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New Method for the Synthesis of Podoblastin Derivatives and 3-Acyltetronic Acids#

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A new and general method for the synthesis of podoblastin derivatives and 3-acyltetronic acids via isoxazoles is described. The key isoxazole intermediates were obtained by 1,3-dipolar cycloaddition reaction of acetylenecarboxylic acid derivatives to nitrile oxides. These isoxazoles were readily converted to the title compounds by hydrogenolysis followed by hydrolysis and cyclization.

There exist a lot of biologically active natural products such as podoblastins, 3-acyltetronic acids, 2-acyl-1,3-cyclohexanediones which have 2-acyl-1,3-dicarbonyl moiety. These compounds have been synthesized from the corresponding 1,3-dicarbonyl compounds by direct acylation with the aid of Lewis acids.[1] However, the yields were not so high, and severe acidic conditions were required. As for the synthesis of lactonic compounds having such a moiety, indirect acylation method, i.e. O-acylation followed by Fries type migration, was reported recently.[2] In connection with our natural product synthesis utilizing 1,3-dipolar cycloaddition reaction,[3] we have examined the synthetic method of 2-acyl-1,3-dicarbonyl compounds starting from readily available acetylenic compounds. We now wish to report a new and general synthetic route for podoblastin derivatives, antifungal metabolites isolated from Podophyllum peltatum L.,[4] and 3-acyl-5-methyltetronic acids via isoxazoles as the key intermediate

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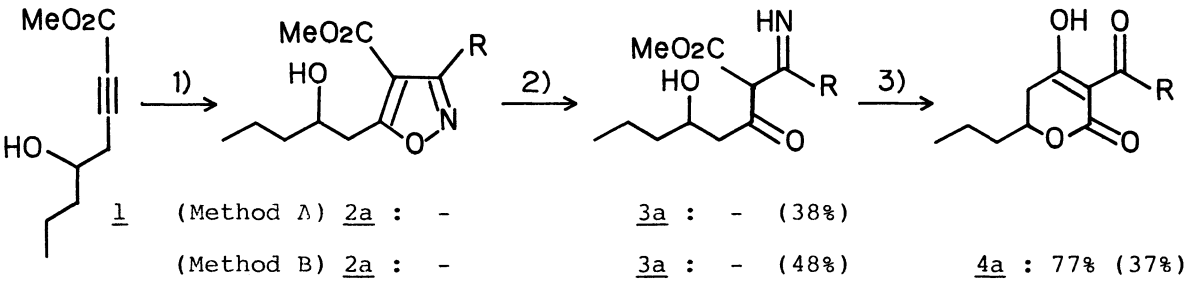
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

(Scheme 1).

Methyl 5-hydroxy-2-octynoate[5] (1) was led to tetrahydropyranyl ether.[6] 1,3-Dipolar cycloaddition reaction of this ether to 1-nitropropane by the Mukaiyama and Hoshino's procedure[7] proceeded in the regiospecific manner to give the desired isoxazole (2a). However, partial thermal decomposition of the THP ether took place simultaneously and a small amount of urethane derivative was also formed. Purification of the isoxazole contaminated with 1 was fairly difficult, therefore the crude 2a contaminated with a small amount of 1 was subjected to the Pd-C catalyzed hydrogenolysis, and imine (3a) was isolated in 38% yield after silica gel column chromatography (Method A).

On the other hand, when 1,3-dipolar cycloaddition reaction was carried out using chloroformate-tertiary amine as the dehydrating agent instead of phenyl isocyanate (Method B), the imine (3a) was obtained in 48% yield after hydrogenolysis. This method is advisable in point of both yields and purification procedures. In addition, chloroformate did not react with the hydroxy group under



1 (Method A) 2a : - 3a : - (38%)

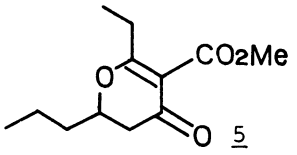
(Method B) 2a : - 3a : - (48%) 4a : 77% (37%)

(Method B) 2b : 61% 3b : 91% (55%) 4b : 70% (39%)

* The values in parentheses are the overall yields from 1.

a : R=CH_3CH_2-

b : R=$CH_3(CH_2)_8$-



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Reaction conditions :

1) (Method A)

i) DHP / p-TsOH ii) RCH_2NO_2 / p-ClC_6H_4NCO / Et_3N / C_6H_6 / reflux / 24h

iii) MeOH / p-TsOH

(Method B)

RCH_2NO_2 / $ClCO_2Me$ / $(iPr)_2NEt$ / r.t. / 48h

2) H_2 / Pd-C / r.t. / 12h

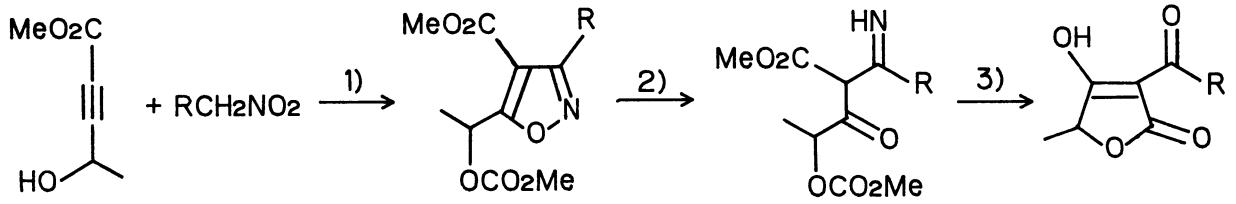
3) 1 mol dm^{-3} NaOH aq. / EtOH / r.t. / 1h

Scheme 1.

the conditions, and therefore, protection of the hydroxy group in 1 was not necessary.

When the imine (3a) was treated with acid, dihydropyrone derivative (5) was yielded as the major product (64%). On the other hand, when 3a was treated under basic conditions, lactonization and hydolysis of the imine function proceeded in the one-pot, and podoblastin derivative (4a) was formed directly in 77% yield. The overall yield of 4a was 37% from 1. In the same manner, unnatural podoblastin derivative 4b, which showed higher antifungal activity, was synthesized in 39% overall yield.

Next, to test the generality of our method, we tried to synthesize 3-acyl-5-methyltetronic acids (Scheme 2). Carolinic acid and carolic acid were isolated as mold metabolic products from Penicillium charlesii G. Smith and have the similar structural moiety as podoblastins.[8] We anticipated that these compounds would be



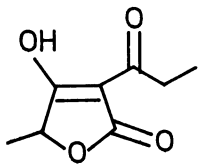
6 7a : R=CH_3CH_2- 8a-8c 9a : 73% 10a : 43% (31%)

7b : R=$MeO_2CCH_2CH_2$- 9b : 49% 10b : 54% (26%)

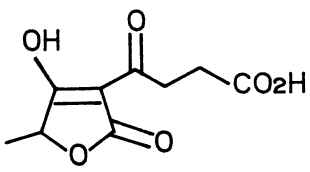
7c : R=$AcOCH_2CH_2CH_2$- 9c : 56% 10c : 47% (26%)

* The values in parentheses are the overall yields from 6.

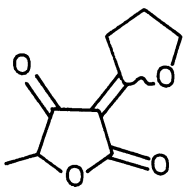
Products :



10a



10b : Carolinic Acid



10c : Carolic Acid

	10a	10b : Carolinic Acid	10c : Carolic Acid
mp	62.5-63.5 °C	136.5-138.0 °C	110.0-113.0 °C
(Lit.[8] mp)	(64.5-65.5 °C)	(141.0-142.0 °C)	(110.0-112.0 °C)

Reaction conditions :

1) $ClCO_2Me$ / $(iPr)_2NEt$ / CH_2Cl_2 / r.t. / 24h 2) H_2 / Pd-C / r.t. / 12h

3) 1 mol dm^{-3} NaOH aq. / Et_2O / r.t. / 1h

Scheme 2.

synthesized starting from methyl 4-hydroxy-3-pentynoate (6).[9]

1,3-Dipolar cycloaddition reactions of 6 with nitro compounds (7) by chloroformate method (Method B) were smoothly proceeded within 24h at room temperature. In contrast to the synthesis of podoblastin derivatives, the hydroxy group of 6 reacted with chloroformate to give methoxycarbonylated isoxazoles (8). But this was not disadvantage for our purpose, since the introduced group is readily removed in the cyclization step. Although 8 was contaminated with small amounts of furoxane and undefined by-products, crude mixtures were hydrogenolized over Pd-C, imines (9) were obtained from 6 in the yields as indicated in the scheme. When 9 were treated similarly as 3 under basic conditions, 3-acyl-5-methyltetronic acids (10) were obtained after recrystallization of crude products. This method seems to be more efficient in the point of overall yields, mildness of the reaction conditions, and ready availability of starting materials.

In conclusion, the above mentioned method is sufficiently general to be applicable to the synthesis of lactonic compounds having 2-acyl-1,3-dicarbonyl moiety.

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