Tetrahedron Letters Vol. 22, pp 735 - 738 0040-4039/81/0215-0735$02.00/0

SYNTHESIS OF (±)-PYRENOPHORIN UTILIZING 1,3-DIPOLAR CYCLOADDITION OF SILYL NITRONATE FOR THE CONSTRUCTION OF 16-MEMBERED RING

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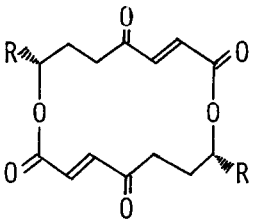
Summary: 1-Methyl-4-nitrobutyl acrylate underwent 1,3-dipolar cycloaddition via its silyl nitronate to give isoxazoline derivative of 16-membered dilactone after acid treatment, from which (±)-pyrenophorin was synthesized.

Recently a number of synthetic method of the 16-membered dilactone metabolites, pyrenophorin (1) and vermiculine (2), have been reported.[1] But every method required multistep process and the overall yields were not so high. For the construction of the 16-membered ring, these methods used the lactonization of hydroxy carboxylic acids[1a-h] except one which utilized the Wadsworth-Emmons modification of the Wittig reaction.[1i]

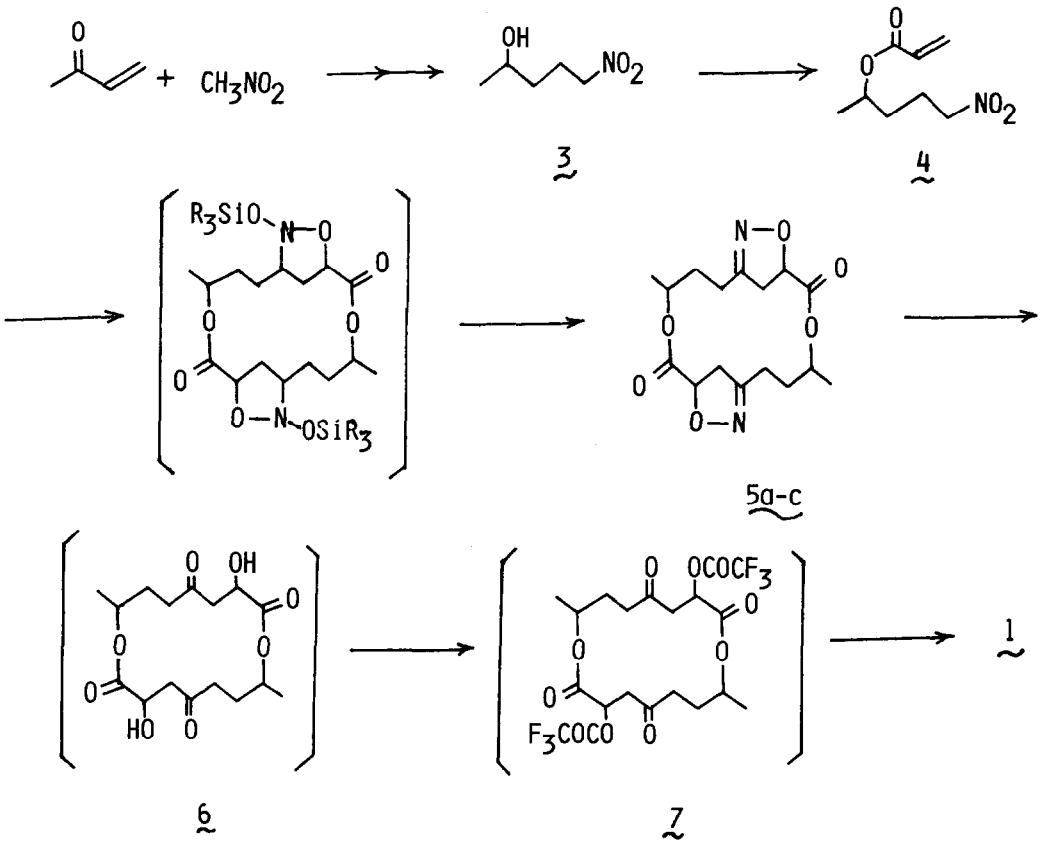
In this communication, we will describe short step synthesis of (±)-pyrenophorin applying 1,3-dipolar cycloaddition of trialkylsilyl nitronate[2] for the construction of the 16-membered dilactone ring.



R = CH_3 Pyrenophorin 1

R = $CH_2C(=O)CH_3$ Vermiculine 2

The nitro alcohol (3, 62%, bp 109 °C/3 mmHg) was prepared by the Michael addition of nitromethane to 3-buten-2-one in the presence of a catalytic amount of aqueous potassium hydroxide followed by the reduction with sodium borohydride.[3] The nitro alcohol was converted to the acrylate (4, 99%, isolated by column chromatography, bp 91-92 °C/0.2 mm Hg) by the reaction with acryloyl chloride and N,N-dimethylaniline in cold benzene. Then dimerization-cyclization of 4 applying 1,3-dipolar cycloaddition of its silyl nitronate was examined.



After stirring a mixture of the acrylate (4, 4.14 mmol), chlorotrimethylsilane (6.21 mmol) and triethylamine (6.62 mmol) in dry benzene (110 ml) at 34-37 °C for 16 days, and 2M hydrochloric acid was added. Extraction with dichloromethane and silica gel column chromatography of the extracts gave a stereoisomeric mixture of dimerization-cyclization products (5) in 85% combined yield. Since the isoxazoline (5) has 4 chiral canters, 6 isomers are possible to exist.[4] Three of them will give (±)-pyrenophorin by the subsequent functional transformation and the other three isomers will give meso-pyrenophorin. The stereoisomeric mixture could be separated into 3 parts by repeated column chromatography [5a(crystals):5b(crystals):5c(oil)=ca 4:1:3, Rf value(solvent: hexane/acetone=5/4): 0.54, 0.46, and 0.41]. All of these three indicated satisfactory spectra(ir, nmr, and mass) and elemental analyses. In order to carry out the 1,3-dipolar cycloaddition via nitrile oxide,[5] phenyl isocyanate was used in stead of chlorotrimethylsilane, but only 5c was obtained. In the consequence of the examination of the effect of concentration, it was clarified that the highest yield was obtained when 1 mmol of 4 was treated with

chlorotrimethylsilane and triethylamine in 25 ml of solvent. It is worthy to note that the concentration is extraordinally high comparing with other cyclization methods. These results are listed in Table 1.

Table 1 1,3-Dipolar Cycloaddition of 4

Concentration of 4 (mmol/ml)	Reagent	Temp.	Time	Yield of 5 (%)
1/5	Et_3SiCl	~ 30 °C	7 days	39
1/15	Et_3SiCl	~ 30 °C	7 days	58
1/25	Et_3SiCl	~ 30 °C	7 days	70
1/50	Et_3SiCl	~ 30 °C	22 days	5
1/25	Et_3SiCl	reflux	20 hrs	30
1/25	Me_3SiCl	~ 35 °C	16 days	85
1/25	PhNCO	~ 30 °C	7 days	34

Solvent:Benzene, Base: Et_3N

Reduction of a mixture of 5 in ethanol-acetic acid-water (15:2:1) in the presence of 10% Pd-C under atmospheric pressure of hydrogen at a room temperature gave 6. After the removal of Pd-C by filtration, the crude 6 was treated with trifluoroacetic anhydride-acetonitrile (1:1) in the presence of a catalytic amount of 4-dimethylaminopyridine at a room temperature. Volatile compounds were removed under reduced pressure and the residue (7) was dissolved in dry dichloromethane. Treatment of the solution of 7 with 4-5 molar equivalents of triethylamine[6] at a room temperature gave (±)- and meso-pyrenophorin (ca 1:1, 67% combined yield from 5; (±)-pyrenophorin: mp 139-140 °C, meso-pyrenophorin: mp 128-128.5 °C). Both of these were confirmed by direct comparison with authentic samples prepared by the alternative method.[1h] Each of the treatment of isolated 5a-c afforded a mixture of (±)- and meso-pyrenophorin. Consequently, each of 5a-c was confirmed to be composed of both precursors of (±)- and meso-pyrenophorin.[7]

References and Notes

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2) As for the syntheses of silyl nitronates and their reactions with simple olefins, see; a) M. V. Kashutina, S. L. Joffe, and V. A. Tartakovskii, Dokl. Acad. Nauk. SSSR, 218, 109 (1974); b) K. Torssell and O. Zeuthen, Acta Chem. Scand., B 32, 118 (1978); c) E. W. Colvin and D. Seebach, J. Chem. Soc., Chem. Commun., 1978, 689; d) S. C. Sharma and K. Torssell, Acta Chem. Scand., B 33, 379 (1979); e) H. Takei, T. Kawara, T. Mukuta, M. Sado, Y. Negishi, and M. Asaoka, Bull. Chem. Soc. Jpn., submitted.

3) H. Shechter, D. E. Ley, and L. Zeldin, J. Am. Chem. Soc., 74, 3664 (1952).

4) To count the number of isomers, if each racemic isomer is counted as 2, 10 isomers are possible to exist.

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6) When large excess of triethylamine was added, the polymerization of pyrenophorin was observed and the yield was decreased.

7) 5a; IR(KBr): 1730 cm^{-1}(C=O). NMR($CDCl_3$):δ=1.32(6H, d, J=7), 1.68-2.17(4H, m), 2.17-2.72(4H, m), 2.85-3.65(4H, m), 4.65-5.60(4H, m). Recrystallization from ethanol gave crystals(mp 217-218.5 °C, sublime~200 °C) which afforded meso-pyrenophorin by subsequent transformation. From mother liquor a mixture of crystals was recovered. The mixture gave (±)-pyrenophorin mainly. 5b; IR (KBr): 1730 cm^{-1}(C=O). NMR($CDCl_3$):δ=1.28 and 1.35(each d, J=6.5 and J=6.0, 6H), 1.68-2.75(8H, m), 2.78-3.35(4H, m), 4.60-5.37(4H, m). It was found that 5b was composed of at least 2 isomers(mp ~195 and ~212 °C) but the isolation of pure isomer could not be achieved. The mixture gave meso- and (±)-pyrenophorin(ca. 2:1) by subsequent functional transformation. 5c; IR (NaCl): 1735 cm^{-1}(C=O). NMR($CDCl_3$):δ=1.30(6H, d, J=6.5), 1.55-2.20(4H, m), 2.20-2.68(4H, m), 3.20(4H, br. d), 4.68-5.23(4H, m). Functional transformation afforded (±)-pyrenophorin mainly.

(Received in Japan 4 November 1980)