Editorial

Total Synthesis of Biologically Active Natural Products

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The inaugural *JACS* Virtual Issue (http://pubs.acs.org/JACSbeta/JVI/index.html) focuses on the total synthesis of natural products. This topic was selected since a significant number of the most highly viewed papers published in *JACS* concern the synthesis of natural products—reflecting the continued vitality and broad interest in this important field of research.

Our intent is to highlight research published in 2007 and in 2008 to date. Among the numerous beautiful contributions in natural products synthesis that were published in this time frame, the 20 that are highlighted in this *JACS* Virtual Issue were selected by the Editors, with the guidance of the number of Web views (weighted for the time since the papers were first published) and reviewer input, particularly regarding their assessment of the novelty and significance of the work.

Synthesis is a discipline that is central to all areas of chemistry. It encompasses the unique ability of chemists to develop new reactions and to design molecules or molecular systems with a desired (or anticipated) set of properties—be they enzyme inhibitors, receptor agonists, fluorescent dyes, transition metal catalysts, molecular devices, nanotubes, modified surfaces, solid-state compositions, or novel polymers. The proactive and creative nature of the *science of chemical synthesis* is unique among all of the physical sciences. This is especially true of research in natural products synthesis.

Research focusing on the synthesis of natural products has its origin in structure determination, which in decades prior to the advent of modern physical and spectroscopic methods was accomplished by degradation and partial synthesis of fragments or, in some cases, by the relay and/or total synthesis of the natural product itself. However, in spite of the remarkable techniques that are now available to the natural product isolation chemist, it is not always possible to assign the complete stereochemistry on the basis of spectroscopic methods. In such cases, chemical synthesis continues to play a significant role in structure determination.

Interest in natural products synthesis has also been fueled by the recognition that many classes of important pharmaceutical agents derive from natural products—β-lactam antibiotics, macrolide antibiotics, and steroid hormones are three illustrative classes of natural products that have given rise to important medicinal agents. Fascination with the role that secondary metabolites play in regulating cellular and other biological processes continues to provide the stimulus for natural products synthesis, as well as research on the development of small-molecule libraries and ultimately drug candidates based on natural product leads. In many cases, the quantities of natural products available from natural sources are so limited that total synthesis is required in order to provide material for further biological characterization, a necessary step to determine if the natural product warrants further exploration as a lead structure for drug development.

Importantly, interest in natural products synthesis has stimulated incredible advances in the development of new synthetic methods and new strategies for synthesis of structurally and stereochemically complex molecules. Even a cursory examination of the workhorse bond-forming reactions in use today—ranging from the multitude of palladium(0)- and nickel(0)-catalyzed coupling reactions, to ruthenium-mediated olefin metathesis and other transition metal-mediated C−C bond-forming reactions, to C−H activation, to the many important and newly emerging methods for asymmetric synthesis and asymmetric catalysis, among many others—reveals that most were not available to the practicing organic or medicinal chemist even two decades ago. Natural products synthesis provides an important forum for testing and demonstrating the synthetic utility of newly developed methods and strategies, as the unique and often complex arrangements of functionality and stereochemistry in natural product targets provide stringent tests. In essence, efforts to apply new methods to complex natural product targets provide a Darwinian selection pressure that ensures that the methodology platforms available to the bench chemist continue to evolve in a highly productive direction.

These themes are beautifully represented by the 20 outstanding papers that appear in this inaugural *JACS* Virtual Issue. Not surprisingly, many of these papers embody more than one of these themes. These papers are organized here, roughly along the lines of the three themes defined above.

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Kishi and Kim's[1] synthesis of mycolactone F represents a case in which the stereochemistry of the natural product was not known with certainty, owing to the difficulty of assigning stereochemistry to the side chain C(11′) and C(13′) hydroxyl groups. This issue was resolved by synthesis and complete characterization of mycolactone F and its "remote diastereomer".

De Brabander[2] initiated the total synthesis of palmerolide A owing to its promising antitumor properties and extremely limited supply from natural sources. De Brabander and co-workers synthesized the originally assigned structure of palmerolide A, only to find that the structure had been misassigned. De Brabander and co-workers deduced the correct relative stereochemistry and synthesized (−)-palmerolide A, the enantiomer of the natural product.

Two other papers in this set also contribute to the assignment of the complete stereochemistry of natural products: (−)-okilactomycin, a novel polyketide antitumor antibiotic, and (+)-frondosin A, a norsesquiterpene with HIB-inhibitory activity. The absolute stereochemistry of these natural products had not been assigned prior to these total syntheses. **Smith** and co-workers'[3] okilactomycin synthesis features a Petasis−Ferrier union/rearrangement to construct the highly congested 2,6-*cis*-tetrahydropyranone ring and a ring-closing metathesis reaction to close the 13-membered ring of the natural product. The frondosin A synthesis by **Trost** and co-workers[4] features use of a ruthenium-catalyzed [5+2]-cycloaddition, a Claisen rearrangement, and a ring expansion to construct the core of the natural product in a highly efficient and selective manner.

Two of the contributions in this set of 20 noteworthy papers illustrate the use of natural products as starting points for drug development. Platensimycin is a recently discovered antibiotic with significant activity against drug-resistant bacteria and, consequently, has attracted the interest of numerous groups worldwide. **Nicolaou** and co-workers'[5] synthesis of carbaplatensimycin focuses on the question of how the natural product binds to the bacterial target, β-ketoacyl-(acyl carrier protein) synthases I/II. This work confirms the role that the platensimycin ethereal oxygen plays in the activity of the natural product. The second paper with a significant medicinal chemistry thrust is on the synthesis of FR901464 and a low picomolar analogue, meayamycin, from the **Koide** group.[6] The syntheses include an impressive diene−ene cross-coupling reaction. Meayamycin was designed to eliminate a source of chemical instability of FR901464 and, significantly, proved to be circa 100 times more potent than the natural product against human breast cancer MCF-7 cell proliferation.

Five additional total syntheses in this *JACS* Virtual Issue were developed with an eye toward studies of mechanism of action and more detailed biological evaluation of the natural products. **Danishefsky and Dai**[7] report strategically interesting total syntheses of spirotenuipesines A and B, which have demonstrated potential to promote the differentiation of neurons and are accordingly of interest for potential treatment of neurodegenerative disorders. **Fürstner and Nagano**[8] present a synthesis of ipomoeassins B and E, which are of interest for their ability to inhibit human ovarian cancer cells. Their synthesis features an interesting strategy for protecting a cinnamic ester during a ring-closing metathesis sequence. Stephacidins A, B and notoamide B are highly cytotoxic alkaloids, with stephacidin B having significant activity against testosterone-dependent prostate LNCaP lymphoma. The syntheses of these compounds reported by **Williams** and co-workers[9] feature an S_N2' cyclization to establish the [2.2.2] bridged bicyclic ring system, as well as the extensive use of microwave reaction technology. **Menche** and co-workers[10] present an efficient synthesis of archazolid A, which displays powerful growth-inhibition activity against a number of murine and human cancer cell lines, and **Markó and Pospísil**[11] similarly present a very brief synthesis of jerangolid D, a compound with intriguing antifungal activity. In all five of these cases, the authors indicate that analogues of the natural products are being synthesized in order to further probe the biological properties of these very interesting structures.

Three additional contributions in this issue are noteworthy for, among other reasons, the methodological advances that they highlight. The first-generation synthesis of (+)-saxitoxin

(1) Kim, H.-J.; Kishi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 1842–1844.
(2) Jiang, X.; Liu, B.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.
(3) Smith, A. B., III; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872–14874.
(4) Trost, B. M.; Hu, Y.; Horne, D. B *J. Am. Chem. Soc.* **2007**, *129*, 11781–11790.
(5) Nicolaou, K. C.; Tang, Y.; Wang, J.; Stepan, A. F.; Li, A.; Montero, A. *J. Am. Chem. Soc.* **2007**, *129*, 14850–14851.
(6) Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Czaicki, N. L.; Koide, K. *J. Am. Chem. Soc.* **2007**, *129*, 2648–2659.
(7) Dai, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 3498–3499.
(8) Fürstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906–1907.
(9) Artman, G. D., III; Grubbs, A. W.; Williams, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 6336–6342.
(10) Menche, D.; Hassfeld, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100–6101.
(11) Pospísil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 3516–3517.

by **Du Bois** and co-workers[12] features a powerful rhodium-catalyzed C−H amination reaction. A palladium-catalyzed silicon-based cross-coupling reaction and a chiral bisphosphoramide-catalyzed allylation reaction using allyltrichlorosilane are prominently highlighted in the synthesis of papulacandin D by **Denmark** and co-workers.[13] Finally, an enantioselective decarboxylative allylation reaction and a ring-closing metathesis reaction to construct a tetrasubstituted chlorine-containing alkene are highlighted in the synthesis of elatol by **Stolz, Grubbs**, and co-workers.[14]

The remaining six contributions constitute beautiful demonstrations of strategy and tactics—as do many of the other papers named above—for the synthesis of structurally complex, stereochemically rich, biologically active targets. **Overman** and co-workers[15] describe the synthesis of (−)-sarain A by a route featuring an enoxysilane−*N*-sulfonyl iminium ion cyclization, a ring-closing metathesis reaction, and an intramolecular Stille macrocyclization. A beautiful transannular Michael reaction cascade sequence is the heart and soul of the salvinorin A synthesis by **Evans** and co-workers.[16] **Baran** and co-workers[17] provide a detailed account of their syntheses of several dimeric pyrrole−imidazole alkaloids by routes that utilize the fundamental chemistry of the 2-aminoimidazole heterocycle as well as a strategically novel fragmentation of an oxaquadricyclane intermediate. The synthesis of (+)-nakadomarin A by **Kerr and Young**[18] showcases the utility of a nitrone−cyclopropane cycloaddition to generate the pyrrolidine functionality within the tetracyclic core. **Watanabe and Nakada**'s[19] synthesis of the κ-opioid receptor agonist (−)-erinacine E features, as the key step, an intramolecular aldol reaction that is coupled with a 1,2-migration of a benzoyl ester protecting group for formation of the strained skeleton of the natural product. Finally, the synthesis of racemic communesin F by **Qin** and co-workers[20] features an intramolecular cyclopropanation of an indole and a subsequent Claisen rearrangement to establish the adjacent quaternary centers in the natural product.

We hope that this collection of papers will provide both the practitioner and the wider chemical community with insight into the significance and excitement that the field of natural products total synthesis continues to hold for organic chemists.

William R. Roush, Associate Editor
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