

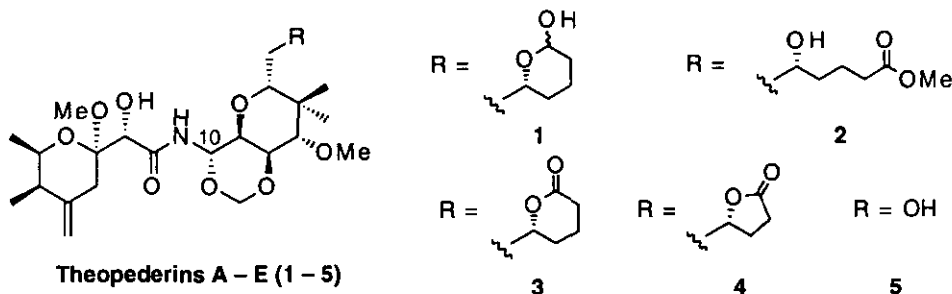
A PRACTICAL SYNTHESIS OF THE KEY INTERMEDIATE FOR THEOPEDERINS—AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-METHYL PEDERATE†

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Abstract —A practical synthesis of the key intermediate for theopederins, methyl pederate (**15**), has been accomplished by means of palladium-catalyzed reactions.

Because of their unique structures and pharmacological properties, theopederins A–E (**1–5**), isolated from *Theonella* sp. by Fusetani and his co-workers¹ in 1992, and their relatives [mycalamides A, B,² onnamide A,³ and pederin⁴] are attractive candidates for total synthesis. They all exhibit strong cytotoxic activities.⁵ Especially, theopederin A (**1**) is remarkable cytotoxic against P388 murine leukemia cells with an IC_{50} value of 0.05 ng/mL.¹ Each possesses a pederic acid unit and an intriguing acylaminal functional group at C-10. The unusual structural features coupled with their biological properties have produced efforts in several laboratories toward their preparation, which have culminated in the synthesis of mycalamide A, B,⁶ onnamide A⁷ and pederin.⁸

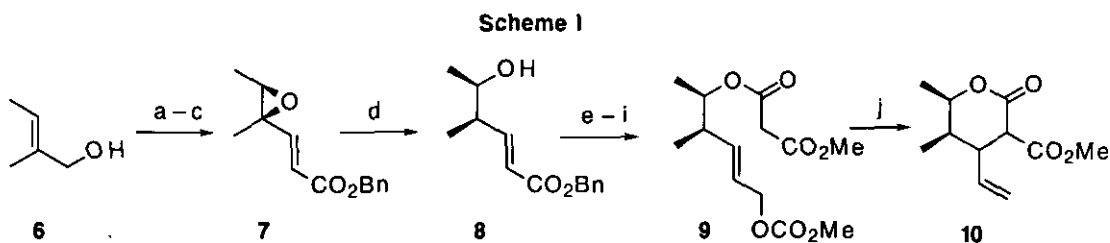


In our first contribution to this area, we would like to describe an enantioselective total synthesis of (+)-methyl pederate (**15**), a key intermediate for the synthesis of theopederins, based upon successive

† This paper is dedicated to Prof. K. Nakanishi on the occasion in his 75th birthday.

palladium-catalyzed reactions.

Tiglic alcohol (**6**) was subjected to the Sharpless asymmetric epoxidation⁹ (cumene hydroperoxide, (-)-DIPT, $\text{Ti}(\text{O}^i\text{Pr})_4$, 3A-MS, CH_2Cl_2 , -70°C) to provide the 2,3-epoxy alcohol with 92% ee, determined by using the Mosher ester analysis.¹⁰ After TPAP oxidation,¹¹ the efficient construction of the *E*-olefin (**7**) (*E*:*Z*=16:1) was accomplished by the method of Masamune and Roush.¹² Palladium-catalyzed hydrogenolysis¹³ of the (*E*)-alkenyloxirane (**7**) was conducted with $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ in the presence of $^t\text{Bu}_3\text{P}\cdot\text{HCO}_2\text{H}\cdot\text{Et}_3\text{N}$ in 1,4-dioxane to furnish the alcohol (**8**) as the major isomer in a 16:1 mixture. Protection of **8** (TBSOTf, 2,6-lutidine) followed by flash chromatography removed the minor isomer to afford the corresponding pure TBS ether, which was transformed into the allylic alcohol derivative (**9**) by sequential DIBALH reduction, carbonate formation (ClCO_2Me , pyridine), deprotection with $^t\text{Bu}_4\text{N}^+\text{F}^-$, and esterification with malonic acid monomethyl ester in the presence of DMAP and [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: WSC]. The pivotal palladium-catalyzed cyclization¹⁴ of the carbonate (**9**)¹⁵ was examined under a wide variety of conditions. As a result of testing, preparative-scale cyclization was best carried out with 5 mol % $\text{Pd}(\text{OAc})_2$ and 20 mol % Ph_3P at 90°C in DMSO. Cyclization conducted on a large scale provided the desired product (**10**) as a 3:1 mixture of diastereomers. The non-stereoselectivity of the cyclization was of little consequence, since both of the products could be converted efficiently to the bicyclic γ -lactone (**11**) (Scheme I).



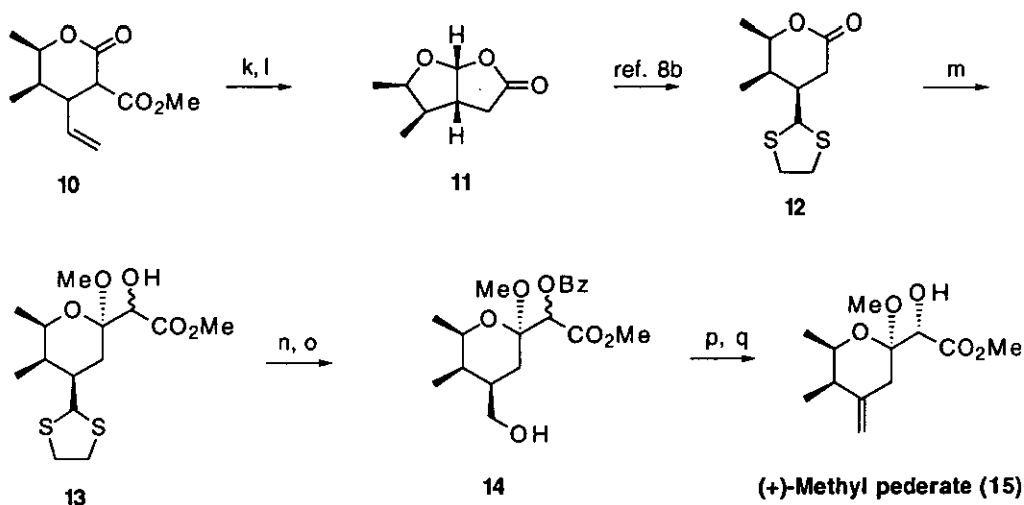
(a) PhMe_2COOH , (-)-DIPT, $\text{Ti}(\text{O}^i\text{Pr})_4$, 3A-MS, CH_2Cl_2 , -70°C (68%), (b) TPAP, NMO, 4A-MS, MeCN, (c) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Bn}$, LiCl, $^i\text{Pr}_2\text{NEt}$, MeCN (2 steps: 67%), (d) $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$, $^t\text{Bu}_3\text{P}$, HCO_2H , Et_3N , dioxane (89%), (e) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 0°C (88%), (f) DIBALH, CH_2Cl_2 , -78°C (95%), (g) ClCO_2Me , pyridine, CH_2Cl_2 (100%), (h) $^t\text{Bu}_4\text{N}^+\text{F}^-$, THF (97%) (i) $\text{HO}_2\text{CCH}_2\text{CO}_2\text{Me}$, WSC, DMAP, CH_2Cl_2 (97%), (j) $\text{Pd}(\text{OAc})_2$, PPh_3 , DMSO, 90°C (69%)

Demethoxycarbonylation¹⁶ (LiAlH_4 , DMF, reflux) of the cyclized products (**10**) followed by ozonolysis (O_3 , MeOH, -78°C ; Me_2S) furnished the aldehyde, which was converted to the bicyclic γ -lactone (**11**).^{8b} After

transformation of **11** into **12**,^{8b} aldol condensation of methyl *O*-(2-methoxy-2-propyl)glycolate with **12** in the presence of LDA, carried out between $-78\text{ }^{\circ}\text{C}$ and $-15\text{ }^{\circ}\text{C}$, afforded the coupled products, which were allowed to react with trimethyl orthoformate and MeOH in the presence of CSA, providing the methoxylated compound (**13**) as a 3:1 mixture of diastereomers. Since attempts at converting **13** to the corresponding ketone were unsuccessful, we adopted the following transformation. After esterification (BzCl, pyridine, DMAP) of **13** followed by dethioacetalization (HgCl₂, HgO, MeCN-H₂O), the resulting aldehyde was reduced with NaBH₄ to furnish the alcohols (**14**). The compounds (**14**) were, on the action of *o*-nitrophenyl selenocyanate and tributylphosphine,¹⁷ converted to the selenides, oxidation of which with 30% H₂O₂ produced the olefins. When a solution of the resulting compounds in MeOH containing NaOMe was stirred at $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, chromatographically separable (+)-methyl pederate (**15**)¹⁸ and (+)-methyl *epi*-pederate¹⁹ were formed in a combined isolated yield of 82%. The spectral properties (¹H NMR, IR) of (+)-methyl pederate (**15**) were identical in all respects to those provided by Nakata (Scheme II).

In conclusion, we have established a practical strategy for the synthesis of (+)-methyl pederate (**15**) by employing successive palladium-catalyzed reactions.

Scheme II



(k) Lil, DMF, reflux (86%), (l) O₃, MeOH, $-78\text{ }^{\circ}\text{C}$; Me₂S; conc HCl, CH₂Cl₂ (93%), (m) MeO₂CCH₂OC(Me)₂OMe, LDA, $-78\text{ }^{\circ}\text{C}$; **12**, $-78\text{ }^{\circ}\text{C} \rightarrow -15\text{ }^{\circ}\text{C}$; HC(OMe)₃, MeOH, CSA, CH₂Cl₂ (71%), (n) BzCl, DMAP, pyridine, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, (o) HgCl₂, HgO, MeCN-H₂O, $62\text{ }^{\circ}\text{C}$; NaBH₄, MeOH, $0\text{ }^{\circ}\text{C}$ (2 steps: 83%), (p) *o*-NO₂PhSeCN, ⁿBu₃P, THF, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$; 30% H₂O₂, THF, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$ (60%), (q) NaOMe, MeOH, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$ (82%)

ACKNOWLEDGMENT

We are very grateful to Dr. Tadashi Nakata (Riken), for sending us copies of the spectral data of (+)-methyl pederate (**15**). This work supported by Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

REFERENCES AND NOTES

1. N. Fusetani, T. Sugawara, and S. Matsunaga, *J. Org. Chem.*, 1992, **57**, 3828.
2. (a) N. B. Perry, J. W. Blunt, M. H. G. Munro, and L. K. Pannell, *J. Am. Chem. Soc.*, 1988, **110**, 4850. (b) N. B. Perry, J. W. Blunt, M. H. G. Munro, and A. M. Thompson, *J. Org. Chem.*, 1990, **55**, 223.
3. (a) S. Sakemi, T. Ichiba, S. Kohmoto, G. Saucy, and T. Higa, *J. Am. Chem. Soc.*, 1988, **110**, 4851. (b) S. Matsunaga, N. Fusetani, and Y. Nakao, *Tetrahedron*, 1992, **48**, 8369.
4. (a) J. H. Frank and K. Kanamitsu, *J. Med. Entomol.*, 1987, **24**, 155. (b) M. Pavan and G. Bo, *Mem. Soc. Entomol. Ital.*, 1952, **31**, 67. (c) *idem*, *Physiol. Comp. Oecol.*, 1953, **3**, 307.
5. A. M. Thompson, J. W. Blunt, M. H. G. Munro, N. B. Perry, and L. K. Pannell, *J. Chem. Soc. Perkin Trans. 1*, 1992, 1335.
6. (a) C. Y. Hong and Y. Kishi, *J. Org. Chem.*, 1990, **55**, 4242. (b) T. Nakata, H. Matsukura, D. Jian, and H. Nagashima, *Tetrahedron Lett.*, 1994, **35**, 8229. (c) T. Nakata, H. Fukui, T. Nakagawa, and H. Matsukura, *Heterocycles*, 1996, **42**, 159.
7. C. Y. Hong and Y. Kishi, *J. Am. Chem. Soc.*, 1991, **113**, 9693.
8. (a) F. Matsuda, N. Tomiyoshi, M. Yanagiya, and T. Matsumoto, *Tetrahedron*, 1988, **44**, 7063. (b) T. Nakata, S. Nagao, N. Mori, and T. Oishi, *Tetrahedron Lett.*, 1985, **26**, 6461 and 6465. (c) T. M. Willson, P. Kocienski, K. Jarowicki, K. Issac, P. Hitchcock, A. Faller, and S. F. Campbell, *Tetrahedron*, 1990, **46**, 1767.
9. T. Martín, C. M. Rodríguez, and S. V. Martín, *Tetrahedron: Asymmetry*, 1995, **6**, 1151.
10. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
11. S. V. Ley, J. Norman, W. P. Griffith, and S. P. Marsden, *Synthesis*, 1994, 639.
12. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.
13. M. Oshima, H. Yamazaki, I. Shimizu, M. Nisar, and J. Tsuji, *J. Am. Chem. Soc.*, 1989, **111**, 6280.
14. recent reviews: (a) C. G. Frost, J. Howarth, and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089. (b) A. Heumann and M. Reglier, *Tetrahedron*, 1995, **51**, 975. (c) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395.
15. It is noteworthy that initial attempts to form the valerolactone derivative from (4*R*,5*R*,2*E*)-5-hydroxy-4-methyl-2-hexenyl acetate resulted in decomposition.
16. A. P. Krapcho, *Synthesis*, 1982, 805 and 893.
17. (a) K. B. Sharpless and M. W. Young, *J. Org. Chem.*, 1975, **40**, 947. (b) P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485.
18. W. R. Roush, T. G. Marron, and L. A. Pfeifer, *J. Org. Chem.*, 1997, **62**, 474.
19. (+)-Methyl *epi*-pederate has stereoselectively been transformed into (+)-methyl pederate (**15**) by 2 steps.²⁰
20. K. Tsuzuki, T. Watanabe, M. Yanagiya, and T. Matsumoto, *Tetrahedron Lett.*, 1976, 4745.