ORGANIC LETTERS

2007
Vol. 9, No. 13
2597−2600

The Total Synthesis of Psymberin

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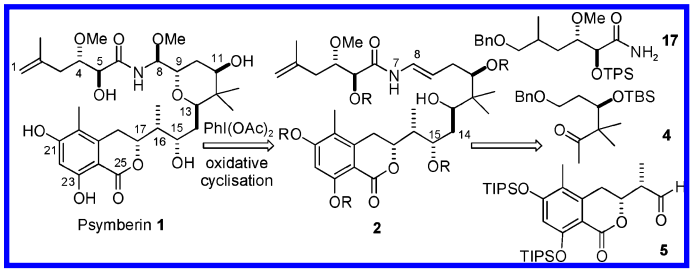
Received May 11, 2007

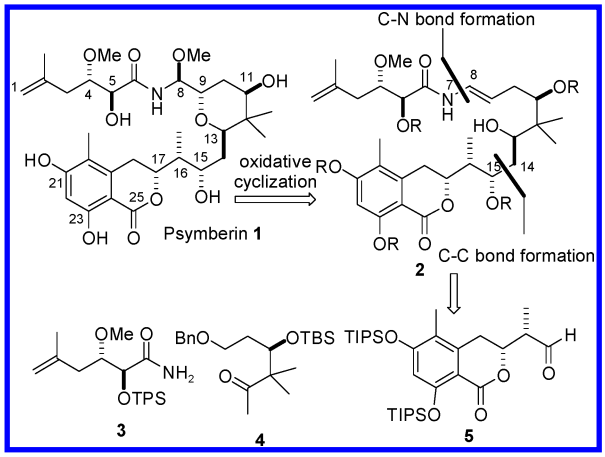
ABSTRACT



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.

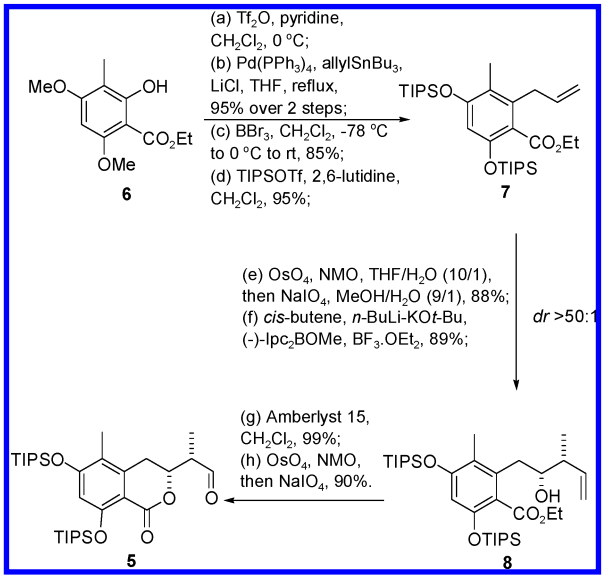
10.1021/ol071068n CCC: $37.00
Published on Web 05/25/2007

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

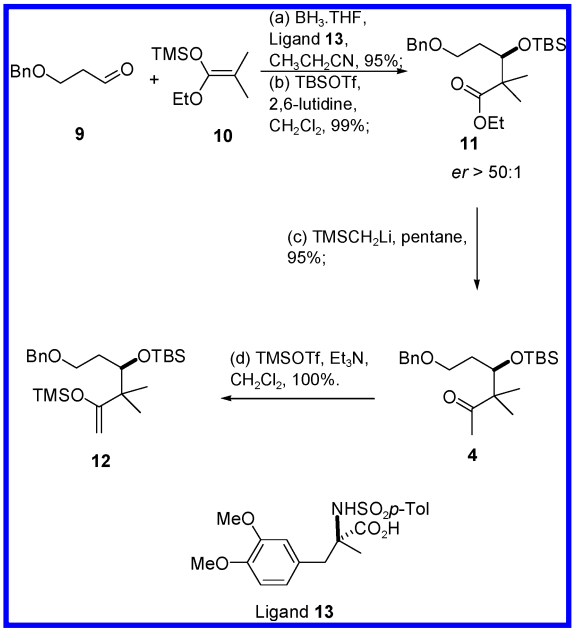
Scheme 2. Synthesis of the Dihydroisocoumarin Unit



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]

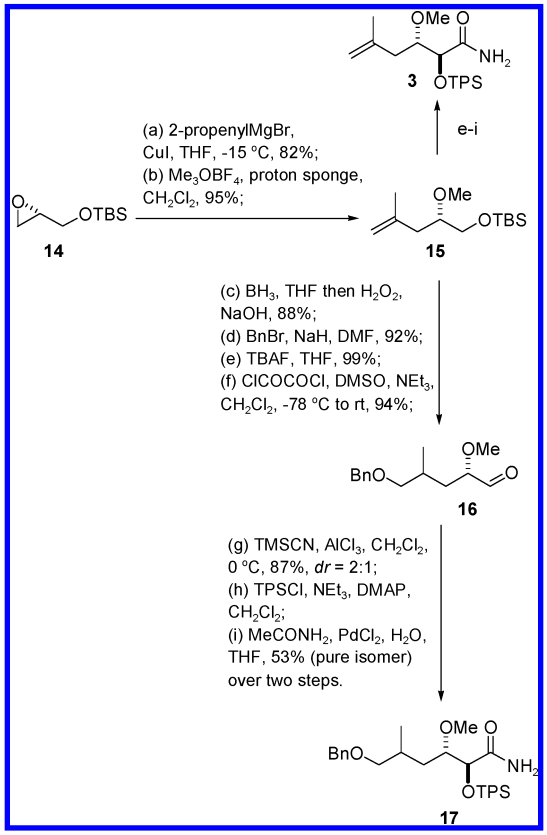
(9) All compounds containing this side chain were a 1:1 mixture of two isomers (*R*, *S*) at C_2 except when otherwise indicated.

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

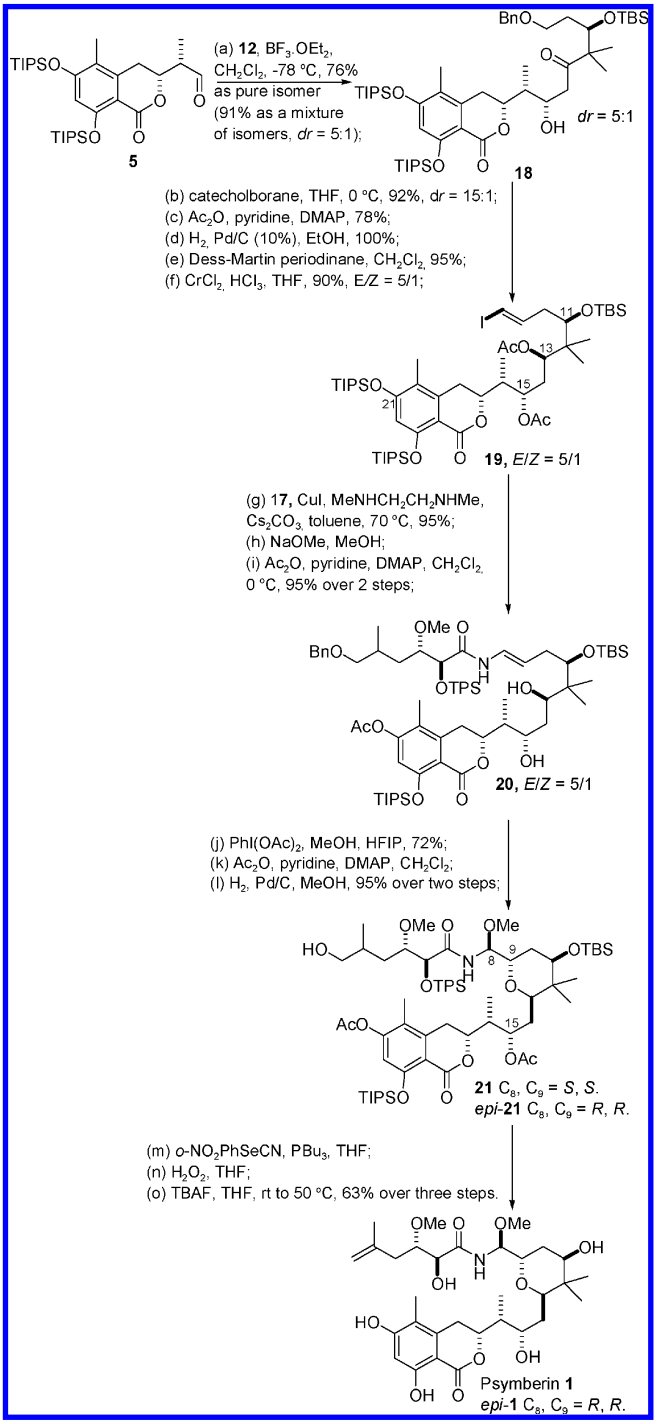
(11) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840 and references cited therein.

(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 (^{1}H, ^{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.

Acknowledgment. We thank Dr. Craig Boyle at SPRI for proofreading our manuscript and Drs. Catherine Strader, John Piwinski, and Satwant Narula at Schering-Plough Research Institute (SPRI) for their strong support of the postdoctoral program.

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.

OL071068N