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THE PROPIOLIC ACID DIANION AS AN ACYL ACETATE EQUIVALENT: THE SYNTHESIS OF (±)-PESTALOTIN

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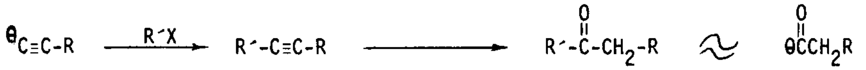
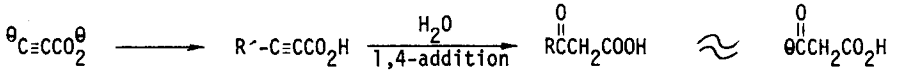
The use of a nucleophilic acyl equivalent is the basis of several valuable synthetic methods.[1] Acetylides potentially represent such acyl synthons if advantage could be taken of a regiospecific hydration procedure (Eqn. 1). The nucleophilic properties of propiolic acid dianion(I) have therefore been evaluated for this purpose on the basis of predicted susceptibility of the β carbon of the conjugated product towards nucleophilic attack (Eqn. 2).[2,3]



$$^{\ominus}\mathrm{C{\equiv}C\text{-}R} \xrightarrow{\mathrm{R'X}} \mathrm{R'\text{-}C{\equiv}C\text{-}R} \longrightarrow \mathrm{R'\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}R} \sim \overset{\mathrm{O}}{\overset{\|}{\ominus\mathrm{C}}}\mathrm{CH_2R} \qquad \text{Eqn. 1}$$



$$^{\ominus}\mathrm{C{\equiv}CCO_2^{\ominus}} \longrightarrow \mathrm{R'\text{-}C{\equiv}CCO_2H} \xrightarrow[\text{1,4-addition}]{\mathrm{H_2O}} \mathrm{R\overset{O}{\overset{\|}{C}}CH_2COOH} \sim \overset{\mathrm{O}}{\overset{\|}{\ominus\mathrm{C}}}\mathrm{CH_2CO_2H} \qquad \text{Eqn. 2}$$

Propiolic acid dianion additions to epoxides proceed in good yields. Subsequent conjugate addition of methanol formally provides the elements of a selective hydration by generating a series of methoxydihydro-α-pyrones(IV). Moreover, this conjugate addition of methanol can proceed either from the acid II (HgO, H_2SO_4, CH_3OH) or from the ester III (HgO, BF_3, CH_3OH or $NaOCH_3$, CH_3OH).[4] Specific examples of IV prepared by these methods are presented in Table I.

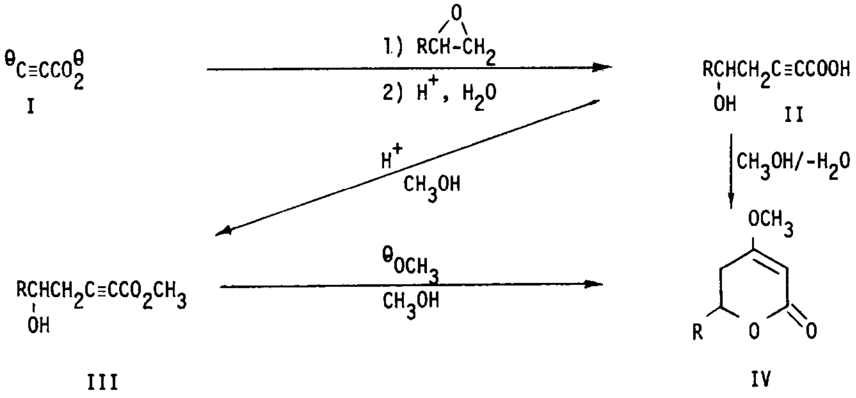
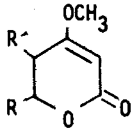


Table I



R	R´	Yield, %[a]	Mp, °C[b]	Nmr, δ ppm[c]
CH_3CH_2-	H-	29	55.0-55.5	1.01 (CH_3, t), 1.7 (CH_2, m), 2.35 ($H_{5a}H_{5e}$, m), 3.71 (CH_3O, s), 4.3 (H_6, m), 5.12 (H_3, s).
C_6H_{13}-	H-	28	39.2-40.0	0.88 (CH_3, t), 1.35 [$(CH_2)_5$, m], 2.38 (H_{5a} H_{5e}, m), 3.71 (CH_3O,s), 4.35 (H_6, m), 5.11 (H_3, s).
C_6H_5-	H-	19	142.5-143.5[d]	2.65 ($H_{5a}H_{5e}$, m), 3.75 (CH_3O, s), 5.24 (H_3, s) 5.41 (H_6, m), 7.4 (C_6H_5, m).
$-CH_2(CH_2)_2CH_2-$		7.4	71.0-71.5	0.8-2.6 (broad multiplet), 3.7 (CH_3O, s), 3.9 (H_6, m), 5.05 (H_3, d, J=1.5 Hz).

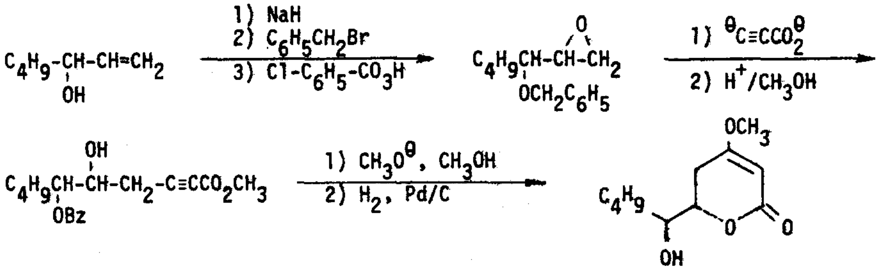
a Overall crude yield starting from propiolic acid; the α-pyrone was obtained using HgO and H_2SO_4.

b All new compounds gave satisfactory elemental analyses.

c $CDCl_3$, TMS.

d Lit.,[5] mp 146-147°.

The utility of propiolic acid dianion in the preparation of polyketides was illustrated by the synthesis of Pestalotin[6,7] and Epipestalotin.[8] Propiolic acid dianion was added to the benzyl ether of 3-hydroxy-1-heptene oxide and the methyl ester prepared of the product. Treatment with sodium methoxide in methanol, hydrogenolysis, and subsequent chromatographic separation gave the desired epimers.



Pestalotin

EXPERIMENTAL SECTION

4-Methoxy-5,6-dihydro-6-ethyl-2H-pyran-2-one (General Procedure)

To a stirred solution of 1 ml (7 mmol) of diisopropylamine in 40 ml of tetrahydrofuran maintained at -45° was added 72 ml (147 mmol) of *n*-butyllithium in hexane. After 10 min, 40 ml of hexamethylphosphoramide (HMPA) was added, followed by 4.3 ml (70 mmol) of propiolic acid. The temperature was allowed to gradually rise to -10° over a 2 hr period and 6.0 ml (70 mmol) of 1,2-epoxybutane was added. The resulting clear, red-brown solution, after stirring for 45 hr at 25°, was concentrated on a rotary evaporator. The residue was diluted with 250 ml of water and washed with methylene chloride until the HMPA was removed. The aqueous solution was then adjusted to pH 1 with concentrated hydrochloric acid, saturated with sodium chloride and extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated to give 5.2 g (52%) of viscous red-brown oil [5-hydroxy-2-heptynoic acid]. The crude acid (1.73 g, 12 mmol) in 20 ml of methanol was treated with 0.26 g (1.2 mmol) of red mercuric oxide and 0.08 ml (1.5 mmol) of sulfuric acid for 18 hr at 25°. The reaction mixture was filtered, concentrated, diluted with ether, and washed with a saturated solution of sodium bicarbonate and brine. After drying over magnesium sulfate, the ether was evaporated to yield 1.05 g (55%) of crude lactone which was purified by recrystallization from ether-pet ether (bp 30-60°) to give white crystals of IV ($R=C_2H_5$, mp 55.0-55.5°, see Table I).

(±)-Pestalotin and (±)-Epipestalotin

A 1:1 epimeric mixture of 1,2-epoxy-3-benzyloxyheptanes, obtained by *m*-chloroperbenzoic acid oxidation of the benzyl ether of 1-heptene-3-ol (Chemical Samples Co.), was added to the propiolic acid dianion as previously described to give a 54% yield of viscous red-brown oil [6-benzyloxy-5-hydroxy-2-decynoic acid]. The crude acid (3.7 g, 13 mmol) was dissolved in 40 ml of a 1% solution of sulfuric acid and stirred at 25° for 24 hr to form 2.91 g (78%) of crude ester [methyl 6-benzyloxy-5-hydroxy-2-decynoate]. The crude ester (1.03 g, 3.0 mmol) was added to a solution of sodium methoxide prepared from 0.015 g (0.70 mmol) of sodium and 10 ml of methanol and stirred for 22 hr at 25°. Work-up gave 0.84 g (82%) of crude lactone [4-methoxy-5,6-dihydro-6-(1-benzyloxypent-1-yl)-2H-pyran-2-one]. After treatment with decolorizing carbon, 0.8 g (2.6 mmol) of the crude lactone was dissolved in 25 ml of ethanol containing 0.2 g of 10% palladium on charcoal and allowed to take up 64 ml (2.6 mmol) of hydrogen. The resulting oil [4-methoxy-5,6-dihydro-6-(1-hydroxypent-1-yl)-2H-pyran-2-one] amounted to 0.52 g (93%).

The diasteriomers were separated on a liquid chromatograph (Waters Associates) using three 12x3/8 inch columns of Porasil A eluted with 20% hexane and 3% isopropanol in ether. The first isomer eluted, (±)-Epipestalotin, was recrystallized from ether-pet ether (bp 30-60°) to give material of mp 71-72° (lit.,[8] mp 72°). (±)-Pestalotin, melted at 81-82° after recrystallization from ether-pet ether (lit.,[8] mp 82°).

1. For a good review, including a conceptual discussion, see D. Seebach, Angew. Chem. Int. Ed., **8**, 639 (1969). For later methods, see R. M. Carlson and J. L. Isidor, Tetrahedron Lett., 4819 (1973) and references cited therein.
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ACKNOWLEDGMENT

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