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Asymmetric Synthesis of the Alkaloid 2,6-Disubstituted Piperidin-3-ols, (-)-Cassine and (+)-Spectaline

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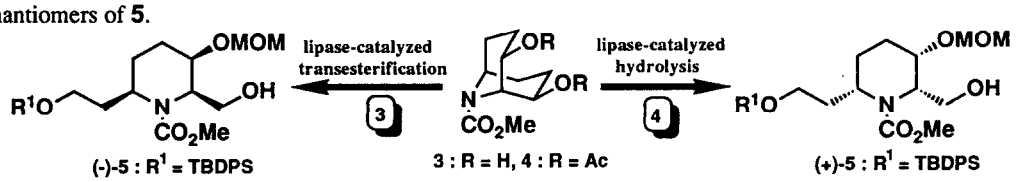
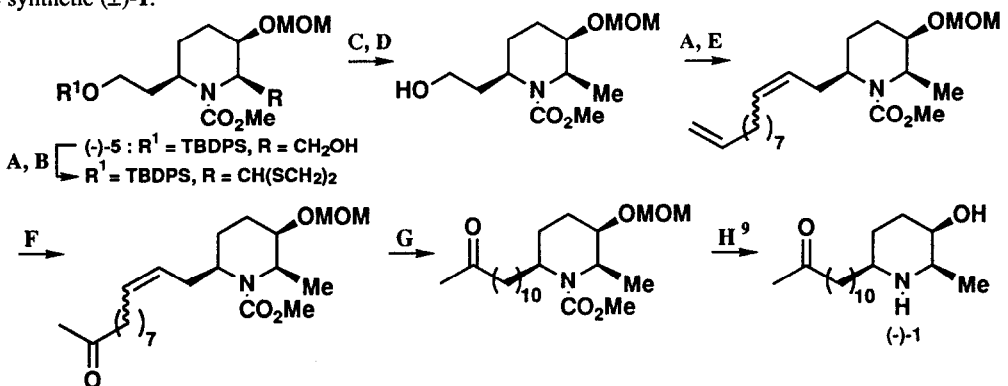
Abstract: The asymmetric total synthesis of (-)-cassine (**1**) and (+)-spectaline (**2**) was achieved by starting with both enantiomers of the homochiral 3-oxygenated 2,6-*cis*-disubstituted piperidine **3**.

A number of the 2,6-disubstituted piperidin-3-ols have been found in *Cassia* or *Prosopis* species,[1] and many of these alkaloids possess interesting pharmacological properties.[2] Although a few chiral syntheses of the piperidin-3-ol alkaloid starting with L-serine[3] or D-glucose[4] have been reported, none of the asymmetric synthesis has yet been reported to date. Recently, we have reported the asymmetric synthesis of both enantiomers of the homochiral 3-oxygenated 2,6-*cis*-disubstituted piperidine **5** based on the lipase-catalyzed transesterification or hydrolysis of the *meso* glycol (**3**) or its diacetate (**4**).[5] In this communication, we describe the first asymmetric synthesis of (-)-cassine (**1**)[6] and (+)-spectaline (**2**)[7] starting with both enantiomers of **5**.

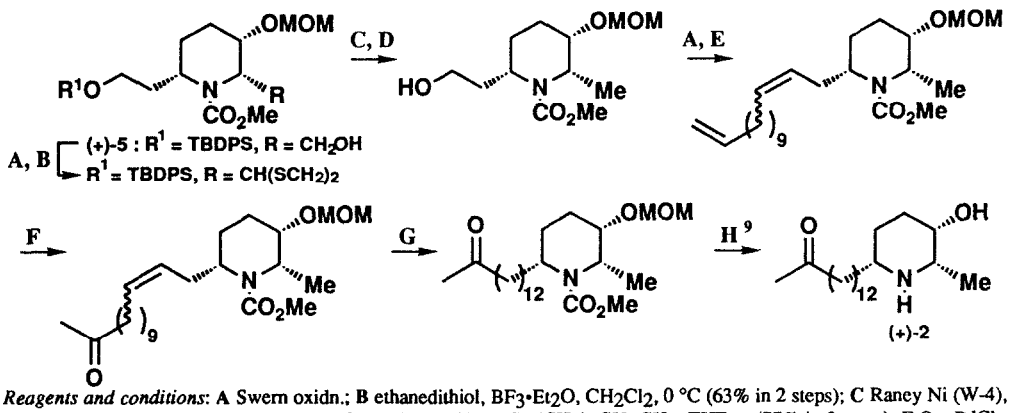


First, we examined the synthesis of (-)-**1** as shown below.[8] The synthetic (-)-**1** {mp 55~57 °C, $[\alpha]_D^{26}$ -0.7 (*c* 0.59, EtOH)} was in accordance with the natural cassine in its physical properties {mp 57~58.5 °C, $[\alpha]_D^{25}$ -0.6 (*c* 8.0, EtOH)}[6a] and possessed the spectral properties (^{1}H and ^{13}C NMR) identical with those of the synthetic (±)-**1**.[6d]



Reagents and conditions: **A** Swern oxidn.; **B** ethanedithiol, BF_3•Et_2O, CH_2Cl_2, 0 °C (63% in 2 steps); **C** Raney Ni (W-4), EtOH, reflux; **D** TBAF, THF, rt (90% in 2 steps); **E** $(Ph)_3P$=$CH(CH_2)_7CH$=CH_2, THF, rt (86% in 2 steps); **F** O_2, $PdCl_2$, CuCl, DMF-H_2O (70%); **G** H_2, 5% Pd/C, MeOH (92%); **H** TMSI, $CHCl_3$, reflux (65%)

Next, we examined the synthesis of (+)-**2** as shown below.[8] The synthetic (+)-**2** {mp 59~61 °C, $[\alpha]_D^{26}$ +9.0 (*c* 1.30, $CHCl_3$)} was in accordance with the natural product in its physical properties including NMR data {$[\alpha]_D^{25}$ +8.0 (*c* 0.27, $CHCl_3$)}[7a] and was identical in its ^1H and ^{13}C NMR data with the synthetic (±)-**2**.[6d]



Reagents and conditions: **A** Swern oxidn.; **B** ethanedithiol, BF_3•Et_2O, CH_2Cl_2, 0 °C (63% in 2 steps); **C** Raney Ni (W-4), EtOH, reflux; **D** TBAF, THF, rt (90% in 2 steps); **E** $(Ph)_3P{=}CH(CH_2)_9CH{=}CH_2$, THF, rt (77% in 2 steps); **F** O_2, $PdCl_2$, CuCl, DMF-H_2O (70%); **G** H_2, 5% Pd/C, MeOH (92%); **H** TMSI, $CHCl_3$, reflux (65%)

In conclusion, we demonstrated the utility of the piperidine **5** as a chiral building block for the synthesis of 3-piperidinol alkaloids and also as a key compound to determine the absolute configuration of this family of alkaloids.

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