

Total Synthesis of (–)-Ovalicine from L-Quebrachitol

Sophie Bath,^a David C. Billington,^b Stephen D. Gero,^a Béatrice Quiclet-Sire*^a and Mohammad Samadi*^a^a Institut de Chimie des Substances Naturelles, C.N.R.S., 91198, Gif-sur-Yvette, Cedex, France^b Institut de Recherches Servier, 11 rue des Moulineaux, 92150, Suresnes, France

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, CH₂Cl₂)}.

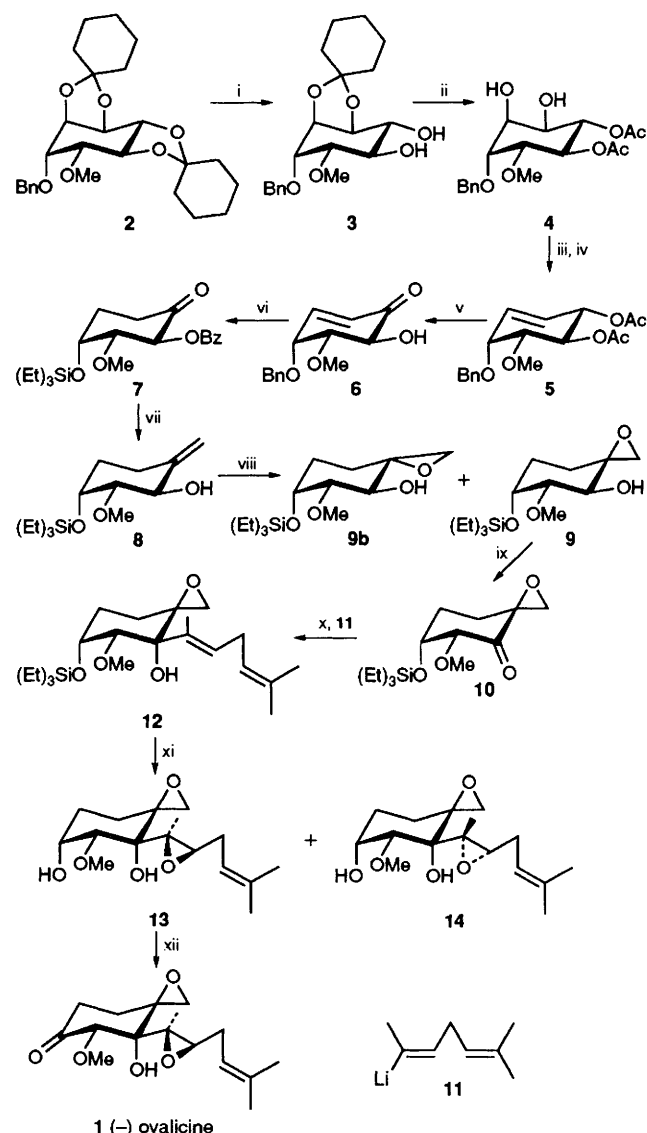
In order to effect a Corey–Winter *cis*-desoxygenation⁵ **4** was first treated with thiophosgene in dichloromethane in the presence of 4-dimethylaminopyridine, and the resulting thio-carbonate was then heated at 120 °C in trimethylphosphite for 24 h. Cleavage of the acetate groups using ammonia in methanol then gave the olefin **5** (82% from **4**). Selective oxidation of the allylic hydroxy group of **5** was achieved using freshly prepared MnO₂ (from MnCl₂ and KMnO₄)⁶ to give the α,β -unsaturated ketone **6** (50%) as an oil {[$\alpha]_D^{25} = -172$ (c 1.2 CHCl₃)}. Catalytic hydrogenation of **6** in ethanol in the presence of palladium gave the dihydrocyclohexanone (85%) which was selectively benzoylated (94%) at the more reactive α -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, CHCl₃)}. 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, CHCl₃)} together with 10% of the *trans* isomer **9b**, {[$\alpha]_D^{25} = -22$ (c 0.62, CHCl₃)}. Swern oxidation⁷ of **9** then gave the keto-epoxide **10** as an oil (88%) {[$\alpha]_D^{25} = -87$ (c 1.15, CHCl₃)}.

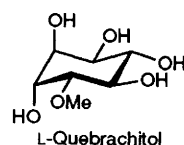
The side chain of (–)-ovalicine was introduced by a Shapiro reaction⁸ between the ketone **10** and the vinyl lithium **11**, prepared *in situ* from 3,3-dimethylallyl bromide and acetone (2,4,6-triisopropylbenzene) sulphonylhydrazone.⁹ The addition product **12** (75%) {[$\alpha]_D^{25} = -75$ (c 1, CHCl₃)} was then epoxidised by the method of Sharpless¹⁰ 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, CHCl₃; lit –88 (c 0.45, CHCl₃)),^{1b} and **14** {[$\alpha]_D^{25} = -69$ (c 0.75, CHCl₃)} 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, CHCl₃; lit. –117 (c 0.4, CHCl₃))^{1†} by oxidation of the secondary alcohol to the corresponding ketone using pyridinium-dichromate.

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Scheme 1 Reagents and conditions: i, HOCH₂CH₂OH, *p*-TSA, CH₂Cl₂; ii, (a) (CH₃CO)₂O, Py, (b) CF₃COOH, THF–H₂O; iii, (a) CSeCl₂, DMAP, CH₂Cl₂, (b) (CH₃O)₃P; iv, NH₃, MeOH; v, MnO₂, CH₂Cl₂; vi, (a) H₂, Pd/C 10%, EtOH, (b) PhCOCl, Py, (c) (Et)₃SiCl, imidazole, DMF; vii, Ph₃P=CH₂, THF; viii, MCPBA, CH₂Cl₂; ix, DMSO, (CF₃CO)₂O, CH₂Cl₂; x, **11**, THF–Toluene –78 °C; xi, (a) (acacO)₂VO, Bu^tOOH, PhH, (b) TBAF, THF; xii, PDC, CH₂Cl₂



Footnote

† Selected spectroscopic data for **1**: mp 90–92 °C (ether–pentane), lit.¹ 94–95 °C (ether–pentane) ¹H NMR (CDCl₃): 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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