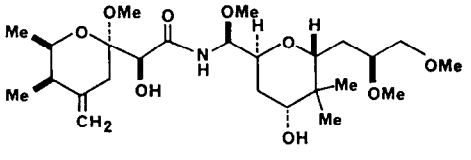
Tetrahedron Letters,Vol.26,No.52,pp 6461-6464,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF (+)-PEDERIN. 1. STEREOCONTROLLED SYNTHESIS OF (+)-BENZOYLPEDAMIDE

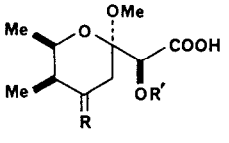
Tadashi Nakata,* Shigeto Nagao, Nobuyuki Mori, and Takeshi Oishi*
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama 351-01, Japan

Summary: (+)-Benzoylpedamide (5), a right half of (+)-pederin (1), was synthesized stereoselectively based on the newly developed method for the synthesis of 1,3-syn- and 1,3-anti-polyols.

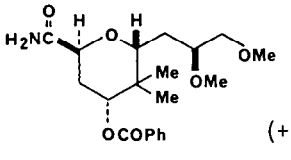
(+)-Pederin (1), a potent insect poison isolated from Paederus fuscipes, exhibits remarkable physiological activities such as inhibition of mitosis in HeLa cells and blocking of protein synthesis. The unique stereostructure of 1 having nine chiral centers has attracted the attention of synthetic organic chemists[1] and the first total synthesis of (+)-pederin (1) has been achieved by Matsumoto and co-workers.[1a] In their synthesis, (+)-acetylpederic acid (2) or (+)-selenoacid (3), a left half of 1, and (+)-benzoylpedamide (5), a right half, were synthesized initially and then combined to (+)-1 at the last stage. We also accomplished the synthesis of (+)-4 corresponding to 3 based on a stereoselective reduction of



(+)-Pederin (1)



(+)-2: R=CH_2, R'=Ac
(+)-3: R=β-CH_2SePh, α-H
R'=Ac
(+)-4: R=β-CH_2SePh, α-H
R'=COPh

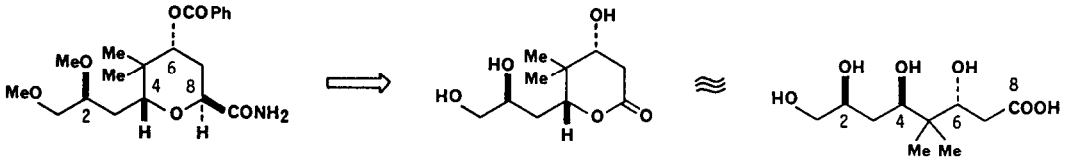


(+)-5

acyclic ketones with $Zn(BH_4)_2$[2] and (+)-5 based on a new synthetic method for stereochemically defined 1,3-polyols[3,4]. A total synthesis of (+)-pederin (1) from (+)-4 and (+)-5 was achieved following essentially Matsumoto's strategy. The synthesis of (+)-5 will be described in this communication and the synthesis of (+)-4 and the total synthesis of (+)-pederin (1) in the following paper.

Retrosynthetic analysis of 5 reveals that 2,4-syn-4,6-anti-triol A could be a precursor and therefore, it is highly expected that previously developed general methods for the syntheses of both 1,3-syn- and 1,3-anti-polyols[3,4] would be applied for the synthesis of A derivative and thus for 5 (Scheme 1).

Scheme 1



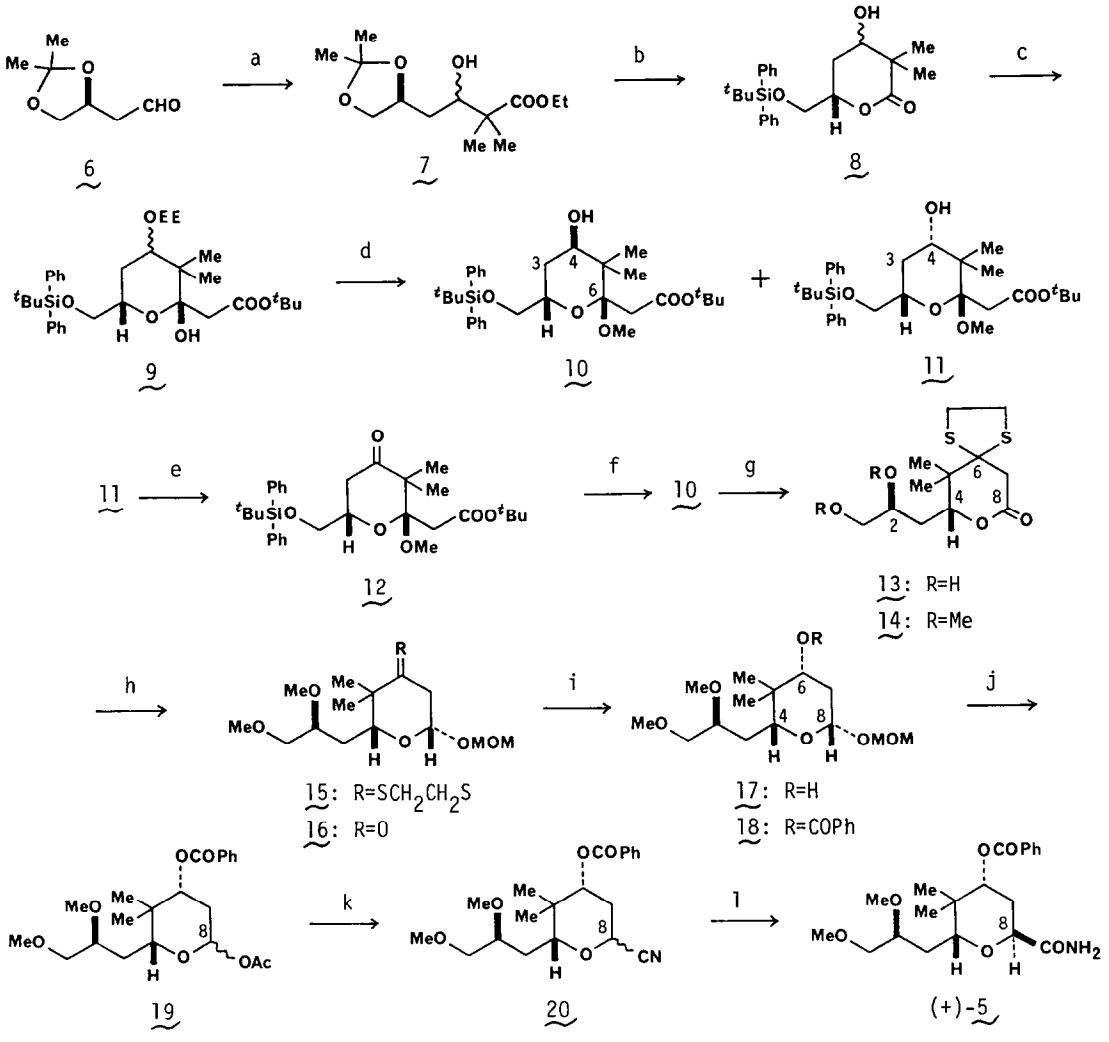
(+)-5 2,4-syn-4,6-anti A

Treatment of aldehyde 6,[5] prepared from (S)-(-)-malic acid, with LDA and i-PrCOOEt in THF at -78° afforded a mixture of β-hydroxy ester 7 in 74% yield. The mixture 7 was converted into δ-lactone 8 in a 3 step sequence: 1. deacetonization (p-TsOH/MeOH); 2. silylation (t-$BuPh_2SiCl$); 3. lactonization (CSA/benzene); 72% overall yield. Protection of the hydroxyl group of 8 as the ethoxyethyl ether and successive treatment with lithium enolate of t-butyl acetate in THF at -78° afforded hemiacetal 9. On treatment of 9 with $CH(OMe)_3$ and CSA in MeOH-CH_2Cl_2, acetalization and deprotection of ethoxyethyl group took place simultaneously producing a mixture of the desired 4β-alcohol 10 and 4α-isomer 11. Separation of the mixture was easily performed by column chromatography to afford alcohols 10[6] and 11[6] in 38% and 37% yields (from 8), respectively. The configurations of the hydroxyl groups were confirmed on the bases of their ^1H NMR data (10: $J_{3\alpha,4}=J_{3\beta,4}=2.9$ Hz; 11: $J_{3\alpha,4}=11.8$ Hz, $J_{3\beta,4}=4.8$ Hz). The undesired isomer 11 was successfully converted into the required 10 following the strategy used in 1,3-syn-polyol synthesis.[3] Namely, PCC oxidation of 11 and successive reduction of the resulted ketone 12 with L-Selectride in THF at -78° produced 4β-alcohol 10 (90%) as a single product. Reduction with K-Selectride used previously[3] gave only unsatisfactory results. On treatment of 10 with ethanedithiol and $BF_3 \cdot Et_2O$ at -30°, acetal-thioacetal interchange at C-6 position and successive lactonization between the 4β-hydroxyl group and the t-butyl ester took place producing δ-lactone 13 (83%). The liberated hydroxyl groups on the side chain in 13 were effectively methylated by treatment with CH_2N_2 in the presence of silica gel in ether[7] to give dimethoxy lactone 14[6] (83%).

The 4,6-anti stereoselection was accomplished by applying the method used in the termination of 1,3-anti-polyol synthesis.[4] DIBAH reduction of 14 in toluene at -78° and successive treatment with $BrCH_2OMe$ and i-Pr_2NEt in refluxing CH_2Cl_2 afforded exclusively the required equatorial MOM acetal 15[6] (88%), which was subjected to the dethioacetalization with NBS affording ketone 16[6] (87%). $LiAlH_4$ reduction of 16 in ether gave the expected 6α(equatorial)-alcohol 17 (98%) as a single product,[4] which on treatment with PhCOCl afforded benzoate 18[6] (100%). The configuration of the 6-hydroxyl group was assigned as equatorial by ^1H NMR analysis (18: $J_{6,7\alpha}=12.0$ Hz, $J_{6,7\beta}=4.6$ Hz).

The 8β(axial)-amide group present in the target molecule was introduced as follows.

Acid treatment of 18 followed by acetylation yielded a 2 : 1 mixture of 8α- and 8β-acetates 19 (86%). The mixture was treated with Me_3SiCN and $BF_3 \cdot Et_2O$ in CH_2Cl_2[8] to give a mixture of 8β- and 8α-nitriles 20[6] (94%) in a ratio of ca. 10 : 1 (by ^1H NMR analysis), 8β-isomer predominating. Finally, treatment of the mixture with $TiCl_4$ in aq AcOH[9] produced 8β-amide 5[6] (87%) and C-8 epimer (10%). The physical data of the major isomer 5 were identical with those of the authentic (+)-benzoylpedamide (mp, mixed mp, ^1H-NMR, $[\alpha]_D$).[10]



Acknowledgement: The authors are grateful to Professor Takeshi Matsumoto (Hokkaido University) for providing the authentic sample of (+)-benzoylpedamide. This work was supported by Special Coordination Funds of the Science and Technology of the Japanese Government.

References and Notes

1. a) F. Matsuda, N. Tomiyoshi, M. Yanagiya, and T. Matsumoto, Tetrahedron Lett., 24, 1277 (1983); M. Yanagiya, F. Matsuda, K. Hasegawa, and T. Matsumoto, ibid., 23, 4039 (1982); F. Matsuda, M. Yanagiya, and T. Matsumoto, ibid., 23, 4043 (1982); T. Matsumoto, F. Matsuda, K. Hasegawa, and M. Yanagiya, Tetrahedron, 40, 2337 (1984). For approaches to the synthesis of 1: b) J. Meinwald, Pure and Appl. Chem., 49, 1275 (1977); M. A. Adams, A. J. Duggan, J. Smolanoff, and J. Meinwald, J. Am. Chem. Soc., 101, 5364 (1979). c) G. S. Cockerill and P. Kocienski, J. Chem. Soc. Chem. Comm., 460 (1982); K. Isaac, P. Kocienski, and S. Campbell, ibid., 249 (1983); P. Kocienski and T. M. Willson, ibid., 1011 (1984).
2. T. Oishi and T. Nakata, Acc. Chem. Res., 17, 338 (1984).
3. T. Nakata, S. Takao, M. Fukui, T. Tanaka, and T. Oishi, Tetrahedron Lett., 24, 3873 (1983).
4. T. Nakata, S. Nagao, and T. Oishi, Tetrahedron Lett., 26, 75 (1985).
5. S. Hanessian, A. Ugolini, and M. Therien, J. Org. Chem., 48, 4427 (1983).
6. ^{1}H NMR spectra were taken on a JEOL GX-400 instrument in $CDCl_3$. 10: NMR δ 1.58 (dt, J=13.7, 2.9 Hz; 3β-H), 1.87 (ddd, J=13.7, 12.5, 2.9 Hz; 3α-H), 3.40 (s; OMe), 3.45 (dt, J=10.0, 2.9 Hz; 4α-H), 3.90 (m; 2β-H), 4.11 (d, J=10.0 Hz; OH), $[\alpha]_D^{18}$ -9.2° (c=1.94, $CHCl_3$). 11: NMR δ 3.29 (s; OMe), 3.98 (dd, J=11.8, 4.8 Hz; 4β-H); $[\alpha]_D^{19}$ +5.4° (c=2.12, $CHCl_3$). 14: NMR δ 3.40, 3.41 (each s; 2xOMe), 3.64 (m; 2α-H), 4.39 (dd, J=10.5, 1.5 Hz; 4β-H); $[\alpha]_D^{19}$ +96.1° (c=1.40, $CHCl_3$). 15: NMR δ 3.386, 3.398, 3.403 (each s; 3xOMe), 4.81 (dd, J=9.8, 2.2 Hz; 8β-H). 16: NMR δ 3.37, 3.39, 3.40 (each s; 3xOMe), 4.85 (dd, J=9.8, 2.9 Hz; 8β-H). 18: NMR δ 3.23 (dd, J=8.8, 2.9 Hz; 4β-H), 3.388, 3.394, 3.398 (each s; 3xOMe), 3.54 (m; 2α-H), 4.93 (dd, J=12.0, 4.6 Hz; 6β-H); $[\alpha]_D^{20}$ -57.2° (c=1.74, $CHCl_3$). 20: 8β-CN; NMR δ 4.96 (dd, J=6.1, 1.7 Hz; 8α-H), 5.18 (dd, J=11.5, 5.1 Hz; 6β-H). 5: NMR δ 0.93, 1.08 (each s; 2xMe), 2.03 (ddd, J=13.2, 10.7, 6.6 Hz; 7α-H), 2.59 (ddd, J=13.2, 4.6, 2.7 Hz; 7β-H), 3.39, 3.42 (each s; 2xOMe), 4.48 (dd, J=6.6, 2.7 Hz; 8α-H), 4.98 (dd, J=10.7, 4.6 Hz; 6β-H), 5.46 (broad s; NH_2).
7. K. Ohno, H. Nishiyama, and H. Nagase, Tetrahedron Lett., 4405 (1979).
8. K. Utimoto and T. Horiie, Tetrahedron Lett., 23, 237 (1982); K. Utimoto, Y. Wakabayashi, T. Horiie, M. Inoue, Y. Shishiyama, M. Obayashi, and H. Nozaki, Tetrahedron, 39, 967 (1983).
9. T. Mukaiyama, K. Kamio, S. Kobayashi, and H. Takei, Chemistry Lett., 357 (1973).
10. 5: mp 145-6°, $[\alpha]_D^{22}$ +20.5° (c=3.22, $CHCl_3$); mixed mp 139-142° (lit[1a] mp 137-8°; $[\alpha]_D^{28}$ +15.9° (c=3.24, $CHCl_3$)).

(Received in Japan 27 August 1985)