and conditions: (a)  $\text{Me}_3\text{OBF}_4$ ,  $\text{CH}_2\text{Cl}_2$ , PVP, rt; filter, concentrate; (b)  $\text{PhMe}$ ,  $\text{Pr}_2\text{NEt}$ , 56,  $40^\circ\text{C}$ , 2 h, cool to  $0^\circ\text{C}$ , then add  $\text{NaBH}_4$  in  $\text{EtOH}$ ; (c)  $\text{LiOH}$ ,  $\text{MeOH}$ , rt; (d)  $\text{BzCl}$ ,  $\text{Pr}_2\text{NEt}$ ,  $\text{PhMe}$ , 70%; (e) DDQ,  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ , 70%; (f) TBAF, THF. Abbreviations: PVP, poly(4-vinylpyridine) (25% cross-linked).

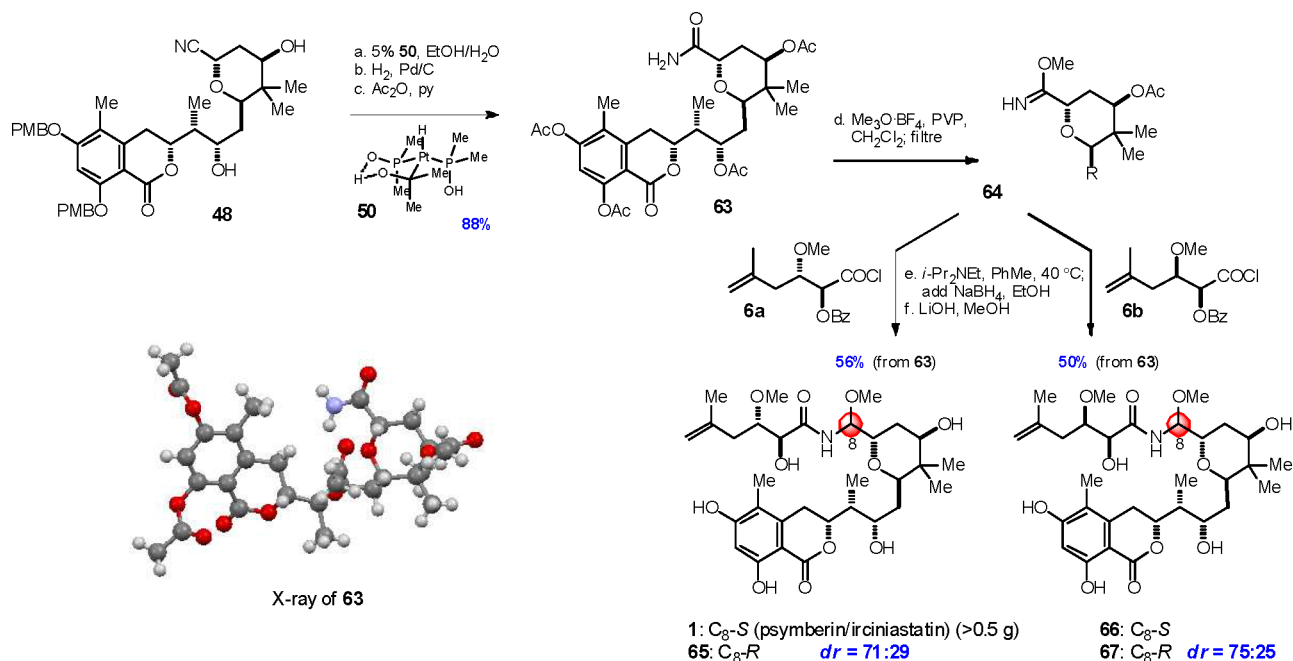
(crude NMR). Only a small amount of fully deprotected material was observed, even when a large excess of fluoride was added. We were unable to neither convert nor purify the crude mixture of compounds 60–62a or 60–62b to a globally deprotected material. However, thorough analysis of the crude  $^1\text{H}$  NMR, spectra hinted that the mixture containing 62a provided a spectral fingerprint congruent with that reported for psymberin.<sup>1</sup>

Although we had defined an end game 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 silyl ether protecting groups. Toward this end, we processed diol 48, obtained from silyl ether 47 via fluoride-mediated deprotection (TBAF, 99%, Scheme 5). As shown in Scheme 7, nitrile 48 was hydrolyzed with the Ghaffar–Parkins catalyst 50,<sup>35,38</sup> followed by hydrogenolytic removal of the *p*-methoxybenzyl protecting groups and peracylation with acetic anhydride. The corresponding crystalline amide 63, obtained in

88% yield (three steps), permitted an unambiguous confirmation of the full stereochemistry as shown via crystallography. As before (Scheme 6), stirring a solution of amide 63 ( $\text{CH}_2\text{Cl}_2$ ) with  $\text{Me}_3\text{OBF}_4$  in the presence of poly(4-vinylpyridine) yielded a crude imidate mixture ( $\rightarrow 64$ ) 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  $40^\circ\text{C}$  for 2 h. The reaction mixture was then cooled to  $0^\circ\text{C}$  and treated with an ethanolic sodium borohydride solution, providing after workup and saponification of the acetate protecting groups with a methanolic  $\text{LiOH}$  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.<sup>37</sup> As noted in the Introduction, a constitutional identical natural product termed irciniastatin was isolated by the Pettit group.<sup>2</sup> Although the relative stereochemistry of irciniastatin was only partly resolved, the assignment dictated it to be a different compound than psymberin (structure 2 in Figure 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.

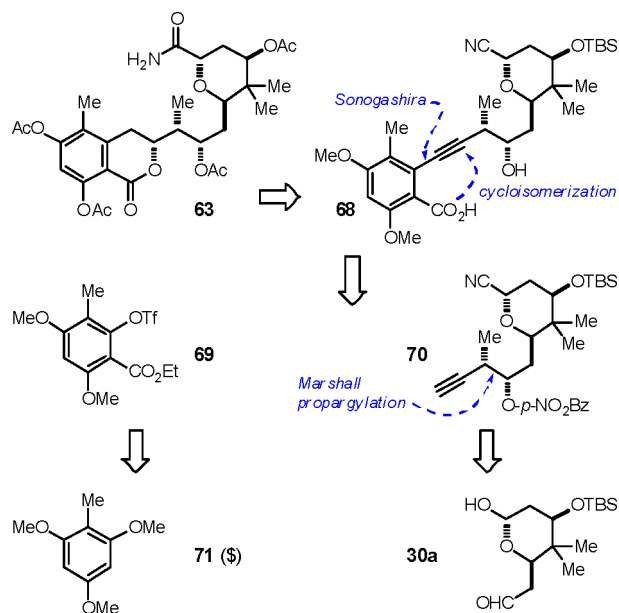
**2.2. Second Generation Synthesis.** Although our first generation synthesis served us well in producing  $\sim 0.5$  g of psymberin (1), introducing the dihydroisocoumarin fragment required an eight-step synthesis of aromatic aldehyde 9, followed by a stereoselective aldol coupling and reductive lactonization. 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 cyclization 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 three steps from commercial trimethoxytoluene (71).<sup>39</sup> Alkynyl fragment 70 in turn would be accessible from lactol 30a via a Marshall propargylation.<sup>40</sup>

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 co-workers in good yield (70%) and excellent diastereoselectivity (dr > 10:1, separable).<sup>40,41</sup> The corresponding reaction with the allenylzinc species derived from 71 ( $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ ,  $\text{Et}_2\text{Zn}$  in THF) led to decomposition.<sup>40b</sup> Acetate displacement with  $\text{TMSCN}$ ,<sup>22</sup> 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,  $\text{PPh}_3$ , in THF) failed<sup>42</sup> and led to elimination (enyne) or recovered starting material. However, exploiting condition developed by Tsunoda et al. ( $N,N,N',N'$ -tetramethylazodicarboxamide,  $\text{PBu}_3$ ,

Scheme 7. Synthesis of Psymberin and Diastereomers<sup>a</sup>

<sup>a</sup>Reagents and Conditions: (a) cat. [PtH(PMe<sub>2</sub>OH)(PMe<sub>2</sub>O)<sub>2</sub>H] (**50**), EtOH/H<sub>2</sub>O, 80 °C, 97%; (b) 10% Pd/C, H<sub>2</sub>, EtOH, 99%; (c) Ac<sub>2</sub>O, pyridine, 92%; (d) **63**, Me<sub>3</sub>OBF<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, PVP, rt; filter, concentrate; (e) crude **64**, PhMe, <sup>t</sup>Pr<sub>2</sub>NEt, **6a** or **6b**, 40 °C, 2 h, cool to 0 °C, then add NaBH<sub>4</sub> in EtOH; (f) LiOH, MeOH.

## Scheme 8. Alternative Synthetic Strategy

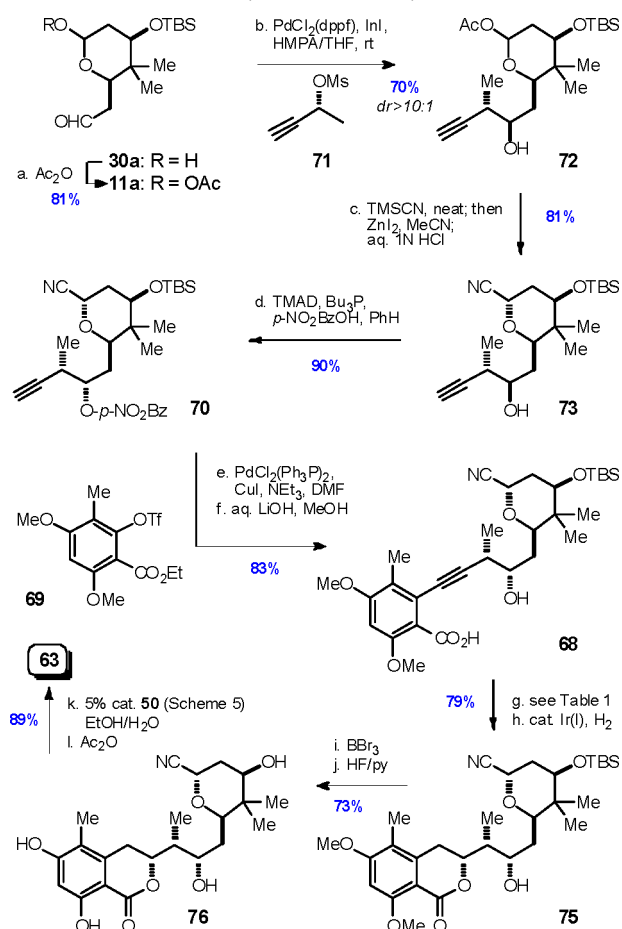


benzene) efficiently provided inverted *p*-nitrobenzoate **70** in 90% yield.<sup>43</sup> Initial model studies to construct the isocoumarin via a one-pot Pd-catalyzed heteroannulation between alkyne **70** and *o*-iodobenzoic acid indicated low conversion and significant amounts of phthalide formation.<sup>44</sup> 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.<sup>45</sup>

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<sup>46</sup> including Brønsted acid<sup>47</sup> (entries 1, 2), InBr<sub>3</sub> (entry 3), and AuCl<sub>3</sub> (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 results reported in the literature.<sup>49</sup> Inspired by the cycloisomerization methodology developed by our group, we explored Zeise's dimer ([Pt-(CH<sub>2</sub>CH<sub>2</sub>)Cl<sub>2</sub>]<sub>2</sub>).<sup>50</sup> 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<sup>51</sup> provided a slight improvement but still favored the undesired *5-exo* product **74b** (entry 7).<sup>52</sup> In the end, we could overturn the regioselectivity favoring the desired *6-endo* product when cationic Au(I) (PPh<sub>3</sub>PAuCl, AgSbF<sub>6</sub>) was engaged as the catalyst (2:1 ratio of **74a**:**74b**, ~60% mass balance, entry 8). The use of (Ph<sub>3</sub>P)AuNTf<sub>2</sub><sup>51</sup> 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 Xphos-ligated AuNTf<sub>2</sub><sup>53</sup> (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<sub>3</sub>) and silyl ether (HF/py) deprotection provided dihydroisocoumarin **76** in 73% yield for the two-step sequence. Ghaffar-Parkins<sup>35</sup> nitrile hydrolysis followed by peracetylation provided a material (compound **63**) that was identical to that

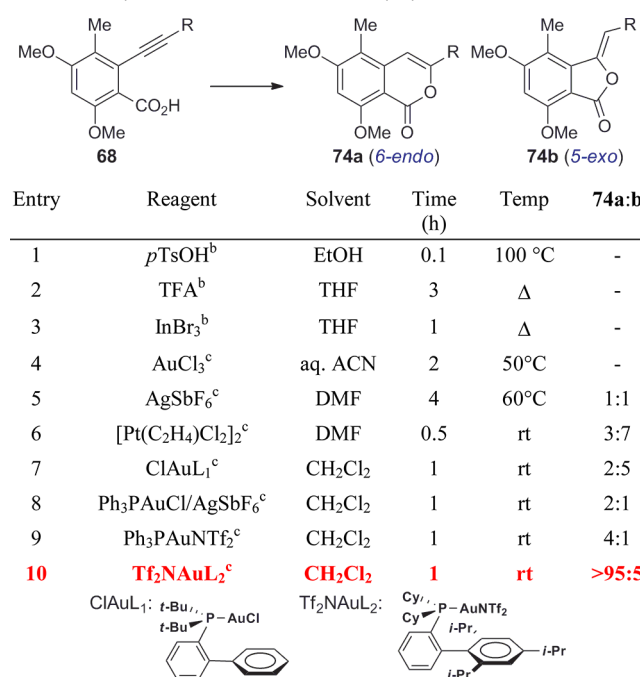
**Table 1. Cycloisomerization of Alkynyl Benzoic Acid 68<sup>a</sup>**



<sup>a</sup>Reagents and Conditions: (a)  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 81%; (b) **55**,  $\text{PdCl}_2(\text{dppf})_2$ , InI, HMPA, THF, rt, 70%, dr > 10:1; (c)  $\text{TMSCN}$  (neat);  $\text{ZnI}_2$ , MeCN; aq 1N HCl, 81%; (d) TMAD,  $\text{Bu}_3\text{P}$ ,  $p\text{-NO}_4\text{BzOH}$ , benzene, 90%; (e) **51**,  $\text{PdCl}_2(\text{PPh}_3)_2$ , CuI,  $\text{Et}_3\text{N}$ , DMF, 40 °C, 83%; (f) aq 1N LiOH, MeOH, 0 °C, 99%; (g)  $\text{AuNTf}_2(\text{Xphos})$  (5 mol %),  $\text{CH}_2\text{Cl}_2$ , rt; (h)  $\text{H}_2$  (1 atm), cat.  $[\text{Ir}(\text{cod})(\text{PCy}_3)(\text{py})]\text{PF}_6$  (2 mol %),  $\text{CH}_2\text{Cl}_2$ , rt, 79% over two steps; (i)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78$  to  $25$  °C, 77%; (j) HF/pyridine, THF, 95%; (k) cat.  $[\text{PtH}(\text{PMe}_2\text{OH})(\text{PMe}_2\text{O})_2\text{H}]$  (**50**),  $\text{EtOH}/\text{H}_2\text{O}$ , 80 °C, 97%; (l)  $\text{Ac}_2\text{O}$ , pyridine, 92%. Abbreviations: TMAD,  $N,N,N',N'$ -tetramethylazodicarboxamide.

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 toward 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 second generation approach offers an attractive late stage introduction of aromatic fragments for SAR around the dihydroisocoumarin structure.

**2.3. 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.<sup>13</sup> The terminal olefin of **1** is distinct from

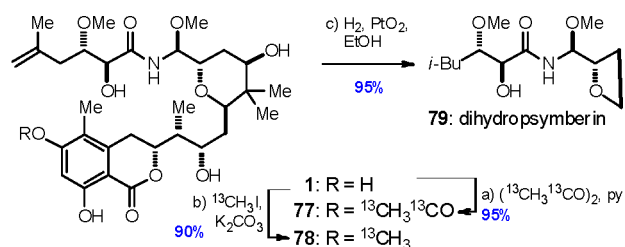


<sup>a</sup>All reactions were performed with 50  $\mu$ mol **68**. <sup>b</sup>20 mol %. <sup>c</sup>5 mol %.

<sup>d</sup>Ratios were determined by <sup>1</sup>H NMR.

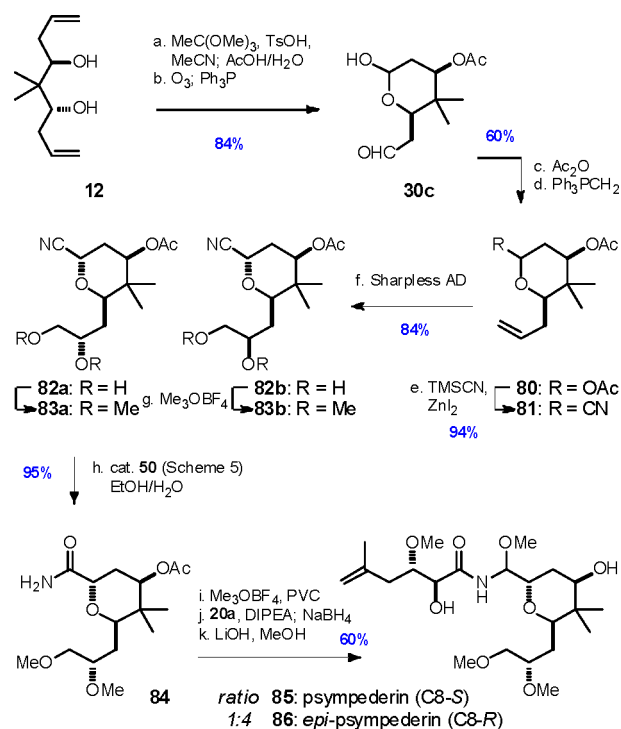
the exocyclic double bond present in other pederin family members. In the subsequent article, we demonstrate that the homoallylic ether in pederin is responsible for the irritant/blistering activity associated with this class of compounds.<sup>5</sup> Although psymberin does not possess blistering activity,<sup>13</sup> hydrogenation of the terminal olefin of psymberin would allow for the preparation of a radiolabeled variant for biological studies. Thus, hydrogenation of psymberin (**1**) over platinum provides 95% of the corresponding dihydropsymberin **79** (Scheme 10). Alternatively, <sup>13</sup>C phenolic methyl ether **78** or acetate **77** was prepared via methylation or acetylation of psymberin **1** (90–95% yield).

**Scheme 10. Synthesis of Methyl-, Acetyl-, and Dihydrosyberin**



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<sub>2</sub>-symmetrical bishomoallylic alcohol **12**, which was monoacetylated via cyclic orthoacetate formation and hydrolysis under



**Scheme 11. Synthesis of a Psymberin–Pederin Hybrid, Psympederin<sup>a</sup>**

<sup>a</sup>Reagents and Conditions: (a) MeC(OMe)<sub>3</sub>, *p*-TsOH, MeCN; AcOH/H<sub>2</sub>O, 88%; (b) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; PPh<sub>3</sub>, 95%; (c) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; (d) Ph<sub>3</sub>PCH<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 60% (two steps); (e) TMSCN, ZnI<sub>2</sub>, MeCN, 94%; (f) hydroxyquinine 9-phenanthryl ether, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, <sup>t</sup>BuOH/H<sub>2</sub>O, 0 °C; OsO<sub>4</sub>, 92%; (g) Me<sub>3</sub>OBf<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 2,6-lutidine, 93%; (h) cat. [PtH(PMe<sub>2</sub>OH)(PMe<sub>2</sub>O)<sub>2</sub>H] (50), EtOH/H<sub>2</sub>O, 80 °C, 95%; (i) Me<sub>3</sub>OBf<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, PVP; filter, concentrate; (j) PhMe, <sup>i</sup>Pr<sub>3</sub>NEt, 6a, 40 °C, 2 h, cool to 0 °C, then add NaBH<sub>4</sub> in EtOH; (k) LiOH, MeOH, 60% (three steps).

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 acetate **80** (mixture of anomers) was treated with trimethylsilyl cyanide<sup>22</sup> in the presence of ZnI<sub>2</sub> 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<sub>4</sub>, *N*-methylmorpholine) revealed an intrinsic facial bias slightly favoring the undesired diastereomer **82b** (**82a**:**82b** = 1:1.4), whereas Sharpless asymmetric dihydroxylation using the (DHQD)<sub>2</sub>PYR or (DHQD)<sub>2</sub>PHAL ligand was nonselective (1:1 ratio).<sup>54</sup> After some experimentation, we found that hydroxyquinine 9-phenanthryl ether (HQP ether) was the optimal ligand for the asymmetric dihydroxylation of **81**,<sup>55</sup> providing a ~3:1 mixture favoring the desired C<sub>15</sub>-S configuration (**82a**). Kocienski and co-workers 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.<sup>56</sup> 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.<sup>56</sup> Nitrile hydrolysis of the major methyl ether **83a** with use of the Ghaffar–Parkins catalyst<sup>55</sup> provided acetylpedamide **84** in 95% yield.<sup>57</sup> The final introduction of the C<sub>1</sub>–C<sub>6</sub> “psymberate” side chain was accomplished via the protocol outlined for the synthesis of psymberin (Scheme 7). Thus, acylation of the imide 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**.<sup>58,59</sup> 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*-acylimide reduction is highly dependent on the presence or absence of the dihydroisocoumarin fragment.

### 3. 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 paper, 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 linear sequence) from three fragments prepared in 7–8 steps (first generation) or 3–8 steps (second generation) each. The synthesis of the central tetrahydropyranyl fragment via a double dehydrogenative allylation developed by Krische and 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 methylimide formation with Me<sub>3</sub>OBf<sub>4</sub>; 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 paper.<sup>13</sup>

### ■ ASSOCIATED CONTENT

#### 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>.

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#### Notes

The authors declare no competing financial interest.

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(58) A similar coupling between benzoylpedamide and the pederin "pederate" fragment in Nakata's<sup>36</sup> pederin total synthesis also yielded a 1:3 mixture of pederin and *epi*-pederin (38% yield).

(59) The natural C<sub>8</sub>-S configuration of **85** was assigned based upon a detailed analysis of <sup>1</sup>H–<sup>1</sup>H coupling constants and 1D- and 2D-NOE correlations, see ref 10a for details.