

Special Issue

Laudio for Professor Clayton H. Heathcock



This special issue of *SYNLETT* continues a tradition of honoring scientists who have not only made impressive contributions to the field of organic synthesis, but have helped to shape it through their innovation. Professor Clayton H. Heathcock has played many leading roles in organic chemistry during his 40-year career at the University of California at Berkeley. His research contributions both exemplify and in many respects stimulated the dramatic transformations that occurred in synthesis during his time. The establishment of new synthetic paradigms, careful analysis of reaction mechanisms and, above all, inspired and succinct approaches to complex molecules are all represented at the highest level in his work.

Heathcock is above all a teacher. His contributions in the classroom, through the well-respected textbook that he coauthored with his colleague, Andy Streitwieser, and the training he provided to the students and postdocs in his research group are obvious reflections of this role. However, all of us in the community of synthetic organic chemists have been taught an enormous amount through his approach to research, his innovative contributions, and the way in which he communicates them.

The concept of stereocontrolled synthesis was still young in the 1970's. The establishment of relative stereochemistry through double bond addition reactions or the introduction of cis or trans relationships in ring systems of well-defined conformation was our level of aspiration. We knew that some carbon-carbon bond-forming processes between acyclic substrates could generate a preponderance of one diastereomer over another, but we had not yet made the jump from trying to understand the phenomenon to attempting to control it. In short, the concept of acyclic diastereoselection was only a shimmer when Heathcock initiated his work on the stereocontrolled aldol addition reaction. His 1977 *JACS* paper entitled "Stereoselection in the Aldol Condensation" made the mechanistic connection between the geometry of the enolate and the stereochemistry of the β -hydroxy ketone or ester product. The key was revealed: if you control the enolate geometry and prevent product equilibration, you can control the configuration of the acyclic product in a predictable fashion.

As with many such innovative discoveries, this simple, precipitating concept triggered a flood of research, including more than 40 papers from Heathcock's lab and thousands from others extending and diversifying this approach to the control of acyclic stereochemistry. However, this first paper was not his only conceptual breakthrough in this field. He and his group were the first to apply the concept of double stereodifferentiation for the control of "Cram's rule selectivity" in additions to chiral aldehydes and to popularize the terms "diastereofacial preference" and "diastereofacial selectivity". Together, these strategies made the polypropionate natural products accessible to total synthesis, opening up interest in macrolide lactones and polyethers that continues to this day.

A research domain of equal importance in demonstrating how much Heathcock has taught us is that of natural product total synthesis. Even his first foray into this field, the synthesis of copaene published just two years after his arrival at Berkeley, demonstrated a conciseness of synthetic planning and experimental virtuosity that foreshadowed his later exploits. Among his subsequent accomplishments are syntheses of bulnesol, occidentalol, lycopodine, lycodine, lycodoline, confertin, parthenin, compactin, dihydromevinolin, fawcettimine, methyl homodaphniphyllate, norsecurinine, vallesamidin, daphnilactone A, isovelleral, methyl homosecodaphniphyllate, secodaphniphylline, bukittinggine, mirabazole C, alloaristoteline, diplamine, thiangazole, petrosin, ACRL toxin IIIb, codaphniphylline, papuamine and haliclonadamin, tantazole B, zaragozic acid, tricolorin A, myxalamide A, preussomerins G and I, cylindricines A and B, isoschizogamine, aspidospermidine, styelsamine B, and spongistatin 2. While "first ascents" are often collected as trophies, the hallmarks of Heathcock's approach – simplicity of synthetic design and a careful attention to experimental detail – also produce "direttissima": more challenging but the most elegant and instructive. His syntheses of the daphniphylline alkaloids, involving few steps, high yields, and dazzling sequences of stereocontrolled ring-forming reactions are among the most impressive ever devised. Even when he and his students have to dig into a long synthesis, the outcome is unique. For example, Heathcock's recent total synthesis of the highly cytotoxic marine natural product, spongistatin 2, was notable not simply for the 113 steps it entailed, but for the yield of the effort: more than 250 mg of the material.

Clayton's quite substantial research accomplishments must be viewed within the framework of Clayton as a mentor and a person. Many of his colleagues and former students can relate stories about the ways in which Clayton allowed his coworkers the free rein necessary to develop fully as scientists. In this way, his researchers were often "forced" to discover something on their own. Clayton would restrain himself from giving students solutions to problems that he felt they could solve. He also involved his students in the writing of papers and reviews, exercises that became invaluable training for their future careers, and he strongly encouraged, indeed, demanded, that everybody participate in discussions at group meetings, in the laboratory, and at his famous Texan chili parties at his home.

We can't leave a discussion of Clayton's interests in "synthesis" without noting a connection with the hobby that he and his wife Cheri have taken up, which is breeding Rhodesian Ridgebacks. Visit the website "www.camelotr.com" to read the story of how this interest evolved and to see some very engaging dog pictures.

Clayton's ability to perceive the key issues in any problem, address them forthrightly, and solve challenges creatively has served him (and us!) equally well in the service he has provided to the American Chemical Society as editor of the *Journal of Organic Chemistry* and to the University of California as Dean of the College of Chemistry. He has had an influence on our science, our students, and our colleagues that will resonate for a long time.

Paul A. Bartlett
Department of Chemistry
University of California at Berkeley

Biographical Sketch

Clayton H. Heathcock

Biodata and education

Born in San Antonio, Texas, July 21, 1936. B.Sc. Abilene Christian College, Texas (1958); Ph.D. University of Colorado (1963); National Science Foundation Postdoctoral Fellow, Columbia University (1963-4).

Professional experience

Supervisor of Chemical Tests Group, Champion Paper & Fiber Company, Pasadena, Texas (1950-60); University of California, Berkeley: Assistant Professor (1964-70); Associate Professor (1970-76); Professor (1976-2004); Chair, Chemistry Department (1986-89); Dean, College of Chemistry (1999-present); Gilbert Newton Lewis Professor, 2003-present); Chair, Medicinal Chemistry A Study Section, National Institutes of Health (1981-83); Chair, Organic Chemistry Division of the American Chemical Society (1985); Chair, Gordon Conference on Stereochemistry (1986); Editor-in-Chief, *Journal of Organic Chemistry* (1989-99); Editor-in-Chief, *Organic Syntheses* (1986); Scientific Advisory Committee, Abbott Laboratories (1986-97); Scientific Advisory Board, Plexxikon (2002-present).

Honors and awards

Alfred P. Sloan Fellow (1967-69); Alexander von Humboldt US Senior Science Award (1978); Miller Research Professor, UC Berkeley (1982 and 1991); Ernest Guenther Award, American Chemical Society (1986); Allan Day Award, Philadelphia Organic Chemists Club (1989); Award for Creative Work in Organic Synthesis, American Chemical Society (1990); Arthur C. Cope Scholar Award, American Chemical Society (1990); Prelog Medal, ETH (1991); American Academy of Arts and Sciences (1991); National Academy of Sciences (1995); Centenary Medal, Royal Society of Chemistry (1996); H. C. Brown Award, American Chemical Society (2002).

Lectureships

DuPont Visiting Professor, Georgia Institute of Technology (1975); ITT Rayonier Lecture, University of Idaho (1976); Martin Friedman Lecture, Rutgers University (1977); Timmie Lecture, Emory University (1978); Iddles Lecture, University of New Hampshire (1982); Liebig Lecture, University of Colorado (1982); Merck Lecture, University of Montreal (1982); Dow Lecture, Texas Christian University, (1983); Reilly Lecture, University of Notre Dame (1985); Bergmann Lecture, Yale University (1987); Greater Manchester Lectureship, University of Salford (1987); Parke-Davis Lecture, Hope College (1988); Prelog Lecture, ETH (1991); George Büchi Lecture, Massachusetts Institute of Technology (1992); Robert Lutz Lecture, University of Virginia (1992); SmithKline Beecham Lecture, Nottingham University (1992); Victor Chambers Lecture, University of Rochester (1993); C. S. Marvell Lecture, University of Illinois (1994); Phi Lamda Upsilon, Rho Chapter Lecture, University of Nebraska (1995); Warner-Lambert Lecture, University of Michigan (1995); Royal Society of Chemistry Centenary Lecture, Edinburgh, Scotland (1996); Bio-Mega/Boehringer Ingelheim Lecture, University of Sherbrooke, (1997); PRI Chemistry Lecture, R. W. Johnson Research Institute (1997); Frontiers in Science Lectures, Texas A&M (1997); Howard Lectures, Universities of Sydney & New South Wales (1998); 50th Frank Burnett Dains Memorial Lecture, Kansas University (1998); 1st Henry Shine Lecture, Texas Tech University (1999); Pfizer Lecture, University of Puerto Rico (2000); Mack Award Lecture, Ohio State University (2000); R. B. Miller Memorial Lecture, University of California, Davis (2001); Mahler Lecture, University of Texas (2002); Hodgson Memorial Lecture, GlaxoSmithKline (2003); Hirata Memorial Symposium, Helsinki (2003).

Berkeley, May 15, 2004

I am honored to have had the privilege for 40 years of serving as mentor to an exceptional group of research coworkers - undergraduate, graduate, and postdoctoral students now numbering more than 150, many of whom have since found their own places on faculties of chemistry or in the research departments of a multitude of pharmaceutical companies around the world.

When I reflect on my academic career, I find it remarkable how far the field of organic synthesis has come since 1964, when I showed up in Berkeley as a *junior* Assistant Professor. My first project was total synthesis of a 15-carbon, tricyclic terpene named *copaene*. From that simple start, my students and I came by 2003 to the total synthesis of a marine polyketide named *atohyrtin C* (*spongistatin 2*), a logistical feat that required chaperoning eight different starting materials through a highly convergent synthesis that required a total of 117 chemical steps and ultimately provided 250 milligrams of the synthetic natural product.

In my view, this where practitioners of organic synthesis must look in the coming decades. It has now been abundantly established that we can synthesize any conceivable natural product. Our challenge now is to establish that we can synthesize any desired natural product, no matter how complex, in meaningful quantity.

Clayton Heathcock