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Facile Enantiodivergent Approach to 5-Hydroxy-5,6-dihydro-2(1*H*)-pyridones. First Total Synthesis of Both Enantiomers of Pipermethystine†

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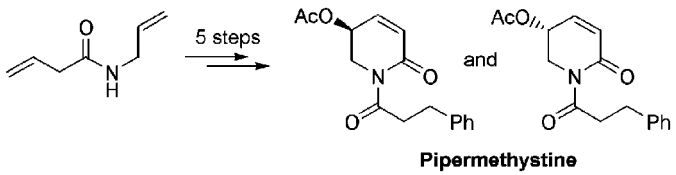
ABSTRACT



A novel enantiodivergent approach to 5-hydroxy-5,6-dihydro-2(1*H*)-pyridones using a ring closing metathesis and a lipase-mediated kinetic resolution as key steps is described and applied to the first synthesis of both enantiomers of pipermethystine.

The 2(1*H*)-pyridone ring system and the corresponding dihydro and tetrahydro derivatives possess structural features found in a wide variety of naturally occurring alkaloids[1] and novel synthetic biologically active molecules.[2] These molecules also have considerable potential in organic synthesis. They are valuable intermediates for the preparation of quinoline[3] and isoquinoline[4] derivatives and indolizidine[5] and quinolizidine[5a] alkaloids with pharmaceutical activity. They are also useful for the preparation of substituted piperidines,[1b] including polyhydroxylated piperidines (azasugars).[6]

There are few methods for preparing chiral nonracemic 5-oxygenated 5,6-dihydro-2(1*H*)-pyridones (**1**, Figure 1),[7]

Figure 1.

and these typically require a large number of synthetic steps, starting from the chiral pool. For example, the best synthesis of a protected 5-hydroxy-5,6-dihydro-2(1*H*)-pyridone described so far utilizes L-glutamic acid as a starting material and requires five steps to prepare the 5(*S*)-5-hydroxy-2-piperidone.[8] Another four steps are needed for selective

† Dedicated to the memory of Professor Jesus H. Rodriquez.

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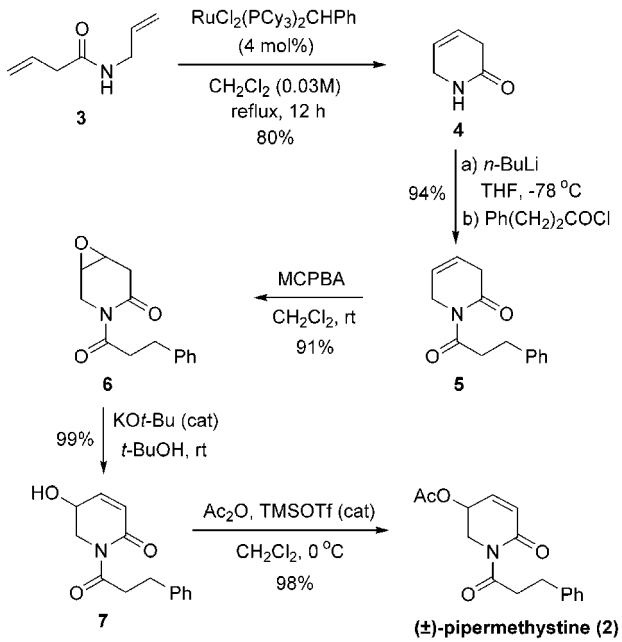
protection of oxygen and nitrogen functionalities and the introduction of the unsaturation at C-3.[4,9] The lack of general and efficient methods for the preparation of such systems is exemplified by the fact that, despite its apparent simple structure, no synthesis of the natural alkaloid pipermethystine (**2**, Figure 1) has been reported since its isolation in 1979.[10] Pipermethystine is the major constituent of the leaves and a minor constituent of the stems of *Piper methysticum* (piperaceae), a large shrub indigenous to the islands of the South Pacific (e.g., Fiji). A ceremonial and social drink, known as kava, is prepared from the roots and stems of *Piper methysticum* and used to induce relaxation. Surprisingly, only two papers regarding the isolation and structure determination of pipermethystine have been reported, but no further information about its absolute configuration or biological properties has been provided.

Associated with our interest in chiral, nonracemic pyridinylmolybdenum complexes as enantiomeric scaffolds for heterocycle synthesis,[11] we have investigated a novel enantiodivergent route to enantiopure 5-hydroxy-5,6-dihydro-2(1*H*)-pyridones starting from acyclic *N*-allyl-3-butenamide (**3**) (Scheme 1), which is easily prepared from commercially available 3-butenoic acid and allylamine.[12]

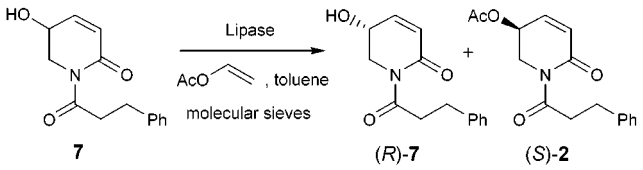
Scheme 1



The ring closing metathesis of **3** using a catalytic amount of Grubbs's ruthenium catalyst $RuCl_2(PCy_3)_2$=CHPh (4 mol %, CH_2Cl_2, reflux)[13] provided the 3,5-dihydro-2(1*H*)-pyridone, **4**, in 80% yield (Scheme 1). Subsequent protection of the secondary amido group with hydrocinnamoyl chloride provided the corresponding imide **5** in 94% yield. The corresponding allylic alcohol **7** was prepared by epoxidation of **5** with MCPBA (CH_2Cl_2, rt, 91%) followed by treatment of the resulting epoxide **6** with a catalytic amount of KO*t*-Bu (*t*-BuOH, room temperature, 99%). Interestingly, both steps can be achieved without chromatographic purification. Compound **6** is apparently base-sensitive since larger amounts of base or longer reaction times resulted in partial migration of the phenethylcarbonyl group from the nitrogen to the oxygen. Standard base-promoted acetylation of **7** afforded a complex mixture of products. However, acetylation of **7** was achieved under acidic conditions [Ac_2O, TMSOTf (cat.), CH_2Cl_2, 0 °C, 98%][14] to provide racemic pipermethystine, **2**, in almost quantitative yield without the need of chromatographic purification (66% overall yield for five steps).

For the enantiodivergent preparation of either antipode of the natural alkaloid in high enantiopurity, a lipase-catalyzed enantioselective acetylation of racemic alcohol **7** was envisaged.[15] Four commercially available lipases[16] were screened for activity and stereoselectivity in a transesterification with vinyl acetate as acetylating reagent and toluene as solvent. The results are shown in Table 1.

Table 1. Enantioselective Transesterification of (±)-**7**



			(*R*)-**7**		(*S*)-**2**	
entry	lipase	time[a]	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]
1	R[d]	–	–	–	–	–
2	PS	5.5 h	47	87	48	79
3	AK	1.5 h	47	82	47	94
4	PPL	17 h	46	88	47	>99.5
5	PPL	4 d	47	>99.5	48	>99.5
6	PPL	11 d	46	>99.5	47	>99.5

[a] Time for reaching 50% conversion (measured by NMR). [b] Yield of pure product after chromatography. [c] Determined by chiral column HPLC. [d] (±)-**7** was recovered in 99% yield after 5 days.

All enzymes except for lipase R showed good activity toward substrate **7**. Lipases AK and PS displayed a high

(6) For the synthesis of 3,4,5-trihydroxylated 2-piperidones, see: (a) Piró, J.; Rubiralta, M.; Giralt, E.; Diez, A. *Tetrahedron Lett.* **1999**, *40*, 4865. (b) Defoin, A.; Sarazin, H.; Sifferlen, T.; Strehler, C.; Streith, J. *Helv. Chim. Acta* **1998**, *81*, 1417. (c) Bouchez, V.; Stasik, I.; Beaupère, D.; Uzan, R. *Tetrahedron Lett.* **1997**, *38*, 7733. (d) Norris, P.; Horton, D.; Levine, B. R. *Tetrahedron Lett.* **1995**, *43*, 7811. For the synthesis and inhibitory activity of 3,4,5-trihydroxypiperidines, see: (e) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007.

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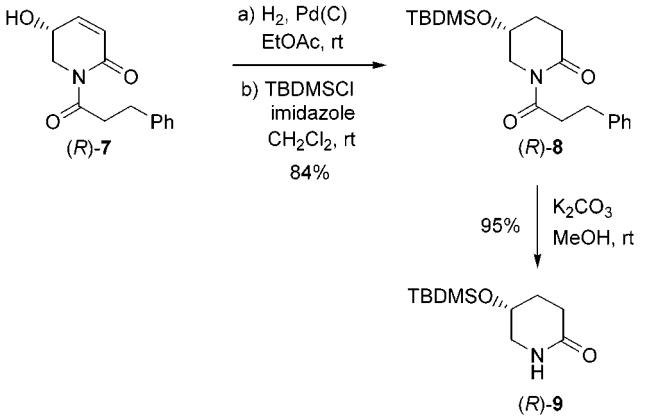
(10) (a) Smith, R. *Tetrahedron* **1979**, *35*, 437. See also: (b) Smith, R. *Phytochemistry* **1983**, *22*, 1055.

activity but only moderate selectivities; 50% conversion[17] was reached after 1.5 and 5.5 h, respectively (Table 1, entries 2 and 3). In contrast, excellent enantioselectivity was achieved using lipase PPL (entries 4−6). Lipase PPL (25 mg/mL) catalyzed in 17 h the enantioselective acetylation of **7** by vinyl acetate (5.0 equiv) in toluene (0.05 M) at room temperature. The presence in the reaction mixture of molecular sieves was essential to reach 50% conversion.[18] The resulting acetate (*S*)-**2** and the unreacted alcohol (*R*)-**7** were readily separated by flash chromatography and obtained in 47% and 46% yields, respectively. While (*S*)-**2** showed an excellent enantiomeric purity (ee > 99.5%),[19] (*R*)-**7** was obtained in only 88% ee[20] (entry 4). However, after 4 days of reaction lipase PPL catalyzed the complete acetylation of the (*S*)-enantiomer of **7** without affecting (*R*)-**7**, providing both (*S*)-**2** and (*R*)-**7** with ee > 99.5% (entry 5). As a dramatic example of the specificity of lipase PPL for (*S*)-**7** as a substrate, no acetylation of (*R*)-**7** was detected even after 11 days of reaction (entry 6). This remarkable selectivity and its associated high enantiomeric purity suggest that this lipase-mediated resolution could be applied to a wide range of 5-hydroxy-5,6-dihydro-2-pyridones.

The antipode (*R*)-**2**, was prepared with >99.5% ee by acetylation of (*R*)-**7** under the same conditions used previously for (±)-**7**. To date, this five-step approach constitutes the first total synthesis of both enantiomers of pipermethystine, as well as the shortest synthesis of a 5-oxygenated 5,6-dihydro-2(1*H*)-pyridone. The catalytic nature of the two key operations (ring closing metathesis and lipase-mediated resolution) lends the sequence to easy scale-up.

The absolute configuration of the enantiomerically pure alcohol (*R*)-**7** was determined by chemical correlation to the known 2-piperidone (*R*)-**9**.[21] *tert*-Butyldimethylsilyl ether (*R*)-**8** was readily obtained by hydrogenation of the double bond and protection of the hydroxyl group of (*R*)-**7**. Finally, *N*-deprotection of (*R*)-**8** (K_2CO_3, MeOH, room temperature) afforded cleanly (*R*)-**9** in 95% yield (Scheme 2).

Scheme 2



In summary, a highly efficient and stereodivergent methodology based on ring closing metathesis and lipase-mediated kinetic resolution has been described for the synthesis of 5-hydroxy-5,6-dihydro-2(1*H*)-pyridones of high enantiopurity (ee > 99.5%). This method has been applied to the synthesis of both enantiomers of pipermethystine, each one obtained in about 32% overall yield through a five-step sequence. The process described herein should prove generally useful for the enantiocontrolled construction of a variety of materials derived from 5-hydroxy-5,6-dihydro-2(1*H*)-pyridones.

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Supporting Information Available: A complete description of the synthesis, characterization data, and copies of proton and carbon NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Conversion measured by proton NMR.

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(19) Enantiopurity of (*S*)- and (*R*)-**2** was measured by chiral column HPLC (Daicel Chiracel AD, see Supporting Information for details).

(20) Enantiopurity of (*R*)-**7** was determined by HPLC after its transformation into (*R*)-**2**.

(21) Although, (*R*)-**9** is known, its optical rotation value has not been reported: (a) Honda, T.; Ishikawa, F. *Chem. Commun*. **1999**, 1065. However, the optical rotation for (*R*)-**9** {$[\alpha]_D$ +12.5 (*c* 1.0, MeOH)} was opposite to that described for (*S*)-**9** {$[\alpha]_D$ −12.1 (*c* 2.0, MeOH), see ref 4}. For other syntheses of (*S*)-**9**, see (b) Herdeis, C.; Heller, E. *Tetrahedron: Asymmetry* **1993**, *4*, 2085. (c) Reddy, P. N.; Han, S.-S.; Chung, K.-H. *Bull. Korean Chem. Soc*. **1998**, *19*, 617.