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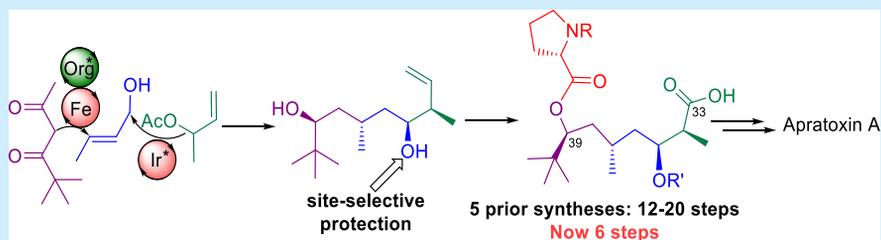
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# Catalysis Driven Six-Step Synthesis of Apratoxin A Key Polyketide Fragment

Na Shao, Jean Rodriguez, and Adrien Quintard\*



**ABSTRACT:** Apratoxin A is a potent anticancer natural product whose key polyketide fragment constitutes a considerable challenge for organic synthesis, with five prior syntheses requiring 12 to 20 steps for its preparation. By combining different redox-economical catalytic stereoselective transformations, the key polyketide fragment could be rapidly prepared. Followed by a site-selective protection of the diol, this strategy enables the preparation of the apratoxin A fragment in only six steps, representing the shortest route to this polyketide.

Polyketides are among the most prominent natural products and given their variety of bioactivity profiles, represent an invaluable inspiration for drug discovery.<sup>1</sup> As a consequence, chemists have for a long time considered polyketide synthesis as a motivation to devise more efficient synthetic routes. However, most syntheses still too often involve lengthy stepwise sequences and activation by multiple stoichiometric reagents. The difficulty at synthesizing polyketides stems from the challenge associated with the control of multiple remote acyclic stereogenic centers required for each distinct chiral reactant or catalyst. Therefore, most solutions consist of the stepwise elaboration of the different functionalities through iterative sequences involving, aside from the molecular skeleton formation, costly changes in the redox states of the carbon chain and protecting group manipulation.

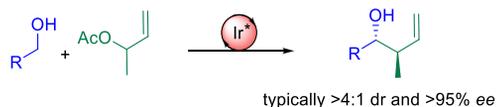
Fulfilling the principles of redox economies,<sup>2</sup> different cascade transformations have been developed where the initial activation step consists of an alcohol dehydrogenation by a metal complex.<sup>3</sup> In situ generating reactive aldehydes, the catalytic cascades can trigger complex enantioselective couplings between initially unreactive alcohols, considerably limiting waste and steps. Meeting these requirements, the Krische group developed a broad array of coupling reactions involving alcohols and pro-nucleophilic carbon donors.<sup>4</sup> In a typical example, enantioselective crotylation of alcohols can be performed directly through the iridium catalyzed condensation of  $\alpha$ -methyl allyl acetate and alcohols (Scheme 1a).<sup>5,6</sup> Such strategies can considerably short-cut the construction of key

natural product fragments which was notably applied in the context of polyketides synthesis.<sup>7</sup>

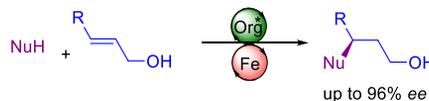
Complementary to these couplings, our group developed the concept of enantioselective multicatalytic borrowing hydrogens (Scheme 1b).<sup>8</sup> Based on a combination between an iron borrowing hydrogen catalyst and a chiral pyrrolidine organocatalyst, such an approach enables the enantioselective condensation of different nucleophiles to allylic alcohols.

## Scheme 1. Examples of Redox-Economic Transformations

### a) Enantioselective redox-neutral coupling:



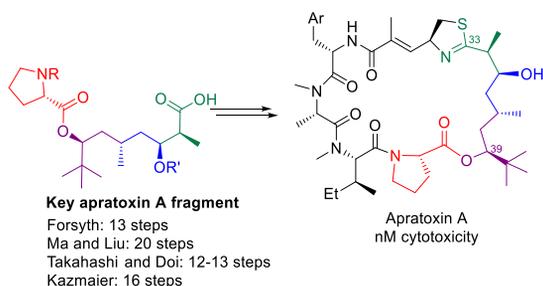
### b) Enantioselective borrowing hydrogen:



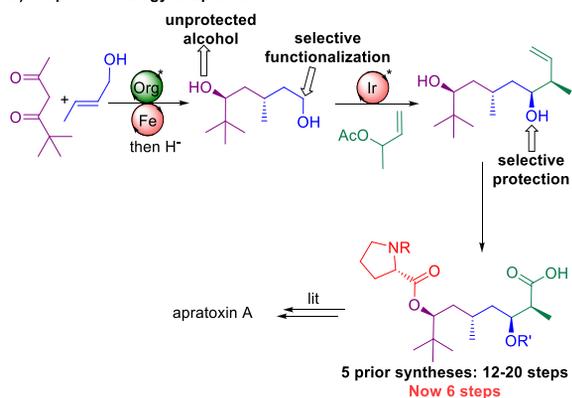
Apratoxins are natural macrolides first isolated in 2001 from *Lyngbya* types cyanobacteria.<sup>9</sup> They feature strong cytotoxic activity at the nM level against various cancer lines. Among the different natural apratoxins and unnatural analogues, apratoxin A (Scheme 2) is the most potent one. The excellent bioactivity profile has pushed organic chemists to develop a wide array of synthetic routes toward its preparation.

**Scheme 2. (a) Apratoxin A and Known Syntheses of the Key Polyketide Fragment; (b) Proposed Strategy**

**a) Apratoxin A and previous routes:**



**b) Proposed strategy to apratoxin A:**

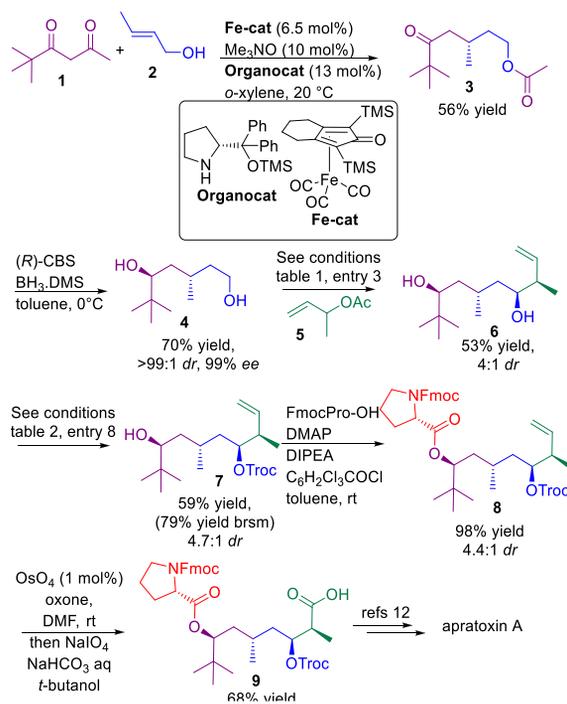


While the preparation of the peptidic part of the natural product is more classical and straightforward, the biggest challenge arises from the stereoselective construction of the complex C33–C39 advanced polyketide fragment. While Nature has engineered powerful enzymes for its construction, for now, chemists have relied on lengthy synthetic sequences for its preparation (Scheme 2a). All these efforts have been summarized in two reviews by Coltart.<sup>10</sup> Illustrating the difficulty at finding a convenient route to assemble this polyketide scaffold and control the different stereocenters, the first synthesis of this fragment by Forsyth required 13 steps and the use of two chiral auxiliaries for the construction of the carbon–carbon bonds.<sup>11</sup> Since then, the groups of Ma and Liu, Takahashi and Doi or Kazmaier have developed alternative strategies all still requiring between 12 and 20 steps and multiple chiral auxiliaries.<sup>12</sup> Synthesis of apratoxin analogues and other doubly protected diol fragments also required 13–14 steps such as in works by Cavalier, Xu, Gilles and Ye.<sup>13</sup> As a result, despite decades of efforts, the shortest sequence to date remains based on a minimum of 12 steps and multiple stoichiometric activating reagents.

Given the above-mentioned progress in the development of redox-economical catalytic transformations, we envisaged that a combination between a multicatalytic borrowing hydrogen and a redox-neutral coupling could provide a fast and highly enantioselective generation of this polyketide motif (Scheme 2b). This strategy would elaborate the desired C33–C39 chain in only three steps directly from widely available products. Development of a subsequent site-selective alcohol protection could unlock the final access to the desired functionalized key polyketide fragment. Herein, we present our success at developing such a strategy, culminating in the concise six-step synthesis of the key polyketide fragment, affording the most efficient to date formal synthesis of apratoxin A. This approach considerably shortens the access to this class of products and should find application in the preparation of other polyketide motifs.

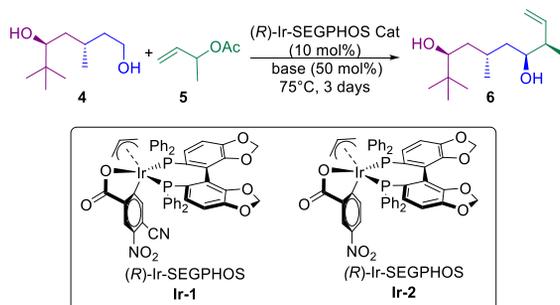
The synthesis started with the condensation of commercial diketone **1** to crotyl alcohol **2** (Scheme 3).<sup>8</sup> By combining iron

**Scheme 3. Six-Step Synthesis of Apratoxin A Fragment**



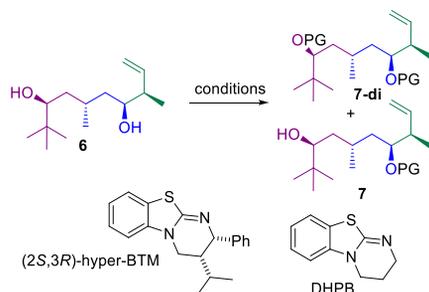
complex **Fe-Cat** and diphenyl prolinol silyl ether **organocat**, the cascade enantioselective borrowing hydrogen/Claisen type fragmentation<sup>14</sup> directly afforded the desired adduct **3** in 56% yield. Following stereoselective CBS reduction of the ketone and simultaneous deprotection of the alcohol, diol **4** could be isolated in 70% yield. The excellent selectivity of the CBS reduction<sup>15</sup> enabled isolation of diol **4** in >99:1 *dr* and improved 99% *ee* after separation upon silica gel chromatography of the minor diastereomer generated.

From this diol, key to the success for a short and efficient synthesis of apratoxin A was the implementation of a selective crotylation of the primary alcohol in the presence of the unprotected secondary alcohol. Even though allylation had been described on other types of scaffolds containing

**Table 1. Optimization of the Crotylation**

Entry	Base	Solvent	Cat.	Concn	Yield % ( <i>dr</i> ) <sup>a</sup>
1	Cs <sub>2</sub> CO <sub>3</sub>	THF (H <sub>2</sub> O, 5 equiv)	Ir-1	0.5 M	26% (3.6:1 <i>dr</i> )
2	K <sub>3</sub> PO <sub>4</sub>	THF (H <sub>2</sub> O, 5 equiv)	Ir-1	0.5 M	44% (3.1:1 <i>dr</i> )
3	K <sub>3</sub> PO <sub>4</sub>	THF	Ir-1	0.5 M	53% (4:1 <i>dr</i> )
4	K <sub>3</sub> PO <sub>4</sub>	THF	Ir-1	1 M	26% (3.4:1 <i>dr</i> )
5	K <sub>3</sub> PO <sub>4</sub>	THF	Ir-1	0.25 M	9% (2.8:1 <i>dr</i> )
6	K <sub>3</sub> PO <sub>4</sub>	THF	Ir-2	0.5 M	trace

<sup>a</sup>*dr* of the isolated product.

**Table 2. Optimization of the Site-Selective Protection**

Entry	Conditions	6/7-di/7 <sup>a</sup>
1	TBSCl or TESCl, base (excess), solvent, 0 to 80 °C (see SI for full conditions)	Conv <5%
2	TBSOTf (1 equiv), imidazole (2 equiv), DMAP (0.5 equiv), DMF, 0 °C to rt	93/6/1
3	TrocCl (1.2 equiv), pyridine (3 equiv), DMAP (5 mol %), DCM, 0 °C to rt	3.3/4/1
4	TrocCl (1.05 equiv), pyridine (2 equiv), DCM, rt	2.2/0.7/1
5	TrocCl (1.05 equiv), DMAP (2 equiv), DCM, rt	0.9/0.2/1
6	TrocCl (1.05 equiv), pyridine (2 equiv), (2 <i>S</i> ,3 <i>R</i> )-hyper-BTM (1 mol %), DCM, rt	1/0.9/1
7	TrocCl (1.05 equiv), pyridine (2 equiv), (2 <i>R</i> ,3 <i>S</i> )-hyper-BTM (1 mol %), DCM, rt	1.3/0.8/1
8	<b>TrocCl (1.05 equiv), DMAP (2 equiv), (2<i>S</i>,3<i>R</i>)-hyper-BTM (1 mol %), DCM, rt</b>	<b>0.3/0.2/1 (59%, 7 yield, 79% brsm)<sup>b</sup></b>
9	TrocCl (1.05 equiv), DMAP (2 equiv), DHPB (1 mol %), DCM, rt	2.4/0.1/1

<sup>a</sup>Determined by <sup>1</sup>H NMR on the crude reaction mixture. <sup>b</sup>brsm = based on recovered starting material.

secondary alcohols notably on 1,3-diols,<sup>16</sup> crotylation proved challenging in the context of unprotected 1,5-diol **4** (Table 1). Among all the tested parameters (see Supporting Information (SI) for additional experiments), we found that the nature of the base, the temperature, the concentration, and the structure of the catalyst were crucial to obtain the desired product. First experiments applying standard conditions with Ir-1 and Cs<sub>2</sub>CO<sub>3</sub> as base afforded the expected adduct **6** in a low 26% yield (entry 1). Under those conditions, formation of **6** was accompanied by a large amount of undesired dehydrogenation of the secondary alcohol to the corresponding ketone. Turning to K<sub>3</sub>PO<sub>4</sub> improved the yield to 44% (entry 2). While the presence of water is often associated with beneficial effects in the crotylation, herein, using dry THF improved both yield and selectivity, providing **6** in 53% yield and 4:1 *dr* (entry 3).

Similarly, crotylation is also mostly time conducted at high concentration (>1 M), which proved detrimental to the present reaction, affording **6** in only 26% yield (entry 4). Using more diluted conditions (0.25 M) also did not prove satisfactory, generating only 9% of the desired adduct with lower diastereocontrol (2.8:1 *dr*) (entry 5). Finally, use of less electron-efficient Ir-2 totally shut down the reactivity in this transformation (entry 6). Altogether, applying conditions of entry 3 with Ir-1 as catalyst and K<sub>3</sub>PO<sub>4</sub> enabled the synthesis of diol **6** in 53% yield and 4:1 *dr*. It is important to highlight that by applying this approach, all the four stereogenic centers of the polyketide chain are constructed in only three steps.

From diol **6**, the site-selective protection of the supposedly less hindered C-35 homoallylic alcohol was then scrutinized (Table 2, see Supporting Information for additional experi-

ments). We focused on the protection by a silyl or a 2,2,2-trichloroethoxycarbonyl (Troc) group, already applied in the synthesis of apratoxin A.<sup>12</sup> Initially, using TBSCl or TESCl did not provide any reactivity (entry 1). Using the more reactive TBSOTf, only the major protection of both alcohols **7-di** was observed with poor conversion, indicating a total lack of site selectivity (entry 2). Turning to the use of TrocCl considerably improved the reactivity (entries 3–8).<sup>17,18</sup> Using pyridine as the base, DMAP did catalyze the formation of the expected monoprotected alcohol **7** together with still a large amount of bis-protected diol **7-di** (entry 3). Using pyridine alone improved the selectivity in favor of the monoprotected alcohol at the expense of the conversion (entry 4). Using an excess of DMAP as base improved the selectivity affording around 25% of the desired monoprotected alcohol together with a large amount of unprotected diol and some bis-protected diol (entry 5). Given these results, we hypothesized that use of a bulkier nucleophilic Lewis base catalyst could improve the site-selective conversion to the monoprotected alcohol. Indeed, using chiral nonracemic isothiourea Hyper-BTM catalysts<sup>19</sup> resulted in a good compromise between conversion and selective monoprotection (entries 6–8). Since both enantiomers of the chiral catalyst provide closely related results (compare entries 6 and 7), this indicates that the selectivity is not arising from a chiral recognition by the enantiopure catalyst but rather due to the nature of the catalyst, disfavoring the acylation at the more hindered C-39 alcohol. This is confirmed by using achiral DHPB,<sup>20</sup> providing a closely related selectivity but at the expense of the conversion (entry 9). Altogether, by combining 1 mol % of (2*S*,3*R*)-hyper-BTM and 2 equiv of DMAP, the desired monoprotected alcohol **7** could be isolated in 59% yield through this site-selective protection (entry 8). Of interest, 20% of the unreacted starting diol could be recovered and reused, providing a 79% yield for this process based on recovered starting material.

With a convenient site-selective monoprotection giving access to **7**, subsequent functionalization of the secondary alcohol with the protected proline derivative and oxidative cleavage of the double bond provided in two subsequent steps the key fragment **9**, a known apratoxin A precursor (Scheme 3).<sup>12</sup>

In conclusion, by appropriately combining redox-economical stereoselective construction of the functionalized carbon chain with site-selective protection of the resulting diol **6**, a short formal synthesis of apratoxin A was developed. The key C33–C39 polyketide fragment, common to all apratoxin A synthesis, could be prepared in only 6 steps while the previous literature syntheses required between 12 and 20 steps. Given the efficiency of this approach and the similarity between apratoxin A and other natural scaffolds, this strategy should also be applied in the future to the efficient synthesis of other polyketides such as tuelarin C or neopeltolide.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) (a) Staunton, J.; Weissman, K. J. Polyketide Biosynthesis: A Millennium Review. *Nat. Prod. Rep.* **2001**, *18*, 380. (b) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J. Nat. Prod.* **2020**, *83*, 770.
- (2) For concept of redox-economies in synthesis, see: (a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854–2867. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021. For other synthetic-economy concepts, see: (c) Trost, B. M. *Science* **1991**, *254*, 1471–1477.
- (d) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201.
- (3) (a) Gunanathan, C.; Milstein, D. Applications of Acceptorless Dehydrogenation and Related Transformations in Chemical Synthesis. *Science* **2013**, *341*, 1229712–1229724. (b) Quintard, A.; Rodriguez, J. Catalytic enantioselective OFF-ON activation processes initiated by hydrogen transfer: concepts and challenges. *Chem. Commun.* **2016**, *52*, 10456–10473. (c) Reed-Berendt, B. G.; Latham, D. E.; Dambatta, M. B.; Morrill, L. C. Borrowing Hydrogen for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7*, 570–585.
- (4) For reviews, see: (a) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. Catalytic Carbonyl Addition through Transfer Hydrogenation: A Departure from Preformed Organometallic Reagents. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (b) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. Catalytic Enantioselective

C-H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (c) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. Metal-catalyzed reductive coupling of olefin-derived nucleophiles: Reinventing carbonyl addition. *Science* **2016**, *354*, aah5133. (d) Kim, S. W.; Zhang, W.; Krische, M. J. *Acc. Chem. Res.* **2017**, *50*, 2371. (e) Santana, C. G.; Krische, M. J. From Hydrogenation to Transfer Hydrogenation to Hydrogen Auto-Transfer in Enantioselective Metal-Catalyzed Carbonyl Reductive Coupling: Past, Present, and Future. *ACS Catal.* **2021**, *11*, 5572.

(5) (a) Kim, I. S.; Han, S. B.; Krische, M. J. anti-Diastereo- and Enantioselective Carbonyl Crotylation from the Alcohol or Aldehyde Oxidation Level Employing a Cyclometallated Iridium Catalyst:  $\alpha$ -Methyl Allyl Acetate as a Surrogate to Preformed Crotylmetal Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (b) Gao, X.; Han, H.; Krische, M. J. Direct Generation of Acyclic Polypropionate Stereopolyads via Double Diastereo- and Enantioselective Iridium-Catalyzed Crotylation of 1,3-Diols: Beyond Stepwise Carbonyl Addition in Polyketide Construction. *J. Am. Chem. Soc.* **2011**, *133*, 12795. (c) Gao, X.; Townsend, I. A.; Krische, M. J. Enhanced anti-Diastereo- and Enantioselectivity in Alcohol-Mediated Carbonyl Crotylation Using an Insoluble Single Component Iridium Catalyst. *J. Org. Chem.* **2011**, *76*, 2350. (d) Kasun, Z. A.; Gao, X.; Lipinski, R. M.; Krische, M. J. Direct Generation of Triketide Stereopolyads via Merged Redox-Construction Events: Total Synthesis of (+)-Zincophorin Methyl Ester. *J. Am. Chem. Soc.* **2015**, *137*, 8900.

(6) For other examples of such redox-neutral couplings: (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. Enantioselective Iridium Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Using Allyl Acetate as an Allyl Metal Surrogate. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. Enantioselective Iridium Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Transfer Hydrogenative Coupling of Allyl Acetate: Departure from Chirally Modified Allyl Metal Reagents in Carbonyl Addition. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Quintard, A.; Rodriguez, J. Enantioselective Ir-Catalyzed Bidirectional Reductive Coupling. *Org. Lett.* **2019**, *21*, 453.

(7) (a) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504. (b) Feng, J.; Kasun, Z. A.; Krische, M. J. Enantioselective Alcohol C-H Functionalization for Polyketide Construction: Unlocking Redox-Economy and Site-Selectivity for Ideal Chemical Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 5467. (c) Sperandio, C.; Rodriguez, J.; Quintard, A. Catalytic strategies towards 1,3-polyols synthesis by enantioselective cascades creating multiple alcohol functions. *Org. Biomol. Chem.* **2020**, *18*, 1025.

(8) (a) Quintard, A.; Constantieux, T.; Rodriguez, J. An Iron/Amine-Catalyzed Cascade Process for the Enantioselective Functionalization of Allylic Alcohols. *Angew. Chem., Int. Ed.* **2013**, *52*, 12883. (b) Roudier, M.; Constantieux, T.; Quintard, A.; Rodriguez, J. Enantioselective Cascade Formal Reductive Insertion of Allylic Alcohols into the C(O)-C Bond of 1,3-Diketones: Ready Access to Synthetically Valuable 3 Alkylpentanol Units. *Org. Lett.* **2014**, *16*, 2802. For a review, see: (c) Quintard, A. Iron-based multi-catalysis: eco-compatible alternative for complex molecules synthesis. *Chem.—Eur. J.* **2021**, *27*, 89.

(9) See for example: (a) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. Total Structure Determination of Apratoxin A, a Potent Novel Cytotoxin from the Marine Cyanobacterium *Lyngbya majuscula*. *J. Am. Chem. Soc.* **2001**, *123*, 5418. (b) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. New apratoxins of marine cyanobacterial origin from guam and palau. *Bioorg. Med. Chem.* **2002**, *10*, 1973. (c) Gutiérrez, M.; Suyama, T. L.; Engene, N.; Wingerd, J. S.; Matainaho, T.; Gerwick, W. H. Apratoxin D, a Potent Cytotoxic Cyclopeptide from Papua New Guinea Collections of the Marine Cyanobacteria *Lyngbya majuscula* and *Lyngbya sordida*. *J. Nat. Prod.* **2008**, *71*, 1099.

(10) (a) Tarsis, E. M.; Rastelli, E. J.; Wengryniuk, S. E.; Coltart, D. M. The apratoxin marine natural products: isolation, structure

determination, and asymmetric total synthesis. *Tetrahedron* **2015**, *71*, 5029. (b) Rastelli, E. J.; Coltart, D. M. *Tetrahedron* **2018**, *74*, 2269.

(11) (a) Chen, J.; Forsyth, C. J. Total Synthesis of Apratoxin A. *J. Am. Chem. Soc.* **2003**, *125*, 8734. (b) Chen, J.; Forsyth, C. J. Total synthesis of the marine cyanobacterial cyclopeptide apratoxin A. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 12067.

(12) (a) Zou, B.; Wei, J.; Cai, G.; Ma, D. *Org. Lett.* **2003**, *5*, 3503. (b) Ma, D.; Zou, B.; Cai, G.; Hu, X.; Liu, J. O. Total Synthesis of the Cyclopeptide Apratoxin A and Its Analogues and Assessment of Their Biological Activities. *Chem.—Eur. J.* **2006**, *12*, 7615. (c) Doi, T.; Numajiri, Y.; Munakata, A.; Takahashi, T. Total Synthesis of Apratoxin A. *Org. Lett.* **2006**, *8*, 531. (d) Numajiri, Y.; Takahashi, T.; Doi, T. *Chem.—Asian J.* **2009**, *4*, 111. (e) Andler, O.; Kazmaier, U. Total synthesis of apratoxin A and B using Matteson's homologation approach. *Org. Biomol. Chem.* **2021**, *19*, 4866. (f) Chen, Q.-Y.; Liu, Y.; Cai, W.; Luesch, H. Improved Total Synthesis and Biological Evaluation of Potent Apratoxin S4 Based Anticancer Agents with Differential Stability and Further Enhanced Activity. *J. Med. Chem.* **2014**, *57*, 3011.

(13) (a) Xu, Z.; Chen, Z.; Ye, T. *Tetrahedron: Asymmetry* **2004**, *15*, 355. (b) Gilles, A.; Martinez, J.; Cavellier, F. Supported Synthesis of Oxoapratoxin A. *J. Org. Chem.* **2009**, *74*, 4298. (c) Gilles, A.; Martinez, J.; Cavellier, F. A flexible synthesis of C33-C39 polyketide region of apratoxin: Synthesis of natural and unnatural analogues. *C. R. Chimie* **2011**, *14*, 437.

(14) Rodriguez, J.; Quintard, A. Acyl transfer strategies as transient activations for enantioselective synthesis. *Synthesis* **2019**, *51*, 1923.

(15) Onda, Y.; Fukushi, K.; Ohsawa, K.; Yoshida, M.; Masuda, Y.; Doi, T. *Heterocycles* **2020**, *101*, 679.

(16) Site selective: (a) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. Protecting-Group-Free Diastereoselective C-C Coupling of 1,3- Glycols and Allyl Acetate through Site-Selective Primary Alcohol Dehydrogenation. *Angew. Chem., Int. Ed.* **2013**, *52*, 3195. (b) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. 1,*n*-Glycols as Dialdehyde Equivalents in Iridium Catalyzed Enantioselective Carbonyl Allylation and Iterative Two-Directional Assembly of 1,3-Polyols. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (c) Feng, J.; Garza, V. J.; Krische, M. J. Redox-Triggered C-C Coupling of Alcohols and Vinyl Epoxides: Diastereo- and Enantioselective Formation of All-Carbon Quaternary Centers via tert-(Hydroxy)-Prenylation. *J. Am. Chem. Soc.* **2014**, *136*, 8911. (d) Shin, I.; Wang, G.; Krische, M. J. Catalyst-Directed Diastereo- and Site-Selectivity in Successive Nucleophilic and Electrophilic Allylations of Chiral 1,3-Diols: Protecting-Group-Free Synthesis of Substituted Pyrans. *Chem.—Eur. J.* **2014**, *20*, 13382.

(17) For leading examples of site selective catalytic functionalization of alcohols, see: (a) Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. A Catalytic One-Step Process for the Chemo- and Regioselective Acylation of Monosaccharides. *J. Am. Chem. Soc.* **2007**, *129*, 12890. (b) Yanagi, M.; Ninomiya, R.; Ueda, Y.; Furuta, T.; Yamada, T.; Sunazuka, T.; Kawabata, T. Organocatalytic Site-Selective Acylation of 10-Deacetylbaconin III. *Chem. Pharm. Bull.* **2016**, *64*, 907. (c) Tay, J. H.; Arguelles, A. J.; DeMars, M. D.; Zimmerman, P. M.; Sherman, D. H.; Nagorny, P. Regiodivergent Glycosylations of 6-Deoxy-erythronolide B and Oleandomycin-Derived Macrolactones Enabled by Chiral Acid Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 8570. (d) Xiao, G. Z.; Cintron-Rosado, G. A.; Glazier, D. A.; Xi, B. M.; Liu, C.; Liu, P.; Tang, W. P. Catalytic Site-Selective Acylation of Carbohydrates Directed by Cation- $\pi$  Interaction. *J. Am. Chem. Soc.* **2017**, *139*, 4346. (e) Li, J.; Grosslight, S.; Miller, S. J.; Sigman, M. S.; Toste, F. D. Site-Selective Acylation of Natural Products with BINOL-Derived Phosphoric Acids. *ACS Catal.* **2019**, *9*, 9794. (f) Nishikawa, Y.; Toda, S.; Matsui, T.; Takada, H.; Takemoto, K.; Hara, O. Site-Selective Acylations of  $\alpha$ - and  $\beta$ -Hydroxyamides in Complex Molecules: Application of Template-Driven Acylation to Disaccharides and a Glycopeptide. *Org. Lett.* **2021**, *23*, 2715. (g) Ashush, N.; Fallek, R.; Fallek, A.; Dobrovetsky, R.; Portnoy, M. Base- and Catalyst-Induced Orthogonal Site

Selectivities in Acylation of Amphiphilic Diols. *Org. Lett.* **2020**, *22*, 3749.

(18) For examples of site-selective acylation of diols: (a) Paterson, I.; Lombart, H.-G.; Allerton, C. Total Synthesis of Elaiolide Using a Copper(I)-Promoted Stille Cyclodimerization Reaction. *Org. Lett.* **1999**, *1*, 19. (b) Reddy, R.; Dietrich, E.; Lafontaine, Y.; Houghton, T. J.; Belanger, O.; Dubois, A.; Arhin, F. F.; Sarmiento, I.; Fadhil, I.; Laquerre, K.; Ostiguy, V.; Lehoux, D.; Moeck, G.; Parr, T. R., Jr.; Rafai Far, A. Bisphosphonated Benzoxazinorifamycin Prodrugs for the Prevention and Treatment of Osteomyelitis. *ChemMedChem.* **2008**, *3*, 1863. (c) Qian, S.; Shah, A. K.; Head, S. A.; Liu, J. O.; Jin, Z. Insights into the structure–activity relationship of the anticancer compound ZJ-101, a derivative of marine natural product superstolide A: A critical role played by the conjugated trienyl lactone moiety. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3411.

(19) (a) Zhang, Y.; Birman, V. B. Effects of Methyl Substituents on the Activity and Enantioselectivity of Homobenzotetramisole-Based Catalysts in the Kinetic Resolution of Alcohols. *Adv. Synth. Catal.* **2009**, *351*, 2525. For reviews, see: (b) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. Enantioselective Catalysis by Chiral Isothioureas. *Eur. J. Org. Chem.* **2016**, *2016*, 5589. (c) Birman, V. B. Amidine-Based Catalysts (ABCs): Design, Development, and Applications. *Aldrichimica Acta* **2016**, *49*, 23.

(20) Kobayashi, M.; Okamoto, S. Unexpected reactivity of annulated 3H-benzothiazol-2-ylideneamines as an acyl transfer catalyst. *Tetrahedron Lett.* **2006**, *47*, 4347–4350.