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The Total Synthesis of Psymberin

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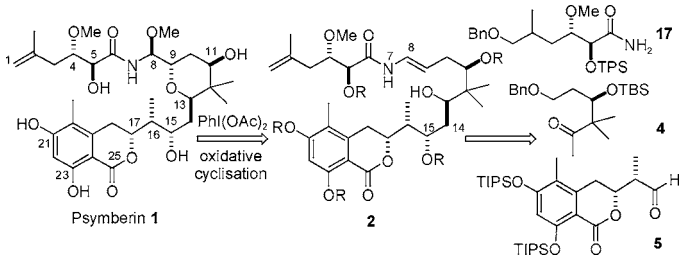
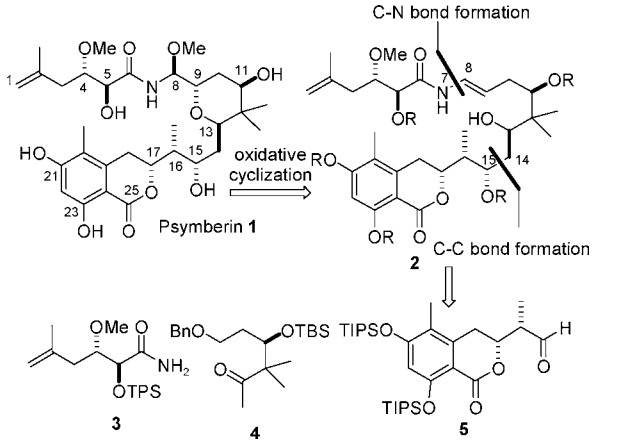
ABSTRACT



The total synthesis of a new member of the pederin family of natural products, psymberin 1, was accomplished. Using a recently reported novel and efficient PhI(OAc)$_2$ mediated oxidative entry to 2-(*N*-acylaminal)-substituted tetrahydropyrans as the key step, this total synthesis was executed in a convergent and efficient manner. The longest linear sequence of this synthesis was 22 steps starting from known 6.

After almost a decade of effort, two research groups[1] independently reported in 2004 the isolation and structure elucidation of a potent anticancer marine natural product. It was named psymberin (**1**) and irciniastatin A by each group, respectively. The C_4 stereochemistry was undefined. 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 unique dihydroisocoumarin unit and an unusual unsaturated acyclic side chain. More importantly, psymberin is an extremely potent and selective cytotoxin compared to other pederin natural products.[1a] Therefore, the total synthesis of psymberin has drawn much attention from the synthetic chemistry community.[2] In 2005, an elegant total synthesis of this natural

Scheme 1. Retrosynthetic Analysis of Psymberin with Use of an Oxidative Cyclization as the Key Step



product was reported by De Brabander's group,[2a] leading to a complete stereochemical assignment of psymberin with an *S*-configuration at C_4 and the conclusion that psymberin and irciniastatin A were identical. To assemble the synthetically challenging pederin common core, we recently reported[3] a novel synthesis of 2-(*N*-acylaminal)-substituted tetrahydro-

(1) (a) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951 and references cited therein. (b) Pettit, G. R.; Xu, J. P.; Chapuis, J. C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149.

(2) Total synthesis, see: (a) Jiang, X.; Garcia-Fortanet, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254 and references cited therein. Formal total synthesis, see: (b) Ning, S.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093. Fragment syntheses, see: (c) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 5175. (d) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 4117. (e) Kiren, S.; Williams, L. J. *Org. Lett.* **2005**, *7*, 2905. Analogue synthesis, see: (f) Jiang, X.; Williams, N.; De Brabander, J. K. *Org. Lett.* **2007**, *9*, 227.

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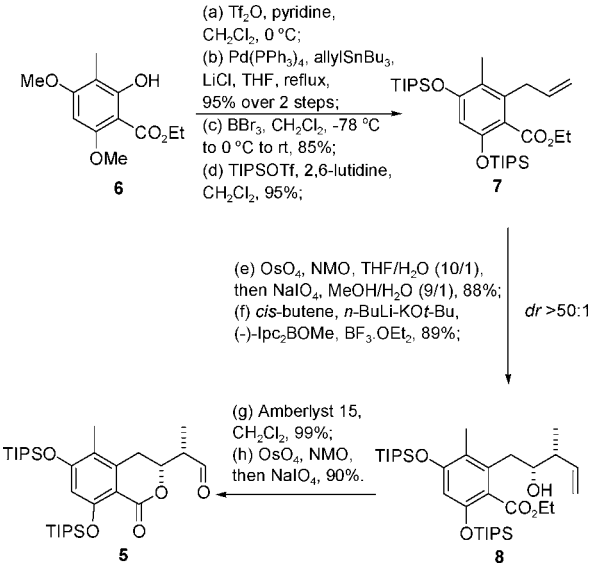
pyrans from enamides using $PhI(OAc)_2$ as an oxidant. Herein, we present a convergent total synthesis of psymberin using this new methodology.

According to our retrosynthetic analysis (Scheme 1), the core α-cyclic-oxy *N*-acyl aminal portion would be obtained from *N*-acyl enamine **2** through the use of the $PhI(OAc)_2$-mediated oxidative cyclization reaction. Enamide **2** potentially would be synthesized from **3**, **4**, and **5** through a CuI-mediated coupling reaction to form the N_7-C_8 bond and a substrate-controlled Mukaiyama aldol reaction to connect $C_{14}-C_{15}$.

Our synthesis started with the preparation of **5** (Scheme 2). Compound **6**[4] was converted to **7** through triflate

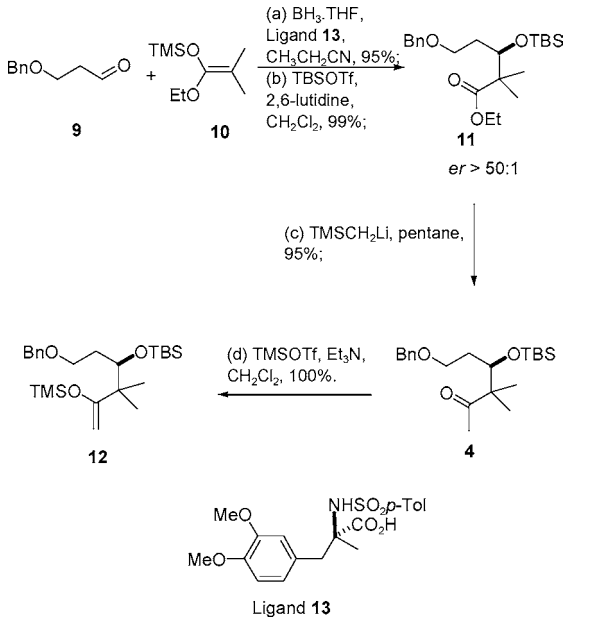
Scheme 2. Synthesis of the Dihydroisocoumarin Unit



formation, allylation, deprotection of the phenolic methyl groups, and protection of the diphenol with TIPS groups. Alkene **7** was treated with $OsO_4/NaIO_4$ followed by a classical Brown crotylation reaction[5] to provide *syn*-**8** with excellent diastereoselectivity (dr > 50:1) and 90% ee, which was determined by chiral OD HPLC. Hydroxyester **8** was converted to **5** through lactone formation in the presence of acid and cleavage of the double bond. In this route, aldehyde **5** was synthesized from **6** in 8 steps (53% overall yield) with excellent diastereoselectivity and good enantioselectivity.

The central linker **4** was quickly synthesized in 89% overall yield in 3 steps from the commercially available aldehyde **9** (Scheme 3). A highly enantioselective Masamune aldol condensation between **9** and **10** gave the secondary alcohol as a single enantiomer (er > 50:1) by Mosher ester analysis with the desired *R*-configuration,[6] which was subsequently protected with a TBS group to give **11**. Treatment

Scheme 3. Synthesis of Ketone **4**



of **11** with $TMSCH_2Li$ in pentane[7] gave ketone **4** in a single operation and was converted to enol ether **12** by treatment with TMSOTf/Et_3N.

For the unsaturated acyclic side chain (Scheme 4), **3**[8] was initially designed to be used as the building block; however, we later found out that the alkene interfered with our $PhI(OAc)_2$-mediated oxidative cyclization reaction. We then proceeded with the synthesis of **17**[9] in which the double bond was temporarily masked. Regioselective epoxide opening of **14** with isopropenylmagnesium bromide gave a secondary alcohol that was protected as a methyl ether with Me_3OBF_4 to give **15**. Ether **15** was converted to **16** in 4 steps via hydroboration, benzylation, deprotection of the TBS group, and Swern oxidation. Aldehyde **16** underwent cyanohydrin formation (dr = 2:1), and the free alcohol was protected as a TPS ether. The nitrile group was hydrolyzed under very mild conditions[10] to give amide **17** (isomers were easily separated at this step). To this point, side chain **17** was prepared in an overall 27% yield in 9 steps.

With all three subunits in hand, we proceeded to complete the synthesis (Scheme 5). A substrate-controlled aldol reaction[11,2c] between **5** and **12** gave ketone **18** in good yield (76% as pure isomer (for two isomers: 91%, dr = 5:1)). Chelation-controlled reduction[12] of ketone **18** provided a

(3) Huang, X.; Shao, N.; Palani, A.; Aslanian, R. *Tetrahedron Lett.* **2007**, *48*, 1967.

(4) **6** was prepared from commercially available 2,4,6-trimethoxytoluene in two steps in 46% yield according to literature procedure. Solladie, G.; Gehrold, N.; Maignan, J. *Tetrahedron*: *Asymmetry* **1999**, *10*, 2739.

(5) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(6) Parmee, E. R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365.

(7) Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000**, *65*, 7456.

(8) Although we did not proceed with compound **3** for the total synthesis, it was prepared efficiently from **14** in 7 steps (Scheme 4) and served as a vehicle to determine the correct sterochemistry at C_5 by spectrum comparison with the psymberin side chain.[2d,e]

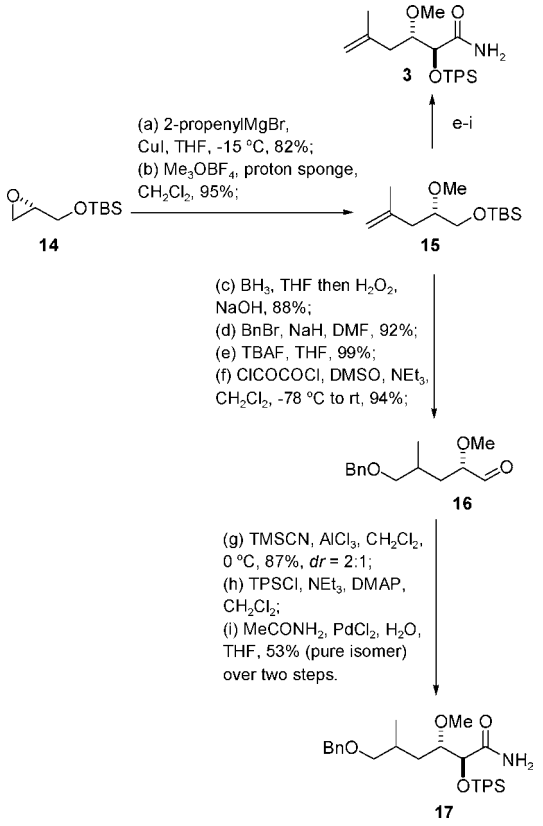
(9) All compounds containing this side chain were a 1:1 mixture of two isomers (*R*, *S*) at C_2 except when otherwise indicated.

(10) Maffioli, S. I.; Marzorati, E.; Marazzi, A. *Org. Lett.* **2005**, *7*, 5237.

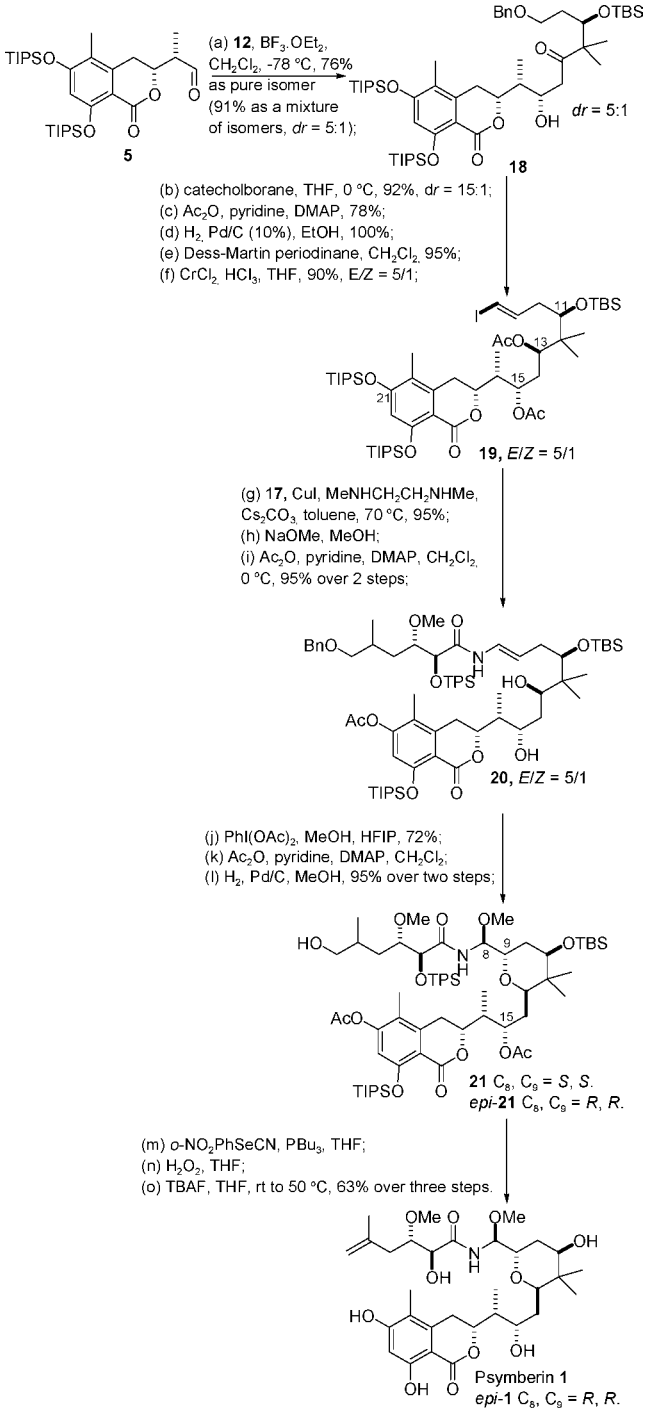
(11) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840 and references cited therein.

(12) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.

Scheme 4. Synthesis of the Acyclic Side Chain



Scheme 5. Completion of the Total Synthesis



secondary alcohol at C_{13} with excellent diastereoselectivity (dr = 15:1),[13] which was transformed to **19** (*E*/*Z* = 5/1) via bis-acetylation at C_{13} and C_{15}, de-benzylation, Dess-Martin oxidation, and Takai vinyl iodide formation.[14] Enamide **20** (*E*/*Z* = 5/1)[15] was synthesized from **19** in three operations: (1) coupling of **19** with **17** by using CuI[16] to give protected *N*-acyl enamine, (2) removal of the C_{13}, C_{15} acetate and O_{21} TIPS groups with NaOMe/MeOH, and (3) selective acetylation of O_{21}. As expected, enamide **20** cyclized slowly but smoothly with use of the $PhI(OAc)_2$-mediated cyclization reaction[3] to give a total of 72% yield of isolated products (60% of two major pairs of diastereomers and 12% of other possible isomers). The major two pairs of diastereomers (30% isolated yield each, C_8, C_9 = *S*, *S* and C_8, C_9 = *R*, *R*[17]) were separately acetylated at C_{15} and debenzylated to give alcohols **21** and *epi*-**21**. The C_1 terminal double bond was revealed by converting **21** and *epi*-**21** to the *o*-nitrophenyl selenide followed by treatment with H_2O_2 at 50 °C.[18] Upon treatment with TBAF at 50 °C, a global deprotection was realized to give the final products **1** and *epi*-**1**. The spectral data (^1H, ^{13}C, optical rotation, MS) of synthetic **1** matched exactly with those reported of natural psymberin.[1,2a]

In conclusion, our novel $PhI(OAc)_2$-mediated oxidative cyclization method[3] was successfully applied to the total synthesis of psymberin, and this further confirmed the assignment of the configuration at C_4.[2a] The synthesis was

(13) Relative stereochemistry at C_{11}, C_{13}, and C_{15} was determined by preparing the C_{11}, C_{13} acetonide and the C_{13}, C_{15} acetonide from the corresponding hydroxy derivatives of **18**.

(14) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(15) It is not necessary to separate the *E* and *Z* isomers since they work equally well in the oxidative cyclization reaction. See ref 3.

(16) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

(17) The *R*,*R* stereochemistry at C_8, C_9 was assigned by using COSY, NOESY, HSQC, and HMBC experiments with the final product *epi*-**1**, see the Supporting Information.

(18) Grieco, P. A.; Takigawa, T.; Schillinger, W. J. *J. Org. Chem.* **1980**, *45*, 2247.

executed in a convergent manner by preparing building blocks **4**, **5**, and **17**. The longest linear sequence of this synthesis is 22 steps starting from the known phenol **6**. This practical oxidative cyclization can be applied to the synthesis of other pederin family natural products as well as analogues of psymberin, and will be reported in due course.

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Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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