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

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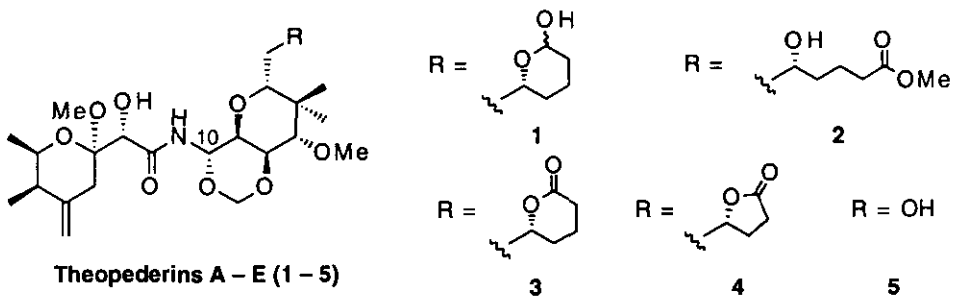
Abstract —A practical synthesis of the key intermediate for theopederins, methyl pederate (**15**), has been accomplished by means of palladium-catalyzed reactions.

Because of their unique structures and pharmacological properties, theopederins A–E (**1**–**5**), isolated from *Theonella* sp. by Fusetani and his co-workers[1] in 1992, and their relatives [mycalamides A, B,[2] onnamide A,[3] and pederin[4]] 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 A[7] and pederin.[8]



Theopederins A – E (1 – 5)

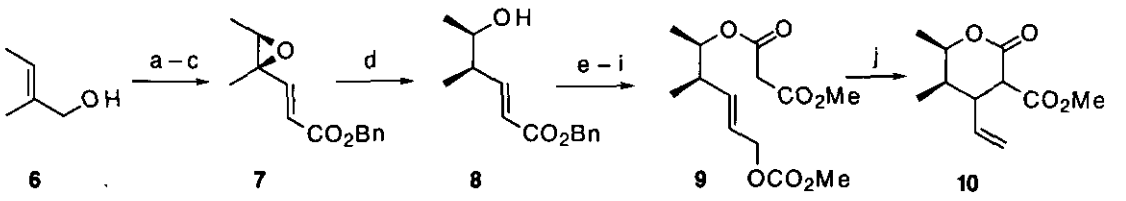
In our first contribution to this area, we would like to describe an enantioselective total synthesis of (+)-methyl pederate (**15**), a key intermediate for the synthesis of theopederins, based upon successive

† 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 epoxidation[9] (cumene hydroperoxide, (–)-DIPT, $Ti(O^iPr)_4$, 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 hydrogenolysis[13] of the (*E*)-alkenyloxirane (**7**) was conducted with $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of $^nBu_3P$-HCO_2H-Et_3N 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 $^nBu_4N^+F^-$, and esterification with malonic acid monomethyl ester in the presence of DMAP and [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: WSC)]. The pivotal palladium-catalyzed cyclization[14] 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 % $Pd(OAc)_2$ 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).

Scheme I



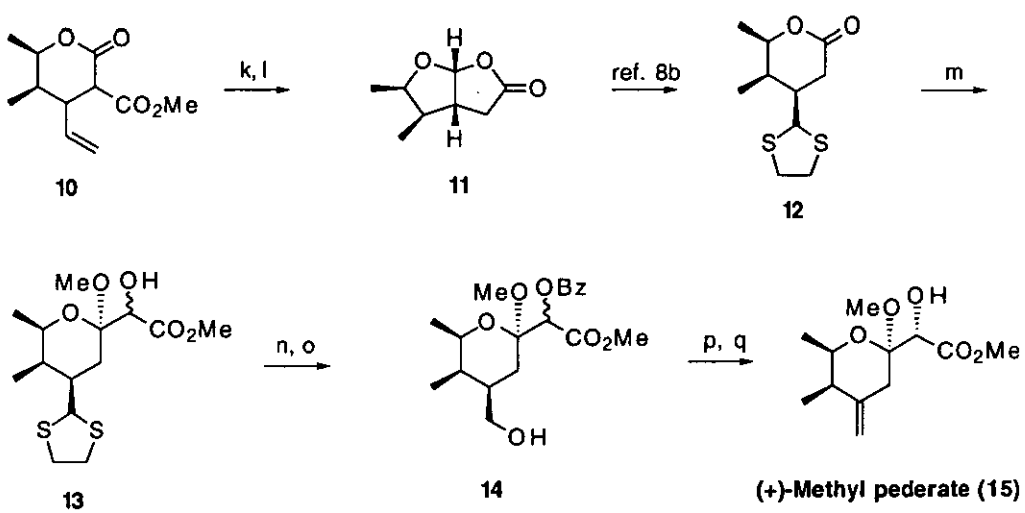
(a) $PhMe_2COOH$, (–)-DIPT, $Ti(O^iPr)_4$, 3A-MS, CH_2Cl_2, –70 °C (68%), (b) TPAP, NMO, 4A-MS, MeCN, (c) $(EtO)_2P(O)CH_2CO_2Bn$, LiCl, $^iPr_2NEt$, MeCN (2 steps: 67%), (d) $Pd_2(dba)_3{\cdot}CHCl_3$, $^nBu_3P$, HCO_2H, Et_3N, dioxane (89%), (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (88%), (f) DIBALH, CH_2Cl_2, –78 °C (95%), (g) $ClCO_2Me$, pyridine, CH_2Cl_2 (100%), (h) $^nBu_4N^+F^-$, THF (97%) (i) $HO_2CCH_2CO_2Me$, WSC, DMAP, CH_2Cl_2 (97%), (j) $Pd(OAc)_2$, PPh_3, DMSO, 90 °C (69%)

Demethoxycarbonylation[16] (LiI, 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**).[8h] After

transformation of **11** into **12**,[8h] aldol condensation of methyl *O*-(2-methoxy-2-propyl)glycolate with **12** in the presence of LDA, carried out between –78 ℃ and –15 °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 ($HgCl_2$, HgO, MeCN-H_2O), the resulting aldehyde was reduced with $NaBH_4$ 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% H_2O_2 produced the olefins. When a solution of the resulting compounds in MeOH containing NaOMe was stirred at 0 °C→rt, chromatographically separable (+)-methyl pederate (**15**)[18] and (+)-methyl *epi*-pederate[19] 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) LiI, DMF, reflux (86%), (l) O_3, MeOH, –78 °C; Me_2S; conc HCl, CH_2Cl_2 (93%), (m) $MeO_2CCH_2OC(Me)_2OMe$, LDA, –78 °C;**12**, –78 °C → –15 °C; $HC(OMe)_3$, MeOH, CSA, CH_2Cl_2 (71%), (n) BzCl, DMAP, pyridine, 0 °C → rt, (o) $HgCl_2$, HgO, MeCN-H_2O, 62 °C; $NaBH_4$, MeOH, 0 °C (2 steps: 83%), (p) *o*-$NO_2PhSeCN$, $^nBu_3P$, THF, 0 °C →rt; 30% H_2O_2, THF, 0 °C → rt (60%), (q) NaOMe, MeOH, 0 °C → rt (82%)

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