A Formal Synthesis of (−)-Mycalamide A

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The mycalamides,[1] onnamides,[2] and theopederins[3] are biologically and synthetically interesting natural products isolated from marine sponges. Many of these compounds possess potent antiviral and antitumor properties due to their ability to arrest protein synthesis.[4] The inhibition of protein synthesis is accomplished by binding to the 80S ribosome and preventing the translocation of the nascent peptide from the A site to the P site. One of the most remarkable aspects of mycalamides A and B is their ability to change the morphology of *ras*-transformed rat NRK-cells back to normal cells by selectively inhibiting the biosynthesis of p21, a G protein.[5] These natural products have attracted a great deal of attention from the synthetic cmmunity. Total synthesis of mycalamide A,[6a,7,8] mycalamide B,[6a,9] onnamide A,[6b] and theopederin D[9] have been recorded. In addition, studies toward their total synthesis have been reported by other groups.[10] Since these molecules are so complex, it is not surprising that the previous total syntheses typically require around 30 linear steps to complete. Through the use of synthetic methodologies developed in these laboratories, we sought to streamline the synthesis.

We focused our efforts on an asymmetric synthesis of (−)-7-benzoylpederic acid **2** and the azide **3** since Nakata et al.[7b] reported their conversion to mycalamide A in three steps (Scheme 1). By envisioning alkene **4** as a flexible building block to several members of these families including mycalamide A, a novel route for its construction was developed that involves two Pd(0)-catalyzed O-π-allyl cyclizations and a novel strategy to create 1,3-dioxan-4-ones. All of the stereochemistry on the trioxadecalin ring derives from either *R*- or *S*-pantolactone. Our strategy to synthesize acid **2** is based on the recently developed Ru-catalyzed alkene−alkyne coupling reaction.[11] The stereochemistry of the pederic acid derives from that of the initial chiral *trans*-2-butene epoxide, which is commercially available. While our synthesis targeted the enantiomer, the natural series is equally accessible simply by using the mirror-image starting materials.

The synthesis of **2** commenced with epoxide **10** (Scheme 2). While the opening of **10** with the Yamaguchi protocol (lithium trimethylsilylacetylide and BF₃·Et₂O)[12] gave capricious results, it cleanly reacted with the corresponding alanate complex to afford the alkyne **9**.[13] A regioselective Ru-catalyzed coupling reaction between alkene **8** and alkyne **9** rapidly gave **7** with the carbon skeleton present in **2**. After protection with TBS−OTf, the less-hindered olefin was chemoselectively dihydroxylated to furnish the diol **11** as a 1:1 diastereomeric mixture. Monobenzoylation followed by oxidative cyclization gave the desired pyran **15** in 18% yield together with a mixture of **14** and **15** (63%) in 1:1 ratio after chromatography on silica gel. Interestingly, diastereomer **14** was in dynamic equilibrium with the desired isomer **15** on silica gel. Subjecting the 1:1 mixture of **14** and **15** to silical gel column chromatography for three cycles provided **15** in 53% yield together with a 2:1 ratio of **14** and **15** (34%). The C(7) stereochemistry, which has been difficult to control in many previous syntheses,[14] is under substrate control. Thus, the stereochemical outcome in the dihydroxylation step is inconsequential. Methylation without migra-

Scheme 1. Retrosynthetic Analysis
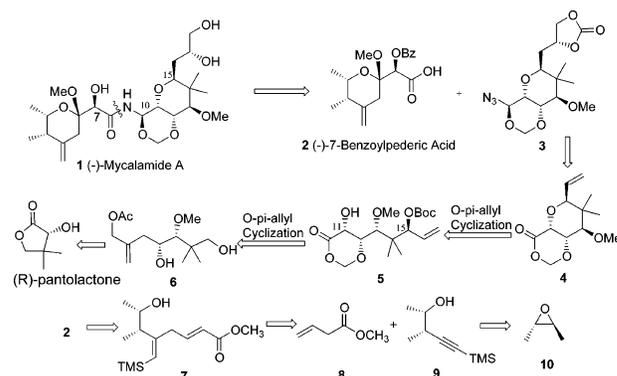
Scheme 2. Synthesis of (−)-7-Benzoylpederic Acid[a]
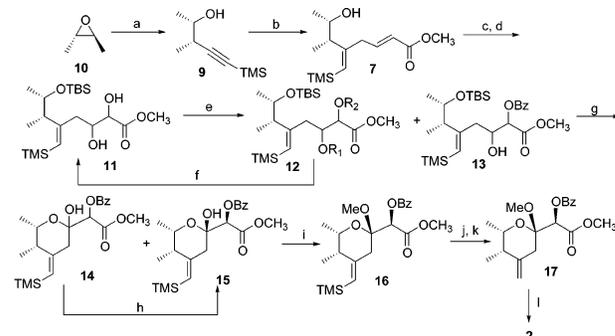
[a] Conditions: (a) TMS acetylene, *n*-BuLi, −78 °C, 20 min; then Me₃Al, −78 °C, 30 min, then −45 °C, 30 min; then **10**, −78 °C, 15 min; then BF₃ etherate, −78 °C, 1 h, quant. (b) **8**, CpRu(CH₃CN)₃PF₆ (10 mol %), acetone, rt, 63%. (c) TBDMSOTi, Et₃N, CH₂Cl₂, quant. (d) OsO₄, NMO, acetone/H₂O, 2 °C, 96% (1/1 dr). (e) DMAP (5 mol %) Et₃N, PhCOCl, CH₂Cl₂, −78 to −40 °C, 70% (96% after f). (f) NaOCH₃, MeOH, 0 °C to room temperature. (g) Dess−Martin Periodianene, NaHCO₃, CH₂Cl₂; then CSA (10 mol %), MeOH, 81%, (h) silica gel. (i) CH₃OTf, LHMDS, DME, −70 °C, 87%. (i) NIS, CH₃CN, 0 °C, 91%. (k) (Ph₃P)₄Pd, Bu₃SnH, 96%. (l) *n*-PrSLi, HMPA, rt, 94%.

tion of the benzoyl group followed by removal of the vinyl TMS afforded **17**. The spectroscopic data (¹HNMR, ¹³CNMR, [α]_D) of **17** match those of Nakata.[14a] A dealkylative saponification of **17** with *n*-PrSLi[15] completed the synthesis of the left-hand side **2**, common to the mycalamide, onnamide, and theopederin families.

The synthesis of the right-hand side azide **3** started from commercially available (*R*)-pantolactone, which was methylated with Ag₂O and excess CH₃I without racemization[16] (Scheme 3). After reduction with DIBAL-H, the resulting lactol was subjected to mediated allylation reaction with 2-(chloromethyl)allyl acetate in aqueous saturated NH₄Cl[17] to produce **6** with a 5:1 diastereomeric ratio favoring **6**. The stereochemistry was confirmed by X-ray analysis. Surprisingly, Pd(0)-catalyzed cyclization exclusively produced the eight-membered ring product **25** (79% yield) wherein the primary alcohol served as the nucleophile (Scheme 4). In contrast, the chemoselectivity was completely switched to form the tetrahydrofuran **18** in 99% yield with the addition of Et₃B. Moffat−

Scheme 3. Synthesis of Azide **3**[a]
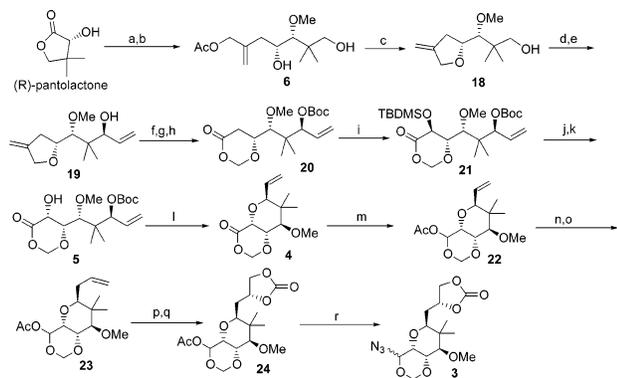
[a] Conditions: (a) Ag₂O, MeI, CH₃CN, 58 °C, 86%, 98% ee, (b) (i) DIBAL-H, CH₂Cl₂, −78 °C; then 2-(chloromethyl)allyl acetate, In powder, sat. aq NH₄Cl, 62% (5/1 dr). (c) PdCl₂(dppf), BEt₃, Et₃N, THF, reflux, 99%. (d) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78 °D, 90% (96% BRSM) (e) vinyl magnesium bromide, MgBr₂ diethyl ether complex, CH₂Cl₂, −78 °C to rt, 96%. (f) n-BuLi, (Boc)₂O, THF, 87% (95% BRSM). (g) (DHQD)₂-PHAL, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, t-BuOH/H₂O; then NalO₄, THF/H₂O, 91%. (h) m-CPBA, 30% Li₂CO₃, CH₂Cl₂, rt, 98%. (i) TBDMSOTf, TEA, CH₂Cl₂, −78 °C, 30 min; then DMDO, acetone, CH₂Cl₂, molecular sieves, −5 °C, 68%. (j) TBAT, benzoic acid, THF, 50 °C, 83%. (k) Tf₂O, pyridine, 0 °C; then NaNO₂, DMF, rt, 75%. (l) Pd₂(dba)₃CHCl₃, dppf, DCE, 70 °C, 58%. (m) DIBAL-H, −78 °C; then pyridine, DMAP, Ac₂O, −78 °C to rt, 100% (1.6/1 dr). (n) 9-BBN, Wilkinson's catalyst; then PCC, DCM, 45 °C. (o) Ph₃P=CH₂, toluene, −40 to −20 °C, 47% over two steps. (p) (DHQD)₂PYR, OsO₄, K₂CO₃, K₃Fe(CN)₆, t-BuOH/H₂O, for α-AcO 74%, 4.3/1 dr; for β-AcO quant., 9/1 dr. (q) Triphosgen, pyridine, DCM, −78 °C, α-AcO 73%, β-AcO 84%. (r) TMSOTf, TMSN₃, CH₃CN, 0 °C, 68% (1.6/1 dr).

Scheme 4. Divergence on Pd(0)-Catalyzed Cyclization of **6**
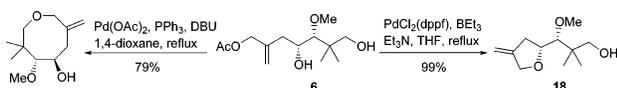
Swern oxidation[18] of **18** followed by vinylmagnesium bromide addition in the presence of MgBr₂·Et₂O[19] gave the allyl alcohol **19** as a single diastereomer. Carbonate formation, selective cleavage of the exocyclic double bond, and a regioselective Baeyer−Villiger oxidation furnished the lactone **20**. The installation of the C(11) hydroxyl group was quite challenging. This was accomplished via a Rubottom oxidation[20] with anhydrous DMDO[21] to give **21**. Addition of 4 Å molecular sieves was crucial to improve both the yield and scalability of this reaction due to the competing protonation/desilylation process. After removal of the TBDMS group with TBAT,[22] the hydroxyl stereochemistry was inverted by activation as a triflate followed by treatment with NaNO₂ in DMF.[23] This is an efficient method to invert the stereochemistry of secondary alcohols. Obviously, many of the methods in the literature employing carboxylic acids as nucleophiles would introduce the dilemma of having to chemoselectively differentiate three different ester groups. The second O-π-allyl cyclization with Pd₂(dba)₃ and dppf as ligand proceeded in a highly diastereoselective fashion to furnish lactone **4**, which was reductively acylated[24] to give quantitative yield of acetates **22** as a separable mixture of α/β (1.6/1) diastereomers. Hydroboration,[25] one-pot PCC oxidation,[26] followed by a Wittig olefination yielded the alkene **23**. After dihydroxylation,[27] carbonate formation, and azide formation, **3** was obtained as a 1.6/1 mixture of α/β C(10) diastereomers. The spectra (¹HNMR, IR) match those reported by Kishi[6a] and Nakata.[7]

In conclusion, an efficient formal synthesis of (−)-mycalamide A was achieved. The left-hand side **2** was synthesized from (2S,3S)-2,3-epoxybutane. The key features include a highly regioselective Ru-catalyzed alkene−alkyne coupling reaction and a novel method

to control the challenging C(7) stereocenter. The right-hand side **3** was synthesized from (R)-pantolactone. The novel features include constructing the trioxadecalin core with two Pd(0)-mediated O-π-allyl cyclizations. The first one is chemoselective, while the second one is highly diastereoselective. Furthermore, a new strategy to construct 1,3-dioxan-4-ones involving 4-methylene tetrahydro-furans[28] has been developed. Three additional steps would be required to complete a total synthesis of mycalamide A.

Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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