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Total Synthesis of Mycalamide A and 7-*epi*-Mycalamide A

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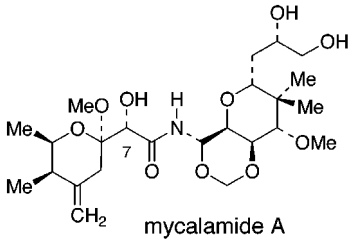
ABSTRACT



mycalamide A

The final stages of a total synthesis of mycalamide A are described. A key step is the aldol reaction (mismatched) of imide 4 and aldehyde 5 which provided a ca. 5:4 mixture of aldols 10a and 10b, with incorrect C(7) stereochemistry. Elaboration of the 10a–10b mixture to mycalamide A required epimerization of C(7) at the stage of *β*-keto imide 11. Alternatively, Swern oxidation of the 10a–10b mixture under conditions that minimize C(7) epimerization led to 7-*epi*-mycalamide A selectively.

Mycalamide A is a member of a group of marine natural products which display potent antiviral and antitumor activity.[1−4] Mycalamide A has been shown to transform *ras*-mutated NRK cells to normal morphology at ≤10 ng/mL concentration through inhibition of P21.[4] The mycalamides also display immunosuppressive activity via inhibition of $CD4^+$ T-cell activation and are significantly more potent than either FK-506 or cyclosporin A in this assay.[5] The mycalamides are structurally related to the onnamides and theopederins, which differ from the mycalamides principally in the C(15) side chain,[6−8] as well as pederin, an insect toxin.[9] As a result of their potent biological properties, this family of natural products has attracted considerable attention as targets for total synthesis. Kishi reported pioneering total syntheses of mycalamides A and B, as well as of onnamide A,[10,11] while Nakata has completed a total synthesis of mycalamide A.[12−14] Kocienski has reported total syntheses of 18-*O*-methylmycalamide B, mycalamide B, and theopederin D.[15−17] In addition, studies on the synthesis of the mycalamides have been reported by Hoffmann[18−20] and ourselves.[21−24] We

(1) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc.* **1988**, *110*, 4850.
(2) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.
(3) Burres, N. S.; Clement, J. J. *Cancer Res.* **1989**, *49*, 2935.
(4) Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull.* **1991**, *39*, 2152.
(5) Galvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, B.; Nadler, L.; Reiser, H. *Eur. J. Immunol.* **1993**, *23*, 283.
(6) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4851.
(7) Matsunaga, S.; Fusetani, N.; Nakao, Y. *Tetrahedron* **1992**, *48*, 8369.
(8) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1992**, *57*, 3828.
(9) Frank, J. H.; Kanamitsu, K. *J. Med. Entomol.* **1987**, *24*, 67, and references therein.
(10) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242.
(11) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693.
(12) Nakata, T.; Matsukura, H.; Jian, D.; Nagashima, H. *Tetrahedron Lett.* **1994**, *35*, 8229.
(13) Nakata, T.; Fukui, H.; Nakagawa, T.; Matsukura, H. *Heterocycles* **1996**, *42*, 159.
(14) We refer to the right-hand, amine component of the mycalamides as "mycalamine".
(15) Kocienski, P.; Raubo, P.; Davis, J. K.; Boyle, F. T.; Davies, D. E.; Richter, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1797.
(16) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 869.
(17) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 1432.
(18) Hoffmann, R. W.; Schlapbach, A. *Tetrahedron Lett.* **1993**, *34*, 7903.
(19) Hoffmann, R. W.; Breitfelder, S.; Schlapbach, A. *Helv. Chim. Acta* **1996**, *79*, 346.
(20) Breitfelder, S.; Schlapbach, A.; Hoffmann, R. W. *Synthesis* **1998**, 468.
(21) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421.
(22) Marron, T. G.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 1581.

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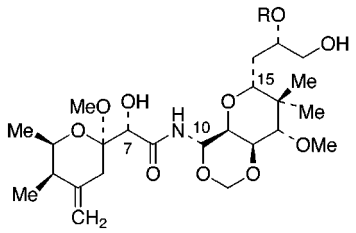
report herein the completion of our total synthesis of mycalamide A (Scheme 1).

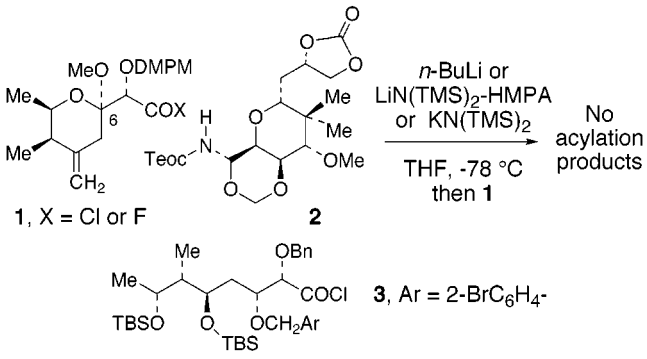
Scheme 1



mycalamide A (R = H)
mycalamide B (R = Me)

One of the significant challenges associated with the synthesis of this family of natural products concerns control of the stereochemistry at the C(7) and C(10) stereocenters. Despite the considerable effort devoted to the synthesis of these molecules, no completely stereoselective route to any member of the family has yet appeared. All syntheses to date, including the synthesis reported herein, have involved generation of mixtures at one or both of these key centers. We correctly predicted and demonstrated as early as 1993 that the C(10) stereocenter could be controlled via the Curtius reaction of a C(10) carboxylic acid precursor.[21] Moreover, we subsequently demonstrated that N-acylation reactions of α-alkoxycarbamates, including **2**, could be accomplished under basic conditions without epimerization of the labile[10] C(10) stereocenter.[25,26] However, our initial efforts to complete a total synthesis were compromised by the steric congestion surrounding the C(6) ketal and C(10)-N units, which prevented the union of **1**[23] and **2**[22] from being successfully accomplished (Scheme 2).[24,25] Moreover, we

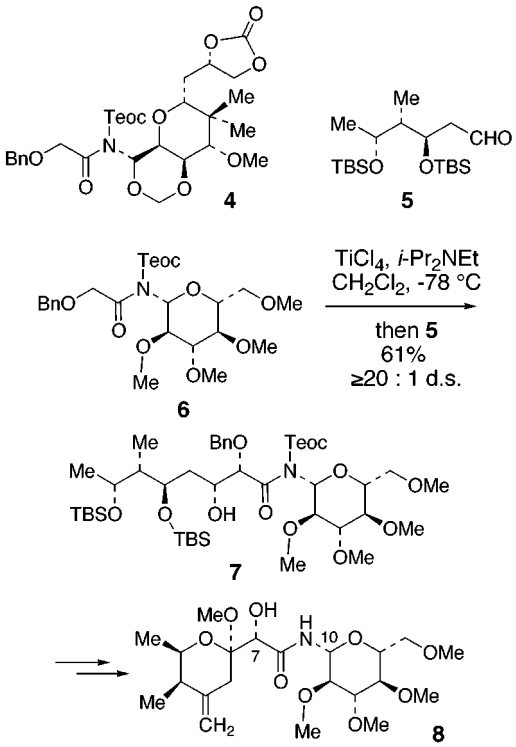
Scheme 2



subsequently discovered that attempted coupling of **2** and the acyclic acid chloride **3** was also unsuccessful, again presumably due to destabilizing steric congestion of the transition state.

These difficulties prompted us to explore a strategy for completing the mycalamide synthesis through the aldol reaction of **4** and **5**, which we successfully modeled by using the readily available *N*-D-glycosyl imide **6** as a surrogate for **4**. We established that the aldol reaction of **5** and **6** provided the syn aldol **7** with ≥ 20:1 selectivity and elaborated this intermediate into the *N*-glycosyl pederamide derivative **8** via an efficient, six-step sequence (Scheme 3).[24] In the course

Scheme 3

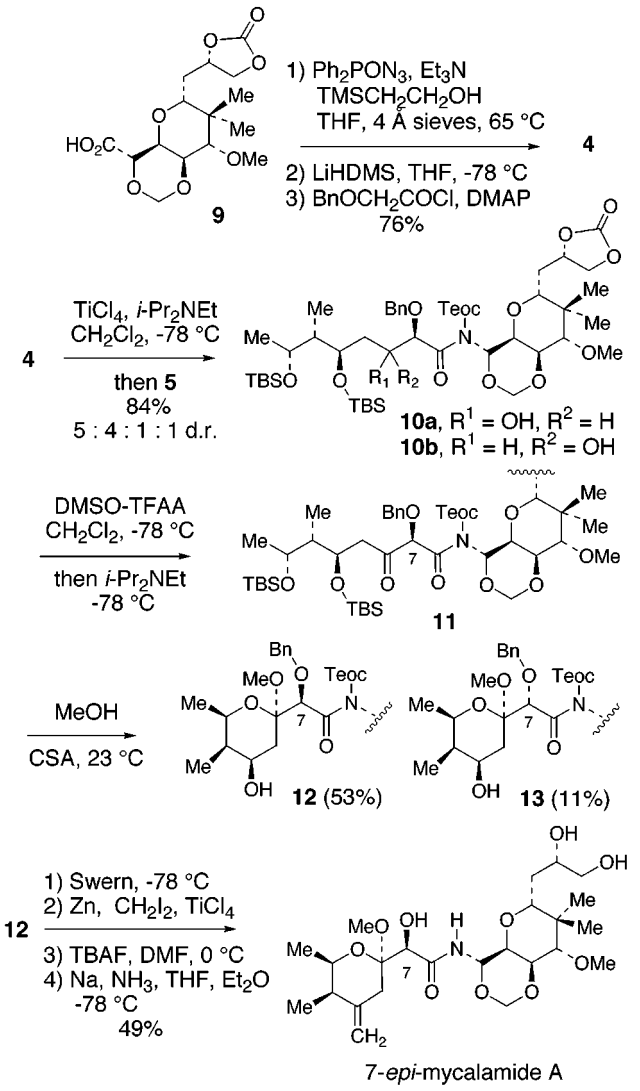


of these studies, we determined that the chlorotitanium enolate of **6** was only moderately diastereoselective (ca. 2:1) in reactions with benzaldehyde and concluded that the excellent stereochemical control in the aldol reaction of **5** and **6** was governed by the intrinsic diastereofacial preference of the *β*-alkoxy aldehyde to favor production of 1,3-anti product.[27] However, since **4** and **6** are in opposite enantiomeric series, we recognized that the **4** + **5** coupling might be a mismatched fragment assembly aldol reaction.[28] Nevertheless, we were optimistic that good results would be achieved since it was not obvious at the outset that the intrinsic diastereofacial selectivity of **4** should be any greater than that of **6**. That is, we anticipated that **5** would be the dominant stereochemical contributor in the targeted aldol reaction with **4**.

(23) Roush, W. R.; Marron, T. G.; Pfeifer, L. A. *J. Org. Chem.* **1997**, *62*, 474.
(24) Roush, W. R.; Pfeifer, L. A.; Marron, T. G. *J. Org. Chem.* **1998**, *63*, 2064.
(25) Marron, T. G. Ph.D. Thesis, Indiana University, 1995.
(26) Roush, W. R.; Pfeifer, L. A. *J. Org. Chem.* **1998**, *63*, 2062.
(27) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
(28) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

The synthesis commenced with the Curtius reaction of carboxylic acid **9**,[22] which provided the 2-trimethylsilylethyl carbamate (Teoc) protected amine **2** in 83% yield under optimized conditions (Scheme 4).[29] Treatment of a mixture

Scheme 4



of **2** and DMAP with LiN(TMS)$_2$ in THF at −78 °C followed by addition of BnOCH$_2$COCl provided imide **4** in 92% yield with complete preservation of the C(10) stereocenter,[26] thereby setting the stage for the key aldol reaction. In the event, the chlorotitanium enolate was generated by treatment of **4** with $TiCl_4$ and *i*-PrNEt$_2$ in CH_2Cl_2 at −78 °C,[30,31] and then a CH_2Cl_2 solution of β-alkoxy aldehyde **5** (1.2−1.5 equiv) was added. This reaction afforded a ca. 5:4:1:1 mixture of four aldols in up to 69% yield, along with 29% of recovered imide **4**. After recycle of **4**, the yield of the mixture of aldols was increased to 84%. The sensitivity of the aldol products to N → O transfer of the Teoc group under even weakly basic conditions (e.g., upon exposure to Et_3N at −78 °C) precluded use of lithium enolate aldol technology. Attempts to perform the aldol reaction using enolborane derivatives generated from **4** were unsuccessful.

The two major isomers **10a** and **10b** could be separated only with considerable loss of material during chromatography, owing to their sensitivity to N → O Teoc group migration.[32] Consequently, the aldol mixture typically was used directly in the following sequence. Oxidation of the mixture with the TFAA−DMSO Swern reagent[33] under non-epimerizing conditions (vide infra) provided the β-keto imide **11** in good yield, with the caveat that it was necessary to add the aldols to the Swern reagent before addition of Et_3N; otherwise, N → O Teoc transfer proved highly competitive with the oxidation reaction. Treatment of crude β-keto imide **11** with camphorsulfonic acid (CSA) in MeOH then provided the epimeric methyl ketals **12** and **13** in 53% and 11% yields, respectively. Ketal **12** was also obtained when partially purified (but separated)[32] samples of either **10a** or **10b** were subjected to the oxidation−ketalization sequence, thus establishing that the two major aldols have the same stereochemistry at C(7). That this center corresponds to the *unnatural* C(7)-*R* stereochemistry was established by elaboration of **12** to C(7)-*epi*-mycalamide A by the following four-step sequence. Oxidation of C(4)-OH by using the standard DMSO−$(COCl)_2$ Swern protocol,[33] followed by Takai−Nozaki methylenation,[34] removal of the Teoc unit by treatment with TBAF in DMF at 0 °C, and then reductive cleavage of the C(7)−*O*-benzyl group and the C(17,18)-carbonate unit provided 7-*epi*-mycalamide A in 49% overall yield. The identity of synthetic 7-*epi*-mycalamide A was confirmed by comparison with ^{1}H NMR data kindly provided by Dr. T. Nakata.[35]

It is clear from these results that the aldol reaction of **4** and **5** followed a totally different stereochemical course than that anticipated on the basis of our earlier studies of the aldol reaction of **6** and **5**.[24] That the two major aldols **10a** and **10b** possess unnatural C(7)-*R* stereochemistry indicates that the chlorotitanium enolate of **4** exerts a significant diastereofacial influence, such that the aldol reaction with **5** is significantly mismatched.[28] This effect was also observed in aldol reactions of **4** and Me_2CHCHO ($TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C), which provided a ca. 10:5:1 mixture of three aldols, the two major isomers of which were assigned C(7)-*R* stereochemistry by spectroscopic correlation with **10a**,**b**. At present we attribute the diastereofacial selectivity

(29) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(30) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(31) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

(32) Aldol **10b** was obtained pure by chromatography, but **10a** was otained as a ca. 5:1:1 mixture with the two minor diastereomers.

(33) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

(34) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.

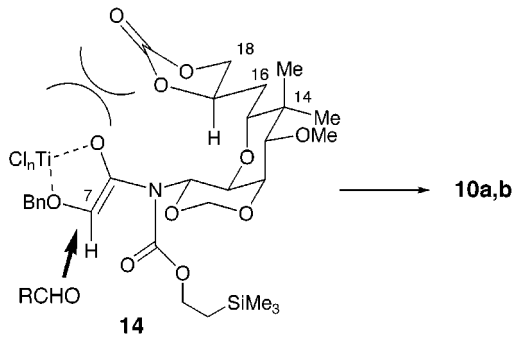
(35) Fukui, H.; Tsuchiya, Y.; Fujita, K.; Nakagawa, T.; Koshino, H.; Nakata, T. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2081.

(36) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.

(37) Molecular mechanics calculations reveal that the C(10)−H eclipses one of the imide carbonyl groups in **4**, although the energy difference between the two C(10)−N rotamers is very small. We assume that this eclipsed conformation is maintained in the chlorotitanium enolate, as indicated in **14**.

of the chlorotitanium enolate **14** to the C(15) side chain (not present in **6**) which effectively blocks the backside of the enolate from approach of the aldehyde (Scheme 5). The

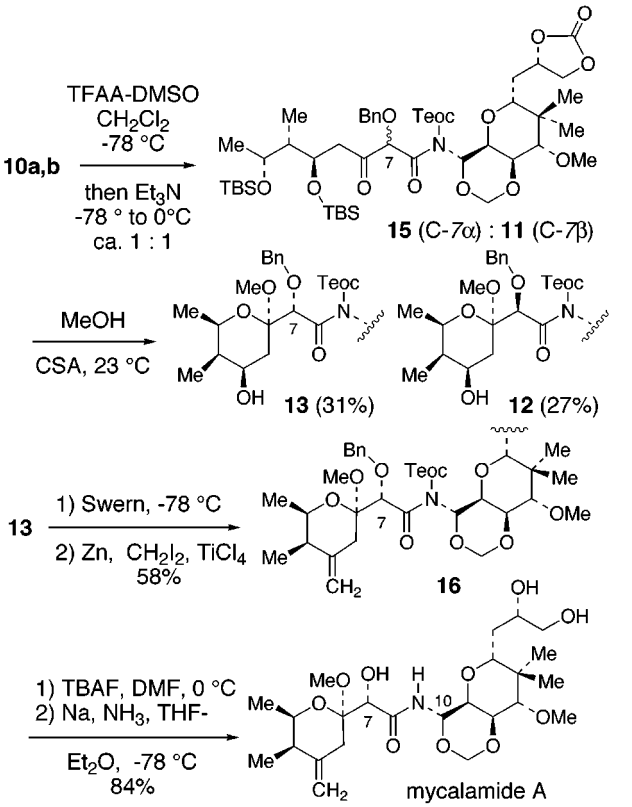
Scheme 5



C(15) side chain is forced to adopt the conformation indicated so as to minimize syn-pentane interactions with the C(14) substituents.[36] Although models indicate that the C(10)-imide functionality can readily adopt a second low-energy conformation by 180° rotation about the C(10)−N bond in **14**,[37] our model analysis indicates that C(17)−O is close enough to interact with the chlorotitanium enolate, perhaps as a ligand on titanium, such that the rotamer depicted in Scheme 5 corresponds to the kinetically dominant one. Aldol reactions of enolate **14** by necessity should occur preferentially from the front face, leading to the 7(*R*)-aldol stereochemistry present in both **10a** and **10b**. However, the factors that contribute to the poor selectivity for chairlike vs boatlike transition states in aldol reactions of **14** (which accounts for the low level of control over the C(6) stereochemistry in the aldol mixture) are unclear at present.

To complete the mycalamide synthesis, we returned to the Swern oxidation of the **10a**,**b** mixture. Merely switching bases from *i*-Pr$_2$NEt to Et$_3$N, and allowing the reaction mixture to warm from −78 to 0 °C after addition of Et$_3$N, provided a ca. 1:1 mixture of **11** and its C(7)-epimer **15** (Scheme 6). Treatment of this mixture with CSA in MeOH then provided an easily separable mixture of **13** (31% for the two-step sequence from **10a**,**b**) and **12** (27% yield). Oxidation of the free C(4)-hydroxyl group of **13** followed by Takai−Nozaki olefination provided **16** in 58% yield. Finally, removal of the 2-(trimethylsilyl)ethyl carbamate (Teoc) by treatment of **16** with TBAF in DMF at 0 °C followed by reductive cleavage of the C(7)−*O*-benzyl ether and the C(17,18) carbonate provided synthetic mycalamide A in 84% yield. The identity of this material was confirmed by comparison with an authentic sample of synthetic my-

Scheme 6



calamide A generously provided by Prof. Kishi.[10] The spectroscopic properties of our synthetic material were also in excellent agreement with data kindly supplied by Prof. Munro.[1,2]

In summary, total syntheses of mycalamide A and 7-*epi*-mycalamide A have been completed. This work nicely illustrates the utility of our carbamate acylation protocol[22,26] for controlling the C(10)-α-alkoxy amide stereocenter of the natural product. Moreover, our synthesis of 7-*epi*-mycalamide A[35] constitutes the first stereoselective synthesis of any member of this family. However, additional efforts will be required for definition of a strategy for control of both the C(10) and C(7) stereocenters of the mycalamides and related natural products—a problem that has not been solved in any of the syntheses reported to date.[10−13,15−17,38−40]

Acknowledgment. Support provided by the National Institutes of Health (GM 38907) is gratefully acknowledged. We also thank Drs. Nakata and Munro for providing spectroscopic data and Prof. Kishi for providing an authentic sample of mycalamide A for comparison.

Supporting Information Available: Experimental procedures for the synthesis of **4**−**19**, *epi*-mycalamide A, and mycalamide A, plus tabulated spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J. *Tetrahedron* **1990**, *46*, 1757.

(39) Kocienski, P.; Jarowicki, K.; Marczak, S. *Synthesis* **1991**, 1191, and references therein.

(40) Nakata, T.; Nagao, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6465. References to earlier syntheses of pederin are cited in this paper.