

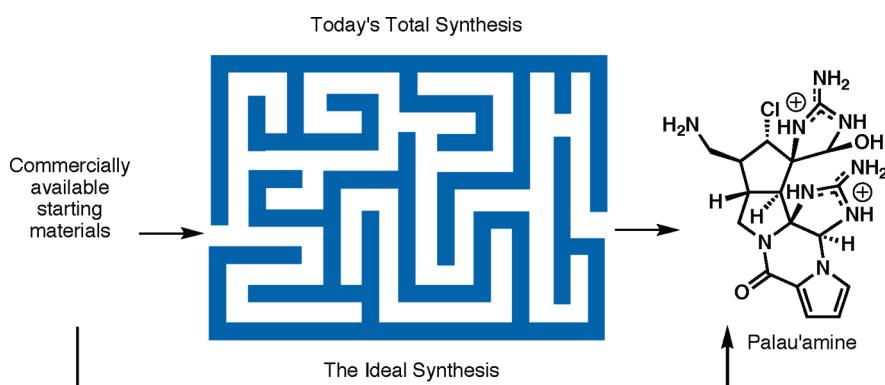
## Aiming for the Ideal Synthesis

Tanja Gaich and Phil S. Baran\*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, 92037 La Jolla, California

[pbaran@scripps.edu](mailto:pbaran@scripps.edu)

Received April 8, 2010



The field of total synthesis has a rich history and a vibrant future. Landmark advances and revolutionary strides in the logic of synthesis have put the practicing chemist in the enviable position of being able to create nearly any molecule with enough time and effort. The stage is now set for organic chemists to aim for “ideality” in the way molecules are synthesized. This perspective presents a simple and informative definition of “ideality” and demonstrates its use during the self-evaluation of several syntheses from our laboratory.

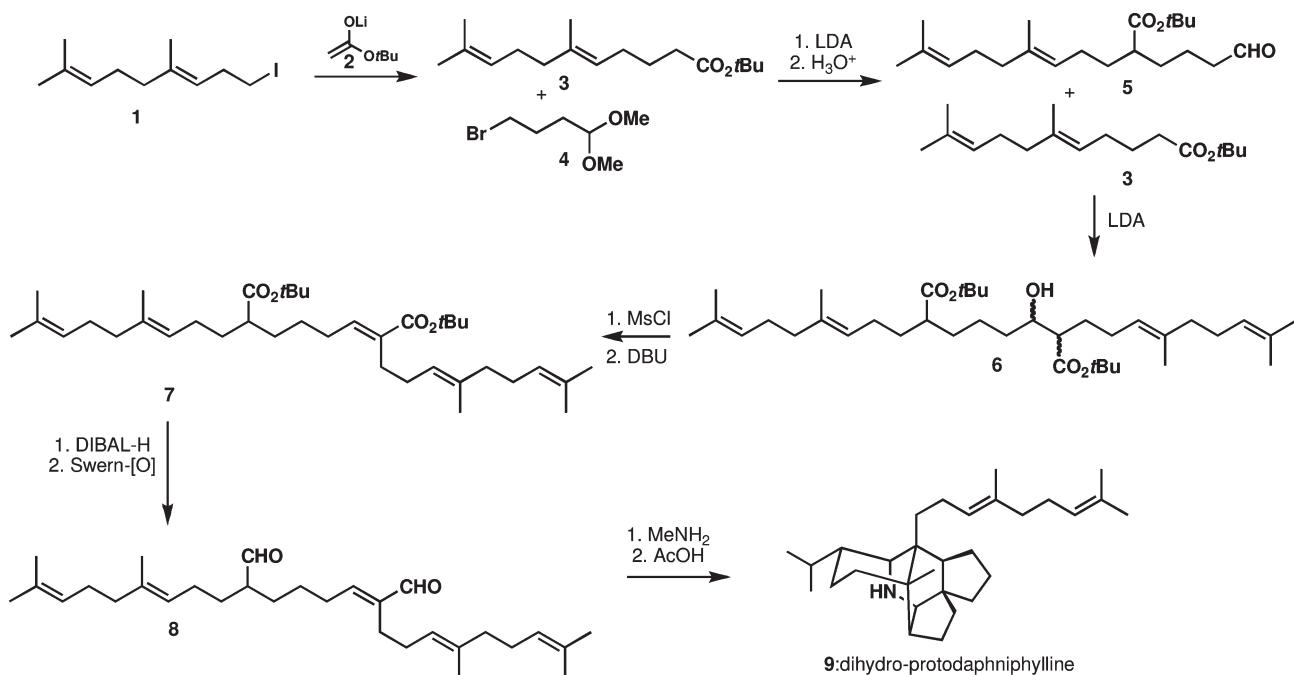
### Introduction

In the 20th century, the art and science of complex natural product total synthesis defined the frontiers of organic chemistry.<sup>1</sup> Throughout these decades, fundamental insights into reactivity and selectivity principles were revealed by these numerous synthetic endeavors. The field of total synthesis has served and continues to serve as the ultimate testing ground for new methodologies and strategies. The capability and power of organic synthesis has thus experienced a dramatic increase putting today’s synthetic chemists in the position to construct molecules of more or less any degree of structural complexity. Consequently, the definition of a “complex” target has undergone considerable revision. However, what yet remains to be reframed, and what we wish to emphasize here, is the need for a “sea-change” in the perception defining *art* in organic synthesis today. This key issue was first addressed by Hendrickson in 1975 when he defined the “ideal synthesis” as one which:<sup>2</sup>

“...creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality.”

This prescient statement truly encompassed and epitomized the “economies” of synthesis design<sup>3</sup> many years before the ideas of atom,<sup>4</sup> step,<sup>5</sup> and redox-economy<sup>6</sup> were formally galvanized. Many factors may be responsible for this—one of them perhaps being that, in 1975, the challenge of organic synthesis was not efficiency so much as feasibility. In other words, the era of rationally planned complex molecule construction was still developing at a blistering pace. To be sure, erythronolide, paclitaxel, paletoxin, brevetoxin, vitamin B<sub>12</sub>, ginkgolide, and hundreds of other natural product targets still awaited completion in 1975. Now, in 2010, the field has reached an awe-inspiring level, with many proclaiming that synthesis has matured.<sup>7</sup> Indeed, it has certainly matured to the point that molecules such as teicoplanin or calicheamicin no longer appear hopelessly complex. But before one declares the science of synthesis as an endeavor in engineering, one only needs to reflect on the inspiring ease with which Nature crafts large (metric ton) quantities of its most complex molecules (e.g., vancomycin and paclitaxel). Total synthesis in this century must therefore be keenly aware of this ultimate challenge: to be able to provide large quantities of complex natural products with a

SCHEME 1. Total Synthesis of Dihydro-protodaphniphylline by Heathcock et al.



minimum amount of labor and material expense.<sup>8</sup> The natural consequence of pursuing such a goal is to embrace the Hendrickson dictum (*vide supra*). Pursuing synthesis in such a way forces the practitioner into the role of an inventor. It also naturally leads to explorations into biology since multiple collaborations can be forged with an ample supply of materials. Finally, scalable syntheses of complex natural products help debunk the myth that such compounds are not economically viable targets in the pharmaceutical industry.

#### Attempting To Quantify the Ideal Synthesis

Over the years, numerous attempts have been made to quantify various parameters of efficiency in chemical synthesis.<sup>9a–d</sup> What follows is our elementary effort to furnish a numerical expression for Hendrickson's conception of an ideal synthesis. The purpose of this simple metric is to aid practitioners of synthesis to easily make comparisons and pinpoint areas for improvement. Thus we define percent "ideality" as follows:

$$\% \text{ideality} =$$

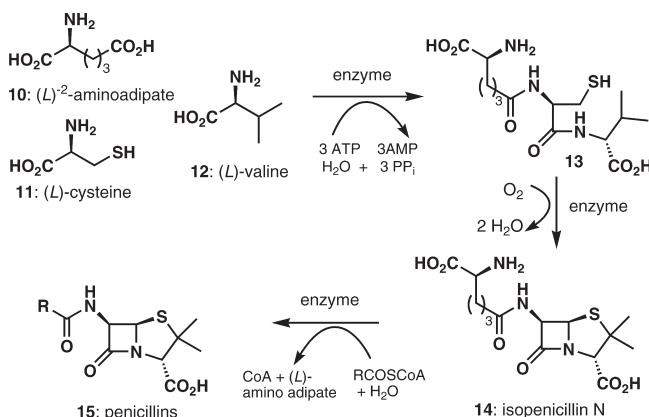
$$\frac{[(\text{no. of construction rxns}) + (\text{no. of strategic redox rxns})]}{(\text{total no. of steps})} \times 100$$

*Construction reactions*, as defined by Hendrickson, are those which form skeletal bonds (C–C and C–heteroatom). *Strategic redox reactions* (another form of construction reaction) have been previously defined as those that directly establish the correct functionality found in the final product, such as asymmetric oxidations and reductions or C–H oxidations.<sup>9c</sup> All other types of reactions fall into the category of a *concession step*: (1) *Nonstrategic redox manipulations* (i.e., reduction of ester to alcohol), (2) *functional group interconversions* (i.e., alcohol to mesylate to azide), and (3) *protecting group manipulations*. The term *concession step* is applied to these types of reactions since it is well

accepted that they require extra effort but are often simply unavoidable. To substantiate the principle of "ideality" in synthesis, the trend-setting synthesis of daphniphyllum alkaloids by Heathcock et al. is showcased in Scheme 1.<sup>10</sup> The synthesis of dihydro-protodaphniphylline (**9**) starts with two C–C bond formations between the lithium enolate of *tert*-butyl acetate and **1**, followed by an alkylation of **3** with **4**, to give after acid hydrolysis compound **5**. The acid hydrolysis is considered as a concession step (protecting group manipulation). What follows is another C–C-bond formation, in this case an aldol reaction of **3** and **5**, to give compound **6**. Aldol product **6** is converted into compound **7** via two concession steps, namely a mesylation and an elimination reaction with DBU, both being functional group interconversions. Diester **7** is transformed into dialdehyde **8** via a reduction/oxidation sequence, therefore representing two nonstrategic redox reactions. Reaction of **8** with methylamine and subsequent treatment with acetic acid complete the synthesis of dihydro-protodaphniphylline **9**. These last two steps build up the carboskeleton with the correct functionality and oxidation states in place and are therefore considered as construction steps. Thus, despite the beauty and groundbreaking nature of this landmark 10-step synthesis it exhibits only 50% ideality.

Not surprisingly, Nature's biosynthesis is often nearly ideal. The biosynthesis of penicillins is just one example of a completely ideal synthesis that confirms this view,<sup>11a</sup> and similar lines of analysis could be used for other famous natural product classes (such as erythronolide, paclitaxel, and vancomycin). Starting from completely unprotected amino acids cysteine, valine, and amino adipate, tripeptide **13** is formed at the expense of three molecules ATP, constituting a construction step (Scheme 2). Thereafter, isopenicillin-*N*-synthase builds up the bicyclic framework characteristic for penicillins via a strategic redox reaction. The last step allows for

## SCHEME 2. Biosynthesis of Penicillins



the introduction of various side chains without any intermediate hydrolysis steps and, therefore, also constitutes a construction step. For this reason, biomimetic syntheses are often incredibly efficient and closer to ideality than abiotic variants.<sup>11b-d</sup>

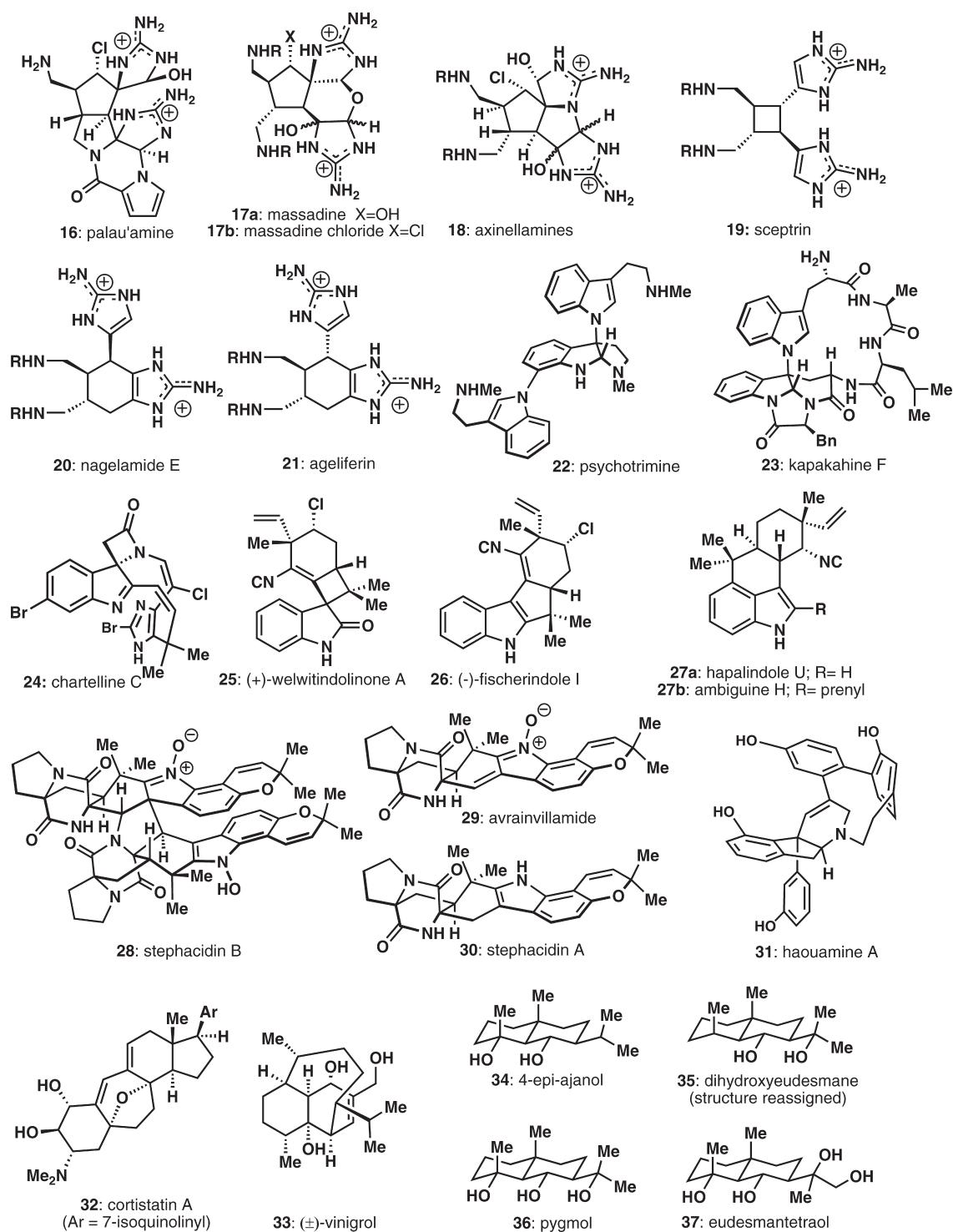
A fair evaluation of a synthetic route of any target structure is inevitably tied to the molecular complexity it exhibits. Therefore, the definition of ideality, as we wish to describe it, is restricted to the comparison of different routes leading to the same target structure. Our intent is to provide the practitioner with a tool for the purpose of self-reflection and evaluation. We are well aware, that “ideality” in synthesis is just one variable for the consideration of a synthetic route. Depending on the purpose of the synthesis, other factors like ease of purification, high overall yields, costs of reagents, etc. will govern the choice of the sequence finally carried through. *In our own work, we have found it useful to evaluate three specific metrics: Overall yield, step count, and percent ideality.* This Perspective details our efforts in aiming for the Hendrickson ideal synthesis in the context of complex natural product synthesis. During the past seven years, the structures shown in Figure 1 were synthesized in our laboratories, and they represent a broad cross-section of small molecule natural product subtypes, ranging from indole alkaloids to pyrrole-imidazole alkaloids to steroid-derived compounds, peptoidal architectures, diterpenes, and polyhydroxylated terpenoids. A previous account from our laboratory showcased several of these natural product syntheses in relation to the chemoselectivity challenge they posed and the planning guidelines used for their construction.<sup>12</sup> In this account, we will examine our total syntheses through the critical (and often harsh) lens of ideality with particular attention paid to deficiencies and areas for further improvement. The natural products will be discussed arbitrarily in order of decreasing nitrogen content.

## Palau'amine, Massadines, and Axinellamines

Palau'amine (**16**),<sup>13</sup> massadines (**17**),<sup>14</sup> and axinellamines (**18**)<sup>15</sup> are marine natural products belonging to the pyrrole-imidazole family possessing a very high degree of complexity.<sup>16</sup> Their highly polar structures exhibit a variety of halogenation patterns and have a very dense arrange-

ment of functionality on their carboskeleton. Especially noteworthy is the guanidinium hemi-aminal functionality (highlighted in red in Scheme 3) that they all share. The well-documented difficulty of installing this critical functional group inspired us to pursue a C–H functionalization approach. By deferring hemi-aminal formation to the advanced stages of the synthesis, it was surmised that concession steps could be minimized. Although there was ample precedence for the oxidation of amines to imines, no method for the oxidation of guanidines was known from the literature. The C–H bond in question electronically resembles that which is adjacent to an amide rather than an amine. Further, with such dense functionality present in these molecules, chemoselectivity issues would need to be overcome. Most worrisome was the problem of overoxidation since it could be easily argued that the product of such a transformation is easier to oxidize than the starting material. After extensive experimentation we found that silver(II) picolinate (**40**)<sup>17</sup> was suitable for the oxidation of **41** to **39** (Scheme 3A). This key reaction enabled our 2008 synthesis of the axinellamines (**18a/b**) and paved the way for the completion of **17a/b** and **16**.<sup>18</sup> The reaction was dramatically improved by adding 10% trifluoroacetic acid<sup>19</sup> (see Scheme 3D) and has subsequently found use in the pharmaceutical industry. In 2010, Aldrich Chemical Co. began selling **40** (\$10/g).<sup>20</sup> Our unified approach to these alkaloids begins with central building block **43**. In the case of **17**, oxidation of **43** to hemi-aminal **44/45** was performed before oxidation of the aminoimidazole moiety (**44/45** → **46**) because the hydroxyl group of the hemi-aminal in **46** was required to form the tetrahydropyran ring in **47**.<sup>19</sup> The third and most complex sibling, palau'amine (**16**),<sup>21</sup> possesses a unique structural feature compared to its two congeners: one pyrrole is embedded in an exquisite hexacyclic framework comprising a trans-fused azabicyclo[3.3.0]octane ring system (e.g. *trans*-5,5-bicycle), previously unseen among natural isolates. This is a central reason why it had eluded synthesis for almost seventeen years since its isolation in 1993. Our initial attempts for a biomimetic approach to **16** failed, presumably due to the very high ring strain imposed by the *trans*-5,5-bicycle (Scheme 3F). The lessons learned thereby inspired an alternative approach that exploited a macrocyclic constitutional isomer (**48a**) (e.g., “macro”-palau'amine Scheme 3E) of **16**, spring-loaded for a transannular ring closure, and enabled by a dynamic equilibrium between the aminoimidazole and amidine form (**48b**, Scheme 3C). For this purpose, **48a** was accessed from **49** with EDCI in the absence of protective groups.

Exposure of **48a** to TFA elicited the desired transformation to yield palau'amine with its characteristic highly strained *trans*-5,5-bicycle. This reaction exemplifies how substrate preorganization and proximity effects can overcome energy barriers, enabling counterintuitive transformations that lead to otherwise difficult to access molecular scaffolds (in this case the *trans*-5,5-bicycle, see Scheme 3E). Another example of this type of strategy will be discussed in the kapakahine section (vide infra). The most striking feature of the logic underpinning these syntheses are the late-stage chemoselective oxidations on completely unprotected intermediates possessing no fewer than nine

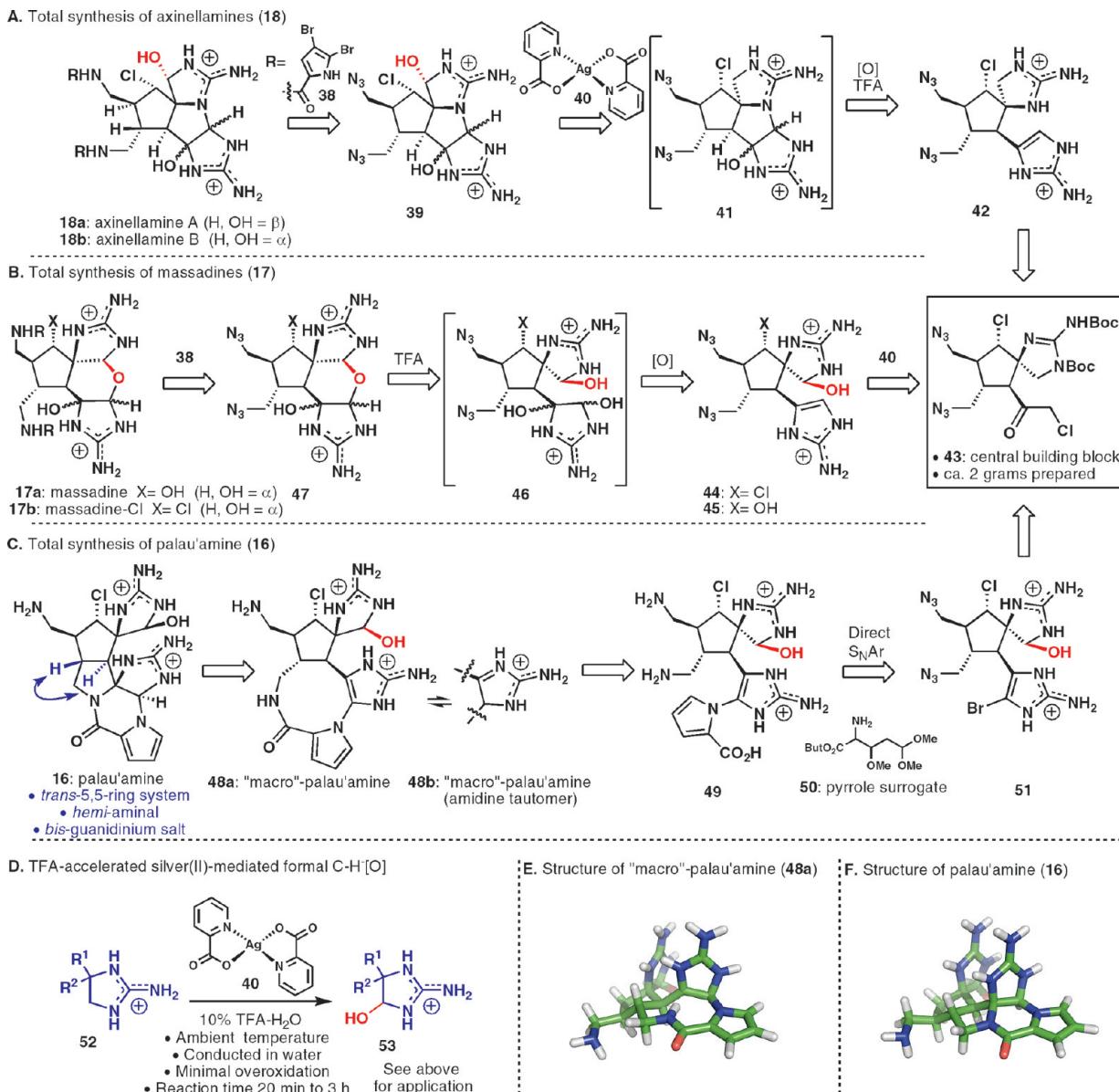
**FIGURE 1.** Structures of natural products recently completed in our laboratories.

nitrogen atoms. Overall, the syntheses of **18**, **17**, and **16** all take place in 25 steps with 32%, 36%, and 36% ideality, respectively. Thus, 60–70% of the steps involved in these total syntheses are concession steps and therefore detract from the appeal of these routes. The overall yields of these routes also suffer as a consequence (2.7% for **18**, 0.6% for **17**, and 0.015% for **16**). Studies are now underway in our laboratories to streamline these routes.<sup>21a,22</sup>

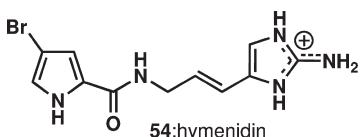
### Sceptrin, Ageliferin, and Nagelamide

Whereas the previous section dealt with marine sponge-derived natural products of the pyrrole-imidazole family that contain a central five-membered ring, the biosynthetic machinery of the same sponges also create beautiful structures possessing cyclobutane and cyclohexane core skeletons. Known as sceptrin (**19**),<sup>23</sup> nagelamide E (**20**),<sup>24</sup> and ageliferin (**21**),<sup>25</sup> they can be biosynthetically traced

## SCHEME 3. Total Syntheses of Axinellamines, Massadines, and Palau'amine



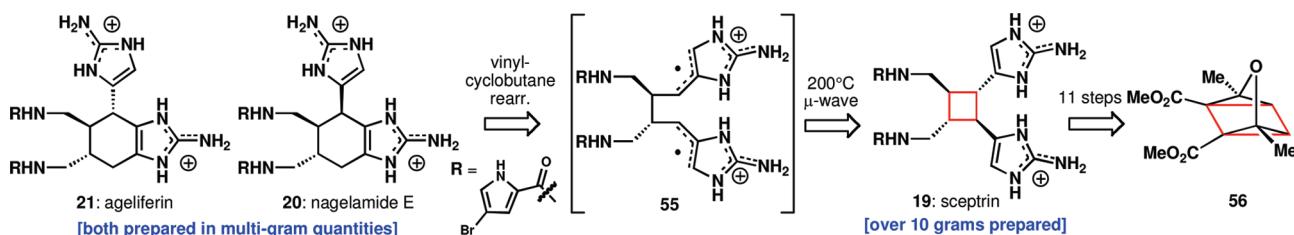
back to the monomeric natural product hymenidin (see inset). At the time our laboratory embarked on their synthesis, it was believed that **19–21** were independently formed via [2 + 2] and [4 + 2] cycloadditions, respectively, of hymenidin.<sup>26</sup>



We formulated an alternative hypothesis in which **21** and **20** were derived from **19** via a formal vinyl cyclobutane rearrangement.<sup>27</sup> This hypothesis proved correct (at least in the laboratory) and allowed for the gram-scale synthesis of these intriguing natural products.<sup>28</sup> Thus, when an aqueous solution of **19** was heated to 200 °C for 1 min in a microwave,

**21** and **20** were produced in synthetically useful yields. Our full account on the subject has shown how the yield of this reaction, which requires microwave irradiation, is counter-ion dependent.<sup>28</sup> The mechanism of this reaction has been hypothesized to proceed via a diradical intermediate.<sup>29</sup> It is interesting that vinylcyclobutane rearrangements are now being invoked in the biosynthesis of completely unrelated marine natural product families.<sup>30</sup> The hypothesis that **19** is an important precursor to other pyrrole-imidazole alkaloids led us to pursue the correct structure of palau'amine (see the previous section) before it was officially revised by Köck in 2007.<sup>13e</sup> Since sceptryn exhibits potential for the treatment of cystic fibrosis and Alzheimer's disease, access to large quantities of this natural product was imperative.<sup>28b</sup> We therefore developed a short, chromatography-free, high-yielding synthesis featuring a rare oxiquadricyclane **56** fragmentation to rapidly build the all-trans tetrasubstituted cyclobutane core.<sup>28,31,32</sup> With a total number of 11 steps

SCHEME 4. Total Syntheses of Sceptryn, Nagelamide, and Ageliferin



and only two protective group manipulations, access to more than 10 g of sceptryn **19** was gained. Although multigram quantities of **19**–**21** were accessed, their syntheses only showed 36% (for **19**) and 42% (for **20** and **21**) ideality, respectively, with overall yields of 24% for **19**, 12% for **21**, and 3% for **20** (Scheme 4). The reason for this shortcoming in ideality lies in two nonstrategic redox reactions, three functional group interconversions, and two protective group manipulations.<sup>33</sup>

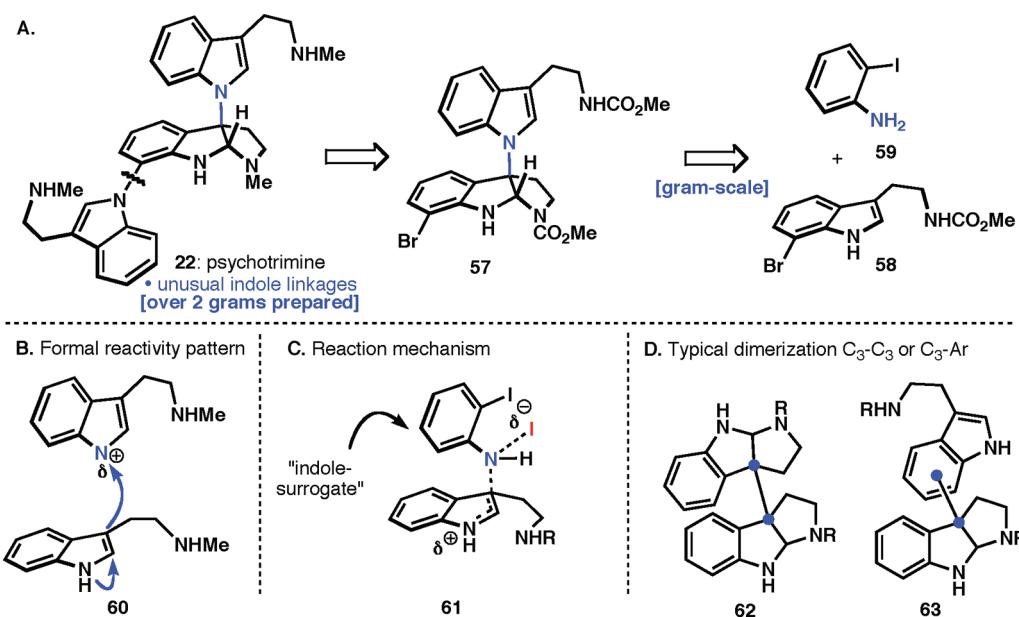
### Kapakahine and Psychotrimine

Psychotrimine (**22**)<sup>34</sup> and kapakahine F (**23**)<sup>35</sup> are interesting examples of how the positioning of a single functional group can stimulate the invention of methodology. Specifically, both natural products are polymeric indole alkaloids that in the case of **22** present a rare N1–C3-connection between two tryptamine residues (indole nomenclature, Scheme 5A). This connectivity is especially curious given the indole heterocycle's inherent preference<sup>36</sup> to dimerize and generate a new *carbon–carbon* bond (typical connectivity depicted in Scheme 5D) rather than a *carbon–nitrogen* bond. In 2006, when the synthesis of **22** began in our laboratories, no methodology for the direct coupling of indoles to give this N1–C3-bond was known. The formal reactivity pattern (depicted in Scheme 5B) requires one “unpoled” indole moiety, which is engaged by a second indole unit via its C3 carbon atom. Embracing this disconnection, a reaction was invented using *o*-idoaniline (**59**) as an “indole

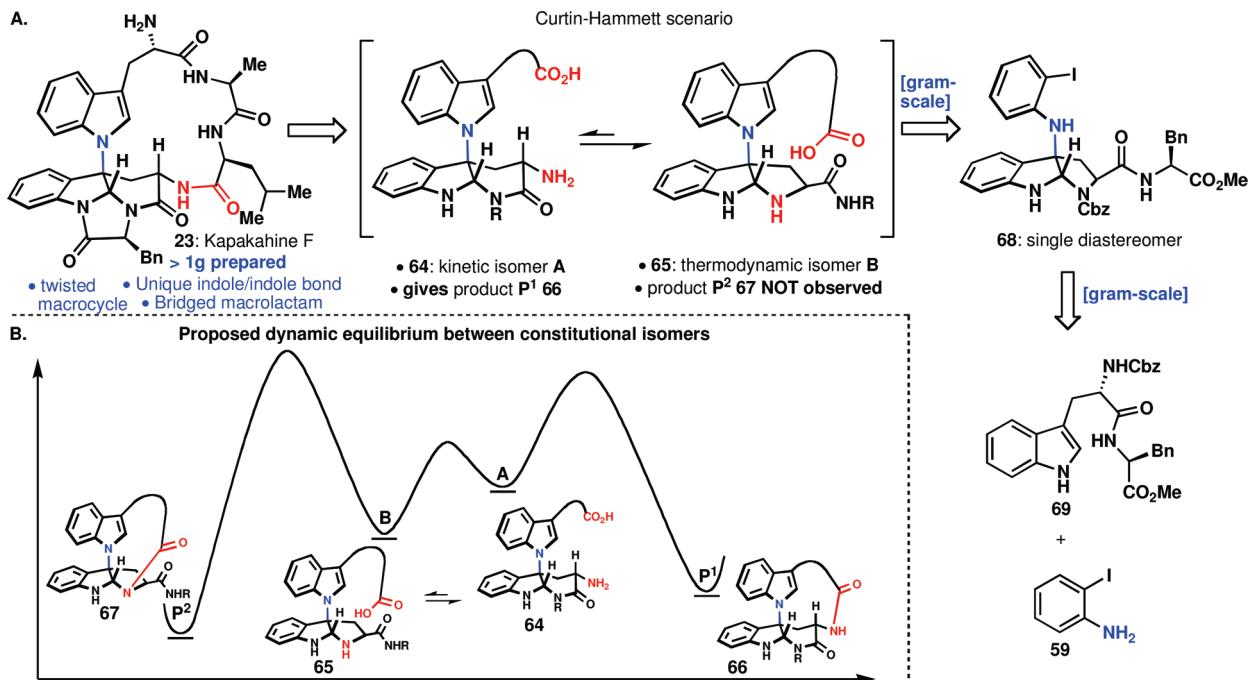
surrogate”.<sup>37</sup> In the event, **59** was oxidatively activated using *N*-iodosuccinimide and combined with **58** via the proposed mechanism depicted in Scheme 5C. Our recent full account on this topic traces the design, development, mechanistic intricacies, and relevant historical context of this methodology.<sup>38</sup> Following Larock annulation (to deliver **57**), Buchwald–Goldberg–Ullmann coupling, and methyl carbamate reduction, a gram-scale, four-step synthesis of **22** was completed.

Kapakahine F (**23**) is a heptacyclic peptide that exhibits the same type of N1–C3 linkage as **22**. The 16-membered twisted (“kapakahine” is Hawaiian for “twisted”) macrocyclic lactam incorporated in this structure, with an embedded α-carboline moiety, poses an additional synthetic challenge. The unique N1–C3 linkage was constructed in the same fashion as in psychotrimine, yielding pyrroloindoline (**68**) as a single diastereomer. Larock annulation and functional group manipulations gave a fused peptide (**65**), which was ready for macrocyclization. By examining the structure of kapakahines, it becomes immediately evident that simple macrocyclization would produce a pyrroloindoline structure analogous to that found in psychotrimine (see structure **67**, Scheme 6B) rather than the kapakahine skeleton **66**, (Scheme 6B). Therefore, the success of the route depended exclusively on the existence of a proposed dynamic equilibrium between pyrroloindoline (**65**) and α-carboline (**64**), of which the latter would undergo macrocyclization in preference to the former.

SCHEME 5. Total Synthesis of Psychotrimine



SCHEME 6. Total Synthesis of Kapakahine F



This constitutes a “Curtin–Hammett-scenario”<sup>39</sup> in which the primary amine in **64** should react faster than the secondary amine in **65**. In accord with our design, when **65** was submitted to macrocyclization conditions, the desired kapakahine scaffold **66** was isolated as major product ( $11:1 = 66:67$ ) in 64% yield. This outcome substantiates the existence of a Curtin–Hammett scenario in which **64** is the kinetic isomer but is removed from the equilibrium due to a lower activation barrier in the macrocyclization reaction (Scheme 6B). In contrast, macrocyclization of **65** is slow due to its higher activation energy.<sup>40</sup>

From the vantage point of ideality, the direct N1–C3 coupling method enabled a concise four-step synthesis of **22** in 43% overall yield and 75% ideality. The clear Achilles’ heel of that synthesis is the reduction of the carbamates in the last step (89% yield), which was necessary to set the proper oxidation state of the methyl groups. This singular concession step was, however, worthwhile since it permitted the other three reactions to take place chemoselectively and eased purification and characterization. In the case of kapakahine F (**23**), an additional five functional group interconversions and one protecting group operation lowered the ideality to 42% over 12 steps with 12% overall yield, primarily due to the stepwise nature of the peptide backbone synthesis.<sup>41</sup>

### Chartellines

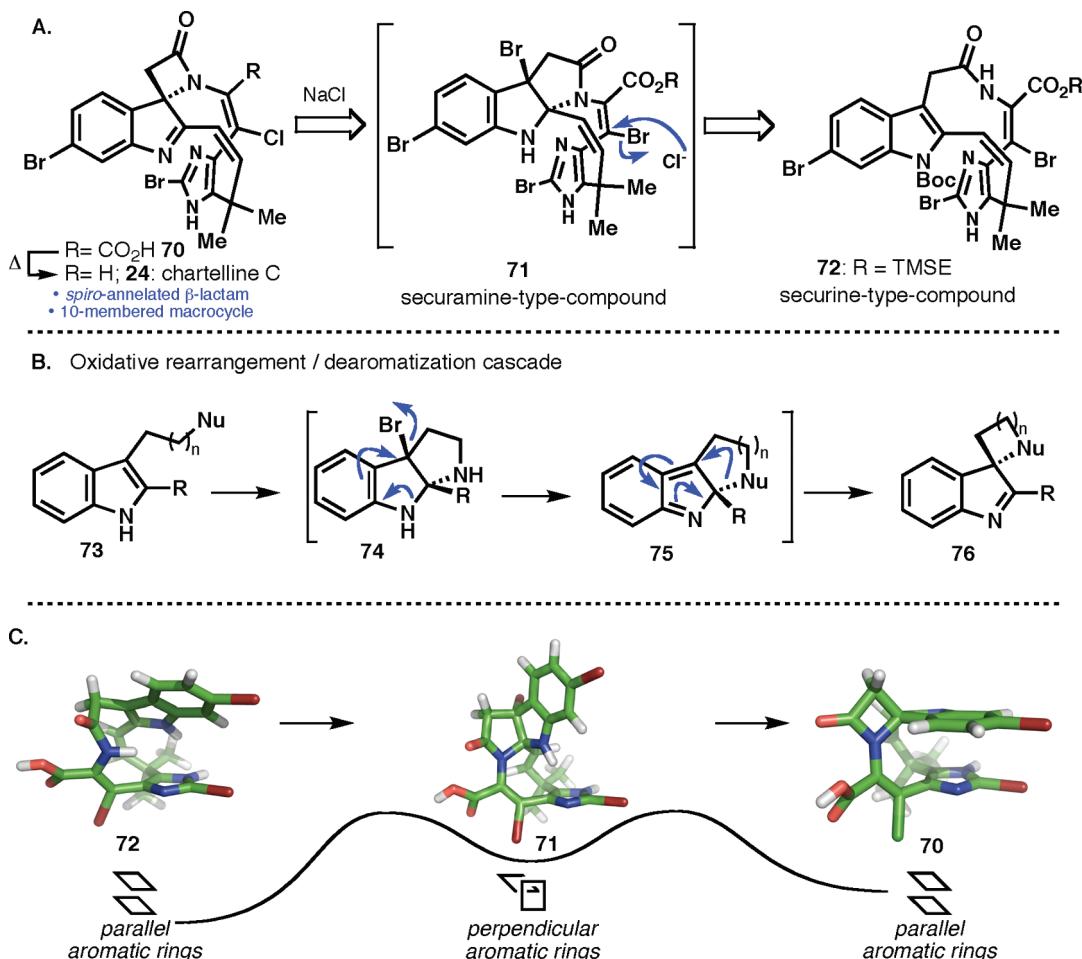
Chartellines constitute a modestly sized family of marine natural products of extremely high molecular complexity.<sup>42</sup> The rarest naturally occurring among them, chartelline C (**24**), contains an indolenine motif with an imidazole embedded in a 10-membered macrocyclic lactam, and a  $\beta$ -lactam attached in a spiro fashion to the indolenine. The indole and imidazole subunits are perfectly positioned for  $\pi$ -stacking, and the overall architecture is folded so as to accommodate the unusual  $\beta$ -lactam ring. Biosynthetically,

the chartellines are related to securines and securamines. Thus, the proposal we put forth contained a highly unusual ring contraction based on fundamentally sound oxidative rearrangement/dearomatization cascade chemistry to form the  $\beta$ -lactam ring (Scheme 7B).<sup>43</sup> Although it was very easy to locate precedent for the failure of the proposed spiro-ring contraction, it was hypothesized that  $\pi$ -stacking and ring conformational effects would overcome this problem (see hypothesized reaction coordinate in Scheme 7C). Securine-type structure **72** was synthesized via standard transformations not mentioned here. Thermolytic Boc-deprotection of compound **72** and subsequent treatment with *N*-bromosuccinimide gave securamine structure type **71**, which upon heating rearranged to give the desired  $\beta$ -lactam of chartelline C.<sup>44</sup> An unusually facile exchange of bromine for chlorine upon standard workup with brine took place, and after decarboxylation of **70** the natural product was obtained in overall 16 steps, 6% yield, and 47% ideality. The synthesis contains three nonstrategic redox reactions, which are used to build up key precursor **72** and largely detract from ideality. Two protecting group manipulations and three functional group interconversions additionally lower the overall ideality.<sup>45</sup>

### Hapalindoles, Fischerindoles, and Welwitindolinone A

Terpene–indole hybrids from marine cyanobacteria have inspired practitioners of synthesis for decades.<sup>46</sup> With 60+ members and growing, there is ample opportunity to imagine how Nature fashioned these natural products and design routes, which mimic some, but not all, of those steps. In 2003, when we embarked on the synthesis of this family, efficiency and practicality was our ultimate objective. A retrosynthesis was designed whose sole purpose was to avoid the most glaring of concession steps: protecting group manipulations.<sup>47</sup> This required a plan that maximizes both

SCHEME 7. Total Synthesis of Chartelline C



convergency and innate reactivity. Therefore, the central strategic disconnection utilized in the course of this synthesis program was the direct formation of a carbon–carbon bond between C3 of the indole moiety and the α-carbon atom of the terpenoid fragment derived from carvone (Scheme 8C).<sup>48</sup> The oxidative radical coupling used for this purpose brings about the great advantage that no prefunctionalization of either fragment is required (compare the hypothetical transformation of **79** to **80** with **81** to **82**, Scheme 8B).<sup>49</sup> This contributes to the step economy of the synthesis and avoids potential protective group manipulations. The assembly of the carvone and indole fragments (in Scheme 8C) was achieved via simple deprotonation and use of a copper(II) oxidant for radical dimerization to give pivotal building blocks **77** and **78a/b**, respectively.

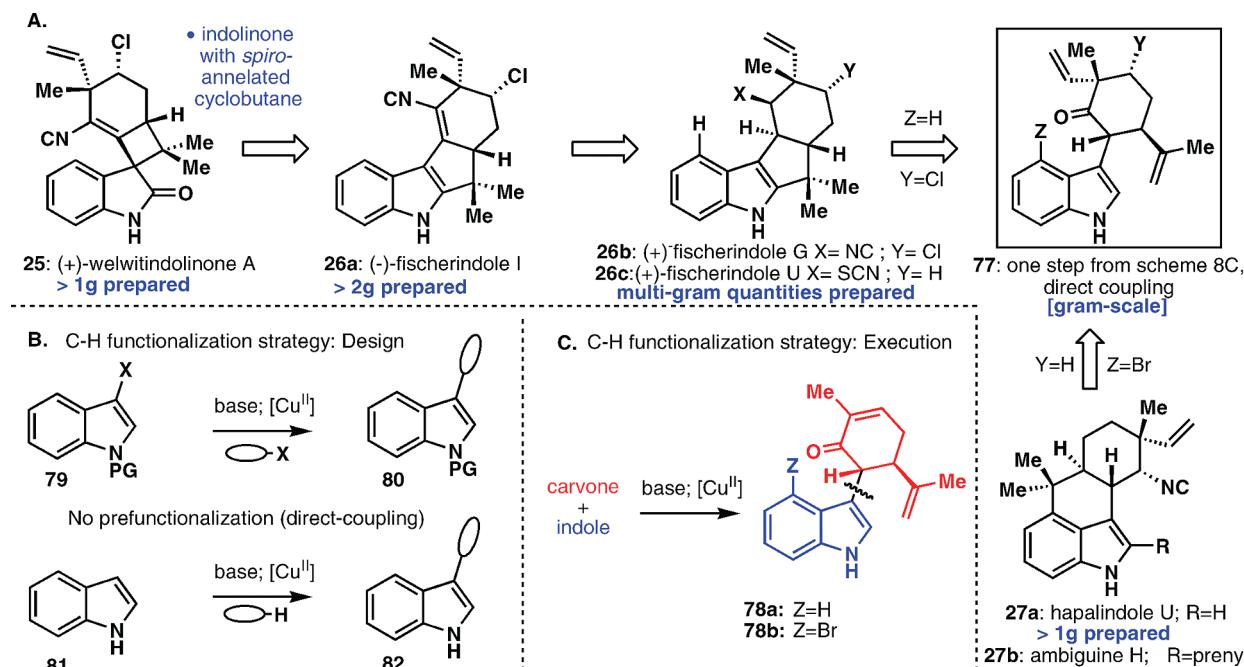
Fischerindoles U (**26c**), G (**26b**), and I (**26a**) were prepared from **77** via a cationic cyclization reaction to give the desired five-membered carbocycle.<sup>8a,48</sup> The total synthesis of welwitindolinone A (**25**) shows parallels to the β-lactam formation in the chartelline C synthesis (see Scheme 8B), where an oxidative ring contraction of a five-membered ring was involved to provide the unique cyclobutane structure element of welwitindolinone A, accompanied with the formation of the oxindole moiety of the natural product. Hapalindole U (**27a**) and ambiguine H (**27b**) were also prepared via compound **77** on a gram scale.<sup>50</sup> The synthesis of **27a** was completed with a ring annulating Heck reaction, whereas for compound **27b** an additional prenylation

reaction was performed. Clearly, the oxidative coupling of indoles and carbonyl compounds was the critical invention that enabled the avoidance of protective group manipulations, provided a generalized approach to this alkaloid family, and hence furnished gram amounts of these natural products. The route to fischerindole I involved eight steps (11% overall yield) leading to an ideality of 75%. Hapalindole U and ambiguine H were synthesized in four steps (24% overall yield) with 75% ideality and six steps (9% overall yield) with 83% ideality, respectively. Welwitindolinone A was synthesized in nine steps (3% overall yield) with 78% ideality.<sup>46b,51</sup>

### Avrainvillamide and Stephacidins A and B

Stephacidins A (**30**) and B (**28**) possess unique structural features, including a very dense functionality and an uncommon oxidation pattern for indole alkaloids. The signature bicyclo[2.2.2]diazaoctane ring system and the dimeric character of stephacidin B granted considerable potential to develop new methodology.<sup>52</sup> Our focus resided on the development of a scalable route to stephacidin A (**30**) (Scheme 9A),<sup>53</sup> a position and chemoselective oxidation of **30** to avrainvillamide **29**,<sup>54</sup> and eventually its dimerization to give stephacidin B (**28**).<sup>54,55</sup> The dimerization of **29** as outlined in Scheme 9B was proposed to be Nature's pathway to **28**, a prospect easily probed with a viable route to **29**. Access to large quantities of **30** relied upon an efficient construction of the distinctive bicyclo[2.2.2]diazaoctane

SCHEME 8. Total Synthesis of Fischerindoles, Hapalindole U, and Welwitindolinone A



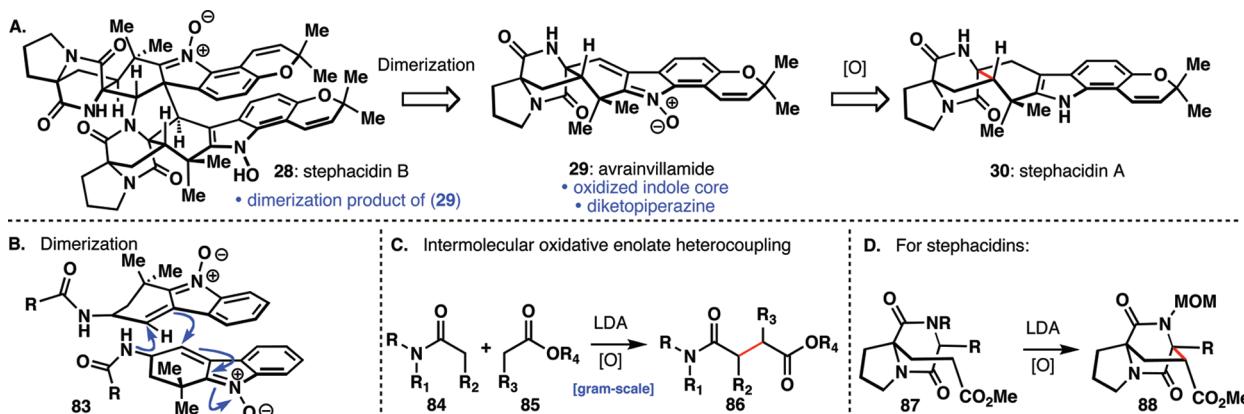
ring system. The strategic bond highlighted in Scheme 9A (structure **30**) in red was thereby gained via an oxidative enolate heterocoupling of an ester and an amide enolate (Scheme 9D). This methodology gave good yields, could be conducted on a preparative scale, and was completely stereoselective.<sup>56</sup> Furthermore, this conversion represented a rare example of two different types of carbonyl compounds (ester **84** and amide **85**) undergoing an oxidative radical heterocoupling. This intermolecular oxidative enolate heterocoupling reaction has since found use in the pharmaceutical industry for the preparation of unsymmetrical, enantio-pure succinate building blocks.<sup>57</sup> Oxidation of stephacidin A to avrainvillamide was conducted with substoichiometric amounts of selenium dioxide and hydrogen peroxide.<sup>58</sup> A spontaneous double-Michael addition of two molecules of **29** gave rise to the dimer stephacidin B. The numbers reveal that, for **30**, **29**, and **28** (16, 17, and 18 steps, respectively), the ideality ranges from 38% for **30**, 41% for **29**, to 44% for **28**. The sequence leading to stephacidin A (**30**) involves 16 steps, among which are seven protecting group manipulations, one

nonstrategic oxidation reaction, and two functional group interconversion.<sup>59</sup>

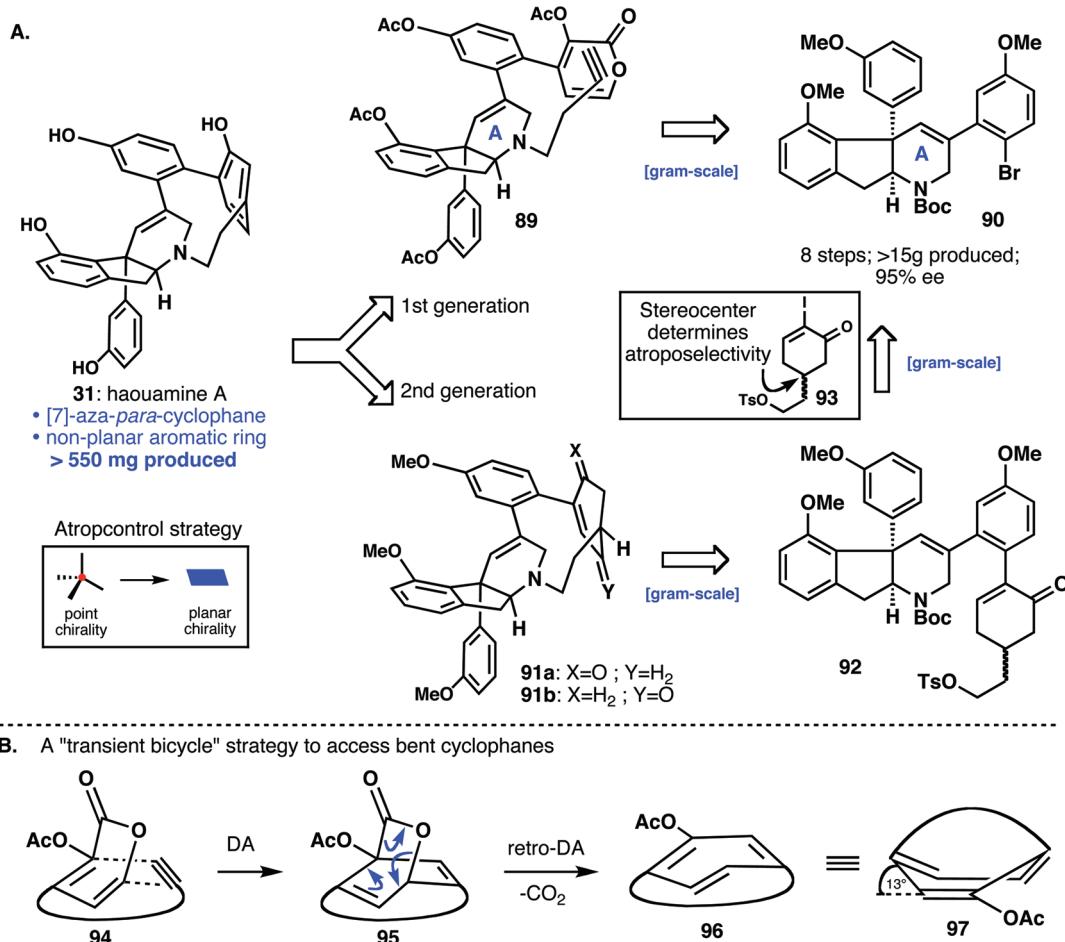
### Haouamine

Cyclophanes are highly strained compounds with an alkyl bridge between nonadjacent positions of an aromatic ring.<sup>60</sup> There are very few examples of this structure motif in natural products,<sup>61</sup> with haouamine A (**31**) representing one of them.<sup>62</sup> Its striking architectural feature comprises a [7]-azaparacyclophane structure element, which makes it a very attractive target for total synthesis. The aromatic ring of the *p*-cyclophane in **31** adopts a strained boat conformation, thereby bending out of plane and imposing considerable ring strain (Scheme 10B). In order to construct this natural product, one must apply a method for ring closure that can overcome this strain. In our first-generation approach, the method of choice was an intramolecular  $\alpha$ -pyrone Diels–Alder reaction with a tethered alkyne (depicted in Scheme 10B), the driving force of this reaction originating from the liberation of carbon dioxide.<sup>63</sup>

SCHEME 9. Total Synthesis of Stephacids A and B and Avrainvillamide



SCHEME 10. Total Synthesis of Haouamine A



Our synthesis commenced with a concise eight-step synthesis of **90** on a multigram scale.<sup>64</sup> We were then able to access Diels–Alder precursor **89** with the two crucial functional groups (alkyne and  $\alpha$ -pyrone) in gram quantities. The Diels–Alder reaction required exposure of **89** to 250 °C in dichlorobenzene for 10 h and provided the desired carbo-skeleton of haouamine in a 10:1 ratio in favor of the desired atropisomer in low yield. In accord with the isolation report, **31** was found to exist as a mixture of rapidly interconverting isomers, which could be explained either by atropisomerism or pyramidal inversion at nitrogen.<sup>65</sup> A collaboration with Genentech was forged to elucidate the biological mode of action for **31**'s anticancer activity. Unfortunately, the first-generation route to **31** could only deliver small quantities that were insufficient for extensive analysis. A second-generation route to **31** was therefore designed with the issues of scalability and atropselectivity in mind.<sup>66</sup> Slightly saturated versions of **31** and *atrop*-**31** were targeted as shown in Scheme 10 (**91a/b**). It was reasoned that these enones would be susceptible to oxidation/aromatization and that atroposelectivity would be easily achieved by transferring their point chirality into the planar chirality of the natural product.

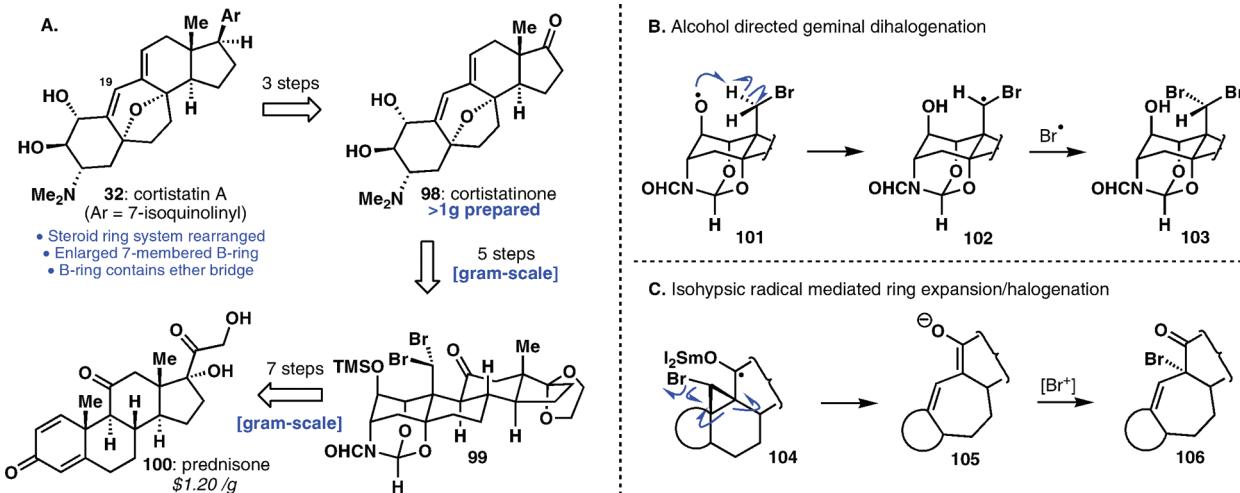
Atropisomers **91a** and **91b** were generated through a high-yielding macro-alkylation and separated by column chromatography. Chemoselective aromatization was achieved with *N*-*tert*-butylenesulfinimidoyl chloride<sup>67</sup> to yield

haouamine A (**31**) and tentative “atrop”-haouamine A, respectively. With both atropisomers in hand, we were able to prove that the isomeric mixture of **31** stems from nitrogen inversion and concomitant conformational tetrahydropyridine rearrangement rather than atropisomerism. As a result of this work, the supply of haouamine for extensive biological evaluation is no longer an issue (samples freely available on request). Both (first- and second-generation) routes were carried out in racemic and enantioselective<sup>68</sup> forms. The racemic first-generation approach is eight steps, with 1% overall yield, and exhibits 50% ideality, whereas the enantioselective first-generation approach consists of 12 steps with 0.6% overall yield and 50% ideality. The racemic second-generation approach includes nine steps with 5% overall yield and 44% ideality versus 13 steps for its enantioselective version with 3% overall yield and 38% ideality. Application and refinement of this strategy to other chiral and strained cyclophanes are underway.<sup>69</sup>

### Cortistatin A

The cortistatins constitute an unusual family of 9-(10,19)-*abeo*-androstane steroids and were isolated from a marine sponge.<sup>70</sup> They feature very potent inhibition of human umbilical endothelial vein cells—with cortistatin A (**32**) as the most potent member (HUVECs, IC<sub>50</sub> = 1.8 nM) without exhibiting any cytotoxicity toward either healthy or cancerous cells. Cortistatin A is a high-affinity ligand for a small set

SCHEME 11. Total Synthesis of Cortistatin A



of protein kinases including ROCK, CDK8, and CDK11.<sup>71</sup> Its outstanding biological activity combined with an unusual array of functionality attracted our attention and led us to pursue a practical semisynthesis given the historical success in the commercialization of steroids through such strategies.<sup>72</sup> Prednisone **100** appeared to be a versatile starter unit to us, as it is inexpensive (\$1.2/g) and already contained 70% of the carbosexkeleton of **32**. The principle highlights of our approach include the construction of a “heteroadamantane” core in ring A (see structure **99**, Scheme 11A), the first example of an alcohol-directed geminal-dihalogenation (Scheme 11B), and an isohypsic ring expansion (Scheme 11C) to establish the B-ring with its correct oxidation state.<sup>73</sup> Cortistatinone (**98**) was accessed on multigram scale in 7% overall yield from prednisone in twelve steps. This critical intermediate could be used to access cortistatin A (**32**) and myriad of related analogues.

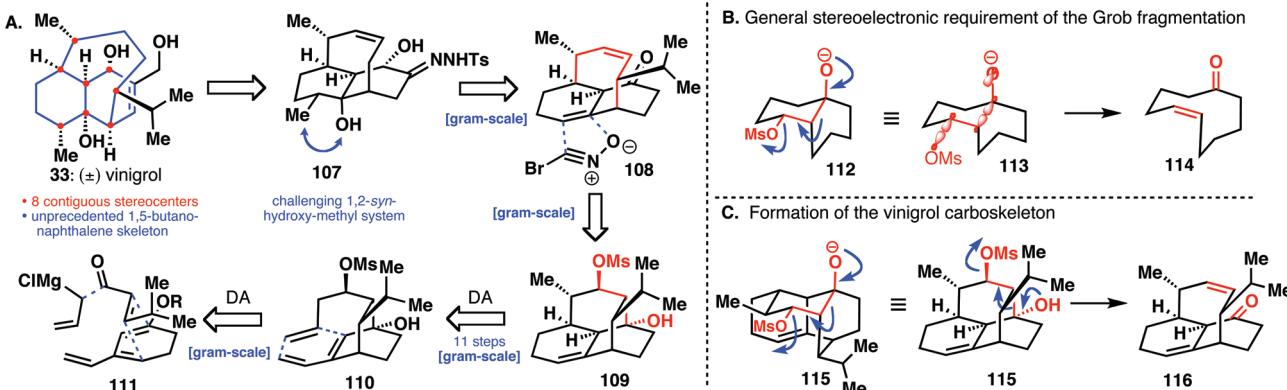
The overall yield was 3% for **32**, with a total of 15 steps, with four construction steps and four strategic oxidations contributing to the 66% ideality of the synthesis. Although the sequence is very short, there is room for improvement. All together five concession steps had to be carried out, one of which was a nonstrategic oxidation, two functional group interconversions, and two protecting group manipulations. Full details of our second-generation route to **32** will be reported in the near future.<sup>70d,74</sup>

### Vinigrol

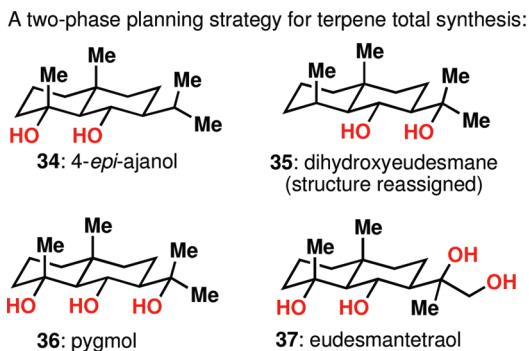
The total synthesis of vinigrol **33** stood as a major challenge in terpene chemistry over the last two decades.<sup>75</sup> The extreme difficulty in preparing this diterpenoid stems from its unprecedented decahydro-1,5-butanonaphthalene ring system, which bears eight contiguous stereogenic centers. Vinigrol can be viewed as a *cis*-decalin system bridged by a four-carbon-atom handle.<sup>76</sup> This makes the structure very rigid and renders any kind of ring closure disfavorable. We therefore envisaged the construction of another readily accessible ring system **109** that could then be fragmented into the vinigrol carbosexkeleton.<sup>77</sup> This progenitor ring system was accessed via two Diels–Alder reactions (**111** → **110** → **109**) as shown in Scheme 12A. Grob fragmentation<sup>78</sup> was planned to occur along the highlighted bonds in **109**, according to the mechanism being depicted in Scheme 12C. For comparison (Scheme 12B), one can see that the stereoelectronic requirements for the Grob fragmentation are perfectly fulfilled, and indeed, the desired transformation proceeded smoothly to give the desired vinigrol skeleton.

With the backbone set in place, the main obstacle to complete the total synthesis of **33** became the installation of the 1,2-*syn*-hydroxymethyl system (shown in **107**). After extensive experimentation, the reaction of *in situ* generated

SCHEME 12. Total Synthesis of Vinigrol



## SCHEME 13. Two-Stage Retrosynthesis for Terpene Total Synthesis



bromonitrile oxide with bis-olefin **108** and concomitant functional group interconversions afforded desired **107**. Up to this point, all reactions were carried out on gram scale, demonstrating the robustness and scalability of the synthetic route. Shapiro reaction of **107** and trapping of the intermediate trianion (double alkoxy plus vinylic anion) with formaldehyde successfully concluded the synthesis of **33**. The synthesis of vinigrol comprises 23 total steps with overall 3% yield.<sup>79</sup> The route suffers from four nonstrategic redox reactions and eight functional group interconversions, but only one protecting group manipulation was carried out. These concession steps are opposed by only seven construction steps and three strategic redox reactions, which results in the relatively low ideality of 43%.<sup>75a,80</sup> Indeed, as will be seen in the following section, our work in the vinigrol arena prompted us to take a step back and question whether there might be a more efficient general strategy for assembling complex terpenes in the laboratory.

#### Chemo- and Site-Selective C–H Oxidation To Access Poly-hydroxylated Terpenoids

On January 12, 2007, we were invited by the editor of *Nature Chemical Biology* to write a review on modern approaches to terpene synthesis.<sup>81</sup> This puzzling invitation (we had only published alkaloid syntheses at that point) was eagerly accepted with the hopes of entering this area and learning about recent trends in the synthesis of such molecules. After pouring through the literature, it became quite clear that the overall modus operandi that chemists use to plan and execute terpene syntheses has not changed over the past several decades. To be sure, organic chemists have become quite adept at building up molecular skeletons but fall short of ideality when functional groups need to be installed. On the other hand, Nature constructs terpenes in two distinct “phases”, referred to as the cyclase and oxidase phases by enzymologists.<sup>82</sup> Inspired by the general biosynthetic terpene pathway, we envisaged a similar two-phase strategic plan, namely the synthesis of a nonoxidized polycyclic precursor, or “cyclase-phase”, and the subsequent selective oxidation of this polycycle, or “oxidase phase” (Scheme 13). As a prelude to more complex terpenes (ingenol and paclitaxel, for instance), we chose the eudesmane terpene family as a proof of principle. In the laboratory, the cyclase phase would take advantage of decades of advances in carbogen construction, whereas the oxidase phase gives one the opportunity to explore fundamental

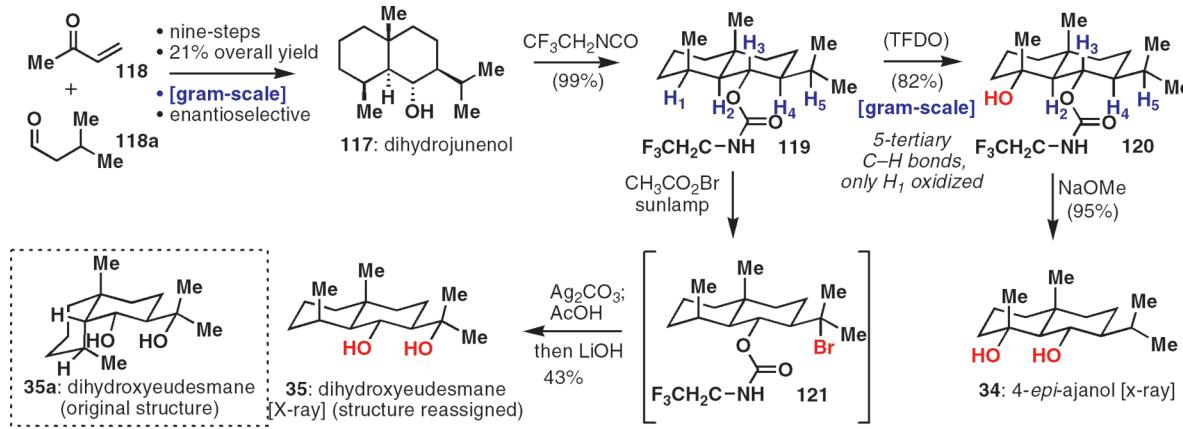
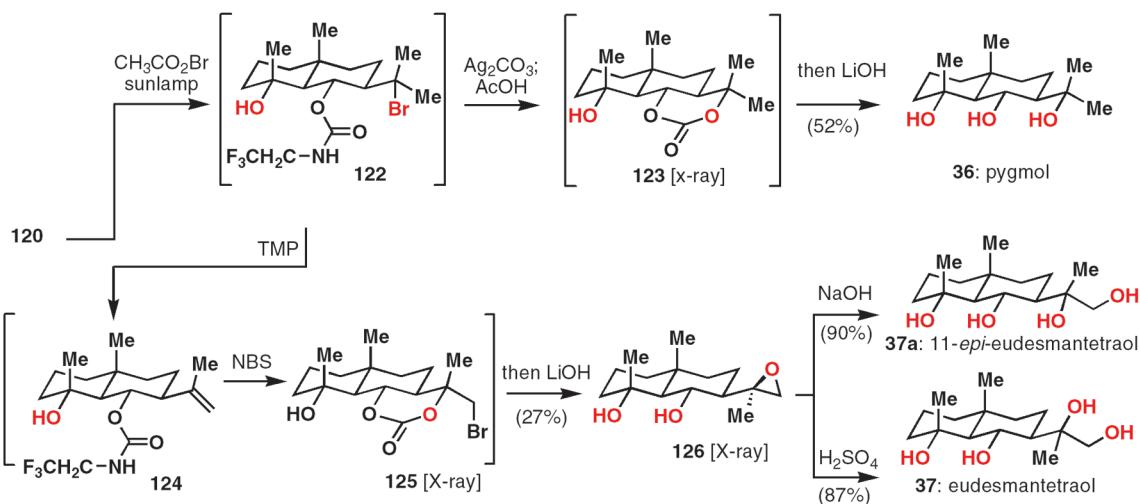
reactivity and invent new methods for selective functionalization of C–H bonds.

Starting from inexpensive and commercially available starting materials (**118a** and **118b**), the enantioselective synthesis of dihydrojunenol **117** was accomplished in nine steps on a gram scale (Scheme 14A).<sup>83,84</sup> 4-*epi*-Ajanol (**34**) and dihydroxyeudesmane (**35**) were targeted first. Both natural products have the same oxidation state (redox isomers), but the position of oxidation differs on the carbon-skeleton, making them ideal test systems for site-selective C–H functionalization. After the trifluoroethyl carbamate directing group was appended onto **117**,<sup>85</sup> adduct **119** was evaluated by X-ray crystallography and NMR spectroscopy to predict the most likely sites of C–H oxidation. Both techniques combined with literature precedence for rapid equatorial C–H oxidation (*vide infra*) pointed to H<sub>1</sub> being oxidized more rapidly with an intermolecular oxidant and H<sub>5</sub> being oxidized under the direction of the trifluoroethyl carbamate group (intramolecular). In accord with this prediction, reaction of methyl(trifluoromethyl)dioxirane (TFDO)<sup>86</sup> with **119** selectively produced compound **120** in very good yields on a gram scale. In contrast, dihydroxyeudesmane (**35**) was accessed by reaction of **119** with acetyl hypobromite, which gave exclusive functionalization of the side chain (H<sub>5</sub>). Conversion of bromide **121** to **35** completed the synthesis. Our NMR data of **35** perfectly matched the isolated material, requiring a structural reassignment of **35a** to **35**, which was supported by single-crystal X-ray analysis.

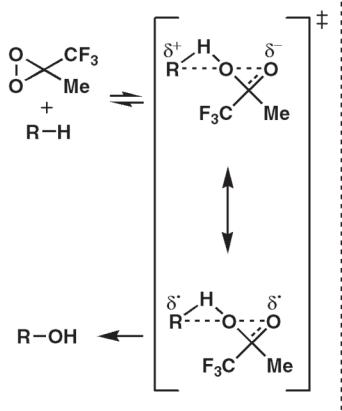
The synthesis of trihydroxylated pygmol (**36**) required an additional C–H-functionalization reaction, which was conducted on 4-*epi*-ajanol precursor **120** using acetyl hypobromite to yield **122** (see Scheme 14B). Conversion to **123** and hydrolysis gave **36** in good yields. For the synthesis of tetrahydroxylated 11-*epi*-eudesmanetetraol (**37a**) and eudesmanetetraol (**37**), epoxide **126** was generated as outlined in Scheme 14B. By either acidic or basic opening of **126**, both natural products were accessed from the same intermediate. It is worth noting that the transformation of **120** to olefin **124** represents a unique example of a formal remote dehydrogenation process. Additionally, if olefin **124** is exposed to Sharpless AD-mix  $\alpha$  or  $\beta$ , a 1:1.5 mixture of **37a**/**37** is obtained, further strengthening the tactical advantage of using a directing group.

To the best of our knowledge, this represents the first example of the use of multiple C–H activation processes to install carbon–oxygen bonds in total synthesis. To summarize, 4-*epi*-ajanol (**34**), dihydroxyeudesmane (**35**), pygmol (**36**), and eudesmanetetraols (**37**) were synthesized in 12,

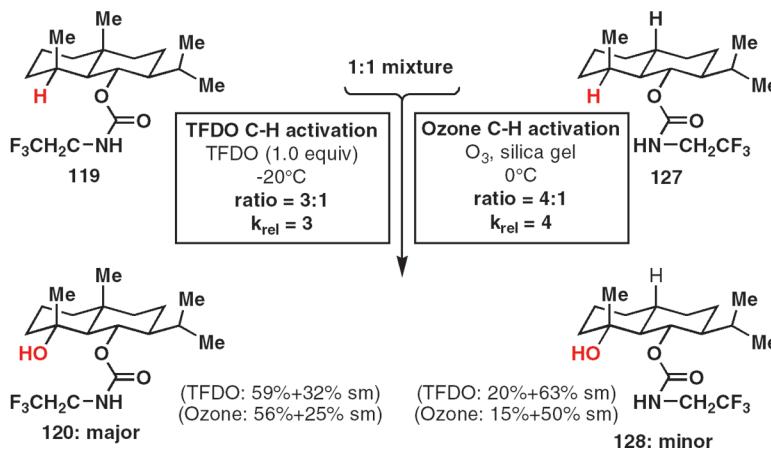
## SCHEME 14. Total Synthesis of Eudesmane Terpenoids Using Site-Selective C–H-Activation Methodology

A. Forward synthetic route to 4-*epi*-ajanol (34) and dihydroxyeudesmane (35)B. Forward synthetic route to pygmol (36), eudesmantetraol (37) and 11-*epi*-eudesmantetraol (37a)

## C. Transition-state model



## D. Strain release phenomenon in tertiary C–H oxidation



12, 13, and 15 steps, with overall yields of 17, 9, 9, and 4%, respectively. As a testament to the underlying logic of this approach, the ideality increased with increasing number of steps starting from 58% ideality for 34 and 35, 62% ideality for 36, and 66% ideality for 37 and 37a. This counterintuitive

increase provides some evidence that C–H activation methodology can indeed contribute to the “economies” of terpene synthesis.

In fact, it has long been appreciated that terpenes, with their diverse oxidation patterns, constitute an ideal playground for

TABLE 1. Overview of the Ideality of the Syntheses Described

natural product	steps	non-strategic redox	PG mani- pulation	FGI	strategic redox	con- struction rxn.	% Ideality
palau'amine ( <b>16</b> )	25	6	4	7	1	7	32
axinellamines ( <b>18</b> )	25	5	5	6	2	7	36
massadines ( <b>17</b> )	25	5	4	7	2	7	36
sceptrin ( <b>19</b> )	11	2	2	3	1	3	36
stephacidin A ( <b>30</b> )	16	1	7	2	0	6	38
avrainingvillamide ( <b>29</b> )	17	1	7	2	1	6	41
kapakahine F( <b>23</b> )	12	1	1	5	0	5	42
ageliferin ( <b>21</b> ) and nagelamide ( <b>20</b> )	12	2	2	3	1	4	42
vinigrol ( <b>33</b> )	23	4	1	8	3	7	43
stephacidin B ( <b>28</b> )	18	1	7	2	1	7	44
chartelline C ( <b>24</b> )	15	3	2	3	2	5	47
haouamine ( <b>31</b> )	12	1	3	2	1	5	50
4- <i>epi</i> -ajanol ( <b>34</b> ), di- hydroxyeudesmane ( <b>35</b> )	12	1	0	4	3	4	58
pygmol ( <b>36</b> )	13	1	0	4	4	4	62
eudesmanetetraol ( <b>37</b> )	15	1	0	4	5	5	66
11- <i>epi</i> -eudesmane- tetraol ( <b>37a</b> )	15	1	0	4	5	5	66
cortistatin A ( <b>32</b> )	15	1	2	2	6	4	66
fischerindole I ( <b>26a</b> )	8	0	0	2	2	4	75
halalindole U ( <b>27a</b> )	4	0	0	1	1	2	75
psychotrimine ( <b>22</b> )	4	1	0	0	0	3	75
welwitindolinone A ( <b>25</b> )	9	0	0	2	3	4	78
ambiguine ( <b>27b</b> )	6	0	0	1	2	3	83

the testing of new selective C–H activation methods.<sup>87</sup> Yet, in order to apply multiple site-selective C–H activation reactions in a synthesis, profound understanding of reactivity trends is required. For instance, the selective oxidation of equatorial C–H bonds over their axial counterparts has been observed for decades, but explanations remain somewhat ambiguous.<sup>88</sup> The eudesmane synthesis prompted us to take a careful look at this phenomenon, specifically the conversion of **119** to **120** (Scheme 14A). On the basis of steric and electronic arguments alone, one might propose that H<sub>5</sub> would react in preference to H<sub>1</sub>, yet the opposite is observed. In our 2009 report, it was hypothesized<sup>83</sup> that such selectivity was due to strain release effects in the transition state during oxidation. As shown in Scheme 14C, a developing positive charge or radical character is observed in the transition state of the TFDO oxidation (this occurs in any reaction of a C–H bond with an electrophilic oxidant).<sup>89</sup> This leads to a bending of the carbon center toward planarity and thus alleviates 1,3 diaxial interactions in the transition state. In collaboration with Professor Albert Eschenmoser, a model system was designed that would provide nearly “unassailable” evidence for a strain-release effect leading to rate acceleration (Scheme 14D).<sup>90</sup> Indeed, model system **127** reacted slower than **119** due to lower ground-state destabilization. Thus, studies on the eudesmanes brought to light strain release as a new reactivity

factor to be considered in planning and understanding the selectivity of C–H activation reactions in complex settings in addition to the well-known effects of steric hindrance and C–H bond nucleophilicity. Time will tell whether the two-phase approach to terpene synthesis will succeed in even more complex settings, and those studies are ongoing in our laboratory.

### Conclusion

“Ideal beauty is a fugitive which is never located.”  
Marquise de Sevigne, Marie de Rabutin-Chantal

Can the same be said for synthesis? Perhaps, but the future of organic synthesis must be in constant search of the ideal synthesis. Efficiency and practicality are the “yardsticks” by which beauty and ideality in synthesis will be judged. The means by which practitioners aim for this goal will differ, but innovation will invariably be the result. “Ideality” in synthesis is only one variable of several that should be considered. It is a useful tool for the purposes of self-reflection and evaluation but NOT an ultimate measure of a synthesis. Although the pursuit of an ideal synthesis may naturally lead to a better route in many instances, certain situations (ease of purifications, inexpensive reagents, higher atom economy,

higher overall yield, etc.) might dictate choosing a path with lower ideality.

In this perspective, we have summarized the past seven years of our own efforts toward ideality in total synthesis (see Table 1 for a numerical summary). Table 1 aims to provide the reader with an overview for estimating the extent that the Hendrickson ideal has been fulfilled for the specific target structures in question. However, as stated previously, it does not provide a method for comparison of syntheses of different target structures because of the strong divergence in their molecular complexity. While attempting to adhere to Hendrickson's vision of an ideal synthesis, we have completed several practical syntheses of complex natural products, along with the discovery of interesting methods, strategies, and fundamental insights into reactivity. We may never achieve a total synthesis characterized by 100% ideality, but such a pursuit serves as a constant source of inspiration.

**Acknowledgment.** This perspective is dedicated to the students and postdoctoral scholars who, through their boundless passion and creativity, have made this research possible (names listed in references). We thank Dr. Shun Su, Dr. Chad A. Lewis, and Jonathan W. Lockner for fruitful discussions and Ian B. Seiple and Dr. Tanja Gulder for assistance with manuscript preparation. We are grateful to Amgen, Bristol-Myers Squibb, Pfizer, Roche, GlaxoSmithKline, Astra Zeneca, Dupont, Searle Foundation, Beckmann Foundation, The Scripps Research Institute, Skaggs Institute for Chemical Biology, the NIH, NSF career, and the Alfred P. Sloan Foundation for funding over the years. The Austrian Science Foundation (FWF) is thanked for a postdoctoral fellowship (J2899) to T.G. The cover artwork was acquired from [http://en.wikipedia.org/wiki/File:Uomo\\_Vitruviano.jpg](http://en.wikipedia.org/wiki/File:Uomo_Vitruviano.jpg).

**Note Added after ASAP Publication.** There were errors in the version published ASAP June 11, 2010. Schemes 2, 3, 14 and Figure 1 were replaced and various text changes were made; the corrected version reposted on June 18, 2010.

## References

- (1) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, 1989. (b) Nicolaou, K. C.; Sorenson, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: Weinheim, New York, 1996; (c) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, 2003; (d) Nicolaou, K. C.; Montagnon, T. *Molecules That Changed the World: A Brief History of the Art and Science of Synthesis and Its Impact on Society*; Wiley: New York, 2008.
- (2) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784.
- (3) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.
- (4) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
- (5) (a) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (c) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197.
- (6) (a) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938. (b) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.
- (7) Such proclamations have been ongoing for decades; see, for example: (a) Service, R. F. *Science* **1999**, *285*, 184. (b) Lowe, D. <http://prospect.rsc.org/blogs/cw/?cat=19>.
- (8) (a) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3. (b) Hudlicky, T.; Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*; Wiley: New York, **2008**; Vol. 130.
- (9) (a) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801. (b) Horvath, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2167. (c) Fuchs, P. L. *Tetrahedron* **2001**, *57*, 6855. (d) Qiu, F. *Can. J. Chem.* **2008**, *86*, 903. (e) For example, chromium trioxide oxidation of a double bond, yielding an  $\alpha,\beta$ -unsaturated ketone, which then has to be reduced to give an allylic alcohol, does not represent a strategic redox reaction, whereas oxidation of the same double bond with selenium dioxide (directly giving the allylic alcohol) does represent a strategic redox reaction.
- (10) (a) Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532. (b) Heathcock, C. H. *Angew. Chem.* **1992**, *104*, 675.
- (11) (a) For further references and reading, see: Baldwin, J. E.; Abraham, E. *Nat. Prod. Rep.* **1988**, *5*, 129. (b) See refs 1 and 3. For additional reviews, see: (c) Kim, J.; Movassagh, M. *Chem. Soc. Rev.* **2009**, *38*, 3035. (d) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000**, *17*, 349.
- (12) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530.
- (13) (a) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376. (b) Kinnel, R. B.; Gehrken, H. P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. (c) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573. (d) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; Van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127. (e) Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320.
- (14) (a) Nishimura, S.; Matsunaga, S.; Shibasaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett.* **2003**, *5*, 2255. (b) Grube, A.; Immel, S.; Baran, P. S.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 6721.
- (15) Urban, S.; Leone, P. D.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731.
- (16) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586.
- (17) Bacon, R. G. R.; Hanna, W. J. *W. J. Chem. Soc.* **1965**, 4962.
- (18) (a) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581. (b) Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maua, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3578.
- (19) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490.
- (20) Aldrich catalog no. 718157
- (21) (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. (b) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551. (c) Weinreb, S. M. *Nat. Prod. Rep.* **2007**, *24*, 931. (d) Arndt, H.-D.; Riedrich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4785. (e) Feldman, K. S.; Fodor, M. D.; Skoumbourdis, A. P. *Synthesis* **2009**, 3162. (f) Heasley, B. *Eur. J. Org. Chem.* **2009**, 1477. (g) Takao, K.-i.; Tadano, K.-i. *Kagaku* **2009**, *64*, 70. (h) Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scclaro, A.; Papeo, G. *Mar. Drugs* **2009**, *7*, 705.
- (22) For other approaches, see: (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319. (b) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535. (c) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880. (d) Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T. *Tetrahedron Lett.* **2002**, *43*, 3699. (e) Poullennec, K. G.; Kelly, A. T.; Romo, D. *Org. Lett.* **2002**, *4*, 2645. (f) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344. (g) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623. (h) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Loewe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203. (i) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559. (j) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.* **2004**, *6*, 735. (k) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679. (l) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 765. (m) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551. (n) Du, H.; He, Y.; Rasapalli, S.; Lovely, C. J. *Synlett* **2006**, 965. (o) Gergely, J.; Morgan, J. B.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 9144. (p) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223. (q) Lanman, B. A.; Overman, L. E. *Heterocycles* **2006**, *70*, 557. (r) Nakadai, M.; Harran, P. G. *Tetrahedron Lett.* **2006**, *47*, 3933. (s) Schroif-Gregoire, C.; Travert, N.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2006**, *8*, 2961. (t) Tan, X.; Chen, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4345. (u) Wang, S.; Dilley, A. S.; Poullennec, K. G.; Romo, D. *Tetrahedron* **2006**, *62*, 7155. (v) Tang, L.; Romo, D. *Heterocycles* **2007**, *74*, 999. (w) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J. *Org. Lett.* **2007**, *9*, 3861. (x) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc.* **2007**, *129*, 12896. (y) Cernak, T. A.; Gleason, J. L. *J. Org. Chem.* **2008**, *73*, 102. (z) Wang, S.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1284. (aa) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8885. (bb) Bultman, M. S.; Ma, J.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6821. (cc) Zancanella, M. A.; Romo, D. *Org. Lett.* **2008**, *10*, 3685. (dd) Sivappa, R.; Mukherjee, S.; Dias, H. V. R.; Lovely, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3215. (ee) Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem.* **2009**, *74*, 5909. (ff) Williams, R. M.; Burnett, C. M. *ACS Symp. Ser.* **2009**, *1009*, 420. (gg) Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.; Tanino, K.; Williams, R. M.; Nishizawa, M. *Chem.—Eur. J.* **2009**, *15*, 6560.
- (23) Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772.
- (24) Endo, T.; Tsuda, M.; Okada, T.; Mitsuhashi, S.; Shima, H.; Kikuchi, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2004**, *67*, 1262.
- (25) (a) Rinchart, K. L. *Pure Appl. Chem.* **1989**, *61*, 525. (b) Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.;

- Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579. (c) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittschof, D.; Rinckart, K. L. *J. Org. Chem.* **1991**, *56*, 2965. (d) Williams, D. H.; Faulkner, D. J. *Tetrahedron* **1996**, *52*, 5381.
- (26) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.
- (27) Baran, P. S.; O'Malley, D. P.; Zografas, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674.
- (28) (a) O'Malley, D. P.; Li, K.; Mauke, M.; Zografas, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 4762. (b) For biological studies of these natural products enabled by gram-scale synthesis, see: Cipres, A.; O'Malley, D. P.; Li, K.; Finlay, D.; Baran, P. S.; Vuori, K. *ACS Chem. Biol.* **2010**, *5*, 195.
- (29) Northrop, B. H.; O'Malley, D. P.; Zografas, A. L.; Baran, P. S.; Houk, K. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 4126.
- (30) Dai, J.; Jimenez, J. I.; Kelly, M.; Williams, P. G. *J. Org. Chem.* **2010**, *75*, 2399.
- (31) Racemic route: Baran, P. S.; Zografas, A. L.; O'Malley, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 3726.
- (32) Enantioselective route: Baran, P. S.; Li, K.; O'Malley, D. P.; Mitsos, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 249.
- (33) For other approaches, see: (a) Hao, E.; Fromont, J.; Jardine, D.; Karuso, P. *Molecules* **2001**, *6*, 130. (b) Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujio, N.; Nikaido, F.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **2002**, *43*, 4377. (c) Pyers, J. I. V.; Warner, J. C.; Cannon, A. S. *Abstracts of Papers*, 225th ACS National Meeting, New Orleans, LA, Mar 23–27, 2003; American Chemical Society: Washington DC, 2003; IEC. (d) Birman, V. B.; Jiang, X.-T. *Org. Lett.* **2004**, *6*, 2369. (e) Kawasaki, I.; Sakaguchi, N.; Khadeer, A.; Yamashita, M.; Ohta, S. *Tetrahedron* **2006**, *62*, 10182. (f) Huijgens, R. W.; Melander, C. *Abstracts of Papers*, 231st ACS National Meeting, Atlanta, GA, Mar 26–30, 2006; American Chemical Society: Washington DC, 2006; ORGN. (g) Tonsiengsom, Ph.D. Thesis, Oregon State University, Corvallis, 2007. (h) Anon. *Chemtracts* **2008**, *21*, 300; (i) Lovely, C. J.; Bhandari, M.; Rasapalli, S. *Abstracts of Papers*, 235th ACS National Meeting, New Orleans, LA, April 6–10, 2008; American Chemical Society: Washington DC, 2008; ORGN. (j) Rajaratnam, M.; O'Doherty, G. A. *Chemtracts* **2009**, *22*, 59. (k) Appenzeller, J.; Tilvi, S.; Martin, M.-T.; Gallard, J.-F.; El-bitar, H.; Dau, E. T. H.; Debitus, C.; Laurent, D.; Moriou, C.; Al-Mourabit, A. *Org. Lett.* **2009**, *11*, 4874. (l) Bhandari, M. R.; Sivappa, R.; Lovely, C. J. *Org. Lett.* **2009**, *11*, 1535.
- (34) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945.
- (35) (a) Nakao, Y.; Yeung, B. K. S.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Am. Chem. Soc.* **1995**, *117*, 8271. (b) Yeung, B. K. S.; Nakao, Y.; Kimmel, R. B.; Carney, J. R.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1996**, *61*, 7168. (c) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *Org. Lett.* **2003**, *5*, 1387.
- (36) For examples, see: (a) Scott, A. I.; McCapra, F.; Hall, E. S. *J. Am. Chem. Soc.* **1964**, *86*, 302. (b) Cheek, G. T.; Nelson, R. F. *J. Org. Chem.* **1978**, *43*, 1230. (c) Balogh-Hergovich, E.; Speier, G. *J. Chem. Soc., Perkin Trans. I* **1986**, 2305. (d) Dryhurst, G. *Chem. Rev.* **1990**, *90*, 795. (e) Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 5637. (f) Ishikawa, H.; Kitajima, M.; Takayama, H. *Heterocycles* **2004**, *63*, 2597.
- (37) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886.
- (38) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137.
- (39) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science: Sausalito, CA, 2004.
- (40) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360.
- (41) For other approaches, see: (a) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125. (b) Espejo, V. R.; Rainier, J. D. *Org. Lett.* **2010**, *12*, 2154.
- (42) (a) Chevrolat, L.; Chevrolat, A. M.; Gajhede, M.; Larsen, C.; Anthoni, U.; Christophersen, C. *J. Am. Chem. Soc.* **1985**, *107*, 4542. (b) Anthoni, U.; Chevrolat, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 4709.
- (43) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714.
- (44) Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028.
- (45) For other approaches, see: (a) Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631. (b) Pinder, J. L.; Weinreb, S. M. *Tetrahedron Lett.* **2003**, *44*, 4141. (c) Korakas, P.; Chaffee, S.; Shotwell, J. B.; Duque, P.; Wood, J. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12054. (d) Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025. (e) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, *33*, 440. (f) Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 3159. (g) Sun, C.; Camp, J. E.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1779. (h) Black, P. J.; Hecker, E. A.; Magnus, P. *Tetrahedron Lett.* **2007**, *48*, 6364. (i) Hecker, E. A. Ph.D. Thesis, University of Austin Texas, 2008. (j) Kajii, S.; Nishikawa, T.; Isobe, M. *Chem. Commun.* **2008**, 3121. (k) Kajii, S.; Nishikawa, T.; Isobe, M. *Tetrahedron Lett.* **2008**, *49*, 594. (l) Sato, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Chem. Commun.* **2009**, 6264.
- (46) (a) Teuscher, E.; Lindequist, U.; Mundt, S. *PZ Wiss.* **1992**, *5*, 57. (b) Avendano, C.; Menendez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65. (c) Klapoetke, T. M.; Goebel, M.; Scheutzw, S.; Boehm, A.; Weis, J. *Nachr. Chem.* **2007**, *55*, 860. (d) Gademann, K.; Portmann, C. *Curr. Org. Chem.* **2008**, *12*, 326. (e) Sanchez, C.; Mendez, C.; Salas, J. A. *Mod. Alkaloids* **2008**, 619.
- (47) For reviews of protecting group free synthesis, see: (a) Hoffmann, R. W. *Synthesis* **2006**, 3531. (b) Young, I. S.; Baran, P. S. *Nature Chem.* **2009**, *1*, 193.
- (48) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450.
- (49) For a full account, see: Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857.
- (50) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.
- (51) For other approaches, see: (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 1815. (b) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331. (c) Muratake, H.; Kumagami, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6351. (d) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6343. (e) Vaillancourt, V.; Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499. (f) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125. (g) Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393. (h) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326. (i) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2000**, *2*, 3517. (j) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001. (k) Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983. (l) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189. (m) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835. (n) Lopez-Alvarado, P.; Garcia-Granda, S.; Alvarez-Rua, C.; Avendano, C. *Eur. J. Org. Chem.* **2002**, *1702*. (o) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120. (p) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovasaka, T. V.; Wood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1270. (q) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087. (r) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421. (s) Banwell, M. G.; Ma, X.; Taylor, R. M.; Willis, A. C. *Org. Lett.* **2006**, *8*, 4959. (t) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643. (u) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287. (v) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448. (w) Chandra, A.; Viswanathan, R.; Johnston, J. N. *Org. Lett.* **2007**, *9*, 5027. (x) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovasaka, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087.
- (52) (a) von Nussbaum, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3068. (b) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160. (c) Nising, C. F. *Chem. Soc. Rev.* **2010**, *39*, 591.
- (53) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 606.
- (54) Baran, P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3892.
- (55) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678.
- (56) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083.
- (57) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.
- (58) For an improved procedure, see: Hafensteiner, B. D.; Escribano, M.; Petricci, E.; Baran, P. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3808.
- (59) For other approaches, see: (a) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329. (b) Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1970**, 1103. (c) Baldas, J.; Birch, A. J.; Russell, R. A. *J. Chem. Soc., Perkin Trans. I* **1974**, *50*. (d) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. (e) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *Tetrahedron* **1993**, *49*, 8471. (f) Domingo, L. R.; Sanz-Cervera, J. F.; Williams, R. M.; Picher, M. T.; Marco, J. A. *J. Org. Chem.* **1997**, *62*, 1662. (g) Williams, R. M.; Sanz-Cervera, J. F.; Sancenon, F.; Marco, J. A.; Halligan, K. M. *Bioorg. Med. Chem.* **1998**, *6*, 1233. (h) Sanz-Cervera, J. F.; Williams, R. M.; Alberto Marco, J.; Maria Lopez-Sanchez, J.; Gonzalez, F.; Eugenia Martinez, M.; Sancenon, F. *Tetrahedron* **2000**, *56*, 6345. (i) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1675. (j) Jin, S.; Wessig, P.; Liebscher, J. *J. Org. Chem.* **2001**, *66*, 3984. (k) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1296. (l) Myers, A. G.; Herzon, S. B. *J. Am. Chem. Soc.* **2003**, *125*, 12080. (m) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078. (n) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (o) Adams, L. A.; Gray, C. R.; Williams, R. M. *Tetrahedron Lett.* **2004**, *45*, 4489. (p) Grubbs, A. W.; Artman, G. D.; Williams, R. M. *Tetrahedron Lett.* **2005**, *46*, 9013. (q) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342. (r) Pichowicz, M.; Simpkins, N. S.; Blake, A. J.; Wilson, C. *Tetrahedron Lett.* **2006**, *47*, 8413. (s) Greshock, T. J.; Grubbs, A. W.; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2262. (t) Wulff, J. E.; Herzon, S. B.; Siegrist, R.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 4898. (u) Greshock, T. J.; Williams, R. M. *Org. Lett.* **2007**, *9*, 4255. (v) Pichowicz, M.; Simpkins, N. S.; Blake, A. J.; Wilson, C. *Tetrahedron* **2008**, *64*, 3713. (w) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573. (x) Frebault, F. C.; Simpkins, N. S. *Abstracts of Papers*, 236th ACS National Meeting, Philadelphia, PA, Aug 17–21, 2008; American Chemical Society: Washington, DC, 2008; CHED.
- (60) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204.

- (61) For other examples, see: (a) Justus, K.; Herrmann, R.; Klammann, J.-D.; Gruber, G.; Hellwig, V.; Ingerl, A.; Polborn, K.; Steffan, B.; Steglich, W. *Eur. J. Org. Chem.* **2007**, 5560. (b) Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. *Angew. Chem., Int. Ed.* **2009**, 48, 6870. (c) Laurindo de Oliveira, P.; Tanaka, C. M. A.; Kato, L.; da Silva, C. C.; Previato Medina, R.; Moraes, A. P.; Sabino, J. R.; de Oliveira, C. M. A. *J. Nat. Prod.* **2009**, 72, 1195. (d) Yoshinari, T.; Ohmori, K.; Schrems, M. G.; Pfaltz, A.; Suzuki, K. *Angew. Chem., Int. Ed.* **2010**, 49, 881.
- (62) Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J. *J. Org. Chem.* **2003**, 68, 293.
- (63) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, 128, 3908.
- (64) Burns, N. Z.; Jessing, M.; Baran, P. S. *Tetrahedron* **2009**, 65, 6600.
- (65) Belostotskii, A. M. *J. Org. Chem.* **2008**, 73, 5723.
- (66) Burns, N. Z.; Krylova, I. N.; Hannoush, R. N.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, 131, 9172.
- (67) Matsuo, J.-I.; Iida, D.; Tatami, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, 75, 223.
- (68) Burns, N. Z.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, 47, 205.
- (69) For other approaches, see: (a) Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, 7, 4309. (b) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, 8, 23. (c) Jeong, J. H.; Weinreb, S. M. *Org. Lett.* **2006**, 8, 2309. (d) Wipf, P.; Furegati, M. *Org. Lett.* **2006**, 8, 1901. (e) Gravel, E.; Poupon, E.; Hocquemiller, R. *Chem. Commun.* **2007**, 719. (f) Liang, G., **2007**; (g) Fürstner, A.; Ackerstaff, J. *Chem. Commun.* **2008**, 2870. (h) Okano, K. *Yuki Gosei Kagaku Kyokaishi* **2008**, 66, 387. (i) Taniguchi, T.; Zaimoku, H.; Ishibashi, H. *J. Org. Chem.* **2009**, 74, 2624.
- (70) (a) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, 128, 3148. (b) Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsukikawa, K.; Yamamoto, H.; Kobayashi, M. *Bioorg. Med. Chem.* **2007**, 15, 6758. (c) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, 48, 4485. (d) Sato, Y.; Kamiyama, H.; Usui, T.; Saito, T.; Osada, H.; Kuwahara, S.; Kiyota, H. *Biosci. Biotechnol. Biochem.* **2008**, 72, 2992. (e) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, 63, 4074.
- (71) Cee, V. J.; Chen, D. Y. K.; Lee, M. R.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2009**, 48, 8952.
- (72) (a) Djerassi, C. *Steroids* **1984**, 43, 351. For reviews on semisynthesis of steroids, see: (b) Cabaj, J. E.; Kairys, D.; Benson, T. R. *Org. Process Res. Dev.* **2007**, 11, 378. (c) Hanson, J. R. *Nat. Prod. Rep.* **2007**, 24, 1342. (d) Nising, C. F.; Bräse, S. *Angew. Chem., Int. Ed.* **2008**, 47, 9389.
- (73) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, 130, 7241.
- (74) For other approaches, see: (a) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, 49, 5931. (b) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, 49, 6610. (c) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, 49, 6613. (d) Kotoku, N.; Sumii, Y.; Hayashi, T.; Kobayashi, M. *Tetrahedron Lett.* **2008**, 49, 7078. (e) Kurti, L.; Czako, B.; Corey, E. J. *Org. Lett.* **2008**, 10, 5247. (f) Lee, H. M.; Nieto-Oberhuber, C.; Shirai, M. D. *J. Am. Chem. Soc.* **2008**, 130, 16864. (g) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2008**, 47, 7310. (h) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, 47, 6650. (i) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, 10, 3413. (j) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, 11, 5394. (k) Dai, M.; Danishefsky, S. J. *Heterocycles* **2009**, 77, 157. (l) Harmata, M.; Calkins, N. L. *Chemtracts* **2009**, 22, 182. (m) Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun.* **2009**, 662. (n) Magnus, P.; Littich, R. *Org. Lett.* **2009**, 11, 3938. (o) Shoji, M. *Yuki Gosei Kagaku Kyokaishi* **2009**, 67, 949. (p) Yamashita, S.; Kitajima, K.; Iso, K.; Hirama, M. *Tetrahedron Lett.* **2009**, 50, 3277. (q) Nicolaou, K. C.; Peng, X.-S.; Sun, Y.-P.; Polet, D.; Zou, B.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2009**, 131, 10587. (r) Simmons, E. M.; Hardin-Narayan, A. R.; Guo, X.; Sarpong, R. *Tetrahedron* DOI:10.1016/j.tet.2010.01.030.
- (75) For reviews, see: (a) Tessier, G.; Barriault, L. *Org. Prep. Proced. Int.* **2007**, 39, 311. (b) Lu, J.-Y.; Hall, D. G. *Angew. Chem., Int. Ed.* **2010**, 49, 2286.
- (76) (a) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, 52, 5292. (b) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, 41, 25.
- (77) Maimone, T. J.; Voica, A.-F.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, 47, 3054.
- (78) Prantz, K.; Mulzer, J. *Chem. Rev.* DOI: 10.1021/cr900386h.
- (79) Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, 131, 17066.
- (80) For other approaches, see: (a) Devaux, J. F.; Hanna, I.; Lallemand, J. Y.; Prange, T. *J. Org. Chem.* **1993**, 58, 2349. (b) Guevel, R. Ph.D. Thesis, The Ohio State University, 1994. (c) Mehta, G.; Reddy, K. S. *Synlett* **1996**, 625. (d) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prange, T. *J. Chem. Res., Synop.* **1996**, 32. (e) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (f) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1997**, 62, 5062. (g) Kito, M.; Sakai, T.; Shirahama, H.; Miyashita, M.; Matsuda, F. *Synlett* **1997**, 219. (h) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, 55, 14369. (i) Gentric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, 5, 1139. (j) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, 68, 6096. (k) Morency, L.; Barriault, L. *Tetrahedron Lett.* **2004**, 45, 6105. (l) Morency, L.; Barriault, L. *J. Org. Chem.* **2005**, 70, 8841. (m) Paquette, L. A.; Efremov, I. *J. Org. Chem.* **2005**, 70, 510. (n) Paquette, L. A.; Efremov, I.; Liu, Z. *J. Org. Chem.* **2005**, 70, 505. (o) Paquette, L. A.; Liu, Z.; Efremov, I. *J. Org. Chem.* **2005**, 70, 514. (p) Souweha, M. S.; Enright, G. D.; Fallis, A. G. *Org. Lett.* **2007**, 9, 5163. (q) Grise, C. M.; Tessier, G.; Barriault, L. *Org. Lett.* **2007**, 9, 1545. (r) Morton, J. G. M.; Kwon, L. D.; Freeman, J. D.; Njardarson, J. T. *Synlett* **2009**, 23. (s) Morton, J. G. M.; Kwon, L. D.; Freeman, J. D.; Njardarson, J. T. *Tetrahedron Lett.* **2009**, 50, 1684. (t) Morton, J. G. M.; Draghici, C.; Kwon, L. D.; Njardarson, J. T. *Org. Lett.* **2009**, 11, 4492. (u) Harmata, M.; Calkins, N. L. *Chemtracts* **2009**, 22, 205. (v) Gentric, L.; Le Goff, X.; Ricard, L.; Hanna, I. *J. Org. Chem.* **2009**, 74, 9337. (w) Crowe, W. E.; Wang, D. *Abstracts of Papers*, 239th ACS National Meeting, San Francisco, CA, Mar 21–25, 2010; American Chemical Society: Washington DC, 2010; ORGN.
- (81) Maimone, T. J.; Baran, P. S. *Nature Chem. Bio.* **2007**, 3, 396.
- (82) (a) Ruzicka, L. *Experientia* **1953**, 9, 357. (b) Davis, E. M.; Croteau, R. *Top. Curr. Chem.* **2000**, 209, 53. (c) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, 88, 3011. (d) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, 105, 4730.
- (83) Chen, K.; Baran, P. S. *Nature* **2009**, 459, 824.
- (84) Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* DOI:10.1016/j.tet.2010.02.088.
- (85) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, 130, 7247.
- (86) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, 22, 205.
- (87) (a) Barton, D. H. R., Ed. *Reason and Imagination: Reflections on Research in Organic Chemistry: Selected Papers of Derek H. R. Barton*; World Scientific: River Edge, NJ, 1996; (b) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437. (c) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, 417, 507. (d) Dyker, G., Ed. *Handbook of C–H Transformations*; Wiley-VCH: Weinheim, 2005; Vols. 1–3. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, 62, 2439. (f) Godula, K.; Sames, D. *Science* **2006**, 312, 67. (g) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, 451, 417. (h) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, 48, 5094.
- (88) For selected examples, see: (a) Varkony, H.; Pass, S.; Mazur, Y. *J. Chem. Soc., Chem. Commun.* **1974**, 437. (b) Schneider, H. J.; Mueller, W. *J. Org. Chem.* **1985**, 50, 4609. (c) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, 111, 6749. (d) Likhotvorik, I. R.; Yuan, K.; Brown, D. W.; Krasutskii, P. A.; Smyth, N.; Jones, M., Jr. *Tetrahedron Lett.* **1992**, 33, 911. (e) Chen, K.; Que, L., Jr. *J. Am. Chem. Soc.* **2001**, 123, 6327. (f) Gomez, L.; Garcia-Bosch, I.; Company, A.; Benet-Buchholz, J.; Polo, A.; Sala, X.; Ribas, X.; Costas, M. *Angew. Chem., Int. Ed.* **2009**, 48, 5720.
- (89) Du, X.; Houk, K. N. *J. Org. Chem.* **1998**, 63, 6480.
- (90) Chen, K.; Eschenmoser, A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, 48, 9705.