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Editorial
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Natural Product Total Synthesis: As Exciting as Ever and Here To Stay

We have travelled far since 1828 and the interest attached to 'total synthesis' has disappeared

Sir Robert Robinson (1936)

The total synthesis of complex natural products still remains among the most exciting and dynamic areas of research, with representative publications in this area routinely ranking among the most-read in every chemistry-focused journal. Three excellent prior summaries of fantastic accomplishments in this area have appeared in 2008,[1] 2013,[2] and 2014,[3] with the creation of virtual issues highlighting many representative publications from those time periods. In all of the editorials accompanying those expertly curated virtual issues, strong cases were made for why total synthesis continues to be an important and topical area of investigation. In this editorial I'd like to address recent topical issues surrounding the future of this field.[4]

Total synthesis and synthetic organic chemistry as a whole provide society a fantastic return on investment with innumerable fundamental and applied tangible advancements. Historically, chemists educated in this area are some of the most sought after in industry, as the skills of making molecules can be utilized for designing an infinite array of translational applications in medicines, agrochemicals, and materials. But the justification for why this pursuit endures goes beyond the simple argument of supplying the demands of a particular labor market.[5] From a fundamental perspective, total synthesis is a barometer and proving ground for new methodologies and new strategies or ways of thinking.[6] Lessons from such endeavors can illuminate unique or underappreciated areas of chemical reactivity. Powerfully simplifying disconnections in the context of an obscure natural product family can have enormous downstream impacts as well. From an applied standpoint, having sustainable and reliable access to biologically active natural isolates can demystify new areas of biology or provide promising candidates for drug discovery.[7] In many cases such pursuits can serve as the only means for structural identification.[8] It is therefore puzzling that so frequently this area of inquiry is criticized or its motives questioned.[9] To be sure, the study of total synthesis does not consume inordinate taxpayer resources relative to other areas (quite the opposite, actually),[10] and among journal readership such studies are of extreme interest to the broad audience based on sheer download statistics. I would argue that based on this statistic alone it is self-evident that the field remains vibrant rather than stale and of little general appeal.

Among outsiders or those disconnected from the intricacies of the field, some may view total synthesis or synthetic organic chemistry as a whole as being a "mature" field,[11] perhaps even being immediately amenable to automation[12] or replacement with artificial intelligence algorithms.[13] In my view, those efforts are certainly worthwhile as long as they don't come at the expense of the very field they wish to simplify. In other words, such efforts do not intimidate, threaten, or provoke fear in the hearts of any practitioner of synthesis. Promises of computational chemistry and combinatorial chemistry displacing the field were made over the years, yet we are still here.[14] Thus, I would predict that our species will become capable of interplanetary colonization long before rooms of machines dramatically reduce the number of employable synthetic chemists or eliminate them all together.[12f]

The perception of synthesis "maturity" is probably due to the field being misunderstood rather than mature. This misunderstanding is partially self-inflicted, as with every large accomplishment in the area one can get the sense that an endpoint has been reached.[15] As a community, we have become quite adept at being able to make anything with enough resources, but we are still decades or perhaps even centuries away from making everything well.[16] The "age of feasibility" [17] did a great job to advertise the former capability and perhaps deemphasize the latter deficiency, thus setting the stage for critics to emerge.

The goals of sustainability and environmentally conscious science underlie the precepts of modern chemistry, and natural product synthesis is no different in that regard. Thus, the field is moving toward simplifying the way molecules can be made[18] so that perhaps one day even the most complex structures can be obtainable by engineers rather than basic scientists. It's not visionary to speculate that computer-designed, fully automated sequences are on the way—that is blatantly obvious. Despite hubristic promises otherwise, that day is still far away. Active practitioners in this area are fully cognizant of this fact but either are too busy doing science to write countless essays, blog posts, and opinion pieces on the subject or simply don't have a platform to do so. Well-designed retrosyntheses can fail even in simple settings, reproducibility is still an issue with precise experimental technique often essential for success,[19] selectivity (chemo, regio, stereo) is frequently hard to predict in complex settings, serendipity still abounds, visceral creativity and persistence determine success, and some of the most powerful disconnections and new reagents need to be invented from scratch—these facts bear repeating, especially to government officials that fund science and the Editors that publish it.[20] These very same bleak facts also underlie the charm and appeal of the area and are the reason that students are still magnetically attracted to it. Indeed, total synthesis programs still evoke an exciting sense of wonder and exploration of the unknown, not to mention the artistic aspects and inherent beauty of the final route. Thus, to state the obvious (to some), the "industry" of synthesis cannot be heroically "disrupted" with engineering advances and promises of utopian automation.[21] That's not to say that certain aspects of synthesis can't be made easier or accelerated with such advances.[22] And that's also not to say that folks like me in the synthesis community would not welcome such a day. Rather, it is still boring old human ingenuity, creativity, and curiosity[23] manifesting through the invention of new enabling methods, catalysts, reagents, and daringly different strategies that will push the field forward with the most "disruptive potential". In fact, many industries (such as drug discovery and development) are moving toward more and more complex targets,[24] and it is widely recognized that synthesis is often a rate-limiting step. For the reasons articulated above, advances in total synthesis and methodology can have a positive impact in making simple what was once

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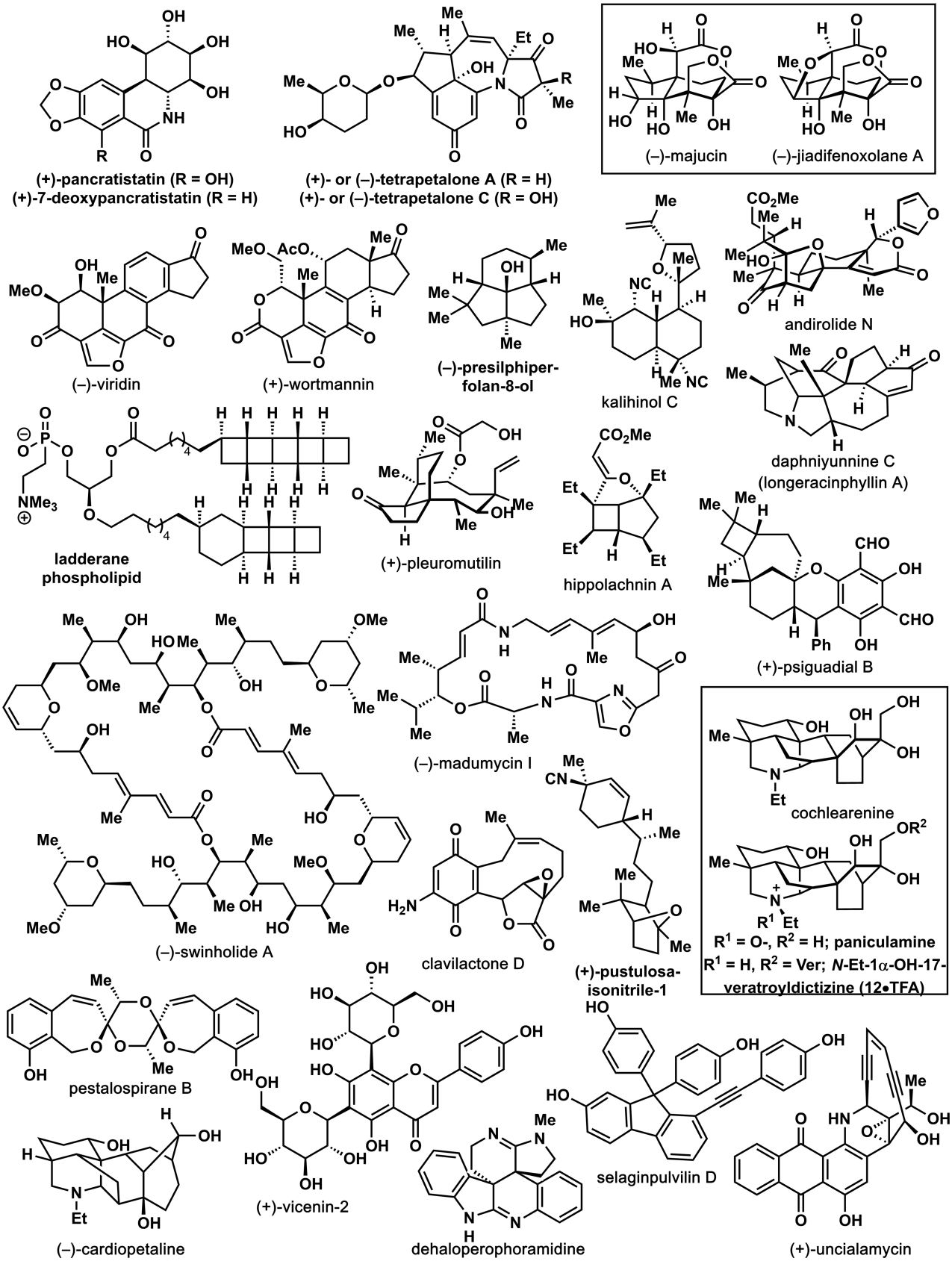

Figure 1. Structures of natural products synthesized as part of selected articles in this issue of *JACS* Select.

complex[21] and making engineer-friendly what was once unimaginable. Unfortunately, it is a mission statement that has less headline-grabbing potential than "3-D printing drugs",[12e] and certainly it is not a focused "moon-shot".[25] But from the vantage point of someone that struggles with synthesis every day in their own lab and through countless hours of consulting with industry, it is reality.

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The selections in this *JACS Select* virtual issue are thus representative of the modern ideals of total synthesis, from striking new strategies and methods applied to complex problems to the powerful application of modern techniques to provide materials of functional importance. The curated papers highlighted here are only a snapshot of the beautiful work in this area. They were chosen from the past 18 months based on referee feedback and popularity (download rates) and limited to 24 selections (17 from *JACS*, 4 from *Organic Letters*, and 3 from *The Journal of Organic Chemistry*). The structures of some of the natural products synthesized in these featured articles are shown in Figure 1.

The **Sarlah** group's enantioselective synthesis of the pancratistatins is a prime example of reaction invention and bold new strategies in action. Through the use of an innovative "arenophile" approach, the alkaloid family can be made from benzene in only a handful of steps, dramatically shortening alternative routes to this family, including those relying on biocatalysis[26] for asymmetry. The **Wood** laboratory recently completed a landmark synthesis of the tetrapetalones using a clever annulation strategy with carefully choreographed operations to furnish the natural products for the first time despite extensive efforts from groups around the world. In a striking feat of two-phase terpene total synthesis, the **Maimone** group accessed (−)-majucin and (−)-jiadifenoxolane A through a series of 10 carefully choreographed oxidations from a minimally oxidized terpene starting material. A testament to the creativity of chemists in assembling similar structures, one is struck by the differing approaches to (−)-viridin and (+)-wortmannin by the **Guerrero** and **Luo** groups, respectively. The former group features a unique intramolecular Heck reaction to rapidly assemble the core, while the latter group utilizes a Pd-catalyzed cascade to convergently assemble the skeleton. A daring stereoselective double-Heck reaction is featured in **Snyder**'s rapid total synthesis of (−)-presilphiperfolan-8-ol. **Shenvi**'s rapid and stereocontrolled path to kalihinol C features a remarkable heterodendralene Diels−Alder reaction followed by an S_N2 reaction on a tertiary center to install the isonitrile motif. A unique biosynthetic hypothesis coupled to a powerful sequence of C−C bond-forming events enabled an unusually concise path to andirolide N by the **Newhouse** group. The tactical combination of a phosphine-promoted [3+2] cycloaddition, silver-catalyzed alkyne cyclization, and Luche radical cyclization enabled the **Li** group to access the complex daphyniphyllene alkaloid longeracinphyllin A. **Burns** and co-workers' recent scalable approach to the ladderanes features a daring late-stage desymmetrization and C−H chlorination and is enabling a fundamental understanding of how these bizarre natural products elicit their function. **Herzon**'s modular assembly of the classic target pleuromutilin sets a high bar for efficiency in reaching complex terpenoid targets and sets the stage for analogues that were previously inaccessible using a semisynthetic approach.[27] The seemingly simple yet densely functionalized cyclobutane-containing natural product hippolachnin A was prepared through an innovative approach by the **Trauner** group, featuring a rarely encountered thiocarbonyl−ylide cycloaddition. **Reisman** and co-workers' creative use of a cyclobutane C−H functionalization process provides a unique pathway to access (+)-psiguadial B that is complementary to the biomimetic approach.[28] **Krische**'s synthesis of (−)-swinholide A is yet another example of the remarkable increase in efficiency obtainable using innovative new methods for catalytic enantioselective C−C bond formation. Indeed, the route to these complex natural products was nearly cut in half (15 steps LLS vs 27 in the shortest previous approach[29]). In the hunt for interesting new antibiotics, **Seiple** and co-workers reported a highly modular and scalable approach to the bacterial ribosome-inhibiting madumycin natural products. A unified total synthesis of complex diterpenoid alkaloids (paniculamine, cochlearenine, veratroyldictyzine) through a brilliantly designed dearomatization/Diels−Alder strategy was accomplished by **Sarpong** and co-workers. **Nicolaou**'s streamlined approach to the uncialamycins paves the way for scalable access to these highly potent cytotoxins through the tactical use of a Friedlander quinoline synthesis and a Hauser annulation. **Snider** and **Li** accomplished a short synthesis and structural reassignment of clavilactone D through an innovative Fe-catalyzed three-component coupling. The **Vanderwal** and **Garson** groups teamed up for a superb synthesis, structural elucidation, and biological evaluation of (+)-pustulosaisonitrile-1. In **Brimble**'s elegant synthesis of pestalospirane B, a biomimetic dimerization/spiroketalization is utilized to access assign the stereochemistry of the natural product. The intricate complexity of (−)-cardiopetaline was expertly addressed by the **Fukuyama** group through a strategically planned Wagner−Meerwein shift of a sulfonyl oxirane. **Suzuki**'s masterful synthesis of vicenin-2 features a rapid and programmable assembly through strategic use of simple 1,3,5-trifluorobenzene as a starting material. The **Sherburn** group's rapid and scalable synthesis of selaginpulvilin D is a remarkable example of a cascade assembly of a natural product with five core C−C bonds being generated in only four simple steps. Finally, the conciseness of **Somfai**'s synthesis of dehaloperophoramidine is a testament to a clever design embedded with domino reactions to reduce reliance on protecting group and refunctionalization chemistry.

The community should consider total synthesis a vibrant and worthwhile pursuit as long as it enables access to functionally useful molecules and/or powerful new methods and strategies are being invented. The selections herein are only the tip of the iceberg and are representative of the exciting developments that continue to be reported. It is likely that the best days of total synthesis are still to come.

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Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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