

SYNTHESIS OF NATURAL (S)-(-)-TULIPALIN B STARTING FROM L-MALIC ACID AS A CHIRAL POOL

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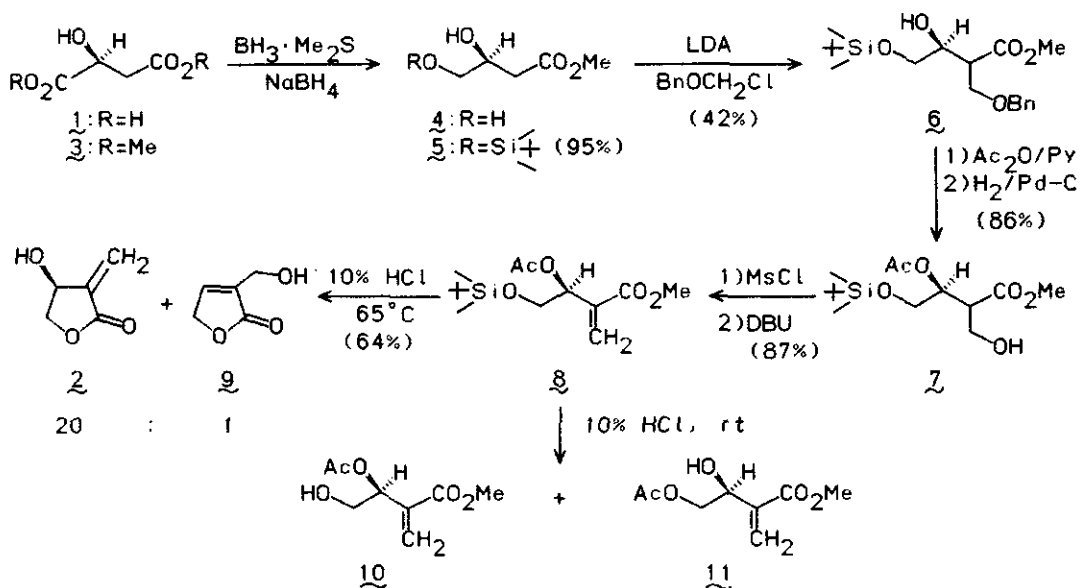
Abstract - The naturally occurring α -methylene- γ -lactone Tulipalin B (**2**) was synthesized enantioselectively starting from L-malic acid as a chiral pool in 15% overall yield.

Malic acid (**1**) has been proven to be an extremely valuable chiral synthon for the enantioselective synthesis of several classes of compounds such as (S)-(-)-carlosic acid,¹ 3-hydroxytetrahydrofuran,² a uracil with a chiral side chain,³ amphotericin B,⁴ avermectin B_{1a} aglycon,⁵ and (+)-pantolactone,⁶ the antibiotic monensin,⁷ and pheromones.^{8,9}

In 1985, Papageorgiou and Benezra¹⁰ described a short synthesis of (+)- and (-)-tulipalin B (**2**),¹¹ a natural product with cutaneous allergenic activity,¹² starting from dimethyl L- and D-malate (**3**) as a chiral pool. The first regiospecific step by enzymatic hydrolysis of **3** is, although important as a successful application of pig liver esterase, not practical for the synthesis in a large scale. And the α -methylenation in their synthesis via the Eschenmoser-Mannich homologation is of relatively low overall yield (11%). We wish to report here an efficient alternative route to **2** from the same synthon.

Dimethyl (S)-(-)-malate (**3**) was converted into methyl 3,4-dihydroxybutanoate (**4**) according to the method by Saito and co-workers.¹³ The selective protection of the primary hydroxyl in **4** by treatment with *t*-butyldimethylchlorosilane gave an β -hydroxy ester (**5**) in 95% yield. The ¹H-nmr spectrum¹⁴ of **5** displayed single *t*-butyl signal (δ 0.90) along with another singlet at δ 0.05 due to the dimethylsilyloxy moiety, the feature evidencing the high selectivity of silylation between two hydroxyls. The benzyloxymethyl as a precursor for the α -methylene moiety was introduced effectively at the α -position of **5** by action of benzyl

chloromethyl ether on the dilithiate of **5**. The reaction proceeded in a highly stereoselective manner¹⁵ and single diastereoisomer of the desired α -benzyloxy-methyl ester (**6**)¹⁶ was isolated in 42% yield. Acetylation of the secondary hydroxyl and subsequent debenzoylation gave an α -hydroxymethyl ester (**7**)¹⁷ in 86% overall yield. The mesylation of **7** followed by DBU-catalyzed elimination of methanesulfonic acid gave an α -methylene ester (**8**)¹⁸ in 87% yield. The ¹H-nmr of **8** displayed characteristic two signals with small coupling constants, at δ 5.84 and δ 6.36, due to the olefinic protons of the α -methylene moiety. Final lactonization was achieved on treatment of **8** with 10% hydrochloric acid at 65°C to give the desired (S)-(-)-**2** ($[\alpha]_D^{24}$ -81.5° (c=0.65, CHCl₃), lit.,¹⁹ $[\alpha]_D^{20}$ -82° (c=1.0, CHCl₃)), in 64% yield, and a small amount of 2(5H)-furanone (**9**).²⁰ When conducted under a moderate condition, the reaction resulted in the formation of a mixture of the desilylated product (**10**) and the acyl-migrated product (**11**) in high conversion rate.



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14. ^1H -Nmr spectra were taken on a JEOL JNM-GSX 270 spectrometer with tetramethyl silane as an internal standard. Coupling constants (\underline{J}) are given in Hz, and following abbreviations are used; s=singlet, d=doublet, t=triplet, quart=quartet, quint=quintet.
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16. Ir (CHCl_3) cm^{-1} ; 3506, 2905, 2850, 1726, 1460, 1435, 1361, 1252, 1167, 1093, 833. ^1H -Nmr (CDCl_3) δ ; 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 2.96 (1H, quart-like, $\underline{J}=6.1$), 3.20 (1H, d-like, $\underline{J}=6.3$, exchangeable with D_2O), 3.58-3.80 (4H, m), 3.72 (3H, s), 3.94 (1H, quint-like, $\underline{J}=6.1$), 4.51 (2H, s), 7.25-7.37 (5H, m).
17. Ir (CHCl_3) cm^{-1} ; 3350, 2949, 2920, 2850, 1735, 1460, 1435, 1371, 1250, 1167, 832. ^1H -Nmr (CDCl_3) δ ; 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 2.06 (3H, s), 2.88 (1H, broad s, exchangeable with D_2O), 2.99 (1H, q, $\underline{J}=5.8$), 3.73 (3H, s), 3.79 (1H, dd, $\underline{J}=11.5, 4.6$), 3.84 (1H, dd, $\underline{J}=12.0, 5.8$), 3.87 (1H, dd, $\underline{J}=11.5, 4.5$), 3.90 (1H, dd, $\underline{J}=12.0, 5.8$), 5.25 (1H, ddd, $\underline{J}=5.8, 4.6, 4.5$).

18. Ir (CHCl₃) cm⁻¹; 2949, 2915, 2850, 1736, 1630, 1437, 1363, 1250, 834. ¹H-Nmr (CDCl₃) δ; 0.05 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 2.10 (3H, s), 3.71 (1H, dd, J=11.0, 6.5), 3.78 (3H, s), 3.84 (1H, dd, J=11.0, 3.5), 5.71 (1H, ddt-like, J=6.5, 3.5, 0.7), 5.84 (1H, t-like, J=0.7), 6.36 (1H, t-like, J=0.7).
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