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TOTAL SYNTHESIS OF dl-PEDERAMIDE

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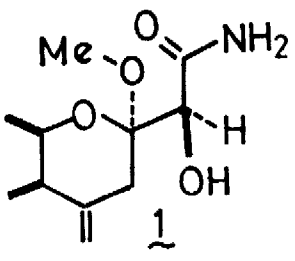
We report here a stereochemically controlled total synthesis of pederamide 1[1], a main hydrolysis product of the structurally unique and powerful insect poison pederin 2[2], in dl-form.



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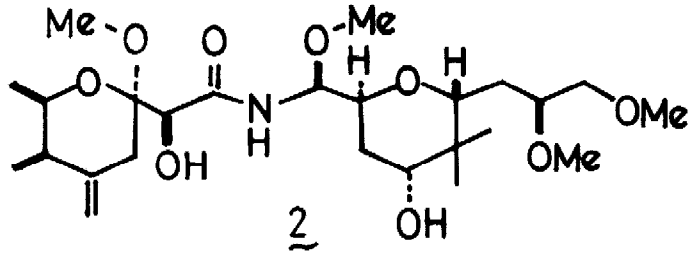

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Analysis of structural and stereochemical features of pederamide indicated that it would be synthesized through selective opening of the tetrahydrofuran ring of a 2,7-dioxabicyclo[3.2.1]octane derivative 8, which in turn seemed obtainable stereoselectively from cis-3-methyl-γ-valero-lactone 3. Treatment of 3[3] with 1 equiv of lithium diisopropylamide at -78° in tetrahydrofuran, followed by alkylation with 1.2 equiv of propargyl bromide gave lactone 4[4] [mp 66-67°, δ_{CDCl_3} 1.15 (3H, d, J=7Hz), 1.25 (3H, d, J=7Hz), 2.00 (1H, t, J=2Hz), 4.60 (1H, qui, J=7Hz)] as a single product in 93% yield. Stereochemistry of the propargyl group was confirmed by the nmr spectral data of 4 in the presence of Eu(fod)$_3$[5]. Reduction of 4 with $LiAlH_4$ in ether at reflux afforded diol 5[4] [95%

mp 53-54°, δ_{CDCl_3} 2.33 (2H, dd, J=7and3Hz)]. Conversion of 5 to ester 6[4] [mp 67-68°, δ_{CDCl_3} 2.51 (2H, d, J=7Hz)] was accomplished in 72% overall yield by successive treatment with (1) DHP-TsOH-CH_2Cl_2, (2) nBuLi-$ClCO_2Me$-THF at -78° and (3) TsOH-MeOH. Reaction of 6 with triethylamine at reflux gave a Z-E mixture of unsaturated ester 7[4)6)], [Z/E=1/3 by nmr. ν_{max}^{neat} 1690, 1640cm^{-1}, δ_{CDCl_3} 4.83(Z) and 5.23(E) (1H, bs)] which on oxidation with m-chloroperbenzoic acid in CH_2Cl_2 yielded an epimeric mixture at C-2 of the 2,7-dioxabicyclo[3.2.1]octane derivative 8[4] [1:1 by nmr. ν_{max}^{neat} 1750cm^{-1}, δ_{CDCl_3} 3.78 and 3.80 (3H, s)] in 49% overall yield. The C-2 position of this and the following ester intermediates was susceptible to isomerization by acids and bases.

The compound 8 was transformed stereoselectively into a tetrahydropyran 9[4] [mp 138-139°, 1:1 epimeric mixture at C-2, δ_{CDCl_3} 3.26 and 3.30 (3H, s), 3.48 (2H, d, J=7Hz), 4.31 (1H, bs)] in 58% overall yield through the following sequence of reactions : (1) Bz(benzoyl)Cl-Py (2) selective opening of tetrahydrofuran ring with 1N HCl-THF at reflux (3) formation of dibenzoate with BzCl-Py (4) methylation (MeOH-AcCl) and (5) debenzoylation (MeOH-MeONa). Selective tosylation of the primary hydroxy group of 9 and subsequent treatment with phenylselenolate anion[7] in absolute methanol gave a 55% overall yield of selenide 10[4] [δ_{CDCl_3} 2.78 (2H, d, J=7Hz)]. Oxidation of 10 with 30% H_2O_2 in tetrahydrofuran followed by elimination of phenylselenic acid in a mixture of benzene and triethylamine (1:1) at reflux afforded an epimeric mixture (1:1) at C-2 of methyl pederate 11, [δ_{CDCl_3} 2.19 (1H, dq, J=3and7Hz), 2.33 (2H, bs), 3.27 (3H, s), 3.80 (3H, s), 3.89 (1H, dq, J=3and7Hz), 4.31 (1H, s), 4.68, 4.80 (each 1H, bs)] and 12[4] [δ_{CDCl_3} 1.90 and 2.73 (2H, AB, J_{AB}=14Hz, J_{AX}=2Hz, J_{BX}=0Hz), 3.31 (3H, s), 4.38 (1H, s)] in 78% overall yield. The mixture gave on oxidation with the Collins reagent a single ketone 13[4] [δ_{CDCl_3} 2.30 and 2.47 (2H, AB, J_{AB}=14Hz, J_{AX}=2Hz, J_{BX}=0Hz)] in 90% yield. Reduction of 13 with $NaBH_4$ in methanol at -78° proceeded in a stereoselective manner, giving methyl pederate 11 in 75% yield together with a 15% yield of 12. Conversion of 11 to amide acetate 14[4] [mp 140-141°, δ_{CDCl_3} 2.20 (3H, s), 2.40 (2H, bs)] was effected without concomitant epimerization at C-2 in 76% overall yield by successive treatment with (1) MeOH-H_2O-NEt_3 at reflux for 24hr (2) Ac_2O-Py and (3) 6-chloro-1-(p-chlorobenzenesulfonyloxy)-benzotriazole[8]

-NEt_3-NH_3-THF. Finally deacetylation of 14 with NH_3 in methanol afforded quantitatively racemic pederamide (mp 129-130°), spectral data (ir, nmr, ms) of which were completely identical with those of the natural material.

REFERENCES AND FOOTNOTES

(1) T. Matsumoto, M. Yanagiya, S. Maeno and S. Yasuda, Tetrahedron Lett., 6297 (1968).

(2) A. Furusaki, T. Watanabe, T. Matsumoto and M. Yanagiya, Tetrahedron Lett., 6301 (1968). For physiological activity see M. Pavan, Sunto delle attuali conoscenze sulla pederina, Universita' di Pavia (1975).

(3) Compound 3[3a] was prepared stereoselectively from trans-2,3-epoxybutane in 48% overall yield through a new sequence of reactions : (1) alkylation with dimethyl malonate (MeOH-MeONa) (2) hydrolysis (KOHaq) (3) decarboxylation (Py at reflux).
3a) J. F. Laporte and R. Rambaud, C. R. Acad. Sci., Ser. C, 262, 1095 (1966).

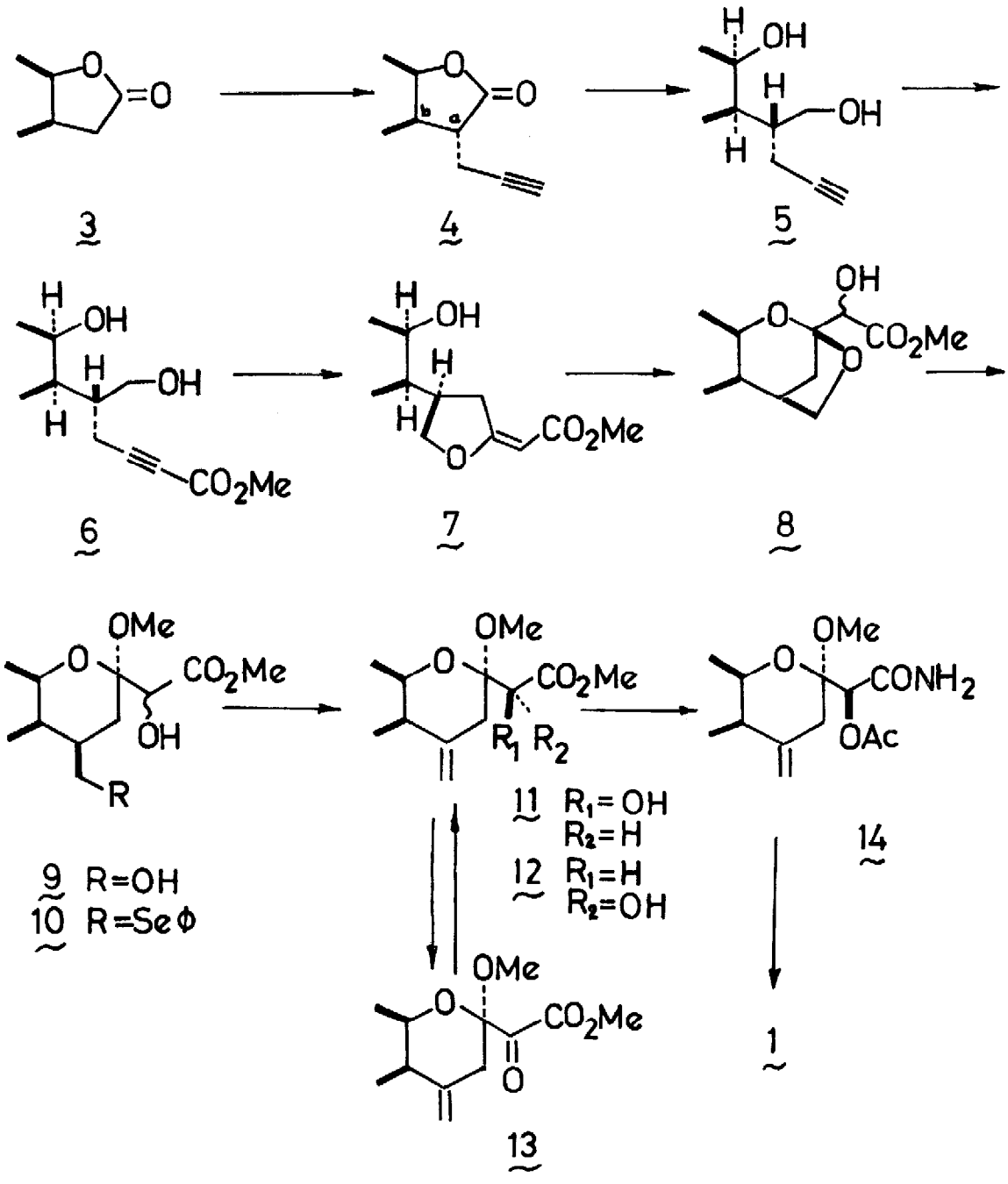
(4) Satisfactory elementary analytical values as well as ms, ir, and nmr spectral data were obtained for this compound.

(5) The nmr spectral data in the presence of $Eu(fod)_3$ of 4 indicated J_{ab}=10Hz (see formula 4). Configuration of the propargyl group was determined by comparing the value of J_{ab} with the corresponding values of related γ-lactones[5a].
5a) M. Petzilka, D. Felix and A. Eschenmoser, Helv. Chim. Acta., 56, 2950 (1973).

(6) Acetate of 7 exhibited dq (3and7Hz) peaks centered at δ 4.87. The alternative tetrahydropyranoid structure for 7 was therefore excluded.

(7) K. B. Sharpless and M. W. Young, J. Org. Chem., 40, 947 (1975).

(8) M. Itoh, H. Nojima, J. Notani, D. Hagiwara and K. Takai, Tetrahedron Lett., 3089 (1974).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4
5
6
7
8
9 R=OH
10 R=SeΦ
11 R1=OH R2=H
12 R1=H R2=OH
13
14
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