Formal Total Synthesis of Benzylpedamide: The Right Half of (+)-Pederin

Degang Liu, Jijun Xue, Zhixiang Xie, Liping Wei, Xianshu Zhang, Ying Li*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. of China
Fax +86(931)8912582; E-mail: liying@lzu.edu.cn

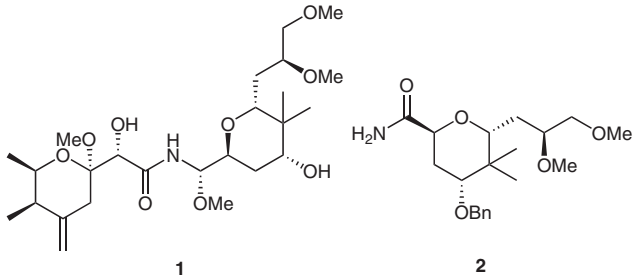
Received 5 February 2008

Abstract: The right half of (+)-pederin was synthesized through a convenient and efficient asymmetric synthesis in 14 steps with 8.3% overall yield. The key step was an iodine-induced heterocyclization to construct the pyran ring. The chiral centers were constructed separately via asymmetric allylation, substrate-controlled diastereoselective reactions, and Sharpless asymmetric dihydroxylation.

Key words: synthesis, pedamide, pederin

The pederin family of natural products, consisting of at least 36 structurally related compounds,[1] is an interesting class of compounds due to their potent cytotoxic activities. For example, pederin (**1**), is an effective insect toxin isolated from *Paederus fuscipes*.[2] It can inhibit mitosis in Hela cells and block protein and DNA biosynthesis, and can act as an antitumor and antiviral agent.[3] The pederin family compounds, except psymberin, have almost an identical tetrahydropyran ring on the left half, but a structurally different tetrahydropyran ring on the right hand side (Figure 1). The two tetrahydropyran rings are bridged by an *N*-acyl aminal linker. The structural similarities between psymberin and other pederin natural compounds have been noted.[4]

Because of their unique structures and unusual biological activities, these compounds are important and interesting synthesis targets. The syntheses towards these compounds had been reported by many researchers[5–9] before. The main contributors are Matsumoto,[6] Nakata,[7] Kocienski,[8] and Rawal[9] and their co-workers. Most of these reported works are focused on the synthesis of the different right molecular segments. Among these various fragments, pedamide[6c] and its analogues[8e,9b] have been adopted as key building blocks in all subsequent syntheses of pederin since Matsumoto et al. reported their seminal work in 1988.[6a] The major synthetic challenge of pedamide is to construct the pyran ring with three chiral centers stereoselectively. We found that iodine-induced heterocyclization was useful for the asymmetric construction of pyran ring. Based on this, a new asymmetric synthesis of optically pure benzylpedamide (**2**) was developed, in which the chiral centers were constructed from asymmetric allylation, substrate-controlled diastereoselective reactions, and Sharpless asymmetric dihydroxylation.



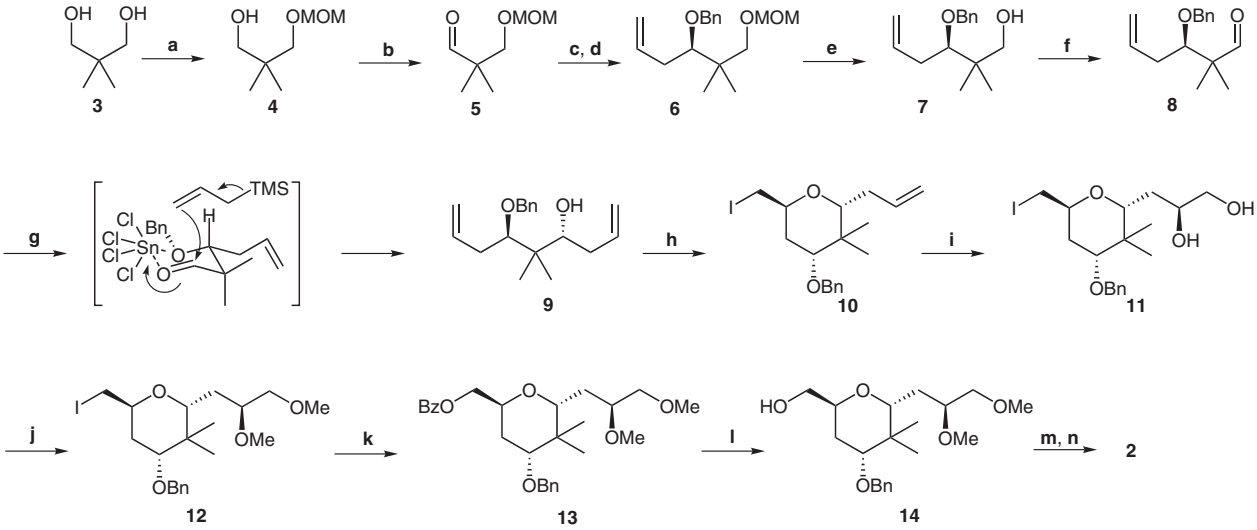
1 2

Figure 1

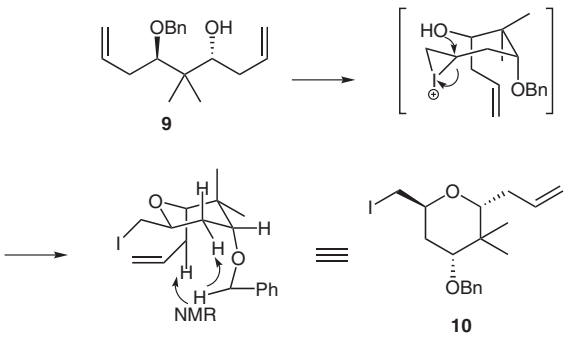
The synthesis started from 2,2-dimethylpropane-1,3-diol (**3**), which was converted into monoprotected alcohol **4** in 85% yield using a published procedure (Scheme 1).[10] The corresponding aldehyde **5** was subsequently obtained in 99% yield by Swern oxidation of **4**. Asymmetric allylation of **5** using Brown's chiral allylborane[11] gave the homoallylic alcohol in 80% ee. However, it was difficult to separate the product from isopinocampheol, the byproduct coming from Brown's borane reagent. Without further purification, therefore, the mixture was treated with BnCl and sodium *tert*-amyloxide (*t*-AmONa) to give ether **6**, which could be separated by column chromatography in 70% yield in two steps. Deprotection of the MOM group in **6** under acidic conditions, followed by Swern oxidation gave aldehyde **8**. Lewis acid mediated diastereoselective allylation of **8** proceeding under $SnCl_4$ chelation[12] control formed a pair of diastereomers in a ratio of 2:1, which were easily separated by column chromatography to give **9** in 39% yield.[13] The configuration of the newly formed chiral center was controlled by the configuration of substrate **8**. In a parallel experiment, reagent-controlled diastereoselective allylation[11] of **8** with Brown's chiral allylborane was carried out. It gave a much lower conversion (about 4%) and a poorer diastereomeric ratio (about 1.4:1). The substrate may be too bulky for Brown's allylborane to chelate.

Treating compound **9** with 1.5 equivalents of I_2 and 1.5 equivalents of $NaHCO_3$ under heterogeneous conditions at 0 °C gave the desired pyran **10** in 87% yield and its epimer in 11% yield.[14] The diastereomers were separated by column chromatography. The diastereoselectivity was controlled by substrate and the addition to the C=C bond was *anti*.[15] The relative configuration of the newly formed chiral center was confirmed by NMR analysis (Scheme 2). This is the first case using iodine to induce the heterocyclization in the synthesis of pederin compounds, although heterocyclization has been reported in the synthesis of this kind of compounds.[5d,f,6d,9c]

SYNLETT 2008, No. 10, pp 1526–1528
Advanced online publication: 16.05.2008
DOI: 10.1055/s-2008-1077788; Art ID: W02708ST



Scheme 1 *Reagents and conditions:* (a) MOMCl, NaH, THF, r.t., 3 h, 85%; (b) DMSO, oxalyl chloride, CH_2Cl_2, –78 °C, 1 h, 99%; (c) (+)-B-allyldiisopinocampheylborane, Et_2O, –95 °C, 80% ee; (d) BnCl, *t*-AmONa, DMSO, r.t., 70% (two steps); (e) HCl (3 M, aq), MeOH, reflux, 3 h, 97%; (f) DMSO, oxalyl chloride, CH_2Cl_2, –78 °C, 1 h, 99%; (g) $SnCl_4$, allyl trimethylsilane, CH_2Cl_2, –78 °C, 4 h, 58%, dr = 2:1; (h) I_2, $NaHCO_3$, Et_2O, H_2O, 0 °C, 8 h, 98%, dr = 8:1; (i) AD-mix-α, $MeSO_2NH_2$, $NaHCO_3$, *t*-BuOH, H_2O, 0 °C, 12 h, 96%, dr = 1.6:1; (j) MeI, NaH, DMF, r.t., 1 h, 98%; (k) BzONa, NMP, 100 °C, 6 h, 93%; (l) K_2CO_3, MeOH, r.t., 4 h, 98%; (m) CrO_3, H_2SO_4, acetone, 0 °C, 2 h; (n) PyBOP, HOBt, DIPEA, NH_4Cl, DMF, r.t., 1.5 h, 83% (two steps).



Scheme 2 Mechanism of cyclization and configuration assurance of product

The last chiral center was constructed from Sharpless asymmetric dihydroxylation.[7f,16] The terminal olefin **10** was treated with commercially available AD-mix-α to form a pair of diastereomers in 96% yield with a diastereomeric ratio of 1.6:1. The major epimer was the desired one and was purified by column chromatography. The configuration of the newly formed chiral center was controlled by the dihydroxylation reagent. The dihydroxylation increased the enantiomeric purity of the product because it transformed most of the enantiomer of **10** into a chromatographically separable diastereomer of **11**. Subsequent dimethylation converted diol **11** into ether **12** in 98% yield without affecting the iodide part at all. The last difficult part of this synthesis was to convert iodide **12** into alcohol **14**. We tried several oxidative and nucleophilic substitution conditions,[17] but all of them failed. Finally, iodide **12** was treated with BzONa in NMP according to the literature[14b] and gave ester **13** smoothly in 93% yield. Removal of the benzoyl group in ester **13** under basic conditions gave **14** in 98% yield. Jones' oxidation of alcohol **14** followed by benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP)–*N*-hydroxybenzotriazole (HOBt)-mediated amidation[7f,18] with NH_4Cl gave the desired benzylpedamide (**2**), the right half of pederin, in 83% yield over two steps.

In conclusion, an efficient and convenient method for the asymmetric synthesis of benzylpedamide (**2**), the right half of bioactive (+)-pederin (**1**), was developed in 14 steps with more than 8% overall yield. The key step is the diastereoselective iodine-induced hetereocyclization. This is a new method for the synthesis of pedamide and will find wide application for the synthesis of similar compounds.

Acknowledgment

We thank the National Natural Science Foundation of China for financial support (Project 20672050).

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