# Total Synthesis of (−)-Ovalicine from L-Quebrachitol

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The first chiral synthesis of (−)-Ovalicine **1** from commercially available L-Quebrachitol in 16 steps and an overall yield of 3.5% is reported.

(−)-Ovalicine, a secondary metabolite similar in structure to the antitumour antibiotic Fumagillin, was first isolated from cultures of *Pseudorotium Ovalis* by Stolk.[1] The observed antibiotic, antitumour and immunosuppressive activities of (−)-**1** led Corey and Dittami to develop a total synthesis of racemic ovalicine from 2,4-dihydroxybenzoic acid.[2]

Here we describe the first chiral synthesis of (−)-Ovalicine **1**, using the naturally occurring optically active L-Quebrachitol as starting material.[3] This starting material, isolated from *Hevea brasiliensis*, was chosen as it contains a C-2 methoxy group, and has an absolute stereochemistry amenable for conversion into (−)-Ovalicine **1**.

L-Quebrachitol was transformed into L-3,4:5,6-di-O-cyclohexylidene-2-O-methyl-*chiro*-inositol using the literature method,[4] which on benzylation with benzyl bromide in DMF gave the fully protected compound **2** (90%). Selective removal of the less stable *trans* acetal was accomplished by trans-acetylation using ethylene glycol in dichloromethane in the presence of a catalytic quantity of *p*-TSA. The resulting diol **3** (70%) was then acetylated (98%), and acid cleavage of the remaining *cis* acetal gave the crystalline diol **4** (77%) {(mp 133 °C heptane, $[\alpha]_D^{25} = -55$ (*c* 1.42, $CH_2Cl_2$)}.

In order to effect a Corey–Winter *cis*-desoxygenation[5] **4** was first treated with thiophosgene in dichloromethane in the presence of 4-dimethylaminopyridine, and the resulting thiocarbonate was then heated at 120 °C in trimethylphosphite for 24 h. Cleavage of the acetate groups using ammonia in methanol then gave the olefin **5** (82% from **4**). Selective oxidation of the allylic hydroxy group of **5** was achieved using freshly prepared $MnO_2$ (from $MnCl_2$ and $KMnO_4$)[6] to give the α,β-unsaturated ketone **6** (50%) as an oil {$[\alpha]_D^{25} = -172$ (*c* 1.2 $CHCl_3$)}. Catalytic hydrogenation of **6** in ethanol in the presence of palladium gave the dihydroxycyclohexanone (85%) which was selectively benzoylated (94%) at the more reactive *alpha*-hydroxy group, and subsequently silylated to give the fully protected ketone **7** (97%).

To introduce the spirocyclic epoxide function, the ketone **7** was first treated with an excess of methyltriphenylphosphorane to give the exocyclic olefin **8** (70%) {$[\alpha]_D^{25} = -85$ (*c* 1.12, $CHCl_3$)}. Epoxidation of the olefin **8** with *meta*-chloroperbenzoic acid gave the *cis* spiro-epoxide **9** as the major product (84%) {$[\alpha]_D^{25} = -60$ (*c* 1.27, $CHCl_3$)} together with 10% of the *trans* isomer **9b**, {$[\alpha]_D^{25} = -22$ (*c* 0.62, $CHCl_3$)}. Swern oxidation[7] of **9** then gave the keto-epoxide **10** as an oil (88%) {$[\alpha]_D^{25} = -87$ (*c* 1.15, $CHCl_3$)}.

The side chain of (−)-ovalicine was introduced by a Shapiro reaction[8] between the ketone **10** and the vinyl lithium **11**, prepared *in situ* from 3,3-dimethylallyl bromide and acetone (2,4,6-triisopropylbenzene) sulphonylhydrazone.[9] The addition product **12** (75%) {$[\alpha]_D^{25} = -75$ (*c* 1, $CHCl_3$)} was then epoxidised by the method of Sharpless[10] using *tert*-butyl hydroperoxide in the presence of vanadium acetylacetonate to give a mixture of two bis-epoxides (72%), which could only be separated on silica gel after desilylation. The isomeric bis-epoxides **13** {$[\alpha]_D^{25} = -83$ (*c* 0.5, $CHCl_3$; lit −88 (*c* 0.45, $CHCl_3$)},[1b] and **14** {$[\alpha]_D^{25} = -69$ (*c* 0.75, $CHCl_3$)} were isolated in the ratio 65:35. The bis-epoxide **13** was then converted into (−)-ovalicine **1** (78%) {$[\alpha]_D^{25} = -115$ (*c* 0.5, $CHCl_3$; lit. −117 (*c* 0.4, $CHCl_3$)}[1†] by oxidation of the secondary alcohol to the corresponding ketone using pyridinium-dichromate.

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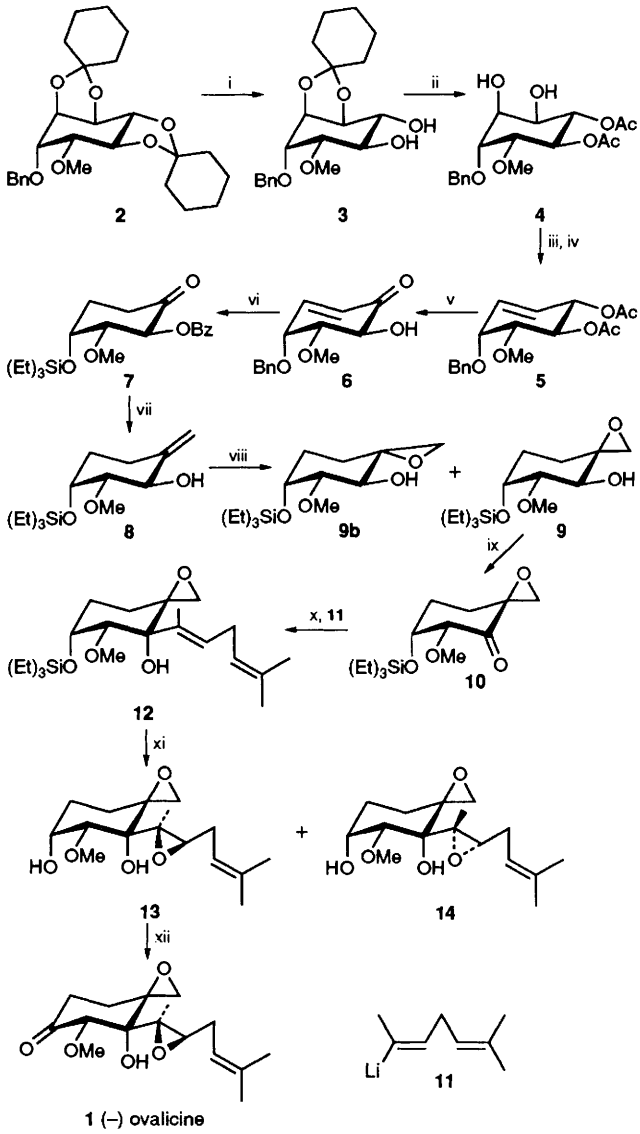
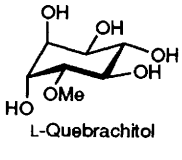



**Scheme 1** *Reagents and conditions*: i, $HOCH_2CH_2OH$, *p*-TSA, $CH_2Cl_2$; ii, (*a*) $(CH_3CO)_2O$, Py, (*b*) $CF_3COOH$, THF–$H_2O$; iii, (*a*) $CSCl_2$, DMAP, $CH_2Cl_2$, (*b*) $(CH_3O)_3P$; iv, $NH_3$, MeOH; v, $MnO_2$, $CH_2Cl_2$; vi, (*a*) $H_2$, Pd/C 10%, EtOH, (*b*) PhCOCl, Py, (*c*) $(Et)_3SiCl$, imidazole, DMF; vii, $Ph_3P{=}CH_2$, THF; viii, MCPBA, $CH_2Cl_2$; ix, DMSO, $(CF_3CO)_2O$, $CH_2Cl_2$; x, **11**, THF–Toluene −78 °C; xi, (*a*) $(acacO)_2VO$, $Bu^tOOH$, PhH, (*b*) TBAF, THF; xii, PDC, $CH_2Cl_2$




L-Quebrachitol

## Footnote

† *Selected spectroscopic data* for **1**: mp 90–92 °C (ether–pentane), lit.[1] 94–95 °C (ether–pentane) $^1$H NMR ($CDCl_3$): 5.18 (t, H-11, $J_{11,10}$ 7.5 Hz); 4.23 (s, 1H, H-2); 3.56 (s, 3H, OMe); 3.18 (br s, 1H, OH); 3.1 (d, 1H, H-7, $J_{7,7'}$ 4.2 Hz); 2.9 (t, 1H, H-9, $J_{9,10}$ 6.5 Hz); 2.73 (d, 1H, H-7′); 2.66–2.46 (m, 3H, H-6, H-6′, H-5); 2.43 (m, 1H, H-10, $J_{10,10'}$ 14.5 Hz, $J_{10,11}$ 7.5 Hz, $J_{10,9}$ 6.5 Hz); 2.15 (m, 1H, H-10′); 1.75 (s, 3H, Me-14); 1.66 (s, 3H, Me-13); 1.43 (m, 1H, H-5); (s, 3H, Me-15).

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