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Editorial

Terpenoid- and Shikimate-Derived Natural Product Total Synthesis: A Personal Analysis and Commentary on the Importance of the Papers That Appear in this Virtual Issue

Introduction. In August 2012, Professor Amos B. Smith III, the Editor-in-Chief of *Organic Letters*, wrote to all of the *OL* Associate Editors, to ask if we would each be willing to Guest Edit a special *OL*, *JOC*, and *JACS* Virtual Issue, on a research topic of our very own choosing. The brief was to highlight outstanding organic chemistry research achievements that had been published in all three journals, over the previous two years, and to provide appropriate expert commentaries on the long-lasting importance and legacy of the individual papers that had been selected.

At about the time of Professor Smith's e-mail, my fellow *Organic Letters* Associate Editor, Professor William Lubell, had just completed his very successful guest editing of a most useful *OL*, *JOC*, *JACS* Virtual Issue on the topic of "*Peptide Chemistry*,"[1] and shortly before him, Professor Carsten Bolm of *JOC* had compiled an equally valuable Virtual Issue on the theme of "*Cross-Coupling Reactions*".[2] Both surveys identified papers that beautifully reflected the state of the art of the two fields in 2012, and both Editors are to be commended for their individual selections, as well as for the insightful commentaries they provided which, collectively, have helped create an enduring reference work that will serve the community well for many years to come.

Inspired by their efforts, and the expert 2008 *JACS* Select on the "*Total Synthesis of Biologically Active Natural Products*",[3] by Professor William R. Roush, I agreed to compile a similar *OL* Virtual Issue on the topic of "*Terpenoid- and Shikimate-Derived Natural Product Total Synthesis*" for publication in July 2013, and I am now pleased to report that this task is complete.

It has been my aim to create a Virtual Issue that contains some of the most meritorious and interesting research papers that have been published in these two synthetic areas over the period July 2011 to May 2013, publications that stand out not only for the novelty and excellence of the organic chemistry they expound but also for their grace and sheer elegance of approach.

I have attempted to do this in a most catholic way, by gathering together papers from team leaders of many different nationalities, age groups, and genders. Although I have populated this Issue primarily with papers from the aforesaid areas, there have been some valuable contributions included from interface disciplines, such as diterpenoid alkaloid synthesis, although the coverage of meroterpenoid natural products (*viz.* terpenoids of mixed biosynthetic origin) has not been my main thrust, by any means. While some readers may feel that I have gone well beyond my remit, by including such work, I have ultimately let the Cornforth 1968 definition of meroterpenoids,[4] and the quality of the published chemistry, finally determine whether a piece of chemistry should or should not be present; plus I wanted this Virtual Issue to have as broad an appeal as possible. With the scope of my coverage defined, I will begin my discussion of the topic of "*Terpenoid- and Shikimate-Derived Natural Product Total Synthesis*", by commenting initially on the importance of complex molecule total synthesis.

The Importance of Complex Molecule Total Synthesis As a Modern-Day Scientific Pursuit. As the number of new reagents and organic reactions continues to grow, so too does the need to test out the genuine synthetic worth of many of these technologies. Complex molecule total synthesis allows us to do this very effectively by pitting many of these new synthetic protocols against the most challenging and uncompromising of synthetic problems. As such, it provides us with a reliable bellwether and magnifying lens on the overall utility of many recently developed synthetic methods in difficult and demanding situations.

Not only does such rigorous testing expose the fundamental weaknesses and shortcomings of the different

(1) Lubell, W. D. *Org. Lett.* **2012**, *14*, 4297.
(2) Bolm, C. *J. Org. Chem.* **2012**, *77*, 5221.
(3) Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 6654.

(4) (a) Cornforth, J. W. *Chem. Br.* **1968**, *4*, 102. (b) For a recent authoritative review on meroterpenoid chemistry, see: Geris, R.; Simpson, T. J. *Nat. Prod. Rep.* **2009**, *26*, 1063.

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synthetic protocols, it also helps to define their spheres of operation. It accurately pinpoints the true success stories of the subject and delineates the precise theaters where such reaction technologies can be strategically deployed. As a result, complex molecule total synthesis imparts power and predictability to the art, science, and practice of modern-day organic synthesis; it is thus a highly important endeavor.

The ever-growing roll call of failed synthetic strategies that we typically see reported in most complex molecule total syntheses not only helps to establish the methodological boundaries of the present-day subject, it also further initiates and drives many of the exciting new synthetic chemistry developments that continually keep appearing in our organic chemistry journals, while also greatly expanding our knowledge and understanding of chemistry as a whole.

Complex molecule total synthesis is thus an enduring pursuit of great scientific worth and of long-lasting value to the subject of chemistry. It is an enterprise that critically underpins the future advancement and absolute vibrancy of our subject. These points aside, there are other reasons why such effort is highly topical, worthwhile, and in need of continuation and support long into the future.

There are numerous, exceedingly rare, natural product molecules continually being discovered that have unique and unusual biological profiles. Many of these have the ability to selectively perturb cells in such a way that the functions and interconnections of various genes, proteins, and signaling pathways can be precisely established and delineated. The total synthesis of such molecules[5] can, on occasion, offer the only reliable method for accessing these substances (or their analogues), in quantities sufficient to allow this type of fundamental biological discovery work to take place. Complex molecule total synthesis thus plays an important enabling role in helping many areas of modern-day biology advance and further develop.[6] It is thus an endeavor that can give us extraordinary new insights into the origins and progression of many human, animal, and plant diseases. Sophisticated total synthesis can, periodically, furnish us with the novel affinity reagents that we need to isolate new proteins or help define the biological targets of some drugs. Schreiber's brilliant work in the histone deacetylase area, with isotopically labeled trapoxins,[7] is just one real-life example of how total synthesis can open up whole new fields of biology in a fundamentally important way that can significantly impact human medicine and drug discovery. However, there are many other examples that we can point to, where synthetically derived complex natural product molecules have made similar biomedically important contributions.

On occasion, complex molecule total synthesis can serve as the only viable method for verifying a postulated structure for a biologically relevant molecule.

In other instances, it offers us the only means whereby we can probe important biosynthetic pathways. One excellent example of this can be found in Walsh's work on the biosynthetic incorporation of 5-chloro-piperazic acid into the kutzneride antifungal natural products.[8]

Complex molecule total synthesis should thus be recognized and appreciated for what it truly is: as an important and genuinely cross-disciplinary research enterprise that helps drive the natural evolution and progression of science as a whole, through the powerful research contributions it makes to chemistry, biology, and human medicine.

Terpenoid- and Shikimate-Derived Natural Product Total Synthesis. If we return now to the specific focus of this themed Virtual Issue, it is probably fair to say that terpenoid- and shikimate-derived natural products are now providing some of the most structurally interesting and biologically relevant target molecules of the 21st Century; molecules whose synthetically challenging structures are offering some of the very greatest challenges for modern-day total synthesis; molecules that can test recently developed synthetic methods to their absolute limits, while also themselves inspiring the design of many new synthetic methods, most especially reactions for complex ring-assembly. For all these reasons, and many biological ones besides, I felt that the community would welcome a Virtual Issue that paid homage to some of the recent synthetic triumphs of these two fields over the past two years.

I have to say, at the outset, that I have been greatly inspired by all of the work that has appeared in this Virtual Issue which I believe is of the very highest academic quality. The papers that it contains not only demonstrate the great intellectual capital that many synthetic organic chemists bring to this discipline but also reveal the remarkable determination with which those individuals prosecute and complete complex research projects, and I have particularly admired the magnificent contributions of some of our younger colleagues, such as Sarah Reisman (Caltech), Jonathan George (U of Adelaide), Chi-Sin Lee (Peking U), Guangxin Liang (Nankai U), Stefan Kirsch (TU Munich), and Craig

(5) (a) (+)-Azinothricin and (+)-kettapeptin: Hale, K. J.; Manaviazar, S.; George, J. H.; Walters, M. A.; Dalby, S. M. *Org. Lett.* **2009**, *11*, 733. (b) (−)-Agelastatin A: Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615. (c) Gram-Scale (+)-Discodermolide: Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (d) Halichondrin, C.; Yamamoto, A.; Ueda, A.; Bremond, P.; Tiseni, P. S.; Kishi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 893. (e) Gram-Scale Spongistatin 1: Smith, A. B., III; Tomioka, T.; Risatti, C. M.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* **2008**, *10*, 4359.

(6) (a) Hale, K. J.; Manaviazar, S.; Lazarides, L.; George, J.; Walters, M. A.; Cai, J.; Delisser, V. M.; Bhatia, G. S.; Peak, S. A.; Dalby, S. M.; Lefranc, A.; Chen, Y.-N. P.; Wood, A. W.; Crowe, P.; Erwin, P.; El-Tanani, M. *Org. Lett.* **2009**, *11*, 737. (b) Hale, K. J.; Manaviazar, S.; George, J. *Chem. Commun.* **2010**, *46*, 4021. (c) Mason, C. K.; McFarlane, S.; Johnston, P. G.; Crowe, P.; Erwin, P. J.; Domostoj, M. M.; Campbell, F. C.; Manaviazar, S.; Hale, K. J.; El-Tanani, M. *Mol. Cancer Ther.* **2008**, *7*, 548.

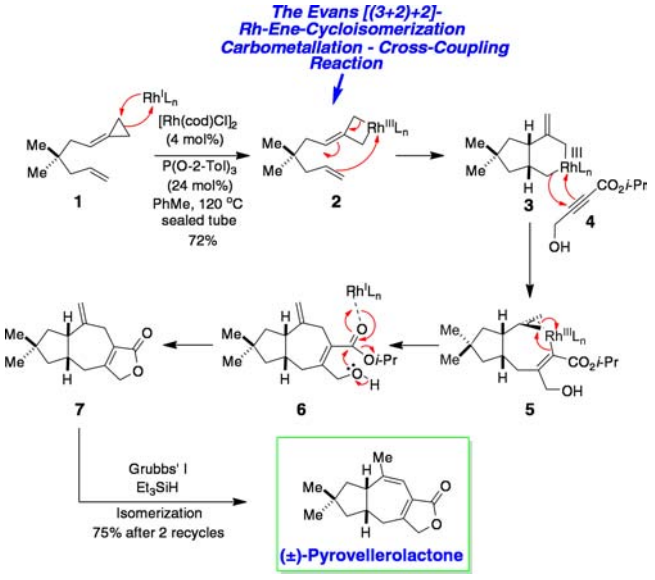
(7) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412.

(8) Jiang, W.; Heemstra, J. R., Jr.; Forseth, R. R.; Neumann, C. S.; Manaviazar, S.; Schroeder, F. C.; Hale, K. J.; Walsh, C. M. *Biochemistry* **2011**, *50*, 6063.

Williams (U of Queensland) to name but a few. Their efforts give me great hope for the well-being of our discipline long into the future, for they show that the talent pool is still strong and great in organic chemistry, and not diminishing in any way at all, despite the many pressures on our field. So, without any further delay, let me give you my personal overview of the significance of the various individual contributions that have been selected for inclusion in this Virtual Issue of *OL*, *JOC*, and *JACS*.

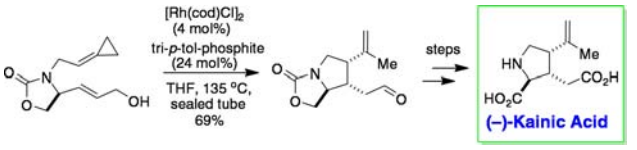
Chemical reactions that can efficiently assemble several carbocyclic rings at once always command the community's attention. One especially powerful example of such a process is provided by Professor P. Andrew Evans' rhodium(I)-catalyzed alkenylidene-cyclopropane Ene-cycloisomerization reaction, which he and his team elegantly

Scheme 1. Part of the Synthetic Strategy Used by Professor P. Andrew Evans To Secure (±)-Pyrovellerolactone



unveiled in their total synthesis of the tricyclic sesquiterpenoid, (±)-pyrovellerolactone, a paper that first appeared in *OL* in early 2013.[9] The key step in this synthesis was the new higher-order [(3 + 2) + 2]-carbocyclization process that it purveyed with the nonsymmetric alkynoate **4** (Scheme 1), which produced the tricyclic adduct **7** alongside the separable regioisomer (rs = 3.5:1), in a combined yield of 92% (72% of **7**). Tricycle **7** was then advanced forward into (±)-pyrovellerolactone by a simple olefin isomerization that involved the Grubbs type-1 catalyst and Et_3SiH. Why the reaction, involving **1** and **4**, stands out is because it builds up the target's three rings in a sequential and highly ordered fashion, while also controlling the *cis*-ring junction stereochemistry that is present with outstanding precision (>19:1 dr). Another notable aspect of the work is the way in which the regiochemical outcome of the butenolide annulation step was controlled by the judicious positioning of the propargylic alcohol in the final carbometalation substrate **4**, an adjustment which favored the formation of adduct **5** in which the newly established metal center was placed directly adjacent to the electron-withdrawing carbonyl, to allow a subsequent seven-membered ring closure to occur followed by lactonization. This was a most impressive reaction cascade, and it came not long after an earlier and equally captivating (−)-α-kainic acid synthesis reported by Evans in *JACS* in 2012,[10] where a lower-order Rh(I)-mediated Ene-carbocyclization underpinned the key skeleton-forming step (Scheme 2). In most of the published literature to date, the majority of metal-catalyzed Ene-cycloisomerization reactions have involved 1,6-enynes, and so, this new process wherein Evans employs 1,6-dienes is of great interest,[11] even if it does involve alkenes that possess activated exocyclic cyclopropene units. Given the high level of molecular complexity that can be readily sculpted with this new chemistry, one can only imagine the likely future target synthesis settings in which it will most probably be deployed over the coming years.

Scheme 2. The Lower-Order Rh(I)-Mediated Ene-Carbocyclization Used by Evans in His (−)-Kainic Acid Total Synthesis



Continuing with the theme of transition-metal-mediated carbocycle formation, I draw attention to another highly unusual ring-forming method that appears in this Virtual Issue, namely, the platinum(IV)-mediated tandem 6-*endo*-*dig* cyclizative-pinacol rearrangement of 3-silyloxy-1,5-enynes developed by Kirsch and his team at the Technical University of Munich, which provides a powerful new entry into complex [3a,7a]-dialkyloctahydro-1*H*-indene ring systems of the type found in many sesquiterpenoid natural products.[12] To demonstrate the utility of this remarkable new method in real-life total synthesis, Kirsch and his team devised a remarkably elegant new synthetic pathway[12] (Scheme 3) to the naturally occurring herbicide, (+)-cyperolone,[13,14] a molecule rendered daunting by the two vicinal quaternary carbon

(9) Evans, P. A.; Inglesby, P. A.; Kilbride, K. *Org. Lett.* **2013**, *15*, 1798.

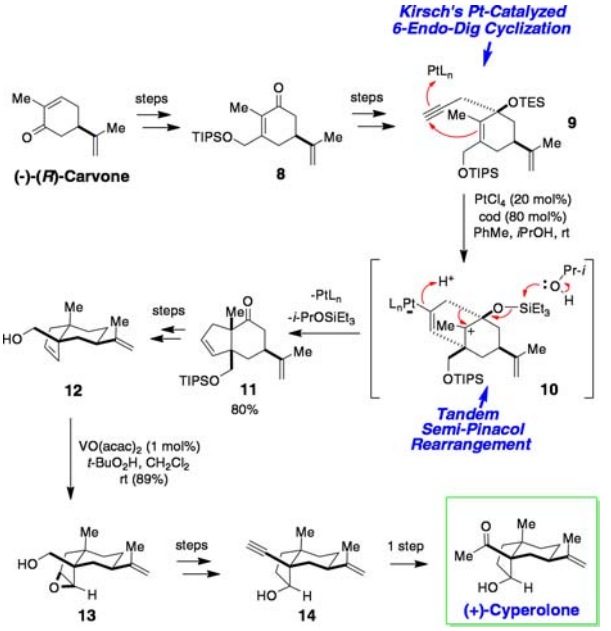
(10) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 3635.

(11) For early work on the Rh(III)-catalyzed Ene-reaction to make pyrrolidines, see: (a) Schmitz, E.; Heuuck, U.; Habisch, D. *J. Prakt. Chem.* **1976**, *318*, 471. For later work from the Grigg laboratory where Wilkinson's catalyst was used to effect cycloisomerization, see: (b) Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1745. For Furstner and Oppolzer's report on the use of a Rh(I)-complex to effect a similar process on allylic acetates: (c) Oppolzer, W.; Furstner, A. *Helv. Chim. Acta* **1993**, *76*, 2329.

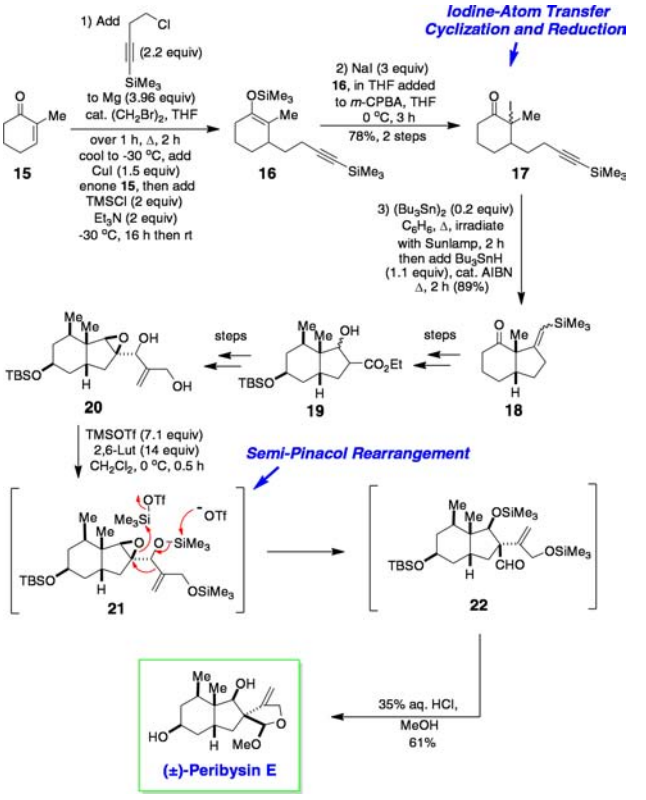
(12) Klahn, P.; Duschek, A.; Liebert, C.; Kirsch, S. F. *Org. Lett.* **2012**, *14*, 1250.

(13) (a) (+)-Cyperalone isolation: (a) Hikino, H.; Aota, K.; Maebayashi, Y.; Takemoto, T. *Chem. Pharm. Bull.* **1966**, *14*, 1439. (b) Hikino, H.; Aota, K.; Maebayashi, Y.; Takemoto, T. *Chem. Pharm. Bull.* **1967**, *15*, 1349. (c) Plant growth inhibitory effects: Komai, K.; Seto, N.; Matsubayasi, K.; Hamada, M. *Zasso Kenkyu (Weed Res. Jp)* **1990**, *35*, 164.

Scheme 3. Some of the Key Steps in Professor Stefan Kirsch's Synthetic Route to (+)-Cyperolone



Scheme 4. A Summary of the Key Highlights in Professor Chin-Kang Sha's Total Synthesis of (±)-Peribysin E



stereocenters that lie at the ring-junction which, in a Cerberus-like way,[15] help guard against synthetic acquisition by the majority of contemporary synthetic methods. Having noted the presence of an isopropenyl group in the target, Kirsch selected (−)-(*R*)-carvone as the starting material for his synthesis, since this contains that stereochemically defined feature. Kirsch then cleverly manipulated the carvone skeleton until he obtained the requisite 3-silyloxy-1,5-enyne needed to implement his plan (compound **9**). Although Kirsch observed that the aforementioned electrophilic cyclization/semipinacol rearrangement could be mediated in 44% yield by $PtCl_2$ (10 mol %) in PhMe at 100 °C, when this catalyst was replaced by the much more electrophilic $PtCl_4$, in the presence of 0.8 equiv of cyclooctadiene, the desired cyclopentene ring annulation occurred at rt with complete stereocontrol, to give **11** in a greatly improved 80% yield on multigram scale, despite the great strain inherently present in the initially formed carbocation intermediate **10**. The bicycle **11** was then deoxygenated and the silyloxy group unmasked, to allow the target's secondary alcohol to be set via a hydroxyl-directed epoxidation on **12**. Alkyne elaboration and reductive epoxide opening thereafter yielded **14** which was readily manipulated into (+)-cyperolone in one more step. While the use of platinum salts for the electrophilic activation of alkynes is not new, the reaction coalition of tandem cationic cyclization and semipinacol rearrangement is, most especially in the context of sesquiterpenoid total synthesis. In the opinion of this Editor, this revolutionary new reaction of Kirsch provides a particularly well thought out way of setting the two seemingly impregnable quaternary stereocenters of (+)-cyperolone. No doubt, we will see other equally remarkable applications of this highly efficient tandem cyclization process effected on other natural product targets in the near future, most especially now that these Pt-catalyzed cyclization conditions have been identified as working in such a highly disciplined way.

Yet another stunning demonstration of the utility of the semipinacol rearrangement in sesquiterpenoid total synthesis[16] can be found in Chin-Kang Sha's 2011 *JOC* paper on the total synthesis of (±)-peribysin E,[17] a potential antimetastasis drug of possible future value for cancer treatment. In this elegant synthesis, we see a 2,3-epoxyallylic alcohol **20** being coaxed into undergoing this type of a rearrangement under extremely mild conditions (Scheme 4) to provide the aldehyde **22**, which thereafter was converted into the natural product by simple deprotection and O-acetalation. While Danishefsky had previously used a different type of semipinacol process in

(14) Semisynthesis: (a) Hikino, H.; Suzuki, N.; Takemoto, T. *Chem. Pharm. Bull.* **1966**, *14*, 1441. (b) Hikino, H.; Suzuki, N.; Takemoto, T. *Chem. Pharm. Bull.* **1967**, *15*, 1395.

(15) Cerberus is the savage three-headed dog (with serpent-like mane and tail), of Greek and Roman mythology, who eternally stands guard at the entrance to Hades (the underworld) to prevent the spirits of the dead from ever leaving; he is thus a creature of fear. Cerberus features in Dante's now famous "Inferno" poem; see: Alighieri, D. *The Divine Comedy: Inferno*, Canto VI.

(16) Review: Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823.

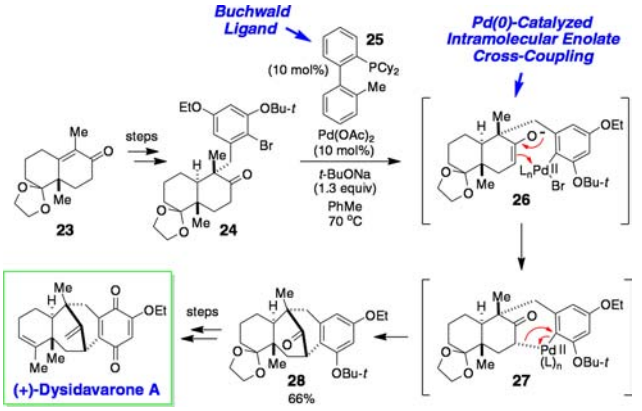
(17) Lee, H.-Y.; Sha, C.-K. *J. Org. Chem.* **2012**, *77*, 598.

(18) Angeles, A. R.; Waters, S. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13765.

his elegant route to (+)-peribysin E,[18] the Sha process was different as well as higher yielding and furnished only a single product. Other notable features of the Sha pathway included his novel synthesis of the α-iodo-ketone **17**, which was submitted to a photochemically induced iodine atom transfer radical cyclization (with catalytic hexabutylditin), to forge the desired *cis*-fused ring system. While such radical cyclizations have been extensively studied by Curran,[19] Crimmins,[20] and Taguchi,[21] among others,[22] these processes are still only used sporadically in complex natural product total synthesis, most especially the variant that we are seeing in this paper on (±)-peribysin E. Overall, there are many fascinating aspects to this total synthesis, which I strongly recommend readers to study in detail.

One truly outstanding example of an unusual transition-metal-mediated cyclization reaction being used to construct a highly strained medium-sized carbocyclic ring can be found in Menche's total synthesis of the naturally occurring antineoplastic terpenoid, (+)-dysidavarone A (Scheme 5).[23]

Scheme 5. Professor Dirk Menche's Use of an Intramolecular Enolate Cross-Coupling in His Asymmetric Total Synthesis of (+)-Dysidavarone A



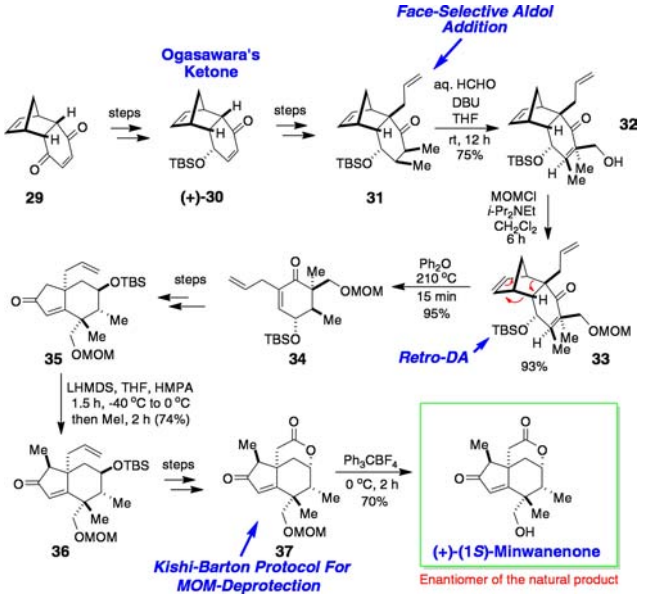
Here the main synthetic challenge resides in construction of the central, highly strained, eight-membered carbocycle, the synthesis of which is rendered particularly daunting by the presence of the bridgehead methylene unit and the alkoxy-quinone that lies annulated onto the eight-membered ring. How Menche overcame these inherent synthetic barriers was to apply an impressive intramolecular enolate cross-coupling reaction on **24**, mediated by $Pd(OAc)_2$ and the Buchwald phosphine ligand **25**.[24] While this internal cyclization undoubtedly benefitted from the presence of a favorable Thorpe–Ingold effect,[25] induced by the quaternary stereocenter present in the tether, as a counterpoint, it was also greatly disadvantaged by the fact that it used an aryl bromide as the internal cross-coupling partner (presumably for stability reasons). Indeed, such a choice would not normally be considered optimal, due to the fact that this same bromide was flanked by two large adjacent groups in the *o*-position, which would naturally disfavor oxidative addition of the Pd(0)-catalyst. These detractions aside, the use of Buchwald's excellent cross-coupling method,[24] by Menche, overcame these formidable obstacles, to furnish the desired product **28** in a noteworthy 66% yield, which is highly commendable, when one considers that most other established enolate arylation cross-coupling protocols all failed to give good results on this most recalcitrant of substrates. As with the (±)-peribysin E work of Sha, a close inspection of this important paper of Menche is strongly advised, since it also describes a greatly improved organocatalytic protocol for preparing the starting Wieland–Miescher ketone **23**.

Although we see Diels–Alder processes generally being used to add elements of permanent molecular complexity to most terpenoid structures, in Mehta's total synthesis of (+)-(1*S*)-minwanenone (*JOC*, 2012),[26] we see it used in a reverse mode, following the execution of a carefully planned and graded functionalization of the cyclohexenone ring in Ogasawara's chiral ketone (+)-**30** (Scheme 6).[27] The latter had originated from **29**, via reduction, O-acetylation, and application of Ogasawara's lipase mediated hydrolysis and kinetic resolution procedure, allied with additional steps.[27] Following implementation of the retro-Diels–Alder process on **33**, the highly substituted cyclohexenone **34** was obtained by what was a most elegant and extremely well-planned route. Besides the synthesis of **34**, there were many other notable transformations reported in the Mehta pathway to this challenging target, not the least of which was the stereospecific enolate C-methylation reaction that was conducted on **35** which, *a priori*, might have been expected to generate a mixture of epimers. However, as we can see, it did not; **36** was obtained as a single product in 74% yield. Mehta's use of the Kishi–Barton trityl tetrafluoroborate deprotection method for cleavage of the MOM ether from **37**,[28] right at the very end of the synthesis, is another item of note, for it left the potentially labile and strained lactone totally undisturbed. All told, this carefully planned synthesis of (+)-(1*S*)-minwanenone by Mehta and Shinde is a beautifully crafted piece of work that is rich in chemistry detail.

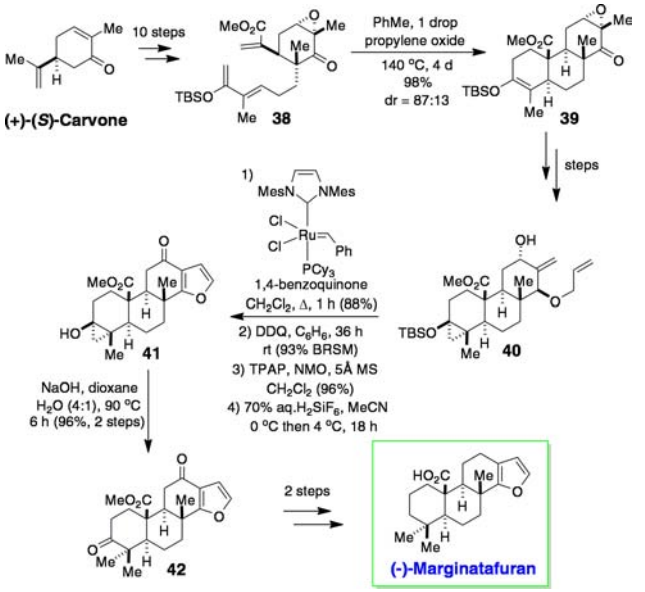
If we pursue the Diels–Alder cycloaddition theme still further, and examine Abad-Somovilla's route to the isospongian diterpenoid (−)-marginatafuran (published in

(19) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
(20) Crimmins, M. T.; Mascarella, S. W. *Tetrahedron Lett.* **1987**, *28*, 5063.
(21) Kitagawa, O.; Miyaji, S.; Sakuma, C.; Taguchi, T. *J. Org. Chem.* **2004**, *69*, 2607.
(22) Review: Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265.
(23) Schmalzbauer, B.; Herrmann, J.; Muller, R.; Menche, D. *Org. Lett.* **2013**, *15*, 964.
(24) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
(25) (a) Review: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735. (b) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080.
(26) Mehta, G.; Shinde, H. M. *J. Org. Chem.* **2012**, *77*, 8056.
(27) Konno, H.; Ogasawara, K. *Synthesis* **1999**, 1135.
(28) Ph_3CBF_4-mediated deprotection of MOM-ethers: (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933. (b) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722. (c) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542.

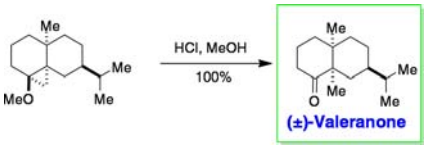
Scheme 6. An Overview of Some of the Highlights of Professor Goverdhan Mehta's Total Synthesis of (+)-(1*S*)-Minwanenone



Scheme 7. Some of the More Noteworthy Transformations in Professor Abad-Somovilla's Synthesis of (−)-Marginatafuran



Scheme 8. Final Stages of Professor Ernest Wenkert's Synthesis of (±)-Valeranone Where Acid-Mediated Alkoxycyclopropane Ring Cleavage Was Effected



JOC in 2012),[29] we see a most aesthetically pleasing and elegant example of an intramolecular [4 + 2]-cycloaddition being used to build this novel terpenoid structure. In this synthesis (Scheme 7),[29] the pivotal step was the implementation of this process on the highly substituted triene **38** which, noticeably, possessed a highly functionalized epoxy ketone in the framework. Strikingly, this reaction proceeded in excellent yield (98%) when run in PhMe at reflux in a sealed tube for 4 days, in the presence of propylene oxide, with **39** being formed with 6.7:1 selectivity. Of course, this reaction nicely set up the furan ring-annulation processes that followed, which involved a ring-closing metathesis on **40** and a regioselective dehydrogenation. Another eye-catching step in this synthesis was the way in which it stationed the geminal-dimethyl grouping within ring-A, via the base-mediated cyclopropanol ring-opening of **41** with aqueous sodium hydroxide at 90 °C. For me, this most unusual reaction stood out as the cornerstone of the synthesis, despite its harshness of approach. Almost certainly, we will see this method applied in other terpenoid natural product total syntheses, in the future, now that this step has been shown to be facile, viable, and high yielding. While acid-promoted alkoxycyclopropane openings of this sort do have significant past precedent in the terpenoid total synthesis literature (see Scheme 8),[30] the base-promoted process on cyclopropanols[31] is a much rarer sight, but a thorough search of the literature does actually reveal a set of papers by Reusch, who first observed and described such base-induced fragmentations, in the early 1970s.[32] Two remarkable examples of his work are shown in Scheme 9.[32]

Importantly, they give us an important insight into why such carbanions form so readily and ultimately get irreversibly protonated (as we see in the conversion of **41** into **42**); it is because they are stabilized homoenolates[33] that can transiently re-engage the carbonyl (in an anion-stabilizing way) on their passage through to the final products! This synthesis of (−)-marginatafuran has thus very topically brought back, into the limelight, this fascinating aspect of the chemistry of cyclopropanols,[31] and their derived homoenolates, except now we are seeing this chemistry applied in a complex target synthesis setting.

(−)-Teucvidin is another furan-containing diterpenoid of structural note belonging to the 19-nor-clerodane family. (−)-Teucvidin was recently constructed in enantiopure form

(29) Gris, A.; Cabedo, N.; Navarro, I.; de Alfonso, I.; Agullo, C.; Abad-Somovilla, A. *J. Org. Chem.* **2012**, *77*, 5664.

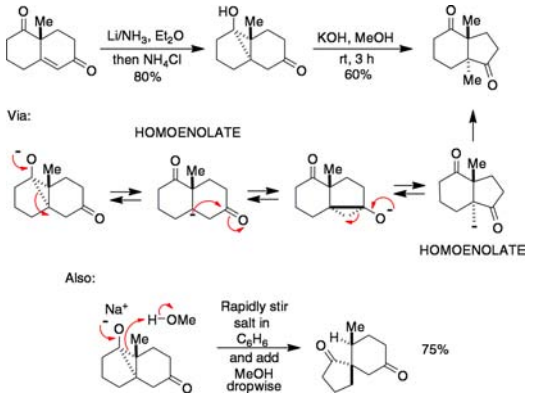
(30) See: (a) The (±)-α-cuparenone and (±)-*β*-vetivone syntheses of: Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267. (b) The (±)-valeranone synthesis of: Wenkert, E.; Berges, D. A.; Golob, N. F. *J. Am. Chem. Soc.* **1978**, *100*, 1263.

(31) For an excellent and authoritative review on the peculiarities of cyclopropanol chemistry, see: Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605.

(32) (a) Venkataramani, P. S.; Karoglan, J. E.; Reusch, W. *J. Am. Chem. Soc.* **1971**, *93*, 269. (b) Grimm, K.; Venkataramani, P. S.; Reusch, W. *J. Am. Chem. Soc.* **1971**, *93*, 270.

(33) dos Santos, A. A.; Commasetto, J. V. *J. Braz. Chem. Soc* **2005**, *16*, 511.

Scheme 9. Base-Induced Cyclopropanol Ring Openings of Reusch



by Lee with his student Xiaozu Liu, via a most interesting sequence that was first published in *Organic Letters* in 2012.[34] The Lee route began with a novel zinc triflate/indium triflate-catalyzed tandem Michael addition−Conia Ene cyclization reaction[35] on **43** (Scheme 10), which diastereoselectively furnished the bicyclic ring system **47** with complete stereocontrol. In this process, two rings and three new asymmetric centers were successively established in a tandem one-pot process that proceeded in an impressive 72% yield! However, this was not the only item of interest that could be found in this paper, for a second highlight was the novel fluoride-induced decarboxylative furan-annulation reaction that was used to advance **48** into **51** in 81% yield. A third item of note was the rarely employed aldehyde allyl enol ether Claisen rearrangement that it marshalled to set the stereocenter that ultimately formed part of the spiro-lactone ring system. After closely perusing this paper, I think that most of us will agree that Lee's (−)-teucvidin synthesis ticks all of the boxes of synthetic greatness for the way in which it assembles this most challenging target.

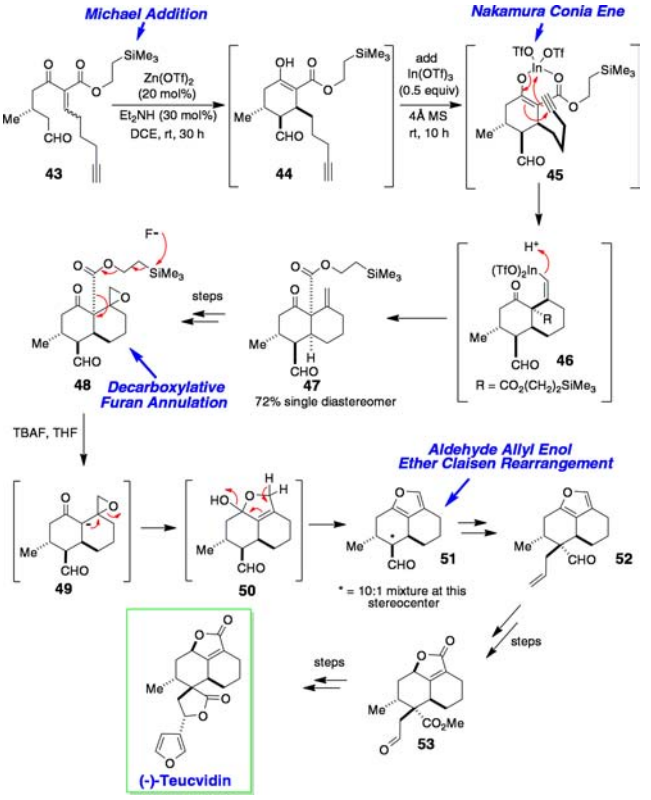
The PAF-inhibitory phomactin terpenoids have long fascinated synthetic chemists, because of the densely crowded skeletal arrays that they proffer, which pose significant difficulties and challenges for total chemical synthesis. The way in which Hsung and Tang chose to tackle the phomactin A synthetic problem was to rely on a new, intramolecular, [3 + 3]-oxo-annulation electrocyclization cascade to build up the ABD-ring system of the target, and notwithstanding the fact that this key step only furnished the desired product **55** in a modest 30% yield (Scheme 11),[36a] it still managed to provide sufficient synthetic material to permit the synthesis to be completed.[36b] One of the key challenges that Hsung and Tang had to address en route to this target was how to

(34) Liu, X.; Lee, C.-S. *Org. Lett.* **2012**, *14*, 2886.

(35) Indium(III) triflate 1,3-dicarbonyl-Conia-Ene reaction: Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264.

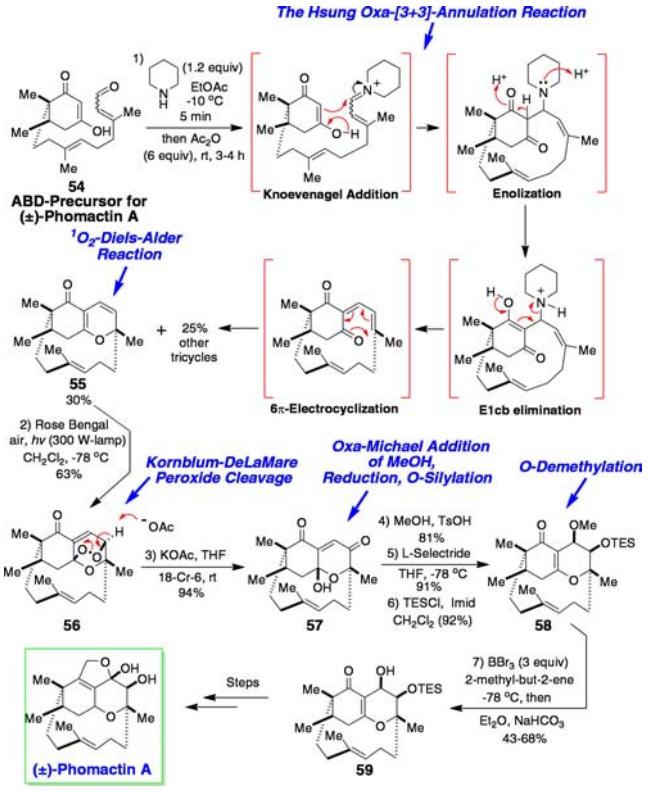
(36) (a) You, L.-F.; Hsung, R. P.; Bedermann, A. A.; Kurdyumov, A. V.; Tang, Y.; Buchanan, G. S.; Cole, K. P. *Adv. Synth. Catal.* **2008**, *350*, 2885. (b) Buchanan, G. S.; Cole, K. P.; Tang, Y.; Hsung, R. P. *J. Org. Chem.* **2011**, *76*, 7027.

Scheme 10. Reaction Highlights from Lee and Liu's Synthetic Route to (−)-Teucvidin



oxygenate the B-ring 2*H*-pyran unit of tricycle **55** stereospecifically. Their very clever opening solution to this problem was to employ a powerful photochemical singlet oxygen Diels−Alder process for this purpose. It is striking that the downward-pointing trisubstituted olefin 'belt' motif of **55** did not adversely complicate this step; rather, it actually aided it, by sterically shielding the underside of the diene, to allow an exclusive top-side approach of the $^1O_2$ to the substrate (as drawn in Scheme 11). The resulting cyclic peroxyacetal **56** was then ruptured in a most unusual way, using a modern-day variant of the classical Kornblum−DeLaMare peroxide ring-cleavage reaction, which furnished **57**, to allow the process of controlled oxygenation of the B-ring to be further continued. One of the ways in which Hsung and Tang increased the oxygen content around this ring was to perform a site-selective oxa-Michael addition on **57** with methanol, under mildly acidic conditions. A stereocontrolled reduction of the keto-group then ensued, followed by O-silylation. This now set up a truly remarkable O-demethylation reaction on **58** with boron tribromide and 2-methyl-but-2-ene at −78 °C, which cleaved the methyl ether *selectively* to give the alcohol **59** in decent yield, *with complete preservation of the nearby TES ether*, and other sensitive features that were present in the target structure! It is very rare indeed that one sees an *O*-methyl ether being successfully cleaved during a complex natural product total synthesis of this sort, yet this is precisely what

Scheme 11. Hsung and Tang's Total Synthesis of (±)-Phomactin A

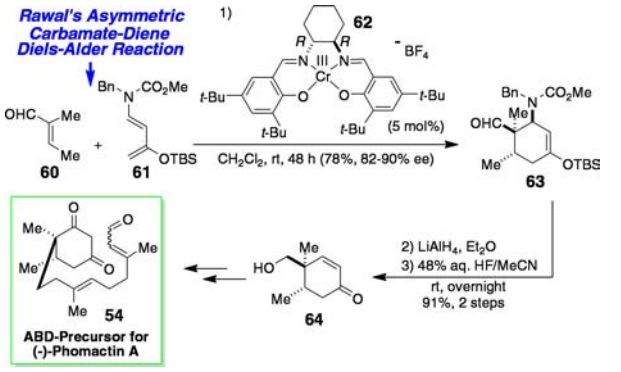


happened here, and very successfully at that! However, before I depart completely from this topic, I would like to draw readers' attention to the fact that Hsung and Tang have actually shown that their (±)-phomactin A synthesis is fully capable of being rendered enantioselective (Scheme 12), through application of a Rawal asymmetric carbamate-diene Diels–Alder reaction[37] on **60** and **61** and further synthetic processing of the cycloadduct **63** to the ABD-precursor **54** needed for securing (−)-phomactin A;[36a] this work was first reported in 2008 but could equally well now be adapted to fashion the enantiomeric (+)-natural product.

Continuing with the topic of electrocyclic ring closure, 2013 saw Professors Lawrence and Sherburn of the ANU in Canberra announce their spectacular total synthesis of the kingianins[38] from the (*Z*,*Z*,*Z*,*Z*)-tetraene intermediate **66**, obtained from the Rieke zinc alkyne semireduction of **65** (Scheme 13). Tetraene **66** was then employed for a thermally mediated 8π-electrocyclization reaction that gave rise to two racemic alcohols **68** and **67** which were both independently taken forward to kingianins A, D, and F, respectively, via TPAP alcohol oxidation to the carboxylic acids, Bauld radical cation Diels–Alder[39] dimerization, and EDC·HCl-mediated amidation.

Their beautiful work in *Angewandte Chemie* built on the earlier 2011 synthetic effort from the Moses group at

Scheme 12. Hsung's Enantioselective Strategy for (−)-Phomactin A



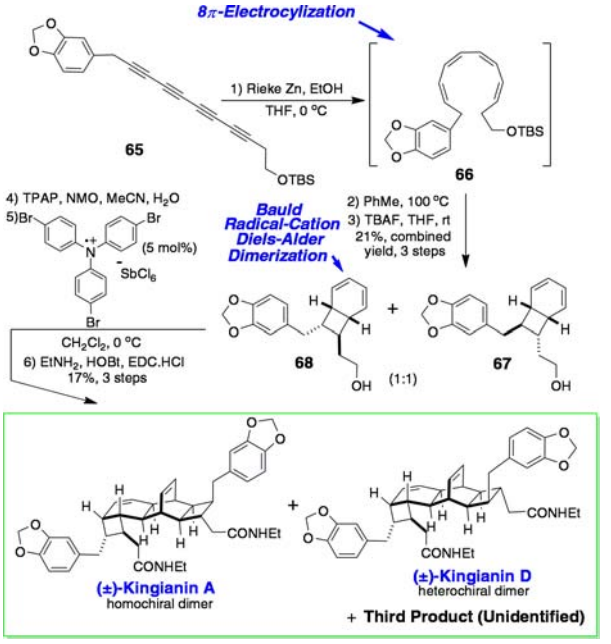
the University of Nottingham, who reported that chemically synthesized prekingianin could not be converted through to (±)-kingianin A by conventional thermally mediated Diels–Alder (DA) chemistry.[40]

Shortly before Lawrence and Sherburn's report, Parker of SUNY[41] had announced a conceptually different pathway to the racemic bicyclo[4.2.0]octadiene **69** in a 2013 *Organic Letters* paper in this Virtual Issue, which used a novel intramolecular iodoetherification reaction to separate it from an otherwise inseparable diastereomer. The resulting pure bicyclo[4.2.0]octa-dienyl alcohol **69** was then elegantly used (Scheme 14) for the *first* total synthesis of (±)-kingianin A, via a tethered intramolecular Diels–Alder cycloaddition. Recognizing Moses' earlier failures on the dimerization of prekingianin through normal thermal DA chemistry,[40] Parker attempted the intramolecular [4 + 2]-cycloaddition of **70** and its *meso* isomer in radical cation mode,[39] to establish successfully the target's skeletal framework for the very first time. Notwithstanding this reaction unexpectedly yielding a pair of *endo* and *exo* cycloadducts **72** and **71** respectively, the primary advantage of Parker's approach to this target stems from the ability to avoid the later synthesis' requirement for a preparative HPLC separation of the kingianin A and D natural products. Indeed Parker's reaction products **72** and **71** could be easily separated from one another by normal SiO_2 flash chromatography. Quite clearly, a much greater level of detail can be found in Parker's original 2013 *Organic Letters* report,[41] which describes a truly brilliant and insightful piece of work.

Although the biosynthetic provenance of (±)-paracaseolide A remains unclear, the molecule's discoverers propose a partial biogenesis that involves a Diels–Alder cycloadditive dimerization of the butenolide **73**, with one component serving as the dienophile and the other as the diene. Spurred on by this insightful Guo hypothesis,[42]

(37) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.
(38) Drew, S. L.; Lawrence, A. L.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 4221.
(39) Harirchian, B.; Bauld, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 1826.
(40) Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2011**, *47*, 10605.
(41) Lim, H. N.; Parker, K. A. *Org. Lett.* **2013**, *15*, 398.
(42) Chen, X.-L.; Liu, H.-L.; Li, J.; Xin, G.-R.; Guo, Y.-W. *Org. Lett.* **2011**, *13*, 5032.

Scheme 13. Lawrence and Sherburn's Biomimetic, Second, Total Synthesis of (±)-Kingianin's A and D in ACIE



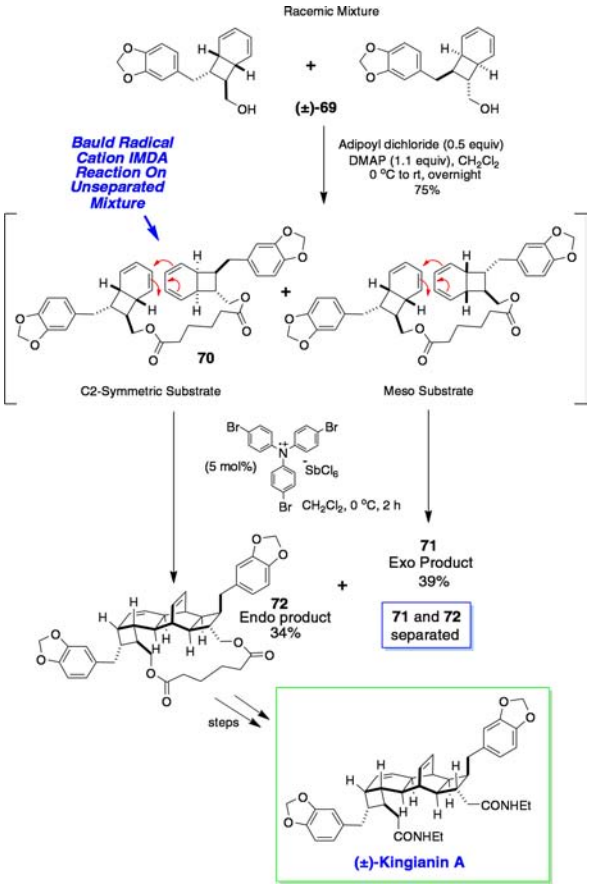
Vassilikogiannakis and his student, Noutsias, crafted a most elegant pathway to the butenolide **73** needed to test out this Diels–Alder proposal in detail.[43] Surprisingly, when they attempted to implement Guo's proposed biosynthetic route, by heating **73** in PhMe in a sealed tube at 110 °C for 12 h, they were unable to bring about the desired cycloaddition. However, when they resorted to a cycloaddition tactic that few of us would ever have dreamed of using, namely, the heating of *neat* **73** at 110 °C in a sealed tube for 12 h, finally, they achieved their goal of obtaining (±)-paracaseolide A in 59% yield (Scheme 15), to complete the first total synthesis of this structurally novel anticancer natural product which, biosynthetically, is probably an oxoquinane structure of meroterpenoid origin.

Following on from this elegant work, we now see another equally scintillating total synthesis of (±)-paracaseolide A being disclosed by Kraus,[44] by a route that takes advantage of some hidden chemistry from Lin and Wu, first published in the *Journal of the Chinese Chemical Society* in 1995,[45] which detailed a very beautiful three-step synthesis of the intermediate **74** (Scheme 16).

Happily, Kraus and Guney were able to repeat the work of Wu without any difficulty, obtaining the desired tetracycle **74** in 20% overall yield over three steps. Then, in a craftsman-like way, we see these two workers convert this compound into (±)-paracaseolide A by some truly well planned transformations that take advantage of the inherent symmetry of **74** and a graded set of phenylsulfoxide *syn*-elimination reactions, as well as various other manipulations. Given that I do not wish to spoil the enjoyment of

(43) Noutsias, D.; Vassilikogiannakis, G. *Org. Lett.* **2012**, *14*, 3565.
(44) Guney, T.; Kraus, G. A. *Org. Lett.* **2013**, *15*, 613.
(45) Lin, C.-C.; Wu, H.-J. *J. Chin. Chem. Soc.* **1995**, *42*, 815.

Scheme 14. Key Tethered Radical Cation Diels–Alder Step in Professor Kathlyn Parker's First Total Synthesis of (±)-Kingianin A

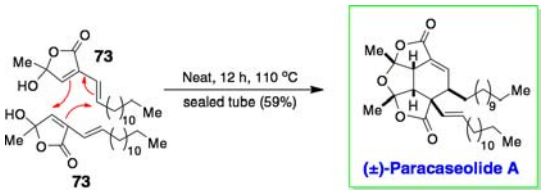


this paper any further, I strongly recommend that you examine this work, which details a synthesis of quite extraordinary beauty.

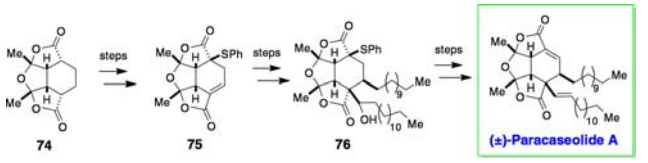
I now wish to comment on yet another first rate *Organic Letters* communication, Professor Jonathan George's paper entitled "Biomimetic Total Synthesis of (±)-Garcibracteatone".[46] It is not very often that one encounters a paper of such extraordinary intellectual quality and sheer practical grace from a chemist of such youth. However, grace is what we see here in this remarkable four-step total synthesis of the highly complex anticancer meroterpenoid, (±)-garcibracteatone. Why this paper stands out is not only because it postulates a remarkable multistep biomimetic radical cascade for the build up of this target structure (Scheme 17) but also because, from the radical **78**, it then goes on to rapidly construct the key precursor needed to test out this impressive new hypothesis (compound **77**), in a mere three steps from readily available phloroglucinol. Experienced synthetic organic chemists, by and large, would not disconnect such a highly complicated polycycle in such a bold and imaginative way, let alone conceive of executing such a daring, multistep, tandem radical cascade that employed such unusual radical

(46) Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162.

Scheme 15. Vassilikogiannakis' Biomimetic First Total Synthesis of (±)-Paracaseolide A



Scheme 16. A Summary of Kraus' Route to (±)-Paracaseolide A

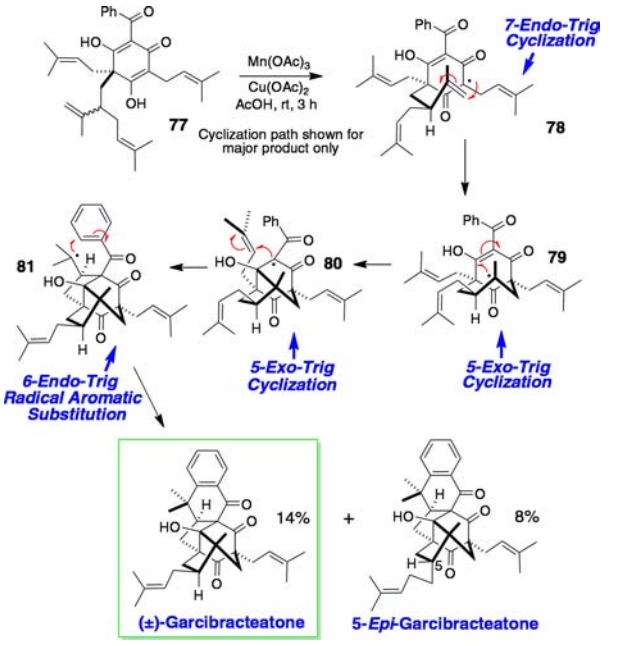


reactions to reach the desired end point. The tandem radical cyclization steps are stunning at every point in the cascade, and the fact that they are used to assemble such a highly strained and multiply caged, intricate, target structure makes them even more remarkable. The 7-*endo-trig* cyclization that initiates the cascade and the aromatic radical substitution that sits right at the very end are simply breathtaking transformations, particularly the latter, because of the extreme rarity with which one sees such reactions successfully applied in a complex molecule total synthesis setting. The fact also that George builds up four new carbocyclic rings and five new stereocenters and creates four new C−C bonds all in one synthetic operation, through the use of only two added reagents ($Mn(OAc)_3/Cu(OAc)_2$) on a single, quite simple, substrate, only adds to the magnitude of his synthetic achievement. For me, the George synthesis of (±)-garcibracteatone is hallmarked with the stamp of excellence, and I put this complex skeletal assembly process on a par with that in the fantastic ionic pentacyclization cascade used by Heathcock in his classic synthesis of dihydro-*proto*-daphniphylline.[47]

The added facet that George and his team have revised the postulated structures of the doitunggarcinones, as a result of completing this total synthesis, and the fact that they have also obtained X-ray crystallographic structures for their two final products in Scheme 17 lend even greater confidence and security to the community's belief in the value and enduring magnitude of this outstanding work. Once more, I recommend that readers examine this excellent paper from the University of Adelaide group.

Yet another fine feast of free radical chemistry is provided by Reisman's *JACS* 2011 synthetic route to

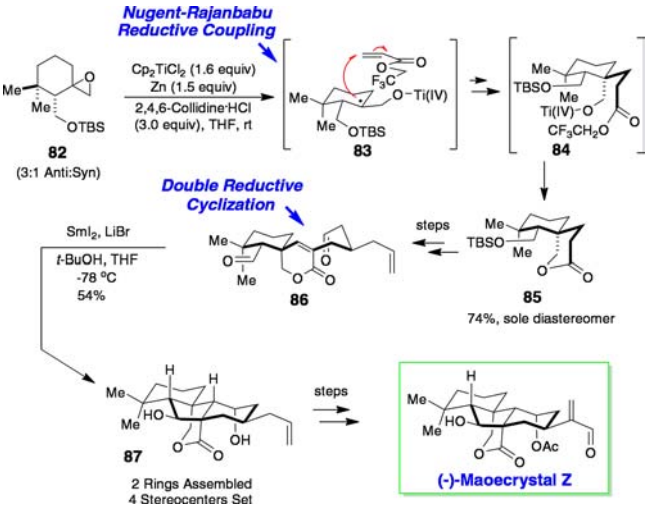
Scheme 17. Professor Jonathan H. George's Cascade Radical Cyclization Sequence for the Biomimetic Total Synthesis of (±)-Garcibracteatone



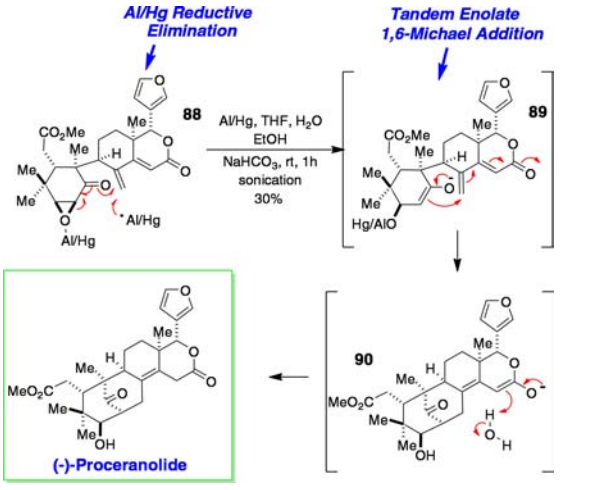
the 6,7-*seco*-*ent*-kauranoid diterpenoid (−)-maoecrystal Z,[48] where two transition-metal-mediated reductive couplings feature at different points in the synthesis (Scheme 18). The first place where we encounter such a reaction is in the assembly of spirolactone **85** from the 3:1 chiral epoxide mixture **82**, using a Nugent−Rajanbabu-mediated Ti(III)-reductive opening[49] and a tandem coupling to the highly electrophilic 2,2,2-trifluoroethyl acrylate, under Gansauer's modified 2,4,6-collidine hydrochloride reaction conditions.[50] Normally, the proton-assisted Gansauer conditions allow for such epoxide reductions to be done catalytically, and ordinary alkyl acrylates generally suffice as viable radicalophiles. However, in the present system, resort very quickly had to be made to a different acrylate reaction partner and to an *excess* of both the Cp_2TiCl_2/Zn and the collidine HCl in order to obtain the desired result. This crucial change from methyl acrylate to 2,2,2-trifluoroethyl acrylate proved essential for attaining a successful final outcome, raising the yield of **85** from 28% to 74%. The second point in the synthesis where a transition-metal-mediated reductive radical coupling played a critical role was in the tandem dialdehyde/ene-lactone cyclization that was attempted on **86**, for which a Flowers SmI_2/LiBr reagent[51] combination proved optimal for tipping the reaction balance heavily in favor of the double cyclization product **87**;

(47) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2554.
(48) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964.
(49) (a) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525. (b) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.
(50) Gansauer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem.—Eur. J.* **2003**, *9*, 531.
(51) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2000**, *122*, 7718.

Scheme 18. Two Key Reductive Coupling Steps in Professor Sarah E. Reisman's Enantioselective Total Synthesis of (−)-Maoecrystal Z



Scheme 19. The Tandem Epoxy-Ketone Reduction-1,6-Michael Addition End Game Used by Professor Craig Williams in His Total Synthesis of (−)-Proceranolide



the key to success here was also performing the reaction in a THF/*t*-BuOH solvent mix at −78 °C. Quite remarkably, the other reagent alliance recommended by Flowers, namely, SmI_2/LiCl, only furnished **87** in low yield under identical circumstances, emphasizing the fundamental differences between the two reagents. The synthetic victory that ensued from use of the former conditions ultimately translated into a 54% yield of **87**, an outstanding result when one examines what was accomplished. With **87** in hand, Reisman advanced forward to complete the first total synthesis of (−)-maoecrystal Z[48] and sign off on a most impressive accomplishment.

The next paper I would like to highlight is the 2012 *JOC* full paper by Williams,[52] which announced his enantioselective total synthesis of molecules of the mexicanolide family of limonoid natural products. There are many notable asymmetric reactions in this general synthetic route, which culminated in the acquisition of (−)-proceranolide, (−)-khayasin, and (−)-cipadonoid B by a common pathway that established their formidable molecular frameworks by yet another powerful reductive cleavage process, applied, on this occasion, on the epoxy ketone **88** (Scheme 19). In this system, all of the standard modern procedures for effecting single-electron epoxide ring opening and tandem enolate 1,6-conjugate addition failed; the methods screened included SmI_2, PhSeNa, and Bu_3SnH among others. Eventually, it was discovered that the seldom-used epoxy-ketone reductant, aluminum−mercury amalgam, ushered this reaction to a successful conclusion, namely, to (−)-proceranolide in 30% yield, which is quite acceptable when one examines what was actually achieved, and one considers the enormous strain that is present in this polycyclic system. This particular natural product was then converted through to the other two target molecules without incident. Williams' synthetic entrance to a family of molecules that has resisted chemical synthesis for many years represents a major highlight of the field. No doubt, we will see other groups applying this mode of reductive cyclization increasingly, over the coming years, now that this report has appeared.

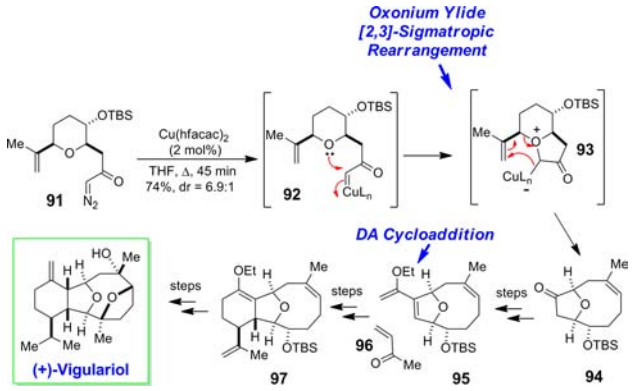
The cladiellin natural products are of interest for their notable anticancer and other biological effects, as well as for their intriguing molecular architectures, which provide a fertile testing ground for the evaluation of new synthetic methods, most especially those involving medium-ring ether synthesis. For many years now, Clark and his team, at the University of Glasgow, have been investigating the sigmatropic rearrangements of *in situ* generated oxonium ylides for the purpose of synthesizing different types of bicyclic medium-ring ether. One very nice application of their valuable synthetic method for fashioning such molecules can be found in their elegant approach to (+)-vigulariol,[53] where ketone **94** was fashioned in high yield (74%) and *ca.* 6.9:1 selectivity from the diazoketone **91** (Scheme 20), under the aegis of Cu(hfacac)$_2$ catalysis in THF at reflux. In their 2013 *JOC* full account of this synthesis, they not only describe these impressive results but also document how **94** was converted into the diene **95** which, in another masterstroke, was subjected to a Diels−Alder reaction with methyl vinyl ketone, to create the core carbon framework needed for eventual elaboration into this natural product. Clark thereafter goes on to discuss his application of variants of this chemistry to other cladiellin syntheses in what is a very thorough account of a most beautiful strategy.

The highly strained, tetracyclic caged structures of the echinopine terpenoids certainly represent a challenge to all synthetic organic chemists interested in strained

(52) Faber, J. M.; Eger, W. A.; Williams, C. M. *J. Org. Chem.* **2012**, *77*, 8913.

(53) Clark, J. S.; Berger, R.; Hayes, S. T.; Senn, H. M.; Farrugia, L. J.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *J. Org. Chem.* **2013**, *78*, 673.

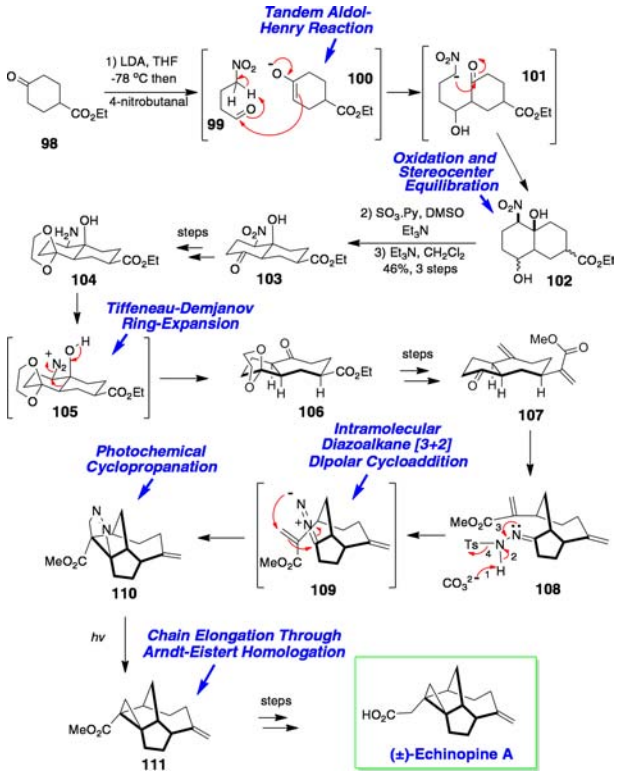
Scheme 20. Professor J. Stephen Clark's Elegant Oxonium Ylide [2,3]-Sigmatropic Rearrangement Strategy for the Total Synthesis of (+)-Vigulariol



molecule total synthesis. Suitably captivated by their unique *cis*-fused bicyclo[5.3.0]decane subsystems, which are punctuated by a cyclopropane unit that possesses two quaternary stereocenters, Liang of Nankai University embarked on the synthesis of echinopines A and B from nitrodecalin **102** (Scheme 21).[54] The latter was available in two easy steps from the commercial ketone **98** by a tandem aldol-Henry reaction sequence involving 4-nitrobutanal. Liang's synthetic plan for assembling the greater part of the echinopine framework centered around modifying a Tiffeneau−Demjanov rearrangement process first reported by Seebach in 1981,[55] which creates *cis*-fused 5,7-carbocycles from *trans*-decalins that have an angular hydroxyl which also forms part of a *cis*-1,2-aminoalcohol system. Such substrates rearrange very readily upon simple diazotization with nitrous acid to afford *cis*-fused bicyclo[5.3.0]decanes stereospecifically in good yield. Application of this rearrangement to the 1,2-aminoalcohol **104** permitted Liang to secure the target **106** in very good yield (77%). Then, in a reaction that has virtually no precedent, Liang effected an innovative intramolecular diazoalkane 1,3-dipolar cycloaddition on **108** to fashion the echinopine core framework, minus the cyclopropane. However, this was not an especially problematical issue for him to rectify, for the latter could be readily fashioned from the resulting pyrazoline **110** by simple photolysis. Liang then processed this tetracycle onward toward echinopines A and B by standard methods. This total synthesis of Liang is one of the most fascinating and original pieces of organic chemistry work to have been published over the past two years. Hence, my desire to include it in this special triptych Virtual Issue.

Another naturally occurring cyclopropanated terpenoid of architectural interest is the pumilaside aglycon, for which a particularly novel strategy for synthetic

Scheme 21. Professor Guangxin Liang's Powerful Synthetic Route to (±)-Echinopine A Involving Intramolecular Diazoalkane 1,3-Dipolar Cycloaddition

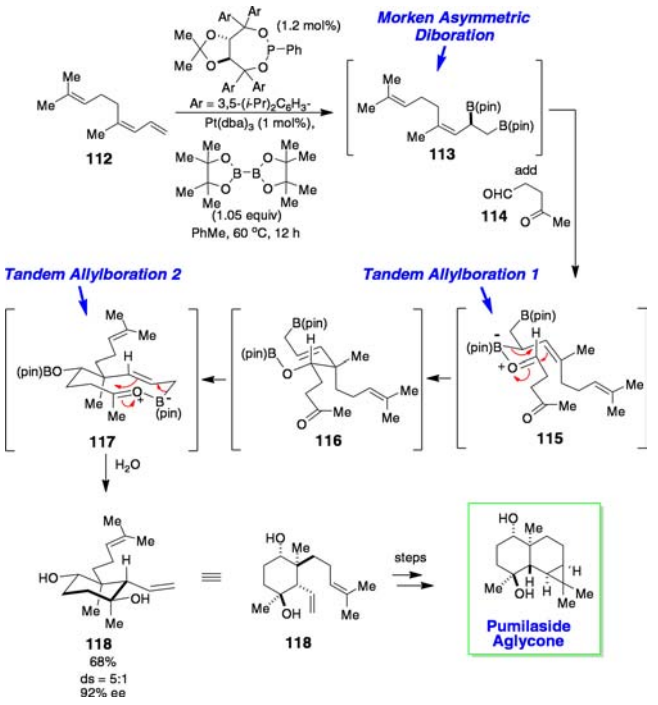


acquisition was published earlier this year in *JACS* by Morken.[56] His approach (Scheme 22) involved the regioselective catalytic asymmetric 1,2-diboration of triene **112** followed by a tandem double allylboration reaction with 4-oxovaleraldehyde **114**, *which collectively built up the cyclohexane* **118** *in 92% ee, adorned by four asymmetric centers, two of which were quaternary*. The process concurrently installed the alkene side chains appropriately tailored for ring-closing metathesis to the decalin, which subsequently permitted further elaboration to the pumilaside aglycon. The remarkable potential of this powerful new ring-construction method is very impressive, as evidenced by the many synthetic applications that appear in this landmark paper. I therefore draw readers' attention to this excellent contribution.

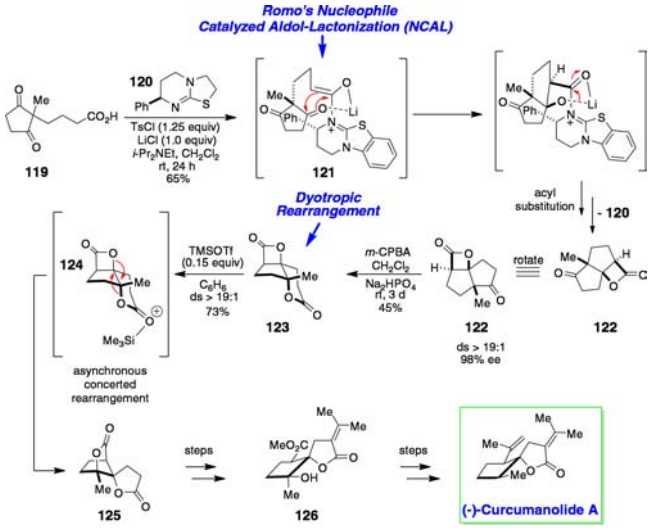
In their purest form, dyotropic rearrangements are reactions in which two σ-bonds are induced to migrate virtually simultaneously in concerted fashion. They are processes that do not feature strongly in the natural products total synthesis literature. However, a recent 2012 *JACS* full paper by Romo[57] has rectified this situation very dramatically by drawing the community's attention to the utility of these methods for creating complex spiro terpenoid target structures such as (−)-curcumanolide A, from the optically active

(54) Xu, W.; Wu, S.; Zhou, L.; Liang, G. *Org. Lett.* **2013**, *15*, 1978.
(55) Weller, T.; Seebach, D.; Davis, R. E.; Laird, B. B. *Helv. Chim. Acta* **1981**, *64*, 736.
(56) Ferris, G. E.; Hong, K.; Roundtree, I. A.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 2501.
(57) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348.
(58) Mulzer, J.; Bruntrup, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 793.

Scheme 22. Professor James P. Morken's Pioneering Catalytic Asymmetric Diboration-Tandem Double Allylboration Route to the Pumilaside Aglycon



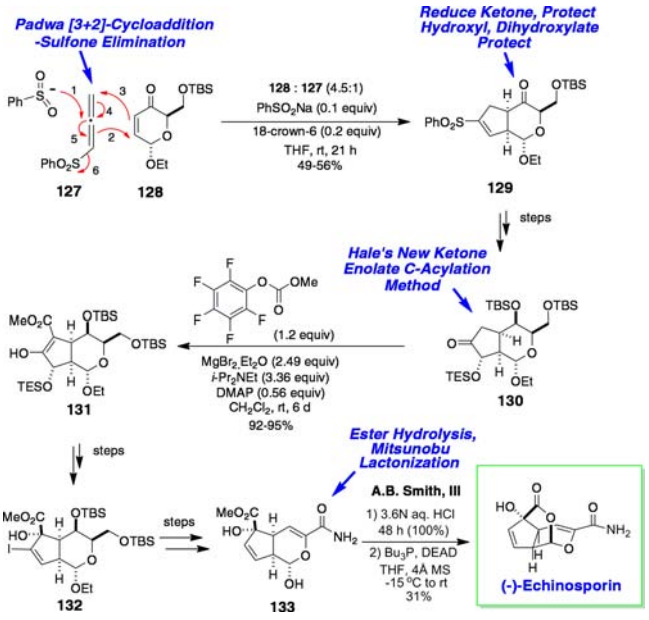
Scheme 23. Professor Daniel Romo's NCAL-Dyotropic Rearrangement Route to (−)-Curcumanolide A



β-lactone **122**, capitalizing on earlier work by Mulzer and Bruntrop,[58] and Romo's own laboratory.[59] Without going into the intricacies of this paper, it does report what looks to be a potentially powerful tandem reaction sequence that has many potential spheres of application (Scheme 23). The kernel of the Romo approach involves (A) performing

(59) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479.

Scheme 24. A Summary of Hale and Flasz's New, Fully Stereocontrolled, Synthetic Route (−)-Echinosporin via Padwa's Allenylsulfone [3 + 2]-Cycloadditive Elimination



Romo's aesthetically pleasing nucleophile-catalyzed aldol lactonization (NCAL) reaction[59] to obtain **122**; (B) subjecting the keto-lactone product **122** to Baeyer−Villiger oxidative ring expansion; and (C) effecting a Lewis acid catalyzed dyotropic ring rearrangement on the product **123**. In the case of (−)-curcumanolide A, compound **125** was then taken forward to the target. Once more, I point you in the direction of this most notable paper.

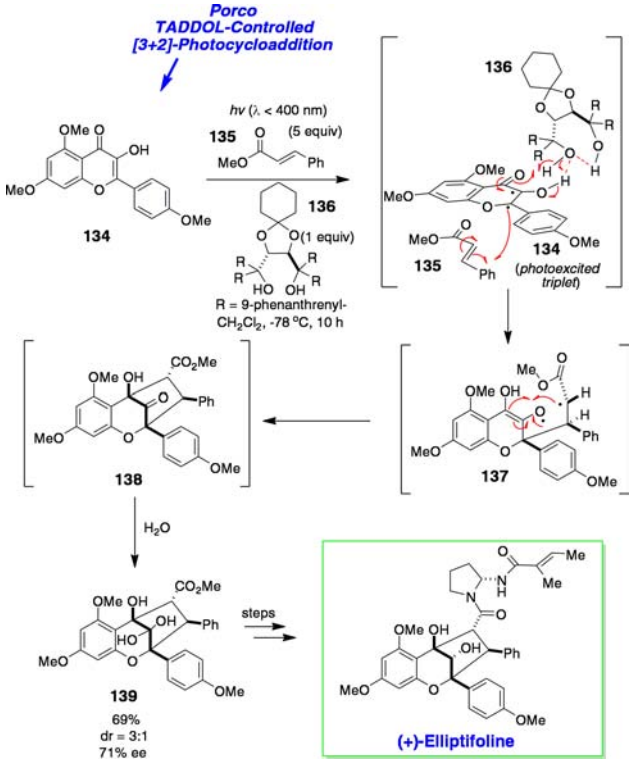
There is growing interest in the community in the development of new [3 + 2]-carbacycloaddition methods,[60,21] and in the refinement of many existing underutilized protocols.[61] Two papers in this Issue that report on novel tactics for this purpose apply them in shikimate-derived natural product systems: the first is by Hale at Queen's University Belfast, on the total synthesis of (−)-echinosporin; the second is by Porco at Boston University, on a concise and highly original new synthetic pathway to the 3-hydroxyflavones, (+)-ponapensin and (+)-elliptifoline.

If we focus initially on the work of Hale, it documents the first use of a Padwa allenylsulfone [3 + 2]-cycloadditive

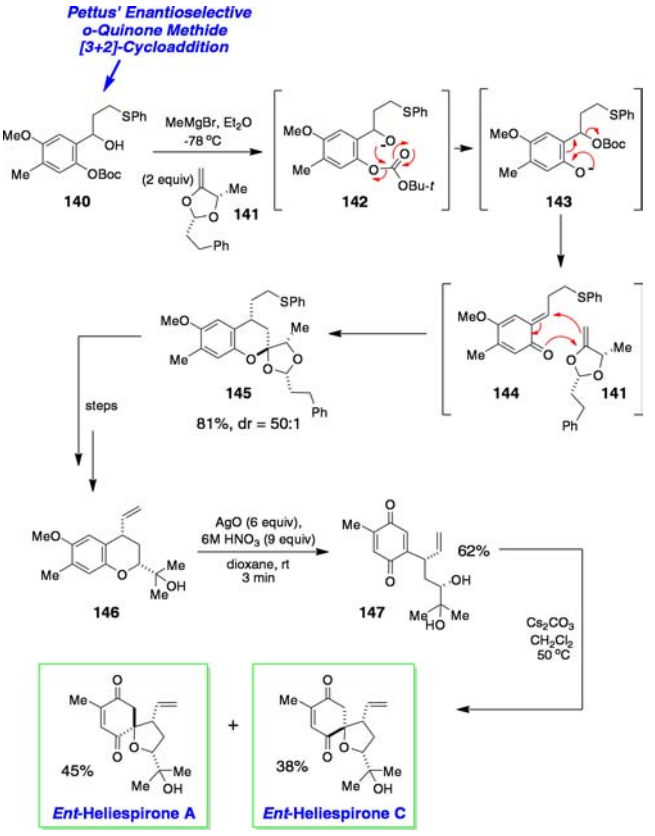
(60) For some recent Pd-catalyzed trimethylenemethane asymmetric methods, see: (a) Trost, B. M.; Maruniak, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6262. (b) Trost, B. M.; Bringley, D. A.; Seng, P. S. *Org. Lett.* **2012**, *14*, 234. (c) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. For a recent paper on a catalytic asymmetric Lu [3 + 2]-carbacycloaddition protocol involving allenoates, see: (d) Han, X.; Wang, S.-X.; Zhong, F.; Lu, Y. *Synthesis* **2011**, 1859. For a method that gives much better product ee, see: (e) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. For Professor Lu's earlier mechanistic work in this area, see: (f) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. For other [3 + 2]-carbacycloaddition methods, see: (g) Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2013**, *135*, 58. (h) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440.

(61) For Professor Michael J. Krische's excellent synthesis of the iridoid natural product, (+)-geniposide, via diastereoselective Lu allenoate [3 + 2]-carbacycloaddition on a pyranone, see: Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849.

Scheme 25. Porco's Elegant Enantioselective Photochemical [3 + 2]-Carbacycloaddition Pathway to (+)-Elliptifoline



Scheme 26. Pettus' Enantioselective *o*-Quinone Methide Diels–Alder Strategy for the Total Synthesis of *ent*-Heliespirones A and C



elimination reaction[62] in the total synthesis of a complex natural product, and it does so in the context of the development of a viable new synthetic route to the antitumor lactone, (−)-echinosporin.[63] In this work,[63] the Padwa methodology[62] reliably delivered the cyclopentenylpyran **129** in 49−56% yield with complete stereocontrol and, in so doing, brought this remarkable reaction out of the shadows (Scheme 24). In this paper, we also see a chemoselective reduction of the ketone group in **129**, a protection of the resulting alcohol, and a face-selective dihydroxylation of the resulting cyclopentenyl-sulfone to obtain **130** after protection. The latter was then submitted to a long list of standard enolate C-acylation methods in an attempt to introduce the C(7)-carboxymethyl substituent. Unfortunately, all of these protocols either failed or performed badly, which forced the development of a new method for enolate C-acylation,[64] based upon ketone enolization with $MgBr_2 \cdot Et_2O$ and Hunig's base in CH_2Cl_2,[65] and capture with methyl pentafluorophenyl-carbonate, in the presence of DMAP; the latter conditions brought about the successful conversion of **130** into **131** in 92−95% yield (a method that has since been further extended and published as a second independent 2013 *Organic Letter*[64]). Thereafter a second face-selective dihydroxylation on **131** was employed to install the challenging C(7)-tertiary hydroxyl, to furnish an intermediate which was then advanced forward toward Smith's advanced hemiacetal **133** by a set of reactions that included use of the Barton ketone iodoolefination reaction[66] to give **132**. The Smith group had previously converted hemiacetal **133** into (−)-echinosporin by simple 3.6 N aqueous HCl hydrolysis and Mitsunobu lactonization, to complete the first total synthesis of this highly challenging target in 1989;[67] the Hale approach again relied on these final two reactions to attain the goal. Another item in the Hale synthesis[63] was the use of 49% aqueous HBF_4 to cleave, chemoselectively, the ethyl glycoside to obtain **133**. The difficulties associated with successfully accomplishing this conversion were extensive, and out of a long list of acids evaluated, this proved to be the one that worked optimally and cleanly. Other workers in the carbohydrate chemistry field should strongly consider using these conditions when

(62) (a) Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 1617. (b) Padwa, A.; Yeske, P. E. *J. Org. Chem.* **1991**, *56*, 6386. (c) Padwa, A.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 3256. (d) Nunez, A., Jr.; Martin, M. R.; Fraile, A.; Garcia Ruano, J. L. *Chem.—Eur. J.* **2010**, *16*, 5443.

(63) Flasz, J. T.; Hale, K. J. *Org. Lett.* **2012**, *14*, 3024.

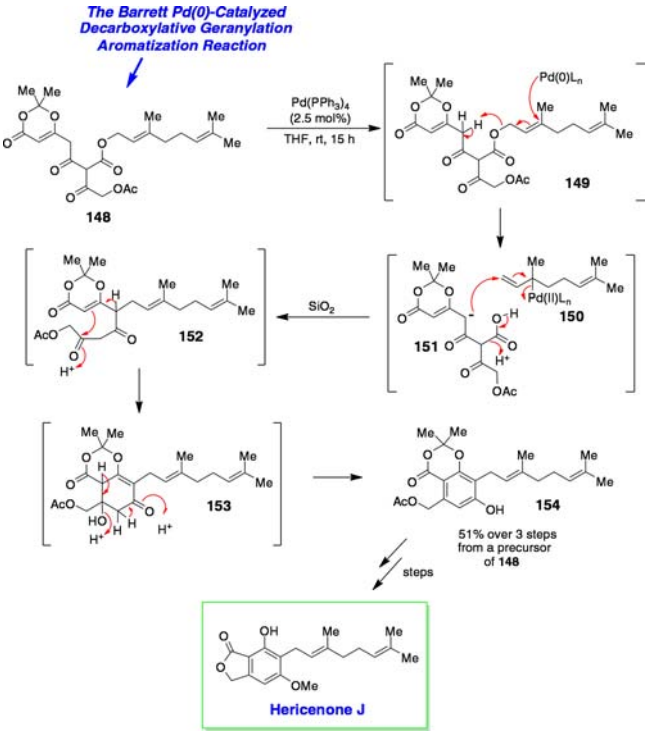
(64) Hale, K. J.; Grabski, M.; Flasz, J. T. *Org. Lett.* **2013**, *15*, 370.

(65) (a) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139. (b) Yost, J. M.; Garnsey, M. R.; Kohler, M. C.; Coltart, D. M. *Synthesis* **2009**, 56.

(66) (a) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470. (b) Barton, D. H. R.; Chen, M.; Jaszberenyi, J. Cs.; Taylor, D. K.; Hartz, R. A.; Smith, A. B., III. *Org. Synth.* **1998**, *74*, 101.

(67) Total synthesis of (−)-echinosporin: (a) Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039. (b) Smith, A. B., III; Sulikowski, G. A.; Sulikowski, M. M.; Fujimoto, K. *J. Am. Chem. Soc.* **1992**, *114*, 2567.

Scheme 27. Barrett's Pd(0)-Catalyzed Decarboxylative Geranylation−Aromatization Reaction Deployed in the Total Synthesis of Hericenone J



attempting to nondestructively cleave protected sugar glycosides, to obtain the corresponding protected reducing sugars, since they worked eminently well here.

In the second [3 + 2]-carbacycloaddition paper that we see highlighted in this Virtual Issue,[68] Porco performs an innovative [3 + 2]-photocycloaddition between **134** and **135**, in the presence of tetrakis-9-phenanthrenyl-TADDOL **136**, to obtain **139** as the major reaction product in 71% ee and 69% yield (Scheme 25). Subsequent reduction of this material gave an alcohol whose ee could be further enriched to >97% by recrystallization. Additional steps thereafter converted this alcohol into (+)-ponapensin and (+)-elliptifoline, to prove that they were actually enantiomers of the two natural products that had originally been isolated; this synthesis was therefore repeated in the opposite enantiomeric series to give the two natural compounds. The great merit of this work lies in the fact it relies solely upon intermolecular hydrogen-bonding effects between the 3-hydroxy-flavone and the stoichiometric chiral additive to bring about the observed asymmetric induction in this extraordinary [3 + 2]-cycloaddition event. Yet again, readers are urged to read this fascinating account, which traverses much new territory.

Still more enantioselective chroman chemistry can be found in Pettus' 2012 *JOC* article on the total synthesis of *ent*-heliespirones A and C (Scheme 26).[69] Here the novelty derives from the chiral auxiliary-mediated, inverse-demand, Diels−Alder reaction between a most unusual β-thiophenoxy *o*-quinone methide **144** and the L-lactic acid derived exocyclic enol ether **141**, allied with the subsequent oxidative cleavage of a further elaborated chroman **146**, which set up a base-mediated oxo-Michael addition onto the quinone **147** for completion of the synthesis of these two challenging targets.

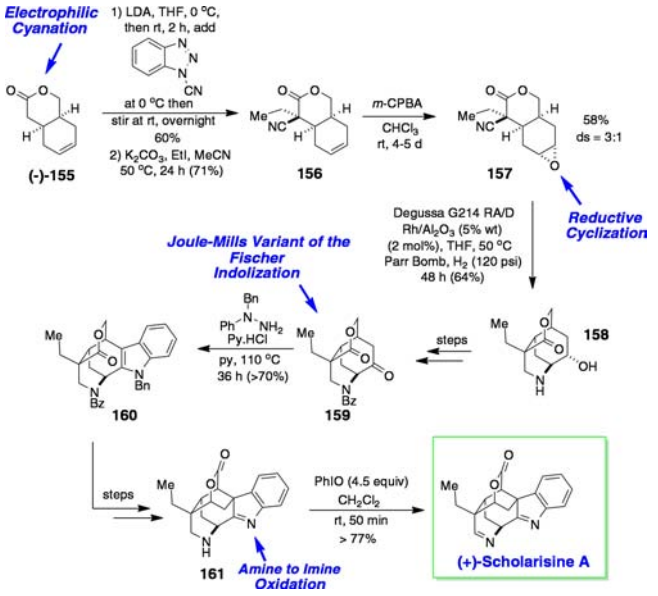
As many of us know, the construction of highly substituted benzenoid nuclei can frequently be problematical. Thus, generally applicable new synthetic procedures that provide rapid access to such systems are always to be welcomed. In an excellent *JOC* article on the total synthesis of the geranyl- and prenyl-functionalized meroterpenoid natural products, angelicoin A, hericenone J, and hericenol A,[70] Barrett and his team at Imperial College report on their discovery and subsequent application (Scheme 27) of a beautifully conceived, Pd(0)-driven, internal enolization/prenylation/geranylation reaction, followed by a decarboxylation and a tandem internal aldol-dehydration (in some cases mediated by silica gel) that provided synthetic access to all three natural products. Given the relative synthetic ease with which Barrett was able to piece together these unusual polycarbonyl aromatic ring precursors, this elegant work appears to offer a substantial synthetic advantage over much previous art for the *ab initio* construction of aromatic meroterpenoids. I therefore encourage readers to study this contribution, in depth, for it is a most enjoyable read of extremely elegant chemistry.

The complex structure of the monoterpenoid alkaloid, (+)-scholarisine A, provides a significant synthetic challenge due to the formidable structural features embodied within the multiply caged array. These include six asymmetric centers, five of which are domiciled in the strained lactone ring, and two of which are quaternary. In 2012, Adams and Smith completed the first total synthesis of this highly challenging molecule. Their *JACS* communication on this topic forms part of this Virtual Issue;[71] it was selected over the more comprehensive full account[72] that Adams and Smith later provided in *JACS*, as the former shows the final route that was developed much more concisely (Scheme 28).

Novel aspects of this total synthesis include the way in which the quaternary carbon stereocenter of the lactone nitrile **156** was constructed. Also of note was the way in which **157** was hydrogenated, to obtain the primary amine, which then engaged in a tandem epoxide ring-opening reaction, under the high pressure conditions that were used to reduce the nitrile, to collectively help establish the beginnings of the target's caged-lactone ring system. The remarkable Joule−Mills variant of the Fischer indole synthesis that elaborated the indole ring

(68) Lajkiewicz, N. J.; Roche, S. P.; Gerard, B.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2012**, *134*, 13108.
(69) Bai, W.-J.; Green, J. C.; Pettus, T. R. R. *J. Org. Chem.* **2012**, *77*, 379.
(70) Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 652.
(71) Adams, G. L.; Carroll, P. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **2012**, *134*, 4037.
(72) Adams, G. L.; Carroll, P. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **2013**, *135*, 519.

Scheme 28. Some of the Key Steps in Professor Amos B. Smith III's Asymmetric Route to the Monoterpenoid Alkaloid, (+)-Scholarisine A



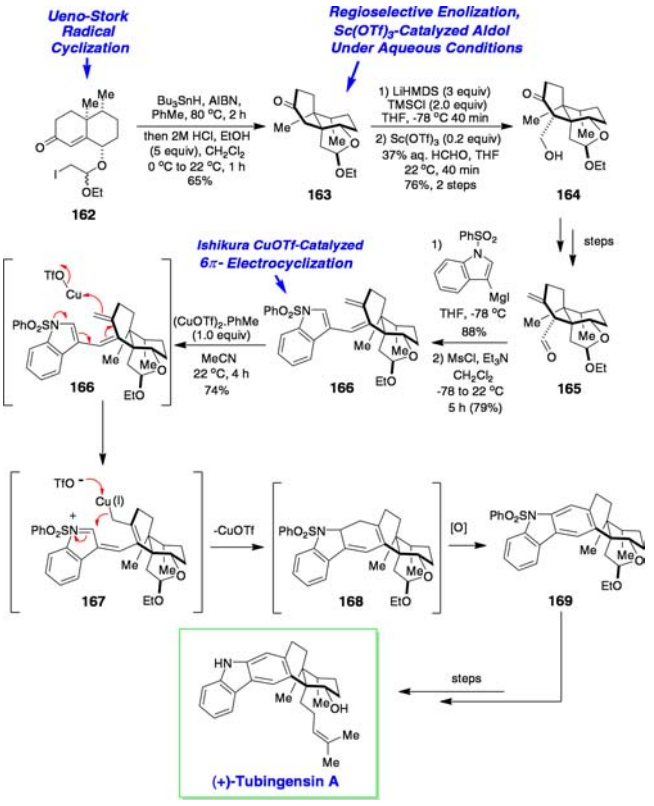
of **160** is another item of great note, most especially for the compatibility with the strained lactone system. This result aside, that very same feature thereafter had to be deleted, to allow the fully developed lactone to eventually be installed, with quaternary center indolimine and all. However, despite this litany of graceful steps, and many additional items of merit besides, Adams and Smith saved the very best transformation of the synthesis until the final step. This involved the piperidine to piperidine-imine oxidation of **161** that was used to obtain (+)-scholarisine A itself, which was mediated by excess iodosobenzene in CH_2Cl_2. This reaction stands out because of the extreme rarity with which one ever sees this transformation applied in total synthesis. Further information on this elegant synthesis can be found in the subsequent full paper[72] that followed this communication.

The second terpenoid alkaloid total synthesis paper that I draw attention to is that of Nicolaou (Scripps) and Li (Shanghai Institute of Organic Chemistry) on the total synthesis of anominine and tubingensin A, via a unified strategy (Scheme 29).[73] In these two syntheses, a common enantiomerically enriched decalin **162** was created via published synthetic methods. The latter was then converted into the tetrahydrofuran-annulated derivative **163** by an application of the Ueno−Stork radical cyclization reaction,[74] and this compound further advanced toward **165** and thence onward to the two target diterpenoid alkaloids themselves. However, why I ultimately picked this paper for inclusion in this Virtual Issue was because of the elegant 6π-electrocyclic ring closure that it effected

(73) Bian, M.; Wang, Z.; Xiong, X.; Sun, Y.; Matera, C.; Nicolaou, K. C.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 8078.

(74) Review: Salom-Roig, X. J.; Denes, F.; Renaud, P. *Synthesis* **2004**, 1903.

Scheme 29. Some of the Key Steps in Professors Kyriacos C. Nicolaou and Ang Li's Asymmetric Route to the Diterpenoid Alkaloid, (+)-Tubingensin A

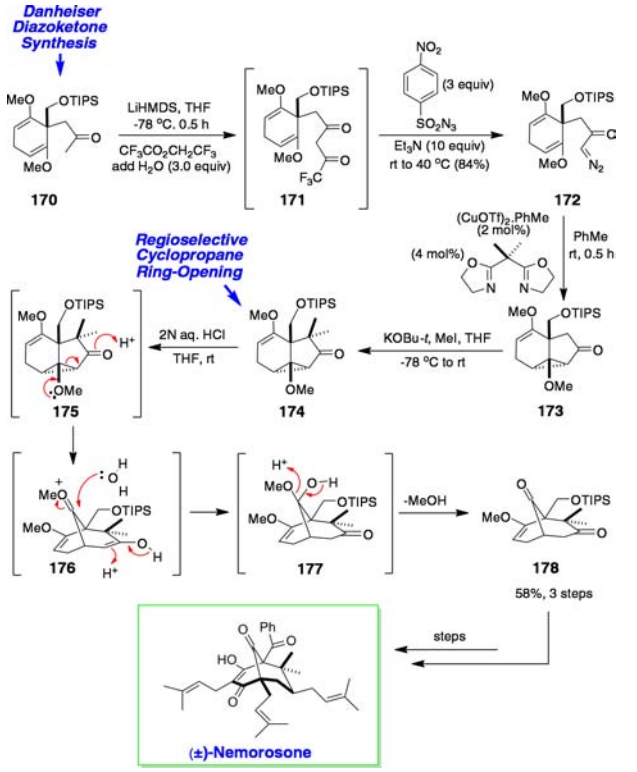


on **166** to create the carbazole ring system of (+)-tubingensin A, a reaction which failed when conducted under standard thermally induced reaction conditions, but which worked very successfully (74% yield) when promoted by CuOTf (1 equiv). This protocol was first applied for carbazole ring synthesis by Ishikura in his beautiful pathway to calothrixins A and B, originally published in *Organic Letters* in 2011.[75] Following this excellent total synthesis of Nicolaou and Li, it is now abundantly clear that the Ishikura copper(I)-catalyzed 6π-electrocyclic ring closure is indeed a general process for carbazole ring construction, and one that the community must take serious note of, now that it has been deployed for a second time in this most synthetically challenging of arenas. While the mechanism of this unusual ring closure is currently unknown, one possibility that I would like to advance is shown in Scheme 29. It invokes the successive intermediacy of **167** and **168**. The latter, of course, would undergo spontaneous oxidative aromatization to **169**, once generated. In the present instance, **169** was then converted through to (+)-tubingensin A to complete a synthesis that stands out for the application of Ishikura's wonderful new carbazole ring-construction method.

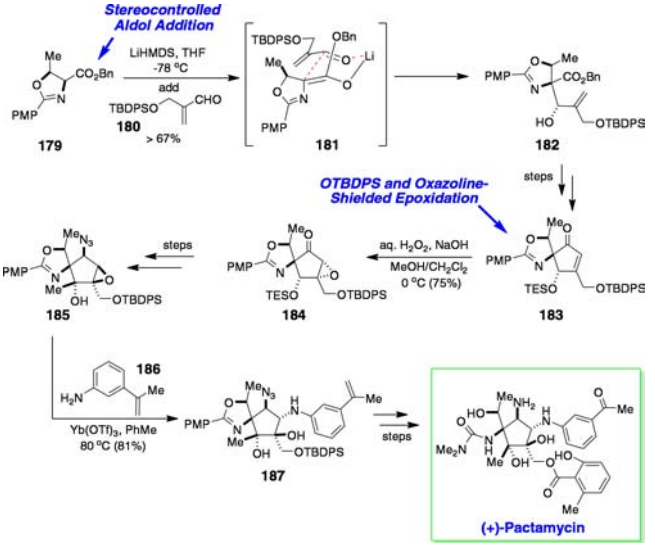
Nakada's powerful new route to (±)-nemorosone[76] is another piece of chemical elegance that I felt duty-bound

(75) Abe, T.; Ikeda, T.; Yanada, R.; Ishikura, M. *Org. Lett.* **2011**, *13*, 3356.

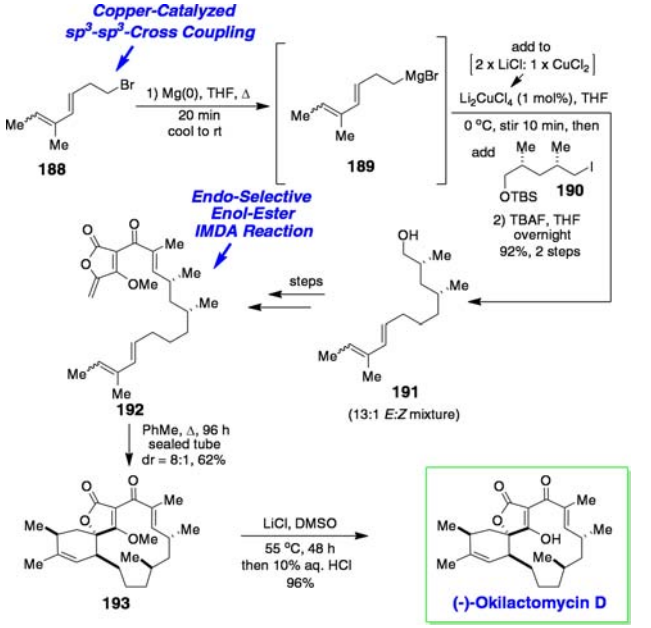
Scheme 30. Some of the Key Steps in Professor Masahisa Nakada's Synthesis of (±)-Nemorosone



Scheme 31. Some of the Key Steps in Professor Stephen Hanessian's Synthesis of (+)-Pactamycin



Scheme 32. Highlights from Professor Thomas R. Hoye's Total Synthesis of (−)-Okilactomycin D



to highlight in this Issue. The Nakada synthesis has many notable aspects, including the way in which it employed the Danheiser protocol[77] to manufacture the α-diazoketone **172** required to forge the tricycle **173** (Scheme 30). The way in which it fashioned the target's bicyclic skeleton was also most appealing. It did so via the acid-induced ring opening of cyclopropane **174**,[30] a reaction that really did require some very clever and insightful synthetic planning!

Nakada's blow-by-blow appendage of all the substituents around this most tricky of ring systems is another *tour de force*. For all these reasons I strongly urge readers to inspect this 2012 *JOC* contribution.

Although some purists and the *Chemical Abstracts Service* (CAS) might say that a total synthesis of pactamycin should not really feature in a special Issue dedicated to the themes I have selected, I disagree, since this particular molecule constitutes yet another example of a "mero-shikimate-derived natural product" (i.e., one of mixed shikimate biosynthetic origin), due to the presence of the amino-acetophenone moiety. I have therefore included the Hanessian 2012 *JOC* Feature Article in this Issue.[78] In this milestone paper, we see Hanessian recounting his numerous synthetic battle plans and experiences for securing this formidable target molecule from L-threonine. While there are far too many interesting reactions contained within this full paper for me to possibly recount here, three of my personal favorites are the aldol reaction that he used to build up the cyclopentenone core **183** (Scheme 31), the face-selective nucleophilic epoxidation that he adopted to produce the epoxide **184**, and the $Yb(OTf)_3$-promoted aminolysis that he effected on **185** (with **186**). The product **187** was then advanced forward to (+)-pactamycin to complete the total synthesis. All

(76) Uwamori, M.; Saito, A.; Nakada, M. *J. Org. Chem.* **2012**, *77*, 5098.
(77) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
(78) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschenes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458.

told, this was a phenomenal chemistry spectacle, and once more, I advocate that readers study this most gripping of accounts.

Finally, I will close my overview of the different papers in this Virtual Issue by briefly highlighting Hoye's concise total synthesis of (−)-okilactomycin D[79] by a strategy that applied a highly stereoselective intramolecular Diels−Alder reaction on the tetronate ene **192** to obtain **193** with 8:1 selectivity (Scheme 32). The synthesis of the IMDA precursor was also notable for the use of a copper-catalyzed sp^3−sp^3 cross-coupling between **189** and **190** to obtain **191**. This is one reaction that truly stands out in this paper, since such C−C-bond-forming reactions are often highly challenging and problematical; however, all went well here. More information on this very nice synthesis can be found in this paper's narrative.

In this Virtual Issue on "*Terpenoid- and Shikimate-Derived Natural Product Total Synthesis*", we have seen some of the world's very best synthetic organic chemists put their own (and other people's) chemical reaction technologies to the very severest of tests, on some of the most chemically demanding target structures that one could ever possibly imagine. We have also seen some of these very same teams attempt to mimic or even surpass Nature for the cascade assembly of certain complex terpenoid- or shikimate-derived structures. We have further witnessed much novel organometallic, organocatalyst, and cycloaddition chemistry being deployed for complex carbocyclic ring assembly, and we have noted many variants of the Diels−Alder process. Indeed, it never ceases to amaze me how so many of my fellow colleagues continue to keep seeing unusual and viable Diels−Alder disconnections in complex target structures that do not appear to lend themselves to such molecular disassembly! We have also received powerful master classes and tutorials, from the different authors, in much highly useful functional group interconversion chemistry which, again, is technology that critically underpins our art.

Finally, may I request the forbearance of all my senior colleagues in the field, and the authors themselves, for the various mechanistic schemes that I have taken the liberty of advancing, alongside my own personal commentaries. Although I have tried to make these closely reflect what is likely happening in most of the reactions discussed, such mechanistic vignettes are *not* intended to be absolutist, or dogmatic, but are there *solely* to assist the undergraduate and graduate student readers to more fully appreciate much of the excellent chemistry that is being presented.

Before I close, I would like to offer my sincerest thanks to Professors Dale Poulter and Peter Stang of the University of Utah, for giving me this opportunity to showcase a few of the many excellent contributions that have appeared in the *JOC* and *JACS* journals, over the past two years. It has been a genuinely informative experience for me personally compiling this Virtual Issue, and I do so hope that my individual selections from these two research fields will prove interesting to the readership, alongside my various summations, which I trust have been illuminatory and valuable.

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(79) Niu, D.; Hoye, T. R. *Org. Lett.* **2012**, *14*, 828.