Biomimetic Synthesis

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Catalyst-Controlled Transannular Polyketide Cyclization Cascades: Selective Folding of Macrocyclic Polyketides

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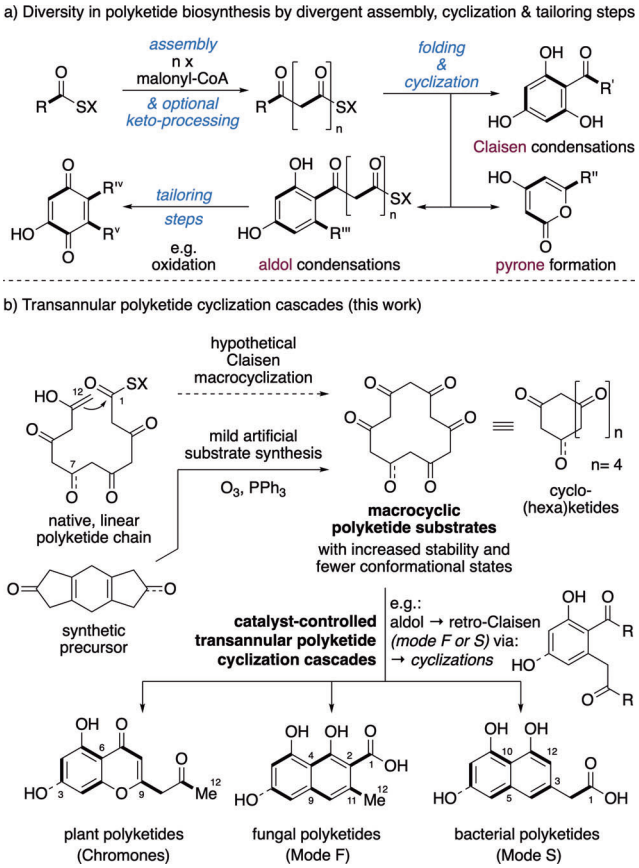
Dedicated to Professor Eric N. Jacobsen on the occasion of his 60th birthday

Abstract: *The biomimetic synthesis of aromatic polyketides from macrocyclic substrates by means of catalyst-controlled transannular cyclization cascades is described. The macrocyclic substrates, which feature increased stability and fewer conformational states, were thereby transformed into several distinct polyketide scaffolds. The catalyst-controlled transannular cyclizations selectively led to aromatic polyketides with a defined folding and oxygenation pattern, thus emulating β-keto-processing steps of polyketide biosynthesis.*

Aromatic polyketides are among the most important natural product scaffolds in medicinal chemistry and essential for antibiotic and cancer research.[1] Their fascinating biosynthesis involves the formation of linear poly-β-carbonyls which are transformed in divergent, enzyme-controlled reaction cascades (Scheme 1 a).[2–6] The selective cyclization of linear polyketide chains to access novel structural versatility has hence attracted enormous interest.[7] However, the extraordinary reactivity and the high number of reactive conformations of native polyketide substrates have hampered the selective catalyst-controlled folding and cyclization.

Our previous efforts were engaged in polyketide cyclizations of artificial aldehyde substrates with pre-organizing aromatic moieties.[8a–g] The mild substrate preparation and the observed control over increasingly complex substrates[8g] thereby indicated the feasibility of small-molecule catalyzed, divergent cyclizations of native polyketides, if the reactivity and selectivity requirements are met. Seminal work by Collie,[9] Birch,[10] Harris,[11] Money,[12] Bringmann[13] and others[14–16] elegantly demonstrated the prospects of using linear polyketide chains as competent substrates in stoichiometric cyclizations, but also that complex product mixtures are obtained with larger systems. Analogous to the early methods for stereoselective synthesis,[17–19] we thus envisaged that macrocyclic polyketide substrates would impart a reduced number of reactive conformations amenable to selective transannular cyclization cascades to various polyketide scaffolds (Scheme 1 b). Notably, the macrocyclic substrates correspond to products of a hypothetical Claisen condensation at the termini of native, linear polyketide chains. Compared to their acyclic congeners, the ring-strain of the macrocycles increases stability preventing uncatalyzed background reactions,[8h] thus allowing to study divergent, catalyst-controlled cyclizations. The biosynthetic pathways would be reentered after a transannular cyclization in subsequent retro-Claisen or retro-aldol reactions, rendering macrocyclic polyketide substrates suitable precursors for aromatic polyketide natural products. Partial reduction of the substrates furthermore emulates β-keto-processing,[2] whereas small-molecule



Scheme 1. a) The divergent biosynthetic pathways lead to remarkable polyketide diversity. b) Macrocyclic polyketide substrates (formal products of Claisen condensations at the termini of native, linear polyketide chains) are prepared from a synthetic precursor by ozonolysis. Divergent, catalyst-controlled transannular polyketide cyclization cascades govern the oxygenation and folding pattern of polyketide natural products, such as the shown examples. F = fungal. S = bacterial (streptomyces). CoA = coenzyme A.

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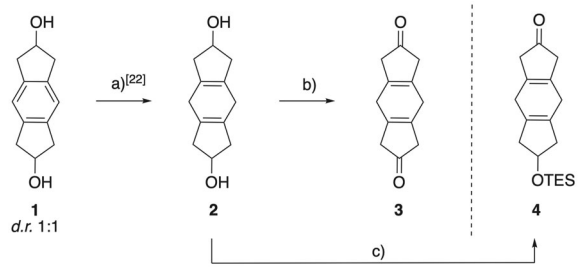
catalyst-controlled cyclizations would provide a means for controlling the oxygenation and folding pattern of plant, fungal or bacterial polyketide natural products.[20]

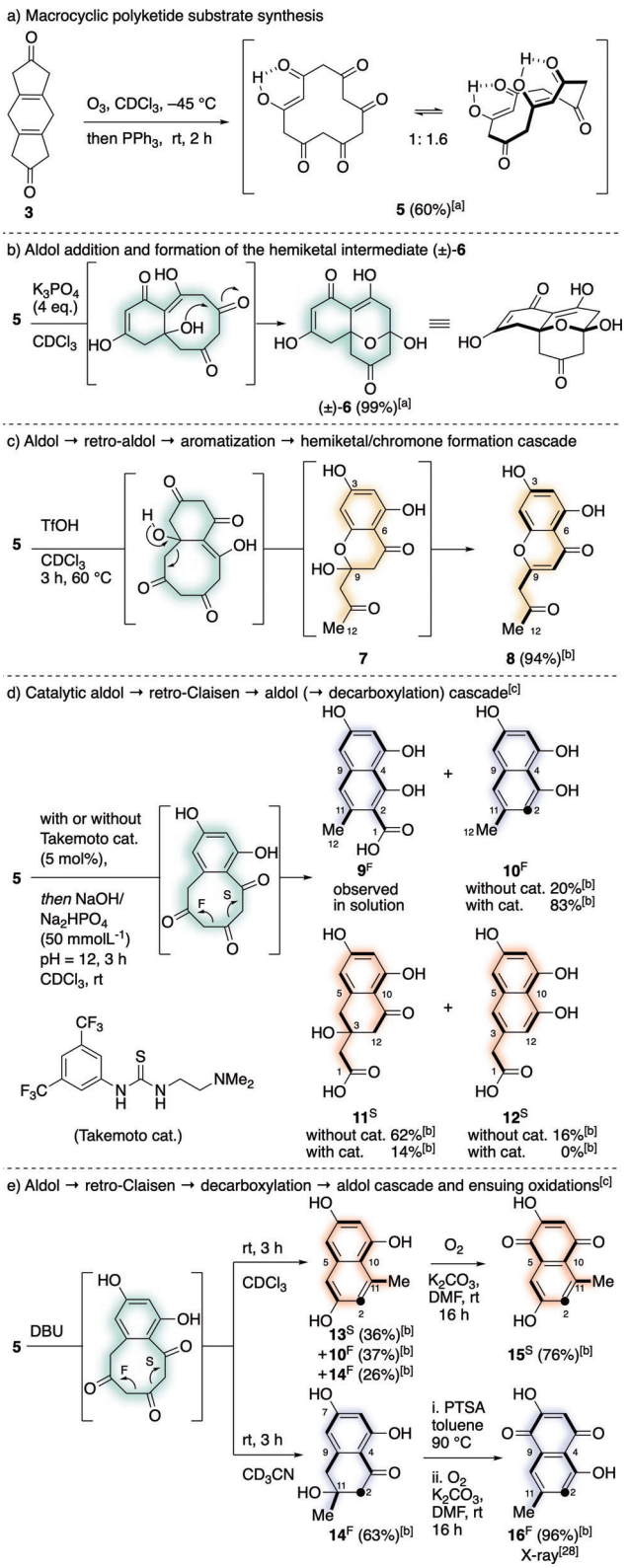
To validate this hypothesis, we selected cyclohexaketides as suitable substrates and prepared the corresponding precursors by a Birch reduction from the aromatic diol **1**[21] followed by a double oxidation to diene **3**, or a monosilylation and oxidation to **4**, respectively (Scheme 2).

A mild two-fold ozonolysis of **3** subsequently allowed the in situ preparation of the desired cyclododecanehexaone **5** as a 1:1.6 mixture of two tautomers (Scheme 3a). Remarkably, the substrate solution was stable for several days at room temperature if kept in the dark, whereas the native, linear polyketide chains spontaneously cyclize even under mild conditions.[23] Having sufficiently diminished the reactivity to circumvent spontaneous transformations, we began the investigation of the selective cyclizations (see Page S15 of the Supporting Information for an overview). Interestingly, the transannular aldol addition was efficiently induced by the addition of K_3PO_4, giving the hemiketal (±)-**6** (99% by NMR) (Scheme 3b). We next explored conditions for cyclization cascades comprising retro-Claisen and retro-aldol transformations to provide the anticipated aromatic polyketide natural products. Notably, the addition of stoichiometric triflic acid (TfOH) led to a selective aldol addition/retro-aldol/aromatization/chromone formation cascade[24] to product **8** in an excellent yield of 94%, while shorter reaction times revealed hemiketal **7** as intermediate (Scheme 3c). With aqueous NaOH/NaH_2PO_4, we observed a divergent and smooth reaction to regioisomeric fungal or bacterial polyketide products **9**–**12**, as determined by the directionality of bond cleavage in the retro-Claisen step (F vs. S, Scheme 3d).[20,24] Interestingly, the fungal and bacterial pathways could converge to an identical polyketide product such as **10**.[25] However, the sensitive naphthoic acid $\mathbf{9}^F$ intermediate with a fungal polyketide pattern was observed in solution, which rapidly decarboxylated to naphthalene-triol $\mathbf{10}^F$ upon isolation. Without catalysts, the bacterial naphthoic polyketides $\mathbf{11}^S$ (62%) and $\mathbf{12}^S$ (16%) are obtained as the major products and were found to be stable.[24] The interconversion of $\mathbf{11}^S$ to $\mathbf{12}^S$ and the decarboxylation of $\mathbf{12}^S$ to $\mathbf{10}^F$ was not observed, further supporting the notion of regiodivergent retro-Claisen reactions. To our delight, the addition of the Takemoto catalyst[26] led to an inversion of regioselectivity

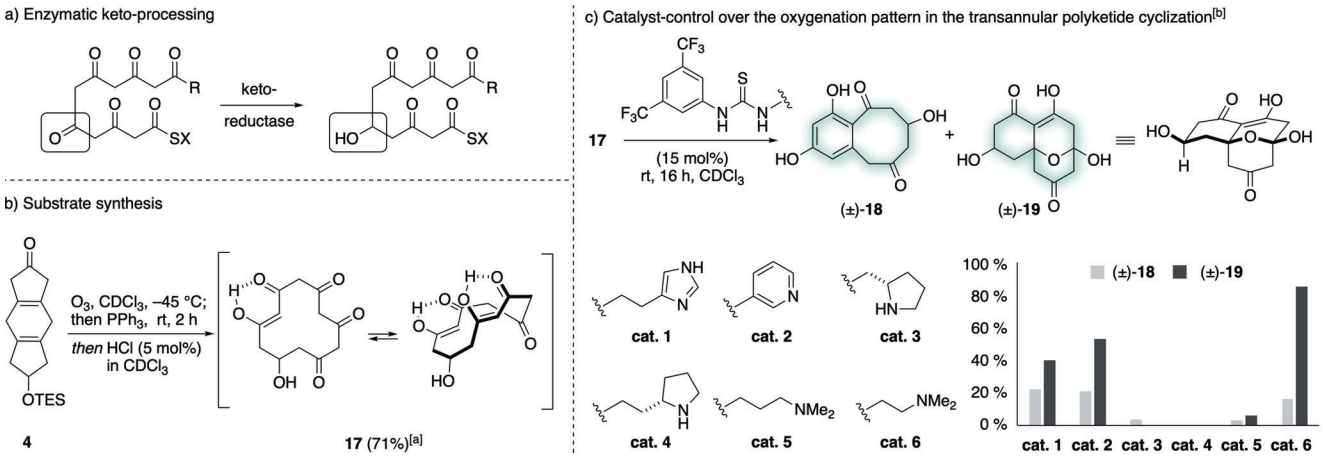


1 *d.r.* 1:1 2 3 4

Scheme 2. Synthesis of precursors **3** and **4** by a Birch reduction:[22] a) Li, MeOH, THF, NH_3, 99%; b) IBX, DMF, 80%; c) i. TESCl, imidazole, DMF, 55% ii. DMP, $KHCO_3$, CH_2Cl_2, 61%. IBX: 2-Iodoxybenzoic acid. DMP: Dess-Martin periodinane.



Scheme 3. Substrate synthesis and transannular polyketide cyclizations. [a] Yield determined by NMR using internal standards. [b] Isolated yield. [c] Polyketide patterns are indicated in bold and the folding modes denoted in superscript and by color code: F (blue, fungal) C(4)-C(9) and C(2)-C(11); S (red, bacterial) C(10)-C(5) and C(12)-C(3);[20,24] undifferentiated (green); chromone (orange). TfOH = triflic acid. PTSA = *p*-toluenesulfonic acid.

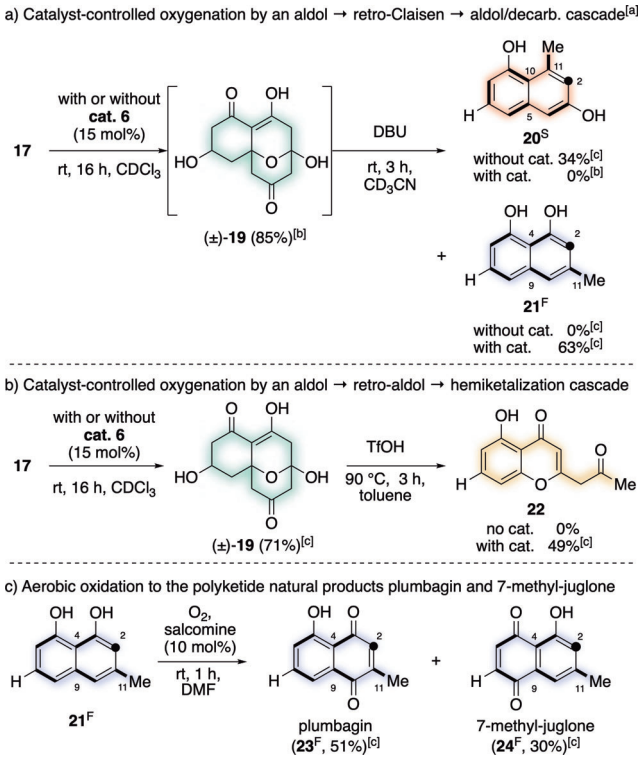


Scheme 4. Transannular cyclization of a partially reduced macrocyclic polyketide substrate with catalyst control over the oxygenation pattern. [a] Yield determined by NMR using an internal standard. [b] Reactions performed with 10.0 μmol of substrate **17** in $CDCl_3$ (7.00 mmol L^{-1}).

(83 % and 14 % isolated yield for $\mathbf{10}^{F}$ and $\mathbf{11}^{S}$, respectively), indicating the viability of small-molecule catalysis to govern polyketide cyclization cascades. Intriguingly, the extent of divergent cyclizations was further noticeable when employing the organic base diazabicycloundecen (DBU), leading to the differently folded product $\mathbf{13}^{S}$ (36 %), together with $\mathbf{10}^{F}$ (37 %) and intermediate $\mathbf{14}^{F}$ (26 %, Scheme 3e).[24] Subsequent aerobic oxidation[27] of $\mathbf{13}^{S}$ led to naphthoquinone $\mathbf{15}^{S}$ (76 %) with reported activity against *mycobacterium tuberculosis*.[28,29] Moreover, **5** treated with DBU in acetonitrile exclusively yielded the fungal intermediate $\mathbf{14}^{F}$ (63 %), which was eliminated to $\mathbf{10}^{F}$ and oxidized to the biologically active naphthoquinone $\mathbf{16}^{F}$ (96 %).[29]

We next set out to investigate whether the oxygenation pattern of partially reduced aromatic polyketide products may be governed by small-molecule catalysis (see Page S35 of the Supporting Information for an overview). To emulate enzymatic keto-processing (Scheme 4a),[2] the partially reduced precursor **4** was ozonolyzed and treated with catalytic amounts of HCl to induce a mild deprotection, affording substrate **17** as a mixture of several tautomers (Scheme 4b). Since five different aldol addition products are feasible from the transannular aldol cyclization of substrate **17**,[24] a precise differentiation is required to control the oxygenation pattern by small-molecule catalysts. Gratifyingly, thiourea catalysts initiated the divergent aldol additions, forming differently oxygenated intermediates (±)-**18** and (±)-**19** (Scheme 4c). The Takemoto catalysts were found to be particularly active and the catalytic performance and selectivity with modifications of the basic functional group and the backbone were thus tested. Experiments with imidazole-based catalyst (**cat. 1**) showed good yields but moderate selectivity (22 % (±)-**18**, 40 % (±)-**19**), whereas a catalyst bearing a pyridine moiety (**cat. 2**) increased the overall yield (21 % (±)-**18**, 53 % (±)-**19**). Catalysts with secondary amine moieties (**cat. 3** or **cat. 4**) led to little or no activity and a propyl-linked tertiary amine (**cat. 5**) also provided low conversions (3 % (±)-**18**, 6 % (±)-**19**). However, the ethylene bridged tertiary amine congener (**cat. 6**) revealed a high selectivity and excellent yields (15 % (±)-**18**, 85 % (±)-**19**).[24] Isolation of the sensitive product (±)-**19** (72 %) allowed to determine the relative diastereomeric configuration (NOE measurements) and also the aldol addition product (±)-**18** with a different oxygenation pattern was isolated in low amounts (10 %). The catalyst-controlled aldol addition was next combined with the developed protocols to complete the cyclization cascades to aromatic polyketide natural products and compared to reactions without thiourea catalysts. Treatment of the partially reduced macrocycle **17** with DBU in acetonitrile without **cat. 6** yielded the unknown naphthalene diol $\mathbf{20}^{S}$, which decomposed over the course of a few hours even under inert conditions (Scheme 5a, 34 %).[24] Strikingly, the transformation of **17** using **cat. 6** affected a catalyst-controlled aldol/ retro-Claisen/ aldol condensation/ decarboxylation cascade to fungal polyketide $\mathbf{21}^{F}$ with excellent selectivity and a 63 % isolated yield. Moreover, while treatment of the macrocycle **17** with excess TfOH only led to decomposition, addition of **cat. 6** (15 mol %) gave (±)-**19** in 71 % isolated yield, which could be converted to chromone **22** using equimolar amounts of TfOH (Scheme 5b, 49 %).[24] To further demonstrate the utility of the catalyst-controlled polyketide cyclization cascades for natural product synthesis, we examined the aerobic oxidation of naphthalene diol $\mathbf{21}^{F}$, which efficiently provided plumbagin ($\mathbf{23}^{F}$) and 7-methyl-juglone ($\mathbf{24}^{F}$) (Scheme 5c).[24,29]

In conclusion, a regioselective methodology for biomimetic polyketide cyclization cascades of macrocyclic polyketide substrates was developed. The substrates showed significantly improved stability, allowing selective cyclizations controlled by small-molecule catalysts that govern the folding and oxygenation pattern of nonreduced and partially reduced aromatic polyketide products. Chromones were obtained by an aldol addition/retro-aldol/aromatization/hemiketalization/ dehydration mechanism, while aromatic polyketides with a fungal or bacterial folding pattern resulted from an aldol addition/divergent retro-Claisen/aldol condensation/decarboxylation sequence. The addition of thiourea catalysts to a partially reduced substrate selectively led to a fungal naphthalene diol, which was aerobically oxidized to naphthoquinone natural products. The synthesis of the 18 isolated



Scheme 5. Catalyst-controlled transannular polyketide cyclization cascades of partially reduced macrocyclic polyketides. [a] Reactions performed with 10.0 μmol of substrate **17** in $CDCl_3$ (7.00 mmol L^{-1}). [b] Yield determined by NMR with an internal standard. [c] Isolated yield.

cyclization products from the macrocyclic substrates underscore the versatility of divergent synthesis and an exciting avenue for regioselective catalysis. It is thus anticipated that this divergent biomimetic late-stage catalysis strategy will provide an alternative to combinatorial polyketide biochemistry. Our current studies focus on the control over linear and angular aromatic structure from larger macrocyclic polyketide substrates, transannular cascades to nitrogen heterocycles and the application of novel catalysis concepts.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biomimetic synthesis · cyclization · natural products · polyketides · regioselectivity

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Biomimetic Synthesis

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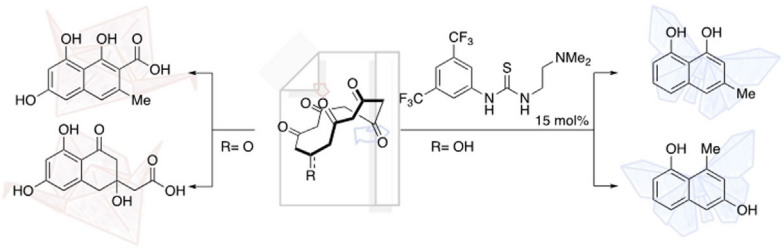

Various aromatic polyketides were prepared from macrocyclic substrates by catalyst-controlled transannular cyclization cascades. The high stability of the macrocyclic polyketides enabled the control of the folding and oxygenation pattern by using small-molecule catalysis. The synthesis of several distinct cyclization products from common precursors highlights the virtues of divergent catalysis and regioselective reaction cascades.