Tetrahedron 69 (2013) 7529–7550

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Toward the ideal synthesis and transformative therapies: the roles of step economy and function oriented synthesis

Paul A. Wender

Department of Chemistry, Department of Chemical and Systems Biology, Stanford University, Stanford, CA 94305-5080, USA

ARTICLE INFO

Article history:
Received 31 May 2013
Available online 7 June 2013

"Much of life can be understood in rational terms if expressed in the language of chemistry. It is an international language, a language for all of time, and a language that explains where we came from, what we are, and where the physical world will allow us to go. Chemical language has great esthetic beauty and links the physical sciences to the biological sciences." from the 'Two Cultures' by Arthur Kornberg[1]

On the special occasion of the awarding of the Tetrahedron Prize, I have been asked to provide an article on our research. In keeping with custom, this will start with some autobiographical background and proceed with an overview of some research conducted by my co-workers and collaborators. At the outset, I wish to acknowledge the many mentors, students, colleagues, family and friends who have figured and continue to figure in this journey. I have had and continue to have the good fortune of working with exceptional co-workers, over 300 and counting including over 70 now in academic positions around the globe and many others in leading positions in industry including directors, VPs, and CEOs. While only some of their projects can be presented here and those at best in abbreviated form, the topics are more fully developed in the referenced primary literature from our laboratory and in references cited therein to noteworthy contributions from other laboratories. Additional contributions from several remarkable friends and scientists whose work is a source of continuing inspiration follow in this issue. I have benefited greatly from many teachers and have had the special benefit and pleasure of conducting research with and being mentored by Bill Stine (Wilkes), Fred Ziegler (Yale) and Gilbert Stork (Columbia). Each has generously shared special insights on chemistry, science and education and each has profoundly influenced my career. They are remarkable. My wonderful colleagues at Harvard and now at Stanford have also figured significantly in shaping our research program and its vision. Of special significance is Jacqueline Bryan Wender, a partner in life, whose wisdom, vision, style, and grace have been and continue to be a source of exceptional inspiration.

Like many fascinated with space travel at the time, I spent much of my childhood literally doing 'research' on rocket fuels and testing their capacity to propel designed model rockets into 'space' in the hills around my home. Some exploded, some burned, but many worked amazingly well. My transition from this 'October Sky'[2] world of model rockets and dreams to the excitement of undergraduate research was guided by Bill Stine. His patience in the laboratory, enthusiasm for science and breadth of interests from piloting planes to competitive tennis, made for extraordinarily diverse and rich learning experiences. Flying in his plane to Syracuse University to record NMR spectra on compounds we made is one of many unforgettable 'research' experiences. It was Bill who encouraged me to think more broadly about chemistry and who with his colleagues at Wilkes put me on the path to graduate school. I arrived at Yale for graduate studies with an interest in biophysical chemistry but found on meeting with faculty that most research programs, whether focused on photochemistry, biosynthesis, mechanistic chemistry, biochemistry or spectroscopy, were heavily involved with and often slowed by problems with making molecules of interest. The message here was clear: if one could learn how to make molecules more quickly and efficiently one would have more time to spend on their study. I knew too little then to understand the broader ramifications of this perception but, as partly elaborated herein, it has indeed been a career long theme taking the form some years later of 'step and time economy' and 'function oriented synthesis' directed at 'the ideal synthesis',[3] a goal we defined in 1985 in a form that most would agree with today:

E-mail address: wenderp@stanford.edu.

http://dx.doi.org/10.1016/j.tet.2013.06.004

'*ideal syntheses [are] those in which the target molecule is assembled from readily available starting materials in one simple, safe, economical, and efficient operation*.'[4]

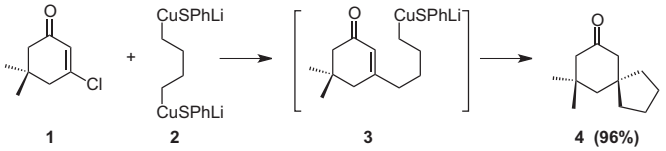
Learning to make molecules thus became the immediate focus of my graduate studies and Fred Ziegler provided the exceptional expertise to make that happen. His group was dynamic and intensely interactive, adding greatly to the learning experience and serving as a model for my own group's operation a few years later. Most days at Yale were rich with discussions about problems and ideas. It was there that I also found time to scour the literature not for some homework assignment but simply to treat myself to what I considered then and now 'recreational reading'. It was there that I first read about arene–alkene photocycloadditions, processes unrelated to my PhD research that later would figure significantly in the start of my own independent research.[5] It was there that I also learned about cuprate chemistry, an experience that would years later figure in my group's introduction of a new family of reagents, organobiscuprates.[6] It was there that I also first explored the fascinating prototropic rearrangement of imines, again unrelated to my research but a subject that was to figure in my own independent research.[7] At Yale, I had the pleasure of conducting a 'methods' project[8] and also completing the first total synthesis of a sesquiterpene by the name of eremophilone.[9] The former in retrospect was an exceptional test of laboratory technique as it required generating liquid HCN several times a week by the dropwise mixing of concentrated sulfuric acid and a saturated solution of NaCN and trapping the resultant bursts of HCN gas (bp=26 °C) in a cold trap. Coffee was not needed on those days. The eremophilone total synthesis elicited less adrenaline but was also rich with learning experiences and indeed provided my initial experimental introduction to organometallic chemistry and photochemistry. Some seeds were thus sown.

My plans for life-after-Yale, while long under consideration, were finalized with unanticipated speed. I had a discussion one morning with Fred Ziegler about possible postdoctoral positions and by the end of that morning Fred told me that Gilbert Stork had accepted me into his group. It was a great day. I arrived at Columbia University in September 1973, at which time Gilbert Stork proposed an exciting idea directed at the synthesis of reserpine. I was thus off exploring the world of heterocycle synthesis. This experience, not unlike my studies at Yale, was enhanced greatly by members of the Stork group and other groups at Columbia, and figured subsequently in projects pursued at the outset of my independent career, including a synthesis of reserpine, and continue to figure in a special collaboration on drug delivery research up to this very day. While I had NIH Postdoctoral Fellowship support for two years, my time with Gilbert Stork, while exceptional,[10] was brief. Within weeks of my arrival at Columbia, I received a call from Robert Woodward asking if I would be interested in a faculty position at Harvard. My subsequent visit went well and was capped by a discussion with Woodward that started, after a full day of science and an evening meal, at 10 PM and ended the following morning around 7. I started at Harvard in July 1974.

At the outset of a journey it is often valuable to have a sense of where one is headed and, from a song of the period, 'a code that one can live by'. The early view that emerged was simple. My interest in chemistry had always been fueled by its potential to address medical problems and that was now integrated with an interest in synthesis. This exciting fusion provided the path forward: advance synthesis and medicine by focusing on and studying molecules that might figure in the prevention, diagnosis or treatment of disease. The questions of which molecules to make and how to achieve clinical relevancy spawned some ideas and plans that remain central to our research even today and are touched upon herein.

At the outset of our independent research, while our synthetic interests focused on specific targets, the structures were selected based on their being representative of more general synthetic and biological problems. Both were important. As for the synthesis component of this fusion, a brief analysis of natural products revealed that while they differ in many ways, they can be universally categorized as acyclic and cyclic and the latter further organized as monocyclic and fused-, bridged- or spirocyclic with most having ring sizes between 3 and 16 members, and containing all carbon or carbon heteroatom compositions. No matter what the specific natural or non-natural target, it was a composite of one or more of these 'general synthetic problems'. A check of the literature at the time revealed that methodology for the construction of rings of seven or more members was not very advanced. In fact, the first syntheses of pseudoguaianes,[11] 5–7 ring systems with interesting biological activities, appeared only in 1976. More complex and more biologically important tiglianes, daphnanes, and ingenanes had not been synthetically approached. Indeed the first member of this large triad of natural product families was not synthesized until many years later (1989).[12] As we noted at the time: '*the facile synthesis and further elaboration of functionalized bicyclo[5.3.0]decanes constitute an objective of considerable dimension in synthesis as suggested, in part, by the number and complexity of natural product families characterized by this subunit (e.g., pseudoguaiane, guaiane, daphnane, tigliane, ingenane, asebotoxin). The significance of this objective is further amplified by [their] potent and varied biological activity and, in particular, significant antitumor or cocarcinogenic activity.*'[13] And so the starting synthetic, biological, and medicinal framework for our studies was put in place.

Our first independent studies were directed at the synthesis of spiro-cycles, seven-membered ring containing natural products, and medium ring containing natural products. While our introduction of the term 'step economy' would come later, it was clear that our approaches were designed with that goal in mind.[14] A method for constructing spiro-cycles using novel organobiscuprate reagents was designed to construct the key quaternary center in '*only one synthetic operation*' (Scheme 1).[6] Our approach to seven-membered rings started with the introduction of a vinylcyclopropane (VCP) into a molecule that upon work up produced a divinylcyclopropane (DVCP), which upon distillative purification underwent a Cope rearrangement to give the seven-membered ring product (Scheme 2). As we noted at the time, '*a particularly attractive feature of [this] method is that the entire annelation sequence can be performed in one synthetic operation, i.e., initial reaction (1,2 addition of the reagent), acidic workup (formation of the divinylcyclopropane), and distillation (rearrangement and purification).*'[15] This strategy for seven-membered ring synthesis subsequently figured in our syntheses of the pseudoguaianes damsinic acid and confertin, both additionally featuring a highly efficient CH activation process (Scheme 3).[13] It also served as a gateway to the bigger synthetic challenges associated with more complex and more biologically important targets, such as the tiglianes, daphnanes, and ingenanes.[16] The reader is referred to work from the groups of Marino[17] and Piers[18] for alternative, contemporaneous DVCP approaches to seven-membered rings.



Scheme 1. Organo-*bis*-cuprates: new reagents for a single step spiroannelation.