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TOTAL SYNTHESIS OF (+)-PEDERIN. 2. STEREOCONTROLLED SYNTHESIS OF (+)-BENZOYLSELENOPEDERIC ACID AND TOTAL SYNTHESIS OF (+)-PEDERIN

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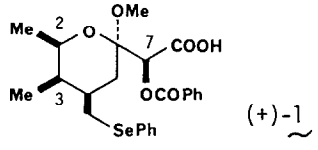
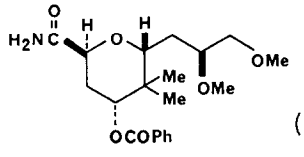
Summary: (+)-Benzoylselenopederic acid (1), a left half of (+)-pederin (3), was synthesized stereoselectively based on the $Zn(BH_4)_2$ reduction and total synthesis of (+)-pederin (3) was accomplished from 1 and the previously synthesized 2.

Having completed the stereoselective synthesis of (+)-benzoylpedamide (2), we turned our attention to the synthesis of (+)-benzoylselenopederic acid (1) corresponding to a left half of (+)-pederin (3) and the total synthesis of (+)-pederin therefrom. Retrosynthetic analysis of 1 suggests that the previously developed stereoselective reduction of acyclic ketones with $Zn(BH_4)_2$[1] would be applied successfully in the introduction of chiral C-2 and C-7 hydroxyl groups in (+)-1 as shown in Scheme 1. In fact, $Zn(BH_4)_2$ reduction was proved to be quite effective in the formation of these chiral centers. We now report the highly stereocontrolled synthesis of (+)-1 and the total synthesis of (+)-pederin (3) from (+)-1 and (+)-2.

Recently, it was reported that optically active α-methyl-β-keto imides or amides were synthesized.[2] These remarkable findings, coupled with the syn-directing $Zn(BH_4)_2$ reduction,

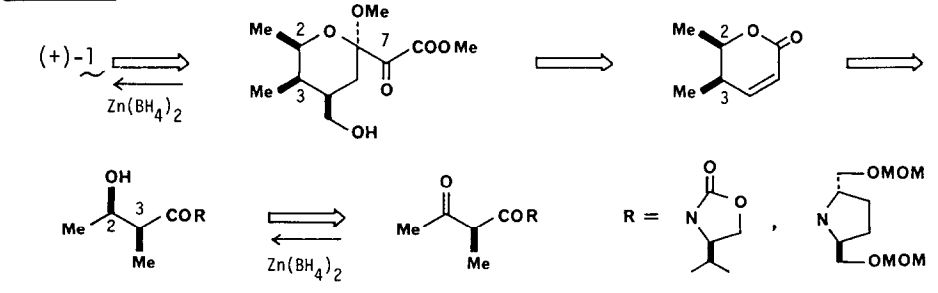


(+)-1

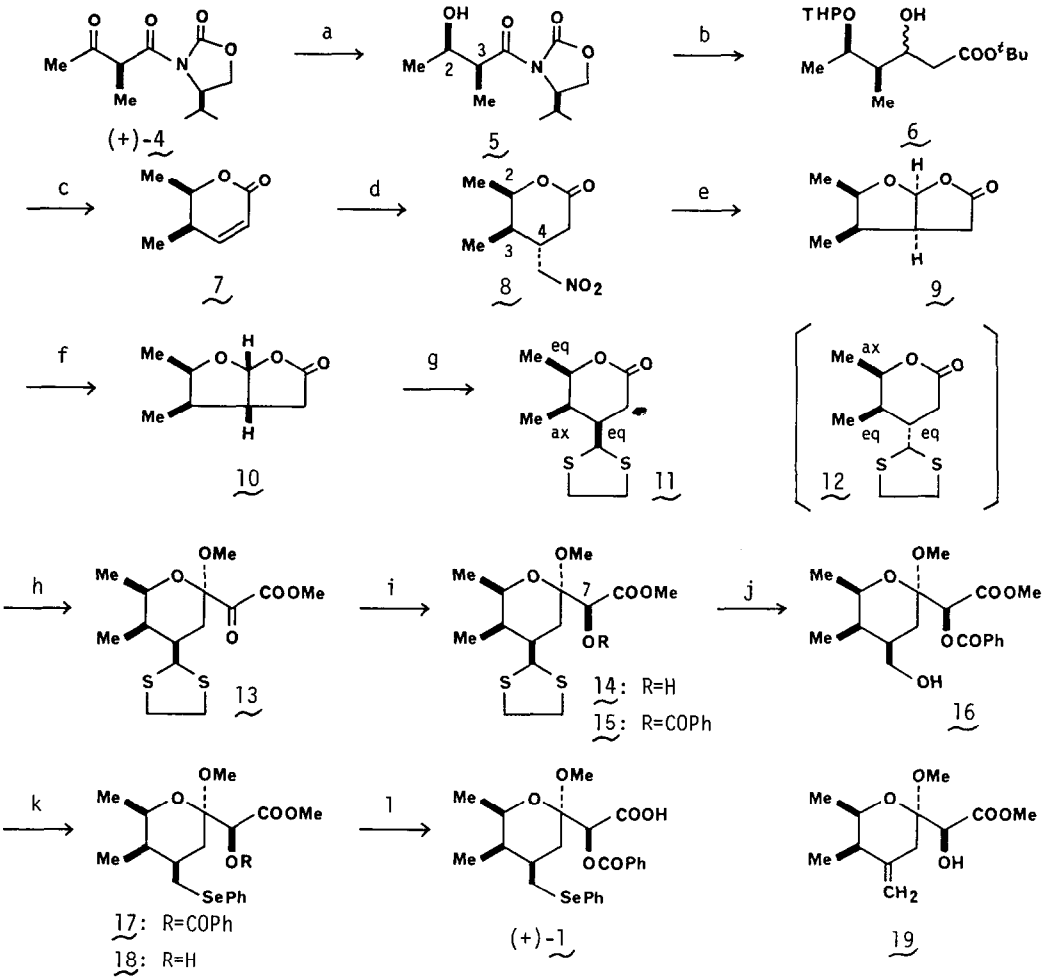


(+)-2

Scheme 1



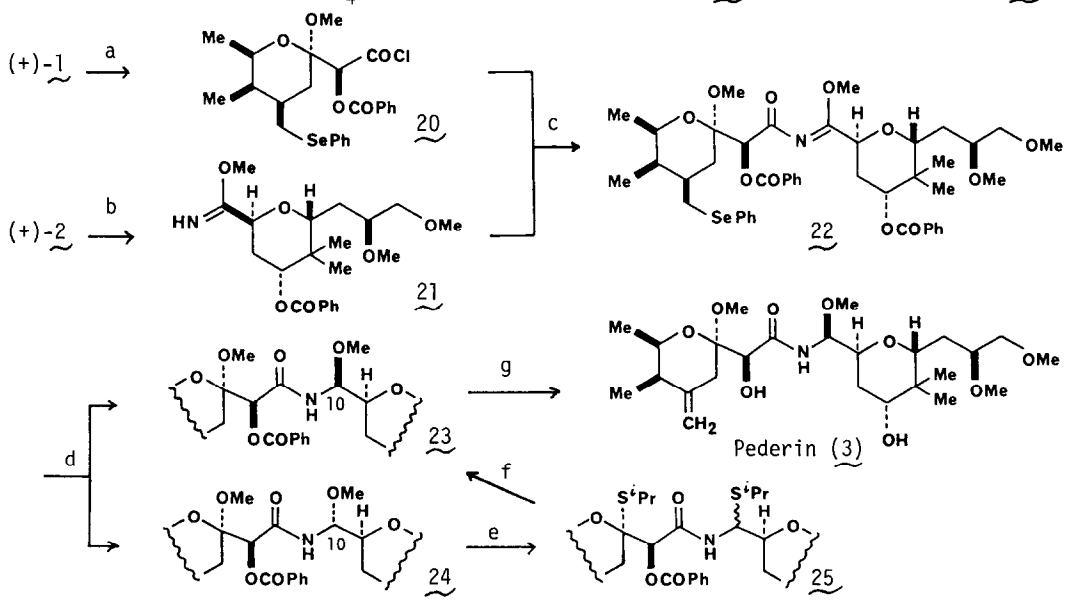
made it possible to synthesize optically active syn-α-methyl-β-hydroxy acid derivative,[2] which would be useful as an important building block in the present synthesis as well as in macrolide synthesis. Thus, optically active (+)-β-keto imide 4[3] was prepared by Evans' procedure[2a] and used as a starting material for pederin synthesis. 4 was subjected to reduction with $Zn(BH_4)_2$ in CH_2Cl_2 at -25° to give the desired syn-5[3] quantitatively with >30 : 1 stereoselection. Imide 5, after protection of the hydroxyl group as the THP ether, was reduced with DIBAH and the resulted aldehyde was treated with lithium enolate of t-butyl acetate in THF producing β-hydroxy ester 6 (80%). Reaction of 6 with p-TsOH in MeOH and successive treatment with p-TsOH in refluxing benzene gave α,β-unsaturated lactone 7 (81%).



a) $Zn(BH_4)_2/CH_2Cl_2/-25°$, b) DHP/p-TsOH; DIBAH/PhMe/-78°; LDA/t-BuOAc/THF/-78°, c) p-TsOH/MeOH; p-TsOH/PhH/reflux, d) $MeNO_2$/Triton B, e) $TiCl_3/Et_3N$, f) c. HCl/CH_2Cl_2, g) $HSCH_2CH_2SH/BF_3{\cdot}Et_2O/CH_2Cl_2$/rt, h) LDA/$MeOC(Me_2)OCH_2COOMe$/THF/-78 -20°; CSA/$CH(OMe)_3/CH_2Cl_2$/MeOH; DMSO/DCC/Py/$CF_3COOH/Et_2O$, i) $Zn(BH_4)_2/Et_2O$/-78°; PhCOCl/DMAP/Py, j) HgO/$HgCl_2$/aq MeCN; $Zn(BH_4)_2/Et_2O$, k) $PhSeCN/Bu_3P$/THF/0°, l) PrSLi/HMPA/rt.

Michael addition of nitromethane to 7 under the conditions reported by Meinwald et al.[4] gave lactone 8[3] having 4α(equatorial)-CH_2NO_2 group (92%).[5] The nitromethyl group of 8 was converted into aldehyde with $TiCl_3$ and Et_3N[6] producing bicyclic lactone 9[3], which was isomerized exclusively to the more stable lactone 10[3] with c. HCl treatment in CH_2Cl_2 (70% from 8). On treatment with ethanedithiol and $BF_3 \cdot Et_2O$, 10 was converted into thioacetal lactone 11[3] (mp 152-152.5°; 81%) having a favourable stereostructure for the next reactions. The isomer 12[3] was obtained from 9 in the same way. 11 was converted into α-keto ester 13 in 3 steps: 1) introduction of glycolic acid moiety (LDA/$MeOC(Me_2)OCH_2COOMe$); 2) conversion of the resulted hemiacetal into the methyl ether and simultaneous deprotection of methoxy i-propyl ether (CSA/$CH(OMe)_3$/MeOH); 3) Moffatt oxidation (DMSO/DCC); 91% overall yield. $Zn(BH_4)_2$ reduction of 13 in Et_2O at -78° yielded the desired 7β-alcohol 14 quantitatively with 17 : 1 stereoselection. Benzoylation of 14 afforded 15 (mp 135-6°; 86%), whose stereostructure was confirmed by X-ray crystallography. Dethioacetalization of 15 followed by $Zn(BH_4)_2$ reduction produced alcohol 16 in 91% yield. Phenylselenation of 16 was accomplished by PhSeCN and Bu_3P treatment[7] giving 17[3] (94%) without hydrolyzing benzoate group. Treatment of 17 with NaOMe gave alcohol 18, which was converted into (+)-methyl pederate (19) by deselenation. ^1H NMR data of 18 and 19 were identical with those of the corresponding authentic samples.[8] Selective hydrolysis of methyl ester of 17 was accomplished by PrSLi treatment in HMPA[9] giving (+)-1 quantitatively.

Then, we examined the total synthesis of (+)-pederin (3) from (+)-1 and (+)-2. Coupling of both segments was carried out in a similar manner reported by Matsumoto et al.[10]; reaction of acid chloride 20 obtained from 1 and imidate 21 from 2 gave N-acylimidate 22 which was immediately reduced with $NaBH_4$. Reduction in EtOH afforded 23[3] (19%) and 10α-isomer 24 (45%),



a) $SOCl_2$/Py/CH_2Cl_2, b) Me_3OBF_4/CH_2Cl_2, c) Et_3N/CH_2Cl_2, d) $NaBH_4$, e) i-PrSH/CSA/CH_2Cl_2, f) $HgCl_2$/Et_3N/MeOH, g) $NaIO_4$; Et_3N/PhH; 1N LiOH/MeOH.

whereas reduction in i-PrOH and CH_2Cl_2 produced 23 (28%) and 24 (30%), the selectivity being slightly improved. Epimer 24 was successfully converted into 23 as follows.[11] Treatment of 24 with i-PrSH and CSA in CH_2Cl_2 gave thioacetal 25 which was treated with $HgCl_2$ in MeOH in the presence of Et_3N[12] to give 23 in 47% yield (from 24) along with epimer 24 (36%). ^1H NMR data of 23 were identical with those of the authentic sample.[10] As 23 has already been converted into (+)-pederin (3),[10] total synthesis of 3 was thus accomplished.

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References and Notes

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2. a) D. A. Evans, M. D. Dennis, T. Le, N. Mandel, and G. Mandel, J. Am. Chem. Soc., 106, 1154 (1984). b) Y. Ito, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., 25, 6015 (1984).
3. ^1H NMR spectra were taken on a JEOL GX-400 instrument in $CDCl_3$. 4: NMR δ 2.33 (s; MeCO), 4.51 (q, J=7.3 Hz; 3-H); $[\alpha]_D^{20}$ +26.5°, $[\alpha]_D^{35}$ +22.9° (c=1.4, CH_2Cl_2). 5: NMR δ 1.17 (d; J=7.1 Hz; Me), 1.21 (d, J=6.4 Hz; Me); $[\alpha]_D^{26}$ -71.8° (c=1.61, $CHCl_3$). 8: NMR δ 2.42 (dd, J=16.0, 10.0 Hz; 5α-H), 2.71 (dd, J=16.0, 6.4 Hz; 5β-H); $[\alpha]_D^{25}$ +74.3° (c=1.11, $CHCl_3$). 9: NMR δ 2.63 (dd, J=19.0, 8.7 Hz; 5-Ha), 2.65 (dd, J=19.0, 4.9 Hz; 5-Hb). 10: NMR δ 2.45 (dd, J=18.1, 3.9 Hz; 5-Ha), 2.88 (dd, J=18.1, 10.7 Hz; 5-Hb). 11: NMR δ 2.26 (dd, J=18.1, 12.0 Hz; 5β-H), 2.90 (ddd, J=18.1, 5.6, 1.2 Hz; 5α-H), 4.33 (d, J=10.0 Hz; SCHS); $[\alpha]_D^{26}$ -12.4° (c=1.45, $CHCl_3$). 12: NMR δ 2.57 (dd, J=15.9, 10.8 Hz; 5α-H), 2.73 (dd, J=15.9, 6.4 Hz; 5β-H), 4.76 (d, J=5.4 Hz; SCHS). 17: NMR δ 3.24, 3.78 (each s; 2xOMe), 5.37 (s; 7-H); $[\alpha]_D^{26}$ +91.9° (c=3.6, $CHCl_3$). 23: NMR δ 5.31 (dd, J=9.8, 3.7 Hz; 10-H), 5.44 (s; 7-H), 6.69 (d, J=9.8 Hz; NH); $[\alpha]_D^{26}$ +67.1° (c=1.55, $CHCl_3$).
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5. Meinwald reported the synthesis of (±)-methyl pederate (19) from (±)-7 via 8 and 12.[4] However, the stereochemistry of most of intermediates has not been discussed. We assigned the stereostructure of 8, 11, and 12 as indicated in the text based on their 400 MHz ^1H NMR data.
6. cf. J. E. McMurry and J. Melton, J. Org. Chem., 38, 4367 (1973).
7. P. A. Grieco, S. Gilman, and M. Nishizawa., J. Org. Chem., 41, 1485 (1976).
8. K. Tsuzuki, T. Watanabe, M. Yanagiya, and T. Matsumoto, Tetrahedron Lett., 4745 (1976).
9. P. A. Bartlett and W. S. Johnson, Tetrahedron Lett., 4459 (1970).
10. F. Matsuda, M. Tomiyoshi, M. Yanagiya, and T. Matsumoto, Tetrahedron Lett., 24, 1277 (1983).
11. Matsumoto et al. extensively studied the epimerization of epi-24 to 23 by acid catalyzed double alkoxy-exchange reaction (see ref. 10).
12. cf. F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, J. Am. Chem. Soc., 99, 4835 (1977).

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