Pergamon

Tetrahedron Letters, Vol. 36, No. 10, pp. 1581-1584, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00093-3

Diastereoselective Synthesis of N-Benzoyl Mycalamine, the Fully Elaborated Trioxadecalin Nucleus of Mycalamide A. Control of the Key N-Acyl Aminal Stereocenter via Carbamate Acylation

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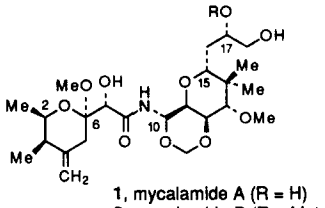
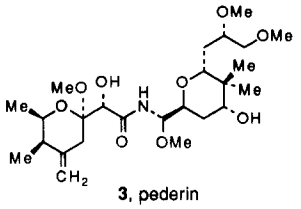
Abstract: A highly diastereoselective synthesis of N-benzoyl mycalamine (8), corresponding to the C(10)-C(18) amine fragment of mycalamide A, is described. The synthesis features a highly stereoselective acylation of carbamate 7 that permits the stereochemistry of the key C(10)-N-acyl aminal center to be controlled.

Mycalamides A (**1**) and B (**2**) are sub-nanomolar inhibitors of protein and DNA synthesis isolated from marine sponges (*Mycale* species)[2] and show promising antiviral, antitumor, and immunosuppressive activity.[3] They are structurally related to pederin (**3**),[4] a potent insect toxin, as well as to the onnamides and the theopederins which differ from the mycalamides principally in the C(15) side chain.[5] All of these compounds contain a pederic acid sub-unit [C(1)-C(8)] and an N-acyl aminal unit at C(10) that is critical to their biological activity.[6]



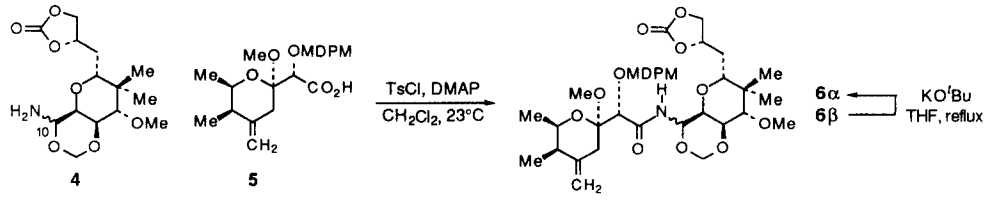
1, mycalamide A (R = H)
2, mycalamide B (R = Me)



3, pederin

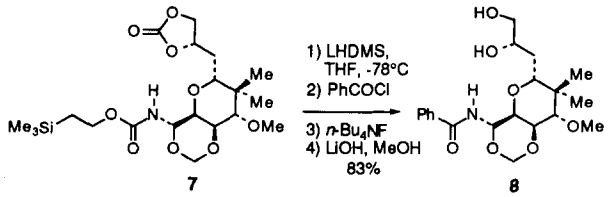
The potent biological properties of the mycalamide-onnamide family, their relative scarcity from natural sources, and their challenging structures have prompted several groups to pursue their synthesis. Kishi has reported pioneering total syntheses of **1** and **2**, as well as of onnamide A,[7] while our group and that of Hoffmann have reported syntheses of structures corresponding to the trioxadecalin ring systems of **1** and **2**.[8,9] Very recently, Nakata reported a formal total synthesis of mycalamide A via synthesis of Kishi's azide precursor to **4**.[10]

Our goal from the outset has been to develop a synthesis that permits the critical C(10) N-acyl aminal unit to be introduced in a highly stereocontrolled manner. Our planning was guided by Kishi's observation that the C(10) aminal **4**, formally an amino glycoside, is configurationally unstable under acidic, basic, and neutral conditions, and that acylation of **4** with the pederic acid unit **5** provided a mixture of α- and β-amide epimers.[7a] Further, Kishi also



4 **5**

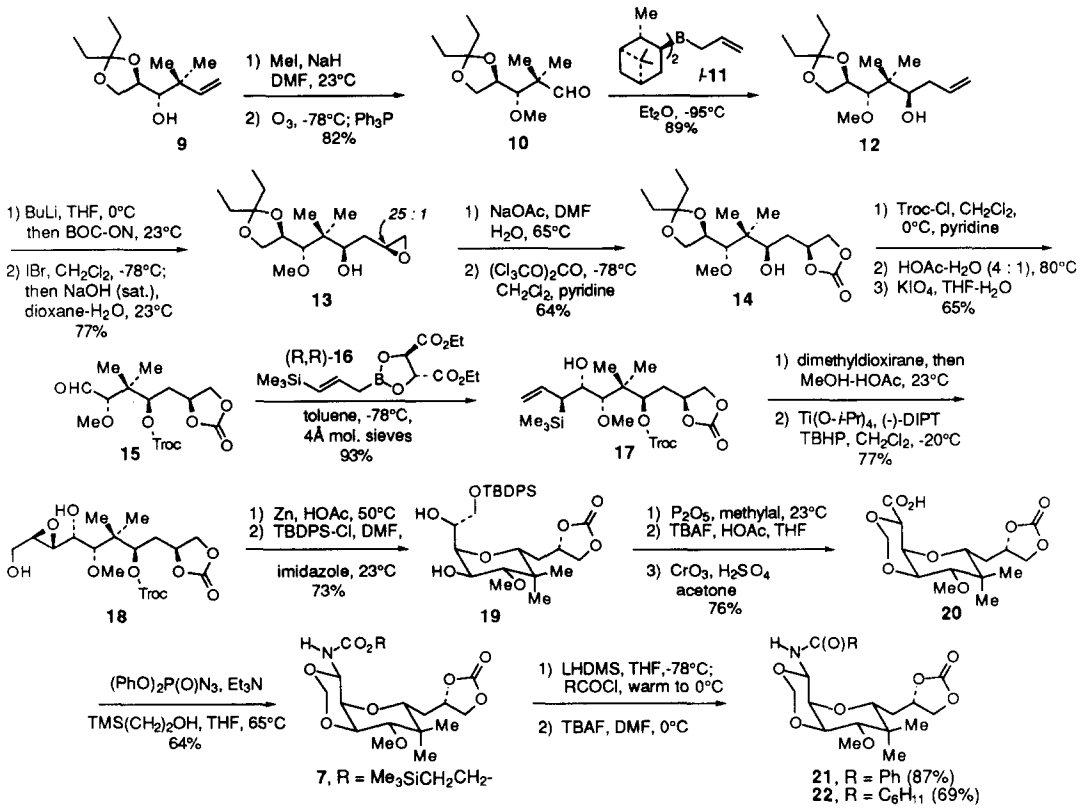
established that the unnatural C(10)-β amide epimer **6β** could be equilibrated with **6α** by treatment with KO-*t*-Bu in THF at reflux, and that the C(17)-C(18) carbonate blocking group could be removed with LiOH in MeOH at room temperature without epimerization of the C(10) N-acyl aminal unit. This suggested to us that the key aminal center could be constructed by acylation of a configurationally stable carbamate precursor,[11] as long as the intermediate carbamate or amide anions were handled at or below ambient temperature. This in turn prompted us to pursue an approach in which the C(10) carbamate is introduced stereospecifically by a Curtius degradation of a carboxylic acid precursor.[8] We report herein the successful demonstration of this strategy in the synthesis of N-benzoyl mycalamine **8** via the highly selective and efficient acylation of carbamate **7**.



Methylation of homoallylic alcohol **9**, prepared as previously described by the asymmetric prenylboration of D-glyceraldehyde 3-pentylidene ketal,[8] followed by ozonolysis of the vinyl group gave aldehyde **10** in 82% yield. Highly diastereoselective allylation of **10** was best accomplished by using Brown's $^{i}Ipc_2BAll$ reagent **11** (prepared from (-)-α-pinene)[12] in Et_2O at -95°C, which gave the desired homoallylic alcohol **12** in 89% yield and ≥98 : 2 diastereoselectivity. Reactions of **10** with other allylmetal reagents (e.g., tartrate allylboronate, $H_2C{=}CHCH_2MgBr$, $H_2C{=}CHCH_2SiPh_2Me$-$TiCl_4$, $H_2C{=}CHCH_2SnBu_3$-$TiCl_4$) were only moderately selective (up to 80 : 20) and the two alcohol diastereomers were inseparable chromatographically.

Our initial strategy called for the vinyl group of **12** to be functionalized by an asymmetric dihydroxylation procedure.[13] Unfortunately, attempted asymmetric dihydroxylation of **12**, or several ether derivatives, with AD-mix-α proceeded with only modest selectivity (≤4 : 1). Recent work by Smith and co-workers prompted us to introduce the requisite diol unit via an iodine monobromide mediated carbonate cyclization.[14] Thus, alcohol **12** was converted into the *t*-butyl carbonate derivative (BuLi, THF, 0°C, then BOC-ON, 23°C, 95%), which was treated with IBr in CH_2Cl_2 at -78°C.[14] Due to the instability of the iodo carbonate, the crude reaction mixture was treated directly with NaOH in aqueous dioxane to furnish epoxy alcohol **13** as a 25 : 1 mixture favoring the desired β epoxide (77% yield from **12**). Regioselective hydrolysis of epoxide **13** (NaOAc, DMF, H_2O, 60°C) followed by selective protection of the C(17)-C(18) diol by using a dilute solution of triphosgene in CH_2Cl_2 at -78°C afforded carbonate **14** in 65% yield overall yield. Protection of the secondary alcohol as a trichloroethyl carbonate (Troc) followed by hydrolysis of the pentylidene ketal (80% HOAc, 80°C) and cleavage of the resulting diol with KIO_4 in aqueous THF gave aldehyde **15** in 65% yield for this three step sequence.

Asymmetric allylboration of **15** with (E)-γ-(trimethylsilyl)allylboronate **16**[15] gave allylsilane **17** in 89% yield and excellent diastereoselectivity (≥98 : 2). Treatment of **17** with a solution of dimethyldioxirane in acetone followed by acid catalyzed Peterson elimination (MeOH, HOAc) then gave the (E)-allylic 1,4-diol in excellent yield (89%). This intermediate was epoxidized by using the Sharpless asymmetric epoxidation procedure, giving **18** in 87% yield.[16,17] It should be noted that both of the allylic alcohols have the ability to direct the epoxidation to the same face of the olefin. Treatment of **18** with zinc in acetic acid resulted in deprotection of the Troc group and cyclization of the resulting secondary alcohol onto the epoxide, yielding the tetrahydropyran system of the natural



product (84% yield). Selective protection of the primary alcohol with TBDPS-Cl (imidazole, DMF, 23°C) then provided the mono TBDPS ether **19** (87%). After considerable experimentation the methylene acetal was introduced in 88% yield by portion-wise addition of P_2O_5 to a solution of diol **19** in dimethoxymethane (methylal).[18] Deprotection of the TBDPS ether by using TBAF in THF buffered with HOAc followed by oxidation of the primary alcohol with Jones' reagent gave carboxylic acid **20** in 86% yield for this one-pot, two step sequence. Finally, Curtius degradation of the carboxylic acid ($(PhO)_2P(O)N_3$, Et_3N, β-(trimethylsilyl)ethanol, 65°C)[19] gave carbamate **7** in 64% yield as a single C(10) epimer.

As a test of our hypothesis that acylation of **7** should proceed without epimerization at C(10), carbamate was treated with 1.1 equiv. of LHDMS in THF at -78°C for 1 h. To this solution was then added 1.1 equiv. of benzoyl chloride, and the resulting mixture was then allowed to warm to 0°C over a 6 h period. Standard workup then provided the intermediate imide in 91% yield that was treated with 2 equiv. of TBAF in DMF at 0°C for 5 min. This provided amide **21** in 87% yield from **7**. The stereostructure of **21** was confirmed by a single crystal X-ray analysis.[20] Similarly, cyclohexyl carboxamide **22** was prepared in 69% yield (unoptimized) from **7** via acylation with $C_6H_{11}COCl$. Finally, treatment of benzamide **21** with LiOH in MeOH at 25°C provided N-benzoyl mycalamine **8** in 95% yield, with no evidence of any epimerization at C(10).

In summary we have developed a highly diastereoselective synthesis of N-benzoyl mycalamine **8** which corresponds to the fully elaborated amino trioxadecalin nucleus of mycalamide A. Additionally, we have

demonstrated that the key C(10) N-acyl aminal stereocenter may be introduced with complete stereochemical control by Curtius degradatation of carboxylic acid **20** followed by a carbamate acylation-deacylation sequence. Application of this technology to the total synthesis of the natural product awaits the completion of a synthesis of pederic acid derivative **5**.

Acknowledgment. Support provided by the National Institute of General Medical Sciences (GM 38907) is gratefully acknowledged.

References

1. Recipient of a fellowship from General Electric Plastics Division, 1993-94.
2. (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc.* **1988**, *110*, 4850.
3. (a) Burres, N. S.; Clement, J. J. *J. Cancer Res.* **1989**, *49*, 2935. (b) Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull.* **1991**, *39*, 2152. (c) Galvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, B.; Nadler, L.; Reiser, H. *Eur. J. Immun.* **1993**, *23*, 283.
4. (a) Frank, J. H.; Kanamitsu, K. *J. Med. Entomol.* **1987**, *24*, 67, and references cited therein. (b) Furusaki, A.; Watanabe, T.; Matsumoto, T.; Yanagiya, M. *Tetrahedron Lett.* **1968**, 6301.
5. (a) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucey, G.; Higa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4851. (b) Matsunaga, S; Fusetani, N.; Nakao, Y. *Tetrahedron* **1992**, *48*, 8369. (c) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1992**, *57*, 3828.
6. (a) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B.; Pannell, L. K. *J. Chem. Soc., Perkin I* **1992**, 1335. (b) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Clark, B. M. *J. Chem. Soc., Perkin I* **1994**, 1025.
7. (a) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. (b) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693.
8. Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421.
9. Hoffmann, R. W.; Schlapbach, A. *Tetrahedron Lett.* **1993**, *34*, 7903. This synthesis provided the unnatural C(10) epimer of a carbamate analogous to **7**.
10. Nakata, T.; Matsukura, H.; Jian, D.; Nagashima, H. *Tetrahedron Lett.* **1994**, *35*, 8229.
11. (a) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, 48, 2424 and refs. therein. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
12. Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614.
13. (a) Review: Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317. (b) Sharpless, K. B.; Amberg, W.; Bennani, G. A. C.; Martung, J.; Heong, K. S.; Kwong, H.-L.; Morikawa, K.; Wang, X.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
14. Duan, J. J.-W.; Smith, A. B., III, *J. Org. Chem.* **1993**, *58*, 3703.
15. Synthesized from allyltrimethylsilane by using the procedure previously described for the γ-dimethylphenylsilyl substituted allylboronate: Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981.
16. Rossiter, B. E., in *Asymmetric Synthesis*; Morrison, J. D., ed.; Academic Press: New York, 1985; Vol. 5; pp 193-246.
17. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
18. Carrewtero, J. C.; Dominguez, E. *J. Org. Chem.* **1993**, *58*, 1596.
19. Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
20. We thank Dr. John Huffman for performing the X-ray structure analysis of **21**. Details are provided in the Indiana University Molecular Structure Center Report No. 94078.

(*Received in USA* 22 *November* 1994; *revised* 3 *January* 1995; *accepted* 9 *January* 1995)