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

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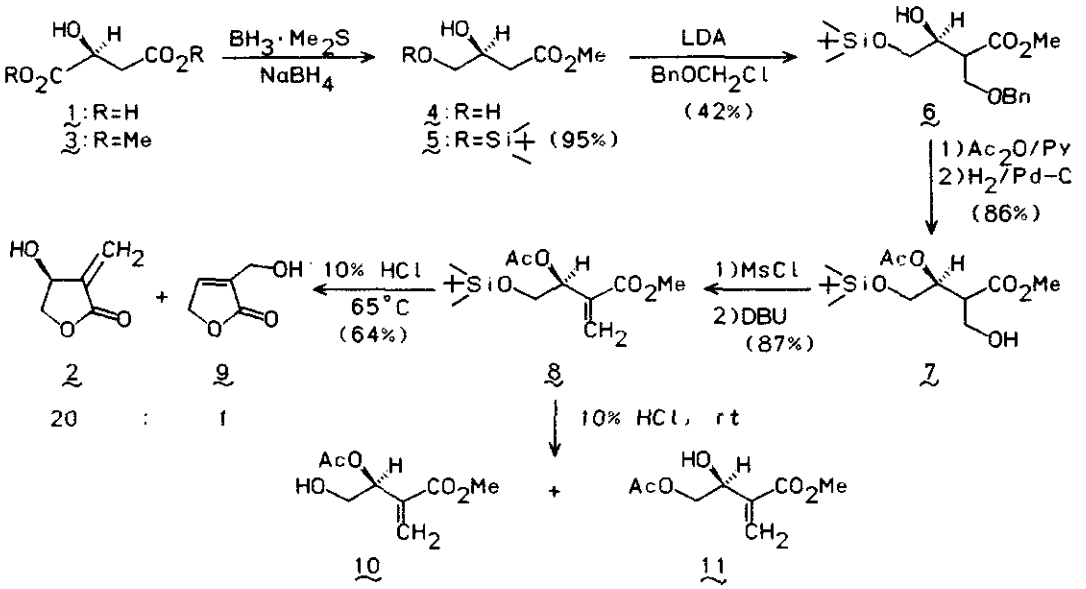
Abstract - The naturally occurring α-methylene-γ-lactone Tulipalin B (2) was synthesized enantioselectively starting from L-malic acid as a chiral pool in 15% overall yield.

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 Benezra[10] 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 ^{1}H-nmr spectrum[14] 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 manner[15] and single diastereoisomer of the desired α-benzyloxymethyl ester (6)[16] was isolated in 42% yield. Acetylation of the secondary hydroxyl and subsequent debenzylation 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 ^{1}H-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, $CHCl_3$), lit.,[19] $[\alpha]_D^{20}$ -82° (c=1.0, $CHCl_3$)), 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.



REFERENCES AND NOTES

1. J. L. Bloomer and F.E. Kappler, J. Chem. Soc., Perkin Trans., 1, 1976, 1485.
2. V.K. Tandon, A.M. Van Leusen, and H. Wynberg, J. Org. Chem., 1983, 48, 2767.
3. H. Hayashi. K. Nakanishi, C. Brandon, and J. Marmur, J. Am. Chem. Soc., 1973, 95, 8749.

4. S. Masamune, P. Ma, H. Okumoto, J.W. Ellingboe, and Y. Ito, J. Org. Chem., 1984, 49, 2834.
5. S. Hanessian, A. Ugolini, and M. Therien, J. Org. Chem., 1983, 48, 4427.
6. D. Wasmuth, D. Arigoni, and D. Seebach, Helv. Chim. Acta, 1982, 65, 344.
7. D.B. Collum, J.H. McDonald, III, and W.C. Still, J. Am. Chem. Soc., 1980, 102, 2118.
8. E. Hungerbühler, R. Naef, D. Wasmuth, D. Seebach, H.-R. Loosli, and A. Wehrli, Helv. Chim. Acta, 1980, 63, 1960.
9. K. Mori, T. Takigawa, and T. Matsuo, Tetrahedron, 1979, 35, 933.
10. C. Papageorgiou and C. Benezra, J. Org. Chem., 1985, 50, 1144.
11. The first synthesis of (-)-tulipalin B starting from isopropylidene-D-glyceraldehyde is described: A. Tanaka and K. Yamashita, Agric. Biol. Chem., 1980, 44, 199.
12. a) J.-P. Corbet and C. Benezra, J. Org. Chem., 1981, 46, 1141; b) P. Barbier and C. Benezra, J. Org. Chem., 1983, 48, 2705; c) Idem, J. Med. Chem., 1986, 29, 868. For a recent review on the subject, see H.M.R. Hoffmann and J. Rabe, Angew. Chem. Int. Ed. Engl., 1985, 24, 94.
13. S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, Chem. Lett., 1984, 1389.
14. ^{1}H-Nmr spectra were taken on a JEOL JNM-GSX 270 spectrometer with tetramethyl silane as an internal standard. Coupling constants (J) are given in Hz, and following abbreviations are used; s=singlet, d=doublet, t=triplet, quart=quartet, quint=quintet.
15. The stereoselectivity in the alkylation of β-hydroxy esters is discussed: G. Fráter, U. Müller, and W. Günther, Tetrahedron, 1984, 40, 1269.
16. Ir ($CHCl_3$) cm^{-1}; 3506, 2905, 2850, 1726, 1460, 1435, 1361, 1252, 1167, 1093, 833. ^{1}H-Nmr ($CDCl_3$) δ; 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 2.96 (1H, quart-like, J=6.1), 3.20 (1H, d-like, J=6.3, exchangeable with D_2O), 3.58-3.80 (4H, m), 3.72 (3H, s), 3.94 (1H, quint-like, 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. ^{1}H-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, J=5.8), 3.73 (3H, s), 3.79 (1H, dd, J=11.5, 4.6), 3.84 (1H, dd, J=12.0, 5.8), 3.87 (1H, dd, J=11.5, 4.5), 3.90 (1H, dd, J=12.0, 5.8), 5.25 (1H, ddd, J=5.8, 4.6, 4.5).

18. Ir ($CHCl_3$) cm^{-1}; 2949, 2915, 2850, 1736, 1630, 1437, 1363, 1250, 834. ^1H-Nmr ($CDCl_3$) 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).

19. a) R. Tschesche, F.-J. Kämmerer, G. Wulff, and F. Schönbeck, Tetrahedron Lett., 1968, 701; b) R. Tschesche, F.-J. Kämmerer, and G. Wulff, Chem. Ber., 1969, 102, 2057.

20. A. Calderon, P. de March, and J. Font, J. Org. Chem., 1987, 52, 4631.

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