Communication

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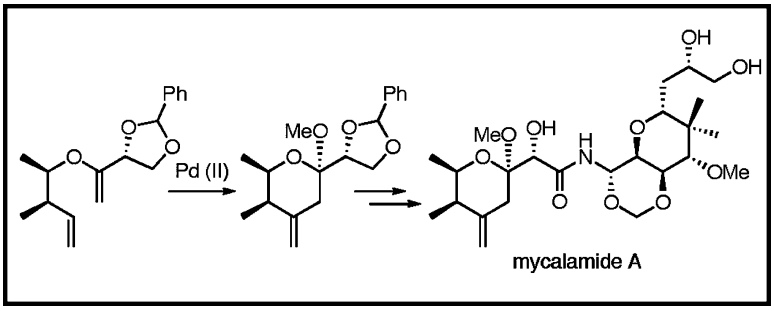

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Total Synthesis of Mycalamide A

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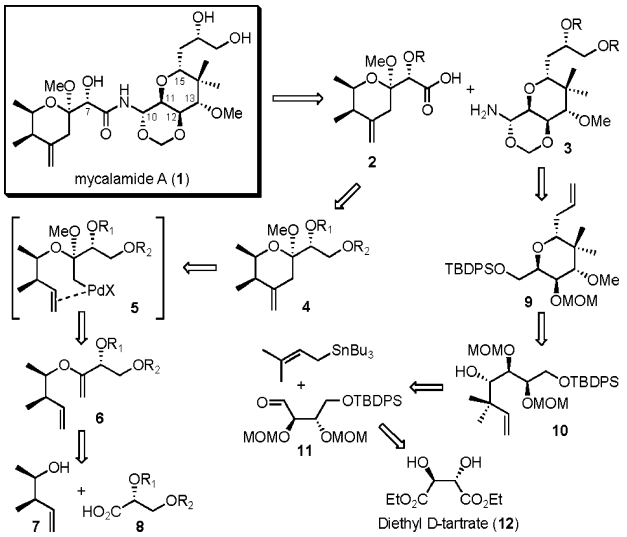
Mycalamides A−D,[1] onnamides A−F,[2] and theopederins A−L[3] belong to a class of structurally related natural products. These compounds possess strong antitumor and antiviral activities, and some members display potencies at subnanomolar concentrations in cells as a consequence of protein synthesis inhibition.[4] In particular, mycalamide A (**1**), isolated from a New Zealand marine sponge of the genus *Mycale*, also exhibits immunosuppressive action by blocking T-cell activation in mice and is significantly more potent than FK-506 and cyclosporine A.[5] The combination of intriguing biological profile, structural complexity, and scarce supply of these natural products has stimulated intense research efforts by synthetic chemists, and total, formal, or partial syntheses of several members of this family of compounds have been reported.[6−9] We report here a convergent synthesis of mycalamide A, wherein the two major parts of the target are synthesized through concise, stereocontrolled routes.

Our plan for the preparation of mycalamide A entailed linking of the pederic acid half (**2**), which is found in all members of the above family of compounds, with the mycalamine half (**3**) through an amide bond (Scheme 1).[6] Diastereoselective formation of this bond has proven challenging, since the aminal group in mycalamine is configurationally unstable under acidic, neutral, or basic conditions.[6a,b] We devised a palladium-catalyzed tandem cyclization sequence to construct the pederic acid framework. The exocyclic double bond containing pyran ring **4** was expected to arise from an intramolecular Heck reaction of σ-alkylpalladium species **5**, which, in turn, was the expected product of a Wacker-type reaction of enolether **6**.[11] Since Pd(0) is produced at the end of the cascade, a secondary oxidant would be required to complete the catalytic cycle. In the challenging trioxadecalin part, five out of the seven carbons in this bicyclic ring system are stereogenic. Further analysis revealed that the oxygenated four-carbon fragment was derivable from the abundant C2 symmetric compound, tartaric acid.

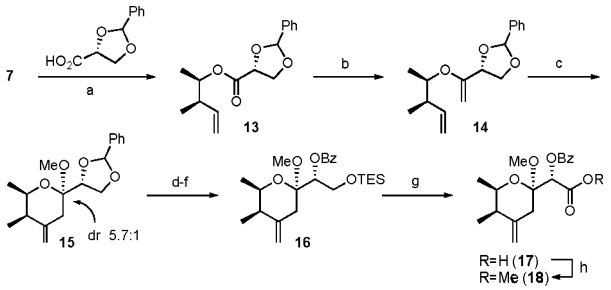
Scheme 2 summarizes the tandem Wacker/Heck route to pederic acid, the left-half of mycalamide A. Esterification of benzylidene-protected glyceric acid[12] with the known homoallylic alcohol **7**,[13] using EDC, followed by Petasis methylenation[14] produced enolether **14**, possessing the carbons necessary for pederic acid and poised for the Pd-catalyzed cyclization sequence. Syringe pump addition of **14** to a mixture containing MeOH, $HC(OMe)_3$, propylene oxide, benzoquinone as the stoichiometric oxidant, and 0.15 equiv of $PdCl_2$ in THF−DMF (20/1) at ambient temperature provided the desired tetrahydropyran **15** in 78% yield as a 5.7:1 mixture of diastereomers. Removal of the benzylidene group and selective TES protection of the primary alcohol followed by benzoylation of the secondary hydroxyl gave **16** in excellent yield. Slow addition of **16** to a mixture of PDC in DMF converted the TES-protected hydroxyl directly to the corresponding acid **17** (83%). For the purpose of characterization, the acid was converted to the corresponding methyl ester (**18**).[15]

The synthesis of the right-half of mycalamide A commenced with diethyl D-tartrate (**12**), which was desymmetrized through a

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of (+)-7-Benzoylpederic Acid[a]



[a] Conditions: (a) EDC, DMAP, CH_2Cl_2, 91%. (b) Cp_2TiMe_2, $PhCH_3$, 80 °C, 85%. (c) $PdCl_2$ (0.15 equiv), benzoquinone, MeOH, $HC(OMe)_3$, propylene oxide, THF/DMF (20/1), 78%. (d) Na, liq. NH_3, EtOH, 93%. (e) TESCl, DIPEA, CH_2Cl_2, 93%. (f) BzCl, DMAP, DIPEA, CH_2Cl_2, 94%. (g) PDC, DMF, 83%. (h) CH_2N_2, Et_2O, quant.

four-step sequence to give the aldehyde **11** in 77% overall yield. (Scheme 3) Chelation-controlled addition of tri-*n*-butylprenylstannane to aldehyde **11** using $ZnBr_2$ introduced the next stereocenter with >50:1 diastereoselectivity.[9c,16] Methylation of **10** (98%) was followed by a new protocol devised to remove both MOM groups under mild conditions. Treatment with $ZnBr_2$ and *n*-BuSH in methylene chloride for a few minutes at room temperature removed both MOM groups and gave diol **19** in 98% yield.[17] Selective benzoylation of C(11)−OH followed by MOM protection of the remaining OH and removal of the benzoyl group afforded alcohol **20** in good yield. Ozonolysis of **20** followed by acetylation produced a lactol acetate, which on treatment with $BF_3{\cdot}OEt_2$ and allyltrimethylsilane in methylene chloride furnished **9** as a single diastereomer in 66% yield from **20**.[8,9c,d,18]

In preparation for the dioxane formation, the TBDPS group was removed, and the resulting alcohol was oxidized under Swern conditions. Treatment of the resulting aldehyde with paraformal-

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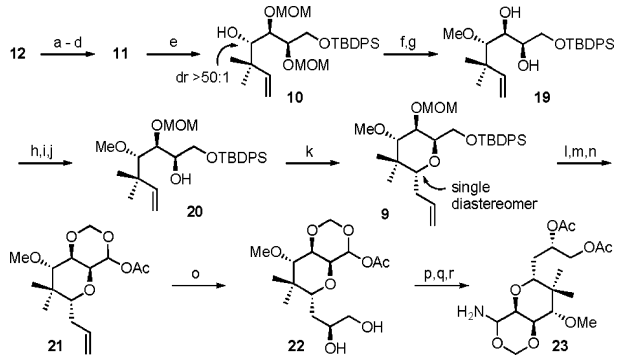
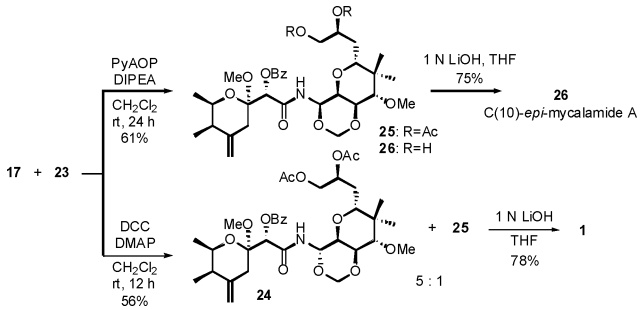
Scheme 3. Synthesis of Mycalamine[a]



[a] Conditions: (a) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2 (quant). (b) LAH, Et_2O (86%). (c) *n*-BuLi, TBDPSCl, THF (quant). (d) $(COCl)_2$, DMSO, Et_3N CH_2Cl_2 (90%). (e) $Me_2CCHCH_2SnBu_3$, $ZnBr_2$, CH_2Cl_2 (90%). (f) NaH, MeI, THF, 98%. (g) $ZnBr_2$ (2.5 equiv), *n*-BuSH (3.0 equiv), room temp (rt), 8 min, CH_2Cl_2, 98%. (h) BzCl, DIPEA, CH_2Cl_2, rt, 11 h, 80%. (i) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, rt, 3 h, 91%. (j) K_2CO_3, MeOH, rt, 3 h, 83%. (k) O_3, Me_2S, CH_2Cl_2; Ac_2O, DMAP, pyr; $BF_3{\cdot}OEt_2$, CH_2CHCH_2TMS, CH_2Cl_2, 66%. (l) TBAF, THF, 91%. (m) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2. (n) $(CHO)_n$, concd HCl, THF; Ac_2O, DMAP, pyr, 63%, dr 5.4:1. (o) OsO_4, $(DHQ)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O, −3 °C (α-AcO 83%, dr 5.0:1; *β*-OAc 85%, dr 5.9:1). (p) Ac_2O, DIPEA, DMAP, CH_2Cl_2, 92%. (q) $TMSN_3$, TMSOTf, CH_3CN, −78 to 0 °C (quant). (r) H_2, Pd/C, EtOAc, 90%.

Scheme 4. Synthesis of Mycalamide A



dehyde and concentrated HCl in THF at −15 to −10 °C directly yielded the 4-hydroxy-1,3-dioxane, which upon acetylation afforded trioxadecalin **21** (57% yield from **9**). After asymmetric dihydroxylation[19] of **21**, the diacetate of diol **22** was treated with $TMSN_3$ and TMSOTf to transform the anomeric acetate to an azide, which on hydrogenation gave the desired mycalamine unit, **23**.

For coupling the two partners, an extensive examination of methods[6a,b] revealed that the reaction proceeded cleanly and in good yield (61%) using PyAOP and *i*-Pr_2NEt in (Scheme 4). However, deprotection of the coupled product with 1 N LiOH in THF gave only C(10)-*epi*-mycalamide A **26**[4c] (75%),[20] which could not be epimerized to mycalamide A.[6a] Gratifyingly, when the coupling of **17** and **23** was carried out using DCC and DMAP in dichloromethane, the predominant product was the desired mycalamide diastereomer, **24**, obtained in a 5:1 ratio along with **25**. Finally, the three esters were removed through hydrolysis using 1 N LiOH in THF to afford mycalamide A in 78% yield.[20]

In conclusion, we have completed a concise and efficient total synthesis of mycalamide A by the convergent coupling of pederic acid piece **17** with mycalamine unit **23**. The left half, (+)-7-benzoylpederic acid, was synthesized in seven steps and 34.6% overall yield from homoallylic alcohol **7** through a route that featured a one-step Pd(II)-catalyzed tandem Wacker/Heck cyclization reaction to prepare the tetrahydropyran ring system. The right half unit, **23**, was synthesized from diethyl D-tartrate (**12**) in 21 steps and 10.5% overall yield. Effective, stereoselective methods were developed for the preparation of either mycalamide A (**1**) or C(10)-*epi*-mycalamide A (**26**).

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra of key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The NMR spectra of our synthetic mycalamide A and *epi*-mycalamide A matched to those of the naturally derived materials. We thank Prof. J. W. Blunt (University of Canterbury, New Zealand) for kindly providing the spectra.

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