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TOTAL SYNTHESIS OF dl-PEDALDEHYDE

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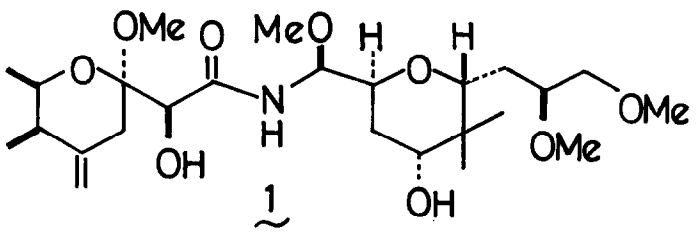
In a previous paper[1] we reported total synthesis of pederamide 2, a hydrolytic cleavage product of the insect poison pederine 1,[2] in the d,l form. We wish to report here a stereochemically controlled total synthesis of dl-pedaldehyde 3,[3] another main moiety of pederine 1.



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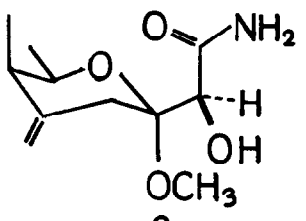

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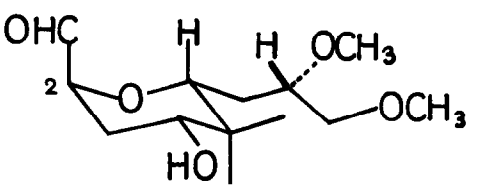
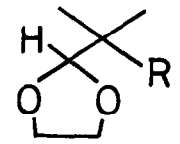


3

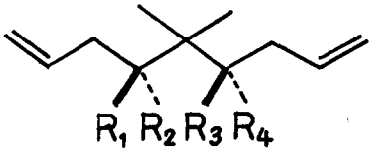
Examination of structural features of pedaldehyde 3 suggested that its C-2 epimer would be synthesized through stereo- and regio-selective opening of oxirane rings of a symmetrical dioxirane 9 with a twofold rotation axis, as shown in the figure. The dioxirane 9 in turn was anticipated to be obtainable by stereocontrolled epoxidation of a symmetrical homoallyl alcohol 7

Acetalization of 3-hydroxy-2,2-dimethylbutyraldehyde[4] with ethylene glycol and a catalytic amount of p-TsOH in benzene (reflux, 20h) afforded an acetal 4[5] [$\delta(CCl_4)$ 0.88 (6H, s), 3.30 (2H, s), 3.85 (4H, m), 4.53 (1H, s)] in 82% yield. Oxidation of 4 with pyridinium chlorochromate[6] in dichloromethane (rt, 3h) gave in 75% yield a half masked dialdehyde 5[5] [$\delta(CCl_4)$

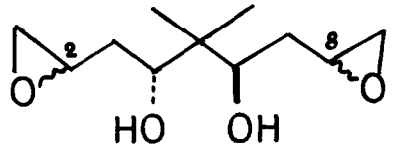
9.53 (1H, s)]. Allylation of 5 by allylmagnesium bromide in ether (0°, 1h) yielded an alcohol 6[5] [δ(CCl_4) 0.84, 0.88 (each 3H, s), 3.46 (1H, dd, J=9 and 4Hz), 4.95 (2H, m), 5.50-6.20 (1H, m), 70%]. Demasking of 6 with 6N-HCl in tetrahydrofuran-water (rt, 20h) and subsequent allylation by the same manner as above afforded a mixture of dl- and meso-glycol (2:1 by glc) in 70% overall yield from 6. The mixture could be separated by column chromatography on silica gel into the dl-glycol 7[5] [mp 59-60°, δ($CDCl_3$) 0.93 (6H, s), 3.65 (2H, dd, J=9 and 4Hz), 5.58 (4H, m), 5.50-6.30 (2H, m)] and the meso-glycol 8[5] [mp 50-51°, δ($CDCl_3$) 3.65 (2H, dd, J=9 and 3Hz), and other peaks almost superimposable upon those of 7]. Stereochemistry of the glycols was determined unambiguously by deducing molecular symmetry of the phenylboronates derived from them on the basis of nmr spectral data.[7] The meso-glycol 8 could be converted to the dl-one 7 through repetition of oxidation (Jones reagent, acetone, 0°, 86%) and reduction (RDB, toluene, -25°, 7:8 = 4.5:1 by glc, 80%). Reaction of the dl-glycol 7 with ^tBuOOH-VO(acac)$_2$[8] in benzene



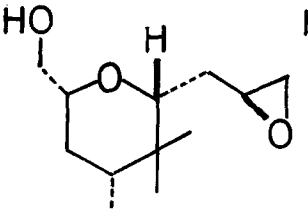
4 R = CH_2OH
5 R = CHO
6 R = $CHCH_2CH{=}CH_2$ (OH)



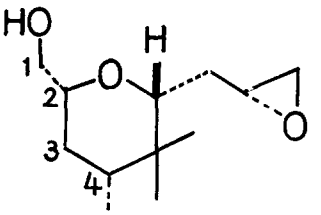
7 $R_1 = R_4 = H$, $R_2 = R_3 = OH$
8 $R_1 = R_3 = OH$, $R_2 = R_4 = H$



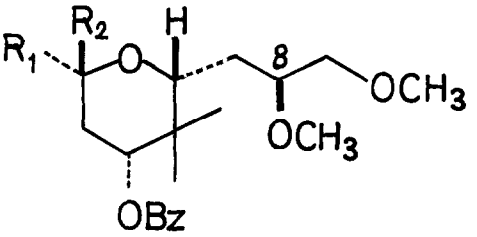
	C-2	C-8
9	----	—
10	----	----



11



12



13 $R_1 = CH_2OBz$, $R_2 = H$
14 C-8 epimer of 13
15 $R_1 = CH_2OH$, $R_2 = H$
16 $R_1 = CO_2CH_3$, $R_2 = H$
17 $R_1 = H$, $R_2 = CO_2CH_3$

(reflux, 1h) gave stereoselectively an isomeric mixture of diepoxides 9 and 10[5] [5:1 by nmr. 9: δ($CDCl_3$) 0.88 (6H, s), 2.51 (2H, dd, J=5 and 3Hz), 2.79 (2H, t, J=5Hz), 3.18 (2H, m), 3.78 (2H, dd, J=7 and 5Hz), 10: δ($CDCl_3$) 2.59 (1H, dd, J=5 and 3Hz), 2.85 (1H, t, J=5Hz), 3.78 (1H, dd, J=10 and 3Hz)] in 57% yield. Separation of the mixture was unsuccessful at this stage. As a by-product (30% yield), an isomeric mixture of tetrahydropyrans 11 and 12[5] [5:1 by nmr (in the presence of $Eu(fod)_3$). δ($CDCl_3$) 0.82, 0.91 (each 3H, s), 2.47 (1H, dd, J=5 and 3Hz), 2.74 (1H, t, J=5Hz)] was obtained. This mixture could not be separated either. The stereostructure 11 of the main tetrahydropyran was shown by the nmr spectrum of the mixture in the presence of $Eu(fod)_3$.[9] The mixture of diepoxides 9 and 10 could be converted to the 5:1 mixture of 11 and 12 by acid treatment (p-TsOH, benzene, reflux, 75%). This mixture was transformed into crystalline dimethoxydibenzoates 13[5] [56%, mp 121-122°, ν($CHCl_3$) 1715, 1605, 1590 cm^{-1}, δ($CDCl_3$) 0.93, 1.12, 3.26, 3.32 (each 3H, s), 4.35 (2H, d, J=5Hz), 4.95 (1H, dd, J=11 and 6Hz)] and 14[5,10] [10%, mp 75-76°, δ($CDCl_3$) 0.93, 1.11, 3.32, 3.34 (each 3H, s), 4.36 (2H, d, J=5Hz), 4.98 (1H, dd, J=11 and 6Hz)] through the following sequence of reactions: (1) masking of the two hydroxyl groups (DHP-p-TsOH, CH_2Cl_2, rt) (2) opening of the oxirane ring (MeOH-MeONa, reflux) (3) methylation of the newly formed secondary hydroxyl group (MeI-NaH, benzene, reflux) (4) demasking (p-TsOH, MeOH) and (5) benzoylation (BzCl-pyridine). Stereochemical homogeneity of the dibenzoates 13 and 14 was confirmed by ^{13}CNMR analysis. Treatment of 13 with a mixture of triethylamine, methanol and water (1:5:1, reflux, 20h) gave selectively a monobenzoate 15[5] [δ($CDCl_3$) 0.92, 1.10, 3.37, 3.38 (each 3H, s), 4.94 (1H, dd, J=10 and 6Hz)] in 86% yield. Oxidation of 15 with Jones reagent in acetone (0°, 1h) and subsequent esterification with CH_2N_2 afforded a methyl ester 16[5] [δ($CDCl_3$) 0.93, 1.13, 3.37, 3.39, 3.73 (each 3H, s), 4.11 (1H, dd, J=12 and 4Hz), 4.95 (1H, dd, J=12 and 5Hz)] in 83% yield. Inversion at C-2 bearing the methoxycarbonyl group in 16 was effected by enolization (LDA, THF, -78°) and subsequent kinetically controlled protonation (addition of HOAc, -78°) to give a 54% yield of an isomeric ester 14[5] [δ($CDCl_3$) 0.93, 1.13 (each 3H, s), 3.42 (6H, s), 3.82 (3H, s), 4.91 (1H, dd, J=12 and 5Hz)] and a 12% yield of 16. The J value of C-2 methine proton [δ4.56 (1H, dd, J=6 and 2Hz)] in 17 indicated axial orientation of the methoxycarbonyl group. Finally, reaction of 17 with DIBAL in toluene (-78°, 30min) afforded dl-pedaldehyde 3[5] [ν(neat) 3400, 1730 cm^{-1}, δ($CDCl_3$) 0.90 (6H, s), 3.38, 3.40 (each 3H, s), 4.23 (1H, J=7 and 2Hz), 9.78 (1H, bs)] in 70% yield.

The condensation of pederamide, pedaldehyde and methanol to pederine is now under investigation.

REFERENCES AND FOOTNOTES

(1) K. Tsuzuki, T. Watanabe, M. Yanagiya and T. Matsumoto, Tetrahedron Lett., 4745 (1976).

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

b) A. Furusaki, T. Watanabe, T. Matsumoto and M. Yanagiya, Tetrahedron Lett., 6301 (1968).

c) For physiological activity see M. Pavan, Sunto delle attuai conoscenze sulla pederina, Universita' di Pavia (1975).

(3) Pedaldehyde has not yet been obtained from pederine.

(4) E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy and K. Folkers, J. Amer. Chem. Soc., 62, 1785 (1940).

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

(6) E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).

(7) The boronate, obtained by reaction of the main glycol 7 with phenylboronic acid in benzene (reflux, 1h), indicated a 6H singlet peak at $\delta(CDCl_3)$ 0.99, while the one from the minor glycol 8 indicated two 3H singlet peaks at δ0.83 and 0.95.

(8) Stereocontrolled cis epoxidation of a cyclic homoallyl alcohol by means of this reagent has been reported [K. B. Sharpless and R. C. Michelson, J. Amer. Chem. Soc., 95, 6136 (1973)]. However, successful example of aliphatic version is not known.

(9) The nmr spectrum in the presence of $Eu(fod)_3$ indicated a quartet peak (J=12Hz) due to the axial proton at C-3. The diacetyl derivative of the isomeric mixture of 11 and 12 exhibited in the nmr spectrum ($CDCl_3$) a double doublet peak (J=11 and 5Hz) due to C-4 methine proton at δ4.68. These coupling constants show the presence of equatorial bonds at C-2 and C-4 positions in 11. Because the original diepoxide 9 has a symmetrical structure as shown by the nmr spectrum (see text), the stereochemistry at C-6 and C-8 is expressed as formula 11.

(10) Compound 14 gave an equatorial methyl ester [$\delta(CDCl_3$) 0.93, 1.13, 3.42, 3.39, 3.78 (each 3H, s), 4.18 (1H, dd, J=12 and 4Hz), 4.98 (1H, dd, J=12 and 5Hz)] different from 16 on successive treatments with (1) NEt_3-MeOH-H_2O (reflux, 20h) (2) Jones reagent and (3) CH_2N_2. Therefore, the stereostructures of compounds 12 and 14 are expressed by formulas 12 and 14, respectively.