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

Xianhai Huang *, Ning Shao, Anandan Palani, Robert Aslanian, Alexei Buevich, Cynthia Seidel-Dugan, Robert Huryk

Department of Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ 07033, United States

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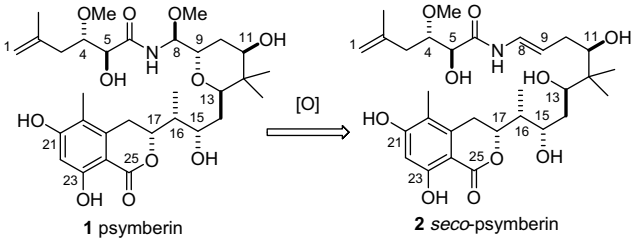
Abstract

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

* Corresponding author. Tel.: +1 908 740 3487; fax: +1 908 740 7664.
E-mail address: xianhai.huang@spcorp.com (X. Huang).

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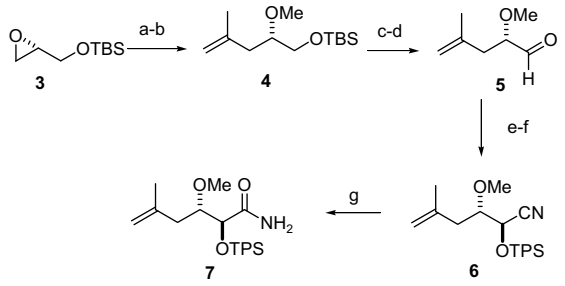


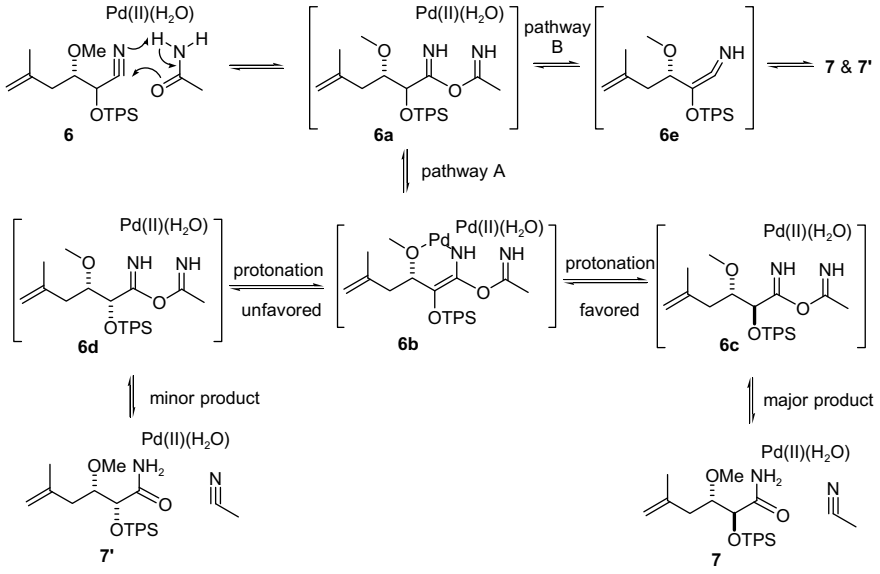
Scheme 2. Synthesis of the acyclic 'psymberate' side chain. Reagents and conditions: (a) 2-propenylMgBr, CuI, THF, −15 °C, 90%; (b) Me_3OBF_4, proton sponge, CH_2Cl_2, 95%; (c) TBAF, THF, 90%; (d) DMP, CH_2Cl_2, 0 °C to rt, 80%; (e) (1) TMSCN, K_2CO_3, Et_2O, 0 °C, rt, 91%; (2) TBAF, THF, 95% dr = 1:1;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

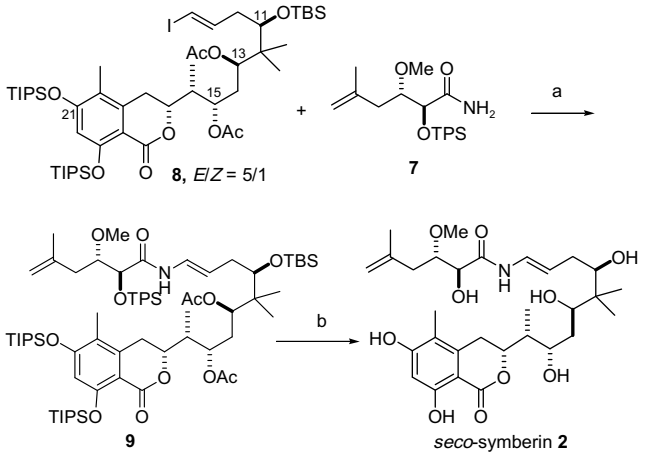
Regioselective epoxide opening of **3** with isopropenylmagnesium bromide gave a secondary alcohol which was protected as a methyl ether with Me_3OBF_4 to give **4**. Ether **4** was converted to **5** in 2 steps via deprotection of the TBS group and Dess–Martin oxidation. Aldehyde **5** underwent basic 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.

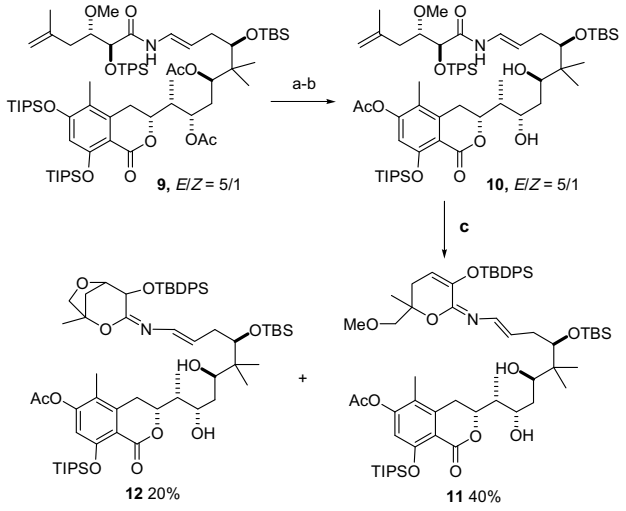
Since we had compound **9** in hand, we also attempted to complete the total synthesis of psymberin with this material (Scheme 5). Cyclization precursor enamide **10** ($E/Z = 5/1$) was synthesized from **9** ($E/Z = 5/1$) in two operations: (1) removal of C_{13}, C_{15} acetate, and O_{21} TIPS groups 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.



Scheme 4. Completion of the synthesis of *seco*-psymberin. Reagents and conditions: (a) CuI, $MeNHCH_2CH_2NHMe$, Cs_2CO_3, toluene, 70 °C, 86%; (b) (1) NaOMe, MeOH; (2) TBAF, THF, rt to 50 °C, 70%.

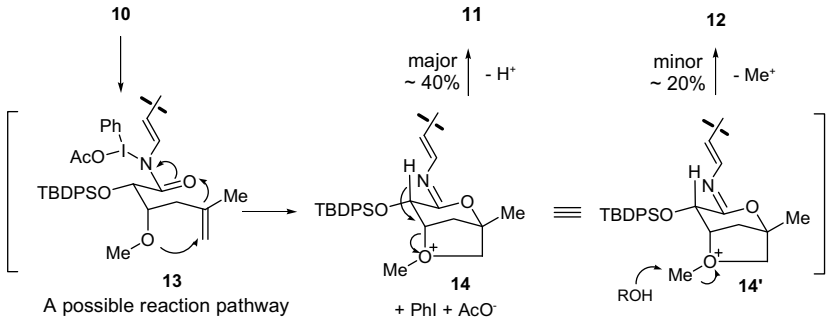


Scheme 5. The discovery of a novel $PhI(OAc)_2$ mediated cascade ring closure reaction. Reagents and conditions: (a) NaOMe, MeOH; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C, 90% over 2 steps; (c) $PhI(OAc)_2$, MeOH, HFIP, 60%.

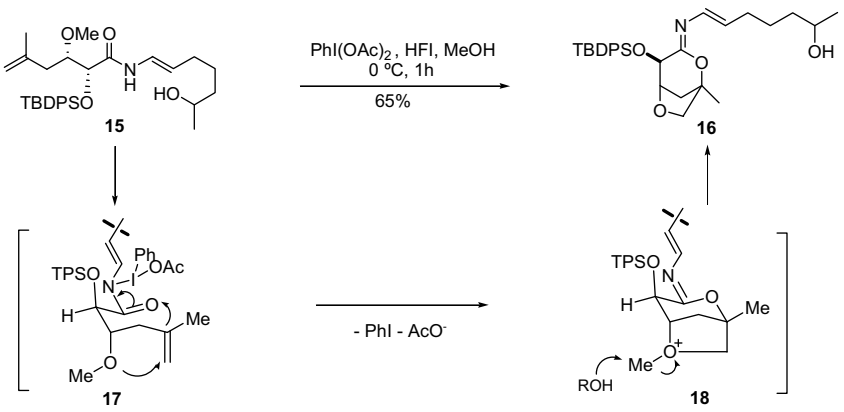
noticed that the enamine double bond was still present in all spectra and the terminal double bond was missing. Among the products isolated, we identified two major products **11** (40%) and **12** (20%). In both compounds, the methoxy group at C_4 disappeared. This surprising result prompted us to wonder what the possible reaction pathway is for the formation of these products. Although it is possible for DIB to complex with simple alkenes[8a] in aqueous media, we did not think that the terminal double bond was involved in the initial step in this case because only very mild conditions were employed and a control reaction showed that the terminal double bond was not affected.[8b]

Herein, we propose a possible reaction pathway for the transformation (Scheme 6). Upon treatment of **10** with DIB, the reagent first coordinates with the electron rich enamide to form a weak iodine nitrogen bond to give **13** (which may dissociate to a tight iron pair).[9] The conformationaly close methoxy group then attacks the terminal double bond followed by ring formation to give intermediate oxonium ion **14** (or **14′**). Intermediate **14** can undergo two possible reactions: (1) the antiparallel proton eliminates using methyloxonium ion as a leaving group (**14**) to give the major product **11**, or (2) external nucleophile (MeOH) attacks the methyloxonium ion (**14′**) to give product **12**. If this hypothesis is viable, we thought that product **11** would not form if the antiparallel proton was not present. To confirm this, we prepared compound **15** in which the stereochemistry at C_5 was inverted. When we subjected **15** to the oxidative cyclization reaction conditions, indeed, the only major product obtained is the bicyclic compound **16**. In this case (Scheme 7), after the formation of intermediate **17**, it undergoes ring closure to give intermediate **18**. There is no antiparallel proton to eliminate in **18**, and the only reaction that can happen is the external nucleophilic attack to give product **16**. At this point, we can not totally rule out the possibility that the interaction between alkenes and oxidants is reversible and the product would be resulted from addition of the nucleophilic amide carbonyl group to the tertiary carbon of the alkene.

In conclusion, we have synthesized the psymberin unsaturated 'psymberate' side chain using commercially available starting material to control the stereochemistry at C_4 and C_5. An unexpected stereochemistry enrichment was



Scheme 6. A possible reaction pathway for the formation of **11** and **12**.



Scheme 7. Further studies of the $PhI(OAc)_2$ mediated ring formation reaction.

observed at C_5. Based on a CuI mediated coupling reaction between vinyl iodide **8** and 'psymberamide' **7**, the synthesis of *seco*-psymberin **2** was completed in an efficient manner. The preliminary biological data of compound **2** support that the 2-(*N*-acylaminal) substituted tetrahydropyran portion of psymberin is crucial for its potent cytotoxic activity. In an attempt to synthesize natural psymberin from the *seco*-intermediate, we discovered a novel $PhI(OAc)_2$ mediated cascade ring closing reaction. A possible mechanistic pathway for the formation of the ring closing product was presented. Further studies and potential synthetic applications of this novel cyclization reaction are underway and the result will be reported in due course.

Acknowledgments

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Supplementary data

Experimental details and spectral data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.016.

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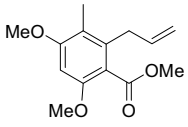

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