

# People, Travel, Seminars, Reading, the Classroom, and Curiosity-Sources of Research Inspiration

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**Abstract.** This manuscript is the outgrowth of a plenary lecture delivered by the author at the 44<sup>th</sup> Congreso Mexicano de Química that was held in Puebla, Mexico from 26-30 September of 2009. In formulating the presentation, consideration was given to thinking about the origins of the ideas that were integral to the formulation of the research to be described. The intent was to address the younger members of the audience – advanced undergraduate and graduate students, and those beginning the process of searching for a job. At a similar stage in my scientific career, I realized the need to formulate research plans in order to complete job applications where they were required. Where do these ideas come from? What factors stimulate one's curiosity? What stimulates one to pursue a particular line of research? Topics discussed within the context of attempting to address these questions include electrohydrocyclization and electroreductive cyclization, and their application to the total synthesis of natural products, the use of nickel salen and triarylaminas as mediators and redox catalysts, the regiospecific rearrangement of cation radicals derived from strained hydrocarbons and the application of the chemistry to the synthesis of a sesquiterpene, and finally, a discussion of the role redox chemistry may play in the expression of the bioactivity of the pseudopterosin class of marine natural products.

**Keyword:** Electrohydrocyclization, redox, chemical synthesis, rearrangements, pseudopterosin.

**Resumen.** Este escrito es el resultado de una conferencia plenaria impartida por el autor en el 44o Congreso Mexicano de Química, realizado en Puebla, México, del 26 al 30 de Septiembre del 2009. Al preparar la presentación, se tomó en consideración el origen de las ideas que motivaron la investigación que se describió. Este intento fue dirigido a los miembros mas jóvenes de la audiencia, a los alumnos de licenciatura y posgrado, y a aquellos en búsqueda de trabajo. En una etapa similar de mi carrera científica, me dí cuenta de la necesidad de formular planes de investigación requeridos para completar las solicitudes de trabajo. ¿De dónde vinieron esas ideas? ¿Cuales son los factores que estimulan la curiosidad? ¿Cual es la motivación para seguir una línea particular de investigación? Los temas que se discuten en el contexto de intentar abordar estas preguntas incluyen la electrohidrociclización y la ciclización electroreductiva, y sus aplicaciones en la síntesis total de productos naturales, el uso del níquel salen y trietilaminas como mediadores y catalizadores redox. las transposiciones regioespecificas de cationes radicales derivados de hidrocarburos tensionados y la aplicación de la química a la síntesis de un sesquiterpeno, y finalmente, se incluye una discusión del papel que la química redox puede jugar en la expresión de la bioactividad de los productos naturales marinos del tipo pseudopterosina.

**Palabras clave:** Electrohidrociclización, redox, síntesis química, transposiciones, pseudopterosinas.

## I. Introduction [1]

At every stage of a scientific career one is challenged by the need to formulate ideas that can serve as the basis for a research project(s). During the early stages of a career this can be a particularly daunting exercise. One has little to no experience, since most of ones' time has been devoted to studying the material presented in textbooks, or focusing upon a research project designed by a mentor.

What are some of the factors that lead one to pursue a particular avenue of research? Of course there are many responses to this query. Some that have guided my choices, and that might be of use for the young scientist include: (1) Attend class. Do so in order to lay the foundation that may later provide a seed that might blossom into a worthwhile project. (2) "Talk chemistry". Each day spend time chatting with your contemporaries about science. Learn about their research. Learn of the unsolved problems they face. Do the problems require a general solution that has not yet been formulated? Spend some time "brainstorming". (3) Read a lot. Each day read articles from the literature and then think about and summarize what you've read. What did you learn? Are there areas of research

that catch your fancy? If so, then be certain not to start a project that the author may have already initiated. When in doubt, contact the author. (4) Attend meetings. Listen to what others have to say. Are some of the ideas/approaches applicable to a research project that you are pursuing, or intend to work on? The opportunity to interact with others provides an excellent setting where one can discuss science, exchange thoughts and opinions, and bounce one's ideas past other persons who can look at them with a critical, but helpful, eye. Occasionally the discussion will trigger threads of thought that lead to the formulation of a research project. As the late Nobel laureate H. C. Brown once wrote: "Tall oaks from little acorns grow" [2]. Again, avoid duplicating what the speaker may already have ongoing in the laboratory. Finally, don't be afraid to tackle new areas that might be unfamiliar to you. Allow your natural curiosity to be drawn outside the box of familiarity that is oftentimes confining.

This manuscript summarizes some of the authors' experiences relating to each of the items referred to above. The present focus is upon organic electrochemistry, and in particular, upon processes that involve the use of a mediator to achieve electron transfer. Within this framework, the topics include

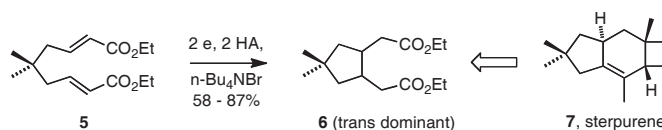
electrohydrocyclization and electroreductive cyclization, and their application to the total synthesis of natural products, the use of nickel salen and triarylaminines as mediators and redox catalysts, the regiospecific rearrangement of cation radicals derived from strained hydrocarbons and the application of the chemistry to the synthesis of a sesquiterpene, and finally, a discussion of the role redox chemistry may play in the expression of the bioactivity of the pseudopterosin class of marine natural products.

We begin with a meeting between the author and Manuel M. Baizer, one of the pioneers and chief architects of the area.

## II. Manuel Baizer and the undergraduate curriculum in organic chemistry at Wisconsin State University, Superior

Manuel M. Baizer is undoubtedly one of the most important figures in the field of organic electrochemistry [3]. Among other important discoveries, he and the members of the research group he headed at Monsanto pioneered the exploration, development, and use of the electrohydrodimerization reaction. As the name implies, the process is initiated electrochemically and leads to dimerization of electron deficient alkenes. The initial reduction leads to an umpolung, or charge reversal, wherein the polarity of the  $\beta$ -carbon changes from electrophilic to nucleophilic [4]. As exemplified in Scheme 1 by the commercially successful electrohydrodimerization of acrylonitrile, the transformation leads to  $\beta,\beta$ -coupling. The scope of the process was extended to include an intramolecular variant referred to as the electrohydrocyclization reaction, exemplified by the conversion of **3** to **4**.

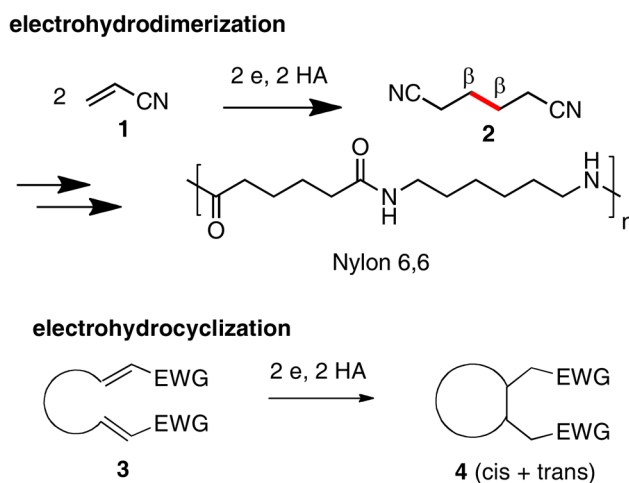
Following his retirement from Monsanto, Baizer assumed an adjunct professorship at UCSB, and became my colleague. His passion for electrochemistry was contagious, and was responsible for rekindling my interest in the field, one that lay dormant from the time I was in graduate school until I met Baizer when he first visited UCSB [5]. Among other projects involving electrochemistry [6], we became interested in exploiting the electrohydrocyclization reaction for the total synthesis of natural products. The tricyclic sesquiterpene called sterpurene (**7**) was selected as our first target structure. Luc Moëns, then a graduate student at UCSB, synthesized and examined the cyclization of the bisenoate, structure **5**. The reaction proceeded in modest to good yields, depending upon the choice of reaction conditions and electrode materials. With the cyclized product **6** in hand, Moëns skillfully transformed it into sterpurene (**7**), thereby completing the first total synthesis of this natural product [7].



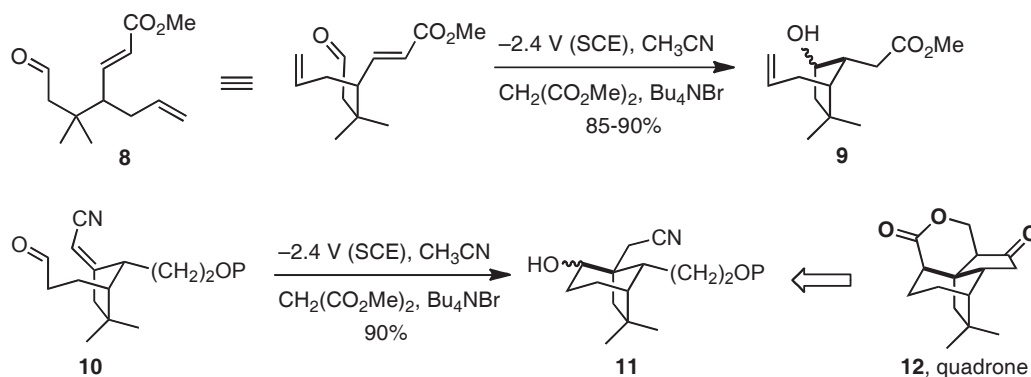
We then turned our attention to an unexplored variation on the theme, one that called for cyclization onto a carbonyl carbon rather than an electron deficient alkene. Its selection as the acceptor was stimulated by the notion that the carbonyl was the most important and useful of all functional groups, an opinion that was formed while I was enrolled in my first course of instruction in organic chemistry at Wisconsin State University in Superior, Wisconsin [8].



Manuel M. Baizer  
(1914-1988)



**Scheme 1.** Examples of electrohydrodimerization and electrohydrocyclization reactions pioneered by Baizer and coworkers.



**Scheme 2.** Two examples of the electroreductive cyclization reaction used en route to the synthesis of the anti-tumor antibiotic called quadrone (**12**).

We termed the electrochemically promoted cyclizations onto a carbonyl unit, electroreductive cyclization reactions [9]. Like the electrohydrocyclization, the overall process requires the consumption of two electrons and two protons. Two examples are shown in Scheme 2; each played an integral role in our development of a total synthesis of the anti-tumor, antibiotic called quadrone (**12**), research accomplished by former graduate students Gregory Sowell and Ron Wolin [10]. The first transformation, **8** to **9**, provided facile access to one of the two five membered rings found in the natural product. Simple functional group manipulation converted it to **10** ( $P = \text{SiPh}_2\text{Bu-t}$ ), the substrate used in the second cyclization. We were gratified to find that the electroreductive cyclization was able to generate the quaternary center found in structure **11** in high yield. This is particularly notable because attempts by other researchers to generate this center by using a variety of conjugate addition strategies frequently met with difficulty [11].

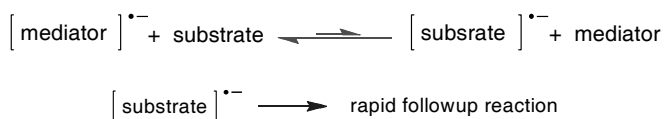
As often occurs, the electroreductive cyclization chemistry proved to be more interesting and more nuanced than was anticipated when we began working in the area [12]. Ultimately, a detailed mechanistic investigation was carried out in collaboration with Professor Albert J. Fry of Wesleyan University, and Joseph Leonetti, who was then a UCSB graduate student [13]. Surprisingly, we discovered that cyclization involved closure of a carbanion onto the carbonyl carbon rather than a radical anion as was initially assumed to be the case. The overall sequence consists of five steps that occur in the following order: (1) reduction of the activated double bond at the cathode, (2) protonation of the radical anion (the rate determining step), (3) addition of a second electron, either from the cathode or from one of the charge carrying species found in the reaction mixture, (4) cyclization of the resulting carbanion onto the carbonyl carbon, and (5) addition of the second proton.

### III. Mediated processes: The Costa Brava Coast of Spain, Münster Germany, and Mexico City

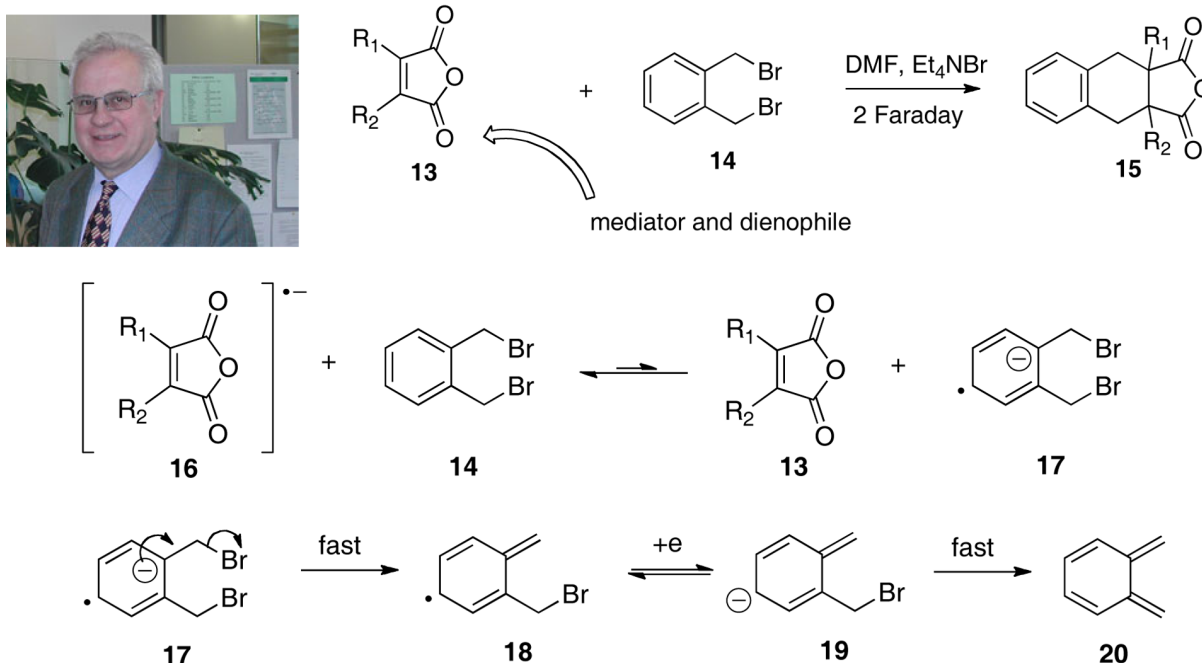
In April of 1995, Professor J. H. P. Utley delivered a seminar at a European Research Conference being held in a facil-

ity located along the Costa Brava Coast of Spain [14]. Of the many intriguing aspects of his presentation, the electrochemically-mediated generation of ortho-quinodimethanes (e.g. **20**) and the resulting Diels-Alder cycloaddition was especially intriguing; one example is illustrated in Scheme 3 [15]. Of particular interest was the fact the process could be initiated at a potential corresponding to the reduction of the anhydride, **13**, despite the fact that it was nearly 400 mV *easier* to reduce than the dibromide, **14**. Nevertheless, the resulting anhydride radical anion **16** was effective in mediating the reduction of the dibromide and its conversion to the quinodimethane **20** in the manner portrayed in Scheme 3.

For persons not used to thinking about electron transfer, the ability to initiate the chemistry of the dibromide, a substance whose reduction occurs at a potential that is 400 mV more negative than the potential that was utilized, might sound incongruous. However, once one realizes that the electron transfer process exemplified in Scheme 3 by the reaction of **14** with **16**, is nothing more than an equilibrium, then the problem no longer seems so challenging. Thus, in just the same way that the success of traditional condensation reactions often depend upon the existence of a follow-up reaction that drains a thermodynamically unfavorable acid-base equilibrium toward the product [16], so too does the success of the electron transfer event depend upon the existence of an equilibrium draining process. In the present instance, the rapid elimination of bromide from intermediates **17** and **19** constitute suitable processes. Thus, we see that regardless of the setting, be it electron transfer or acid-base chemistry, the issue is one of identifying one or more processes that can tip the equilibrium in the direction that is desired.



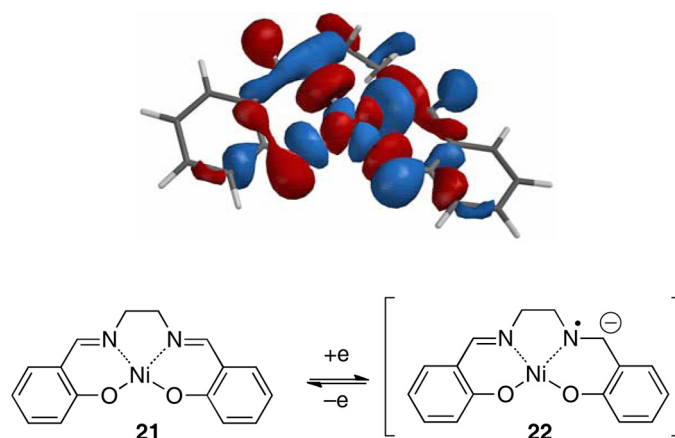
Intrigued by Utley's findings, we wondered whether it might be possible to perform electrohydrocyclization and electroreductive cyclization reactions using a mediator. Inspired by



**Scheme 3.** Photo of J. H. P. Utley, and an example of an electrochemically mediated formation and use of a quinodimethane in a Diels-Alder cycloaddition.

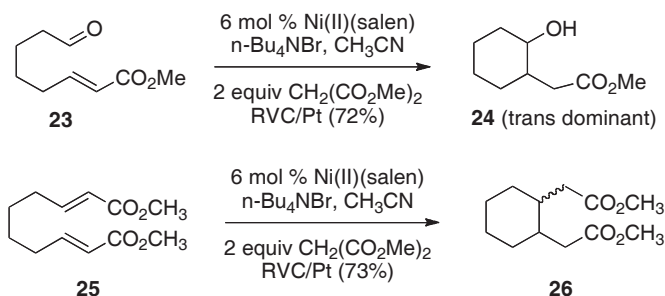
Professor Elisabet Dunach successful use of nickel complexes [17], James Miranda, then a graduate student at UCSB, elected to study both nickel (II) salen and cobalt (II) salen as possible mediators [18]. The reactions described below were carried out at a potential corresponding to that of the mediator, in much the same way that a sensitized photolysis is conducted by choosing a wavelength corresponding to that needed to produce the excited state of the sensitizer,  $S^*$ . In the photochemical process,  $S^*$  transfers both energy and spin information to the substrate, while in the electrochemical process, the reduced (or oxidized) form of the mediator transfers charge. For the chemistry to be described below, we focus upon radical anion character that resides on the ligand portion of the reduced nickel salen [19], a viewpoint that is consistent with the SOMO map shown in Figure 1, the map being generated from a B3LYP/6-31G(d) calculation [20].

As illustrated in Scheme 4, both electroreductive and electrohydrocyclization reactions proved amenable to mediation using 6 mol % of nickel (II) salen, with a reticulated vitreous carbon (RVC) cathode, a platinum anode, and dimethyl malonate as the proton donor; acetonitrile proved to be a suitable solvent and  $n\text{-Bu}_4\text{NBr}$  a suitable supporting electrolyte. Like the Utley case described above, the mediator was easier to reduce than the substrate *viz.*,  $E_p(\text{nickel (II) salen}) -2.1\text{ V}$ , and  $-2.7\text{ V}$  (vs  $\text{Ag}/\text{AgNO}_3$ ) for **23**, the electroreductive cyclization substrate. While nickel (II) salen proved to be an effective mediator, cobalt salen did not. In this case, the thermodynamic impasse imposed by the  $>1$  volt difference between the peak potential for the reduction of cobalt salen (ca  $-1.6\text{ V}$ ) and the electroreductive cyclization substrate, **23**, is simply too large to overcome.



**Fig. 1.** Visualization of the radical anion character of reduced form of nickel salen: reaction and SOMO map resulting from a B3LYP/6-31G(d) calculation; notice the substantial electron density on the ligand.

Upon further inspection of the reaction mixture obtained following the mediated electrolysis of **23**, we discovered the presence of a substantial quantity of aldehyde **31** (25%; note Scheme 5), a substance that does not form when the starting material is reduced directly. Its formation, therefore, must be linked to the presence of the mediator. How? A clue was uncovered when we elected to examine the dimethyl salen analog, **32**, as a possible mediator (note Scheme 5). In this case, the reduced form, *viz.* **22a**, did not serve as an effective electron transfer agent. Rather than producing the electrore-



**Scheme 4.** Nickel salen mediated electroreductive cyclization and electrohydrocyclization reactions.

ductive cyclization product **24**, only the side product formed. The current flow dropped to zero after only 15 min and the mediator was consumed.

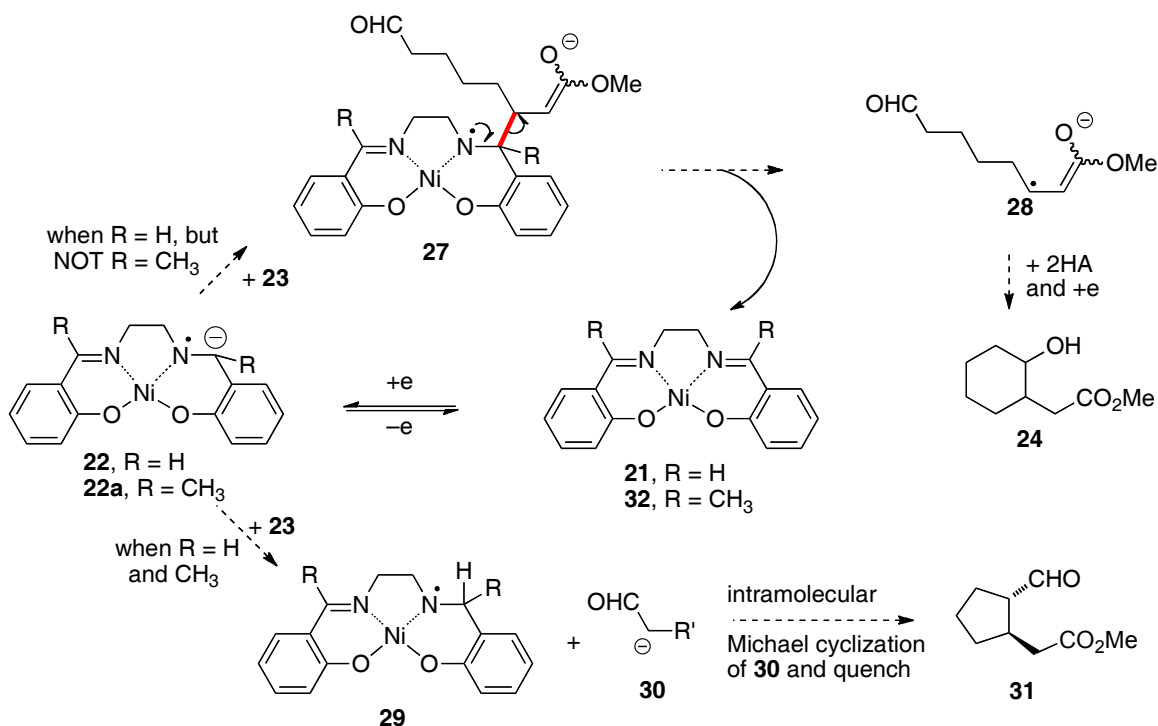
To account for the chemistry shown in Scheme 4 as well as that described in the previous paragraph, we suggest the mechanism illustrated in Scheme 5. The ligand centered form of the reduced nickel salen, viz. **22**, can either undergo conjugate addition to the  $\beta$ -carbon of the unsaturated ester **23** leading to the formation of **27**, or participate in an acid-base reaction leading to the formation of the partially saturated ligand, **29**, and enolate **30**. A subsequent intramolecular Michael addition, followed by a proton quench leads to the side product, **31**. The product of the conjugate addition step, **27**, can undergo a one electron cleavage reaction leading to the regeneration of nickel (II) salen (**21**) and radical anion **28**, a substance that is

known to participate in the mechanistic pathway leading to the electroreductive cyclization adduct **24** [13]. We postulate that the differing behaviour of the two salen complexes, **21** and **32**, is consistent with this scheme, noting that **22a**, the radical anion derived from the dimethyl derivative is simply too crowded to allow conjugate addition to occur, but is not so hindered that the acid-base pathway is shut down. Ultimately, the latter pathway leads to consumption of the mediator and accounts for the current dropping to zero. These ideas are illustrated in structural formulation **33** that is portrayed at the bottom of Scheme 5.

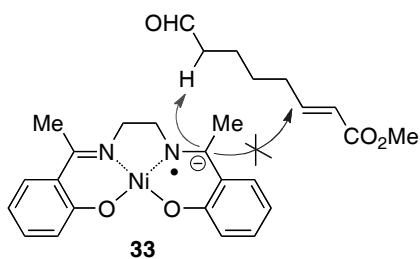
#### IV. Münster, Germany: Hans Schäfer and Waldemar Adam

In November of 2000, I was privileged to attend and speak at a symposium entitled “Electron Transfer in Inorganic and Organic Chemistry” that was held at the Westfälische Wilhelms-Universität in Münster, Germany [21]. Organized by Professor Hans Schäfer and his colleagues, the symposium featured many outstanding talks. My attention was drawn to one delivered by the exceptionally prolific scientist, Professor Waldemar Adam, who spoke of the rearrangement chemistry of cation radicals derived from strained hydrocarbons, and in particular, those possessing the bicyclo[2.1.0] framework [22].

I was intrigued by the possibilities that seemed to be inherent to the transformation of the hypothetical strained

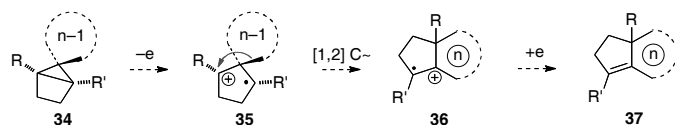


**Scheme 5.** Mechanistic hypothesis used to account for the outcome of the mediated electroreductive cyclization.

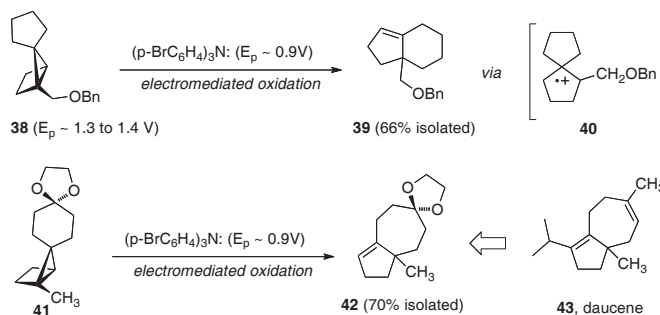


hydrocarbon **34** whose structure is shown in Scheme 6. The sequence begins with the loss of an electron from **34** to afford a cation radical **35** that subsequently undergoes a [1,2] carbon migration leading to **36**; this is followed by the return of an electron to **36** to afford the rearranged product, **37**. The transformation appeared as though it might provide (a) an interesting and unusual entry point to natural product structures possessing the bicyclo[n.3.0] framework, and (b) an opportunity to study cation radical chemistry. Use of the process in a total synthesis would require the identification of the structural features that would ensure that the migration, exemplified by the conversion of **35** to **36**, occur with a high level of regiochemical control.

Once again we elected to use a redox mediator, in this instance tris(4-bromophenyl)amine [23]. Its oxidation at  $\sim 0.9$  V (vs Ag/AgNO<sub>3</sub>) afforded the aminium cation radical which then served as a homogeneous oxidant toward the strained hydrocarbon substrates **38** and **41**. The transformations illustrated in Scheme 7, carried out by my former graduate student Young Sam Park, are illustrative [24-26]. They are notable for two reasons viz., (1) both of the rearrangements



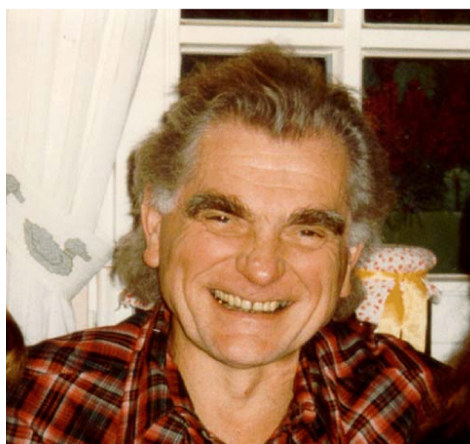
**Scheme 6.** Reaction pathway and potential utility for the construction of the bicyclo[n.3.0] framework.



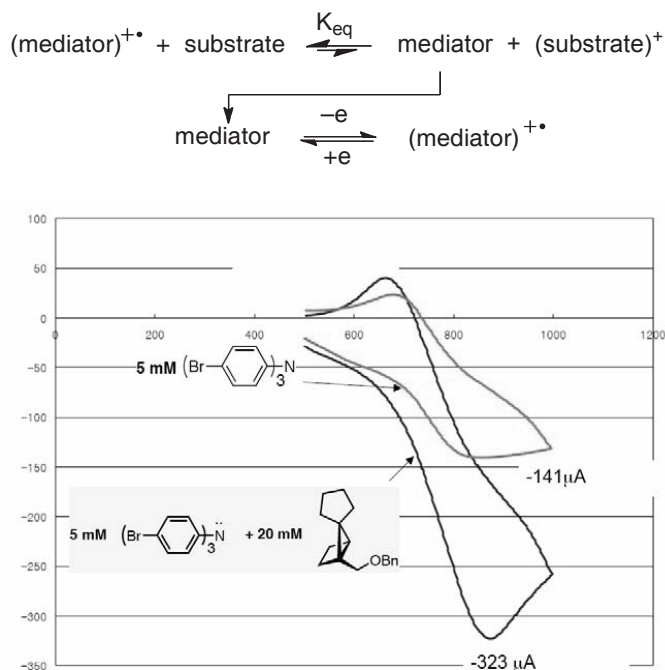
**Scheme 7.** Two examples of electrochemically mediated rearrangements of strained hydrocarbons: application to the synthesis of daucene (**43**).

occur with complete regiochemical control, the migration occurring to the carbon that is best able to stabilize a positive charge, and (2) the conversion of **41** to **42** represents the first instance of migration leading to the formation of a seven membered ring and served as the key step of our total synthesis of the sesquiterpene called daucene (**43**), thereby demonstrating the feasibility of using the approach as an entry to natural products.

The use of cyclic voltammetry provided an opportunity to obtain explicit evidence that electron transfer between the mediator and the substrate actually occurs. The redox behavior of tris(4-bromophenyl)amine is illustrated by the magenta colored curve shown in Figure 3. Thus, in the absence of substrate, one observes current flow indicating the oxidation of the mediator to its cation radical form, and reduction of the latter to regenerate the mediator, i.e., a standard redox couple. This result differs substantially from that which is observed when the substrate, in this case the benzyloxy-methyl substituted derivative **38**, is added and the voltammogram of the resulting mixture is recorded. Now there is more current corresponding to the oxidation of the mediator than is observed in the absence of the substrate (note the blue curve). The additional current is referred to as a “catalytic current”; its appearance is due to the return of the



**Fig. 2.** Photos of Professors Waldemar Adam (left) and Hans Schäfer (right)



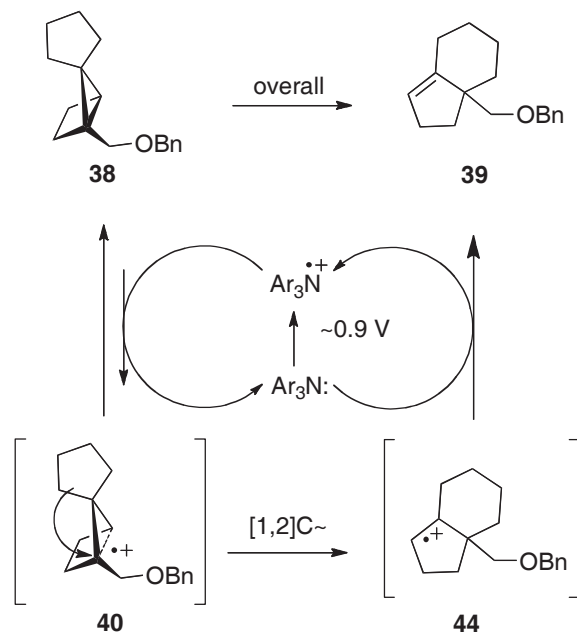
**Fig. 3.** Voltammetry illustrating the so-called “catalytic current”.

mediator to the original redox couple after it has removed an electron from the substrate, in the manner illustrated at the top of Figure 3.

Mechanistically, we suggest that the chemistry proceeds in the manner shown in Scheme 8. It begins with oxidation of the mediator to afford the aminium cation radical that then serves as the oxidizing agent that converts the strained hydrocarbon **38** to **40**. Once **40** forms, a Wagner-Meerwein shift converts it to the rearranged framework **44**. Invariably, the migration occurs toward the carbon bearing the alkyl group rather than hydrogen, that is, toward the center that can best stabilize a positive charge. The sequence is completed by reduction of the rearranged intermediate, **44**, in what surely must be the most exergonic step of the entire series of reactions, as well as the most effective step to drain the unfavorable redox equilibrium between the mediator and substrate toward the product.

## V. Visits to Mexico in 2008 and 2009: the Institute of Chemistry Library at UNAM

My UCSB colleague Professor Robert Jacobs, whose photo is shown here, contacted me a number of years ago asking whether I would like to become involved with a project involving a class of marine natural products called the pseudo-pteropsins (note Figure 4) [27]. My group’s efforts were to focus upon their chemistry, and his group upon the pharmacology. Jacobs, a co-discoverer of the substances, had been studying their pharmacological properties for some time [28].



**Scheme 8.** Mechanistic hypothesis: selective rearrangement toward the carbon that can best stabilize a positive charge.



Their bioactivity profile is characterized by their anti-inflammatory and wound healing properties. In particular, they are known to: (a) inhibit inflammation by blocking the infiltration of leukotrienes and prostaglandins, (b) modulate neutrophil infiltration into the site of injury, (c) inhibit neutrophil degranulation, (d) accelerate wound closure in guinea pigs, and

(e) bind to adenosine receptors. In addition, pseudo-pteropsin A methyl ether (PsA OMe, **46**) has gone through a phase IIA clinical trial. Structurally, the pseudo-pteropsins are tricyclic diterpene glycosides. One of the rings is an electron rich catechol to which is appended a sugar at either position 9 or 10; the most common sugars are of the xylose, fucose or arabinose variety.

In September of 2008, I visited and delivered a seminar at the Universidad Nacional Autónoma de México (UNAM). At one point during the day, my host, Dr. Bernardo Frontana-Urbe, headed off to teach a class. When asked what I wanted to do during that time, I responded that I would like to visit the UNAM Institute of Chemistry Library (note the photo) [29]. What a wonderful library it is! I was impressed by the fine collection of journals as well as the array of recently published books that were at my fingertips. Literally, like a child in a candy store [30], I looked at the covers, read the titles, and thumbed through many of the books. I was especially attracted to one entitled “Molecules and Medicine”, written by E. J.



Library of Instituto de Química, UNAM.

Corey, Barbara Czakó, and László Kürti [31]. Since we had shown that the pseudopterosins bind to GPCRs of the adenosine variety [32], I was particularly attracted to the passages appearing on pages 77-79. They highlighted the role of G-protein coupled receptors (GPCRs) in chemical signaling. One statement in particular caught my attention. It read: "When the receptor is occupied by its ligand, its three-dimensional shape (conformation) changes in a way that switches on an associated intracellular enzyme." I began to wonder whether the pseudopterosins might bind in an analogous manner and

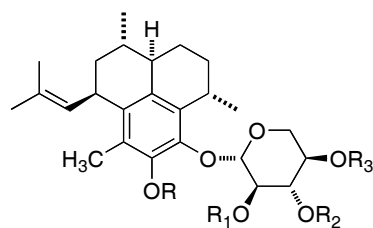
undergo a conformation change that would trigger the receptor to change its conformation and lead the expression of bioactivity. This begs the question: what type of conformational change might trigger the receptor to respond? Could it be something as simple as conformational equilibration amongst the many possible rotamers of the natural product? Or is there some chemistry involved, perhaps something where the pseudopterosin is converted to an intermediate whose conformation has been changed and is then returned to its original form via a fully reversible sequence of steps?

The most likely sites for chemistry to take place on the pseudopterosin framework include the pi-unit of the isobutenyl side chain, the benzylic carbons, the sugar, and the catechol subunit. Since redox processes are common in biological settings, we turned our attention toward the possible oxidation of the electron rich aromatic ring and the chemistry that might follow that event.

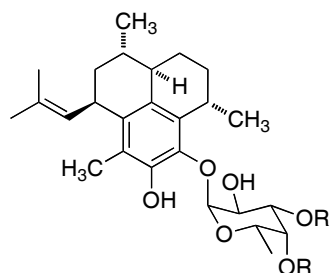
We began by investigating the voltammetric behavior of the iso-PsE derived acetone 51 whose structure is illustrated in Figure 4 [33,34].

Scanning toward progressively more positive potentials reveals current flow indicative of an oxidation leading to a cation radical. As illustrated in Figure 5, no current is observed when the direction of the scan is reversed, this in an effort to observe the reduction of the cation radical back to the starting material. We conclude, therefore, that under the conditions used to record the measurement, there is a follow-up reaction that removes the initially formed cation radical at a rate that is greater than the timescale of the reverse scan.

What is the nature of the follow-up reaction? Does it involve a conformational change? A preparative scale oxida-



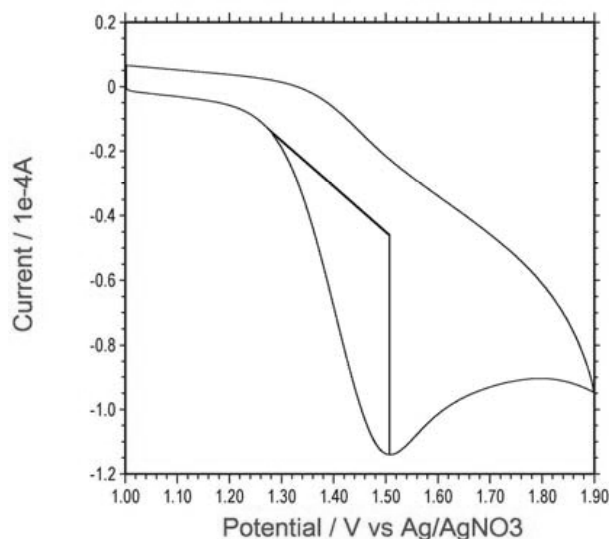
- 45, pseudopterosin A (PsA),  $R = R_1 = R_2 = R_3 = H$   
 46, PsA O-methyl ether,  $R = CH_3$ ,  $R_1 = R_2 = R_3 = H$   
 47, PsB,  $R_1 = Ac$ ,  $R = R_2 = R_3 = H$   
 48, PsC,  $R_2 = Ac$ ,  $R = R_1 = R_3 = H$   
 49, PsD,  $R_3 = Ac$ ,  $R = R_1 = R_2 = H$



- 50, iso-PsE,  $R = H$   
 51, iso-PsE derived acetone,  
 $R = C(Me)_2$

Figure 4. Structures for a variety of pseudopterosin natural products



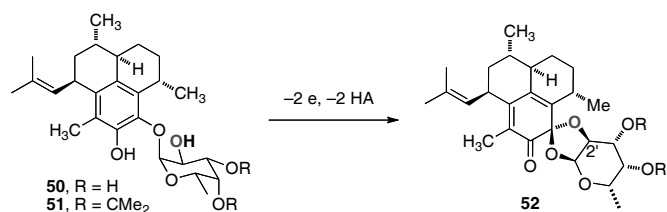


**Fig. 5.** Cyclic voltammetry showing the irreversible oxidation of the iso-PsE derived acetonide **51**.

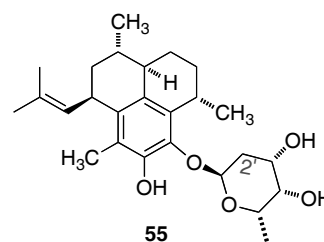
tion of **51** was carried out using hypervalent iodine as the oxidant.<sup>34</sup> Isolation and characterization of the product revealed the formation of keto ketal **52**, a product resulting from the attack of the C-2' hydroxyl group of the sugar onto an oxidized form of the catechol ring system.

We put forth the mechanistic hypothesis shown in Scheme 9 to suggest what might occur in a biochemically relevant setting. The sequence begins with a one-electron oxidation and is followed by an acid-base reaction, perhaps involving a histidine residue found in the receptor acting as a general base. Removal of a second electron affords the captodatively-stabilized cation **53**. Cyclization of the pendant C-2' hydroxyl group onto the site of charge affords **54**, in a process that is clearly accompanied a conformational change. Since each step ought to be fully reversible, this hypothesis provides both a pathway for conformational change as well as the option of returning the pseudopterosin to its starting point, or resting state.

To address the notion that the conformational change might be relevant to the expression of bioactivity, Dr. Wei Zhong, a postdoctoral scholar in my group at UCSB, syn-

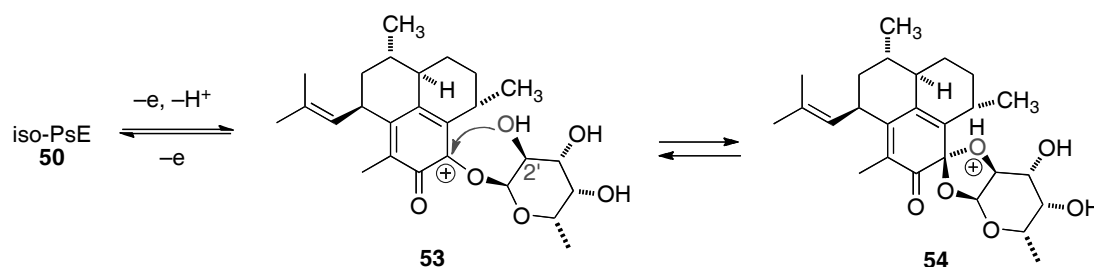


thesized the C-2'-deoxy derivative **55**. Mr. Daniel Day, a graduate student in Jacobs' group, then assessed its ability to promote the growth of HUVEC cells, one of the characteristics associated with the pseudopterosins [35]. If correct, then our hypothesis predicts that cell growth should either disappear or be greatly diminished. It disappeared. While this result accords with our working hypothesis, we have yet to demonstrate that removal of the C-2' hydroxyl group causes the observed effect. The relationship between cause and effect has yet to be established. The ongoing additional experimentation is clearly required.



## VI. Concluding remarks

I hope this excursion through a few of our past and ongoing research projects will serve to provide guidance, however brief and simple, to those persons beginning their scientific career. Always be curious. Always ask questions. Chances are good that their pursuit will lead to interesting and oftentimes unanticipated outcomes. Have fun, and enjoy the scientific endeavor!



**Scheme 9.** A possible biochemically-relevant conformational change

## References

- 1 The science described in this manuscript is the outgrowth of a plenary lecture delivered by the author at the 44th Congreso Mexicano de Química organized by the Sociedad Química de México that was held in Puebla, Mexico from 26-30 September of 2009.
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