Trends in Chemistry

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Forum

Retrosynthetic polyketide disconnections for unnatural aromatics

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Polyketide synthases are extraordinarily complex enzymatic machineries that govern the assembly and cyclization of poly-β-carbonyl intermediates to an enormous diversity of natural products. Captivatingly, this biosynthetic strategy is transferable to the retrosynthetic analysis of unnatural aromatics, enabling strategic biomimetic polyketide cyclizations to design an extensive range of otherwise unrelated aromatic products.

Aromatic structures are among the most common scaffolds in functional materials and bioactive molecules, with most pharmaceuticals containing at least one aromatic moiety. Not surprisingly, methods to prepare aromatic products are of permanent interest and a vast number of protocols have already been developed for the construction and functionalization of aromatic scaffolds. In stark contrast to these approaches, nonreducing and partially reducing polyketide synthases assemble aromatic natural products by a catalyst-controlled late-stage diversification [1]. Remarkably, this precisely regulated cyclization of poly-β-carbonyl chains is unparalleled by nonenzymatic synthetic methods and enables the generation of a vast set of structurally diverse aromatic natural products.

The chemotherapeutic agent doxorubicin represents a notable example for this intriguing biosynthetic process, illustrated by the depicted folding pattern that delineates the polycyclization based on several pertinent aldol condensation reactions (Figure 1A). The biosynthesis of fasamycin C is another instructive assembly process that comprises the cyclization of an extended tridecaketide chain [2]. Besides the linear tetracyclic moiety, a highly substituted biaryl motif is hereby formed in a stereoselective fashion to afford an enantioenriched atropisomer with (S_a)-configuration.

Strikingly, a generalized consideration of retrosynthetic polyketide disconnections in regular aromatic structures towards poly-β-carbonyl chains offers an effective approach to identify synthetic strategies not only for the numerous naturally occurring aromatics, but also for a wide array of unnatural aromatic scaffolds. While regarding the different oxidation states of the ketide units, polyketide disconnections largely delineate the biomimetic synthesis of common aromatic units such as substituted benzenes, naphthalenes, and anthracenes with various oxygenation patterns, typically through arene-forming aldol and Claisen condensation steps, among others (Figure 1B).

Identifying the full set of possible polyketide disconnections not only reveals the entire disassembly to highly reactive poly-β-carbonyl and related precursor chains, but also the potential for partial dissections to smaller stable aromatic synthons. These can be prepared by various methods, allowing a combination with the main polyketide cyclizations to access a most significant scope of natural and unnatural products.

The ideal characteristics of polyketide cyclizations were rapidly recognized for the biomimetic synthesis of various aromatic natural products based on the visionary biosynthetic concepts by Collie, Robinson, Birch, and other pioneers [3]. Money and Scott achieved the preparation of the natural product orsellinic acid (**3**) from a pyranopyrone precursor **1** by *in situ* generation of the reactive tetraketide intermediate **2** using aqueous potassium hydroxide, ultimately triggering an arene-forming aldol cyclization and a decarboxylation process (Figure 1C) [4]. Moreover, a twofold polyketide cyclization was elegantly realized by Yamaguchi and coworkers by a $Ca(OAc)_2$ promoted double aldolization for the synthesis of a polyoxygenated anthracene scaffold **5** [5]. The polycarbonyl intermediate **4** was thereby prepared by a dual Claisen condensation using acetoacetate dianions and a phenyl dicarboxylate ester as stable aromatic precursor, so that the formation of only two of the three aromatic rings through a more stable intermediate was required.

Native linear polyketide chains exhibit an extraordinarily high reactivity, leading to a large number of reactive conformational states and consequential unselective cyclizations, even under mild conditions. To enable controlled and divergent polycyclizations, Sparr and colleagues therefore synthesized a macrocyclic polyketide substrate **6**, existing as a mixture of tautomers with significantly increased stability [6]. Intriguingly, the restricted conformational freedom within the restrained ring system of cyclohexaketide **6** provided sufficient stability for selective transannular polyketide cyclization cascades involving retro-Claisen or retro-aldol reactions to form multiple distinct aromatic natural products. Triflic acid thereby efficiently triggered an aldol → retro-aldol → aromatization → chromone formation cascade to form the product **7** in an excellent yield of 94%. Notably, a divergent reaction cascade was induced by the addition of the Takemoto catalyst, leading to an inverted regioselectivity to afford the fungal polyketide product **8** in 83% yield by a catalytic aldol → retro-Claisen → aldol → decarboxylation cascade process.

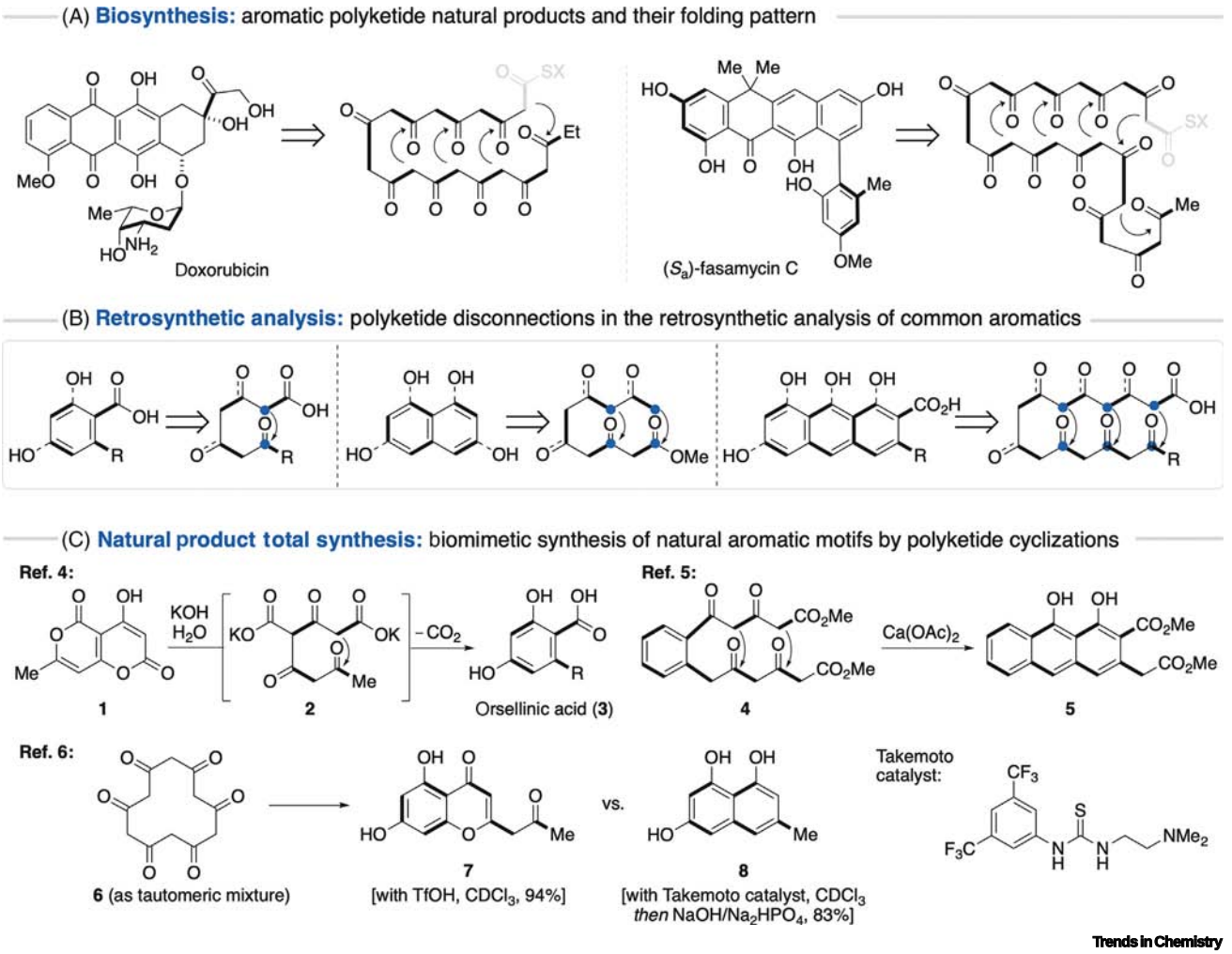

Figure 1. Retrosynthetic polyketide disconnection of natural aromatics. (A) Representative aromatic polyketide natural products and the corresponding folding modes in their biosynthesis. (B) Generalized retrosynthetic analysis of aromatics by considering polyketide disconnections. (C) Selected total syntheses of aromatic natural products featuring biomimetic polyketide cyclizations. Bold bonds depict ketide units in the folded chains and the configuration of stereogenic axes in atropisomeric products. Functionalities in grey are decarboxylatively cleaved in later biosynthetic steps. See [4–6]. Abbreviation: TfOH, triflic acid.

A most striking feature of transferring biosynthetic strategies to small-molecule catalysis is the possibility to design transformations of unique unnatural systems incompatible with enzymatic reactions. For instance, analogous to the biosynthetic assembly of atropisomeric polyketide natural product fasamycin C (Figure 1A) [2], a coordinated folding and cyclization of artificial substrates identified by retrosynthetic polyketide disconnections enables the development of stereoselective methods to prepare a broad range of atropisomers with small-molecule catalyst control. Besides natural products, countless relevant atropisomeric aromatic products are utilized as bioactive compounds, pharmaceuticals, chiral catalysts, and ligands for asymmetric synthesis. The Sparr group hence explored biomimetic arene-forming strategies [7] for the synthesis of versatile atropisomeric scaffolds using designed small-molecule catalysts [8].

A structurally predefined ketoaldehyde **9**, with aryl and vinyl groups as surrogates to the fully disassembled polyketide chain, was investigated by means of substrate activation through dienamine formation with a suitable secondary amine catalyst (Figure 2A) [9]. The *o*-disubstitution pattern of the phenyl ring and the *Z*-configuration of the alkene thus directed the nucleophilic α-carbon atom precisely over the keto group. The congested transition states of the addition and dehydration steps thereby allow a highly stereoselective process and by employing the pyrrolidinyl-tetrazole catalyst **10**, various unsymmetrically substituted 1,1′-binaphthalene-2-carbaldehydes **11** were obtained with high enantioselectivities.

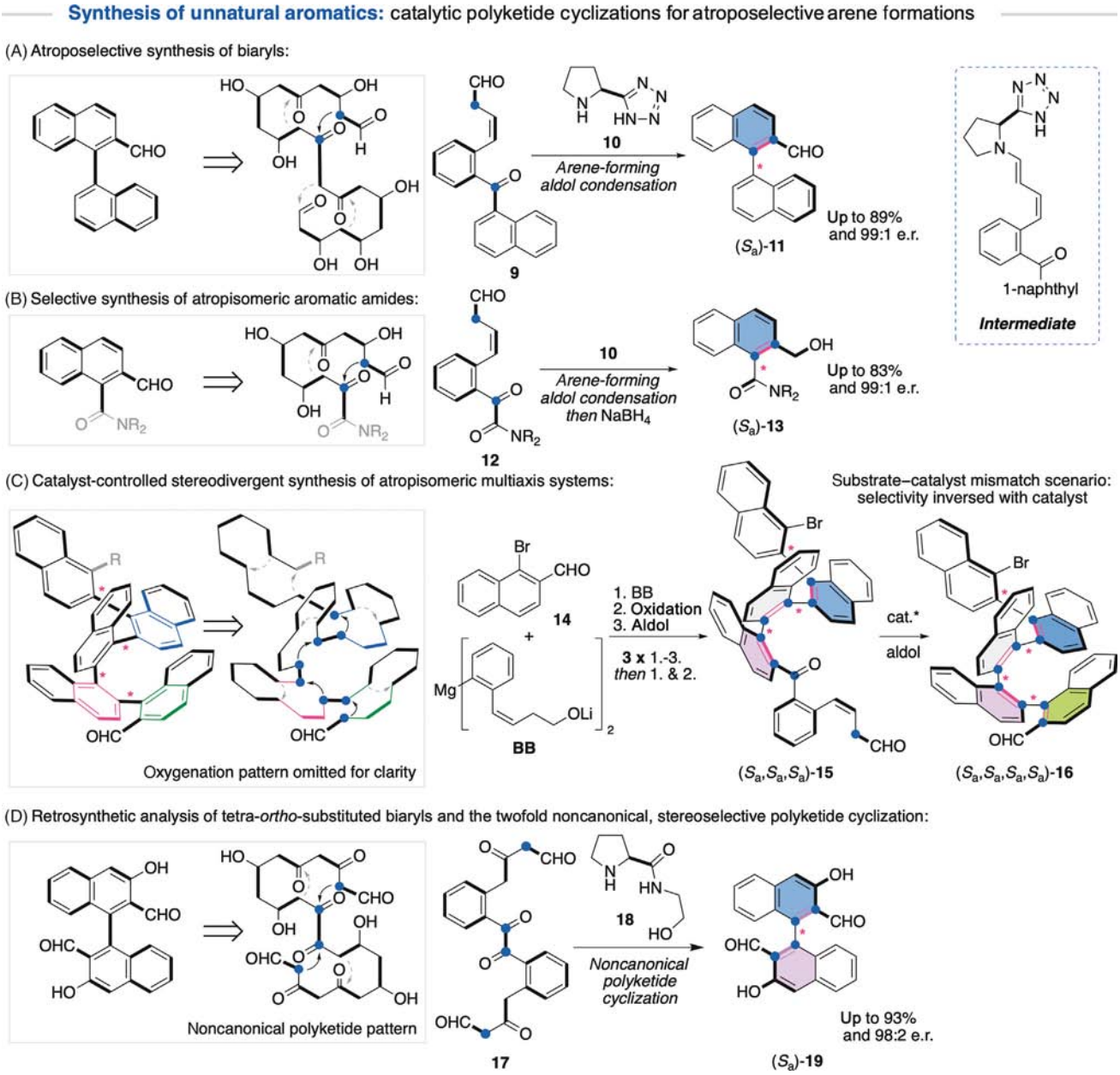

Figure 2. Retrosynthetic polyketide disconnections for unnatural aromatics. (A) Arene-forming aldol condensation for the catalyst-controlled stereoselective synthesis of atropisomeric biaryls. (B) Polyketide disconnection and synthesis of atropisomeric aromatic amides. (C) Analysis of atropisomeric multiaxis systems. Four strategic cyclizations were identified in the retrosynthetically disassembled polyketide chain to stereodivergently control each stereogenic axis individually with small-molecule catalysts. (D) Disconnections of tetra-*ortho* substituted biaryls for a noncanonical polyketide cyclization. Bold bonds depict ketide units in the folded chains and the configuration of stereogenic axes in atropisomeric products. Cyclizations with dashed arrows (grey) are identified but excluded for the forward synthesis. Cyclizations with unbroken arrows (black) were further considered for the developed synthetic approaches.

The generality of this arene-forming strategy was further confirmed by the secondary amine-catalyzed enantioselective synthesis of atropisomeric aromatic amides **13** featuring rotationally restricted Ar–CO bonds (Figure 2B) [10]. Notably, the optimized reaction of the cyclization step combined with an ensuing $NaBH_4$ reduction yields the corresponding hydroxymethyl amides **13** with considerably increased configurational stability. Nearly complete stereoselectivity was observed with catalyst

10, typically within half an hour reaction time at ambient temperature, underscoring the efficiency of the arene-forming aldol condensation identified by the retrosynthetic polyketide disconnections.

Molecular architectures with several stereogenic axes offer a particularly broad range of structurally well-defined topologies. For instance, atropisomeric *o*-arylenes display a characteristic helical shape in their secondary structure and the stereodivergent preparation of atropisomeric multiaxis scaffolds is therefore of critical importance, considering their synthetic utility in asymmetric catalysis or molecular recognition. The possibility of a stereodivergent synthesis of *o*-naphthylenes by individually controlling all stereogenic axes by small-molecule catalysts was thus investigated (Figure 2C) [11]. Three rounds of building block addition, *in situ* oxidation, and stereoselective aldol condensation controlled either by catalyst **10** or cinchonidine-derived ion-paring catalysts, followed by a final building block addition and an *in situ* oxidation, provided aldehyde substrate **15** with three configurationally defined stereogenic axes. A particularly effective activation strategy was thereby required to overcome the intrinsic stereochemical preference as revealed in prior substrate-controlled reactions. Notably, this requirement in the substrate–catalyst mismatch cases is fulfilled in the efficient polyketide aldol reactions, allowing individual catalyst stereocontrol over all four stereogenic axes of **16**.

Another notable advantage of biomimetic catalysis is the opportunity to employ substrates with noncanonical polyketide patterns to reach beyond the poly-β-carbonyls. Intriguingly, noncanonical polyketide disconnections of pertinent tetra-*ortho* substituted atropisomeric biaryls conclusively reveal the consequent feasibility of a twofold arene-forming aldol condensation with catalyst stereocontrol (Figure 2D) [12]. In the forward synthesis, the folding mode of noncanonical hexacarbonyl ketide **17** with a central α-diketo moiety was efficiently controlled by a proline-derived catalyst **18**, presumably by spanning a somewhat larger hydrogen-bond network for the biomimetic polyketide cyclization. By means of a twofold arene-forming aldol condensation, a wide range of functionalized tetra-*ortho* substituted binaphthalenes (**19**) were prepared with high enantioselectivity and up to 93% yield. An enantioenriched helicene, chiral diene ligand, and ion-pairing catalyst were prepared from the products, emphasizing the synthetic utility of the noncanonical polyketide cyclization to tetra-*ortho* substituted biaryl products.

Concluding remarks

By identifying retrosynthetic polyketide disconnections, a broad range of structurally distinct aromatic scaffolds are accessible by efficient biomimetic cyclizations of various polyketide substrates. It is expected that identifying the polyketide pattern in unnatural aromatics during retrosynthetic analysis will continue to inspire the development of synthetic strategies and pertinent methodologies to various unique aromatic frameworks, particularly in combination with selective and catalyst-controlled substrate activation concepts to fold increasingly complex polyketide chains.

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Declaration of interests

No interests are declared.

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