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Simple and Efficient Synthesis of (+)-Methyl 7-Benzoylpederate, a Key Intermediate toward the Mycalamides

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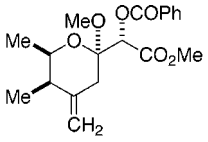
ABSTRACT



(+)-Methyl 7-benzoylpederate

A simple and efficient method for the synthesis of (+)-methyl 7-benzoylpederate, the left half of pederin, mycalamides, onnamides, and theopederins, was developed. The key reactions include the Evans asymmetric aldol reaction, a thioacetalization–lactonization, a stereoselective Claisen condensation, and a Takai–Nozaki olefination. The synthesis requires only nine steps and proceeds in 26% overall yield.

Mycalamide A (**1**; Figure 1),[1] isolated from a New Zealand marine sponge of the genus *Mycale*, exhibits in vivo potent antitumor and antiviral activity and immunosuppressive action via inhibition of T-cell activation.[2] Structure elucidation revealed its striking resemblance to the unique structure of pederin (**2**), a strong insect toxin isolated from *Paederus fuscipes*.[3] The onnamides[4] and theopederins,[5] which are structurally related compounds, were isolated from a Japanese marine sponge of the genus *Theonella*. Their unique structure and potent biological activity have attracted the attention of numerous synthetic organic chemists:[6−15] total syntheses have been reported for pederin,[6−8] mycalamides A[9,10] and B,[9,11] onnamide A,[12] and theopederin D.[13] As all of these natural

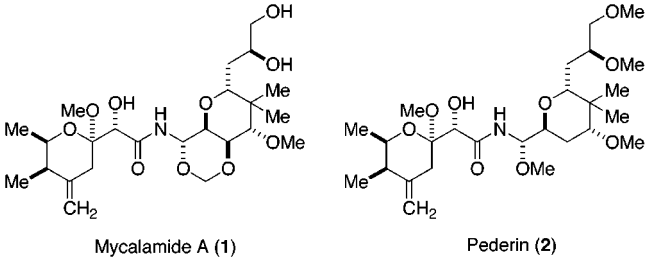


Figure 1. Structures of mycalamide A (**1**) and pederin (**2**).

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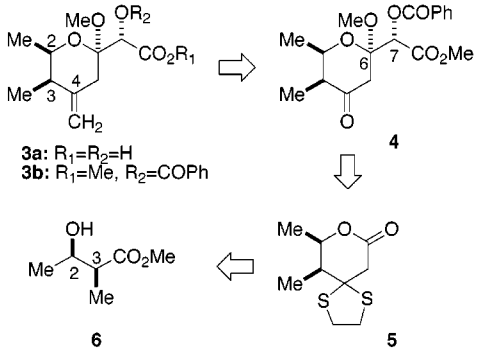
compounds contain an identical pederic acid (**3a**) as the left half, various methods for the syntheses of pederic acid derivatives **3** have been reported in these synthetic studies.[6−8,14] However, more efficient syntheses of pederic acid derivatives **3** are still required for further studies on the total synthesis of this mycalamide family and detailed examination of their biological activity. We herein describe a substantially improved, simple, and highly efficient synthesis of (+)-methyl 7-benzoylpederate (**3b**), which is the key intermediate in our total synthesis of **1**.[10]

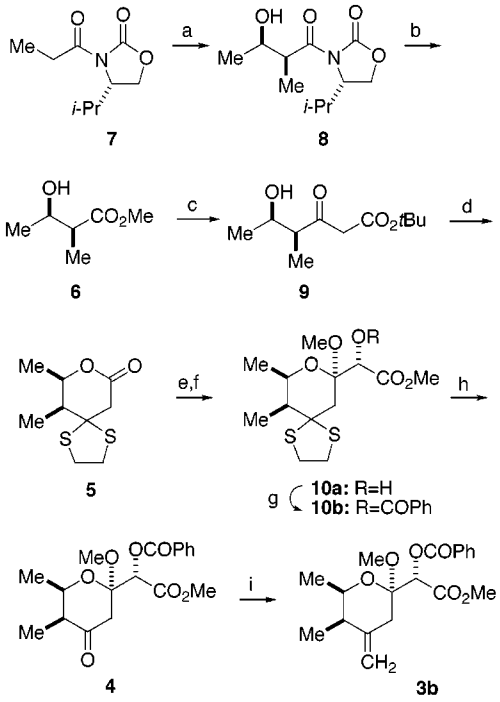
Our synthetic strategy for **3b** is outlined in Scheme 1. The C4-*exo*-methylene unit is introduced to the ketone **4** at the final stage. The key step involves the construction of the C6−C7 bond with concomitant control of the C6 and C7 stereochemistry via a diastereoselective Claisen condensation of the δ-lactone **5** and a glycolate unit. The δ-lactone **5** can be prepared from the optically active 2,3-*syn*-hydroxy ester **6**.

Scheme 1



The synthesis of (+)-methyl 7-benzoylpederate (**3b**) started with an Evans asymmetric aldol reaction using chiral propionimide **7**[16] derived from L-valine (Scheme 2). Reaction of the boron enolate of **7** with acetaldehyde provided the 2,3-*syn*-alcohol **8** with excellent stereoselectivity in 91% yield. Treatment of **8** with NaOMe in MeOH effected the alcoholysis to give methyl ester **6**[17] without any racemization in 70% yield. Reaction of the ester **6** with the lithium enolate of *tert*-butyl acetate at −15 °C afforded a 10:1 equilibrium mixture of β-keto ester **9** and its enol tautomer in 94% yield. The mixture was converted into the desired δ-lactone **5** in one step: upon treatment with 1,2-ethanedithiol in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2, thioacetalization and lactonization took place simultaneously,[18] giving a 17:1 mixture of **5** and its C3 epimer in 90% yield. The δ-lactone **5** has an ideal structure toward the target compound **3b**: it retains the 2,3-*syn*-dimethyl substituents, it possesses a masked ketone for introduction of the *exo*-methylene unit, and it has a lactone carbonyl group for introduction of the glycolate unit in the development of the side chain.

Scheme 2[a]



[a] Reagents and conditions: (a) Bu_2BOTf, CH_2Cl_2, Et_3N, −78 to 0 °C; MeCHO, −78 to 0 °C (91%); (b) NaOMe, MeOH, 0 °C (70%); (c) LDA, *t*-BuOAc, THF, −78 to −15 °C (94%); (d) $BF_3{\cdot}Et_2O$, $HSCH_2CH_2SH$, CH_2Cl_2, −40 °C to room temperature (90%); (e) LDA, $MeOC(Me)_2OCH_2CO_2Me$, THF, HMPA, $ZnCl_2$-ether, −78 to −40 °C; (f) CSA, $CH(OMe)_3$, MeOH, CH_2Cl_2, room temperature (82% from **5**); (g) PhCOCl, DMAP, pyridine, room temperature (98%); (h) $(CF_3CO_2)_2IPh$, MeCN, H_2O, −5 °C to room temperature (80%); (i) Zn, CH_2I_2, $TiCl_4$, THF, room temperature (79%).

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In most previous syntheses of pederic acid derivatives **3**, the glycolate units were introduced to the corresponding δ-lactone derivatives with low stereoselectivity of the C7-hydroxyl group:[6a,7b,8a,14a,b] therefore, oxidation followed by stereoselective reduction of the resulting ketone was necessary for the stereoselection.[6a,7b] With the δ-lactone **5** in hand, our attention was focused on introduction of a methyl glycolate unit to **5** with direct stereocontrol of the C7-hydroxyl group. After several attempts, we found that in the Claisen-type condensation of **5** and a methyl glycolate derivative, addition of $ZnCl_2$ improved both the yield and the stereoselectivity.[19] The condensation of **5** with the lithium enolate of $MeOC(Me)_2OCH_2CO_2Me$ in THF was undertaken in the presence of HMPA and ethereal $ZnCl_2$ at −78 to −40 °C for 19 h to afford the coupling product. Subsequent treatment with CSA and $CH(OMe)_3$ in $MeOH-CH_2Cl_2$ gave the desired 7α-hydroxy ester **10a** as the single isomer in 82% yield (two steps) along with recovered **5** (8%). In the absence of HMPA, the coupling reaction was interminably slow, and elevation of the reaction temperature beyond −30 °C led to significant substrate destruction. The present reaction would proceed with excellent stereoselection via the thermodynamically stable zinc-chelated intermediate **i** as shown in Figure 2,[19] in which the C7 substituent occupies an equatorial position.

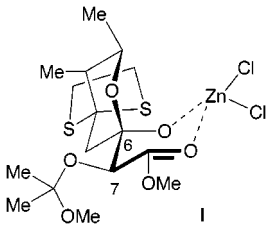

Figure 2.

Completion of the synthesis of (+)-methyl 7-benzoylpederate (**3b**) was achieved via introduction of the C4-*exo*-methylene unit as follows. Protection of the alcohol **10a** with PhCOCl and catalytic DMAP in pyridine gave the benzoate **10b** in 98% yield. Dethioacetalization of **10b** with bis(trifluoroacetoxy)iodobenzene in aqueous MeCN[20] cleanly afforded ketone **4** in 80% yield. Finally, introduction of an *exo*-methylene to the labile ketone **4** was achieved by a Takai−Nozaki olefination:[14c,21] treatment of **4** with Zn, CH_2I_2, and $TiCl_4$ in $THF-CH_2Cl_2$ provided (+)-methyl 7-benzoylpederate (**3b**) in 79% yield.[22,23] The spectral data (^1H, ^{13}C NMR, and $[\alpha]_D$) of the synthetic **3b** were identical with those of the authentic sample[10b] prepared previously by this group.

In summary, we have developed a very simple and efficient synthesis of (+)-methyl 7-benzoylpederate (**3b**), the left half of the mycalamide family, in only nine steps and with 26% overall yield from chiral propionimide **7**.[24]

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Supporting Information Available: Full experimental details and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Treatment of **3b** with *n*-PrSLi in HMPA produced 7-benzoylpederic acid (**3c**) (R_1 = H, R_2 = COPh) (96%), which was employed as the left half in our total synthesis of mycalamide A.[10b]

(23) The Wittig reaction of **4** using $PhP_3P^+MeI^-$ and *n*-BuLi produced methyl pederate (**3d**; R_1 = Me, R_2 = H)[6a,7b] (31%) and α,β-unsaturated ketone (17%) by elimination of MeOH.

(24) Our previous procedure for the synthesis of **3b** needed 21 steps and resulted in 17% overall yield starting from Evans chiral propionimide derived from D-valine.[7b,10b] Other recent procedures for the synthesis of pederic acid derivatives starting from Evans chiral propionimides: Roush group, synthesis of **3e** (R_1 = H, R_2 = DMPM), 14% overall yield in 15 steps;[14c] Toyota−Ihara group, synthesis of **3d** (R_1 = Me, R_2 = H), 6% overall yield in 21 steps.[14d]