Natural Products Synthesis

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Temporary Restraints To Overcome Steric Obstacles: An Efficient Strategy for the Synthesis of Mycalamide B**

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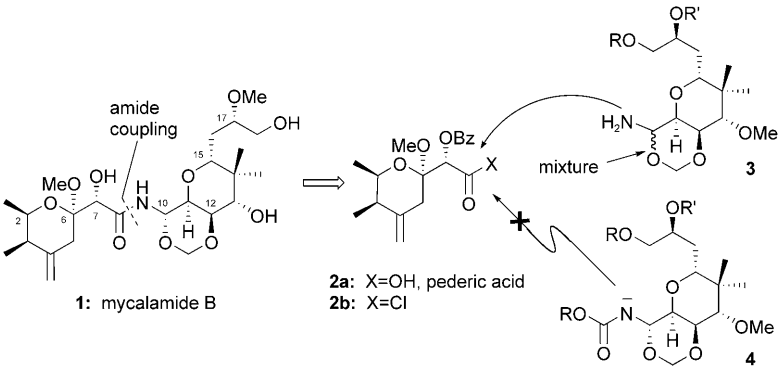
In memory of Michael P. Cava

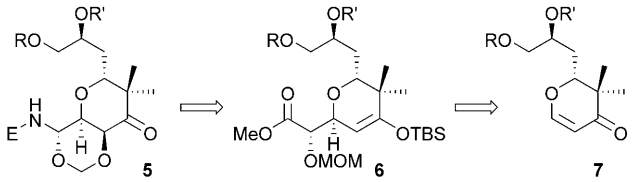
A fundamental concept in synthesis planning is that of convergence. Rather than the incremental, step-by-step assembly of a linear synthesis, a convergent route involves the assembly of two or more advanced fragments of a molecule in a key step, thereby reducing the arduousness of the exercise. While desirable in principle, a convergent path does not guarantee success. The steric bulk associated with advanced fragments can frustrate established reactions and thwart the coupling step. Herein, we describe a convergent synthesis of mycalamide B, wherein steric hurdles are overcome through the use of "chemical handcuffs" to temporarily restrain portions of a molecule, thereby enabling a coupling reaction that would otherwise fail.[1] We also demonstrate the successful extension of our route to pederamine, the right-hand part of pederin, to the more-oxygenated mycalamine system.



Scheme 1. Previous coupling approaches to mycalamide B. Bz = benzoyl.

Sponges of the genus *Mycale* have yielded a diverse group of intricate bioactive natural products.[2] Noteworthy among these are the mycalamides, highly cytotoxic substances that are members of the pederin family of compounds.[3] For example, mycalamide B displays 0.6 nM and 1.3 nM antiproliferative activity against A549 and P388 cancer cell lines, respectively.[4,5] Given their potent anticancer activities, research groups from around the world have pursued the chemical synthesis of the mycalamides and their related natural products, and impressive successes have been recorded.[6–8] Although creative routes have been developed for the synthesis of the two halves of these molecules—the pederic acid and the trioxadecalin parts—no solution has yet been developed for the stereocontrolled coupling of the two fully elaborated halves of mycalamides. At the heart of the problem is that free mycalamine (**3**) readily epimerizes under acidic, basic, and neutral conditions, eroding the stereochemical information at the C10 position (Scheme 1), such that acylation of a free mycalamine component with a pederic acid derivative proceeds with modest selectivity at best.[9] On the other hand, acylation of a carbamate-protected mycalamine unit (e.g., **4**) has been accomplished in a stereocontrolled manner, but only with simpler electrophiles, not with the fully elaborated pederic acid unit.[10] A solution to this coupling difficulty would allow a truly convergent synthesis of the natural product and open up the possibility of concise, stereocontrolled syntheses of many members of the family, as well as their analogues.

The route we envisioned for the synthesis of mycalamide B hinged on two key transformations: 1) the conversion of dihydropyranone **7** into the highly functionalized trioxadecalin framework of the mycalamine unit (Scheme 2) and 2) the stereocontrolled coupling of mycalamine unit **4**, or a derivative thereof, with a pederic acid component (**2**; Scheme 1). The successful realization of these two transformations was expected to provide a route to mycalamide B that would be significantly shorter than those reported previously. A solution to the first of these processes was incorporated in the design of our pederin synthesis, but that for the second process was not evident at the outset.[8c] Specifically, the Mukaiyama–Michael reaction of an appropriately substituted ketene-acetal with dihydropyranone **7**



Scheme 2. Retrosynthetic analysis of the mycalamine unit. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

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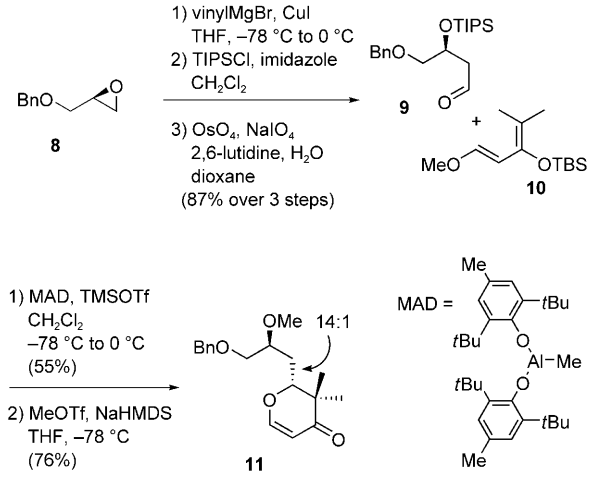
was expected to give silylenol ether **6**, the epoxidation and further elaboration of which would pave the way to mycalamine unit **5**. An efficient strategy to **5** was expected to provide ample material for overcoming the acylative-coupling hurdle.

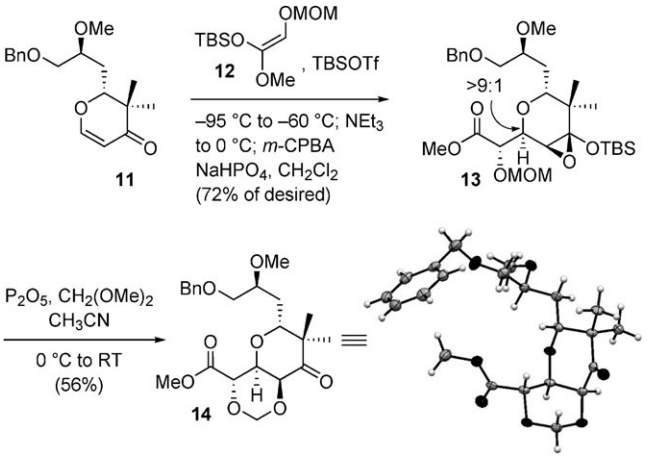
The required dihydropyranone was synthesized in five steps from commercially available benzyl-(*S*)-glycidyl ether (**8**; Scheme 3). Vinyl-cuprate addition to **8**, protection of the free hydroxy group with TIPSCl, and a Johnson–Lemieux



Scheme 3. Synthesis of dihydropyranone **11**. Bn = benzyl, HMDS = hexamethyldisilazide, THF = tetrahydrofuran, TIPS = triisopropylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

oxidative cleavage of the vinyl unit provided aldehyde **9**. The formal hetero-Diels–Alder reaction between aldehyde **9** and Danishefsky-type diene **10** was promoted using Yamamoto's MAD Lewis acid in conjunction with TMSOTf and afforded the expected dihydropyranone in good yield and with high diastereoselectivity.[11–13] Quenching the reaction mixture with aqueous acid gave the free alcohol directly, which was methylated in a separate step to furnish dihydropyranone **11**.

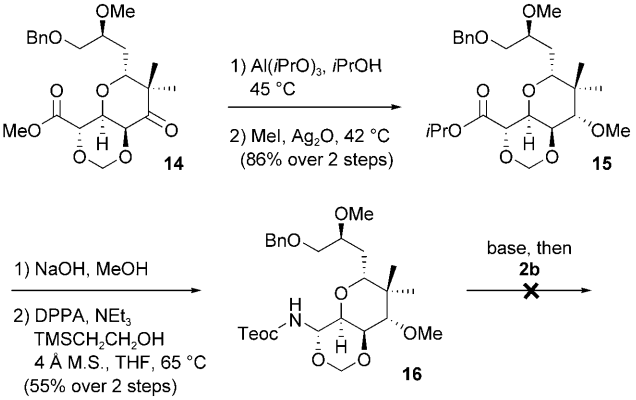
Further elaboration of dihydropyranone **11** to the densely functionalized mycalamine core was achieved in a highly efficient manner and with good diastereoselectivity. Initial studies showed that the Mukaiyama–Michael reaction of MOM-protected silylketene acetal **12**[14] with dihydropyranone **11** proceeded in 5 minutes at −78 °C using TBSOTf as a catalyst. However, the expected silylenol ether product (cf. **6**) was accompanied by significant amounts of the corresponding ketone. After some experimentation, it was found that rather than isolating the intermediate enol ether, it could be epoxidized in situ to afford silyl epoxide **13** in good yield and high diastereoselectivity (Scheme 4). Interestingly, the epoxide was sufficiently stable so as to allow its purification by chromatography. This one synthetic operation set four new stereocenters, three of which are retained in the final product, and installed most of the required parts of mycalamine. Silyl epoxide **13** was treated with P_2O_5 in dimethoxymethane and acetonitrile to arrive at trioxadecalin **14**, the X-ray structure of which confirmed the arrangement of all the newly



Scheme 4. Synthesis of the trioxadecalin core. *m*-CPBA = *meta*-chloroperbenzoic acid.

introduced stereocenters relative to the enantiomerically pure starting material, **8**.[15,16]

The next hurdle that had to be crossed before arriving at the coupling precursor was reduction and methylation of the C13 ketone. Selective reduction of the ketone was expected to be challenging, based on consideration of the steric and electronic factors in the two interconverting chair–chair conformations of **14**. Indeed, borohydride reduction proceeded with complete selectivity for the undesired diastereomer. On the other hand, Meerwein–Ponndorf–Verley (MPV) reduction, carried out by gently heating the reaction mixture, gave the desired alcohol as the only diastereomer, albeit as the isopropyl ester (Scheme 5).[17] Methylation of the alcohol had to be carried out under neutral conditions using silver oxide in methyl iodide to avoid epimerization of the C10 stereocenter.[18] In preparation for the key coupling step, the ester was hydrolyzed and the resulting acid was transformed by the Curtius rearrangement and trapping to give the Teoc-protected mycalamine unit **16**. Disappointingly, but in accord with earlier reports,[6c] all attempts to acylate **16** with pederic acid chloride (**2b**) were unsuccessful. The failure of this acylation step stands in contrast to the analogous acylation used successfully in our synthesis of pederin.[8c]



Scheme 5. Synthesis of mycalamine unit and attempted coupling. Teoc = 2-(trimethylsilyl)ethoxycarbonyl, DPPA = diphenylphosphoryl azide.

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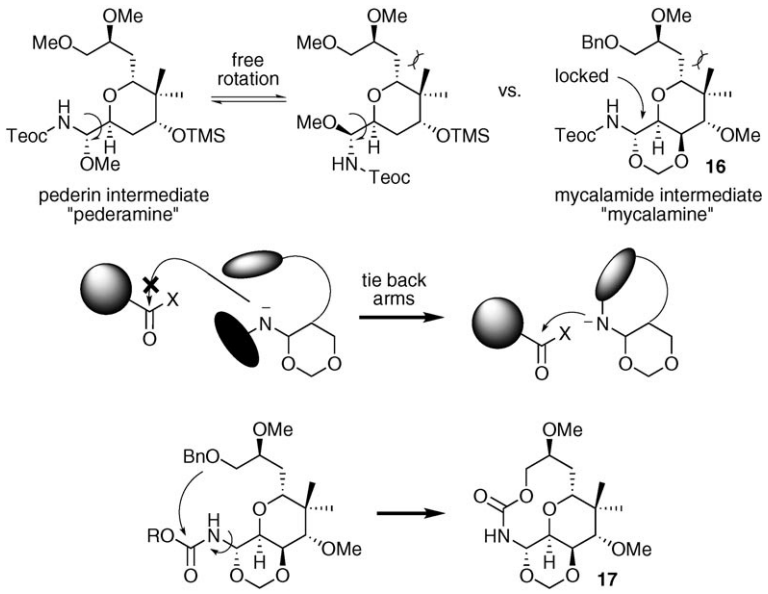
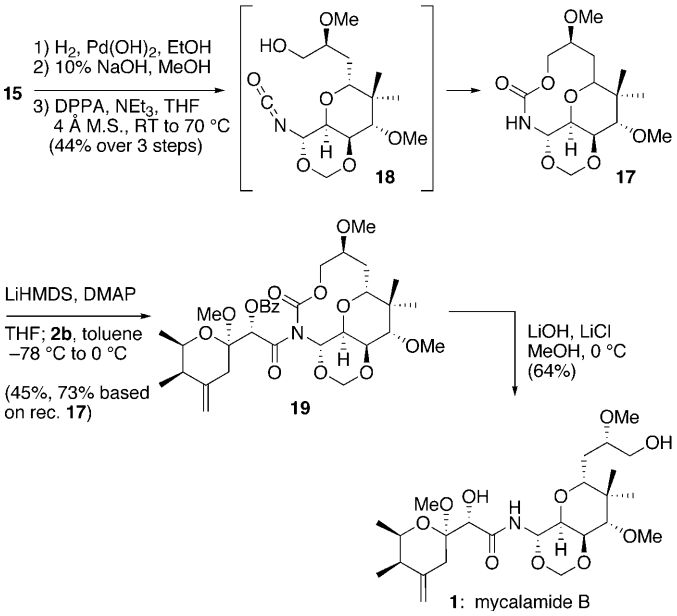


Scheme 6. The handcuff solution for overcoming steric obstacles.

Our analysis of the above problem and a possible solution are illustrated in Scheme 6. In both pederamine and mycalamine, the dialkoxypropyl "arm" is expected to be oriented toward the pyran oxygen, so as to avoid the gem-dimethyl group. However, whereas the deprotonated nitrogen atom in pederamine can freely rotate away from the blocking arm into an orientation that allows acylation, the mycalamine nitrogen is locked by the dioxane ring. Conceptually, if the arm could be constrained—or handcuffed—to the amine, then the nitrogen would be forced to point outwards, making it accessible to the acylating agent. The plan was to tie the nitrogen to the interfering propyl side chain through a 10-membered cyclic carbamate linkage. In addition to restraining the molecule, the cyclic carbamate would protect both the amine and the alcohol, and increase the acidity of the former for the acylation step.[19] Not only are such cyclic carbamates uncommon, but the desired compound is also quite rigid and, ignoring the dioxane ring, represents an example of a system having "inside-outside" stereoisomerism.[20]

The above concerns notwithstanding, synthesis of the cyclic carbamate was straightforward (Scheme 7). Hydrogenolysis over palladium hydroxide on carbon cleanly removed the benzyl group from the C18 hydroxy group. Saponification of the ester followed by treatment with diphenylphosphoryl azide (DPPA) and triethylamine provided the acyl azide, which underwent the Curtius rearrangement upon heating.[21] The resulting isocyanate, **18**, was intercepted intramolecularly by the primary alcohol to cleanly provide the sought-after cyclic carbamate. To the best of our knowledge, this is the first 10-membered cyclic carbamate employed in an organic synthesis exercise.

With tricycle **17** in hand, we turned our attention to its coupling with pederic acid. We were delighted to find that deprotonation of **17** with LiHMDS followed by acylation with pederic acid chloride **2b** gave the desired product (**19**, Scheme 7). The success of the acylation confirmed our hypothesis that the cyclic carbamate would overcome the steric issues encountered by us and others and, for the first time, allowed access to the full mycalamide framework with complete control of the aminal stereocenter. Although the coupling reaction was an important step towards the natural product, the selective hydrolytic cleavage of the carbamate unit over the amide was critical to completing the synthesis. Hydrolysis of the latter would separate the two units that had been so painstakingly assembled. Consideration of known reactivity patterns did not provide clear direction on the relative electrophilicity of the two carbonyl groups toward nucleophiles, although the amide carbonyl group was expected to be more reactive. For example, *N*-acyloxazolidinones are known to react primarily at the amide carbonyl, although the steric environment around the amide carbonyl can reverse the expected chemoselectivity.[22] Examination of the molecular model of **19** showed the carbamate carbonyl to be constrained and sterically more-accessible to nucleophilic attack than



Scheme 7. Coupling and synthesis of mycalamide B. DMAP = 4-(dimethylamino)pyridine.

the amide carbonyl. In addition, the C7 hydroxy group that resulted from hydrolysis of the benzoate group was expected to favor the desired pathway through intramolecular addition and transacylation to the carbamate carbonyl. Indeed, we found that removal of the benzoyl group and opening of the carbamate occurred upon treatment with lithium hydroxide in the presence of lithium chloride in methanol, thus giving us mycalamide B (**1**) with a small amount of recovered **17**.[23]

To summarize, we have developed a stereocontrolled synthesis of mycalamide B, the cornerstone of which is the use

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of temporary restraints to enable coupling of the fully elaborated mycalamine and pederic acid units. The total synthesis requires 14 steps from commercially available starting materials in the longest linear sequence and proceeds in 2.6% overall yield. In addition, the synthetic route features 1) a one-pot Mukaiyama-Michael/epoxidation sequence to introduce three new stereocenters found in the natural product, 2) the intramolecular trapping of the isocyanate from a Curtius rearrangement to produce a rigid, bridged 10-membered cyclic carbamate, and 3) the selective opening of the cyclic carbamate over hydrolysis of the amide linkage. This strategy is expected to enable the synthesis of other members of this large family of highly cytotoxic natural products well as provide rapid access to significant quantities of these compounds for biological and target identification studies.

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