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NEW SYNTHESIS OF (±)-PESTALOTIN AND (±)-EPIPESTALOTIN

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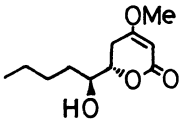
A new synthesis for the preparation of (±)-pestalotin (1) and (±)-epipestalotin (1') was successfully accomplished by utilizing the following two reactions: The partial reduction of 2-benzyloxyhexanoic acid (3) to 2-benzyloxyhexanal (6) via corresponding 3-acylthiazolidine-2-thione 5, and the $TiCl_4$-promoted reaction of the aldehyde 6 with diketene.

Pestalotin (1) is a synergist of gibberellin from the phytopathogenic fungus, Pestalotia cryptomeriaecola, isolated by Kimura et al.[1] It has a 5,6-dihydro-4-methoxy-2H-pyran-2-one skeleton with one hydroxyl group on the side chain, the stereochemistry of which is threo-configuration.[1), 2)]



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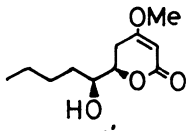
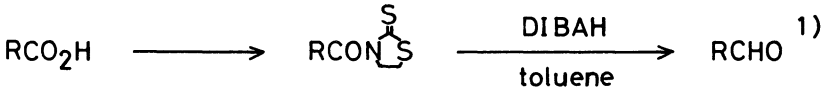
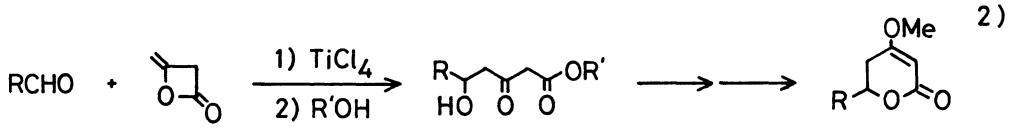


1'

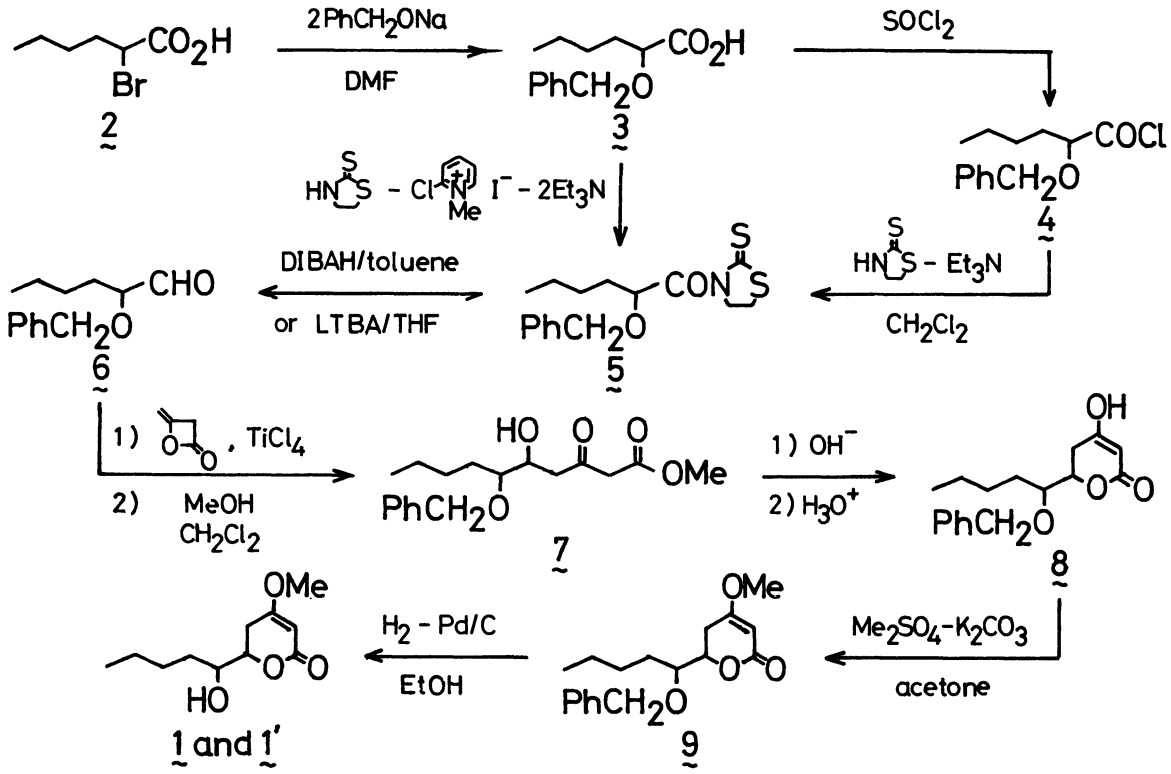
In the preceding paper we reported a convenient method for the partial reduction of carboxylic acid to aldehyde via 3-acylthiazolidine-2-thione with diisobutylaluminum hydride (DIBAH).[3] We also reported the preparation of δ-hydroxy-β-ketoester



by the reaction of aldehyde with diketene in the presence of $TiCl_4$.[4] The ketoesters were converted to (±)-kawain and (±)-dehydrokawain,[4] possessing a 5,6-dihydro-4-methoxy-2H-pyran-2-one skeleton, in good yields.



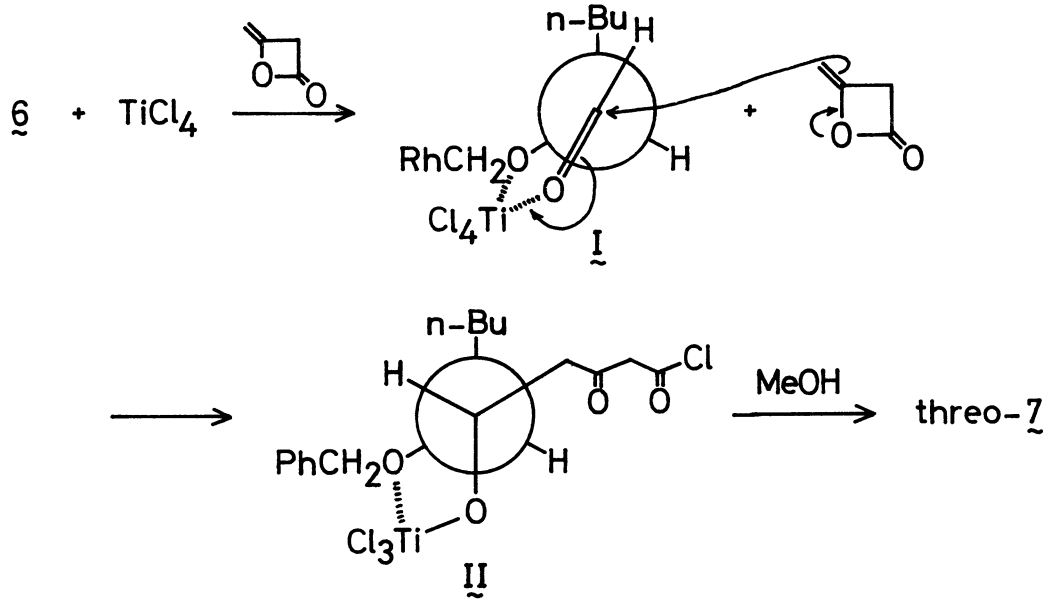
We now wish to describe a new synthetic route to (±)-pestalotin (1) and (±)-epipestalotin (1')[5] utilizing the above mentioned two reactions. Reaction of easily available 2-bromohexanoic acid (2) with two equivalents of sodium benzyl alcoholate at 60°C for 2 h in DMF, prepared in situ from benzyl alcohol and sodium hydride, afforded 2-benzyloxyhexanoic acid (3) (bp 142-144°C/ 0.9 mmHg) in 63% yield. The acid 3 was converted to the corresponding 3-acylthiazolidine-2-thione 5 either by a two-step procedure in 90% yield via acid chloride 4 (bp 110°C/ 1.5 mmHg) or by a single-step procedure in 77% yield using 2-chloro-1-methylpyridinium iodide[6] as a coupling reagent. The partial reduction of 5 with DIBAH in toluene[1] at -78°C gave the key



intermediate, 2-benzyloxyhexanal (6) in 80% yield. The thione 5 was also partially reduced to 6 (bp 90-92°C/ 0.45 mmHg) in 91% yield with lithium tri-t-butoxyaluminum hydride (LTBA) in THF at -40°C for 2 h.[7] The aldehyde 6 and diketene were treated with $TiCl_4$ at -78°C for 15 min in dichloromethane, followed by addition of excess methanol. The mixture was then allowed to stand at -20°C for 1 h to give δ-hydroxy-β-ketoester 7,[8] which was then lactonized to dihydrohydroxypyrone 8 in 67% yield (based on 6) by successive treatment of the crude ketoester 7 with aqueous 0.1N-NaOH and then with 2N-HCl solution at room temperature. Methylation of 8 with dimethyl

sulfate in acetone led to dihydromethoxypyrone 9. The pyrone 9 was hydrogenolyzed over 10% Pd/C to give the epimeric mixture (85:15) of 1 [9] and 1' in nearly quantitative yield, which were separated by thin layer chromatography on silica gel developed by ether-petroleum ether (9:1). The IR and NMR spectra of these products[10] were fully consistent with those of the previously reported natural and synthesized ones.

As mentioned above, the predominant formation of 1 over 1' is rationally explained by assuming the fixed conformation of the aldehyde 6 by coordination of $TiCl_4$ to the two oxygen atoms of 6 as illustrated below. Nucleophilic attack of



diketene to I may occur from the less hindered site of the carbonyl group, i.e., the right side of the figure I, to give preferentially threo-product II, which on methanolysis gives threo-7. Subsequent reactions from 7 to 1 and 1' are expected to proceed with complete retention of configuration to afford 1 as a predominant product.

REFERENCES AND NOTES

1) a) Y. Kimura, K. Katagiri, and S. Tamura, Tetrahedron Lett., 1971, 3137, b) Y. Kimura and S. Tamura, Agric. Biol. Chem., 36, 1925 (1972).

2) G. A. Ellestad, W. J. McGahren, and M. P. Kunstmann, J. Org. Chem , 37, 2045 (1972).

3) T. Izawa and T. Mukaiyama, Chem. Lett., 1977, 1443.

4) T. Izawa and T. Mukaiyama, Chem. Lett., 1975, 161.

5) Previously reported syntheses of pestalotin and epipestalotin: a) ref. 1b, b) D. Seebach and H. M. Meyer, Angew. Chem. Int. Ed. Engl., 13, 77 (1974), c) R. M. Carlson and A. R. Oyler, Tetrahedron Lett., 1974, 2615, d) K. Mori, M. Oda, and M. Matsui, Tetrahedron Lett., 1976, 3137, e) A. Takeda, E. Amano, and S. Tsuboi, Bull. Chem. Soc. Jpn., 50, 2191 (1977).

6) To a mixture of 3 and 2-chloro-1-methyl-pyridinium iodide in dichloromethane was added a dichloromethane solution of two equivalents of triethylamine at -20°C and allowed to stand at room temperature for 6.5 h. See E. Bald, K. Saigo, and T. Mukaiyama, Chem. Lett., 1975, 1163.

7) The partial reduction of 3-acylthiazolidine-2-thione with LTBA will be reported in the near future.

8) This ketoester 7 was contaminated with a small amount of 8.

9) Mp 82-83°C (lit.[5b] 82°C).
Anal. Found: C, 61.87; H, 8.49%. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.22%.

10) 1 : IR(KBr) 3430, 1700, 1615, and 1230 cm^{-1}; NMR($CDCl_3$) δ=0.9 (t, 3H), 1.0-1.8 (m, 6H), 2.25 (dd, J=17 and 5Hz, 1H), 2.75 (br s, 1H), 2.8 (ddd, J=17, 13, and 2Hz, 1H), 3.7 (m, 1H), 3.75 (s, 3H), 4.3 (dt, J=13 and 5Hz, 1H), and 5.1 (d, J=2Hz, 1H); MS(70eV), m/e 214 (M^+) and 127 (base peak).
1' : IR(neat) 3400, 1680, 1615, and 1220 cm^{-1}; NMR($CDCl_3$) δ=0.9 (t, 3H), 1.0-1.9 (m, 6H), 2.25 (dd, J=17 and 4.5Hz, 1H), 2.85 (ddd, J=17, 12, and 2Hz, 1H), 3.75 (s, 3H), 3.95 (m, 1H), 4.3 (dt, J=12 and 4.5Hz, 1H), and 5.1 (d, J=2Hz, 1H).

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