The mycalamides, onnamides, and theopederins 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. 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. These natural products have attracted a great deal of attention from the synthetic community. Total synthesis of mycalamide A, mycalamide B, onnamide A, and theopederin D have been recorded. In addition, studies toward their total synthesis have been reported by other groups. Since these molecules are normally and synthetically interesting natural products isolated from marine sponges, their conversion to mycalamide A in three steps (Scheme 1) by envisioning alkene and alkyne cyclizations and a novel strategy to create 1,3-dioxan-4-ones. All of the stereochemistry on the trioxadecaline ring derives from either R- or S-pantolactone. Our strategy to synthesize acid is based on the recently developed Ru-catalyzed alkene–alkyne coupling reaction. 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 (Scheme 2). While the opening of 10 with the Yamaguchi protocol (liothium trimethylsilylacetylide and BF3·Et2O) gave capricious results, it cleanly reacted with the corresponding alanate complex to afford the alkyl 9. A regioselective Ru-catalyzed coupling reaction between alkene and alkyl 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 (7) stereochemistry, which has been difficult to control in many previous syntheses, is under substrate control. Thus, the stereochemical outcome in the dihydroxylation step is inconsequential. Methylation without migration of the benzyl group followed by removal of the vinyl TMS afforded 17. The spectroscopic data (1HNMR, 13CNMR, δ17 of 17 match those of Nakata. A dealkylative saponification of 17 with n-PrSLi15 completed the synthesis of the left-hand side 2, common to the mycalamide, onnamide, and theopederin families.

The synthesis of the right-hand side 3 started from commercially available (R)-pantolactone, which was methylated with Ag2O and excess CH3I without racemization (Scheme 3). After reduction with DIBAL-H, the resulting lactol was subjected to mediating allaylation reaction with 2-(chloromethyl)allyl acetate in aqueous saturated NH4Cl 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 trihydrofuran 18 in 99% yield with the addition of Et3B. Moffat–
ester groups. The second
This is an efficient method to invert the stereochemistry of
Swern oxidation 18 of
Ru-catalyzed alkene
2
A was achieved. The left-hand side
activation as a triflate followed by treatment with NaNO 2 in DMF. 23
furnish lactone
protonation/desilylation process. After removal of the TBDMS
allowed by a Wittig olefination yielded the alkene
23
(1.6/1 dr).

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 trioxadecaline core with two Pd(0)-mediated O-aryl alkyne coupling reactions. 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 tetrahydrofurans 28 has been developed. Three additional steps would be required to complete a total synthesis of mycalamide A.

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University) for sending us part of Dr. Hong C. Y.’s thesis, Professor T. Nakata (RIKEN) for providing us the 1H NMR of
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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References


JAC038787R
produced dihydrobenzofuranone 23 (R = H) in 85% yield. Note that in this case, the substitution pattern about the furan ring is different from that encountered with the acyclic dicarbonyl compounds. More than likely the initial step involves O-alkylation to give 21 as a transient species. Further reaction of this material with base results in cyclization to 22, which then undergoes a subsequent aromatization. A similar series of reactions was used to prepare furan 24.

When 2-acetylcyclohexanone was used, employing sodium methoxide as the base, ring opening of the intermediate adduct 25 to give 30 takes precedence over deacetylation, presumably as a consequence of the stability of the anion formed. This circumstance can be avoided, however, by the use of a formyl group in place of the acetyl group to activate the cyclic ketone. Thus, DBP reacted with the sodium salt of 2-formylcyclohexanone (26) to give, the same fashion as 31, using the commercially available (R)-3-methylcyclohexanone. Furan 32 was then treated with sodium amalgam to give (R)-menthofuran in 85% overall yield.

In conclusion, the DBP approach is a general method for the synthesis of C-2 and C-3 substituted furans. In addition to its ease of removal, the pendant sulfone at C-4 offers a convenient and versatile site for further elaboration (via alkylation or Julia coupling). This strategy toward furans clearly could be applied to more complex targets. We are currently investigating the scope and limitations of this protocol.

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Supplementary Material Available: Experimental procedures and spectroscopic data for new compounds (5 pages). Ordering information is given on any current masthead page.

Total Synthesis of Mycalamides A and B
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Summary: A total synthesis of mycalamides A (1) and B (2) was accomplished in an enantiomerically pure form, establishing unambiguously their absolute configuration.

Mycalamides A (1) and B (2) and onnamide A have recently been isolated from marine sponges.\(^1\) Naturally, they are strikingly similar to pederin (3), the vesicatory principle of staphylinid beetles \(\text{Paederus}\).\(^3\)
Each of these natural products exhibits remarkable biological activity, and we are intrigued by the acylaminal group, such as the one found at the C-10 position of mycalamides. For example, it may be activated by eliminative cleavage of the C-10 carbon-oxygen bond, and if so, the additional ring system found in other functional groups, such as the one found at the C-10 position of mycalamides, may play an important role in the origin of the biological activity. For example, it may be used as the starting material for the synthesis of right half of mycalamides.

We chose methyl α-D-glucopyranoside as the starting material for the synthesis of right half of mycalamides because of their obvious structural similarity. With small modifications of the functional group transformations known in the carbohydrate literature, this substance was converted into the alcohol 4 (αD +33.3°, CHCl3) in over 65% overall yield. A seven-step sequence of routine synthetic reactions (1) Swern oxidation, (2) Wittig reaction, (3) CH2N2/Pd(OAc)2/ Et2O/0 °C, (4) H2/Pd- (OH)2 on C/ EtOAc/room temperature then H2/PtO2/ AcO/room temperature; (5) (t-Bu)2CuCl2/SiCl3/imidazole/CH2Cl2/room temperature; (6) C2H5CHO/NaH/THF/room temperature; (7) n-BuNF/THF/room temperature) allowed the introduction of the geminal dimethyl groups at the C-14 position in 62% overall yield, i.e. 4 → 5. We planned to incorporate the C-17,18 glycol via the terminal olefin 6. As direct methods did not yield fruitful results, after heating at 6 (αD +77.9°, CHCl3) in five steps (1) Swern oxidation; (2) Horner-Emmons olefination; (3) DIBAL/CH2Cl2/78 °C; (4) H2/Rh on Al2O3/EtOAc/room temperature; (5) o-NO2C6H4SeCN/P(n-Bu)3/CH2Cl2/room temperature, followed by MCPBA treatment in 79% overall yield. Application of the recently developed asymmetric oxyamination [OsO4/N,N,N'-bis(4,4,5,5-trimethylbenzyl)-(S,S)-1,2-diphenyl-1,2-diaminoethane/CH2Cl2/−90 °C] gave a 5:1 mixture of the two possible glycols, which were then transformed to the corresponding carbonates and separated on silica gel to yield the desired carbonate 7 (75% overall yield; αD +66.7°, CHCl3) along with the corresponding undesired carbonate (13% yield). The undesired carbonate was recycled in 65% overall yield via the olefin 6. The C-17 stereochemistry in 7 was assigned on the basis of three pieces of evidence. First, the asymmetric osmylation of 6 in the presence of the antipode of the chiral diamine yielded an inverted ratio (ca. 1:1) of the two possible glycols. Second, Sharpless asymmetric epoxidation [diethyl tartrate/Ti(i-PrO)4/t-BuOOH/CH2Cl2] of the allylic alcohol prepared from 5,17 followed by DIBAL reduction, yielded a 6:1 mixture of the expected 1,2- and 1,3-glycols. The 1,2-glycol thus obtained was found to be identical with the major glycol which expected 1,2- and 1,3-glycols. The 1,2-glycol thus obtained was found to be identical with the major product of which was correlated with 7.20

In order to construct the B ring, we needed to introduce

(4) Mycalamides and onnamide are known to exhibit antiviral and antitumor activity: Burres, N. S.; Clement, J. J. Cancer Res. 1989, 49, 2935. See also the references cited in ref 1 and 2. Pedrin is known to be a powerful insect toxin and a potent inhibitor of protein biosynthesis: see the references cited in ref 3.
(5) The numbering of compounds used in this paper corresponds to that of mycalamides: see structures 1 and 2.
(6) Purchased from Pfanstiehl Laboratories, Inc.
(7) Satisfactory spectroscopic data (1H and 13C NMR, MS, HR MS, IR, MS) were obtained for all the new compounds reported.
(8) This transformation required a six-step sequence of reactions, (1) MeOCH2CH2OMe/ p-TsOH; (2) (n-Bu)2SnO, followed by p-TsCl/Me2N treatment; cf. Munave, R. M.; Szmant, H. H. J. Org. Chem. 1986, 51, 1832; (3) Me/AgO; (4) NaBH4; (5) C2H5CHO/NaH; (6) NaH/CH2Cl2/room temperature; (7) t-BuNF/THF/room temperature. The stereochemistry of the two possible glycols, the major product of which was selected on the basis of three pieces of evidence. First, the asymmetric osmylation of 6 in the presence of the antipode of the chiral diamine yielded an inverted ratio (ca. 1:1) of the two possible glycols. Second, Sharpless asymmetric epoxidation [diethyl tartrate/Ti(i-PrO)4/t-BuOOH/ CH2Cl2] of the allylic alcohol prepared from 5, followed by DIBAL reduction, yielded a 6:1 mixture of the expected 1,2- and 1,3-glycols. The 1,2-glycol thus obtained was found to be identical with the major glycol which expected 1,2- and 1,3-glycols. The 1,2-glycol thus obtained was found to be identical with the major product of which was correlated with 7.

(11) For a large scale preparation, we used (1) CH2Cl2/aqueous NaOH/C2H5CHO/Me3NO/NCf and (2) Li/AcOH/room temperature in place of the step 3 for safety reasons.
(12) These included a vinylcuprate reaction on the tosylate and iodide prepared from 5.
(15) This recycling was carried out in four steps, (1) 0.5 N NaOH/room temperature; (2) HClO4/room temperature; (3) isobutyric anhydride/125 °C; (4) asymmetric osmylation.
(16) This allylic alcohol was prepared from
(17) This allylic alcohol was prepared from
(18) This allylic alcohol was prepared from
(19) This allylic alcohol was prepared from
(20) This allylic alcohol was prepared from
TMSOTf in acetonitrile, followed by ozonization and acetalization, to furnish the dimethyl acetal of the C-11 position. This was accomplished by treatment of the axially disposed aldehyde group or its equivalent at Propargyltrimethylsilane in connection with work on the conformational analysis of C-glycosides.

For the stereochemical outcome of this type of C-glycosidation, see: Lewis, M. D.; Cha, J. K.; Kishi, Y. J. Am. Chem. Soc. 1982, 104, 4976.

Propargyltrimethylsilane was first used by Dr. Wu in these laboratories in connection with work on the conformational analysis of C-glycosides.

(21) For the stereochemical outcome of this type of C-glycosidation, see: Lewis, M. D.; Cha, J. K.; Kishi, Y. J. Am. Chem. Soc. 1982, 104, 4976. Propargyltrimethylsilane was first used by Dr. Wu in these laboratories in connection with work on the conformational analysis of C-glycosides.

the dimethyl acetal 8 (α+63.9°).

When warmed up to room temperature, this reaction yielded the corresponding chloride, which was directly used for the next azide displacement reaction. The overall yield of this sequence was comparable with the one reported in the text but its reproducibility was not as high as the other.

(22) When warmed up to room temperature, this reaction yielded the corresponding chloride, which was directly used for the next azide displacement reaction. The overall yield of this sequence was comparable with the one reported in the text but its reproducibility was not as high as the other.

(23) HR MS (FAB, NaI): calcd for C16H12N9O7M+ (M+ Na) 344.1456, found 344.1456. [α]D = +5.8° (c 0.97, CHCl3). 1H NMR (major isomer, CDCl3): 5.08 (3 H, s, C-14 CH3), 5.21 (2 H, s, C-14 CH2), 1.70 (1 H, m, C-16 H), 3.17 (1 H, dd, J = 4.5, 12.6 Hz, C-18 H), 3.31 (1 H, dd, J = 3.3, 12.6 Hz, C-18 H), 3.79 (1 H, t, J = 3.3 Hz, C-15 H), 3.86 (1 H, dd, J = 3.3, 12.6 Hz, C-15 H). 13C NMR (major isomer, CDCl3): 142.9 (1 H, m, C-16 CH), 141.3 (2 H, s, C-14 CH2), 105.3 (3 H, s, C-14 CH3), 105.3 (1 H, m, C-16 H), 3.17 (1 H, dd, J = 4.5, 12.6 Hz, C-18 H), 2.60 (3 H, s, OCOCF3), 2.26 (1 H, m, C-16 H), 3.01 (1 H, d, J = 3.6 Hz, C-13 H), 3.40 (3 H, s, OCH3), 5.41 (3 H, s, OCH3), 3.67 (1 H, m, C-17 H), 3.70 (1 H, m, C-15 H), 3.87 (1 H, m, C-15 H), 3.87 (1 H, m, C-15 H), 3.90 (1 H, dd, J = 4.9, 12.1 Hz, C-18 H), 4.36 (1 H, dd, J = 2.6, 12.1 Hz, C-18 H), 4.63 (1 H, d, J = 2.6, 12.1 Hz, C-18 H), 4.83 (1 H, m, C-17 H), 5.20 (1 H, d, J = 6.6 Hz, OCH3). IR (CCl4): 2120, 1823 cm-1.

(24) HR MS (FAB, NaI): calcd for C16H12N9O7NaM+ (M+ Na) 366.1745, found 366.1738. [α]D = +5.8° (c 0.97, CHCl3). 1H NMR (CDCl3): 5.02 (3 H, s, C-14 CH3), 1.05 (3 H, s, C-14 CH3), 1.62 (1 H, m, C-16 H), 3.01 (1 H, d, J = 3.6 Hz, C-13 H), 3.40 (3 H, s, OCH3), 5.41 (3 H, s, OCH3), 3.67 (1 H, m, C-17 H), 3.70 (1 H, m, C-15 H), 3.87 (1 H, m, C-15 H), 3.90 (1 H, dd, J = 4.9, 12.1 Hz, C-18 H), 4.36 (1 H, dd, J = 2.6, 12.1 Hz, C-18 H), 4.63 (1 H, d, J = 2.6, 12.1 Hz, C-18 H), 4.83 (1 H, m, C-17 H), 5.20 (1 H, d, J = 6.6 Hz, OCH3). IR (film): 2119, 1739 cm-1.

yielded a mixture of α-16 (58% yield) and β-16 (40% yield) and α-17 (59% yield) and β-17 (26% yield), respectively. The diastereomers were readily separable by chromatography to yield stereochemically pure products. Both β-16 and β-17 were found to isomerize to the corresponding natural diastereomers upon treatment with base (t-BuOK/THF/reflux). It is interesting to note that β-16 isomerized almost exclusively to the natural diastereomer while β-17 epimerized to reach a 1:1 mixture of the natural and unnatural diastereomers. Mycalamides A (1) and B (2) were obtained from α-16 and α-17 in two steps (1) t-BuOK/THF/room temperature for α-16 and LiOH/MeOH/room temperature for α-17; (2) DDQ/H₂O-CH₂Cl₂/room temperature in 60% and 69% overall yields, respectively. On comparison of 1H and 13C NMR, IR, MS, [α]D, and TLC data, the synthetic materials were found to be identical with an authentic sample of mycalamides A and B.

The reported synthesis has good a preparation for the preparation of various analogues of mycalamides. In this regard, it is also interesting to note that some of the intermediates should be useful for the construction of the right half of onnamide A. Lastly, it is worthwhile to point out that this synthesis has unambiguously established the absolute stereochemistry of mycalamides A and B, which had tentatively been assigned on the basis of their structural similarity to pederin.

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**Supplementary Material Available:** Experimental details for the coupling reactions to form 16 and 17 and spectroscopic data for the key natural and mycalamides A and B (13 pages). Ordering information is given on any current masthead page.

(32) On potassium tert-butoxide treatment, the carbonate group in 16 or the acetate group in 17 was hydrolyzed. It was observed that these substrates decomposed slowly in the basic conditions, so epimerization was stopped at approximately 60% completion for preparative purposes to yield the epimerized natural diastereomer in 42% yield (67% corrected yield).

(33) HR MS (FAB, Na⁺): calcd for C₆H₁₄NO₃Na⁺ (M⁺ + Na⁺) 362.0494, found 362.0493.

(34) Supplementary Material Available: Experimental details for the reaction conditions.

(35) We are indebted to Professors Ferry and Munro for a sample of mycalamides A and B.