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Synthesis of *seco*-psymberin/irciniastatin A: the discovery of a novel $PhI(OAc)_2$ mediated cascade cyclization reaction

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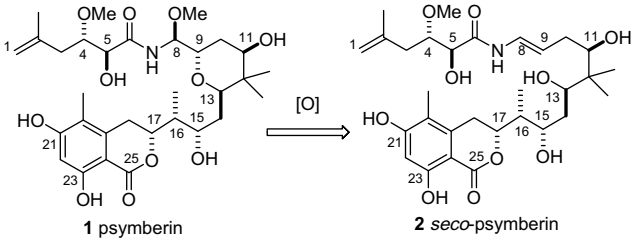
Abstract

The psymberin unsaturated 'psymberate' side chain **7** was synthesized in 7 steps (36% yield) with good diastereoselectivity using commercially available starting material to control the stereochemistry at C_4 and C_5. The synthesis of *seco*-psymberin was completed in an efficient manner based on a CuI mediated coupling reaction between vinyl iodide **8** and 'psymberamide' **7**. In an attempt to synthesize natural psymberin from the *seco*-intermediate, a novel $PhI(OAc)_2$ mediated cascade ring closing reaction was discovered. A possible mechanistic pathway for the formation of the ring closing product was presented.

Keywords: Total synthesis; *seco*-Psymberin; 'Psymberate' side chain; (Diacetoxyiodo)benzene; Oxidative cyclization

The structure of psymberin (**1**)/irciniastatin A was identified by two research groups[1] independently in 2004 after almost a decade of effort. This natural product is extremely potent against various human cancer cell lines with unprecedented selectivity[1a] for its class. This compound is a new member of the pederin family[1a] in that it shares the common pederin α-cyclic-oxy *N*-acyl aminal core (C_6–C_{13}, Scheme 1). However, its structure is unique within this class as this core is flanked by a novel dihydroisocoumarin unit and an unusual unsaturated acyclic side chain. The total synthesis of psymberin has drawn much attention from the synthetic chemistry community[2] including our recent total synthesis.[3] The key in our approach is the assembly of the synthetically challenging pederin common core using our recently reported[4] novel $PhI(OAc)_2$ mediated oxidative cyclization to synthesize 2-(*N*-acylaminal) substituted tetrahydropyrans from enamides. The rational behind this is that the natural product psymberin (**1**) may be synthesized in nature from *seco*-psymberin **2** through a natural oxidation process in a 'biomimic' way. Based on this hypothesis, we became interested in synthesizing and testing compound **2** for biological activity. Herein, we report our synthetic effort toward *seco*-psymberin involving an efficient route to synthesize the unsaturated 'psymberate' side chain, and the discovery of a novel $PhI(OAc)_2$ mediated cascade cyclization reaction in this process.



Scheme 1. A possible 'biomimic' formation of psymberin from *seco*-psymberin.

According to our retrosynthetic analysis, *N*-acyl enamine **2** (*seco*-psymberin) can be synthesized through a CuI-mediated coupling reaction to form the N_7–C_8 bond and a substrate controlled Mukaiyama aldol reaction to

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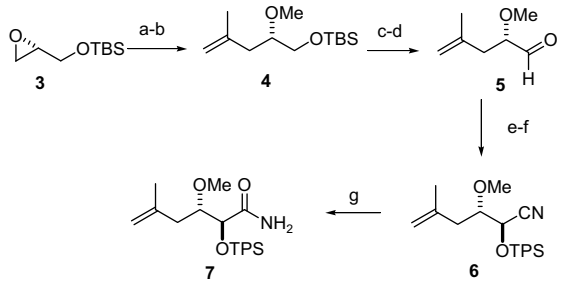


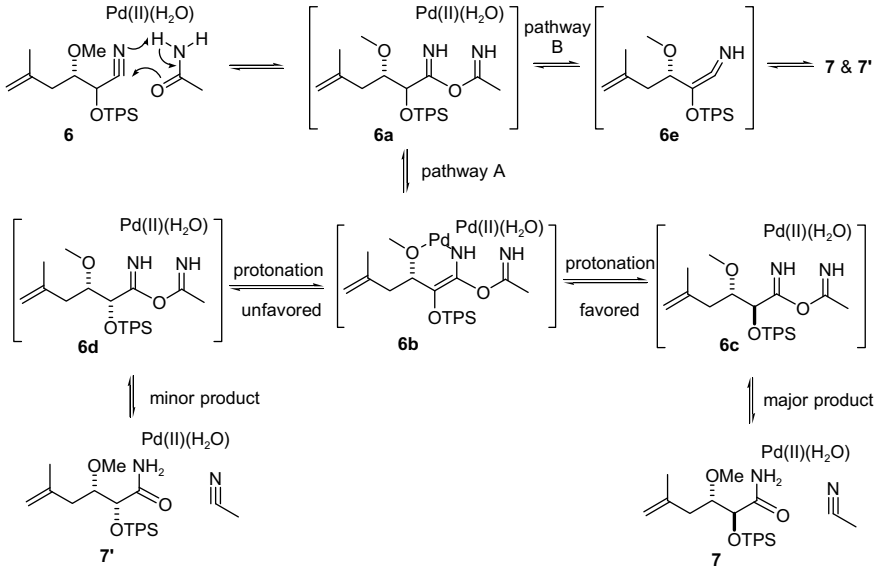
Scheme 2. Synthesis of the acyclic 'psymberate' side chain. Reagents and conditions: (a) 2-propenylMgBr, CuI, THF, −15 °C, 90%; (b) Me_3OBF_4, proton sponge, CH_2Cl_2, 95%; (c) TBAF, THF, 90%; (d) DMP, CH_2Cl_2, 0 °C to rt, 80%; (e) (1) TMSCN, K_2CO_3, Et_2O, 0 °C, rt, 91%; (2) TBAF, THF, 95% dr = 1:1; (f) TPSCl, NEt_3, DMAP, CH_2Cl_2, 95%; (g) $MeCONH_2$, $PdCl_2$, H_2O, THF, 71% (pure isomer).

connect C_{14}–C_{15}. Our synthesis started with the preparation of unsaturated 'psymberamide' side chain **7** (C_1–N_7). Although a few research groups have reported the synthesis of the 'psymberate' side chain,[5] we decided to employ a commercially available chiral precursor (**3**) to set up the C_4 chiral center (Scheme 2).

Regioselective epoxide opening of **3** with isopropenylmagnesium bromide gave a secondary alcohol which was protected as a methyl ether with Me_3OBF_4 to give **4**. Ether **4** was converted to **5** in 2 steps via deprotection of the TBS group and Dess–Martin oxidation. Aldehyde **5** underwent basic cyanohydrin formation (dr = 1:1), deprotection of the TMS group with TBAF, and protection of the free alcohol as a TPS ether to give nitrile **6**. At this point, we did not attempt to improve the stereoselectivity at C_5. When the nitrile was subjected to hydrolysis under very mild conditions,[6] we successfully obtained amide **7** not only in good yield but also in good diastereoselectivity (3:1 to 5:1 in favor of the desired product, isomers were easily separated at this step with silica gel column chromatography). This is a surprising but satisfactory result. We hypothesized that the enrichment of the stereoselectivity might be an equilibration process involving a six-membered intermediate (Scheme 3). After initial palladium mediated proton transfer between **6** and acetamide to form intermediate **6a**, **6a** can isomerize to palladium chelated intermediate **6b** (pathway A). Upon protonation, the favored intermediate **6c** will prevail and further transform to the desired major product **7**. To this point, side chain **7** was prepared in an overall 36% yield in 7 steps with good diastereoselectivity. An alternative mechanistic pathway (Scheme 3, pathway B) is also possible. This involves the initial conversion of **6a** to ketenimine **6e**. Subsequent hydration of **6e** followed by diastereoselective protonation would lead to the major product **7**.

With amide **7** in hand, we proceeded to complete the synthesis (Scheme 4). Vinyl iodide **8**[3] was coupled with compound **7** using CuI[7] under Buchwald conditions to give protected *N*-acyl enamine **9**, and the major product *E*-isomer was separated at this stage. Upon treatment of *E*-**9** with NaOMe/MeOH followed with TBAF at 50 °C, a global deprotection was realized to give *seco*-psymberin **2**. With **2** in hand, we studied its antiproliferation activity in a human lung cancer cell line (HOP62), and found that it was weakly active ($IC_{50} > 1 \times 10^4$ nM). This result suggests that the 2-(*N*-acylaminal) substituted tetrahydropyran portion of psymberin is crucial for its potent cytotoxic activity.

Since we had compound **9** in hand, we also attempted to complete the total synthesis of psymberin with this material (Scheme 5). Cyclization precursor enamide **10** ($E/Z = 5/1$) was synthesized from **9** ($E/Z = 5/1$) in two operations: (1) removal of C_{13}, C_{15} acetate, and O_{21} TIPS groups with NaOMe/MeOH, (2) acetylation of O_{21}. Surprisingly, when we subjected compound **10** under the $PhI(OAc)_2$ mediated cyclization reaction, the reaction was rather complex. After isolation of the products and careful NMR analysis, we



Scheme 3. Possible mechanism for the stereochemistry enrichment at C_5.