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A NEW 3-ACYL-4-HYDROXY-2-PYRONE SYNTHESIS AND ITS APPLICATION TO TOTAL SYNTHESIS OF (±) PODOBLASTIN A, B AND C[1)]

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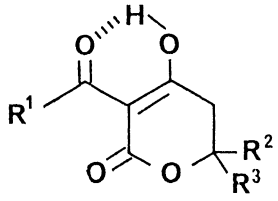
A new general method for preparation of 3-acyl-4-hydroxy-2-pyrones has been developed. The new method includes a Fries type rearrangement of enol-acyl group toward adjacent carbon atom, by which the new and potent fungicides, podoblastin A, B and C have been synthesized for the confirmation of the structures.

In the preceding letter[2)], the authors have reported the isolation and structure elucidation of naturally occurring antifungal dihydropyrones, podoblastin A, B and C from Podophyllum peltatum L. We now wish to report a new general synthetic route toward 3-acyl-4-hydroxy-5,6-dihydropyrones (I) via Fries type acyl migration of enol acyl group of β-keto-δ-valerolactone toward α-position of the δ-lactone as the key step. According to this method, the first total syntheses of podoblastin A, B and C have been accomplished.

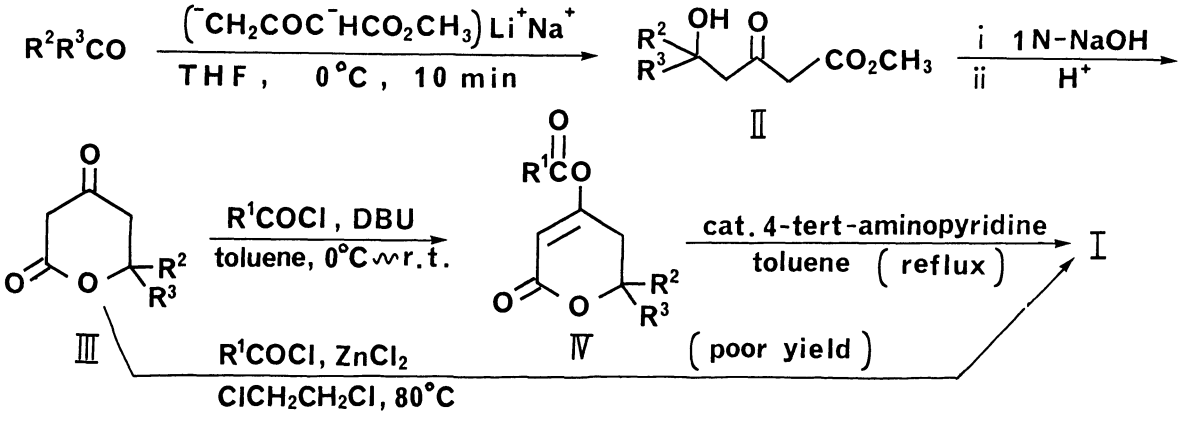


I

podoblastin A $R^1 = CH_3(CH_2)_{10}$
podoblastin B $R^1 = CH_2{=}CH(CH_2)_9$
podoblastin C $R^1 = CH_3(CH_2)_{12}$

R^2 = n-Pr, R^3 = H

Synthesis of this type of pyrones (I) was already reported by Glein et al.[3)] which requires a δ-substituted (R^1) acetoacetate ester and a β-alkyl (R^2 and R^3) acrylate ester for starting materials.



However, this method is not convenient, since both of the starting materials are not readily available except for a methyl analog and require a number of additional steps. In contrast, the new method is simple and versatile. The synthetic route of I are described as follows.

4-Hydroxy-2-oxoesters (II) are readily available as shown in the scheme according to the Weiler's method.[4] Subsequent hydrolysis of the ester gave hydroxy acid which was lactonized spontaneously on acidification to 2,4-tetrahydropyrane-dione (III) in good yield. Several conditions for direct C-acylation of III by acid chlorides were tried, but without complete success. C-Acylated pyrone (I) was not obtained even in a trace and O-acylated pyrone (IV) was the main product. This is in accord with observed preferential O-acylation of cyclohexane-1,3-dione system in the presence of a base.[5] In contrast to the base catalyzed acylation, Lewis acid catalysts were known to give C-acylated product.[6] In fact, $ZnCl_2$ catalyzed acylation of III gave 3-acyl-4-hydroxy-5,6- dihydropyrone (I) in poor yields(~18%) as shown in Table 1.

Table 1 Direct C-acylation of III into I

Substrate	R^2-	R^3-	Acid catalyst	R^1-	Product	Yield(%)[7]
III a	n-Pr	H	$ZnCl_2$[a]	$C_{11}H_{23}$	podoblastin A	15
III a	n-Pr	H	CF_3SO_3H[b]	$C_{11}H_{23}$		0
III a	n-Pr	H	$AlCl_3$[a]	$C_{11}H_{23}$		0
III a	n-Pr	H	$ZnCl_2$	$C_{13}H_{27}$	podoblastin C	18
III a	n-Pr	H	$ZnCl_2$	CH_2=CH(C_9H_{18})		0[c]
III b	Me	Me	$ZnCl_2$	C_2H_5		12
III c	Me	Me	$ZnCl_2$	C_4H_9		17

Reactions were carried out in refluxing $ClCH_2$-CH_2Cl for 2 hours. a) 1.1eq. vs III b) 0.05eq. vs III c) 2-Hydroxy-dodecanoic acid was a sole isolated product(35% yield).

In order to improve the yield, rearrangement of the enol ester (IV) into I was studied extensively, since 4-acyloxycoumarins have been converted into 3-acyl devivatives via related acyl migration.[8] But, common tertiary organic amines could not provide an efficient preparation of the migrated product in the present system. It was finally accomplished by the use of a catalytic amount (0.05 mol %) of 4-tertiaryaminopyridine under reflux in toluene as shown in Table 2.

By means of this method, the total syntheses of podoblastin A, B and C have been first performed as follows. Treatment of dianion of methyl acetoacetate with butyl aldehyde in dry THF at 0-5°C gave methyl 5-hydroxy-3-oxo-octanoate(IIa,67% yield, b.p.92-98°C/0.45mmHg). The hydroxy ester(IIa,R^2=n-Pr, R^3=H) was hydrolyzed with aqueuos N-NaOH followed by acidification with conc-HCl at 0 C to give pure crystals of lactone(IIIa, 91% yield).[9]

Dodecanoyl chloride (2.40g,0.011mol) was added to a solution of the 4-hydroxy-5,6-dihydropyrone(IIIa,1.56g,0.01mol) and DBU(1,8-diazabicyclo(5.4.0)-7-undecene, 1.69g,0.011mol) in toluene(20ml) at 0°C and stirred for 2 hours. Water was added to the reaction mixture which was subsequently extracted with toluene.

Table 2 Rearrangement of IV into I

Substrate	R^2-	R^3-	Catalyst	R^1-	Time(hr)	Yield[c]	Product[d]
IV a-1	n-Pr	H	A[a]	$C_{11}H_{23}$	3	75	podoblastin A
IV a-2	n-Pr	H	A	$CH_2=CH(C_9H_{18})$	3	73	podoblastin B
IV a-3	n-Pr	H	A	$C_{13}H_{27}$	3	67	podoblastin C
IV a-4	n-Pr	H	A	C_2H_5	2	82	
IV a-5	n-Pr	H	A	C_4H_9	2	78	
IV a-6	n-Pr	H	B[b]	C_4H_9	2	77	
IV b	Me	Me	A	C_8H_{17}	3	74	
IV b	Me	Me	B	C_8H_{17}	3	75	
IV c	i-Pr	H	A	C_8H_{17}	3	78	
IV d	Me	Et	A	C_8H_{17}	3	72	

Reactions were carried out in refluxing toluene.
a) A: pyrrolidinopyridine(0.05mol%) b) B:4-dimethylaminopyridine(0.05mol%) c) overall isolated yield from III. d) All products were characterized by ^{1}H-NMR,IR and MS spectra.

The organic layer was washed with aq. 5% HCl and brine, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was practically pure 4-dodecanoyloxy-5,6-dihydro-6-propyl-2-pyrone(IVa-1,3.18g, 0.0094mol)[10] and could be used for the next rearrangement reaction without further purification. The 4-acyloxypyrone(IVa-1,1.00g,0.003mol) and 4-pyrrolidinopyridine (0.02g,5mol%) were heated under reflux in toluene(6ml) for 3 hours, and toluene was removed under reduced pressure. The crude product was purified through a silica gel column(CH_2Cl_2) to give 0.75g of podoblastin A(Ia)[11] in 75% overall yield from IIIa. Podoblastin B(Ib)[12] and C(Ic)[13] were similarly synthesized in 73% and 67 % overall yields, respectively. The chromatographic behavior(GLC,TLC and HPLC) and spectroscopic data(^{1}H,^{13}C-NMR and UV) of synthetic (±)-podoblastin A, B and C were identical to those of natural mixture of (-)-podoblastins. Thus, the proposed structures of podoblastin A, B and C have been confirmed unambiguously.

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References

1) Part 2 in the series of "Studies on Podoblastin."

2) M.Miyakado, S.Inoue, Y.Tanabe, K.Watanabe, N.Ohno and H.Yoshioka, Chemistry Letters, 1982, 1539.
3) S.Glein and R.Glein, Bull.Soc.Chim.Fr., 288 (1968).
4) S.N.Huckin and L.Weiler, Can.J.Chem., 52, 2157(1974).
5) For example,see; N.Ono, T.Yoshimura, T.Saito, R.Tamura, R.Tanikaga and A.Kaji, Bull.Chem.Soc.Jpn., 52, 1716(1979).
6) N.A.Rogers and H.Smith, J.Chem.Soc., 341(1955), Y.Uchiyama and M.Sasaki, Japan.Pat. 118,448(1977).
7) Other products were resinous material resulting from the decomposition of the pyrone ring.
8) T.Ukita, S.Nojima and M.Matsumoto, J.Amer.Chem.Soc., 72, 5143(1950).
9) Recrystallized from EtOH, m.p.68.5°C, Element.Anal. Calcd for C(61.52%)H(7.85%) found C(61.80%)H(7.85%), ν_{max}^{film} 1690,1580,1400,1290cm^{-1}, ^{1}H-NMR (60.0MHz,$CDCl_3$): δ 4.60(m,1H),3.50(d,J=7Hz,2H),2.60(d,J=3Hz,1H),2.45(d,J=8Hz,1H),1.60(br,4H), 0.95(t,3H).
10) ν_{max}^{film} 2930,1760,1720,1140cm^{-1}, ^{1}H-NMR(60.0MHz,$CDCl_3$): δ 5.90(d,J=2.0Hz,1H), 4.40(m,1H),2.50(t,J=8.0Hz,2H),2.40(d,J=7.0Hz,2H),1.26(brs,20H),0.95(t,J=8.0Hz, 6H).
11) m.p.41.0-42.0°C, λ_{max}^{EtOH}272nm(log ε 4.01)and 217(3.82), ν_{max}^{film} 2910,2850,1695, 1560,1475,1085,915 and 885 cm^{-1}, ^{13}C-NMR(25.0MHz,$CDCl_3$): δ 204.9(s),195.5(s), 164.6(s),103.5(s),73.8(d),38.6(t),38.0(t),36.8(t),32.1(t),29.6(t,methylene carbons),22.5(t),22.8(t),18.1(t),14.9(q) and 13.9(q), ^{1}H-NMR(90.0MHz,$CDCl_3$): δ 17.9(s,1H),4.39(m,2H),3.03(t,J=8.0Hz,2H),2.65(d,J=6.0Hz,1H),2.64(d,J=5.0Hz,1H), 1.27(brs,22H) and 1.03(t,J=8.0Hz,6H), HRMS: Calcd for $C_{20}H_{34}O_4$(M^+)338.242, found 338.244, MS:(70eV,DI)m/z 338(M^+,rel.int.,30),320(6),295(17),277(20), 211(100),198(58),193(39),180(17),165(13),155(13),141(13),129(21),97(28),69(28) and 55(46).
12) Oil, λ_{max}^{EtOH}274nm(log ε 4.00)and 215(3.80), ν_{max}^{film} 2920,2850,1700,1560,1460, 1060,910 and 860 cm^{-1}, ^{13}C-NMR(25.0MHz,$CDCl_3$): δ 204.7(s),195.2(s)164.3(s), 139.3(d),114.2(t),103.5(s),73.7(d),38.6(t),38.1(t),36.9(t),33.9(t),29.5(t, methylene carbons),29.1(t),25.3(t),18.1(t) and 13.7(q). ^{1}H-NMR(90.0MHz,$CDCl_3$): δ 17.8(s,1H),5.80(m,1H),5.00(m,2H),4.38(m,2H),3.02(t,J=8.0Hz,2H),2.56(d,J=6.0Hz, 1H),2.55(d,J=5.0Hz,1H),1.25(brs,20H) and 0.91(t,J=8.0Hz,3H), HRMS:Calcd for $C_{20}H_{33}O_4$(M^+)336.224, found 336.227, MS:(70eV,DI)m/z 336(M^+,rel.int.,8),318(6), 293(7),275(13),233(15),211(100),193(66),180(32),165(27),97(25),69(23) and 55(42).
13) m.p.52.0-53.0°C, λ_{max}^{EtOH} 273nm(log ε 4.03) and 217(3.79), ν_{max}^{film} 2910,2850,1695, 1555,1470,915 and 885cm^{-1}, ^{13}C-NMR(25.0MHz,$CDCl_3$):δ 204.9(s),195.4(s),64.6(s), 103.5(s),73.8(d),38.7(t),38.2(t),36.9(t),32.1(t),29.8(t),29.6(t,methylene carbons),25.3(t),22.9(t),18.2(t),14.3(q) and 13.9(q). ^{1}H-NMR(90.0MHz,$CDCl_3$): δ 17.9(s,1H),4.39(m,2H),3.02(t,J=8.0Hz,2H),2.63(d,J=6.0Hz,1H),2.62(d,J=5.0Hz,1H), 1.25(brs,26H) and 0.95(t,J=8.0Hz,2H). HRMS: Calcd for $C_{22}H_{38}O_4$(M^+)366.278,found 366.280, MS:(70eV,DI)m/z 366(M^+,rel.int.,31),348(7),323(25),305(16),279(8), 235(6),211(100),198(61),193(34),180(15),165(11),155(12),141(10),129(19),97(25), 69(25) and 55(40).

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