FEATURE ARTICLE

ChemComm
www.rsc.org/chemcomm

Tandem reactions, cascade sequences, and biomimetic strategies in total synthesis

K. C. Nicolaou,[ab] Tamsyn Montagnon[a] and Scott A. Snyder[a]

[a] *Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA*

[b] *Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA. E-mail: kcn@scripps.edu*

Received (in Cambridge, UK) 25th September 2002, Accepted 10th December 2002
First published as an Advance Article on the web 16th January 2003

Cascade reactions and biomimetic strategies are being increasingly applied to the construction of natural and designed molecules. Such processes, in which ideally a single event triggers the conversion of a starting material to a product which then becomes a substrate for the next reaction until termination leads to a stable final product, are highly desirable not only due to their elegance, but also because of their efficiency and economy in terms of reagent consumption and purification. Often, these multistep, one-pot procedures are accompanied by dramatic increases in molecular complexity and impressive selectivity. The discovery of new molecular diversity from Nature and the demand for more efficient and environmentally benign chemical processes dictates and invites the further development of such synthetic strategies and tactics as we move into a new age of chemical synthesis. Within this article, a number of instructive examples of such synthetic strategies from the principal author's laboratories are discussed.

Professor K. C. Nicolaou, born in Cyprus and educated in England and the US, is currently Chairman of the Department of Chemistry at The Scripps Research Institute where he holds the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Professorship in Chemical Biology as well as Professor of Chemistry at the University of California, San Diego. His impact on chemistry, biology and medicine flows from his works in organic synthesis described in over 550 publications and 50 patents and his dedication to chemical education as evidenced by his training of more than 330 graduate students and postdoctoral fellows. His recent book titled Classics in Total Synthesis, which he co-authored with Erik J. Sorensen, is used around the world as a teaching tool and source of inspiration for students and practitioners of organic synthesis.

Tamsyn Montagnon was born in Hong Kong in 1975. She received her BSc in Chemistry with Medicinal Chemistry from the University of Leeds which was followed by a move to the University of Sussex where she obtained a DPhil in 2000 for research, conducted under the supervision of Professor P. J. Parsons, towards the synthesis of complex natural products including the squalestatins and triptoquinone C. She was awarded a GlaxoWellcome post-doctoral fellowship and joined Professor K. C. Nicolaou's group in January 2001. Her research interests include natural product synthesis, medicinal chemistry, and reaction methods and mechanisms.

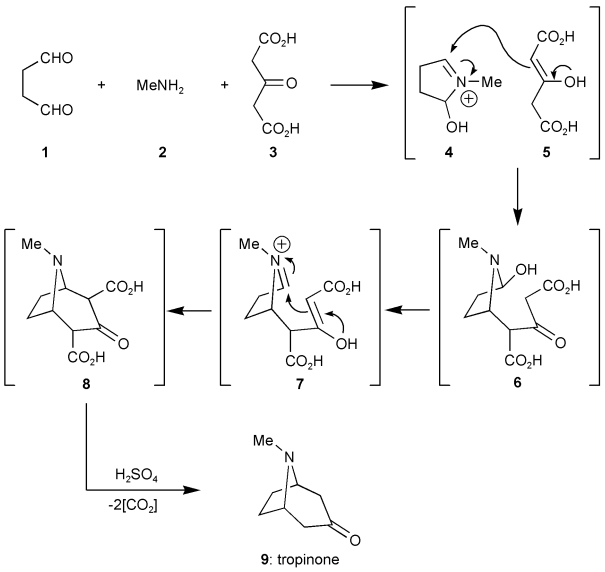
Scott A. Snyder, born in Palo Alto, California, in 1976, spent his formative years in the suburbs of Buffalo, New York. He received his BA in Chemistry, summa cum laude, from Williams College, Williamstown, Massachusetts, in 1999, where he explored the hetero Diels–Alder reaction with Professor J. Hodge Markgraf. He then began graduate studies with Professor K. C. Nicolaou, where he has devoted attention to the chemistry and biology of the marine-derived antitumor agent diazonamide A. He is the recipient of a Barry M. Goldwater Fellowship in Science and Engineering, a National Science Foundation Predoctoral Fellowship, and a Graduate Fellowship from Pfizer, Inc. His research interests include complex natural product synthesis, reaction mechanism and design, and application of these fields to chemical biology.

Introduction

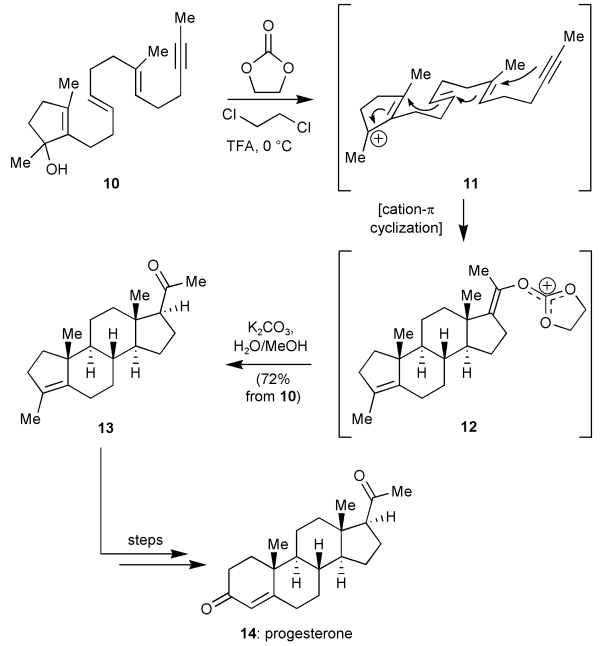
Today, as never before, synthetic chemists are facing Herculean tasks in the form of the total syntheses that they are endeavoring to undertake because of the continual upsurge in molecular complexity and diversity within the targeted natural products. Although each campaign is facilitated by an equally expanding number of technologies endowing tools for our attempts to outsmart these molecular chimeras, the general challenges are still being intensified. The demand continues to rise for solutions and strategies that surpass their predecessors in terms of creativity, with the additional proviso of concurrently striving to reap a richer harvest from such expeditions. Not only do we seek to bequeath the next generation of experimentalists with a superior arsenal to tackle their chosen puzzles, but we also aspire, for the present, to be able to probe the chemical biology of complex molecules by gaining efficient access to designed analogues. With all of these objectives at the vanguard of our stratagems it quickly becomes obvious that our chances of achieving a lucrative outcome are greatly enhanced if we make every effort to improve our efficiency in forging new bonds, particularly carbon–carbon bonds. In this respect, cascade and tandem reactions have long been recognized as providing an admirable set of strategies and tactics. Indeed, their esteemed lineage can be traced back to the formative years of the practice of total synthesis when, in 1917, one of its founding fathers, Sir Robert Robinson, achieved the landmark, one-pot biomimetic synthesis of tropinone (**9**, Scheme 1) from succindialdehyde (**1**), methylamine (**2**), and either acetone or a salt of acetonedicarboxylic acid (**3**).[1] This 'gold standard' was once again attained in 1971 with W. S. Johnson's synthesis of progesterone (**14**, Scheme 2), wherein a series of cation-π cyclizations was exploited to assemble the entire carbon framework of this steroid in a single operation.[2] If we are to successfully emulate the elegance of these works and concomitantly advance the state of the art, current and future practitioners will need to delve deeply in search of creative insight and, in addition, will be required to hone their comprehension of the kinetics of multi-component transformations as well as the fundamentals of reaction mechanisms.

In this review, we have elected to focus on unique tandem sequences and reaction cascades developed in our laboratories as part of our efforts directed towards the expedient total synthesis of intricate and architecturally novel natural products. We hope that by organizing the delineated examples into three

DOI: 10.1039/b209440c



Scheme 1 Robinson's elegant biomimetic union of succindialdehyde (**1**), methylamine (**2**) and acetonedicarboxylic acid (**3**) in his 1917 total synthesis of tropinone (**9**).[1]



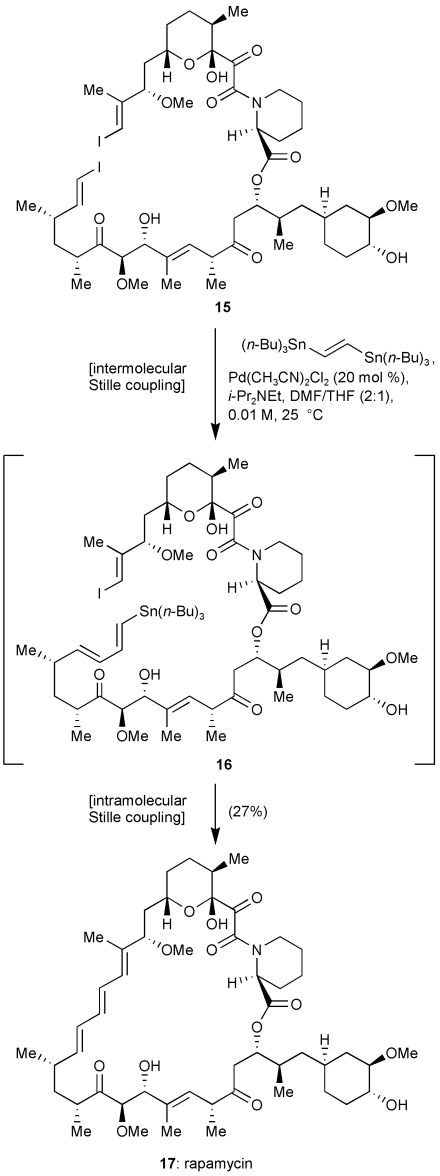
Scheme 2 Johnson's elegant cation-π cyclization to fashion the core scaffold of progesterone (**14**). (1971)[2]

broad categories (intermolecular, intramolecular and biomimetic case studies) the different approaches for the design and implementation of techniques to rapidly increase molecular complexity will be analyzed, compared, and contrasted. Our goal is not only to demonstrate the effectiveness (and limits) of synthetic technologies in the context of some of the most strenuous synthetic problems that have faced the chemical community, but also to provide inspiration that may lead to the design and execution of even more impressive cascade events to fashion molecular complexity in the future.

Designed synthetic cascade sequences and tandem reactions

Intermolecular variants

We begin with a molecule whose aesthetic appeal is undeniable, but, which also possesses an equally enticing biological profile in the form of potent immunosuppressive properties. This natural product, rapamycin (**17**, Scheme 3), is named after its

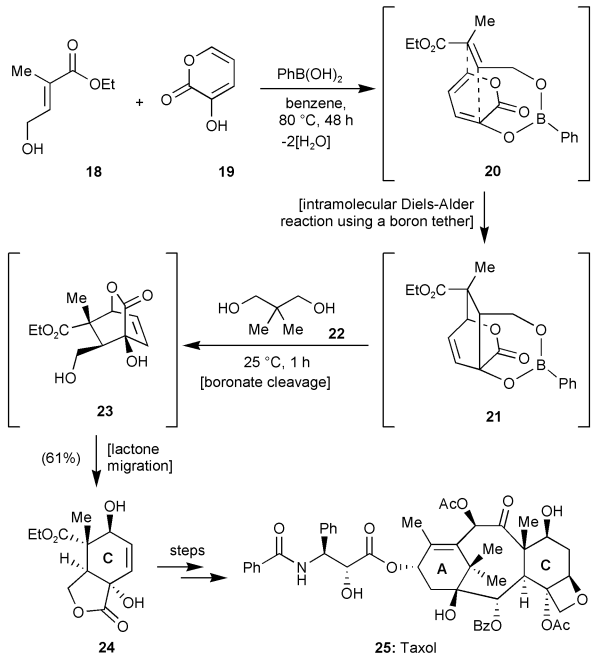


Scheme 3 Iterative Stille cyclization strategy ('stitching macrocyclization') employed in the final step of the total synthesis of rapamycin (**17**). (1993)[4]

biological and geographical sources, the bacteria *Streptomyces hygroscopius* found in soil samples from the island of Rapa Nui.[3] Its structure harbors a 29-membered macrocycle adorned with a number of challenging structural features as exemplified by the conjugated all *trans*-triene motif whose installation is most salient to our purpose here. Our appreciation of the sensitive nature of this domain was garnered from experience with similar polyolefinic arrays and dictated a strategy wherein its incorporation would constitute a late-stage operation. This approach bore fruit and the daring final step of the first total synthesis of rapamycin (**17**), completed by our group in 1993, comprised of a unique stitching macrocyclization using a double inter-/intramolecular Stille coupling.[4–6] Implementation of this iterative use of coupling reactions required the synthesis of an advanced linear precursor (**15**) with a vinyliodide attached to each end; significantly, the macrocyclization conditions were anticipated to be mild enough such that fully deprotected starting material could be productively engaged in this rather dramatic finale. Indeed, the cyclization and concomitant

insertion of the two remaining carbon atoms was achieved in an elegant domino fashion by an initial intermolecular palladium-catalyzed reaction with *trans*-1,2-bis-(tri-*n*-butylstannyl)ethylene to afford the intermediate (**16**), followed by a second, this time intramolecular, Stille reaction that secured the requisite all-*trans* geometry for the triene and furnished rapamycin (**17**) in 27% yield.

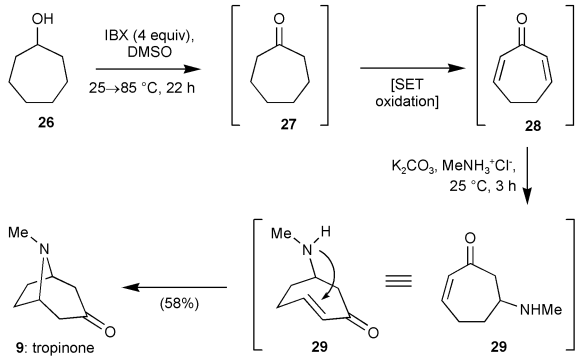
On a par with rapamycin, the gauntlet issued by the structural elucidation[7] of Taxol™ (**25**, Scheme 4) was an event that



Scheme 4 The total synthesis of Taxol™ (**25**) featuring a unique Diels–Alder-based reaction sequence to fashion C-ring intermediate **24**. (1994)[9]

provided a target molecule whose conquest was destined to become one of the most hotly contested and exciting adventures of the late 1980's and early 1990's, as numerous groups worldwide strove to access this important anticancer agent through chemical synthesis.[8] In our approach to this formidable molecular architecture[9–11] we sought to harness the power of the Diels–Alder reaction on two occasions, the most notable being as a potential means to stereoselectively attain the highly substituted cyclohexene ring **24**. Implementation of this design element, however, required a deliberate adaptation of the reaction components to both deviate the cycloaddition course from its intrinsic bias for one regiochemical outcome towards the alternate, desired regioisomer and to enhance the reaction yield. Thus, in this industrious chain of events based upon precedent established by Narasaka,[12] the combination of pyrone **19** and the vinylogous ester **18** with phenylboronic acid in refluxing benzene afforded **24** in 61% yield. The sequence relied upon exploiting the equilibrium that exists between alcohols, boronic acids, and the corresponding boronate esters, to provide a temporary tether that facilitated an intramolecular Diels–Alder reaction furnishing the desired adduct (**21**) having also enforced the desired 'unnatural' regiochemistry. The tether was subsequently removed upon work-up through the addition of a suitable diol (**22**) to sequester the boronic acid, initiating a spontaneous lactone migration that completed the assembly of **24**. This key fragment (**24**) was ultimately incorporated into the right-hand side of the gross structure of Taxol™ (**25**) by way of further elaboration, thereby facilitating the eventual total synthesis of this celebrated natural product.

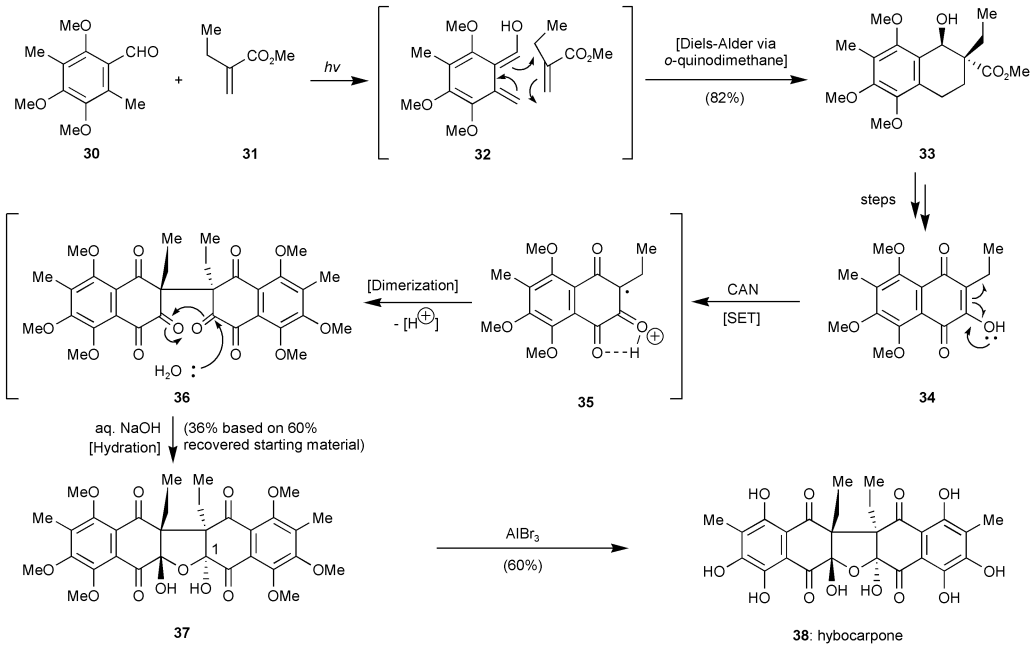
In the introduction to this article we alluded to the fact that the proud history of cascade reactions originated in the pioneering synthesis of tropinone (**9**) achieved by Sir Robert Robinson.[1] In a similar vein, we have also recently synthesized this historic natural product ourselves. Our approach, however, is very different and was predicated upon the application of our recently developed novel methodology for the introduction of unsaturation adjacent to the carbonyl group of ketones and aldehydes.[13] In this instance, the one-pot construction of tropinone (**9**) began from cycloheptanol (**26**, Scheme 5) and



Scheme 5 Use of IBX-mediated oxidation events to convert cycloheptanol (**26**) to cycloheptadienone (**28**), a precursor converted to tropinone (**9**) in the same pot. (2002)[13]

utilized the versatile hypervalent iodine(v) oxidant, IBX, to mediate two distinct transformations. First, IBX was employed to oxidize the alcohol to its corresponding carbonyl, a transformation that delivered the requisite functionality to allow iterative installation of a double bond at both positions adjacent to the newly acquired ketone (**27**). This process could be rationalized by invoking a single electron transfer (SET) mechanism where IBX was engaged to oxidize the ketone's enol tautomer, apparently through the corresponding enolic radical cation, at elevated temperatures. In this manner, cycloheptadienone (**28**) was generated and the synthesis of tropinone (**9**) was subsequently completed in 58% yield through double Michael addition of methylamine (**2**) to **28** in the presence of K_2CO_3, with the final steps of this remarkable cascade constituting an *in situ* formal synthesis based on precedent from Bottini and Gal.[14]

We continue with the theme of SET-mediated reactions in our next example, a recently accomplished total synthesis of the natural product hybocarpone (**38**, Scheme 6), a secondary metabolite which possesses an unprecedented C_2-symmetric molecular architecture built upon a dinaphtho[2,3-b:2,3-d]furan-tetrone skeleton.[15] Hybocarpone (**38**) was isolated in 1999 from mycobiont cultures derived from the lichen *Lecanora hybocarpa* and was found to have potent cytotoxic properties against the murine mastocytoma P815 cell line.[16] Intrigued by its structure and alluring biological profile, we initiated a program directed towards its synthesis based upon the retrosynthetic analysis whereby the central tetrahydrofuran unit was dissected, yielding two monomeric units which resembled its putative biogenetic origins.[17] Accordingly, our first target was naphthazarin **34** which was synthesized *via* a route featuring a Diels–Alder reaction of *o*-quinodimethane **32**, unmasked by a UV promoted excitation of **30**, with methyl 2-ethylacrylate (**31**).[18] In the crucial cascade step, **34** was subjected to the action of ceric ammonium nitrate (CAN) in order to induce SET and a subsequent dimerization event followed by hydration to furnish **37**, thus introducing the requisite symmetry element and justifying our original proposition. We had opted for a radical mode of reaction for the designed dimerization due to the known ability of radical species to react in situations where the local environment is sterically hindered such as that seen about the bond bridging the two monomeric naphthazarin units of hybocarpone (**38**). The

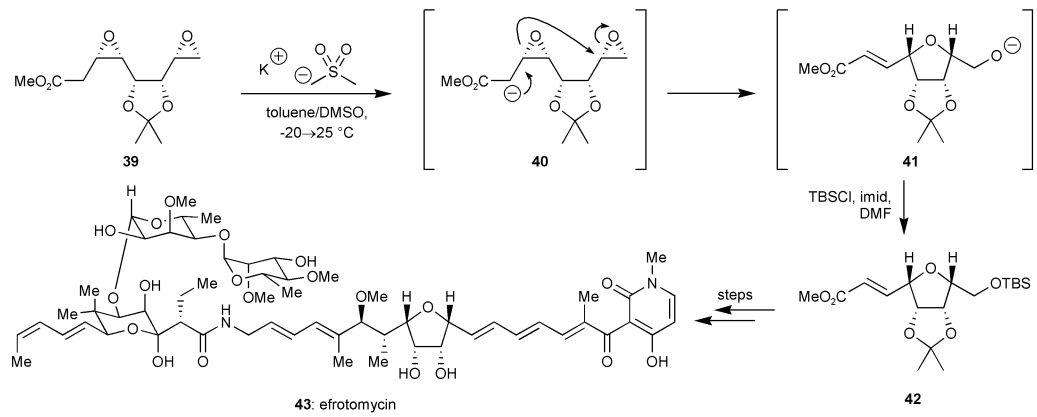


Scheme 6 Dimerization–hydration cascade of a naphtharazin (**34**) to hybocarpone hexamethyl ether (**37**) initiated by single-electron transfer (SET). (2001)[15]

dimerization–hydration cascade adduct was initially isolated as a mixture of only two separable stereoisomers, an impressive result given the number of possible product isomers. Additionally, the minor component could be readily converted to the desired major product (**37**) upon exposure to traces of acid through inversion of the stereochemistry at C-1 driven by the thermodynamic stability of **37**. Our expedient and aesthetically pleasing construction of hybocarpone (**38**) was then finalized by deprotection of **37** as mediated by $AlBr_3$ to afford the natural product in 60% yield. It had taken an arduous search to identify CAN as the oxidant of choice and to delineate the optimum conditions for a successful outcome to the oxidative coupling and hydration reactions. These hurdles are an indication of both the sensitivity of the systems involved and the challenges associated with the generation of highly reactive intermediates which then need to be coaxed down the desired reaction pathway, considerations that add to the impressive nature of the cascade sequence achieved in this synthesis.

Intramolecular variants

Our opening gambit in this section relates to a sequence developed during our asymmetric total syntheses of two striking architectures that characterize the most prominent members of a class of complex anti-bacterial and growth-promoting agents called the elfamycins (Scheme 7).[19] The stereoselective and efficient construction of the central unit of these molecules, a heavily substituted tetrahydrofuran ring, defines one of the major synthetic hurdles presented by aurodox (goldinomycin) and efrotomycin (**43**). By initially enlisting a Sharpless asymmetric epoxidation reaction to effect kinetic resolution of a prochiral allylic alcohol, the source of enantioselectivity for this synthesis was readily reconciled. The same powerful reaction was later reiterated to initiate the serial assembly of the two epoxides exhibited by **39** whose ultimate function was to serve as relay functionalities in the crucial cascade sequence. Upon treatment of **39** with the potassium salt of DMSO, removal of the acidic proton adjacent to the methylcarboxylic ester caused fragmentation of the adjacent epoxide to afford the corresponding alkoxide intermediate which was ideally situated to conclude the cascade sequence with a 5-*exo*-tet cyclization to furnish the fully substituted tetrahydrofuran (**41**); subsequent *in situ* trapping of the alkoxide **41** with TBSCl then completed the sequence leading to **42**. With the goal of stereoselective compilation of the tetrahydrofuran achieved with admirable

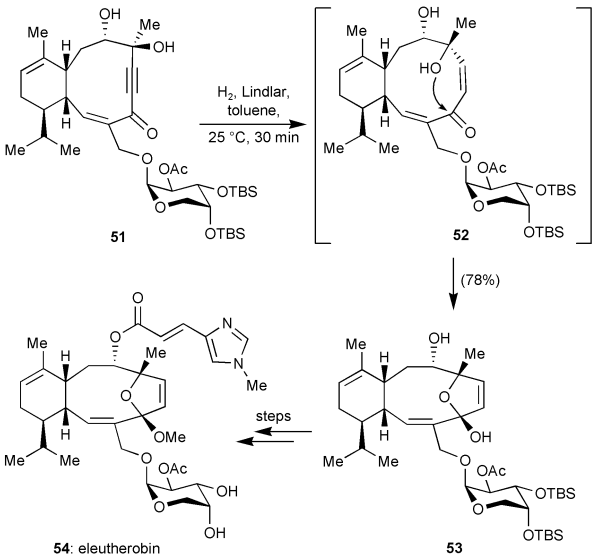


Scheme 7 Development of a unique fragmentation–cyclization cascade to synthesize tetrahydrofurans proved critical in stereoselectively fashioning the central portion of the antibiotic efrotomycin (**43**). (1985)[19]

efficiency, **42** was subsequently elaborated to the targeted structures.

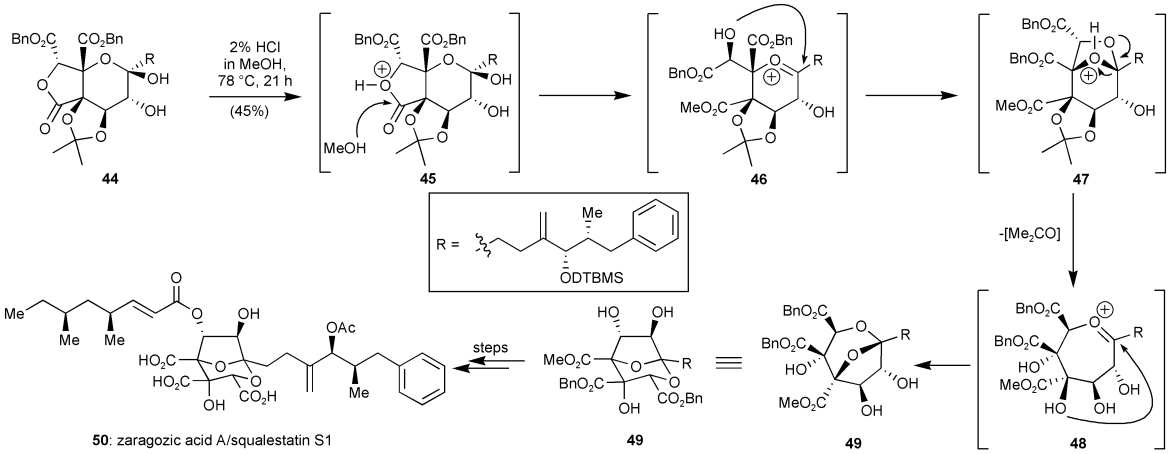
A tetrahydrofuran ring is also a central unit within the structure of the zaragozic acids (*e.g.* zaragozic acid A, **50**, Scheme 8), which are fungal metabolites with useful serum cholesterol-lowering properties discovered almost simultaneously by researchers at Merck[20] and Glaxo.[21] These molecules captivated synthetic chemists in the early 1990's due mainly to the highly oxygenated bicyclic ketal core exhibited within their complex frameworks. Upon initial inspection, construction of this central motif appears to be a daunting prospect; however, the preponderance of oxygen functionality, despite its demand for multifarious protecting groups, held the key to facile assembly based upon ketalization equilibria. Successful implementation of this principle in the construction of the zaragozic acid core was predicated upon a rearrangement which could drive the reaction course towards the final ketal form of the natural product by virtue of its thermodynamic stability relative to the other possible isomers. It was our conjecture that to reach such a homochiral intermediate, the intrinsic theme proposed by the contiguous array of four hydroxy groups should be exploited and installation attempted sequentially, beginning from a prochiral diene and applying the venerable Sharpless asymmetric dihydroxylation.[22,23] It was in this manner that we were able to rapidly access our key intermediate **44**. A feature worthy of note is that within the complex protecting group requirements of **44**, we had designed the incorporation of two protecting groups, an acetonide and a lactone, to serve not only to simplify the protection of four functional groups but to act as essential participants in the rearrangement. The use of the rare di-*tert*-butylmethylsilyl (DTBMS) group was found to be crucial due to the intolerance of a number of other common alternatives to the acidic rearrangement conditions. A stepwise view of the rearrangement itself is profitable since the connectivity of the overall transformation is somewhat hidden; thus, a series of simple transformations was initiated when **44** was treated with methanolic 2% aq. HCl. Initially, protonation of the lactone facilitated esterification and released the hydroxy group allowing it to attack a proximal oxonium cation formed by the action of acid on the hemiketal moiety present in the starting material (**45**→**47**). The ketal so-formed (**47**) was then opened in the opposite sense to reveal a new oxonium cation (**48**) which was trapped by a pendant hydroxyl to furnish the desired bicyclic-ketal (**49**), whose stability ensured that it constituted the major product of this operation. It is pertinent to emphasize that the mechanistic detail postulated above does not account for the intricate interplay between the many equilibrating structures that were present in reality, but seeks instead to précis the overall conversion. The first total synthesis of zaragozic acid A (**50**) was successfully finalized from this product (**49**) by the requisite deprotection reactions and side-chain attachment. The focus, in this instance, on comprehending reaction thermodynamics and kinetics is an apt illustration of the type of analysis required to turn a conceptual cascade into a tangible and impressive event.

A notable domino reaction sequence that draws upon fundamental aspects seen in both the previous examples described in this section was accomplished during our syntheses of the sarcodictyins (A and B)[24] and eleutherobin (**54**, Scheme 9).[25,26] These marine-derived,[27] potent antitumour agents are



Scheme 9 Critical reduction–cyclization sequence to complete the core architecture of eleutherobin (**54**). (1998)[24–26]

characterized by the possession of a rigid tricyclic skeleton wherein also lay the secret to a successful synthetic approach to their construction. Once again, the bridging oxygen atom permitted the strategic disconnection that began the unravelling of these structures and provided the key to the stereoselective assembly of both targets. An intuitive and simplifying disconnection then removed two carbons from the 10-membered ring, whose insertion in the synthetic direction was anticipated as potentially being facilitated through the addition of both termini of acetylene to two carbonyls. In the event, a cyclization precursor was effectively constructed on the scaffold provided by (+)-carvone into which the acetylene was fruitfully stitched, thereby affording **51**. Reduction of the triple bond in **51** using Lindlar's catalyst not only provided the corresponding double



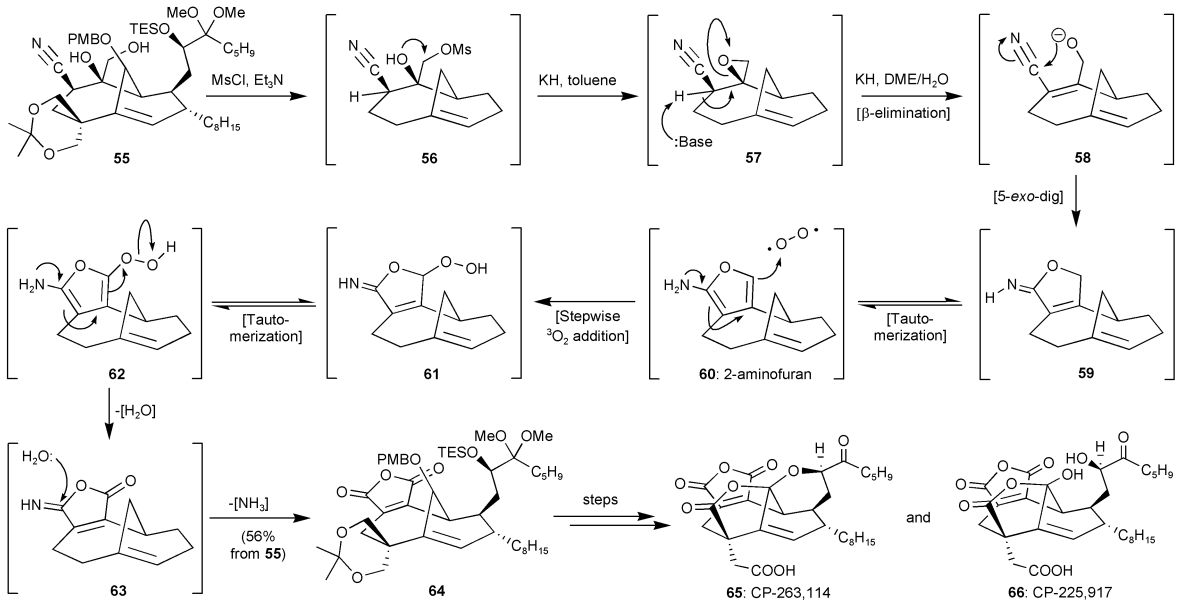
Scheme 8 Thermodynamically driven, acid-catalyzed rearrangement of **44** to generate the core scaffold of zaragozic acid A (**50**). (1994)[22]

bond with the correct *Z*-geometry (**52**) but also triggered a collapse in the rigidity of the 10-membered ring inducing formation of the desired bridged bicycle, with the correct stereochemistry, by bringing the adjacent hydroxy group into close proximity to the ketone. Overall, this sequence, which ultimately furnished **53** in a striking 78% yield, is a fine illustration of how creativity in design can maximize the number of discreet functions one can elicit by the inclusion of a single, carefully selected functional group (in this case a carbon–carbon triple bond), to enrich the course of a synthesis.

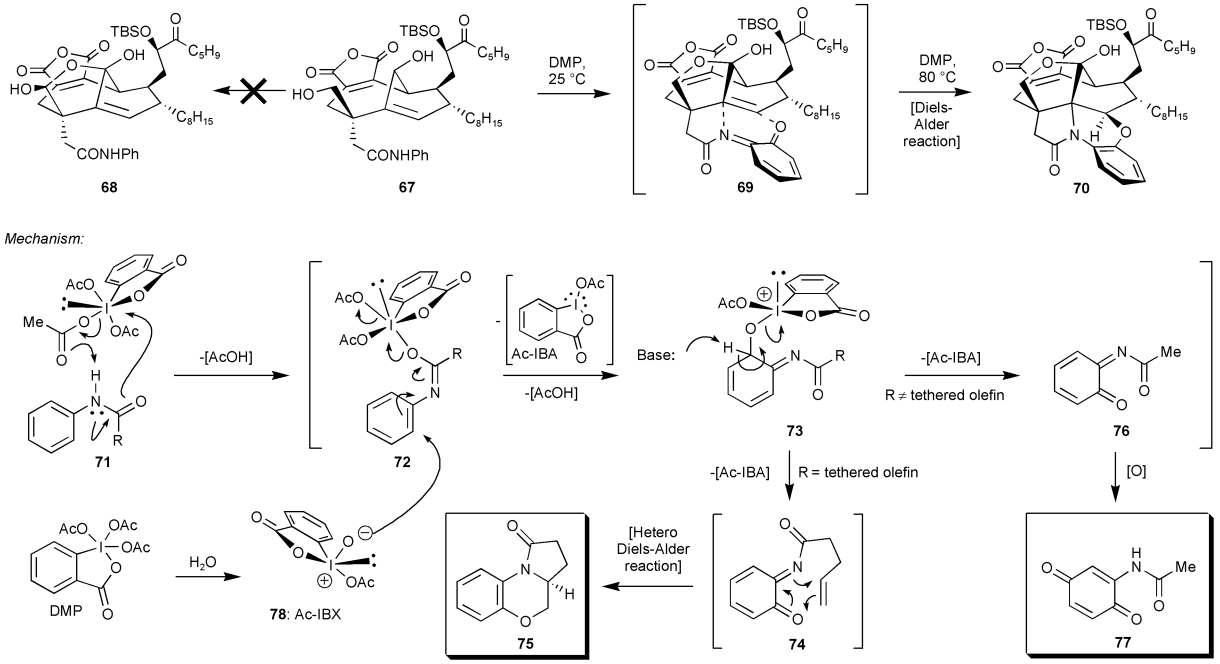
One criterion for the design of a cascade that we have overlooked, thus far, is as a tool to allow the fleeting access to unstable chemical entities *en route* to a desired product. The premier example of this concept from the annals of this group comes within the recent conquest of the infamous CP molecules (**65** and **66**, Scheme 10).[28,29] Amongst the myriad synthetic hurdles presented by these fungal metabolites with diabolically intricate structures was the installation of the fused maleic anhydride moiety. The innocence of this seemingly simple structural unit veils the resistance its hindered position and unique attributes contributed to our attempts to effect its synthesis. After a host of failed strategies, descriptions of which are far beyond the scope of this review, an inspirational and daring plan was conceived that involved enlisting a 2-aminofuran (such as **60**) to harvest oxygen, hence mediating construction of the anhydride from a more accessible species in a lower oxidation state. Synthesis of the 2-aminofuran, a rare chemical entity, was envisaged to be possible considering its tautomeric form, an iminobutenolide such as **59**, given that we had established a precedent in accessing the analogous butenolides by a β-elimination pathway from an appropriately situated epoxyester. In practice, through unprecedented orchestration *via* controlled reagent addition, we were able to begin from the cyanodiol **55**, mesylating this intermediate selectively at the primary position to yield **56**, followed by treatment with a stronger base (KH in toluene) to mediate epoxide formation (**57**) and with subsequent β-elimination, furnishing alkoxycyanide **58**. This intermediate then spontaneously underwent a 5-*exo*-dig cyclization to yield the iminobutenolide, whose tautomer was the coveted 2-aminofuran (**60**). Yet, even at this point, the cascade was only partially complete, as 2-aminofuran **60** underwent autooxidation by trapping triplet oxygen from air, and the peroxide so-formed **62** obligingly expelled both water and ammonia to bring the cascade to a climax, giving the desired product **64** in an impressive 56% yield.

The total synthesis[28,29] of the CP molecules (**65** and **66**) offers us a second domino sequence worthy of comment, although this event is of interest on a completely different basis as it serves to illustrate how a prepared mind can disentangle an anomalous observation or an unanticipated reaction product and consequently enrich the harvest garnered from a synthetic endeavor. To set the scene, during the exploration phase of our synthetic efforts towards the CP molecules, the locking-up of an ester by its transformation into a stable γ-lactone upon the unmasking of a proximal hydroxyl functionality seriously impeded our progress.[28] We envisaged circumvention of this irritating occurrence through replacement of the ester with a less reactive aniline amide.[30] It was with the inclusion of this adaptation that we were trying to advance the synthesis by attempting to effect an oxidation affording the hydroxylactol **68** from the diol **67** using DMP; however, the product isolated from this reaction was actually found to be **70**, formed as the result of a unique cascade reaction sequence.[31] Extensive investigations were undertaken with the aim of clarifying the mechanism involved in this transformation;[32] the results strongly implied mediation by both DMP and Ac-IBX (**78**) acting in synergy (see Scheme 11). We believe that DMP activates the anilide (**71**→**72**) allowing the nucleophilic oxide ligand of Ac-IBX (**78**) to attack the adjacent position initiating a rearrangement furnishing the corresponding *o*-imidoquinone (**74**), a heterodiene, that may participate in an inverse electron demand Diels–Alder reaction when a suitable olefin is appended nearby (intermolecular cycloaddition examples were also shown to be possible).[32] In the absence of a suitable olefin, the imidoquinone (**76**) may be attacked for a second time by a nucleophilic molecule of Ac-IBX (**78**) to yield the corresponding *p*-quinone (**77**, see Scheme 11).[33]

The ubiquity and prominence of quinones and their cycloadducts in Nature inspired us to pursue the application of these two reactions within a total synthesis context. To this end we targeted the epoxyquinomycins which are a class of natural products with an enviable biological profile including antibiotic and anti-inflammatory activity.[34] We were able to engender, in four synthetic operations, the shortest total synthesis yet reported of the most potent member of this family, epox-

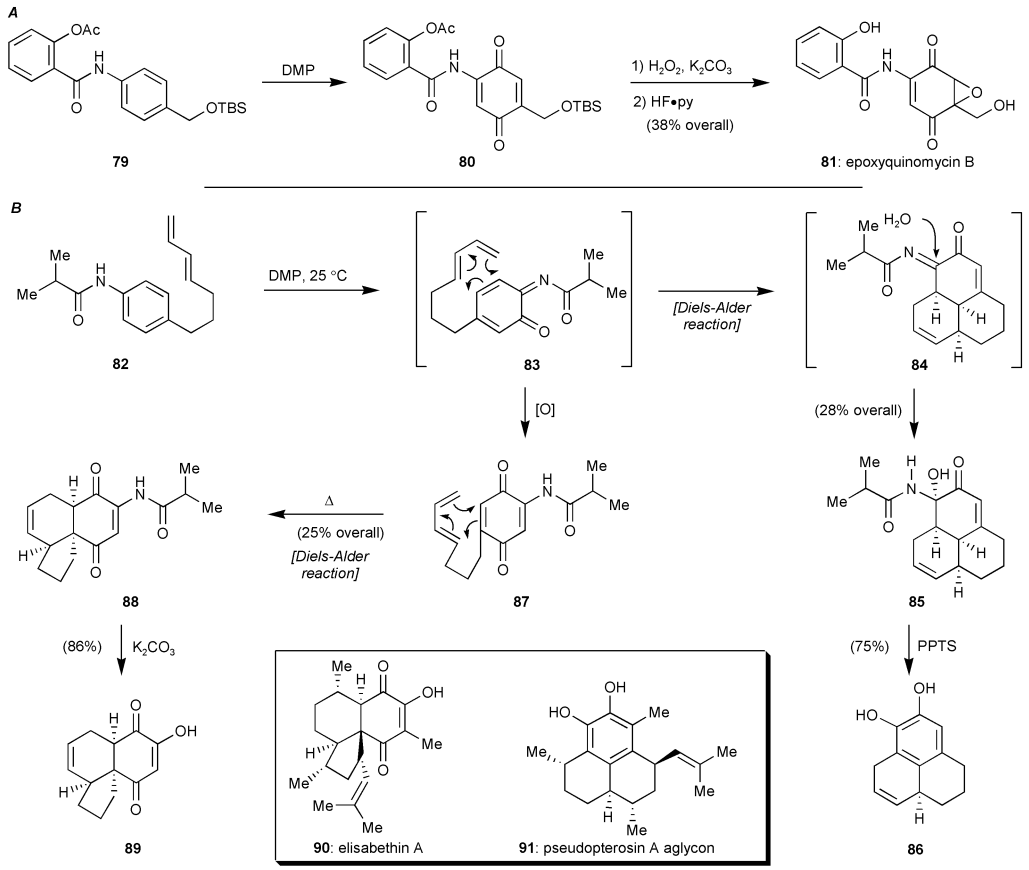


Scheme 10 The designed cascade sequence enabling generation of the coveted maleic anhydride portion (**64**) of the CP-molecules (**65** and **66**). Note: appendages on the core of the intermediates have been removed for clarity. (1999)[29]



Scheme 11 Cascade sequences discovered by serendipity as part of the CP-campaign: Dess–Martin periodinane-initiated polycyclization reaction through the intermediacy of *o*-quinodimethanes (**69**) and proposed mechanism for the observed transformations. (2000)[31–33]

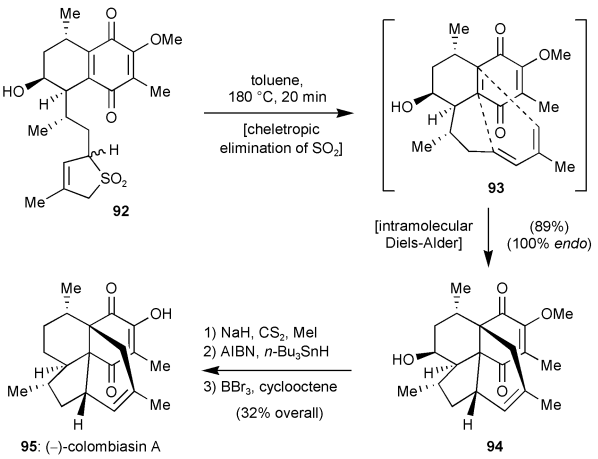
yquinomycin B (**81**), by enlisting the anilide to *p*-quinone tandem oxidation sequence (**79**→**80**, Scheme 12A).[33,35] In our second application of this new method, we unveiled a fascinating link between two seemingly disparate classes of natural products produced by a single organism, the elisabethins such as **90** and pseudopterosins like **91**, thereby suggesting that Nature may also be party to this divergent domino sequence in an analogous form.[33,36] Our suspicions concerning this buried relationship were confirmed when treatment of anilide **82** with DMP at ambient temperature led to two products from unrelated Diels–Alder cycloadditions (see Scheme 12B). The first adduct was an unusual hydroxyketamide (**85**), with diverse chemical potential that has since been explored in detail.[33] One of the myriad options available to **85** was its elaboration upon



Scheme 12 Use of the DMP-initiated cascade in chemical synthesis: *A*) facile generation of the key quinone needed for epoxyquinomycin B (**81**); *B*) generation of both elisabethan A and pseudopterosin A aglycon frameworks from the same starting material (**82**). (2001)[35,36]

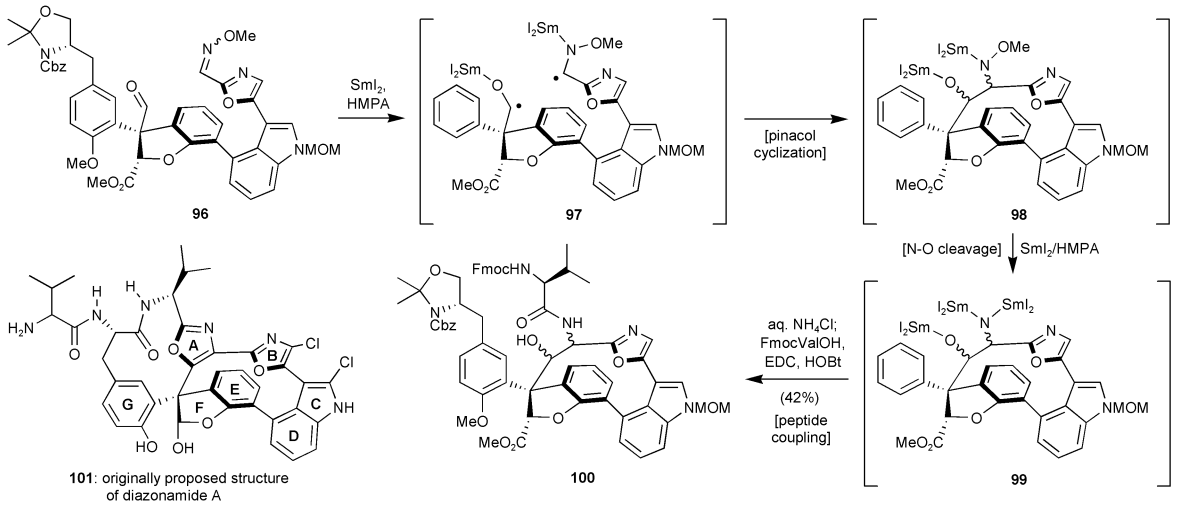
treatment with PPTS and H_2O to furnish the core structure (**86**) of the pseudopterosins (**91**). However, an alternative pathway was also accessible if intermediate **83** was intercepted and oxidized by a second addition of Ac-IBX (**78**) instead, resulting in quinone **87** which could then react as a dienophile to afford cycloadduct **88**, an entity which was converted to **89** upon treatment with K_2CO_3. This latter product (**89**) strongly resembles the gross structure of elisabethin A (**90**). Taken cohesively, these unique chapters of the CP research program demonstrate that to dismiss an unplanned and undesired deviation from one's synthetic designs can mean losing a golden opportunity to discover and develop fundamental knowledge in organic chemistry.

Leaving the wealth of this total synthesis behind us, but staying within the confines of the elisabethin terpenoid architecture, in 2000 a bioassay guided isolation from the West Indian coral *Pseudopterogorgia elisabethae* yielded colombiasin A (**95**, Scheme 13), a potent antibiotic against *Mycobacterium tuberculosis* H37Rv.[37] Colombiasin A (**95**) exhibits an additional challenge over her elisabethin siblings in that its structure is rigidified and further compacted by an additional bridging 6-membered ring appended to the central framework at one of the two adjacent quaternary centers present. We opted to exploit the power of the Diels–Alder cycloaddition reaction in the construction of these hindered quaternary centers; indeed, when our successful total synthesis is considered as a whole it becomes obvious that we drafted the more electron deficient double bond of the methoxyquinone into the role of a participating dienophile on two separate occasions to assemble the skeleton of colombiasin A.[38] The second of these events is the focus of this current synopsis as it constituted a cascade of two pericyclic reactions. After asymmetric construction of the sulfone **92**, the latter was heated in toluene at 180 °C to first unmask a diene (**93**), by means of cheletropic elimination of SO_2, which was then coerced to participate in the final Diels–Alder reaction which furnished the complete tetracyclic skeleton in the form of **94**. Radical deoxygenation, followed by an initially thorny demethylation, finally ceded the coveted natural product, (−)-colombiasin A (**95**).

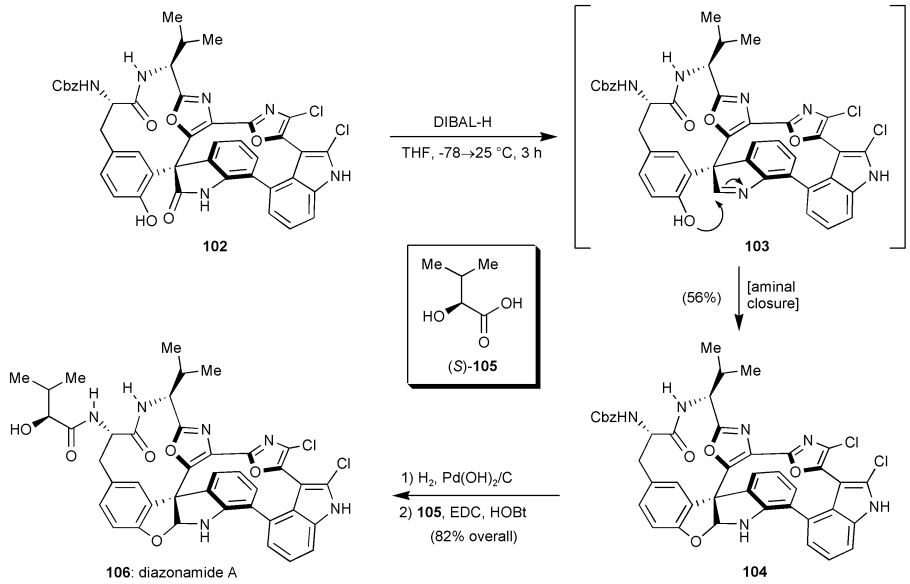


Scheme 13 Cheletropic elimination of SO_2 to unmask a diene for participation in an intramolecular Diels–Alder event leading to the stereospecific construction of the two quaternary centers possessed by (−)-colombiasin A (**95**). (2001)[38]

We finish this section with two vignettes from different chapters of our most recently accomplished endeavor, the total synthesis of a secondary metabolite from the colonial ascidian *Diazona angulata* named diazonamide A (**106**, Schemes 14 and 15). Impressive *in vitro* cytotoxicity and a formidable architecture has inspired many groups to become engrossed in attempts to synthesize this rather demonic molecule; unfortunately, the original structural assignment[39] had to be revised based upon new insights[40] gained in 2001 (**101**→**106**) and to date our total synthesis of **106** stands alone as the only completed effort.[41] A cursory inspection of the diazonamide structures, original (**101**) or revised (**106**), discloses a testing 12-membered macrocycle containing an inflexible biaryl unit. We were enticed by the vision of achieving the requisite formation of such a motif by means of the addition of a ketyl radical to a highly competent radical acceptor in the form of an oxime[42] in a hetero-pinacol type coupling. The prowess of SmI_2 in the generation of ketyl radicals led to its selection as a mediating reagent for our crucial macrocyclization event, a decision reinforced by recent reports[43] that it could also induce scission of N–O bonds allowing us to entertain the alluring prospect of accomplishing cyclization, reduction and peptide coupling in a tandem one-pot operation. Gratifyingly, with only modest tuning of reaction conditions we were indeed able to realize the desired domino sequence when oxime **96** was treated with SmI_2/HMPA followed by the addition of FmocValOH, EDC and HOBt to elicit the formation of product **100** in 42% yield (see Scheme 14).[44] As such, an amino alcohol motif had been installed with far greater efficiency than is possible through the more conventional step-wise approaches available for accomplishing this overall transformation, and the process



Scheme 14 Rapid construction of a functionalized macrocycle (**100**) using a novel hetero-pinacol coupling protocol targeting the originally proposed structure of diazonamide A (**101**). Note that the tyrosine substituents have been deleted in the intermediates for clarity. (2001)[44]



Scheme 15 Generation of the highly strained animal ring system within diazonamide A (**106**) through a reductive-cyclization cascade sequence. (2002)[41]

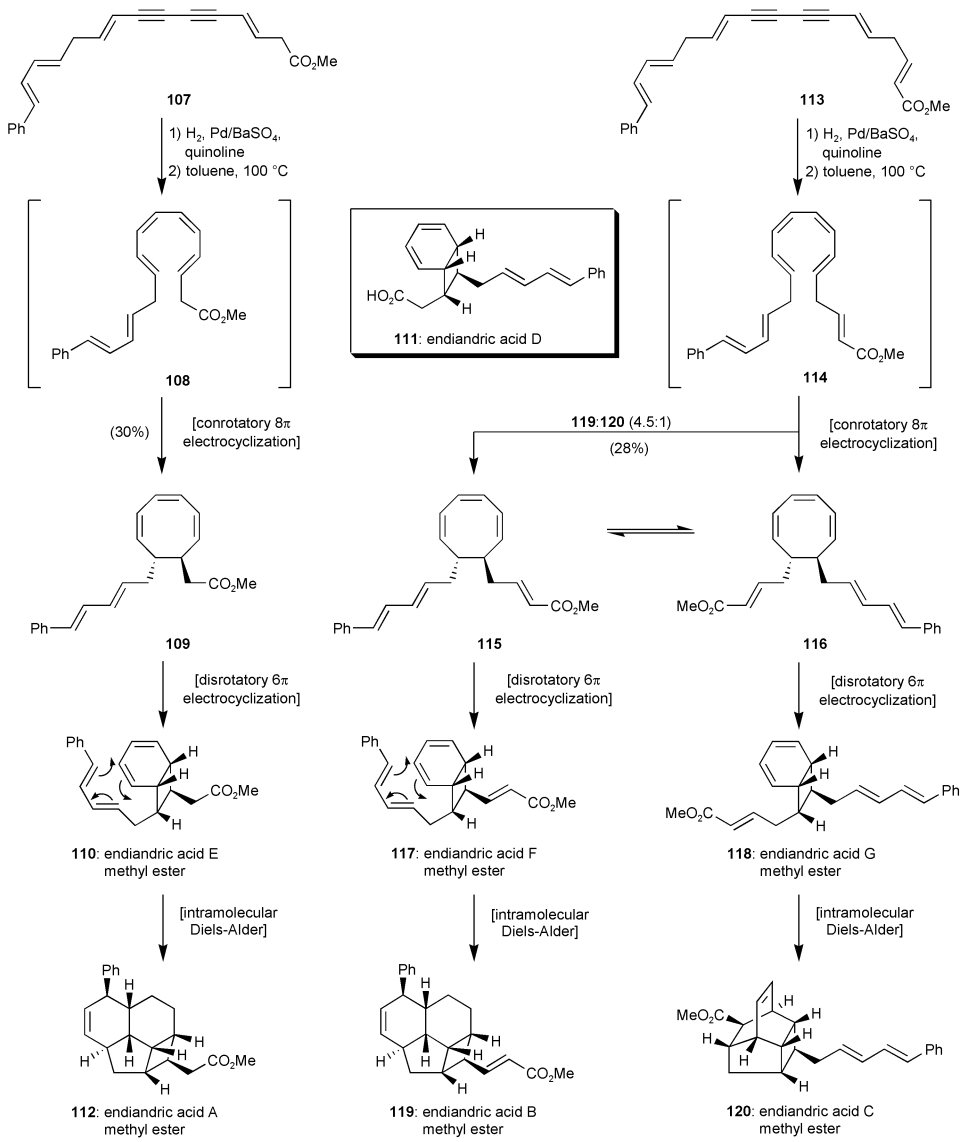
constituted the first successful use of a hetero pinacol cyclization to fashion a ring size of greater than seven.

We were also required to overcome the defiant barrier of substantial ring strain in the closing stages of our synthesis of the structurally corrected diazonamide A (**106**, Scheme 15), where we envisaged that a tandem reduction–cyclization sequence could assemble the final array of rings.[41] Thus, the advanced intermediate amide **102** was treated portion-wise with DIBAL-H, inducing reduction of the amide (**102**) to an imine (**103**) that was suitably disposed to engage the proximal phenolic residue in domino fashion to achieve the final ring closure furnishing **104**. All that was then mandatory to complete the synthesis were two cursory finishing touches, namely a hydrogenolytic deprotection and coupling of the resultant amine with the isovaleric side-chain (**105**) to yield the long sought after prize, diazonamide A (**106**).[41]

Biomimetically inspired cascade sequences

Since we have elected to focus on natural products as our final objectives in synthesis it is perhaps palpable that before embarking on an expedition toward a particular molecule, we should consider how the target was originally assembled by Nature and whether it is possible for us to emulate her graceful strategy in the laboratory. Implementing this principle has long been a mainstay of retrosynthetic analysis in our group, the corollary being that several of our most pleasing cascade sequences have been inspired from Nature's exquisite biosynthetic pathways.

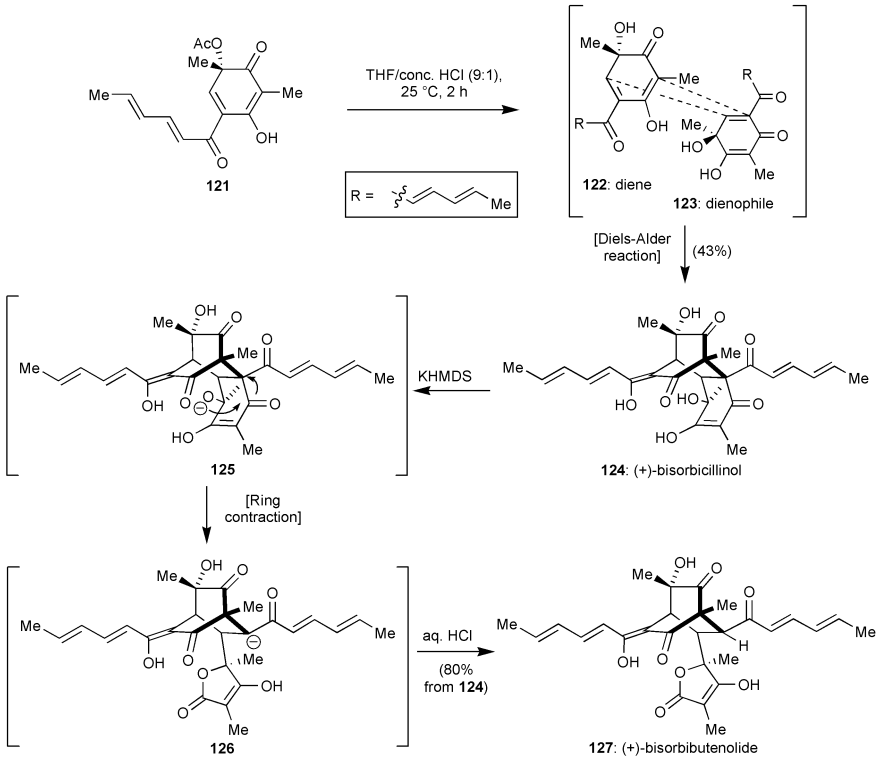
Our initial foray into the 'biomimetic' area of synthesis was sparked by a curiosity discovered in the endiandric acid family of natural products isolated by Black and co-workers from the endemic Australian plant *Endiandra introrsa*.[45] The puzzle lay in the observation that these compounds (which possess eight stereocenters) exist as racemic mixtures, a highly atypical occurrence for molecules derived from natural sources where homochiral enzymes are, in general, intimately involved in templating and orchestrating their syntheses. In response to this unusual finding, Black advanced an intriguing proposal in which it was suggested that the 'biosynthesis' of these secondary metabolites was initiated from achiral polyunsaturated precursors and progressed through a series of non-enzymatic electrocyclizations to furnish endiandric acids E–G (**110**, **117**, **118**, Scheme 16, shown as their methyl esters), followed by a terminating Diels–Alder reaction affording the final adducts, endiandric acids A–C (**112**, **119**, **120**). The provocative nature of this elegant proposal, heightened by the fact that endiandric acid D (**111**, which cannot undergo further elaboration by Diels–Alder cycloaddition due its stereochemistry) was merely anticipated having not yet been isolated, stimulated us to attempt to test and hopefully translate the hypothesis into an actual chemical synthesis. Thus, we chose to exploit the theoretically well-understood, but at the time relatively under-explored, electrocyclizations involving initial disrotatory 6π, followed by conrotatory 8π electron reaction modes starting from a linear unsaturated precursor and proceeding under the governance of the Woodward–Hoffmann rules.[46] Encoded in the geometry of these precursors would be the information necessary to engender the stereocontrolled construction of all the rings and chiral centers. Having these objectives in mind the requisite precursors (**107** and **113**) were assembled in short order to enable a systematic study of the endiandric acid cascade. With a mix of trepidation and a culpable sense of excitement, **107** was treated with Lindlar's catalyst and quinoline under carefully monitored conditions, followed by brief exposure of the resulting material to an elevated temperature (100 °C). Gratifyingly, it was possible to isolate endiandric acid A methyl ester (**112**) from this mixture in 30% yield. The power of this cascade can only be fully appreciated when one recognizes that in a single operation a simple linear precursor had been converted into a complex tetracycle with complete relative control over the formation of eight stereocenters. Similarly, we were able to synthesize endiandric acids B and C as their methyl esters (B, **119** and C, **120**) beginning with hydrogenation of polyene **113** in a combined yield of 28% and *ca.* 4.5 : 1 (**119** : **120**) ratio following the same resplendent cascade reaction sequence. When the temperature elevation was excluded from the protocol, it was then possible to interrupt the cascades and isolate all the intermediate endiandric acids D–G (**110**, **111**, **117**, **118**) from the respective reaction mixtures as their methyl esters. With these successful results in hand, we had aptly demonstrated that Black's insightful hypothesis regarding a non-enzymatic biogenic origin for the endiandric acids was feasible and, concurrently, supplied a powerful and edifying cascade for the archives of our group. The enviable performance of this cascade in generating molecular complexity remained unchallenged in our efforts until the conception of the next two exemplars described below, namely the biomimetic total syntheses of the (+)-bisorbibutenolide (**127**) and trichodimerol (**131**).



Scheme 16 The total synthesis of endiandtric acid methyl esters A–C (**112**, **119**, **120**) by a biomimetically inspired cascade sequence. (1982)[46]

The bisorbicillinoids[47] are a class of natural products isolated from various distinct species of fungi and endowed with a disparate set of biological profiles which reflects their structural diversity.[48,49] This variety conceals a common biological ancestry which is believed to be predicated upon dimerization pathways of sorbillicin and its enantioselectively oxidized congener, sorbicillinol (**122**). These biosynthetic hypotheses have captivated a number of groups,[48*a*,*b*] including ours.[50] Nevertheless, the reduction of these incisive theoretical postulates to laboratory blueprints was obviously challenging, but was deemed to be the only means by which a true empirical insight into the key processes could be provided. Our initial goal in this endeavor was to find a method to controllably generate sorbicillinol (**122**) or a protected form thereof (*e.g.* **121**) from sorbicillin, an aspiration finally achieved after many failures by treating sorbicillin with dry $Pb(OAc)_4$ in degassed acetic acid followed by purification using chiral HPLC in order to accomplish separation of the two enantiomers. To our delight, hydrolysis of the acetate **121** in acidic media (or as mediated by base with subsequent acidification) afforded the Diels–Alder adduct (+)-bisorbicillinol (**124**) in 43% yield, presumably through the fleeting intermediacy of **122** and its tautomer **123**. This remarkable Diels–Alder reaction proceeded with complete regio- and diastereocontrol (*endo* selectivity) generating four stereogenic centers, two of which are quaternary. However, this experiment does not constitute the end of the tale because *in situ* treatment of this tricyclic adduct with KHMDS initiated the next maneuvre in the domino series by deprotonating a tertiary alcohol within **125**, leading to an alkoxide which engaged the nearby carbonyl group in an anionic rearrangement to contract the fused ring affording (+)-bisorbibutenolide (**127**) in high yield (80%, see Scheme 17).[50] Overall, this sequence substantiates the original biosynthetic hypotheses developed by Abe for these members of the bisorbicillinoids.[48*a*,*b*]

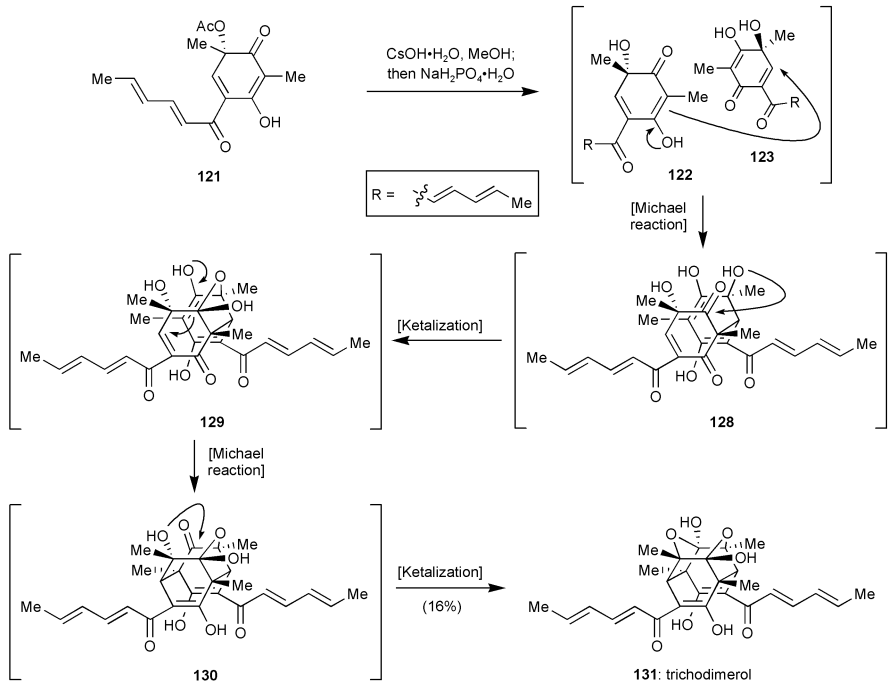
Following this success, we next turned our attention to trichodimerol (**131**), an inhibitory agent against lipopolysaccharide-induced production of tumor necrosis factor α (TNF_α) in human monocytes (then considered a promising lead for the treatment of septic shock).[49] In 1999 we had delineated a detailed proposal for the biosynthesis of **131** in which we suggested that sequential, double Michael addition/ketalization events starting from the same fleeting derivative (**122**) of sorbicillin as we had utilized in our approach to (+)-bisorbibutenolide (**127**) could be used to access trichodimerol (**131**). We postulated that the crucial parameter to control the switch from one dimerization pathway (toward bisorbibutenolide **127**) to a second (toward trichodimerol **131**) was control of water content, since an excess of this species would likely inhibit the



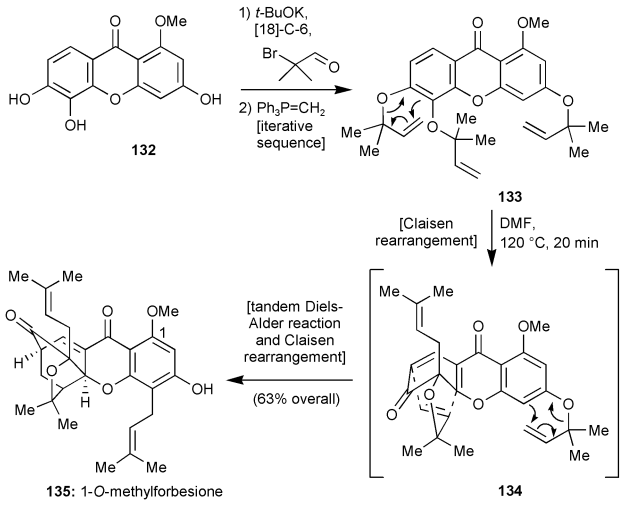
Scheme 17 Cascade sequences featured in the biomimetic syntheses of the bisorbicillinoids. (1999)[50]

ketalization steps intrinsic to the latter option. Indeed, after extensive and exacting fine-tuning of the reaction conditions combined with a vigilant limitation of the water present to stoichiometric quantities, the proposed biomimetic synthesis of trichodimerol (**131**) was accomplished through treatment of **121** with $CsOH{\cdot}H_2O$ in MeOH followed by neutralization with finely powdered $NaH_2PO_4{\cdot}H_2O$ at ambient temperature over the course of 12 h (see Scheme 18).[50] This extraordinary dimerization event produced eight chiral centers in one cascade, no less than six of which are fully substituted quaternary carbons; the process occurred fully in accordance with our postulated biosynthesis. We were subsequently able to exploit this aesthetically pleasing sequence to produce a number of designed analogues of trichodimerol (**131**), demonstrating its practical applicability as well.[50c,51]

Along related lines, we were recently able to confirm a biosynthetic hypothesis first proposed over thirty years ago by Quillinan and Scheinmann[52] for the construction of numerous secondary metabolites, particularly isolates of the Guttiferae family, by the synthesis of 1-*O*-methylforbesione (**134**, Scheme 19) using a tandem double Claisen rearrangement/Diels–Alder strategy.[53] Testing the viability of this scenario first required



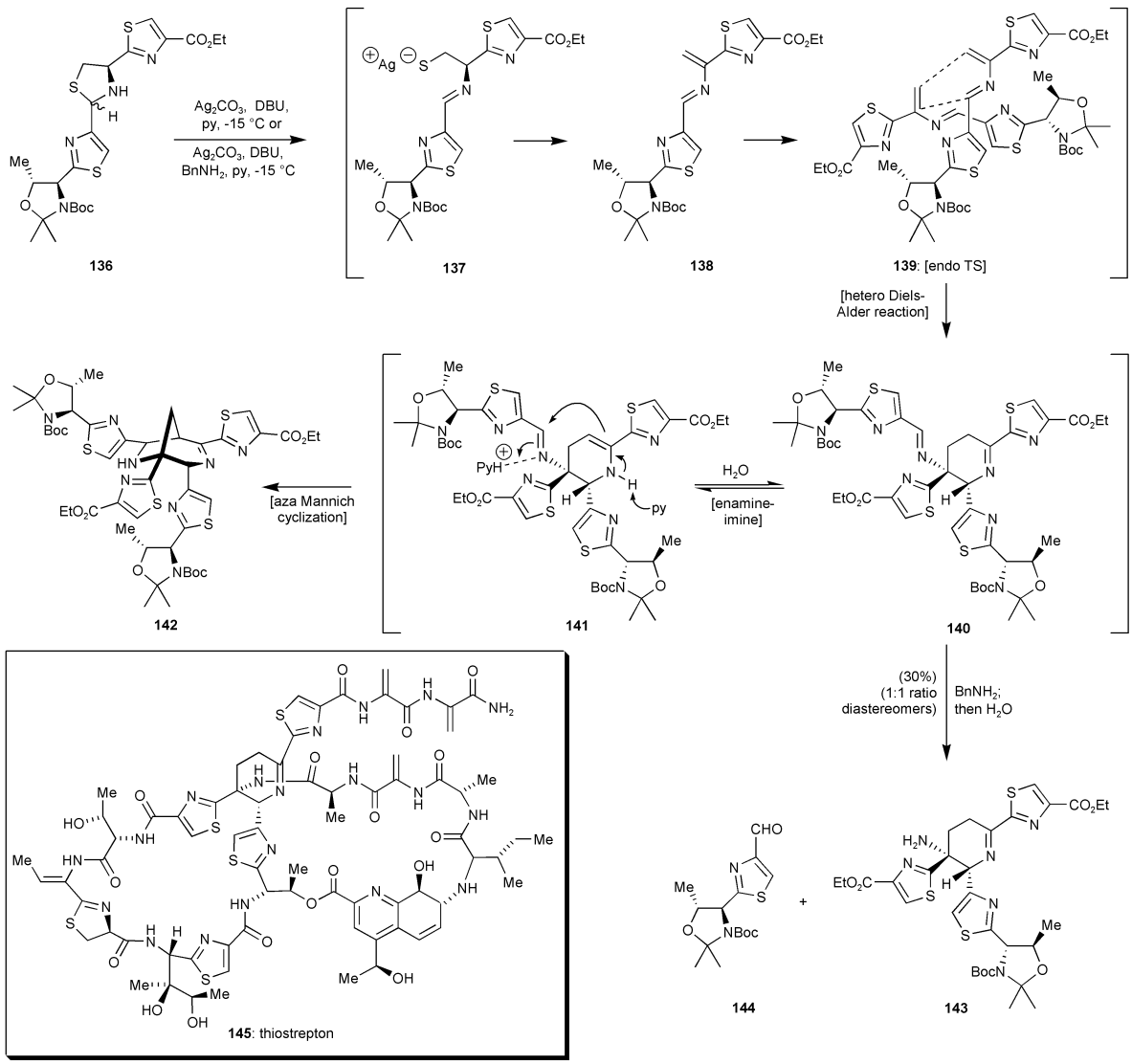
Scheme 18 Total synthesis of trichodimerol (**131**) through a dimerization event based on a double Michael/double ketalization sequence. (1999)[50]



Scheme 19 Putative biomimetic total synthesis of 1-*O*-methylforbesione (**135**) *via* a cascade sequence featuring two Claisen rearrangements and an intramolecular Diels–Alder reaction. (2001)[53]

construction of xanthone **132**, which we achieved in three steps from known starting materials. This material (**132**) was then converted to the cascade precursor by an iterative alkylation/Wittig reaction series to yield **133**. Gratifyingly, when the prenylated xanthone **133** was heated at 120 °C for 20 min, the desired product, 1-*O*-methylforbesione (**135**), was isolated in 63% yield, presumably *via* two Claisen rearrangements and a Diels–Alder reaction whose precise position in the order of events remains unverified.[53] Once again, this elegant cascade illustrates the power of pericyclic reactions in the rapid and efficient construction of molecular complexity from simple precursors, a concept greatly magnified when more than one of these processes is applied in a tandem fashion.

We end this account with an indomitable molecule that demands a particularly intense level of deliberation and imagination to assemble successfully, explicitly the antibiotic thiostrepton (**145**, Scheme 20).[54] This large thiopeptide structure exhibits a rigid bicyclic framework whose fulcrum is a challenging quaternary carbon housed within a unique dehydropiperidine domain, a motif which we have chosen to construct by a route based upon a biomimetic retrosynthetic analysis[55] wherein the dimerization cascade of an azadiene (**138**) plays a pivotal role. In the elegant biosynthetic studies by Floss and co-workers[55] it had been proposed that following dehydration of two serine residues, a [4+2] cyclization event followed by redox adjustment could form the 6-membered didehydropiperidine ring in thiostrepton. We elected to implement this strategy through the use of a thiazolidine precursor



Scheme 20 Biomimetic pathway based on a hetero Diels–Alder dimerization of imines to forge the central didehydropiperidine portion of thiostrepton (**145**). (2002)[57]

(**136**) that could be readily assembled from L-cysteine and L-threonine. With **136** in hand, the scene was then set to test the hetero Diels–Alder[56] cascade proposal. Towards this end, cleavage of the thiazolidine (**136**) was realized upon treatment with Ag_2CO_3 and catalytic amounts of DBU at −15 °C, an event that we presume also initiated an elimination to generate the coveted azadiene (**138**) which acted as both diene and dienophile. The hetero Diels–Alder dimerization proceeded regio- and endoselectively; no facial preference, however, was observed with the result that the product was formed as a diastereomeric mixture.[57,58] During the early exploration phases into this ambitious cascade, we were perturbed by the observation of a by-product (**142**) which constituted a large proportion of the resulting product mixture. The bridged bicyclic core of this contaminant apparently arose from the stereospecific aza-Mannich reaction of the intermediate **141** (a tautomer of our desired Diels–Alder adduct, **140**) that proceeded in preference to the desired hydrolysis of imine **140**. To our delight, we were able to modify the protocol to exorcise this bothersome deviation by opting for transamination as a replacement for the original water quench. Thus, incorporation of stoichiometric amounts of benzylamine into the procedure fruitfully achieved this objective and allowed isolation of the desired product **143** in 30% yield (based on a maximum yield for dimerization of 50%). In addition, we recovered aldehyde **144** in 34% yield that could then be recycled to **136**, thus enhancing the efficiency of this rather sophisticated and elegantly choreographed sequence.

Epilogue and future perspectives

For almost a century, cascade reactions and biomimetic sequences have been recognized as an attractive feature of elegant strategies for the expedient total synthesis of natural products and other complex molecules. It is only in the last two to three decades, however, that the potentially enormous dividends arising from the use of such strategies and tactics have been fully appreciated and translated into an impressive number of ingenious applications in the realm of chemical synthesis.[59] Indeed, judging from the flurry of reports in the literature in 2002[60] from the field of chemical synthesis alone, the trend appears to be continuing with an unabated and accelerated pace.

To incorporate such a powerful sequence into a designed scheme wherein a starting material is programmed to provide a product that then becomes the substrate for the next reaction (under the activating influence of heat, light, various reagents or catalysts) may very well be the key to conveniently accessing the more complex architectures and diverse targets of the future, due to the efficient and clean manner in which multiple bonds are often forged in these processes. Indeed, if we follow this paradigm as we move onwards through the new century, we may find the conduits for synthesis that have unparalleled efficacy and scope with which we can reach even the most puzzling members of Nature's large library of molecules. It is appropriate in closing our discussion to end, as we did with our examples, by paying homage to Nature's prowess because in the aspirations we have just delineated we must acknowledge that the master artisan is Nature herself and, for certain, we can be inspired and learn much from an apprenticeship under her mentoring.

It is with enormous pride and pleasure that we wish to thank our collaborators whose names appear in the references and whose contributions made the described work possible and enjoyable. We gratefully acknowledge the National Institutes of Health (USA), Merck & Co., DuPont, Schering Plough, Hoffmann-La Roche, GlaxoWellcome, Rhone-Poulenc Rorer, Amgen, Novartis, Abbott Laboratories, Bristol-Myers Squibb, Boehringer Ingelheim, Zeneca, CaPCURE, American BioScience, Array BioPharma, the George E. Hewitt Foundation, the Skaggs Institute for Chemical Biology, Pfizer (fellowship to S. A. S.), and the National Science Foundation (fellowship to S. A. S.) for supporting our research programs.

Notes and references

1 R. Robinson, *J. Chem. Soc*., 1917, 762.
2 (*a*) W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Myers, T. A. Bryson and D. H. Miles, *J. Am. Chem. Soc*., 1971, **93**, 4330; (*b*) W. S. Johnson, M. B. Gravestock and B. E. McCarry, *J. Am. Chem. Soc*., 1971, **93**, 4332; (*c*) M. B. Gravestock, W. S. Johnson, B. E. McCarry, R. J. Parry and B. E. Ratcliffe, *J. Am. Chem. Soc*., 1978, **100**, 4274.
3 (*a*) C. Vézina, A. Kudelski and S. N. Sehgal, *J. Antibiot*., 1975, **28**, 721; (*b*) S. N. Sehgal, H. Baker and C. Vézina, *J. Antibiot*., 1975, **28**, 727.
4 K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa and P. Bertinato, *J. Am. Chem. Soc*., 1993, **115**, 4419.
5 A. D. Piscopio, N. Minowa, K. Chakraborty, K. Koide, P. Bertinato and K. C. Nicolaou, *J. Chem. Soc., Chem. Commun*., 1993, 617.
6 K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty and N. Minowa, *J. Chem. Soc., Chem. Commun*., 1993, 619.
7 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc*., 1971, **93**, 2325.
8 K. C. Nicolaou, D. Hepworth, N. P. King and M. R. V. Finlay, *Pure Appl. Chem*., 1999, **71**, 989.
9 K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladourous, K. Paulvannan and E. J. Sorensen, *Nature*, 1994, **367**, 630.
10 K. C. Nicolaou and R. K. Guy, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 2079.
11 (*a*) K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros and E. J. Sorensen, *J. Am. Chem. Soc*., 1995, **117**, 624; (*b*) K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada and P. G. Nantermet, *J. Am. Chem. Soc*., 1995, **117**, 634; (*c*) K. C. Nicolaou, Z. Yang, J.-J. Liu, P. G. Nantermet, C. F. Claiborne, J. Renaud, R. K. Guy and K. Shibayama, *J. Am. Chem. Soc*., 1995, **117**, 645; (*d*) K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan and R. Chadha, *J. Am. Chem. Soc*., 1995, **117**, 653.
12 K. Narasaka, S. Shimada, K. Osoda and N. Iwasawa, *Synthesis*, 1991, 1171.
13 K. C. Nicolaou, T. Montagnon, P. S. Baran and Y.-L. Zhong, *J. Am. Chem. Soc*., 2002, **124**, 2245.
14 A. T. Bottini and J. Gal, *J. Org. Chem*., 1971, **36**, 1718.
15 K. C. Nicolaou and D. Gray, *Angew. Chem., Int. Ed*., 2001, **40**, 761.
16 M. A. Ernst-Russell, J. A. Elix, C. L. L. Chai, A. C. Willis, N. Hamada and T. H. Nash, *Tetrahedron Lett*., 1999, **40**, 6321.
17 A number of monomeric species resembling naphthazarin **34** have been isolated from natural sources, see: Y. Yamamoto, H. Matsubara, Y. Kinoshita, K. Kinoshita, K. Koyama, K. Takahashi, V. Ahmadhuam, T. Kurokawa and I. Yoshimura, *Phytochemistry*, 1996, **43**, 1239.
18 H. Sletter and H. Kuhlmann, *Synthesis*, 1979, 29.
19 (*a*) R. E. Dolle and K. C. Nicolaou, *J. Am. Chem. Soc*., 1985, **107**, 1691; (*b*) R. E. Dolle and K. C. Nicolaou, *J. Am. Chem. Soc*., 1985, **107**, 1693.
20 J. D. Bergstrom, M. M. Kurtz, D. J. Rew, A. M. Amend, J. D. Karkas, R. G. Bostedor, V. S. Bansal, C. Dufresne, F. L. VanMiddlesworth, O. D. Hensens, J. M. Liesch, D. L. Zink, K. E. Wilson, J. Onishi, J. A. Milligan, G. Bills, L. Kaplan, M. Nallin Omstead, R. G. Jenkins, L. Huang, M. S. Meinz, L. Quinn, R. W. Burg, Y. L. Kong, S. Mochales, M. Mojena, I. Martin, F. Pelaez, M. T. Diez and A. W. Alberts, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 80.
21 (*a*) M. J. Dawson, J. E. Farthing, P. S. Marshall, R. F. Middleton, M. J. O'Neill, A. Shuttleworth, C. Stylli, R. M. Tait, P. M. Taylor, H. G. Wildman, A. D. Buss, D. Langley and M. V. Hayes, *J. Antibiot*., 1992, **45**, 639; (*b*) P. J. Sidebottom, R. M. Highcock, S. J. Lane, P. A. Procopiou and N. S. Watson, *J. Antibiot*., 1992, **45**, 648.
22 (*a*) K. C. Nicolaou, A. Nadin, J. E. Leresche, E. W. Yue, S. La Greca, T. Tsuri and Z. Yang, *Angew. Chem., Int. Ed. Engl*., 1994, **33**, 2187; (*b*) K. C. Nicolaou, A. Nadin, J. E. Leresche, E. W. Yue and S. La Greca, *Angew. Chem., Int. Ed. Engl*., 1994, **33**, 2190; (*c*) K. C. Nicolaou, E. W. Yue, Y. Naniwa, F. De Riccardis, A. Nadin, J. E. Leresche, S. La Greca and Z. Yang, *Angew., Chem. Int. Ed. Engl*., 1994, **33**, 2184.
23 K. C. Nicolaou, E. W. Yue, S. La Greca, A. Nadin, Z. Yang, J. E. Leresche, T. Tsuri, Y. Naniwa and F. De Riccardis, *Chem. Eur. J*., 1995, **1**, 467.

24 (*a*) K. C. Nicolaou, S. Kim, J. Pfefferkorn, J. Xu, T. Ohshima, S. Hosokawa, D. Vourloumis and T. Li, *Angew. Chem., Int. Ed.*, 1998, **37**, 1418; (*b*) K. C. Nicolaou, J. Xu, S. Kim, J. Pfefferkorn, T. Ohshima, D. Vourloumis and S. Hosokawa, *J. Am. Chem. Soc.*, 1998, **120**, 8661.

25 K. C. Nicolaou, J. Xu, S. Kim, T. Ohshima, S. Hosokawa and J. Pfefferkorn, *J. Am. Chem. Soc.*, 1997, **119**, 11353.

26 K. C. Nicolaou, F. van Delft, T. Ohshima, D. Vourloumis, J. Xu, S. Hosokawa, J. Pfefferkorn, S. Kim and T. Li, *Angew. Chem., Int. Ed.*, 1997, **36**, 2520.

27 (*a*) For sarcodictyin's isolation, see: M. D'Ambrosio, A. Guerriero and F. Pietra, *Helv. Chim. Acta*, 1987, **70**, 2019; (*b*) M. D'Ambrosio, A. Guerriero and F. Pietra, *Helv. Chim. Acta*, 1987, **71**, 964. For the isolation of eleutherobin, see: T. Lindel, P. R. Jensen, W. Fenical, B. H. Long, A. M. Casazza, J. Carboni and C. R. Fairchild, *J. Am. Chem. Soc.*, 1997, **119**, 8744.

28 K. C. Nicolaou and P. S. Baran, *Angew. Chem., Int. Ed.*, 2002, **41**, 2678.

29 (*a*) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, H.-S. Choi, W. H. Yoon, Y. He and K. C. Fong, *Angew. Chem., Int. Ed.*, 1999, **38**, 1669; (*b*) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. C. Fong, Y. He, W. H. Yoon and H.-S. Choi, *Angew. Chem., Int. Ed.*, 1999, **38**, 1676; (*c*) K. C. Nicolaou, J.-K. Jung, W. H. Yoon, Y. He, Y.-L. Zhong and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **112**, 1829; (*d*) K. C. Nicolaou, J. Jung, W. H. Yoon, K. C. Fong, H.-S. Choi, Y. He, Y.-L. Zhong and P. S. Baran, *J. Am. Chem. Soc.*, 2002, **124**, 2183; (*e*) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. C. Fong and H.-S. Choi, *J. Am. Chem. Soc.*, 2002, **124**, 2190; (*f*) K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, J. Jung, H.-S. Choi and W. H. Yoon, *J. Am. Chem. Soc.*, 2002, **124**, 2202.

30 J. C. Martin and J. A. Franz, *J. Am. Chem. Soc.*, 1975, **97**, 6137.

31 K. C. Nicolaou, Y.-L. Zhong and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **39**, 622.

32 K. C. Nicolaou, P. S. Baran, Y.-L. Zhong and K. Sugita, *J. Am. Chem. Soc.*, 2002, **124**, 2212.

33 K. C. Nicolaou, K. Sugita, P. S. Baran and Y.-L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2221.

34 (*a*) N. Matsumoto, T. Tsuchida, M. Umekita, N. Kinoshita, H. Iinuma, T. Sawa, M. Hamada and T. Takeuchi, *J. Antibiot.*, 1997, **50**, 900; (*b*) N. Matsumoto, H. Iinuma, T. Sawa, T. Takeuchi, S. Hirano, T. Yoshioka and M. Ishizuka, *J. Antibiot.*, 1997, **50**, 906; (*c*) N. Matsumoto, T. Tsuchida, R. Sawa, H. Iinuma, H. Nakamura, H. Naganawa, T. Sawa and T. Takeuchi, *J. Antibiot.*, 1997, **50**, 912.

35 K. C. Nicolaou, K. Sugita, P. S. Baran and Y.-L. Zhong, *Angew. Chem., Int. Ed.*, 2001, **40**, 207.

36 K. C. Nicolaou, Y.-L. Zhong, P. S. Baran and K. Sugita, *Angew. Chem., Int. Ed.*, 2001, **40**, 2145.

37 A. D. Rodríguez and C. Ramírez, *Org. Lett.*, 2000, **2**, 507.

38 (*a*) K. C. Nicolaou, G. Vassilikogiannakis, W. Mägerlein and R. Kranich, *Angew. Chem., Int. Ed.*, 2001, **40**, 2482; (*b*) K. C. Nicolaou, G. Vassilikogiannakis, W. Mägerlein and R. Kranich, *Chem. Eur. J.*, 2001, **7**, 5359.

39 N. Lindquist, W. Fenical, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 2303.

40 (*a*) J. Li, S. Jeong, L. Esser and P. G. Harran, *Angew. Chem., Int. Ed.*, 2001, **40**, 4765; (*b*) J. Li, A. W. G. Burgett, L. Esser, C. Amezcua and P. G. Harran, *Angew. Chem., Int. Ed.*, 2001, **40**, 4770.

41 K. C. Nicolaou, M. Bella, D. Y.-K. Chen, X. Huang, T. Ling and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2002, **41**, 3495.

42 (*a*) E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, 1983, **24**, 2821; (*b*) D. J. Hart and F. L. Seely, *J. Am. Chem. Soc.*, 1988, **110**, 1631; (*c*) P. A. Bartlett, K. L. McLaren and P. C. Ting, *J. Am. Chem. Soc*, 1988, **110**, 1633.

43 (*a*) G. E. Keck, T. T. Wager and S. F. McHardy, *Tetrahedron*, 1999, **55**, 11755; (*b*) J. L. Chiara, C. Destabel, P. Gallego and J. Marco-Contelles, *J. Org. Chem.*, 1996, **61**, 359; (*c*) G. E. Keck, S. F. McHardy and T. T. Wager, *Tetrahedron Lett.*, 1995, **36**, 7419.

44 K. C. Nicolaou, X. Huang, N. Giuseppone, P. B. Rao, M. Bella, M. V. Reddy and S. A. Snyder, *Angew. Chem. Int., Ed.*, 2001, **40**, 4705.

45 (*a*) W. M. Bandaranyake, J. E. Banfield, D. St. C. Black, G. D. Fallon and B. M. Gatehouse, *J. Chem. Soc., Chem. Commun.*, 1980, 162; (*b*) W. M. Bandaranayake, J. E. Banfield and D. St. C. Black, *J. Chem. Soc., Chem. Commun.*, 1980, 902; (*c*) W. M. Bandaranayake, J. E. Banfield, D. St. C. Black, G. D. Fallon and B. M. Gatehouse, *Aust. J. Chem.*, 1981, **34**, 1655; (*d*) W. M. Bandaranayake, J. E. Banfield and D. St. C. Black, *Aust. J. Chem.*, 1982, **35**, 557; (*e*) W. M. Bandaranayake, J. E. Banfield, D. St. C. Black, G. D. Fallon and B. M. Gatehouse, *Aust. J. Chem.*, 1982, **35**, 567; (*f*) J. E. Banfield, D. St. C. Black, S. R. Johns and R. I. Willing, *Aust. J. Chem.*, 1982, **35**, 2247.

46 (*a*) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin and J. Uenishi, *J. Am. Chem. Soc.*, 1982, **104**, 5555; (*b*) K. C. Nicolaou, N. A. Petasis, J. Uenishi and R. E. Zipkin, *J. Am. Chem. Soc.*, 1982, **104**, 5557; (*c*) K. C. Nicolaou, R. E. Zipkin and N. A. Petasis, *J. Am. Chem. Soc.*, 1982, **104**, 5558; (*d*) K. C. Nicolaou, N. A. Petasis and R. E. Zipkin, *J. Am. Chem. Soc.*, 1982, **104**, 5560.

47 The term 'bisorbicillinoids' was introduced by us to describe all dimeric natural products derived from sorbicillin.

48 (*a*) N. Abe, T. Murata and A. Hirota, *Biosci. Biotechnol. Biochem.*, 1998, **62**, 661; (*b*) N. Abe, T. Murata and A. Hirota, *Biosci. Biotechnol. Biochem.*, 1998, **62**, 2120; (*c*) O. Shirota, V. Pathak, C. F. Hossain, S. Sekita and K. Takatori, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2961.

49 (*a*) Trichodimerol (**131**) has been isolated independently from four different sources: (*a*) R. Andrade, W. A. Ayer and P. P. Mebe, *Can. J. Chem.*, 1992, **70**, 2526; (*b*) G. A. Warr, J. A. Veitch, A. W. Walsh, G. A. Hesler, D. M. Pirnik, J. E. Leet, P.-F. M. Lin, I. A. Medina, K. D. McBrien, S. Forenza, J. M. Clark and K. S. Lam, *J. Antibiot.*, 1996, **49**, 234; (*c*) O. Shirota, V. Pathak, C. F. Hossain, S. Sekita, K. Takatori and M. Satake, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2961; (*d*) N. Abe, T. Murata and A. Hirota, *Biosci. Biotechnol. Biochem.*, 1998, **62**, 661.

50 (*a*) K. C. Nicolaou, R. Jautelat, G. Vassilikogiannakis, P. S. Baran and K. B. Simonsen, *Chem. Eur. J.*, 1999, **5**, 3651; (*b*) K. C. Nicolaou, K. B. Simonsen, G. Vassilikogiannakis, P. S. Baran, V. P. Vidali, E. N. Pitsinos and E. A. Couladouros, *Angew. Chem., Int. Ed.*, 1999, **38**, 3555; (*c*) K. C. Nicolaou, G. Vassilikogiannakis, K. B. Simonsen, P. S. Baran, Y.-L. Zhong, V. P. Vidali, E. N. Pitsinos and E. A. Couladouros, *J. Am. Chem. Soc.*, 2000, **122**, 3071.

51 A synthesis of enantiomerically pure trichodimerol (**131**) using an oxidation–Michael–ketalization strategy was also reported by D. Barnes-Seeman and E. J. Corey, *Org. Lett.*, 1999, **1**, 1503.

52 A. J. Quillinan and F. Scheinmann, *J. Chem. Soc., Chem. Commun.*, 1971, 966.

53 K. C. Nicolaou and J. Li, *Angew. Chem., Int. Ed.*, 2001, **40**, 4264.

54 (*a*) J. F. Pagano, M. J. Weinstein, H. A. Stout and R. Donovick, *Antibiot. Annu.*, 1955–1956, 554; (*b*) J. Vandeputte and J. D. Dutcher, *Antibiot. Annu.*, 1955–1956, 560; (*c*) B. A. Steinberg, W. P. Jambor and L. O. Suydam, *Antibiot. Annu.*, 1955–1956, 562.

55 U. Mocek, Z. Zeng, D. O'Hagan, P. Zhou, L.-D. G. Fan, J. M. Beale and H. G. Floss, *J. Am. Chem. Soc.*, 1993, **115**, 7992.

56 (*a*) For an example of a similar dimerization, see: G. Wulff and H. T. Klinken, *Tetrahedron*, 1992, **48**, 5985; (*b*) G. Wulff, H. G. Lindner, H. Bohnke, A. Steigel and H. T. Klinken, *Liebigs Ann. Chem.*, 1989, 527; (*c*) G. Wulff and H. Bohnke, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 90.

57 K. C. Nicolaou, M. Nevalainen, B. Safina, M. Zak and S. Bulat, *Angew. Chem., Int. Ed.*, 2002, **41**, 1941.

58 For a recent review of the Diels–Alder reaction in total synthesis, see: K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. E. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668.

59 (*a*) For selected reviews on the topic of cascade and domino reactions in synthesis, see: A. J. McCarroll and J. C. Walton, *Angew. Chem., Int. Ed.*, 2001, **40**, 2224; (*b*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*c*) R. A. Bunce, *Tetrahedron*, 1995, **51**, 13103.

60 (*a*) For a selected number of instructive examples of cascade strategies and biomimetic syntheses reported in 2002 see: P. S. Baran and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 7904; (*b*) M. E. Layton, C. A. Morales and M. D. Shair, *J. Am. Chem. Soc.*, 2002, **124**, 773; (*c*) D. A. Vosburg, C. D. Vanderwal and E. J. Sorensen, *J. Am. Chem. Soc.*, 2002, **124**, 4552; (*d*) M. Shoji, J. Yamaguchi, H. Kakeya, H. Osada and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2002, **41**, 3192; (*e*) A.-L. Dhimane, C. Aïssa and M. Malacria, *Angew. Chem., Int. Ed.*, 2002, **41**, 3284; (*f*) L. A. Paquette and F. Geng, *J. Am. Chem. Soc.*, 2002, **124**, 9199.