Natural Products

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Total Synthesis of Myceliothermophins C, D, and E**

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***Abstract:** The total synthesis of cytotoxic polyketides myceliothermophins E (**1**), C (**2**), and D (**3**) through a cascade-based cyclization to form the trans-fused decalin system is described. The convergent synthesis delivered all three natural products through late-stage divergence and facilitated unambiguous C21 structural assignments for **2** and **3** through X-ray crystallographic analysis, which revealed an interesting dimeric structure between its enantiomeric forms.*

Natural products containing a tetramic acid structural motif are of interest because of their often unusual and challenging structures and wide range of biological activities.[1] Isolated from *Myceliophthora thermophila,* myceliothermophins E (**1**), C (**2**), and D (**3**) (Figure 1) exhibit potent cytotoxic properties against a number of human cancer cell lines, namely hepatoblastoma (HepG2, $IC_{50} = 0.28\ \mu g\,mL^{-1}$ for **1**; $0.62\ \mu g\,mL^{-1}$ for **2**), hepatocellular carcinoma (Hep3B, $IC_{50} = 0.41\ \mu g\,mL^{-1}$ for **1**; $0.51\ \mu g\,mL^{-1}$ for **2**), lung carcinoma (A-549, $IC_{50} = 0.26\ \mu g\,mL^{-1}$ for **1**; $1.05\ \mu g\,mL^{-1}$ for **2**), and breast adenocarcinoma (MCF-7, $IC_{50} = 0.27\ \mu g\,mL^{-1}$ for **1**; $0.52\ \mu g\,mL^{-1}$ for **2**).[2] Total syntheses of these compounds and their siblings myceliothermophins A[2] and B[2] have been achieved through a strategy involving an intramolecular Diels–Alder process of a polyunsaturated aldehyde for the casting of their *trans*-fused decalin system.[3a] Given the difficulties encountered with the preparation and Diels–Alder reactions of polyunsaturated aldehydes as substrates,[4] we sought an alternative strategy for the construction of the decalin system embedded in these natural products. Herein, we report an efficient total synthesis of **1**, **2**, and **3** featuring an unusual cascade sequence of reactions[5] for the stereoselective construction of their rare *trans*-fused decalin system, and confirm unambiguously their structures through X-ray crystallographic analysis of **2**.

The strategy for the total synthesis of myceliothermophins E (**1**), C (**2**), and D (**3**) was based on the retrosynthetic analysis depicted in Figure 1. The requisite decalin aldehyde system **4** was to serve as a precursor to **1**, **2**, and **3** through appropriate manipulation, attachment of the pyrrolidinone structural motif (**5**), and further functional group adjustments. Aldehyde **4** was traced back to the simpler *trans*-fused decalin system **6** featuring two methyl groups, one of which being angular. The uniquely challenging decalin system **6** was expected to arise from a sequential rearrangement of epoxide **9** to aldehyde **8**, and enolization of the latter followed by Robinson-type annulation (via **7**) as depicted in Figure 1. The implementation of this cascade strategy for the synthesis of key building block **6** required extensive experimentation to define appropriate conditions as discussed below.

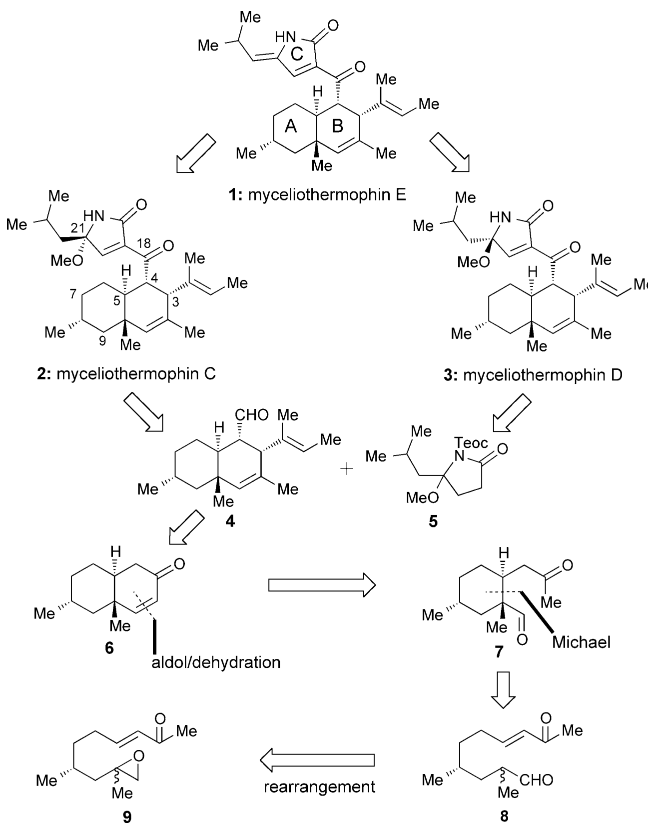

Figure 1. Structures of myceliothermophins E (**1**), C (**2**), and D (**3**) and retrosynthetic analysis.

Decalin key building block **6** was prepared from (±)-citronellal derivative **10**[6] as shown in Scheme 1 A (for cost effectiveness, racemic material was employed, although both enantiomers are also commercially available). Thus, treatment of **10** under Corey–Chaykovsky conditions[7] furnished the corresponding epoxyolefin (96% yield, ca. 1:1 d.r.) which was subjected to ozonolysis/Me_2S reduction to afford the corresponding epoxyaldehyde (ca. 1:1 d.r.). The latter was

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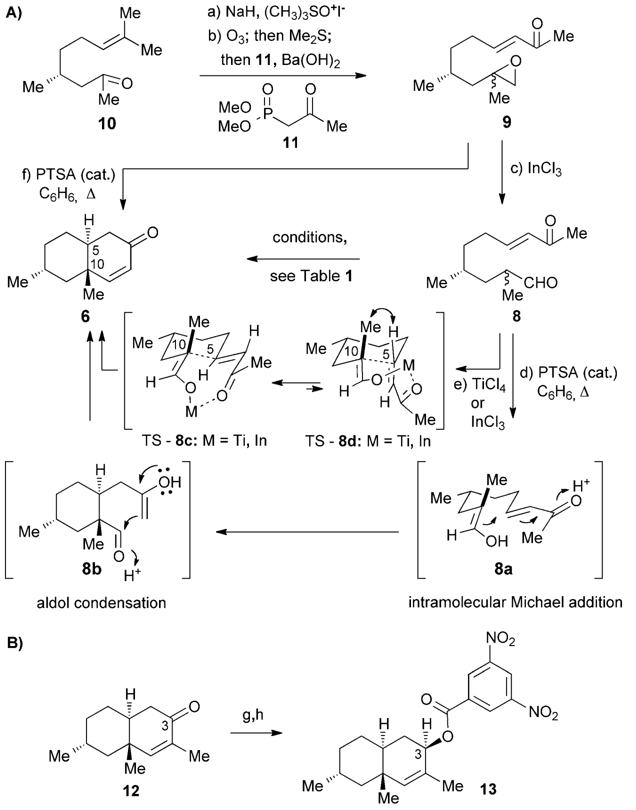


Scheme 1. Preparation of decalin system **6** and 3,5-dinitrobenzoate **13**. A) Reagents and conditions: a) NaH (1.3 equiv), $(CH_3)_3SO^+I^-$ (1.3 equiv), DMSO, 0°C, 3 h, 96% (ca. 1:1 d.r.); b) O_3; then Me_2S (3.0 equiv), CH_2Cl_2, −78°C, 1 h; then $Ba(OH)_2$ (1.1 equiv), **11** (1.1 equiv), THF:H_2O (10:1), 0°C, 2 h, 84% (ca. 1:1 d.r.); c) $InCl_3$ (0.5 equiv), CH_2Cl_2, 25°C, 0.5 h, 85% (ca. 1:1 d.r.); d) PTSA (0.1 equiv), benzene, reflux, 3 h, 92% (ca. 3:1 d.r.); e) see Table 1, entry 5: $TiCl_4$, M.S. 4 Å, CH_2Cl_2, 25°C, 72 h, 23% (ca. 10:1 d.r.); entry 6: $InCl_3$, C_6H_6, 45°C, 5 h, 30% (ca. 4.5:1); f) PTSA (0.1 equiv), benzene, reflux, 3 h, 65% (ca. 3:1 d.r.). B) Reagents and conditions: g) $NaBH_4$ (1.2 equiv), MeOH, 0°C, 1 h, 61% (d.r. ≥ 20:1); h) 3,5-C_6H_3-$(NO_2)_2COCl$ (1.2 equiv), DMAP (2.0 equiv), CH_2Cl_2, 25°C, 2 h, 95% (d.r. ≥ 20:1). PTSA = *p*-toluenesulfonic acid.

then condensed with ketophosphonate **11** under $Ba(OH)_2$ conditions[8] to afford α,β-unsaturated ketoepoxide **9** as a mixture of diastereomers (ca. 1:1 d.r.) in 81% yield for the two steps. Exposure of this intermediate to catalytic amounts of $InCl_3$[9] resulted in the formation of ketoaldehyde **8** in 85% yield (ca. 1:1 d.r.). At this point, an extensive survey of conditions was undertaken in order to develop the devised cascade to convert these substrates (**9** or **8**) to the desired decalin system **6** (see Table 1). Surprisingly, none of the usual basic conditions employed (e.g. NaOMe/MeOH, proline/DMSO, $Zr(OiPr)_4/CH_2Cl_2$)[10] produced any of the desired product, leading instead to decomposition or no reaction (Table 1; entries 1, 2, and 3). Interestingly, however, the intended cascade bis(cyclization) (**8**→**8a**→**8b**→**6**, Scheme 1A) was observed under certain protic (e.g. HCl) or Lewis acidic conditions with good to excellent diastereoselectivities, albeit in low yields (Table 1; entries 4, 5, and 6). The better selectivities observed with $TiCl_4$ and $InCl_3$ (ca. 10:1 and 4.5:1 d.r., respectively) in favor of the shown diastereomer **6** versus its diastereomer (5-*epi*-**6** or 10-*epi*-**6**, not shown)[11] can be attributed to the preferred metal-templated cyclic transition state TS-**8c** (in which the HOMO of the enolate and the LUMO of the enone are aligned for favorable overlap) as compared to the transition state TS-**8d**, which suffers from unfavorable steric interaction between H5 and the methyl group at C10 (see Scheme 1A). Finally, the cascade bis(cyclization) of ketoaldehyde **8** to decalin **6** was found to proceed in excellent yield (92%) and good diastereoselectivity (**6**: 5-*epi*-**6** or 10-*epi*-**6** ca. 3:1) in the presence of catalytic amounts of PTSA in refluxing benzene (Table 1; entry 7). The direct conversion of epoxide **9** to decalin **6** was also achieved under the same conditions, albeit in only 65% yield (ca. 3:1 d.r.). The latter cascade reaction presumably proceeds via aldehyde **8**, formed upon initial epoxide rearrangement, through the same pathway (**8**→**8a**→**8b**→**6**, Scheme 1A). The relative stereochemical configuration of the major decalin diastereomer **6** was established unambiguously through X-ray crystallographic analysis (see ORTEP, Figure 2A)[12] of its crystalline 3,5-dinitrobenzoate derivative **13** (Scheme 1B, m.p. 92–94°C, EtOAc:hexanes (1:1)) and NMR spectroscopic comparison. Compound **13** was prepared from enone **12** ((ca. 3:1 d.r.), obtained from the ethyl counterpart of **9** through the same cascade reaction) by $NaBH_4$ reduction (d.r. ≥ 20:1 at C3, 61%) and benzoylation of the resulting allylic alcohol with 3,5-$C_6H_3(NO_2)_2COCl$ (95%) as shown in Scheme 1B.

Table 1: Optimization of the cyclization of ketoaldehyde **8** to decalin system **6**.[a]

Entry	Conditions	*t* [h]	*T* [°C]	Yield [%][b]	d.r.[c]
1	NaOMe, MeOH	2	25	decomp.	–
2	proline, DMSO	24	25	n.r.	–
3	$Zr(OiPr)_4$, CH_2Cl_2	24	25	n.r.	–
4	1.0 M HCl/Et_2O, THF	72	25	35	3:1
5	$TiCl_4$, M.S. 4 Å, CH_2Cl_2	72	25	23	10:1
6	$InCl_3$, C_6H_6	5	45	30	4.5:1
7	PTSA, C_6H_6	5	reflux	92	3:1

[a] Reactions were performed on 1.0 mmol scale of ketoaldehyde **8**. [b] Combined yields of isolated products. [c] Diastereomeric ratio (C5 or C10 epimer; **6:** major isomer) was determined by ^1H NMR spectroscopic analysis of crude product **6**. n.r. = no reaction.

Having secured the coveted enone decalin system **6** in decagram quantities from the readily available citronellal derivative **10**, we proceeded to functionalize it (initially as a mixture until chromatographic separation became convenient, see below) to the next required key intermediate, aldehyde **4**, as shown in Scheme 2. Thus, deprotonation of **6** (ca. 3:1 d.r.) with LDA at −78°C, followed by quenching the resulting enolate with 1*H*-benzothiazole-1-methanol[13] (**14**) furnished the expected hydroxymethyl product (**15**, ca. 3:1 d.r.) which was immediately (because of its relative instability) protected as a TBS ether (TBSCl, DMAP cat., imidazole) to afford compound **16** (ca. 3:1 d.r.) in 81% overall yield for the two steps. The next task, that of installing the required side chain at C3 of our growing intermediate, proved rather intransigent with several direct tactics such as vinyl or acetylene attachments failing to produce the desired

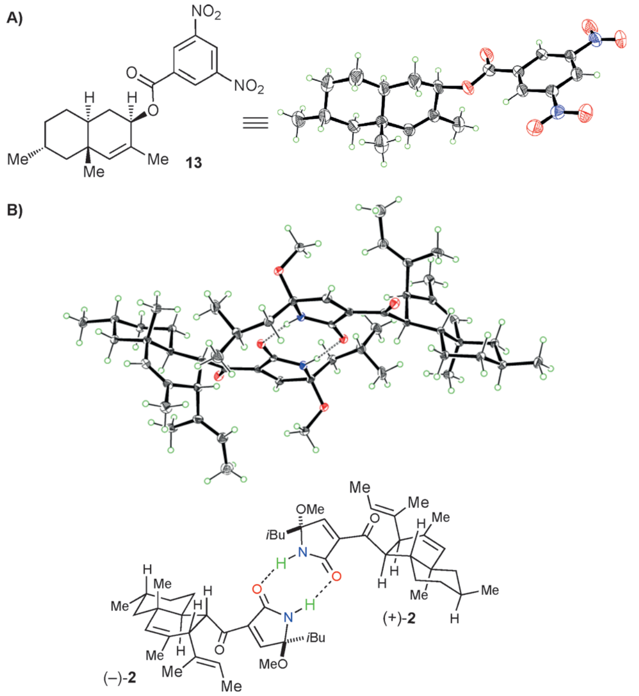
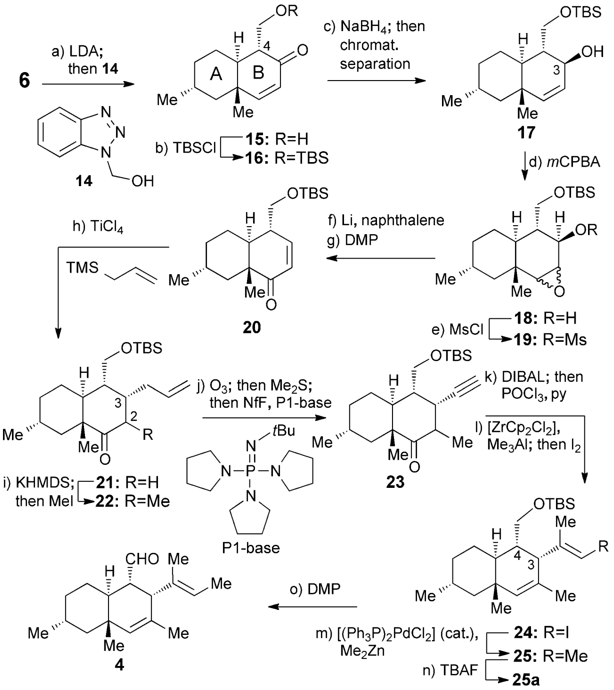


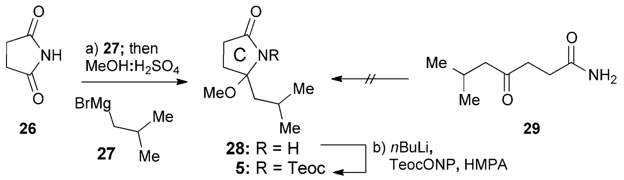
Figure 2. ORTEP representation of A) 3,5-dinitrobenzoate (±)-**13** and B) synthetic myceliothermophin C ((±)-**2**). Thermal ellipsoids at 30% probability. gray = C, red = O, blue = N, green = H for both ORTEP plots.



Scheme 2. Synthesis of aldehyde **4**. Reagents and conditions: a) **6** (ca. 3:1 d.r.), LDA (3.0 equiv), then **14** (2.0 equiv), THF, −78 °C, 0.5 h; b) TBSCl (1.2 equiv), DMAP (0.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 0 °C, 2 h, 81% for the two steps (ca. 3:1 d.r.); c) $NaBH_4$ (1.0 equiv), MeOH, −10 °C, 1 h, then flash column chromatography, 65% for pure alcohol **17**; d) *m*CPBA (1.5 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 0 °C, 10 h, 92% (ca. 2:1 d.r.); e) MsCl (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C, 1 h, 97% (ca. 2:1 d.r.); f) lithium naphthalide (2.0 equiv), THF, −30 °C, 3 h, 83% (ca. 2:1 d.r.); g) DMP (1.1 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 95%; h) allyltrimethylsilane (1.1 equiv), $TiCl_4$ (1.2 equiv), CH_2Cl_2, −78 °C, 2 h, 98%; i) KHMDS (2.0 equiv), MeI (2.0 equiv), THF, −78 °C, 4 h, 87% (d.r. ≥ 20:1); j) O_3; then Me_2S, CH_2Cl_2, −78 °C, 1 h; then NfF (1.2 equiv), P1-base (3.0 equiv), DMF, 0 °C, 3 h, 82%; k) DIBAL (1.0 equiv), CH_2Cl_2, −78 °C, 0.5 h, 98%; then $POCl_3$ (5.0 equiv), pyridine, MeCN, 70 °C, 12 h, 81%; l) $[ZrCp_2Cl_2]$ (2.0 equiv), Me_3Al (5.0 equiv), CH_2Cl_2, −20→25 °C, 24 h; then I_2 (1.1 equiv), 25 °C, 24 h, 81%; m) Me_2Zn (2.0 equiv), $[(Ph_3P)_2PdCl_2]$ (5 mol%), THF, 0 °C, 3 h, 94%; n) TBAF (1.1 equiv), THF, 70 °C, 5 h, 91%; o) DMP (1.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 0.5 h, 95%. NfF = nonafluorobutanesulfonyl fluoride, P1-base = phosphazene base P1-*t*Bu-tris(tetramethylene), LDA = lithium diisopropylamide, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane.

products. Other methods involving palladium π-allyl complexes[14] as intermediates derived from the corresponding allylic alcohol (i.e. **17**) also failed to functionalize the C3 position as desired. This challenge was finally overcome through an indirect pathway involving 1,3 transposition of the enone moiety, followed by 1,4 addition to the newly generated enone as shown in Scheme 2. Thus, $NaBH_4$ reduction of **16** afforded allylic alcohol **17** stereoselectively (ca. 3:1 d.r. at C5 or C10; d.r. ≥ 10:1 at C3). At this stage, column chromatography allowed separation of the major diastereomer leading to pure allylic alcohol **17** (65% yield). Epoxidation of this compound with *m*CPBA led to a mixture of diastereomeric hydroxyepoxide **18** (ca. 2:1 d.r., inconsequential), which was mesylated to give **19** in 97% yield (ca. 2:1 d.r., inconsequential). Exposure of this mixture to Li naphthalide[15] at −30 °C induced the expected radical-based rearrangement, generating, upon oxidation of the resulting mixture of allylic alcohols using DMP,[16] enone **20** in 79% overall yield for the two steps. Upon extensive experimentation, it was found that slow addition of allyltrimethylsilane to enone **20** in CH_2Cl_2 in the presence of $TiCl_4$ (Hosomi–Sakurai reaction)[17] led, exclusively, to the expected ketoolefin **21**, which possesses the desired α-configuration at C3, in 98% yield as confirmed by NOESY correlation between H3 and H4 of subsequent intermediate **25a**. It should be noted that both the slow addition and low temperature are crucial in securing the high stereoselectivity and yield in this reaction. Another notable observation at this step was the fact that the corresponding vinyl cuprate reagent (derived from 2-*cis*-2-butenyllithium and CuCN) reacted with enone **20** to afford the opposite C3 epimer (C3-*epi*-**21**, not shown). These contrasting results may be due to the bulkiness of the TBS group within the substrate (i.e. **20**). The precise mechanistic rationale for this interesting observation is still under investigation. Generation of the enolate from **21** (KHMDS, THF, −78 °C) followed by quenching with MeI furnished the corresponding methylated product (**22**) in 87% yield (d.r. ≥ 20:1; C2 configuration: inconsequential; not assigned). Ozonolysis/reduction of the olefinic moiety in **22** (O_3; Me_2S) followed by treatment of the resulting aldehyde with nonafluorobutanesulfonyl fluoride (NfF) and phosphazene base P1-*t*butyl-tris(tetramethylene) (P1-base) furnished smoothly terminal acetylene **23** in 82% yield.[18] Reduction of the carbonyl group within the latter compound with DIBAL followed by dehydration ($POCl_3$, py) then led to the corresponding acetylenic olefin, which was subjected to sequential zirconium-promoted carboalumination/iodination[19] (81% yield) and Pd-catalyzed Negishi coupling[20] with Me_2Zn (94% yield) to give intermediate **25** via vinyl iodide **24**. Desilylation of the latter (TBAF, 91% yield) followed by DMP oxidation of the resulting alcohol (**25a**) led to the coveted aldehyde **4** (95% yield).

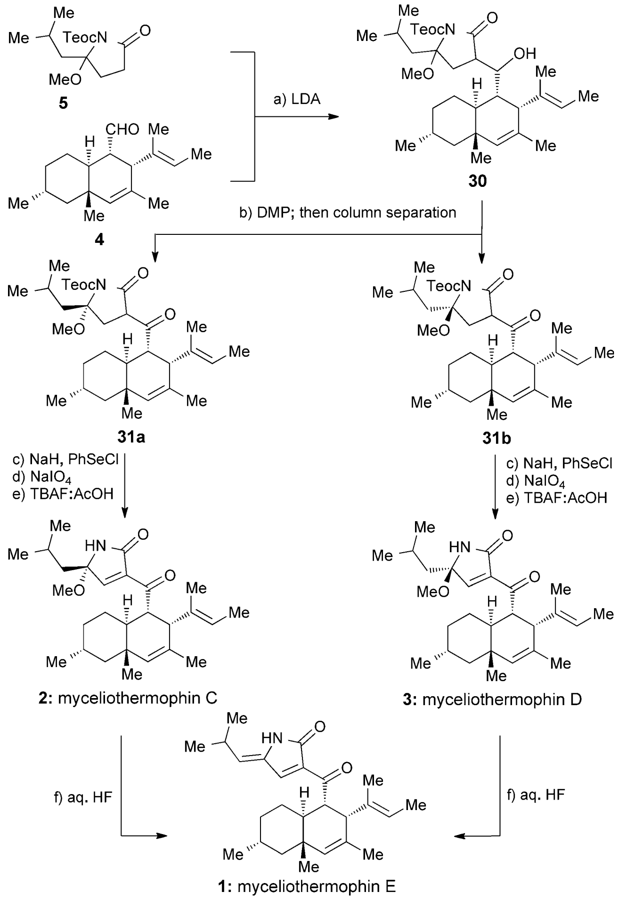
The construction of the other requisite fragment, building block **5**,[21] was achieved in two steps from succinimide (**26**) as shown in Scheme 3. Thus, treatment of **26** with isopropyl Grignard reagent **27** in THF at ambient temperature,



Scheme 3. Synthesis of pyrrolidinone building block **5**. Reagents and conditions: a) **27** (3.0 equiv), THF, 25°C, 24 h; then MeOH:H_2SO_4 (10:1), 62%; b) *n*BuLi (1.2 equiv), TeocONP (1.2 equiv), HMPA (1.0 equiv), THF, −78°C, 10 h, 82%. TeocONP = 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate, HMPA = hexamethylphosphoramide.

followed by quenching with MeOH containing 10% conc. H_2SO_4 at 0°C, furnished lactam **28** in 62% yield.[22] It should be noted that the use of H_2SO_4 was essential for the success of this reaction, for without it only open-chain product ketoamide **29** was obtained upon quenching with MeOH. Furthermore, exposure of the latter compound to the same MeOH:H_2SO_4 solution failed to produce appreciable amounts of the desired cyclic product (i.e. **28**), as did other acidic conditions (e.g. PTSA, PPTS, HCl aq.).[3a] Free pyrrolidinone **28** was found to be rather labile, slowly hydrolyzing in air at ambient temperature to open-chain compound **29**. It was, therefore, immediately protected as its Teoc derivative **5** (*n*BuLi, TeocONP, 82% yield) ready for coupling with aldehyde **4**.

Scheme 4 depicts the coupling of fragments **4** and **5** and the divergent elaboration of the coupling product to the targeted myceliothermophins C (**2**) and D (**3**) and thence **1**. Thus, treatment of **5** with LDA (THF, −78°C) followed by addition of **4** to the resulting anion at −78°C furnished alcohol **30** in 85% yield (mixture of four diastereomers). Oxidation[23] of this mixture with DMP afforded diastereomeric ketones **31a** and **31b** (90% combined yield, ca. 1:1 d.r.), which were chromatographically separated and subjected to the same three-step sequence required for their elaboration to the targeted natural products **2** and **3** [1) phenyl selenylation (NaH, PhSeCl); 2) oxidation/syn elimination ($NaIO_4$, 78% yield for the two steps);[24] and 3) removal of the Teoc group (TBAF:AcOH, 92% yield)]. Synthetic myceliothermophin C (**2**; racemic) crystallized from an EtOAc solution upon slow evaporation to provide colorless crystals [m.p. 167°C (decomp) (EtOAc)] suitable for X-ray crystallographic analysis,[12] a fortunate occurrence for it gave us the opportunity to confirm unambiguously its original NMR-based structural assignment and that of its sibling, myceliothermophin D (**3**).[25] As shown in Figure 2, X-ray crystallographic analysis of



Scheme 4. Completion of the total synthesis of myceliothermophins E (**1**), C (**2**), and D (**3**). Reagents and conditions: a) LDA (1.0 equiv), then **4**, THF, −78°C, 0.5 h, 85%; b) DMP (5.0 equiv), CH_2Cl_2, 25°C, 6 h, 90% combined for **31a** and **31b** (ca. 1:1 d.r.); c) NaH (1.1 equiv), THF, 25°C, 0.5 h; then PhSeCl (1.0 equiv), −78°C, 0.5 h; d) $NaIO_4$ (2.0 equiv), MeCN, 25°C, 2 h, 78% for the two steps; e) TBAF:AcOH (1:1) (2.0 equiv), THF, 0→25°C, 5 h, 92%; f) 47% aq. HF, MeCN, 0→25°C, 2 h, 81%.

(±)-**2** not only proved the original assignments for **2** and **3** by Wu et al.,[2] but interestingly also showed a dimeric form for **2** in the solid state involving the two enantiomers of the molecule within the crystal lattice (see ORTEP representation, Figure 2). Apparently, the two enantiomeric molecules of myceliothermophin C (**2**) are held together by hydrogen bonding involving their pyrrolidinone moieties. Myceliothermophin E (**1**) could be generated from either **2** or **3** by treatment with aq. HF in 81% yield as shown in Scheme 4.

Involving a rare cascade sequence[5] to construct the *trans*-fused decalin system of the myceliothermophins, the described chemistry (which can also be applied to an enantioselective process) renders myceliothermophins E (**1**), C (**2**), and D (**3**) readily available for biological investigations. The developed cascade bis(cyclization) for the construction of the *trans*-fused decalin system provides a practical alternative to the cumbersome Diels–Alder approach, which requires difficult to access polyunsaturated aldehydes as substrates. The developed synthetic technologies may be applied to the construction of related natural products and designed analogues in racemic or enantiomeric forms for further structure–activity relationship studies.[26]

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