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Asymmetric synthesis of the C1–C6 portion of the psymberin using an Evans chiral auxiliary

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ABSTRACT

The C1–C6 region of the potent cytotoxic agent psymberin has been synthesized. The key transformations of the synthesis are an auxiliary-controlled addition of a Sn(II)-glycolate enolate to an aldehyde to yield the *anti*-aldol product and transforming the primary alcohol into a terminal olefin utilizing organoselenium chemistry.

Introduction

In 2004, two groups independently reported the isolation and structural elucidation of a constitutionally identical acyl aminal **1** (Fig. 1). Pettit[1] isolated the extremely potent toxin from the South Pacific sponge Ircinia ramose whereas Crews[2] and co-workers also obtained the acyl aminal **1** from the crude extracts of an inconspicuous sponge, *psammocinia* sp., located from the waters of Papua New Guinea. The Pettit group named the compound as irciniastatin A and the Crews group named it as psymberin on the basis of its proposed biogenesis from symbiotic bacteria.[3]

Psymberin most closely resembles the pederin family[4] of natural products defined by the presence of a functionalized cyclic ether derivative, but psymberin is unique to the pederin family (Fig. 1) because of the presence of a highly substituted dihydroisocoumarin moiety as well as a terminal six carbon amide appendage. The configuration of the amide side chain of psymberin and irciniastatin, was previously reported. Initially the stereochemical assignment at the C4 position and the 5*S* configuration was proposed based on the analogy to other natural products in the pederin family. Recently, William's and co-workers[5] reported the stereochemical assignment of the C1–C6 region using ^{1}H and ^{13}C NMR chemical shift homology and a corroborating X-ray crystal structure. They postulated that the stereocenters at C4 and C5 have an anti-relationship. Floreancig and co-workers[6] established the stereochemical configuration of this fragment to be the 4*S*, 5*S* by the syntheses of all four stereoisomers of psymberic acid and comparison of the acid mediated cyclization products of these isomers to the product of psymberin's acidic methanolysis. Later De Brabander and co-workers[7] and Huang et al.[8] synthesized and made a complete stereochemical assignment of psymberin with an *S*-configuration at C4 and they concluded that psymberin and irciniastatin A were structurally identical. Other synthetic approaches to psymberin were attempted by Smith et al.,[9] Crimmins[10] as well as an interesting approach to the amide side chain by Iwabuchi and co-workers.[11] Recently Smith and co-workers[12] and De Brabander and co-workers[13] have also developed a second generation synthesis of this family of natural products.

Psymberin also displays some unique biological activity which was discovered at the SCI Development Therapeutic in vitro Screening Program. Psymberin displayed exceptional cytotoxicity below 2.5 nM against one colon cell cancer line (HCT-116) three melanoma (MALME-3M, SK-MEL-5, and UACCC-62) and a breast (MDA-MB-435) cancer cell line.[2,14] Recently De Brabander has revealed some fascinating structure–activity relationships (SAR) as well as biochemical studies suggesting that psymberin may have more than one biological function.[15] These interesting structural features as well as the interesting biological activity render this compound a synthetic target.

Results and discussions

Here we report the synthesis of anti-isomer of methyl ester of psymberic acid (C1–C6 fragment) **4** using the auxiliary-controlled aldol addition of Sn(II)-glycolate enolate of **8** to aldehyde **7** as a

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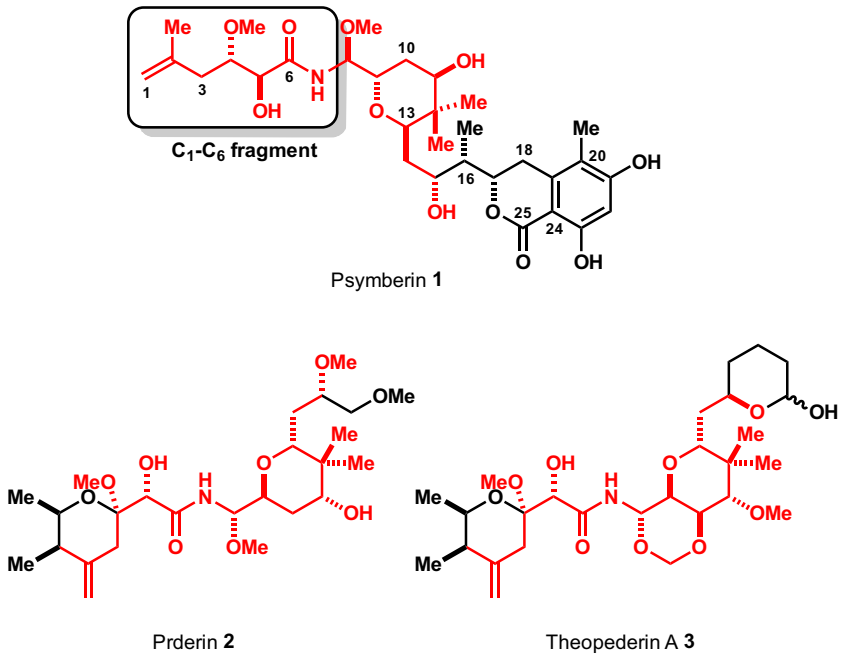
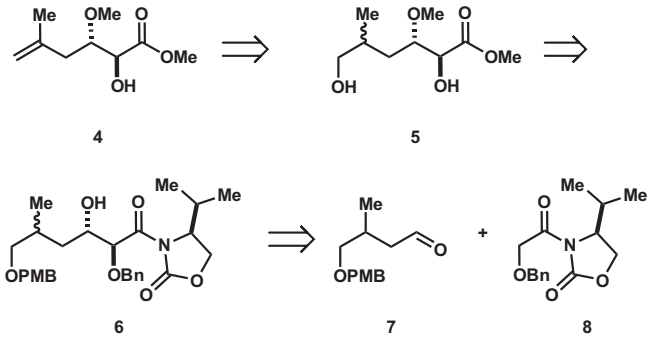


Figure 1. Structure of psymberin and representative acylaminal-containing cytotoxic agents.



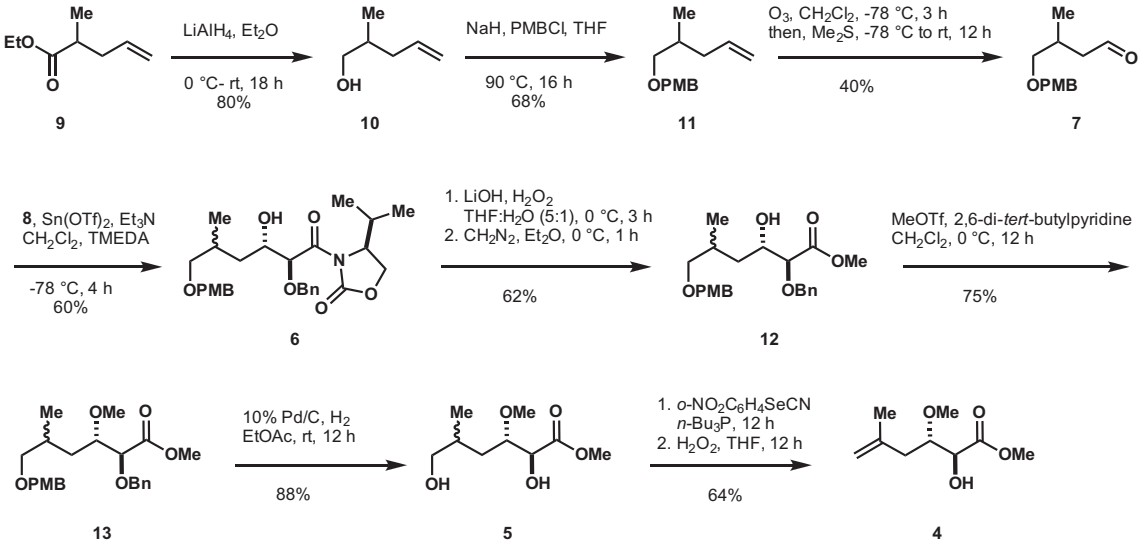
Scheme 1. Retrosynthetic analysis.

key reaction. Though psymberin belongs to the pederin family of natural products, psymberin **1** has distinct structural features from other members of the pederin family. For example, psymberin contains a six carbon amide side chain and a dihydroisocoumarin subunit and a structurally less-complex acyclic side chain. In this work, our synthetic strategy was to prepare anti configuration of methyl ester of psymberic acid and to compare methyl esters spectral data with the reported spectral data for the amide side chain of **1**. Notable features of this synthetic strategy include the implementing a modified protocol developed by Grieco[17] to transform the primary alcohol to an olefin in the presence of a secondary alcohol as well as the application of Evans auxiliary-controlled addition reaction to obtain the anti diastereoselective fragment **6**.

Retrosynthetically, psymberic ester **4** can arise from diol **5** by selective elimination of the primary alcohol over the secondary alcohol developed by Grieco et al.[16] (Scheme 1). The diol can arise from **6** through a three step reaction sequence which included: removal of the chiral auxiliary, esterification followed by hydrogenation. The anti diastereomer **6** is the predicted product of an asymmetric aldol addition reaction using Evans auxiliary-controlled addition reaction between aldehyde **7** and α-oxygenated amide derivative **8**.

The key bond forming reaction to obtain the anti-selectivity at the C4 and C5 positions on the amide side chain was achieved by an Evan's aldol reaction. The acylated oxazolidinone **8** was subjected to the Evans Sn(II) glycolate enolate protocol using aldehyde **7** and α-oxygenated amide derivative **8** to yield the *anti* aldol product **6** in 60% yield (Scheme 2). The stereochemical rational for the selectivity of the reaction remains to be unclear.[17] However, Mukaiyama et al. postulate that in this reaction the product equilibration is slow. They assume the stereochemical outcome is determined by the possible binding of TMEDA to the divalent tin enolate. This binding of TMEDA will change the coordination geometry of tin from tetragonal to octahedral and possibly favor a boat like transition state over the traditional chair transition state.[17,18]

The aldehyde **7** was accessed from ozonolysis of alkene **11**, which was generated from ethyl-2-methyl 4-pentenoate **9** by a LAH reduction followed by PMB protection of the resulting alcohol **10** by 4-methoxybenzyl chloride. The amide **6** was obtained by a previously reported procedure by Evans et al. with benzyloxy acetyl chloride.[19] Having the diastereomer **6** in hand, attention was turned to implicate several methods to protect the free hydroxy group in presence of the amide auxiliary. However, yields were insufficient and the starting material could not be recovered. Therefore, the chiral auxiliary was first removed with lithium hydroxide and hydrogen peroxide to obtain the free acid. The acid was immediately converted to methyl ester **12** by treating with diazomethane, which was subsequently o-methylated with methyl trifluoromethanesulfonate to provide methyl ether **13** (88% ee). Deprotection of the benzyl and PMB protecting groups under palladium-catalyzed hydrogenation provided compound **5**. The primary alcohol was selectively converted to the primary selenide using the protocol developed by Grieco et al.[16] in presence of the secondary alcohol. Treatment of alcohol **5** with 2-nitrophenylselenocyanate and tributyl phosphine gave the intermediate selenide



Scheme 2. Synthesis of C1–C6 portion of psymberin.

which was immediately oxidized with hydrogen peroxide to give the olefin **4** which was spectroscopically identical (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$) to the methyl ester reported by Floreancig and co-workers.[6]

Conclusion

In conclusion, we have developed a viable strategy for the formation of chiral C1–C6 region of the psymberin side chain using Evan's chiral auxiliary. The synthesis was completed in 10 linear steps from the ethyl 4-methylpentenoate **9**. Significant transformations are Evans auxiliary-controlled addition reaction, formation of olefin from primary alcohol.

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Supplementary data

Supplementary data associated (^{1}H and ^{13}C NMR spectra of all new compounds) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.153.

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