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TOTAL SYNTHESIS OF (+)-PEDAMIDE. A NEW, REMOTE CONTROLLED ASYMMETRIC INDUCTION

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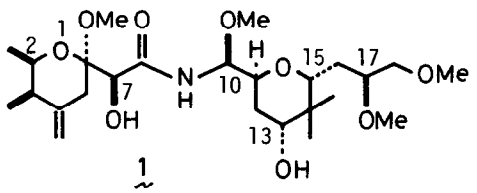
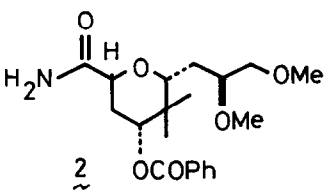
Abstract: Total synthesis of optically active pedamide 2, one of the tetrahydropyran moieties of the potent insect poison pederine 1, was achieved by employing a new, remote controlled asymmetric reduction of a ketone as key step.

Pederine 1[1], the potent insect poison isolated from Paederus fuscipes, has been shown to exhibit remarkable physiological activities, such as inhibition of mitosis in HeLa cells and blocking of protein synthesis in 80S ribosomes at concentration of 1 - 10 ng/ml. Since the natural product is not readily available, a practical chemical synthesis of 1 seems important for studying its chemical and physiological properties. For the total synthesis of 1, a logical route is to connect the two optically active tetrahydropyran moieties through an N-(1-methoxyalkyl)amide group. Previously we reported a stereocontrolled synthesis of (±)-pedaldehyde, the right hand side moiety of 1[1d]. Preliminary experiments showed, however, that adoption of this route to the synthesis of optically active pedaldehyde derivatives was not easy. In this paper we report a new synthesis of pedamide 2, a key pedaldehyde equivalent for the total synthesis of 1, in an optically active form through a new, remote controlled asymmetric induction.



1

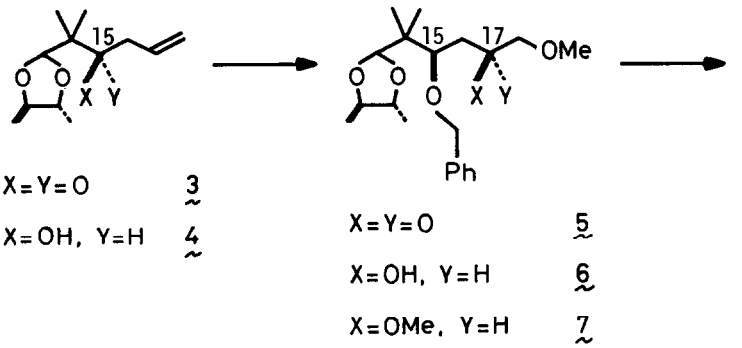


2

A 1,5-asymmetric induction in the reduction of an optically active acetal ketone 3[2b,3] from (-)-(2R,3R)-2,3-butanediol was successfully performed with lithium aluminum hydride at -123 °C in an ether-toluene mixture (1:1) to give (+)-alcohol 4[2a] having the desired 15R-configuration[4] (pederine numbering) in 74% enantiomeric excess[5] (98% yield). The alcohol 4 (74% e.e.) was converted into a dialkoxy ketone 5[2b] in 76% overall yield by the sequence (1) protection of the C-15 hydroxyl group as benzyl ether ($PhCH_2Cl$, ^tAmONa, DMSO, r.t., 2 h), (2) oxidation of the double bond (mCPBA, CH_2Cl_2, r.t., 12 h), (3) opening of the

epoxide group employing sodium methoxide (MeOH, r.t., 2 days), and (4) Collins oxidation (CH_2Cl_2, r.t., 30 min). Reduction of 5 with lithium tri-tert-butoxyaluminum hydride (ether, -78 °C, 30 min) afforded in 95% yield a (-)-alcohol 6[2a], which possessed the desired S-configuration [(15R*,17S*):(15R*,17R*)>10:1][6] at the new chiral center (C-17). Construction of the side chain moiety of 2 was completed by methylation of the new hydroxyl group (MeI, NaH, PhH, reflux, 2 h) to give a (-)-acetal 7[2a] in 93% yield.

Demasking of 7 with 3N-HCl in acetone (reflux, 5 h) and Grignard reaction with allylmagnesium bromide (ether, r.t., 10 min) afforded an alcohol 8[2a] (about 1:1 epimeric mixture at C-13) in 78% overall yield from 7. Removal of the benzyl protecting group was effected by sodium in liquid ammonia (-78 °C, 30



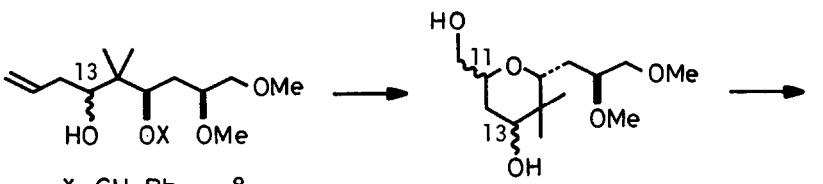
X=Y=O 3

X=OH, Y=H 4

X=Y=O 5

X=OH, Y=H 6

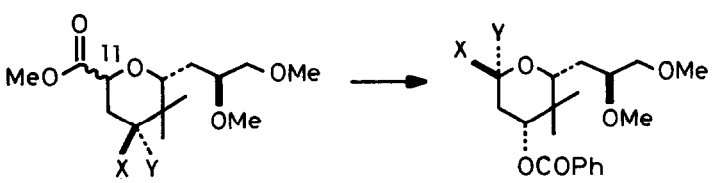
X=OMe, Y=H 7



X=CH_2Ph 8

X=H 9

10



X=Y=O 11

X=H, Y=OH 12

X=CO_2Me, Y=H 13

X=H, Y=CO_2Me 14

X=$CONH_2$, Y=H 2

min) to yield an olefinic diol 9[2a] (74%). Tetrahydropyran derivative 10[2a] was obtained as a mixture of stereoisomers at C-13 and C-11 by oxidation (mCPBA, CH_2Cl_2, r.t., 12 h) and successive acid treatment (p-TsOH H_2O, PhH, reflux, 10 min), in 86% overall yield from 9. The control of the stereochemistry of the secondary alcohol at C-13 on the tetrahydropyran ring was achieved in 68% overall yield through Jones oxidation (An, r.t., 12 h), followed by esterification (CH_2N_2, ether, r.t., 30 min) to 11[2a] and reduction with sodium borohydride (EtOH, -78 °C, 30 min) to afford predominantly (9R)-alcohol 12[2b,7] (about 1:1 epimeric mixture at C-11, 89%). After protection of the hydroxyl group as benzoate (PhCOCl, Py, r.t., 12 h, 94%), stereocontrol at C-11 bearing the methoxycarbonyl group was effected by enolization (iPr_2NLi, THF, -78 °C, 30 min) and subsequent kinetically controlled protonation (addition of HOAc at -78 °C) to give a 54% yield of the desired ester 13[2a,8] and a 12% yield of its epimer 14[2a]. The two epimers could be separated by silica gel chromatography and the minor epimer 14 was recycled. After a hexane solution of the resultant ester 13 was seeded by addition of a few crystals of racemic 13[1d], separated racemic crystals were removed and the mother liquor was concentrated to afford optically purified 13, which had $[\alpha]_D$ +23.1° (c=2.2, $CHCl_3$). The (+)-ester 13 was transformed to (+)-benzoylpedamide 2[2a] in 79% overall yield by the following sequence: (1) hydrolysis of the methoxycarbonyl group (Et_3N, H_2O, MeOH, r.t., 12 h), (2) acid chloride formation ($SOCl_2$, DMF, CH_2Cl_2, reflux, 3 h), and (3) amidation (NH_3, CH_2Cl_2, 0 °C, 20 min). Optically pure (+)-2[9] was obtained by recrystallization from hexane and had $[\alpha]_D$ +15.9° (c=3.2, $CHCl_3$) and mp 137 - 138 °C.

References and Notes

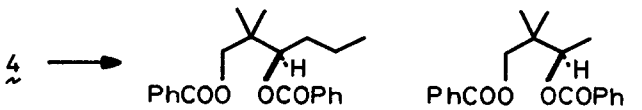
(1) (a) Structure: T. Matsumoto, M. Yanagiya, S. Maeno, and S. Yasuda, Tetrahedron Lett., 6297 (1968). A. Furusaki, T. Watanabe, T. Matsumoto, and M. Yanagiya, ibid., 6301 (1968). (b) Physiological activities: M. Pavan, Sunto delle attuali conosenze sulla pederina, Universita' di Pavia (1975). (c) Synthesis of (±)-pederamide (left hand side moiety): K. Tsuzuki, T. Watanabe, M. Yanagiya, and T. Matsumoto, Tetrahedron Lett., 4745 (1976). (d) Synthesis of (±)-pedaldehyde: K. Tsuzuki, Y. Nakajima, T. Watanabe, M. Yanagiya, and T. Matsumoto, ibid., 989 (1978). (e) An independent synthesis of (±)-pedaldehyde and (±)-pederamide· J. Meinwald, Pure Appl. Chem., 49, 1275 (1977); M A. Adams, A. J. Duggan, J. Smolanoff, and J. Meinwald, J. Am. Chem. Soc., 101, 5364 (1979).

(2) (a) Satisfactory spectral and analytical data were obtained for this compound. (b) Satisfactory spectral data were obtained for this compound.

(3) The acetal ketone 3 was prepared in 51% overall yield from 3-hydroxy-2,2-dimethylpropanal by the sequence (1) acetalization by (-)-(2R,3R)-2,3-butane-

diol (p-TsOH·H_2O, PhH, reflux, 8 h), (ii) oxidation by pyridinium chlorochromate (CH_2Cl_2, r.t., 2 h), (iii) Grignard reaction (CH_2=$CHCH_2MgBr$, ether, r.t., 10 min), and (iv) Jones oxidation (An, 0 °C, 30 min).

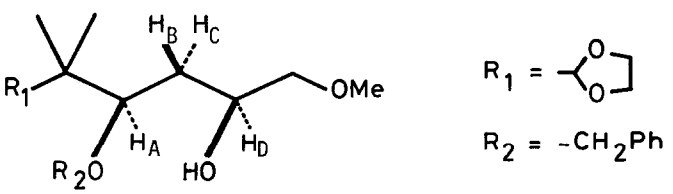
(4) The R-configuration of 4 was determined by leading it to a dibenzoate i (74% e.e.) and comparing its optical rotation [$[\alpha]_D$ -31.2° (c=2, $CHCl_3$)] with that of a closely related dibenzoate ii [65% e.e., $[\alpha]_D$ -32.4° (c=2, $CHCl_3$); I. Ojima, T. Kogure, and M. Kumagai, J. Org. Chem., 42, 1671 (1977)].



i ii

(5) The enantiomeric excess was obtained by nmr spectra. By addition of Eu(fod)$_3$, unresolved signals due to the acetal proton of each diastereoisomer were observed as separate singlet peaks. The ratio of S values for these peaks was 0.76.

(6) The assignment is based on the ^1H nmr spectral data of an (±)-alcohol iii obtained from the corresponding (±)-ketone by a similar treatment. The 400 MHz spectrum ($CDCl_3$) of iii showed peaks due to H_A, H_B, H_C, and H_D at δ 3.69, 1.68, 1.79, and 3.96 respectively, with J_{BC}=13.0 Hz, J_{AB}=J_{BD}=8.5 Hz, J_{AC}=J_{CD}=4.0 Hz. These data are compatible with stereostructure iii. On the contrary the C-17 epimer exhibited peaks at δ 1.59 (H_B) and 1.54 (H_C) with J_{BC}=13.0 Hz, J_{AB}=J_{CD}=9.0 Hz, J_{AC}=J_{BD}=3.0 Hz.



iii

(7) Equatorial orientation of the hydroxyl group was confirmed by the J values of the C-13 methine proton in 13 [δ(CCl_4) 4.78 (dd, J=5 and 12 Hz, 1H)] and those in 14 [δ(CCl_4) 4.90 (dd, J=5 and 12 Hz, 1H)].

(8) The J values of the C-11 methine proton in 13 [δ(CCl_4) 4.43 (dd, J=2 and 6 Hz, 1H)] indicated axial orientation of the methoxycarbonyl group.

(9) Optical purity was confirmed by the nmr spectra of 2 in the presence of the chiral shift reagent, Eu(tfc)$_3$.

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