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SYNTHESIS OF (+)-(6R:1'R)-PESTALOTIN AND (+)-(6R:1'S)-EPIPESTALOTIN

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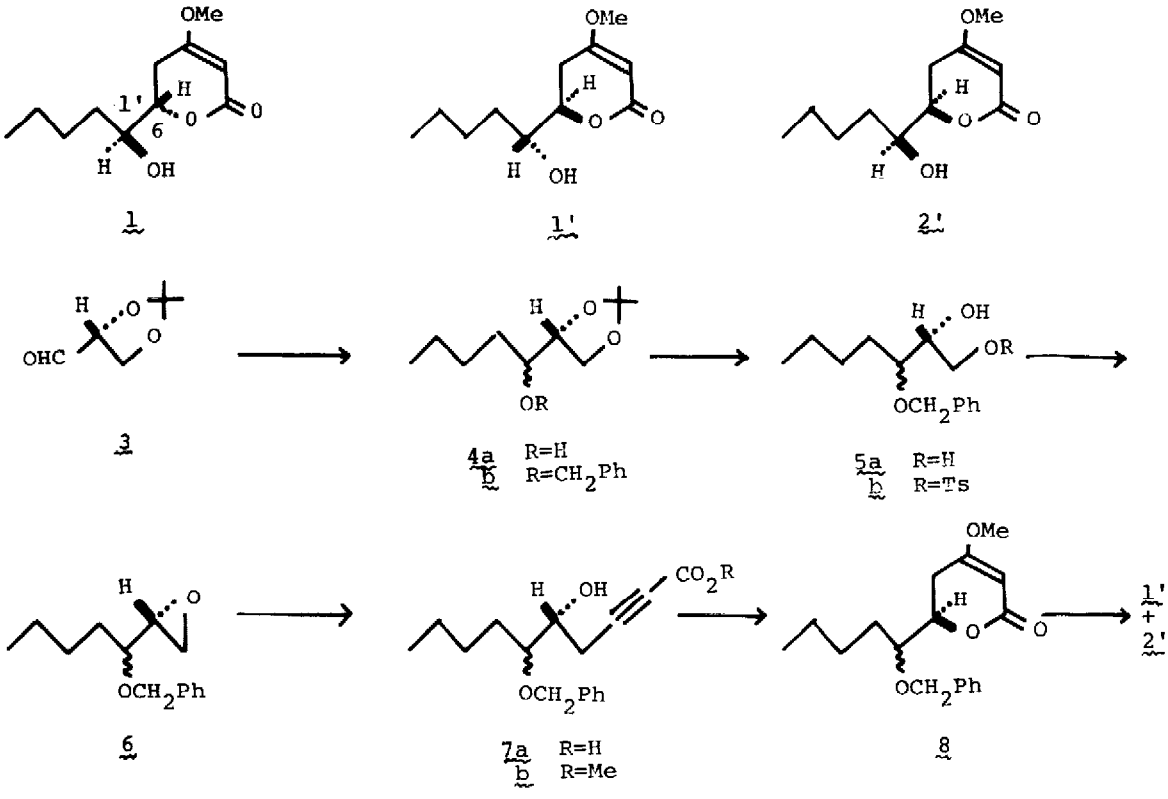
(-)-Pestalotin (1) is a gibberellin synergist isolated from culture broth of Pestalotia cryptomeriaecola Sawada[1] and possesses (6S:1'S)-stereochemistry.[2,3] As a part of our project to synthesize natural products from chiral epoxides, we prepared (+)-(6R:1'R)-pestalotin (1') and its 1'-epimer (2') from D-glyceraldehyde acetonide (3) confirming the 6S-stereochemistry of the natural product.

Reaction of n-BuMgBr in ether with 3 gave an epimeric mixture of 4a(53% yield), bp 91-98°/6mm, n_D^{23} 1.4377; $[\alpha]_D^{23}$ +16.8° (c=2.65, C_6H_6). This was converted ($PhCH_2Cl$/NaOH/DMSO; 30-40°, 2h) to the corresponding benzyl ether 4b (92% yield), bp 129-134°/0.6 mm, n_D^{24} 1.4869 ; $[\alpha]_D^{24}$ +22.9° (c=3.07, C_6H_6). Hydrolysis (dil HCl/MeOH; 60°, 1h) of 4b gave a glycol 5a (87% yield), bp 131-136°/0.35mm, n_D^{26} 1.5086 ; $[\alpha]_D^{26}$ +3.17° (c=3.03, C_6H_6), which was tosylated (1 eq TsCl/C_5H_5N; -10°, 2h) to give 5b. This was treated with KOH soln (room temp, 0.5h) to give an epoxide 6, the key intermediate, in 82% yield from 5a, bp 125-133°/3mm, n_D^{23} 1.4948 ; $[\alpha]_D^{23}$ -7.39° (c=2.68, C_6H_6). Subsequent steps were carried out according to Carlson's general method of α-pyrone synthesis.[4] The epoxide 6 was reacted with the dianion derived from propiolic acid (2 eq $i\text{-}Pr_2NLi$/THF/HMPA) to give 7a, which was esterified to 7b (41% yield from 6). Treatment of 7b with NaOMe/MeOH gave 8. This was hydrogenolyzed (H_2/Pd-C/EtOH) to give a mixture of 1' and 2'. Chromatographic separation (SiO_2/n-hexane-ether) gave 904 mg of crystalline 2' from earlier fractions and 361 mg of crystalline 1' from later fractions starting from 18.5g of 6. (+)-(6R:1'R)-Pestalotin separated as plates from C_6H_6-n-hexane, mp 85.0-86.0°, $[\alpha]_D^{24}$ +87.9° (c=0.428, MeOH).[5] The IR and NMR spectra were



entirely identical with those of the natural enantiomer (1) kindly provided by Dr. Y. Kimura of this Department. (+)-(6R:1'S)-Epipestalotin (2') crystallized as needles from C_6H_6-n-hexane, mp 92.5-93.5°, $[\alpha]_D^{24}$ +73.3° (c=1.44, MeOH).[6] The biological activities of these stereoisomers will be reported later.

REFERENCES AND FOOTNOTES

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5. The rotation of the natural pestalotin (1) of mp 84-85° is reported to be $[\alpha]_D$ -86.2° (c=0.14, MeOH)[2]. Our enantiomer is therefore optically pure.
6. The IR spectrum (nujol) of 2' [3360 (m), 1695 (s), 1685 (s), 1635 (s) cm^{-1}] is quite different from that of 1' [3440 (m), 1710 (s), 1625 (s) cm^{-1}] especially in fingerprint region. In the NMR spectrum of 2' the signal due to C-1' proton appears at δ=3.87 (m), while that of 1' appears at 3.62 (m).
7. All the compounds specified with bps or mps gave satisfactory spectral and analytical data.