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Toward the Synthesis of Mycalamides A, B and Onnamide A: A Highly Stereoselective Synthesis of the Trioxadecalin Ring System

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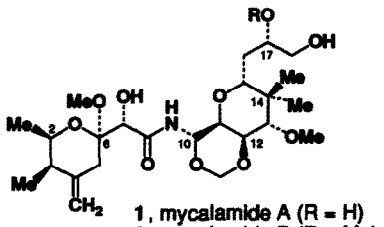
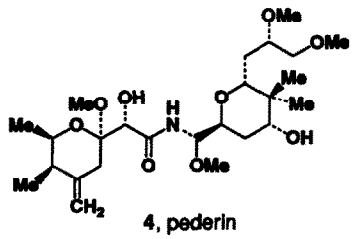
Abstract: A highly diastereoselective synthesis of the trioxadecalin ring system (**5**) of mycalamides A, B and onnamide A is described.

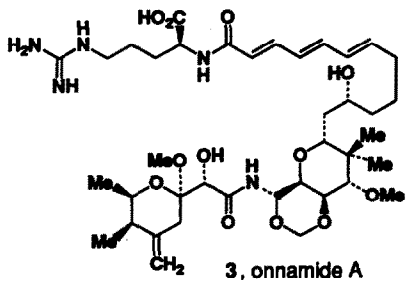
Mycalamides A (**1**), B (**2**), and onnamide A (**3**) are structurally related anti-tumor antibiotics isolated from marine sponges of the *Mycale* and *Theonella* genera.[1,2] These compounds are very potent antiviral agents, and have been shown to have promising antitumor activity.[3] They also show a striking structural resemblance to pederin (**4**),[4] a potent insect toxin. Each contains a pederic acid subunit [C(1)-C(8)] and an interesting acylaminal functional group at C(10) that may contribute to their biological properties.[5a]



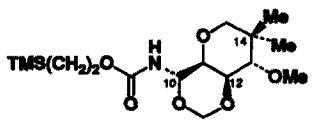
1, mycalamide A (R = H)
2, mycalamide B (R = Me)



4, pederin

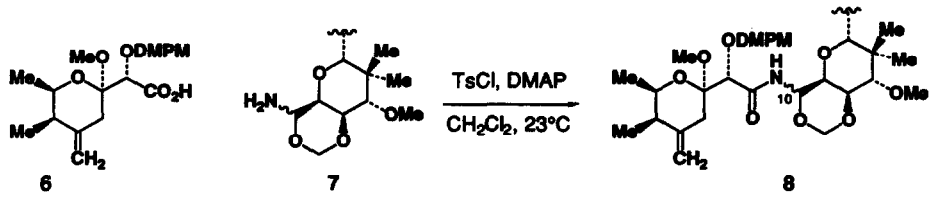


3, onnamide A



5

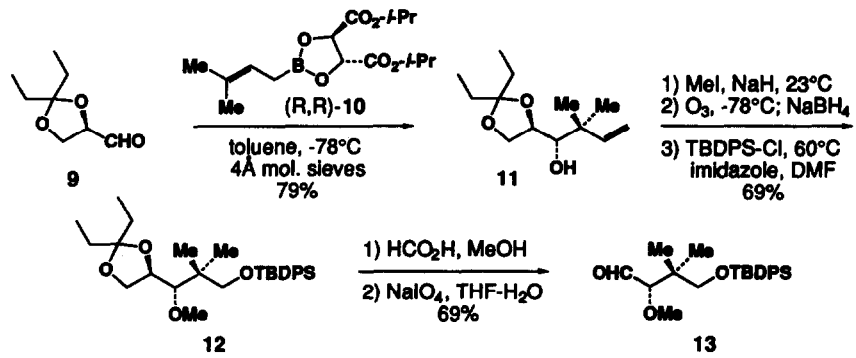
Total syntheses of **1-3** have been reported by Hong and Kishi.[5] A key step in these syntheses is the tosyl chloride mediated coupling of acid **6** and amines **7**. Unfortunately, the C(10) aminal unit of **7** is configurationally unstable under acidic, basic, and neutral conditions, and consequently mixtures of amides **8** were obtained. It was demonstrated, however, that the unnatural C(10)-β epimers may be recycled by equilibration in the presence of KO-*t*-Bu in THF at reflux.[5a]



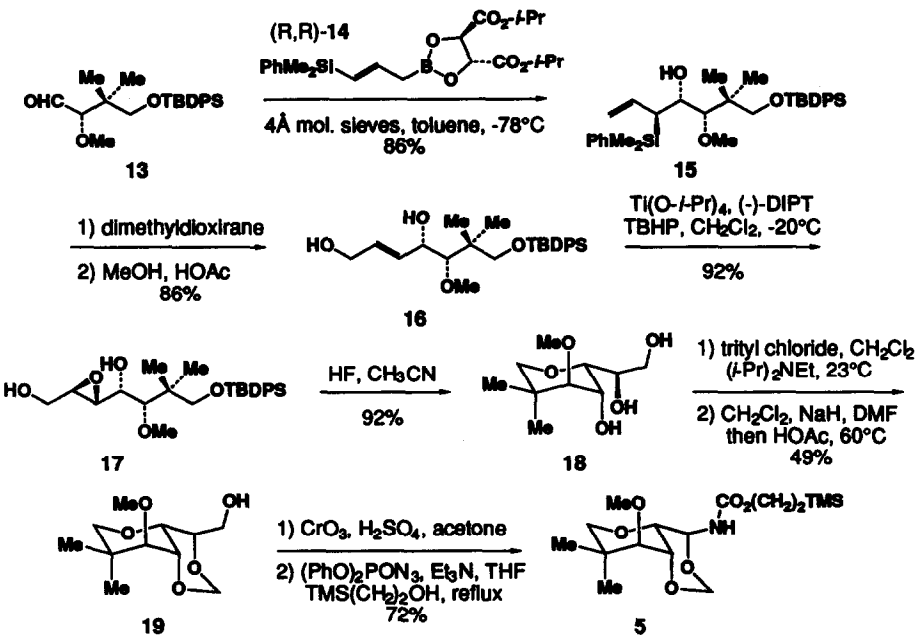
6 7 8

We report herein a highly stereoselective synthesis of **5**, which represents the trioxadecalin nucleus of **1-3**. A key feature of our synthesis is the stereocontrolled introduction of the C(10)-amine as a carbamate derivative via a Curtius rearrangement. Our synthesis also has considerable stereochemical generality, since all four stereocenters in **5** are controlled by using asymmetric synthesis techniques.

Our synthesis originates from D-glyceraldehyde pentylidene acetal **9**, which is easily prepared in two steps from D-mannitol.[6] Treatment of **9** with the (R,R)-diisopropyl tartrate modified prenylboronate **10**[7] in toluene at -78°C provided alcohol **11**[8] in 79% yield and with ≥99 : 1 selectivity as determined by GC analysis.[9] Addition of homoallylic alcohol **11** to a stirred solution of NaH in DMF followed by treatment with methyl iodide yielded the corresponding methyl ether in excellent yield (93%). Ozonolysis of the terminal olefin (CH_2Cl_2-MeOH (3:2), -78°C) followed by a reductive work-up ($NaBH_4$, EtOH) gave the requisite primary alcohol (86% yield) which was protected as a *tert*-butyldiphenylsilyl ether under standard conditions (TBDPS-Cl, imidazole, 60°C, DMF, 86% yield). Hydrolysis of the pentylidene ketal (formic acid-MeOH, 23°C) and periodate cleavage of the resulting diol ($NaIO_4$, THF-H_2O, 23°C) afforded aldehyde **13** (78%). Dropwise addition of **13** to a stirred solution of (R, R)-(E)-γ-[dimethylphenylsilyl]allylboronate **14**[10] in toluene at -78°C provided **15** in 86% yield and with ≥99 : 1 diastereoselectivity. Oxidation of the terminal olefin with dimethyldioxirane (acetone, K_2CO_3, 23°C) followed by acid catalyzed Petersen elimination provided allylic alcohol **16** in 86% yield for this one pot sequence. Epoxidation of **16** by using standard Sharpless conditions (Ti(O*i*-Pr)$_4$, (-)-DIPT, TBHP, -20°C) then provided epoxy diol **17** in 92% yield as a single isomer (>99:1).[11] Interestingly, both hydroxyl groups of **16** are capable of directing the epoxidation to **17**.



9 11 12 13



Simultaneous deprotection of the TBDPS ether and cyclization of the epoxyalcohol was carried out by treating **17** with HF (50 equiv.) in acetonitrile at ambient temperature, thereby providing **18** in 86% yield. Treatment of **18** with trityl chloride (1.1 equiv., *i*-Pr_2NEt, CH_2Cl_2, 23°C) afforded the corresponding mono trityl ether (85% yield). After considerable experimentation, the methylene acetal was introduced by using NaH and bromochloromethane in DMF.[12] The crude reaction mixture was then treated with acetic acid at 60°C which provided **19** in 58% yield. Jones' oxidation of the primary alcohol (91%) followed by Curtius rearrangement ($(PhO)_2PON_3$, Et_3N, THF, reflux)[13] in the presence of 2-trimethylsilylethanol gave the desired carbamate **5** in 79% yield. The stereochemistry of **5** was confirmed by a NOE study performed on the carboxylic acid precursor.[14] This analysis establishes that **19**, the intermediate carboxylic acid and **5** preferentially adopt the indicated conformations which correspond to the minor conformation of the trioxadecalin ring system of the natural products.[1b]

In summary we have developed an efficient and highly diastereoselective synthesis of the mycalamide-onnamide trioxadecalin nucleus **5**. Additional efforts directed toward the total synthesis of mycalamides A, B and onnamide A will be reported in due course.

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

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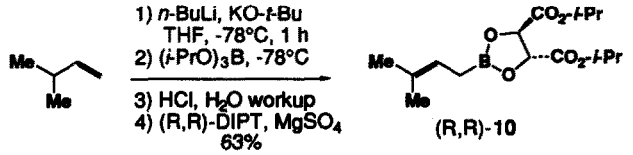
7. Prenylboronate (R, R)-**10** was synthesized starting from 3-methyl-1-butene by using our standard crotylboronate synthesis (Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339). For other chiral prenylating reagents, see ref. 4e and Brown, H. C.; Jadhav, P. K. *Tetrahedron Lett.* **1984**, *25*, 1215.



8. The spectroscopic properties (400 or 500 MHz ^{1}H NMR, IR, mass spectrum) of all new compounds are in complete agreement with the assigned structures. Correct C,H analyses were obtained for **11**, **12**, **15**, **16**, **17**, the trityl ether of **18**, and **5**.
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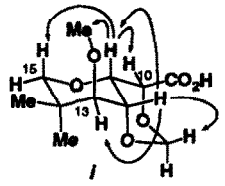
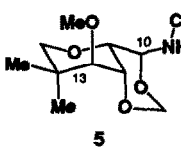
14. NOE and J data for carboxylic acid *i* and carbamate **5** are summarized below. Molecular mechanics calculations (MMX) confirmed that the indicated conformation of *i* is ca. 5.5 kcal/mol more stable than the alternative cis-decalin conformer. However, **5** and the isomeric conformation were calculated to be within ca. 0.5 kcal/mol of each other. A detailed conformational analysis of these trioxadecalin systems will be presented in a subsequent full paper.



i

$J_{10,11}$ = 1.2 Hz
$J_{11,12}$ = 1.4 Hz
$J_{12,13}$ = 2 Hz
$J_{13,15eq}$ = 1.2 Hz



5

$J_{10,11}$ = 4.2 Hz
$J_{11,12}$ = 4.0 Hz
$J_{12,13}$ = 5.6 Hz
(at 80°C)

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