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Synthesis of the Trioxadecalin-Part of Mycalamide B

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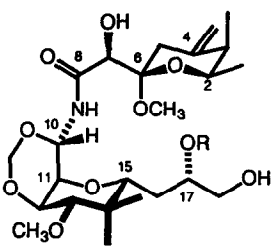
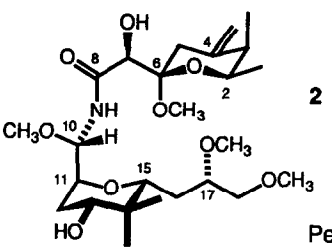
Abstract: *A stereoselective synthesis of the trioxadecalin part of mycalamide B has been realized starting from 2,4,3,5-dimethylene-L-xylose. The C-10-aminal stereocenter is generated by a Curtius degradation.*

The recently discovered mycalamides **1** [1] inhibit protein and DNA synthesis at 0.1 nanomolar concentrations.[2] The mycalamides belong to the class of natural products which includes pederin **2**,[3] a compound that has been known for decades. Simultaneously to the mycalamides the related onnamide,[4] and more recently the theopederins [5] were isolated from marine sources and have been characterised. These compounds differ from either mycalamide or pederin mainly in the nature of the C-15 side chain.



1

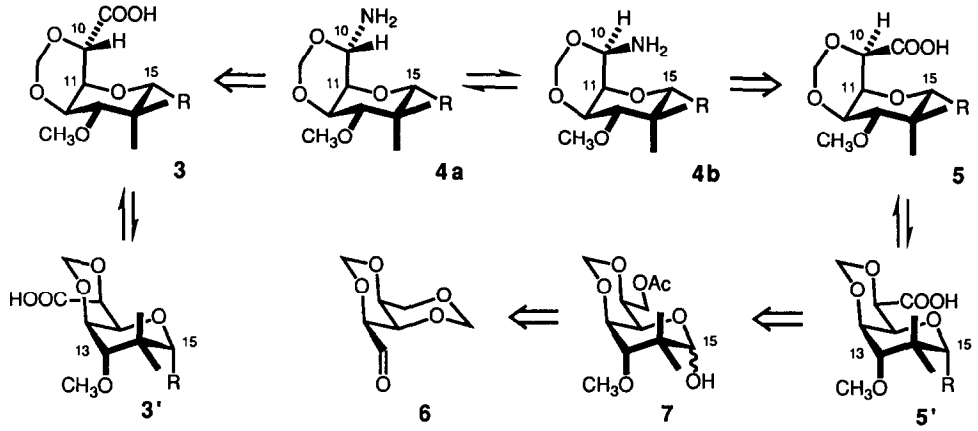
Mycalamide
A : R = H
B : R = CH_3



2

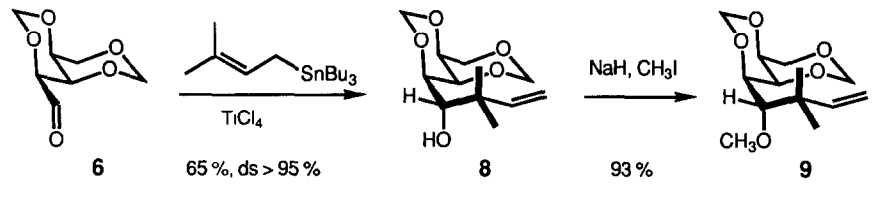
Pederin

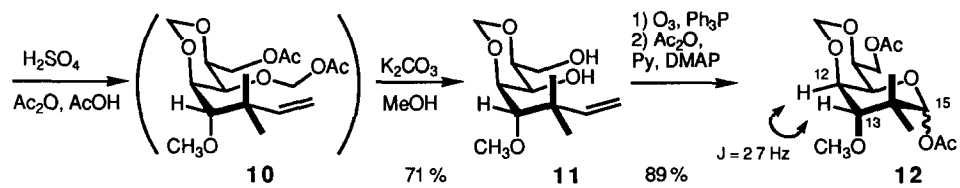
The limited amounts of these compounds available from biological sources has stimulated synthetic efforts directed first at pederin [6] and then at the mycalamides. The ground was broken by Kishi's mycalamide synthesis.[7] These researchers also reached onnamide A by a clearly improved route.[8] An important finding of these studies was the configurational lability of a C-10-aminal center of synthetic intermediates such as **4**. Therefore such intermediates should either be avoided in a next generation of synthetic efforts because of their stereochemical lability. Alternatively, this very feature could be exploited to advantage. We opted for the latter in the context of generating the aminal function by a Curtius degradation of either the carboxylic acid **3** or **5**. Actually, of all four ongoing synthesis [9,10] of mycalamide that we are aware of, three chose the Curtius route to this key structural unit of the mycalamides. The recent paper [9] of the Roush group, describing the synthesis of **3** (R = H) and its Curtius degradation, prompted us to disclose our different approach to the trioxadecalin unit of the mycalamides.



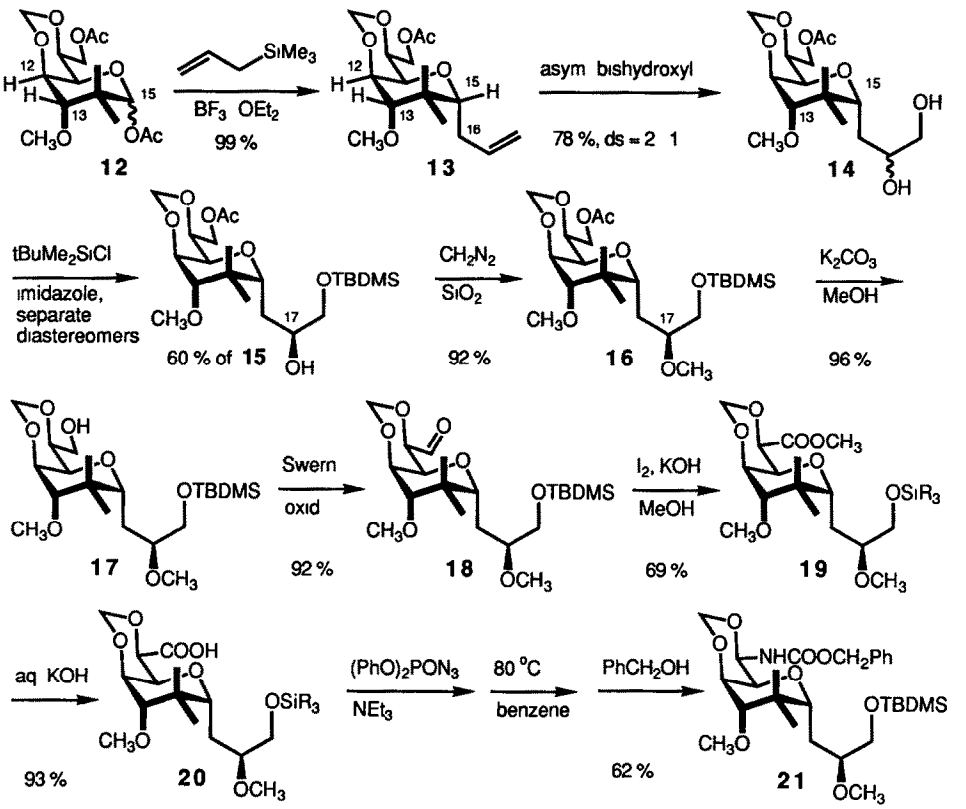
Roush [9] reported that the acid **3** (R = H) exists in the inverted cis-decalin conformation **3'**. This should hold even more so for the C-10 epimeric acid **5** and its derivatives, which should definitely prefer the conformation **5'** in order to avoid placement of the carboxyl group over the tetrahydropyran ring. We wanted to exploit this conformation, which would allow the introduction of the C-16 to C-18 side chain at C-15 from the axial direction, cf. intermediate **7**. This led us to consider the well known aldehyde **6** as the starting point of our synthetic efforts.

2,4,3,5-Dimethylene-L-xylose (**6**) was prepared in three steps [11] from D-sorbitol. First, we considered an allylboration reaction under reagent control of diastereoselectivity to convert the aldehyde **6** into the homoallyl alcohol **8** using the appropriate chiral allylboronate.[12] However, once it became apparent, that this particular stereochemistry could be attained under substrate control of diastereoselectivity when using allylsilanes,[13] the reaction of **6** with tributylprenylstannane became the method of choice. Methylation of the alcohol **8** to the ether **9** followed by acetolysis of the more labile terminal dioxane ring, similar to a procedure developed by Pandit,[14] resulted eventually in the diol **11** in 71% yield. Ozonolysis and acetylation of the intermediary lactol led to the lactol acetates **12** as a 2:1 anomeric mixture in 89% yield. The indicated cis-decalin conformation followed from the H-12/H-13 coupling constant of 2.7 Hz (2.4 Hz in the other anomer) in the ^{1}H-NMR spectrum.





At this point the stage was set for the introduction of the C-16/C-18 side chain. This was effected by Lewis acid mediated reaction with allyltrimethylsilane [15] and led in 99% yield to the allyl compound **13**. Here a definitive proof of the stereochemical assignment was possible from the ^{1}H-NMR-data: H-15 and H-13 showed a W-coupling of 1 Hz. The "axial" methyl group showed NOE contacts to H-13 and H-15, the "equatorial" methyl group to H-13, H-15, and H-16. The elaboration of the side chain followed the pattern set by Kishi.[7] Thus, asymmetric bishydroxylation with dihydroquinine-9-phenanthrylate [16] gave 78% of a 2:1 diastereomeric mixture of diols **14**. The primary hydroxyl group was protected as the TBDMS ether at which stage the diastereomers could be separated by chromatography. The major diastereomer **15** was assigned the desired 17-(S)-configuration, based on a comparison of the δ_C-values for C-15 and C-17 of the two diastereomers. Here we applied an empirical rule [17] regarding the chemical shifts of diastereomeric γ-hydroxy-ethers. The secondary hydroxyl group of **15** was then converted to the methyl ether as required for mycalamide B by the action of diazomethane on silica gel.[18]



At this point the Curtius degradation could be addressed: To this end the acetate was removed and the resulting C-10-carbinol **17** was oxidized to the carboxylic acid **20**. Such transformations can be effected directly, cf. ref. [9]. We, however, chose a three step sequence involving the aldehyde **18**, and the ester **19**. The Curtius rearrangement was initiated in the standard manner with diphenyl phosphoryl azide. Upon heating of the resulting acyl azide, the intermediate isocyanate was trapped by benzyl alcohol to furnish 62% of a single carbamate **21**. This demonstrated the feasibility of the Curtius approach to the key intermediates **4** for mycalamide syntheses.

Our approach profited from the choice of the aldehyde **6** as the starting material, which allowed a very efficient elaboration of the bicyclic frame work as well as attachment of the C-16/C-18 side chain. However, this led us to the C-10-epimeric acid **5**, rather then the "natural" epimer **3**. Of course, cleavage of the carbamate **21** should generate **4b** which would equilibrate with the desired **4a**. However, it appears more attractive to epimerize C-10 at the level of the aldehyde **18** or the ester **19**. This is why we chose a three step oxidation of the alcohol **17** to the acid **20**. The driving force for such an epimerisation, cf. **5'** → **3'**, could be a coupled cis-decalin ring inversion to the conformer **3**, relieving the 1,3-diaxial interaction between the C-13 and C-15 substituents. Studies are underway to test the feasibility of this proposal.

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