Assignment of Configuration

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Total Synthesis of (+)-Apiosporamide: Assignment of Relative and Absolute Configuration**

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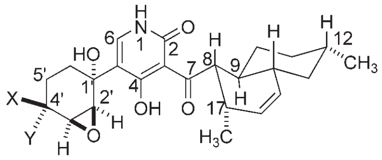

1 (apiosporamide): X = OH; Y = H
2 (YM-215343): X = Y = O

Apiosporamide (**1**) was isolated from the fungus *Apiospora montagnei* Saccardo (Amphisphaeriaceae) in 1994 by Gloer and co-workers.[1] This unique 4-hydroxy-2-pyridinone exhibits potent antifungal activity against the coprophilous fungus *Ascobolus furfuraceus* and exhibits antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*. Recently, the corresponding ketone YM-215343 (**2**) was identified and shown to demonstrate cytotoxicity against HeLa S3 cell cultures.[2] Structural assignments of **1** (and **2**) have proven challenging. Although homonuclear and heteronuclear 2D NMR spectroscopic experiments permitted the assignment of the relative configuration of the decalin ring, the configuration of the epoxydiol system could not be determined unambiguously. The latter moiety was tentatively assumed to have an all-*syn* topology. Unfortunately, the stereochemical features of the *trans* decalin portion present an independent ^{1}H NMR spectroscopic system relative to the cyclohexanediol moiety owing to the planarity of the central pyridinone linkage. Lastly, the substitution pattern of the pyridinone ring was assumed by comparison with the ^{13}C NMR spectroscopic chemical shifts of **1** with ilicicolin H, which was previously described and confirmed by total synthesis as a 5-aryl-4-hydroxy-3-acyl-2-pyridone.[3] Some examples of this family include militarinone A,[4] oxysporidinone,[5] fischerin,[6] and funiculosin.[7] Herein, we report a convergent total synthesis of (+)-apiosporamide (**1**) and its subsequent oxidation to yield YM-215343 (**2**). Our efforts have established the assignments of the relative and absolute configurations, which confirm the antipodal relationship of our synthetic materials with the naturally occurring metabolites.

To address the structural ambiguities of **1**, we chose to explore a convergent plan for stereocontrolled syntheses of the *trans*-decalin and the epoxydiol components. This strategy required appropriate functionalization of each subunit for the late stage formation of the central pyridone. Additionally, we sought to devise general, stereodivergent schemes that would permit the flexibility necessary to examine the substantial stereochemical issues previously outlined.

Studies of the cyclohexanediol portion of **1** began with the synthesis of nonracemic 4-hydroxy-2-cyclohexenones. The multigram preparation of **4** (Scheme 1) utilized (−)-quinic acid as a chiral-pool precursor through formation of the pure acetonide **3** as described by Danishefsky and co-workers.[8] Consideration of the appropriate functionality for direct linkage with the decalin component as well as subsequent pyridone ring formation led us to examine the enolate condensation of *N*-(4-methoxybenzyloxy)azetidin-2-one (**5**) with **4**.

Techniques for the incorporation of intact β-lactams are rare.[9] Although the ring strain of **5** incorporates the desired activation for coupling operations, the limited prospects for addition reactions with unsubstituted β-lactams suggest issues of incompatibility that arise from enolate instability, self-condensation, and acylation of alkoxide intermediates. Thus, we were gratified to find that the hydroxamic acid derivative **5** led to solutions of dependable enolates.[10] The starting β-lactam **5** was readily obtained through procedures described by Reinhoudt and van Elburg.[11] Complete deprotonation was initially recorded through reaction with LiHMDS for 2 h

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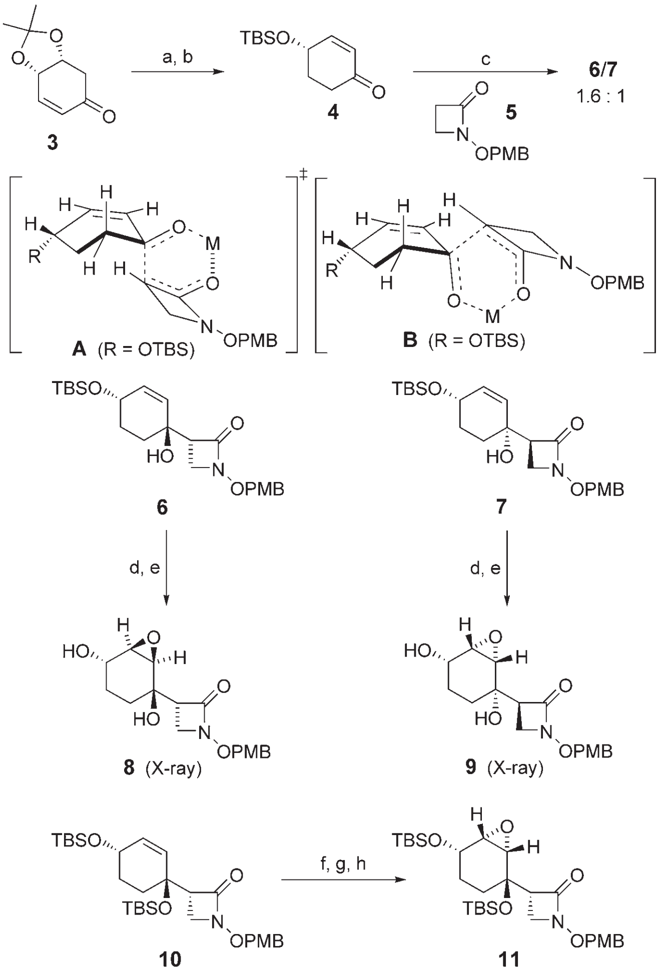
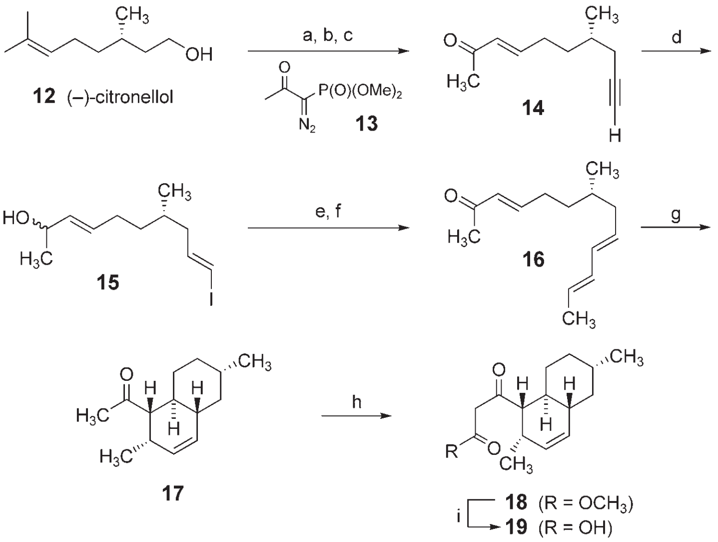


Scheme 1. Formation of β-lactam diastereomers **8**, **9**, and **11**. a) H_2, $Pd(OH)_2/C$, 97%; b) DBU, TBSCl, heat, 72%; c) KHMDS, THF, −78 °C, 2 h; then **4** at −78 °C; 97%, (d.r. 1.6:1); d) cat. $[Mo(CO)_6]$, *t*-BuOOH, benzene/CH_2Cl_2 (5:1 by *v*/*v*), 80 °C, 2 h; 66%; e) cat. aq. H_2SiF_6, CH_3CN/*t*BuOH (9:1 by *v*/*v*), 22 °C, 80%; f) TBAF, 0 °C, 98%; g) MCPBA, CH_2Cl_2, $NaHCO_3$, 54%; h) TBSCl, imidazole, CH_2Cl_2, 100%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBS = *tert*-butyldimethylsilyl; HMDS = 1,1,1,3,3,3-hexamethyldisilazane; TBAF = tetrabutylammonium fluoride; MLPBA = *meta*-chloroperoxybenzoic acid.

at −78 °C. Although the enolate decomposed upon warming to −40 °C, the addition of simple aldehydes at −78 °C immediately led to the formation of addition adducts in 80–95% yields.[12] In the case of cyclohexenone **4**, these experiments gave the two readily separated β-lactam diastereomers **6** and **7** (1.2:1) in high yields, (Scheme 1) without evidence of competing α deprotonation or conjugate addition. The stereochemical features of **6** and **7** are rationalized by arrangements **A** and **B** (Scheme 1), which illustrate nucleophilic addition to either face of the carbonyl group while minimizing nonbonded interactions with the α-methylene of the starting ketone. Coordination with the lithium cation is not essential as reactions in the presence of 12[crown]-4 produced similar product ratios. This conclusion was supported when the reactions were increased to multigram levels, as the use of KHMDS afforded diastereomers **6** and **7** (1.6:1 d.r.) in 97% yield. Although modest improvements in stereocontrol were recorded,[13] the overall efficiency, scale, and ease of separation for reactions with KHMDS proved most advantageous for these efforts.

The relative stereochemistry within the cyclohexane ring of **1** was investigated through the epoxidation of **6** and **7** with catalytic molybdenum hexacarbonyl and *tert*-butylhydroperoxide,[14] to yield a single oxirane in each case. Coupling constants derived from ^1H NMR spectroscopic data for these materials failed to provide a clear basis for stereochemical assignments. However, mild hydrolysis of the TBS ethers gave the crystalline diols **8** and **9**, which were unambiguously assigned by X-ray diffraction studies.[15] Internally directed reactions were confirmed, and led to the use of the secondary allylic alcohol derived from **10** for Henbest epoxidation and silyl protection to yield diastereomer **11**. Further studies to prepare sufficient quantities of the remaining fourth diastereomer that corresponds to the C4′ epimer of **11** encountered several problems. Comparisons of ^1H NMR spectroscopic data for various derivatives of **8**, **9**, and **11** with the reported ^1H NMR spectroscopic characteristics of apiosporamide were not feasible. The presence of the pyridone ring of **1** effectively inverts the relative positions of chemical shifts observed for the hydrogen atoms of the neighboring oxirane moiety. Thus, each β-lactam of Scheme 1 was independently advanced in the synthetic pathway.

The decalin portion of **1** was prepared through an intramolecular Diels–Alder reaction that began with (*S*)-citronellol (**12**; Scheme 2). Oxidation[16] of **12** with TEMPO



Scheme 2. Formation of the *trans*-decalin **19**. a) Cat. TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 70%; b) **13**, K_2CO_3, MeOH, RT, 82%; c) cat. OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH/H_2O (1:1 by *v*/*v*), 94%; then, $NaIO_4$, aq. THF (1:1); then $H_3CC(O)CH_2P(O)(OMe)_2$, K_2CO_3, 91% (13:1 *E*/*Z*); d) $[Cp_2Zr(H)Cl]$, CH_2Cl_2, RT; then I_2, 77%; e) $[Pd(PPh_3)_4]$ (5 mol%), (*E*)-BrZnCH=CHCH$_3$ (2.5 equiv), THF/Et_2O/pentane (4:4:1), −30 °C→RT; 74%; f) Dess–Martin periodinane, py, CH_2Cl_2, 90%; g) $EtAlCl_2$, toluene, −78 °C→RT, 72% (> 97:3 d.r.); h) LiHMDS, THF, −78 °C→0 °C; then HMPA at −78 °C; then MeOC(O)CN, 62%; i) KOH, aq. MeOH, 0 °C, 81%. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy radical, Cp = cyclopentadienyl, HMPA = hexamethylphosphoric triamide.

and treatment with the Ohira–Bestmann reagent **13**[17] provided a volatile alkyne. Selective oxidative cleavage of the trisubstituted olefin followed by treatment with $H_3CC(O)CH_2P(O)(OMe)_2$ led to the conjugated enone in **14** (13:1 *E*/*Z*). The *syn* hydrozirconation of **14** followed by treatment with iodine yielded the *E* alkenyl iodide **15** with concomitant reduction of the ketone.[18] Facile Negishi coupling[19] with (*E*)-prop-1-enylzinc(II) bromide cleanly delivered a single diene diastereomer without the need for protection strategies to prevent the competing Heck reaction, and subsequent mild oxidation recovered the intact enone of **16**.

The Lewis acid mediated intramolecular Diels–Alder reaction of **16** proceeded in toluene at −78 °C with subsequent warming to 22 °C. Excellent stereoselectivity was observed, and the *trans* decalin **17** was assigned by ^1H NMR spectroscopy. Decalin **17** arises through an *exo* bridging arrangement with *endo* positioning of the ester function; a chairlike conformation of the tether is adopted with a pseudoequatorial disposition of the methyl substituent.[20] The corresponding thermal cycloaddition (toluene, 180 °C) occurred with poorer stereocontrol (d.r. 70:30). Deprotonation of **17** under kinetic conditions and C-acylation according to the Mander protocol[21] gave pure β-ketoester **18**, which was then used to produce the labile carboxylic acid **19** prior to coupling studies.

The synthesis of **1** was pursued from **11** (Scheme 3). Although several pathways were examined, superior results involved the initial nucleophilic opening of **11** to give the *N*-alkoxyamine **20** for quantitative *N*-acylation with the carboxylic acid **19**. Subsequent acyl activation in the presence of DBU resulted in ring closure to form **21**. Reduction with samarium diiodide yielded the dihydropyridone **22** with selective N−O bond cleavage. Subsequent oxidation with bromotrichloromethane, based upon our previous studies,[22] gave the expected 4-hydroxy-2-pyridinone for final deprotection to afford (+)-apiosporamide (**1**). The spectral data of **1** proved to be identical to that reported for the naturally occurring **1,** but the optical rotation was opposite.[1,23,24] Further confirmation was obtained by the Dess–Martin oxidation[25] of synthetic **1** to yield the antipode of **2**, (+)-YM-215343,, which was validated by comparison with published data for the natural product.[2,26] Although the structural homology of pyridones **1** and **2** suggest evidence of a common biogenesis, we did not assume homochirality. However, the characterization of these natural products provides physical and spectral data that uniquely identify the synthetic **1** and **2** compared to other diastereomers of this series.

In conclusion, we have established the relative and absolute configuration of apiosporamide and have illustrated an efficient strategy for the synthesis of complex pyridinones. The use of unsubstituted β-lactams as β-alanine enolate equivalents has been demonstrated. Finally, the conversion of synthetic (+)-apiosporamide into (+)-YM-215343 has been described and has confirmed the antipodal relationship to the natural products.

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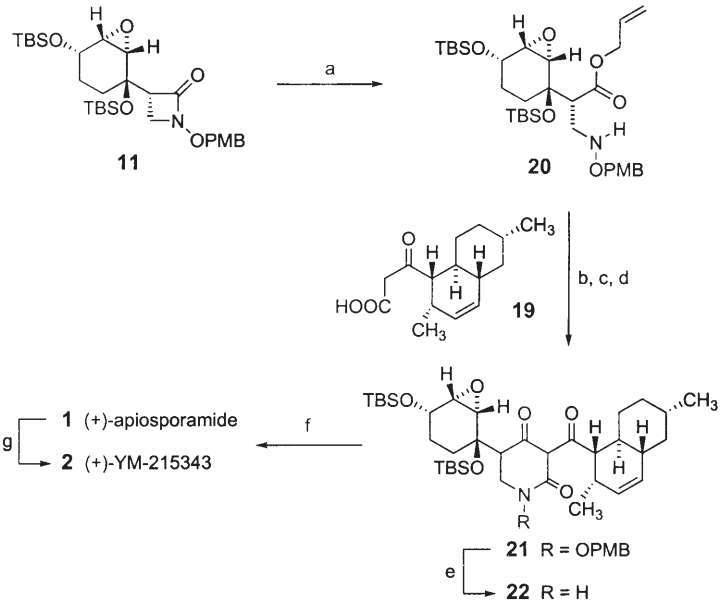

Scheme 3. Synthesis of apiosporamide (**1**). a) Allyl alcohol, *n*BuLi (1 equiv); then **11**; −78 °C→RT; 80 %; b) BOP, Et_3N, MeCN, RT, 99 %; c) $[Pd(PPh_3)_4]$, pyrrolidine, CH_2Cl_2, 85 %; d) BOP, CH_2Cl_2, DBU, −20 °C, 56 %; e) SmI_2, THF, 98 %; f) $BrCCl_3$, TMG, 65 %; then HF·pyr, THF, 75 %; g) Dess–Martin periodinane, CH_2Cl_2, 92 %. BOP = benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, TMG = 1,1,3,3-tetramethylguanidine.

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[15] a) Crystal data for **8**: colorless plate, $0.50\times0.24\times0.08\,\text{mm}^3$, $C_{17}H_{21}N_1O_6$, $M=335.35$, orthorhombic, space group $P2_12_12_1$, $a=5.6693(2)$, $b=10.2239(3)$, $c=28.4168(10)$ Å, $V=1647.10(10)$ Å^3, $T=111(2)$ K, $Z=4$, $\rho_{\text{calcd}}=1.352\,\text{Mg}\,\text{m}^{-3}$, $\mu=0.1026\,\text{mm}^{-1}$, $2\theta_{\text{max}}=60.02$, $\text{Mo}_{\text{K}\alpha}$ ($\lambda=0.71073$). A total of 23151 reflections were measured, of which 4801 were independent ($R_{\text{int}}=0.032$). Final residuals were $R1=0.0382$ and $wR1=0.0406$ (for 4385 observed reflections with $I>2\sigma(I)$, 301 parameters, 0 restraints) with GOF = 1.029, Flack parameter −0.2(7), and largest residual peak $0.603\,\text{e}\,\text{Å}^{-3}$ and hole $-0.198\,\text{e}\,\text{Å}^{-3}$; b) crystal data for **9**: colorless plate, $0.20\times0.18\times0.10\,\text{mm}^3$, $C_{17}H_{21}NO_6$, $M=1099.67$, orthorhombic, space group $P2_12_12_1$, $a=5.8978(2)$, $b=7.5734(3)$, $c=35.1598(13)$ Å, $V=1570.46(10)$ Å^3, $T=112(2)$ K, $Z=4$, $\rho_{\text{calcd}}=0.108\,\text{Mg}\,\text{m}^{-3}$, $\mu=0.108\,\text{mm}^{-1}$, $2\theta_{\text{max}}=60.06$, $\text{Mo}_{\text{K}\alpha}$ ($\lambda=0.71073$). A total of 16372 reflections were measured, of which 4597 were independent ($R_{\text{int}}=0.031$). Final residuals were $R=0.0502$ and $wR2=0.1108$ (for 4319 observed reflections with $I>2\sigma(I)$, 247 parameters, 46 restraints) with GOF = 1.056, Flack parameter −0.1(10), and largest residual peak $0.388\,\text{e}\,\text{Å}^{-3}$ and hole $-0.415\,\text{e}\,\text{Å}^{-3}$. CCDC-274063 (**8**) and -274064 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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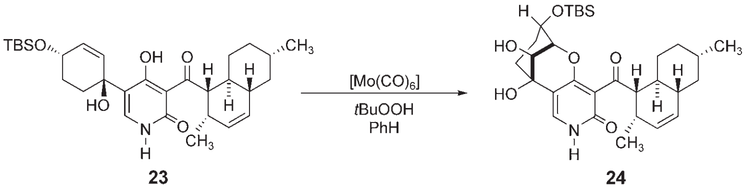
[23] Optical rotation data for naturally occurring apiosporamide was recorded as $[\alpha]_D=-97.4°$ ($c=0.0004$ MeOH). Characterization of synthetic **1**: $R_f=0.12$ (19:1 CH_2Cl_2/MeOH); $[\alpha]_D^{24}=+108°$ ($c=0.40$, MeOH); IR (film): $\tilde{\nu}=3248$ (br), 3072, 3006, 2953, 2925, 1656, 1652, 1602, 1544, 1455, 1214, 1063, 1021, 964 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): $\delta=7.45$ (s, 1H), 5.51 (m, 1H), 5.31 (d, $J=9.8$, 1H), 4.30 (dd, $J=11.2$, 5.7 Hz, 1H), 4.04 (ddd, $J=5.9$, 5.9, 3.1 Hz, 1H), 3.53 (d, $J=3.2$ Hz, 1H), 3.32 (dd, $J=3.2$, 3.1 Hz, 1H), 2.73 (m, 1H), 2.11 (dd, $J=13.0$, 9.0, 1H), 1.85 (dd, $J=12.1$, 2.5 Hz, 1H), 1.78–1.70 (m, 2H), 1.70–1.56 (m, 3H), 1.52–1.37 (m, 2H), 1.30–1.20 (m, 1H), 0.94 (ddd, $J=12.8$, 12.1, 3.3 Hz, 1H), 0.87–0.76 (m, 1H), 0.84 (d, $J=6.5$ Hz, 3H), 0.74 (d, $J=7.2$ Hz, 3H), 0.71 ppm (ddd, $J=12.4$, 12.4, 12.4 Hz, 1H); ^{13}C NMR (101 MHz, MeOH): $\delta=211.7$, 179.5, 164.2, 139.9, 132.7, 131.7, 116.7, 108.8, 70.6, 67.1, 60.5, 57.6, 54.3, 43.3, 43.2, 37.6, 36.7, 34.4, 32.5, 31.6, 31.0, 25.8, 23.0, 18.4 ppm; HRMS: *m*/*z* calcd for $C_{24}H_{32}NO_6$ $[M+H]^+$ 430.2224; found: 430.2225.

[24] Due to the anticipated similarities of ^{1}H and ^{13}C NMR spectroscopic data, and the discrepancy in the specific optical rotation in **1**, the route was adapted for independent preparation of three diastereomers with the *syn* relationship between the epoxide and tertiary alcohol (as in **8** and **9**). All of these isomers demonstrated great instability and underwent opening of the oxirane, as illustrated in the formation of **24** through directed oxidation of **23**. Interestingly, five-membered-ring products were not observed. Additional information will be provided in a full account.



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[26] Synthetic and natural **2** were identical in all respects, except for rotation. Optical rotation for natural YM-215343 was recorded as $[\alpha]_D^{25}=-44°$ ($c=0.10$ MeOH), and synthetic **2** was $[\alpha]_D^{24}=+47°$ ($c=0.225$ MeOH). Diastereoisomer **25** proved to be stable and spectroscopically similar to apiosporamide. However, oxidation gave ketone **26** which was clearly diastereomeric to **2**.