Volume 31 | Number 4 | April 2014 | Pages 403–606

NPR

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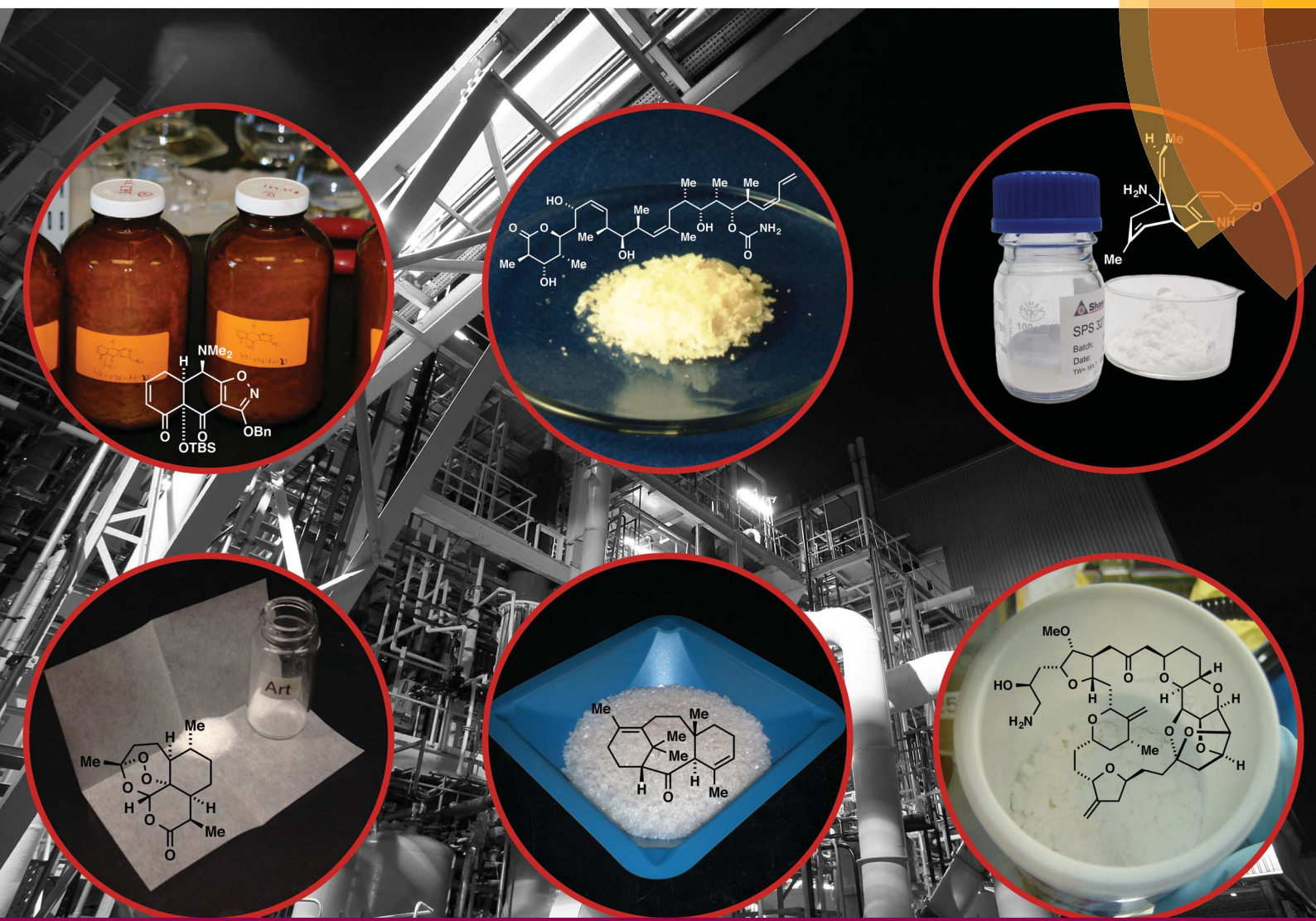

Themed issue: Natural Product Synthesis

ISSN 0265-0568

ROYAL SOCIETY OF CHEMISTRY

HIGHLIGHT

Phil S. Baran *et al.*

Natural product synthesis in the age of scalability

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HIGHLIGHT

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Natural product synthesis in the age of scalability

Cite this: *Nat. Prod. Rep.*, 2014, **31**, 419

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Received 9th September 2013

DOI: 10.1039/c3np70090a

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The ability to procure useful quantities of a molecule by simple, scalable routes is emerging as an important goal in natural product synthesis. Approaches to molecules that yield substantial material enable collaborative investigations (such as SAR studies or eventual commercial production) and inherently spur innovation in chemistry. As such, when evaluating a natural product synthesis, scalability is becoming an increasingly important factor. In this *Highlight*, we discuss recent examples of natural product synthesis from our laboratory and others, where the preparation of gram-scale quantities of a target compound or a key intermediate allowed for a deeper understanding of biological activities or enabled further investigational collaborations.

1 Introduction

Predicting the future can be a precarious undertaking. In many fields of scientific inquiry, it is often serendipitous discoveries that guide an area in a new direction. In other cases, the rediscovery of a known yet underappreciated observation can catalyze investigations into a new area. In contemplating the future of natural product synthesis, it seems apparent that the age of practicality is beginning to dawn. Retrospectively, the field has gone through eras that demonstrated proof-of-concept (urea), biomimicry (tropinone, *daphniphyllium* alkaloids), feasible complexity (strychnine, vitamin B-12, erythronolide), programmability (prostaglandins, ginkgolide), and finally in pushing the limits of chemical synthesis (palytoxin, erythropoietin).[1] From a view of 20,000 feet, the awe-inspiring progress of the field—going from natural products like urea and acetic acid to calicheamicin and taxol in 170 years—has led to a troubling perception by those outside the field that synthesis has reached a state of maturity, with only incremental advances to be had.[2] In reality, this vibrant field is still full of unique opportunities that can have a direct impact on the well-being of both organic chemistry and mankind as a whole.

With the demonstrated ability to prepare highly complex molecules, the most obvious 'next' direction for this field is not the synthesis of complex natural products as an end unto itself, but rather the procurement of tangible and meaningful quantities of these systems within the constraints of an academic setting. Over time, the community has come to recognize this as the next frontier and concepts such as "economies" of synthesis[3] and aiming for "ideality"[4] by avoiding protecting groups[5] or functional group manipulations (C–H functionalization[6]) have become increasingly important during the planning and execution of a synthesis. However, this "awakening" among those that practice natural product synthesis is nothing new for those working in process departments in industry, where the requirement of scalability often results in a dramatic magnification of complexity. Indeed, remarkable and inspirational feats of brilliance take place on a daily basis in companies that manufacture medicines, agrochemicals, and other society-enhancing materials on the metric-ton scale, though these efforts are usually described in the quiet storm of the patent literature. In this article, we highlight recent examples from our laboratory and others, where the primary goal of a complex natural product synthesis program is to achieve a scalable preparation of a target, or perhaps even a potential blueprint for commercial scale production.

The importance of considering 'accessibility' can be correlated to the dramatic rise of interest in the applications of fullerene chemistry; this only occurred *after* a scalable method was invented for their preparation.[7] In a similar vein, the discovery of a workable approach to construct a natural product of limited availability can only be viewed as the first step (*i.e.*, demonstration of feasibility) if real-world applications of a natural product (*i.e.*, potential in pharmaceutical, agrochemical, and flavor industries) can actually be sought. Learning from the molecules of nature, both in terms of function (biology) and structure (SAR) requires gram quantities of a compound – a goal sometimes remised in synthesis efforts. The goal of scalability, which may be seen as a constraint, can act as inspiration for exceptional creativity when integrated into the planning of a natural product synthesis.

It is clear that there are many inherent advantages to approaching natural product synthesis with scalability in mind, but how does one define scalability? Scalability (or even an assessment of commercial viability) is a summation of many weighted factors, for example: (1) step count; (2) the level of

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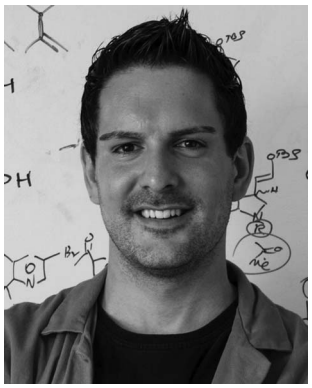
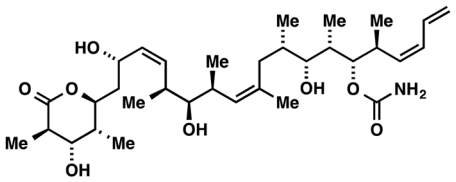
complexity of chemistry used; (3) stereochemical complexity and control; (4) chemical stability of each process and intermediate; (5) overall yield; and (6) operational complexities (such as dilution, isolation, and purification). The relative weighting given to each of these factors is a feature of the environment (culture) of the organization doing the assessment, the projected amount to be produced (grams, kilograms or metric tons), and the magnitude of the problem being addressed (as a guide to potential return on investment). A classic example of a scalable total synthesis that solved a major supply issue is that of (+)-discodermolide (**1**). This polyketide, originally isolated in minute quantities from a deep-sea sponge, was a promising drug candidate for the treatment of cancer. However, its clinical evaluation was hampered by a lack of material, which motivated many groups to pursue its total chemical synthesis. In a landmark achievement, that has already been reviewed elsewhere,[8] Stuart Mickel and his team at Novartis[9] finally succeeded in synthesizing 60 g of **1**, (Scheme 1), by taking inspiration from previous work of the Marshall,[10] Smith,[11] and Paterson[12] groups.



Dr Christian A. Kuttruff was born in 1984 in Donaueschingen, Germany and received a B. Sc. in chemistry from the Technical University of Munich in 2006. After having conducted his M. Sc. research at Harvard University with Professor Tobias Ritter, he moved back to Germany where he completed his Ph.D. in organic chemistry under the supervision of Professor Dirk Trauner, at the University of Munich. Supported by a Feodor Lynen research fellowship, he is currently pursuing postdoctoral research with Professor Phil S. Baran at The Scripps Research Institute (TSRI), focusing on the synthesis of ingenol and analogs thereof.

Dr Martin D. Eastgate was born in England in 1977 and received his undergraduate degree from the University of Surrey in 1999. After completing Ph.D. studies at the University of Cambridge (UK) in 2002, working with Dr Stuart Warren, he moved to the University of Illinois at Urbana-Champaign to conduct postdoctoral research with Prof. Scott E. Denmark. Martin began his career at Bristol-Myers Squibb in 2005 and is currently a Senior Principal Scientist in Chemical Development.



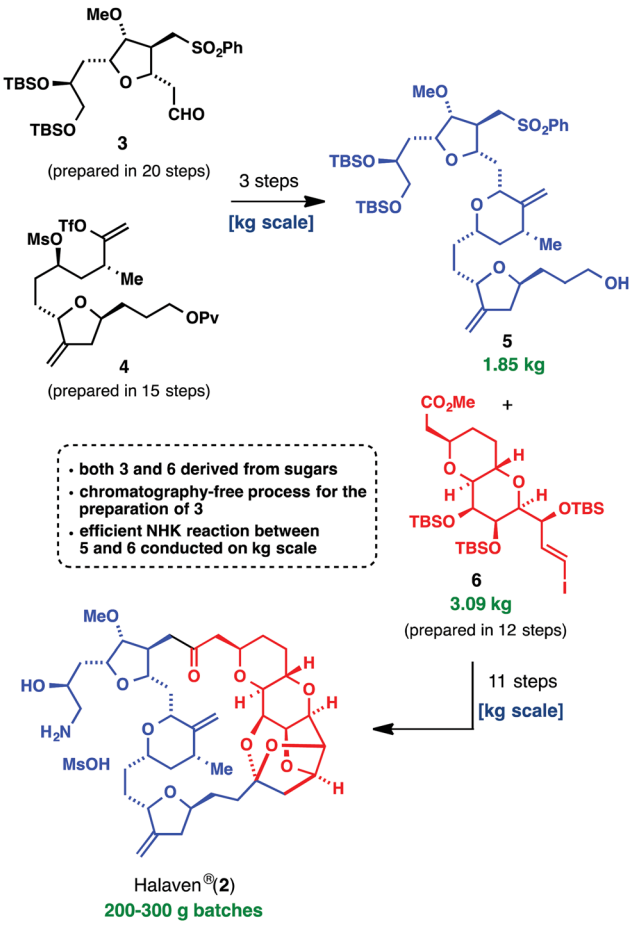
(+)-discodermolide (**1**)
60 g prepared

Scheme 1 The Novartis synthesis of (+)-discodermolide (**1**) overcame a major supply issue.

The most awe-inspiring example of a positive tangible outcome from the combination of basic research into the synthesis of a system, and a correctly weighted assessment of 'scalability', is Halaven®[13] (**2**, E7398, INN eribulin mesylate). Most chemists in industry and academia alike would have considered using total synthesis to support clinical development and commercialization of this compound a 'fool's errand,' but the Kishi group and Eisai Inc. did not.[14] The fact is that this compound solves a major clinical problem, so taking on the issues (length of synthesis, stability limitations, stereochemical problems, *etc.*) had a big payoff (reducing the relative weighting or importance of these factors in assessing the viability of a commercial chemical synthesis). As depicted in Scheme 2, a highly convergent approach, combined with powerful methodology for stitching together key fragments **5** and **6** (Nozaki–Hiyama–Kishi (NHK) coupling) and a strategy of targeting crystalline intermediates were all key elements that culminated in this landmark accomplishment.[15]

In the context of this *Highlight*, scalability in an academic setting refers to the formation of gram-scale quantities of the final product or an advanced key intermediate (that can diverge to analogs). Thus, the route should be viable to address real biological and structural questions, such as preparing enough material for *in vivo* testing and extensive SAR studies. Although a gram-scale synthesis does not guarantee that the process would be scalable in an industrial setting, targeting such

Prof. Phil S. Baran was born in New Jersey in 1977 and received his undergraduate education from NYU with Professor David I. Schuster in 1997. After earning his Ph.D. with Professor K. C. Nicolaou at The Scripps Research Institute (TSRI) in 2001, he pursued postdoctoral studies with Professor E. J. Corey at Harvard until 2003, at which point he began his independent career at TSRI, rising to the rank of Professor in 2008. His laboratory is dedicated to the study of fundamental organic chemistry through the auspices of natural product total synthesis.



Scheme 2 The commercial synthesis of Halaven® (**2**), a landmark achievement in process chemistry.

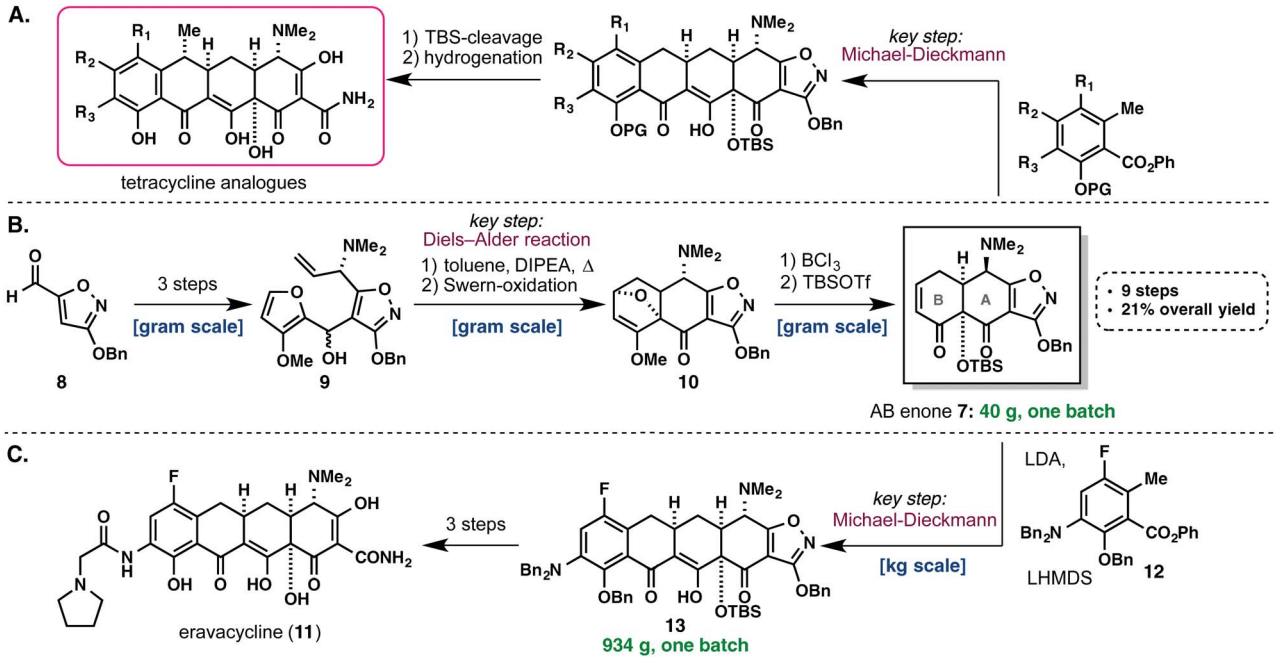
quantities in an academic environment (*i.e.*, a minimal amount of labor) is still several orders of magnitude above the norm in the field. From an industrial perspective, scaling up a route that has already delivered gram quantities of material is more likely to require only process and engineering improvements rather than a complete revision of the synthetic strategy. The goal of scalability can spur retrosynthetic creativity and act as a truer test of the strategy being demonstrated. For true applicability and to answer important questions such as bioactivity, making the bonds of a molecule may no longer be enough justification for embarking on a synthesis. Below, we describe some recent highlights of scalable natural product synthesis emerging from our laboratory and others.

2 Discussion

2.1 Recent syntheses from various groups

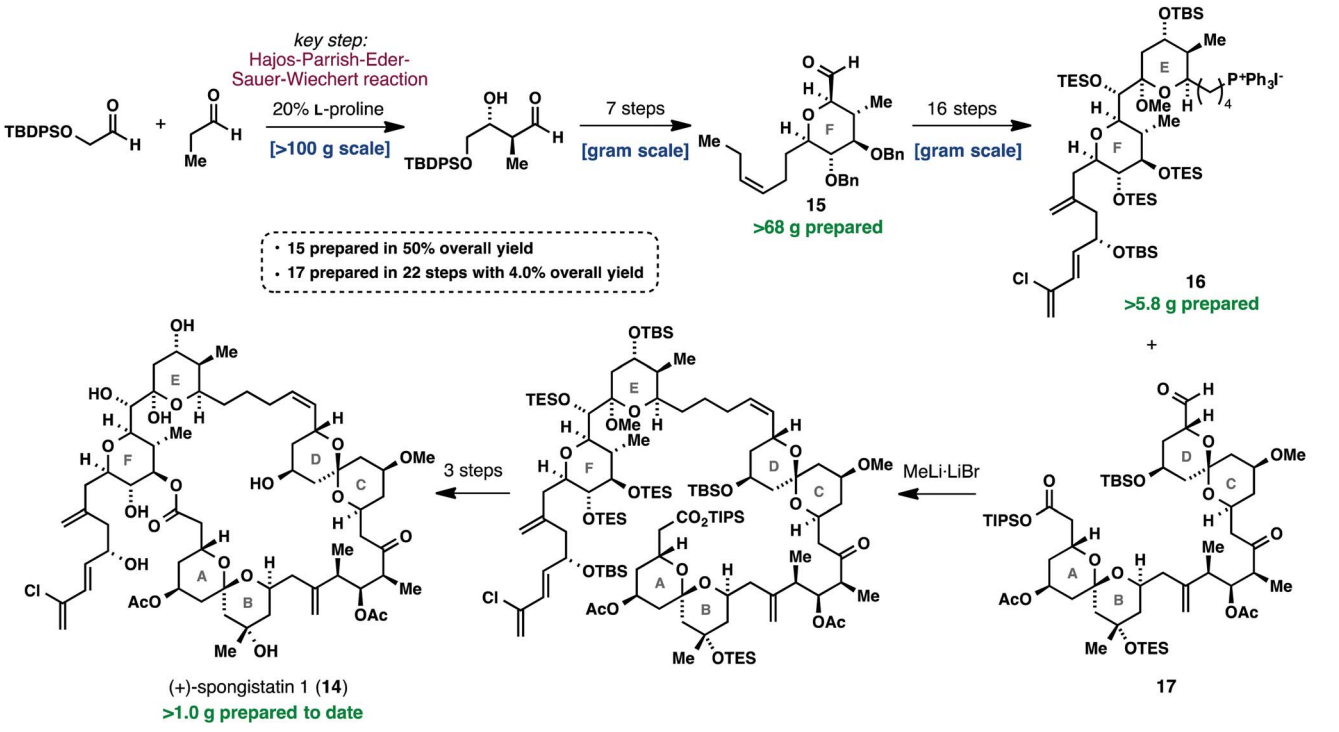
2.1.1 Tetracycline (Myers/Tetraphase, 2005–2013). Myers' convergent approach to the tetracyclines is a great example of how a scalable synthesis of a key intermediate *en route* to a natural product can fuel the discovery of entirely new drug candidates. These broad-spectrum polyketide antibiotics have been widely used in human and veterinary medicine, but, due to the development of tetracycline-resistant strains, there is an unmet need for novel tetracycline drugs. Pioneering work in this field has been achieved by the Myers' group, who published a landmark synthetic approach to the tetracycline class of antibiotics in 2005.[16] Using this route, over 3,000 fully synthetic tetracyclines have been prepared to date. Central to their strategy was the synthesis of a highly versatile intermediate, AB enone **7**,[17] which enabled the convergent construction of novel tetracycline antibiotics (Scheme 3, A).[18] Naturally, the route to **7** had to be practical and amenable to large-scale synthesis and consequently, the synthetic approaches to this building block have become more and more practical and efficient with every new generation. In 2007, Myers published their first practical and enantioselective approach to **7** (Scheme 3, B).[17] The route started from **8**, which can be accessed in multi-hundred gram amounts from commercially available 3-hydroxy-5-iso-xazolecarboxylate (not shown) by *O*-benzylation followed by DIBAL reduction. In a three-step sequence, **8** was transformed into carbinol **9**. In the key step of the sequence, **9** underwent an intramolecular Diels–Alder reaction to give a mixture of 4 diastereomeric cycloadducts, which, after Swern oxidation, could be readily separated by flash column chromatography to afford **10**. Finally, boron trichloride mediated opening of the oxabicyclic ring system and demethylation, followed by TBS protection of the tertiary hydroxyl-group, afforded 40 g of the AB enone **7** in 21% overall yield, over nine steps from commercial material. Slight modifications of this route have allowed for the preparation of >20 kg batches of the AB enone. The availability of large-scale batches of **7** has both enabled the discovery and the development of eravacycline (**11**), the first fully synthetic tetracycline analog in clinical development, from Tetraphase Pharmaceuticals. In their process route,[19] the key Michael–Dieckmann cyclization between **7** and **12** was carried out on kg-scale and afforded **13** in 93.5% yield. This compound was transformed into eravacycline (**11**) in 3 more steps, including TBS-cleavage, hydrogenolysis and amide bond formation. Using this process, several kg of **11** have been prepared to date to support clinical studies. Finally, a third- and fourth-generation route to **7** has recently been published by Myers that is not only shorter than previous routes, but also amenable of structural modifications of the AB-ring enone.[20]

2.1.2 Spongistatin 1 (Smith, 2008). A classic example of a natural product that displays remarkable biological activity, but where its development as a drug is clearly hampered by material availability, is (+)-spongistatin 1 (**14**).[21] This macrolide is one of the most potent tumor cell growth inhibitors discovered to date and numerous research groups from various disciplines have studied this fascinating molecule. Its potency is only surpassed by its scarcity: only 35 mg of (+)-spongistatin 1 (**14**) out of 13 tons (!) of wet sponge had been isolated by the Pettit group. Although several research groups have successfully accomplished a total synthesis of **14**[22]—each of them a seminal achievement—none of them were short and scalable enough to provide gram quantities of spongistatin 1 (**14**) until 2008, when Smith's group reported the first gram-scale synthesis of **14**[23] (Scheme 4). One major difficulty in Smith's earlier efforts was the lack of a large-scale access to the F-ring fragment **15**;



Scheme 3 A. Myers' approach to fully synthetic tetracycline analogues; B. Practical route to the key AB enone; C. Process route to the fully synthetic fluorocycline antibiotic eravacycline (**11**).

however, the group eventually overcame this problem in their third-generation synthesis, that commenced with an intermolecular Hajos–Parrish–Eder–Sauer–Wiechert reaction.[24] With over 68 g of **15** in hand, the synthesis of the EF Wittig salt **16** was addressed, following a previously reported 16-step sequence[25] to provide >5.8 g of the target fragment. The completion of the third-generation route to spongistatin 1 (**14**) required four more steps, including a Wittig union of the EF-fragment **16** with aldehyde **17**, selective deprotection of the TES ethers and TIPS esters, Yamaguchi macrolactonization and global deprotection.



Scheme 4 Smith's gram-scale synthesis of (+)-spongistatin 1 (**14**).

Using this route, a total of 1.009 g of (+)-spongistatin 1 (**14**) was prepared in 31 steps (longest linear sequence based on the EF fragment), with an overall yield of 3.1%, thus allowing for further SAR studies.[26]

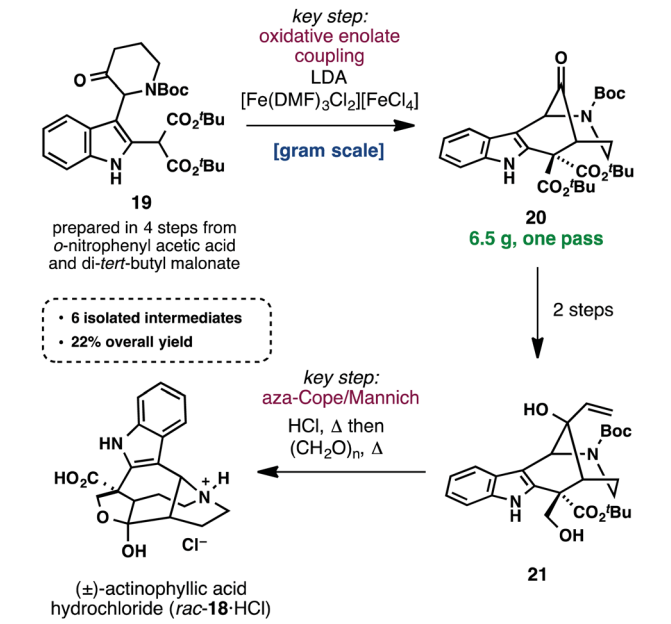
2.1.3 Actinophyllic acid (Overman, 2010). Actinophyllic acid (**18**) is an indole alkaloid that was isolated from the leaves of the tree *Alstonia actinophylla* in 2005 by Carroll *et al.* as part of a program aiming at the identification of potential lead candidates for the treatment of cardiovascular disorders.[27] It was found to be a potent inhibitor of carboxypeptidase U (CPU), an enzyme involved in the blood fibrinolysis process. Due to its intriguing structure and promising biological activity, **18** has found wide interest among the synthesis community.[28]

Besides a very recent synthesis by Martin and coworkers[29] that hinges on a cascade reaction to efficiently build a central precursor, leading to actinophyllic acid (**18**) and related analogs, the strategy of Overman[30] still remains unique in its elegance and brevity. His second-generation synthesis of **18** is shown in Scheme 5 and starts from ketone **19**, which was rapidly prepared on a multigram-scale in 4 steps, from commercially available starting materials (not shown). In the first key step of the synthesis, treatment of **19** with LDA and a preformed iron complex under optimized conditions effected an oxidative dienolate coupling[31] to afford **20** on scales up to 10 g. The tetracyclic ketone **20** was next elaborated to hydroxy ester **21** in two steps. In the second key step, exposure of this intermediate to 5 N HCl, followed by reaction with paraformaldehyde at elevated temperatures promoted deprotection and an aza-Cope/Mannich reaction. This afforded *rac*-actinophyllic acid (**18**) in 22% overall yield, in a sequence that proceeds *via* only six isolated intermediates.

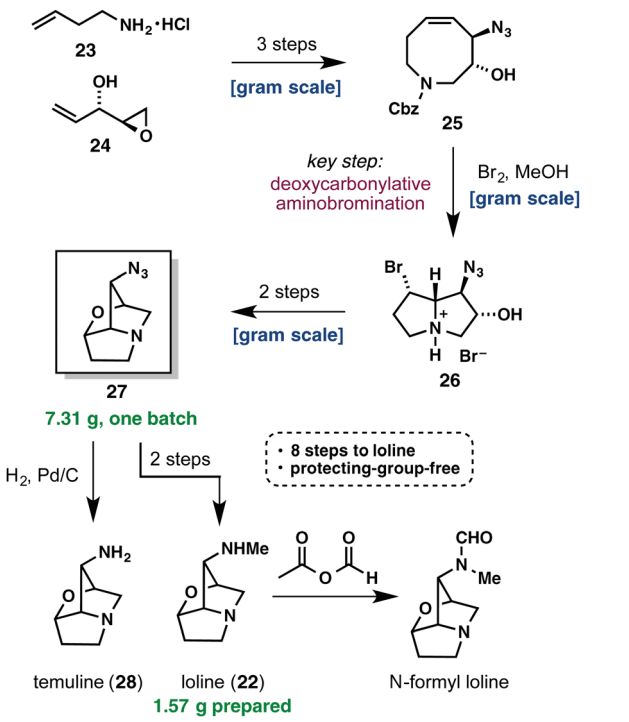
2.1.4 Loline (Trauner, 2011). An example of how a scalable and practical total synthesis evolved from a demand of material from other research areas is Trauner's synthesis of loline (**22**). This small alkaloid belongs to the family of 1-aminopyrrolizidines (or lolines), which were isolated over a century ago from tall fescue grass.[32] The loline alkaloids are produced by endophytic fungi and appear to provide chemoprotection to their plant hosts, mainly due to their insecticidal activities. They have been the subject of various biological studies, but many aspects of their chemical ecology are still not fully understood. The absence of an efficient chemical synthesis of loline (**22**), together with the request of biologists for investigational supplies, motivated Trauner's group to develop a short and scalable total synthesis of loline alkaloids (Scheme 6).[33]

Their synthesis starts from commercially available butenylamine **23** and the known chiral epoxy alcohol **24**. In the streamlined version of the synthesis, these building blocks are transformed into the eight-membered azido alcohol **25**. In the key step of the synthesis, treatment of **25** with bromine in methanol triggers a deoxycarbonylative aminobromination, to give bicyclic pyrrolizidinium **26**. A subsequent Finkelstein reaction and a Williamson ether synthesis yielded the heterotricyclic core of the loline alkaloids. More than 7 g of azide **27** were prepared and served as the branching point for the synthesis of various loline alkaloids, including 1.57 g of loline (**22**) itself.[34] This short and scalable approach enabled the production of sufficient quantities of loline alkaloids for the investigation of the biological role of loline alkaloids by several of the group's collaborators.

2.1.5 Huperzine A (Herzon, 2011; Shasun Pharma Solutions Limited, 2012). (−)-Huperzine A (**29**) is a quinolizidine alkaloid that can be isolated from various *Huperzia* species. It has been used for centuries in traditional Chinese medicine, mainly for the treatment of schizophrenia, fever, blood



Scheme 5 Overman's efficient synthesis of (±)-actinophyllic acid (**18**).



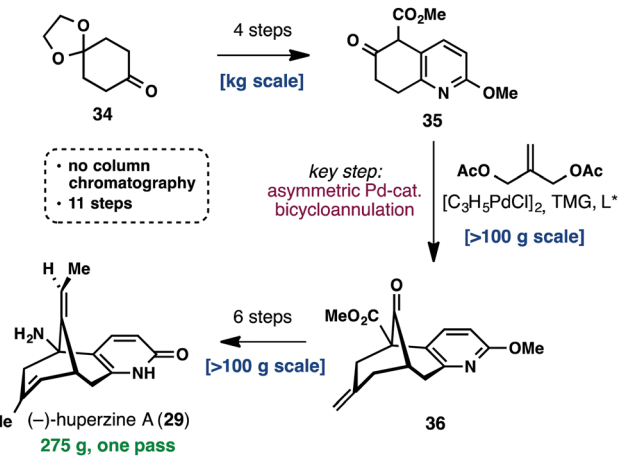
Scheme 6 Trauner's scalable synthesis of loline alkaloids.

disorders and loss of memory.[35] As one of the most potent and selective acetylcholinesterase inhibitors and NMDA receptor antagonists, (−)-huperzine A (**29**) also possesses neuroprotective properties and is currently being investigated as a promising candidate for the treatment of Alzheimer's disease. Unfortunately, there is a lack of supply of natural (−)-huperzine A (**29**), due to its low-yielding extraction (100 kg of dried plant yield 10 g of **29**) and the limited supply of the plant (which requires 20 years to reach maturity). Consequently, there has been a need for a scalable and cost-effective total synthesis of (−)-huperzine A (**29**), to support current biological investigations.

In 2011, the group of Seth Herzon published a scalable synthesis of (−)-huperzine A (**29**) that is depicted in Scheme 7.[36] The starting point of their synthesis was chiral cyclohexenone **30** and dihalopyridine **31**, which were converted into cyanoketone **32** in two steps. **32** was then subjected to a carefully optimized palladium-catalyzed intramolecular enolate heteroarylation, the key step of the sequence. The cyclized product **33** was finally transformed into 1.6 g of (−)-huperzine A (**29**) in a five-step sequence. The synthesis proceeded in only eight steps and in 35–45% overall yield.

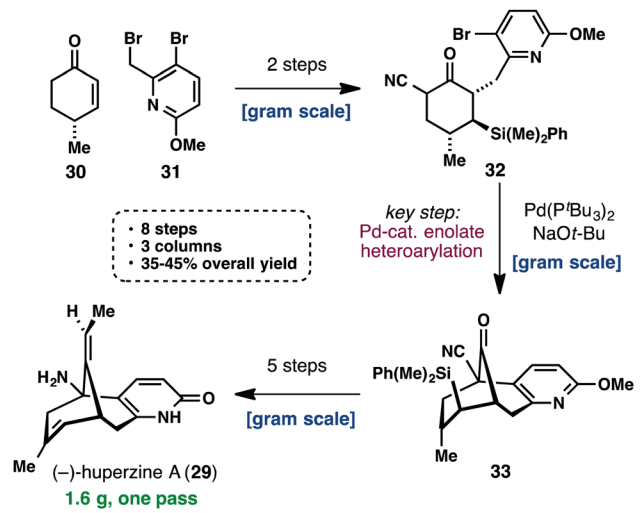
Shortly after Herzon's report, Shasun Pharma Solutions Ltd. published a large-scale route to (−)-huperzine A (**29**) that could be performed safely and economically on an industrial scale.[37] The reported process, shown in Scheme 8, required 11 chemical steps and drew inspiration from Xia and Kozikowski's previous approach.[38] It starts from commercially available 1,4-cyclohexanedione monoethylene ketal (**34**), which was transformed into tetrahydroquinalone intermediate **35** in four steps. The subsequent asymmetric palladium-catalyzed bicycloannulation of β-ketoester **35** to **36** was carried out under optimized conditions.

The conversion of compound **36** into (−)-huperzine A (**29**) required six more steps. Using this route, 275 g of (−)-huperzine A (**29**) were synthesized under cGMP conditions. Notably, all the reactions were carried out on a kilo- or decagram-scale in a chromatography-free process that is capable of providing large quantities of (−)-huperzine A (**29**) for the pharmaceutical or nutraceutical industries.

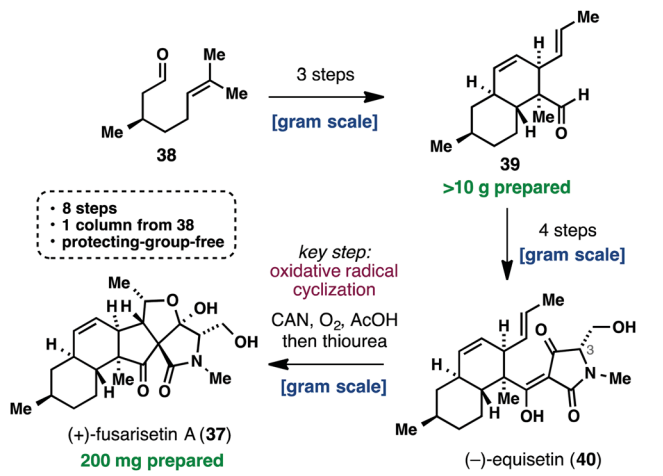


Scheme 8 Large-scale route to (−)-huperzine A (**29**) developed by Shasun Pharma Solutions Ltd. (TMG = tetramethylguanidine, L* = ligand).

2.1.6 Fusarisetin A (Theodorakis, 2012). Fusarisetin A (**37**) is a fungal metabolite that was isolated in 2011 from the soil fungus *Fusarium* sp. FN080326 and reported to exhibit fascinating biological activities, including the inhibition of acinar morphogenesis, cell migration, and cell invasion in MDA-MB-231 breast cancer cells, without displaying any significant cytotoxicity.[39] Thus, this compound has spurred considerable interest amongst scientists, and several groups have succeeded in the total synthesis of both (−)-fusarisetin A (not shown) and (+)-fusarisetin A (**37**).[40] Theodorakis recently published an optimized route to (+)-fusarisetin (**37**) that is scalable and provided enough material for further biological studies (Scheme 9).[41] Their synthesis started from (*R*)-citronellal (**38**), which was rapidly and stereoselectively transformed into aldehyde **39** on a decagram scale. A four-step sequence, consisting



Scheme 7 A scalable synthesis of (−)-huperzine A (**29**) by Herzon.



Scheme 9 Theodorakis' scalable total synthesis of (+)-fusarisetin A (**37**).

of a Reformatsky reaction, DMP oxidation, aminolysis and Dieckmann condensation furnished a 1 : 1 mixture of (−)-equisetin (**40**) and C3-*epi*-equisetin (not shown). This mixture was then subjected to a bio-inspired oxidative radical cyclization under optimized conditions, to build the *trans*-decalin moiety present in (+)-fusarisetin A (**37**). The implementation of this key step was essential for the success of the synthetic strategy and allowed for the preparation of 200 mg of the natural product. The synthetic sequence proceeded without protecting groups, in only 8 steps and 5% overall yield, requiring only one chromatographic purification. The prepared material allowed for further investigations on the bioactivity of **37**, demonstrating its potential as a lead structure for new inhibitors of cancer metastasis.[41]

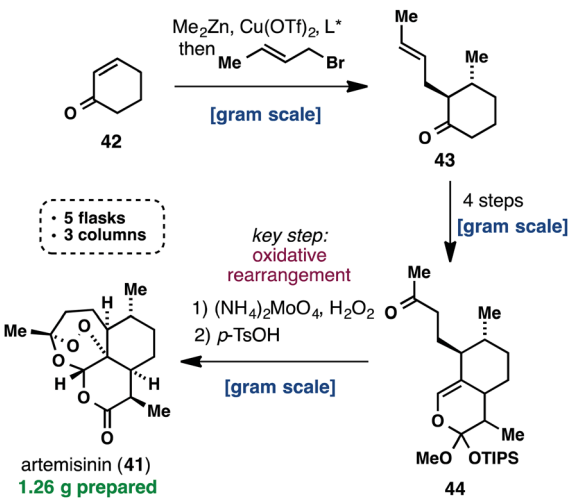
2.1.7 Artemisinin (Cook, 2012). (+)-Artemisinin (**41**) is currently the most effective drug against *Plasmodium falciparum* malaria as part of an artemisinin-based combination therapy (ACT).[42] Although it can be isolated on an industrial scale from *Artemisia annua*, the market price of artemisinin (**41**) has fluctuated widely and traditional extraction does not provide enough material to meet the worldwide demand. Interestingly, recent efforts towards a cheaper and more efficient production of artemisinin (**41**) have mainly taken place in the areas of synthetic biology,[43] semisynthesis[44] and plant engineering,[45] while there has been a lack of practical approaches using a straightforward total synthesis. Despite the fact that all the total syntheses of artemisinin, until 2010,[46] were impressive from a feasibility point of view, none of them provided a solution for the low-cost synthesis of **41**. This changed when Cook's group recently published a scalable synthesis of artemisinin (**41**), which provides a blueprint for the cost-effective production of **41** and its derivatives (Scheme 10).[47] Key to their successful strategy was the use of reaction cascades that rapidly built complexity, starting from the cheap feedstock chemical, cyclohexenone (**42**). The latter was first subjected to a one-pot conjugate addition/alkylation sequence, to give ketone **43**. A three-step sequence consisting of formylation, cycloaddition and a Wacker-type oxidation, yielded 9.4 g of methyl ketone **44**.

The challenging formation of the unusual peroxide bridge was initially met with failure, but was eventually realized by a reaction with singlet oxygen to give **41** amongst other oxidized intermediates. The entire synthetic sequence was conducted on a gram scale, required only three chromatographic purifications and was carried out in only five flasks. Considering the low cost of the commodity chemicals used and the conciseness of Cook's synthesis, it is certainly worth being further investigated.

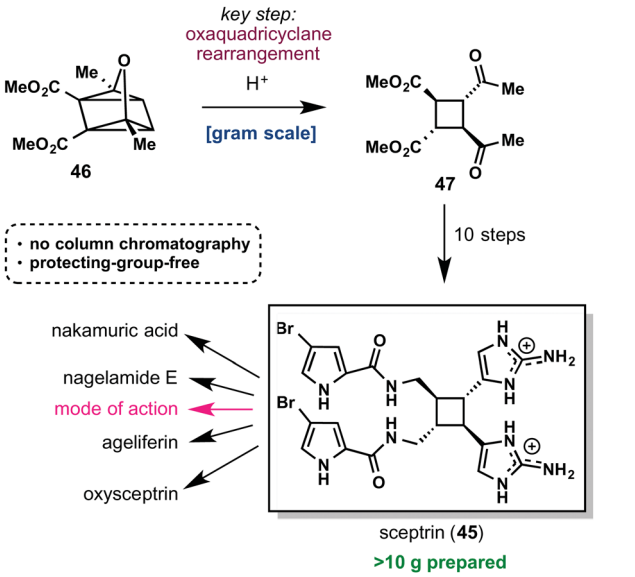
2.2 Total syntheses from the Baran group

2.2.1 Sceptrin (2004). One of the earliest examples of how a scalable total synthesis from our laboratory enabled novel biological insights is sceptrin (**45**), a pyrrole–imidazole alkaloid, isolated in 1981 from *Agelas sceptrum*.[48] It is of considerable pharmaceutical interest, since it exhibits a broad array of biological activities, including antibacterial/antifungal, anti-muscarinic, anti-histaminic and anti-HIV activity. Its inhibitory activity on somatostatin also renders it a potential treatment for cystic fibrosis and Alzheimer's disease. We developed a practical, short and high-yielding synthesis of **45**, as summarized in Scheme 11.[49] The sequence starts with a rare fragmentation of oxiquadricyclane **46** to rapidly build the all-*trans* tetrasubstituted cyclobutane core present in **45**. A 10-step sequence gave access to more than 10 g of sceptrin (**45**). The material that was prepared not only served as a synthetic precursor to other alkaloids (nakamuric acid, nagelamide E, ageliferin and oxysceptrin; structures not shown), but also enabled a collaboration with the Vuori group at the Sanford–Burnham Institute. The Vuori group subsequently found that sceptrin (**45**) is also able to inhibit cell motility—a feature that could be harnessed to treat aggressive tumors.[50]

2.2.2 Psychotrimine (2008) and Kapakahine F (2009). Psychotrimine (**48**) was isolated in 2004 from the leaves of the South American shrub *Psychotria rostrata*, with no reported bioactivity.[51] When we first engaged in the total synthesis of



Scheme 10 Cook's scalable route to (+)-artemisinin (**41**).

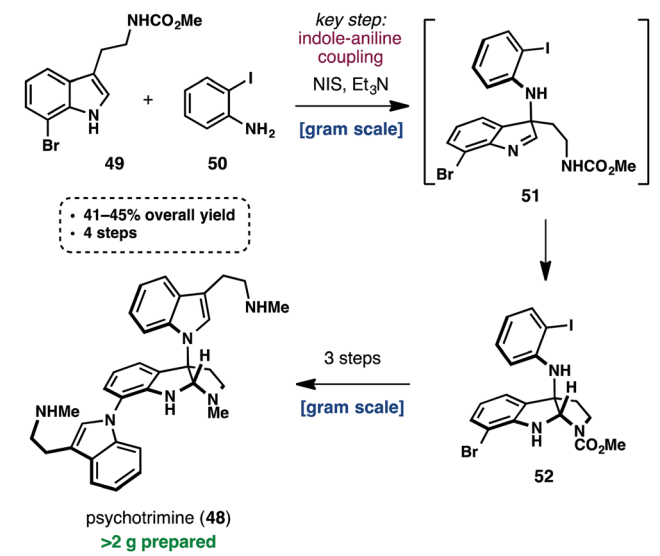


Scheme 11 Short and scalable total synthesis of sceptrin (**45**).

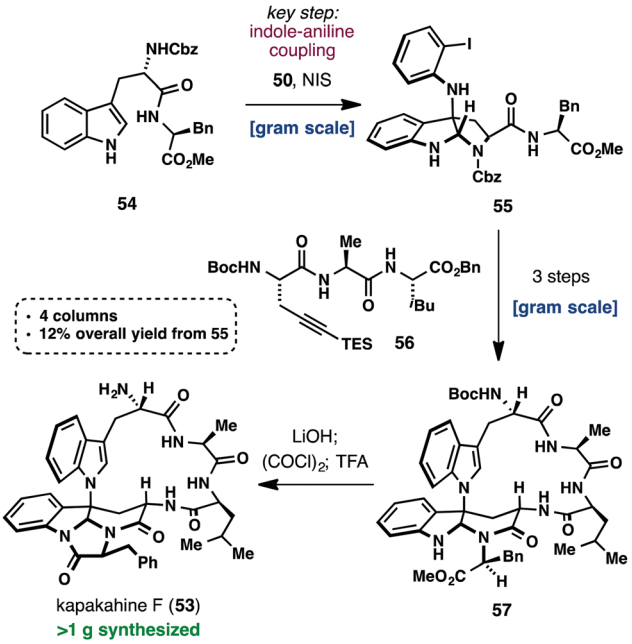
48,[52] no methodology was available for the direct coupling of indoles and anilines to afford the peculiar N1–C3 linkage (indole nomenclature) present in **48**. After extensive investigations, a new method for the oxidative C–N bond formation between indoles and anilines was found. Thus, treatment of the readily available tryptamine **49** with 2-iodoaniline (**50**) and *N*-iodosuccinimide (NIS) gave (*via* intermediate **51**) pyrroloindoline **52** (Scheme 12). Conversion of **52** to the target required only three more steps and provided over 2 g of psychotrimine (**48**), in an overall yield of 41–45%. With ample quantities of **48** available through this synthesis, we initiated a fruitful collaboration with the Romesberg group. It was found that **48** disrupts the cytoplasmic membranes of both Gram-negative and Gram-positive bacteria, resulting in reasonably potent antibacterial activity.[53] These findings might also explain why such alkaloids are manufactured by plants as part of their defense mechanism.

Having established a powerful methodology to construct the N1–C3 connection present in **48**, we next targeted kapakahine F (**53**), a heptacyclic peptide with an intriguing structure that exhibits the same type of linkage.[54] Considering its scarcity (only 0.8 mg of **53** were isolated from 4.0 kg of sponge material) and the lack of understanding of its bioactivity and mode of action, we developed a scalable route that is depicted in Scheme 13.[52b,55]

In analogy to the synthesis of **48**, the route to kapakahine F (**53**) started with the formation of the N1–C3 linkage by subjecting the protected dipeptide **54** and iodoaniline (**50**) to NIS, to yield the coupling product **55**. Next, Larock annulation with tripeptide **56** followed by reductive cleavage of the Cbz-group afforded a mixture of amino acids (not shown), which after EDC/HOAt coupling afforded the macrocycle **57**. Finally, basic hydrolysis of the methyl ester **57**, followed by imidizolone formation afforded >1 g of kapakahine F (**53**) in 12% overall yield (starting from **54**). Notably, all but the last step were carried out on a gram-scale and only 4 column chromatography events were required.



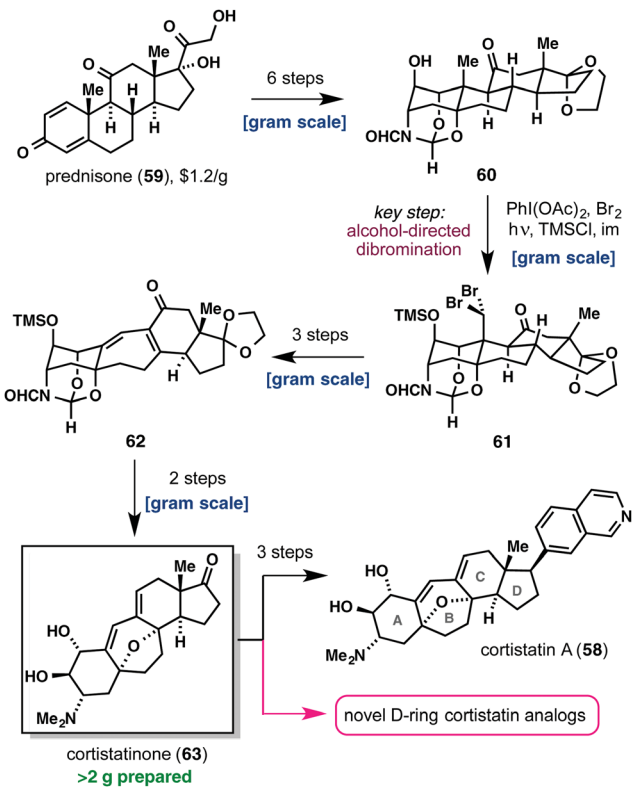
Scheme 12 Gram-scale synthesis of psychotrimine (**48**).



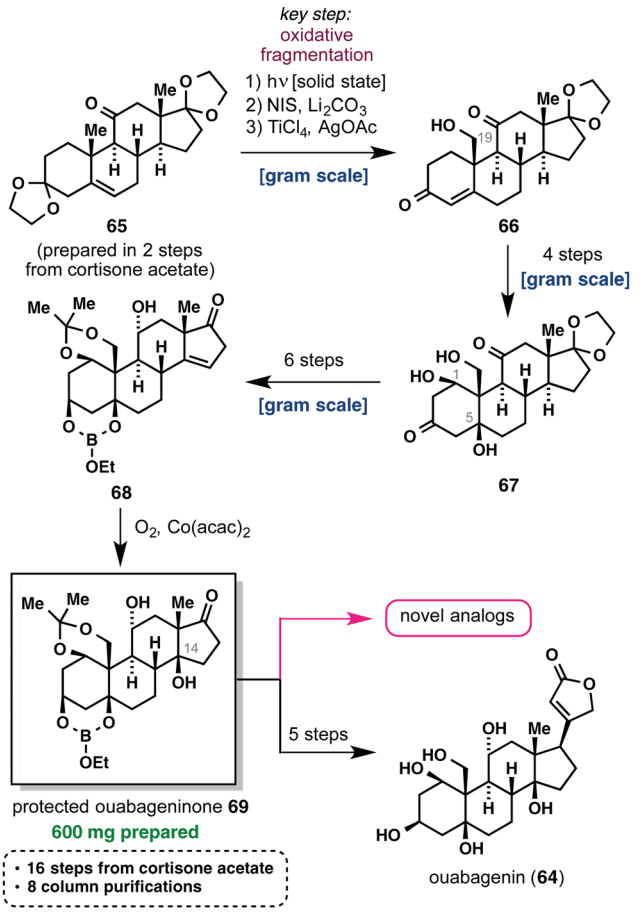
Scheme 13 Scalable total synthesis of kapakahine F (**53**).

Having solved the material supply problem of **53** with our synthesis, the compound (and its SAR) is currently being studied in collaboration with a pharmaceutical company.

2.2.3 Cortistatin A (2008). The cortistatins belong to a family of marine 9-(10,19)-*abeo*-androstane steroids that were



Scheme 14 Synthesis of (+)-cortistatin A (**58**).

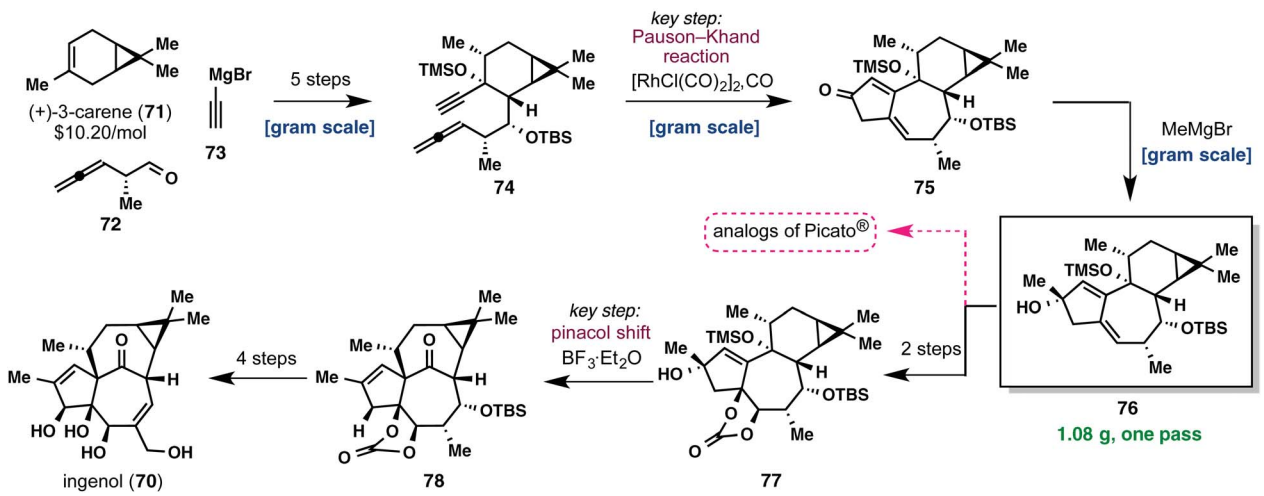


Scheme 15 Scalable synthesis of ouabagenin (**64**).

isolated from the sponge *Corticium simplex* in 2006.[56] They immediately attracted wide attention due to their potent anti-angiogenic properties, rendering them promising therapeutics to combat tumor progression. We selected (+)-cortistatin A (**58**), the most highly functionalized and potent member of the family, as a target and developed a scalable synthesis that was amenable to the generation of analogs (Scheme 14).[57]

Aiming for an economically feasible synthesis, a semi-synthetic approach was chosen. Prednisone (**59**) was selected as the starting material, mainly due to its low cost ($1.2/g) and the fact that it contains 70% of the carbon atoms present in **58**. In the forward direction, **59** was transformed into **60** in six steps. In one of the key steps of the sequence, the treatment of **60** with $PhI(OAc)_2$ and bromine under photochemical irradiation effected the first alcohol-directed, geminal dihalogenation of an unactivated methyl group to date. Compound **61** was then elaborated in five steps and in gram scale to cortistatinone (**63**), the key intermediate and branching point of the synthesis. Cortistatinone (**63**) was finally converted into (+)-cortistatin A (**58**) and a variety of analogs (not shown) that were subsequently tested for bioactivity. The ready availability of synthetic analogs enabled by this synthesis has led to a number of collaborations with both pharmaceutical companies and academic groups.

2.2.4 Ouabagenin (2013). Ouabagenin (**64**) is a polyhydroxylated steroid and belongs to the family of cardenolides.[58] Along with other bioactive steroids, such as digoxin and digitoxin, its parent glycoside, ouabain,[59] is used in the treatment of congestive heart failure. Due to the complex structure of **64**, novel heterocyclic analogs thereof, with improved properties (*e.g.*, broader therapeutic index) are largely inaccessible. In collaboration with Leo Pharma, the Baran group has engaged in a *de novo* synthesis of **64** that, *via* the intermediacy of a diversifiable intermediate, would allow for the synthesis of new analogs of **64**.[60] Considering the scalability and economical feasibility, we planned a semi-synthetic route, that would follow a quasi-biomimetic oxidation strategy (relaying both stereochemical and redox information where possible) and would start from cheap and abundant cortisone acetate. The latter was converted to protected adrenosterone **65** in two steps (Scheme 15). In the first redox-relay event of our synthesis, a solid-state Norrish type I reaction, followed by a reagent-controlled oxidative fragmentation of the formed cyclobutane

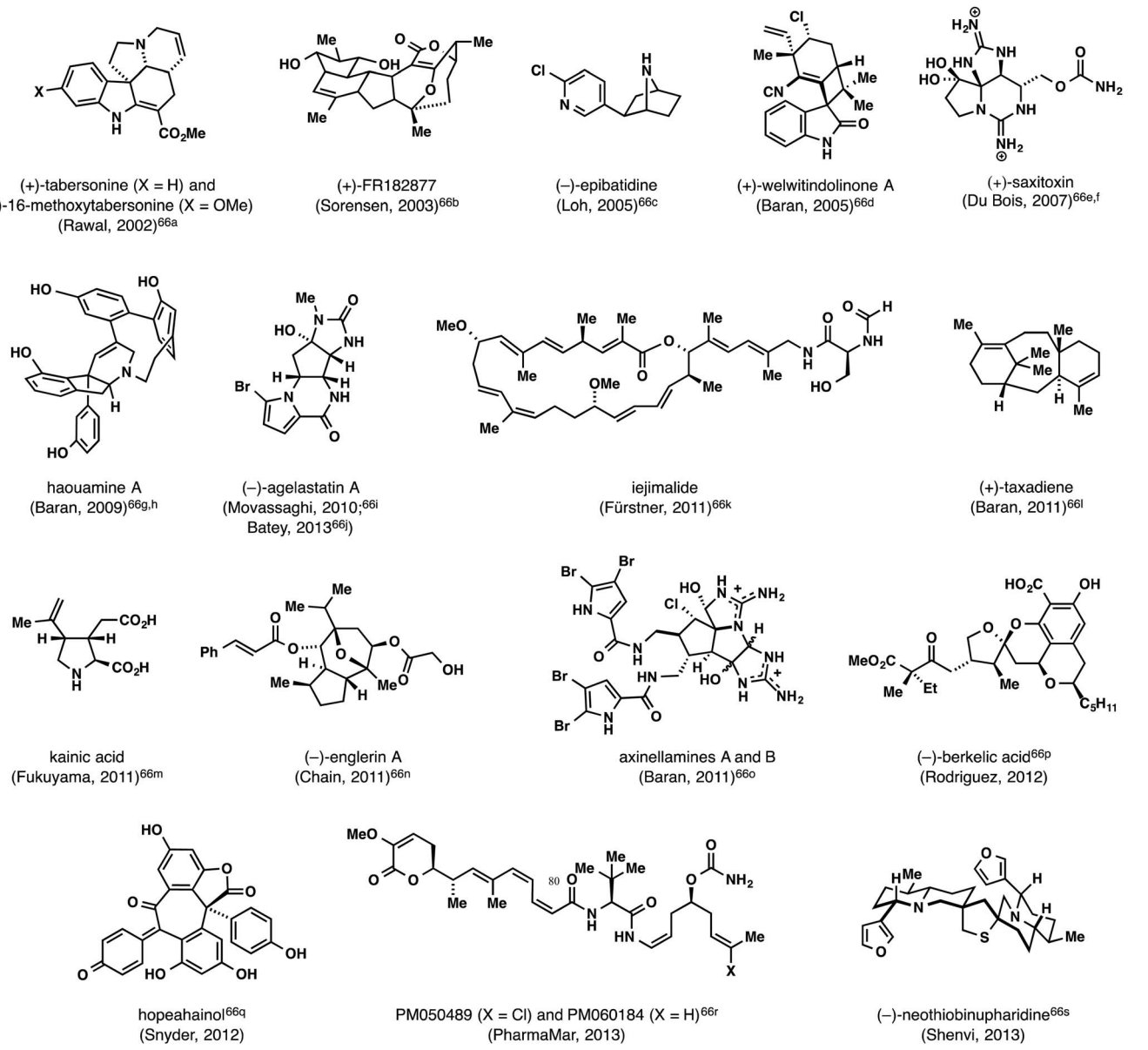


Scheme 16 A 14-step synthesis of ingenol (**70**).

and subsequent hydrolysis, furnished the C19-hydroxyl group in **66**. This alcohol then served to facilitate the introduction of further hydroxyl groups at C1 and C5, which were installed in four steps *via* epoxidation and hydride attack. A sequence of six more steps from **67** furnished **68**, which was then poised for the final redox-relay event. A Mukaiyama hydration afforded the key intermediate, protected ouabageninone (**69**), which is the branching point for the synthesis of both ouabagenin (**64**) and various analogs that are currently being evaluated at Leo Pharma.

2.2.5 Ingenol (2013). Ingenol (**70**) is a diterpenoid first isolated by Hecker in 1968 from *Euphorbia ingens*.[61] Ingenol esters display remarkable biological properties such as anti-cancer and anti-HIV activities, derived from their interaction with protein kinase C.[62] In particular, ingenol mebutate (Picato®, ingenol 3-angelate, not shown) was recently approved by the FDA as a first-in-class treatment for actinic keratosis, a pre-cancerous skin condition, and has completed Phase II clinical trials for the topical treatment of basal cell carcinomas.[63] The current supply of both ingenol (**70**) and ingenol mebutate is limited to direct isolation, and none of the previous synthetic routes to ingenol (**70**)[64] are amenable to large-scale synthesis. As a result, Leo Pharma initiated a partnership with the Baran group, with the goal of designing a total synthesis of ingenol (**70**) that would solve the supply issue and allow for the creation of analogs of Picato® with improved properties.[65]

Our synthesis, shown in Scheme 16, started from inexpensive 3-carene (**71**), which was elaborated in five steps into **74**. The key allenic Pauson–Khand reaction delivered dienone **75**, which was further transformed into carbinol **76**. Intermediate



Scheme 17 A small selection of further natural products that have been accessed in a scalable fashion but are not covered as part of this *Highlight*.

76 represents the 'cyclase-phase' endpoint of our synthesis and at the same time a branching point for the synthesis of a variety of novel analogs of Picato®. Most notably, all the steps of the cyclase phase were carried out on a gram scale, and the route is currently being scaled up, in conjunction with Leo Pharma, to provide larger quantities of the Pauson–Khand product **75**. In the 'oxidase-phase' of our synthesis, **76** was elaborated into carbonate **77**, the substrate for the second key step of our synthesis. The treatment of **77** with $BF_3 \cdot OEt_2$ under optimized conditions effected a pinacol shift, setting the strained *in*,*out*-stereochemistry and affording ingenane **78**. In a sequence of four more steps, the target ingenol (**70**) was completed, resulting in the shortest, most scalable and diversifiable synthesis of ingenol (**70**) thus far. Current efforts focus on the synthesis of novel analogs made possible only through a strategically designed total synthesis.

3 Conclusions

In the 21st century, the demand for natural products remains high. They often act as starting points for drug discovery, along with being tools to learn about biologically important processes.

It cannot be disputed that all too often constraints in availability limit further investigation, due in no small part to a perception that complex natural products are not amenable to SAR studies or eventual commercial scale production. The future of natural product synthesis should be to address this perception and to pursue approaches to molecules that yield sufficient material for further development. In this highlight article, we have given a snapshot of this ever-increasing area, but it is certainly not exhaustive. For those interested in a more complete picture, Scheme 17 depicts a selection of further natural products that have been prepared in a scalable fashion.[66]

To conclude, pursuing natural product synthesis with the mind-set of a process chemist can have many positive outcomes. For example, it will often illuminate areas of potential chemical innovation that can have broad applications in other areas of synthesis. From an application standpoint, scalability makes it inherently easier to pursue the medicinal chemistry of a target, since, with ample material, not only the final product but all of the intermediates along the way can be deeply modified in SAR studies. Finally, the robustness and reproducibility of syntheses that are conducted and optimized on a larger scale bode well for potential commercial production.

4 Acknowledgements

We thank Yoshihiro Ishihara for helpful discussions. C. A. K. is grateful to the Alexander von Humboldt-Foundation for providing a Feodor Lynen-Postdoctoral Fellowship.

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