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Palytoxin: an inexhaustible source of inspiration—personal perspective

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In memory of Professors Robert Burns Woodward (1917–1979), Toshio Goto (1929–1990), and Yoshimasa Hirata (1915–2000)

Abstract—A personal perspective is given on the research programs which have originated from, or are related to, the marine natural product palytoxin. The subjects discussed include: acyclic stereocontrol, Ni(II)/Cr(II)-mediated coupling reaction, stereochemical assignment via organic synthesis, universal NMR database, chiral NMR solvents, conformational analysis of *C*- and *O*-glycosides, diamond-lattice analysis, Type II O blood group determinant *C*- and *O*-trisaccharides, *s*MMP/*s*MGP, and CH_2-bridged Watson-Crick base-pair models.

In the summer of 1974, with mixed feelings, I left Nagoya to join the faculty of Harvard University. I was sad in leaving my home country but, at the same time, I could not refuse the opportunities that would be presented in this new environment. On arrival in Cambridge, we initiated a new research program—acyclic stereocontrol. Our motivation originated from the question around the strategy and tactics for a synthesis of the polyether class of antibiotics such as monensin and lasalocid A. In a broad sense, we were interested in advancing a general (empirical) rule to predict the stereochemical course for a given acyclic system. We were aware that difficulties might be encountered in this approach. Nevertheless, we could not deny the temptation of testing its feasibility and practicability for its enormous potential.

After a considerable induction period, this program gained momentum, resulting in the total synthesis of lasalocid A in 1978 and monensin in 1979.[1,2] Through these studies, we advanced several empirical rules to predict the major product for a given reaction. Related to the synthesis of the left half of monensin, we observed that hydroboration of the *trans*-olefin **1** gave an 8:1 mixture of **2** and its diastereomers. At that time, this level of stereoselectivity was amazingly high, and we realized that the origin of this remarkable stereoselectivity might be related to the conformational preference of the sp^3–sp^2 system. The pioneering work by Wilson, Herschbach and others showed the preferred conformation of this type of system to be eclipsed.[3] Three possible eclipsed conformations are those with the S (small), M (medium), or L (large) group being eclipsed with the olefinic bond. Among these, the one shown in Fig. 1 is considered to be the most preferred, because of the least steric compression—note that the smallest group is eclipsed with R_2. Assuming that this conformational property is reflected at the transition state, the reagent is

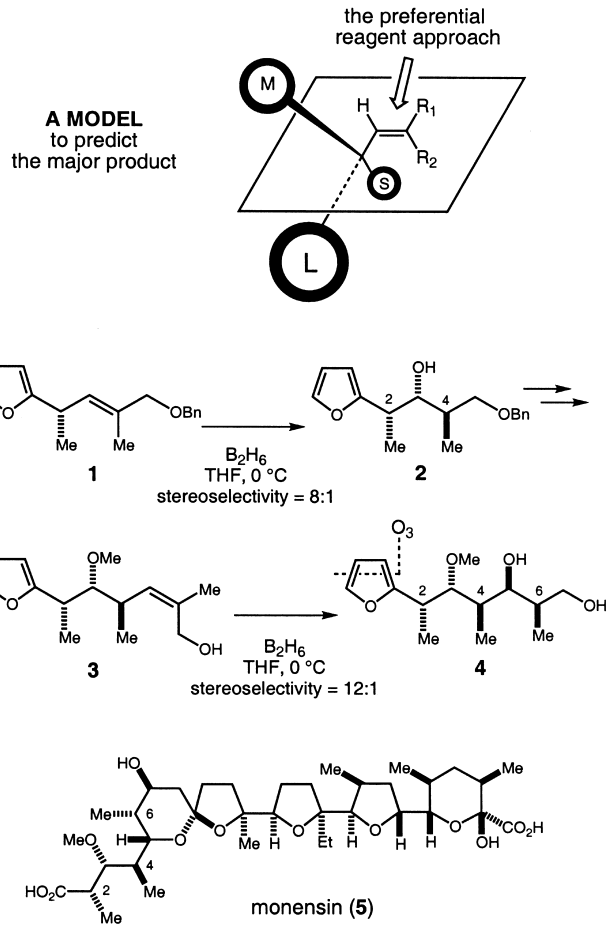

Figure 1.

Keywords: palytoxin; acyclic compounds; stereochemistry; stereocontrol.

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expected to approach the olefin preferentially from the sterically less-crowded side, namely the same side as the M group. This model may not accurately represent the transition state for this process, but it allowed us to predict the major product for different substrates. Indeed, this model suggested the remaining two stereogenic centers present in the left half of monensin could be introduced by hydroboration of the *cis*-olefin **3**.

The MCPBA epoxidation of trisubstitued *trans*-olefin **6** (R=Me) yielded a >20:1 mixture of the epoxide **7** (R=Me) and its stereoisomer. Assuming that the oxidant is pre-complexed with the 1°-OH and 2°-OBn groups cooperatively, we predicted, and proved, the major stereoisomer to be **7** (R=Me); thus, the epoxide was formed through the conformer **A**. Curiously, the stereoselectivity observed for the MCPBA epoxidation of the corresponding disubstituted *trans*-olefin **6** (R=H) was only 3:2, even though the major product was the one predicted by this model. At first glance, this result was disappointing, but we soon realized that it was pointing out an additional value of this model. Among the three eclipsed conformations, the conformational preference of **A** over **B** and **C** should be more significant for the trisubstitued *trans*-olefin than the disubstituted *trans*-olefin—compare the steric compression due to R=Me/Me (conformer **B**) or R=Me/CH_2OBn (conformer **C**) for the former with the steric compression due to R=H/Me (conformer **B**) or R=H/CH_2OBn (conformer **C**) for the latter. This analysis immediately suggested that the poor stereoselectivity observed for the disubstituted *trans*-olefin could be improved by placing a temporary (removable after the epoxidation), sterically demanding group such as TMS on the olefinic group as in **6** with R=TMS. It should be noted that, consistent with this model, both tri- and disubstituted *cis*-olefins **9** gave a >20:1 stereoselectivity (Fig. 2).[4,5]

In a similar analysis of examples scattered in the literature, we recognized that the stereochemical outcome for osmylation of allylic alcohols and their derivatives could be formulated by a simple empirical rule. Regarding this empirical rule, it should be noted that: (1) ether-type protecting groups of allylic alcohols do not significantly

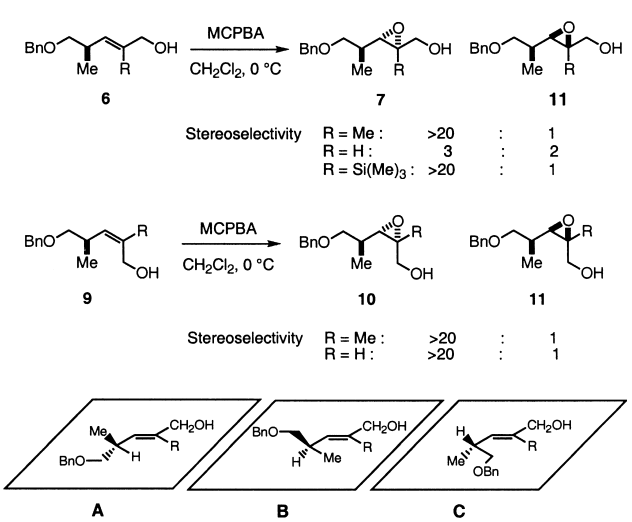


Figure 2.

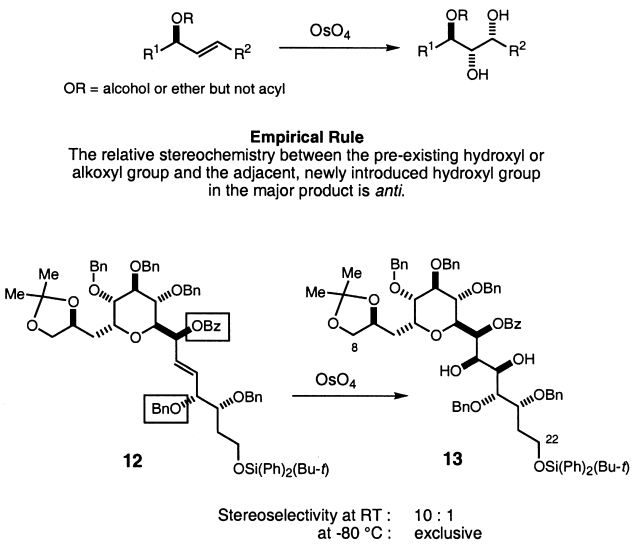


Figure 3.

affect the degree of stereoselectivity, whereas acyl-type protecting groups reduce the stereoselectivity significantly; (2) the degree of stereoselectivity for *cis*-olefins is higher than that for the corresponding *trans*-olefins; (3) for the cases where a hydroxyl or alkoxyl group is present at both ends of the olefinic bond, their effects are additive. With this rule, we could identify the allylic benzylether benzoate **12** to be the key synthetic intermediate for the synthesis of the C8–C22 segment of the marine natural product palytoxin. Osmylation of **12** gave the desired product in excellent yield (Fig. 3).[6,7]

Another intriguing case has recently been discovered in this general area. In connection with the development of a practical synthesis of the right half of the marine natural product halichondrin (vide infra), vinyliodide **15** was envisioned as the C20–C26 building block. We anticipated the desired product **15** is preferentially formed from **14** via an S_N2' process, based on two assumptions: (1) among the three possible conformers, the two eclipsed conformers shown in Fig. 4 are preferred and (2) the 2°-OH group delivers $LiCu(Me)_2$.[8]

Before leaving this subject, it would be worthwhile to make a general comment on the combined application of these rules with fast-developing asymmetric processes. As these rules are concerned with the reactivity inherent in the substrate structures, one can imagine that the

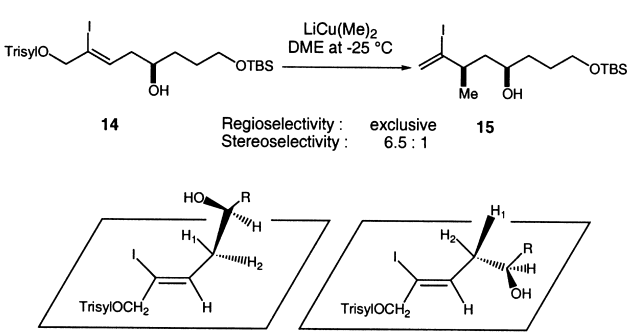


Figure 4.

stereoselectivity should improve in the presence of a chiral reagent for a matching case but decline for a mismatching case.[9] Indeed, this general statement is supported by numerous examples from this and other laboratories.

From 1979 through 1980, I was deeply disheartened. On 8 July 1979, Professor Bob Woodward, my postdoctoral mentor and then colleague, was struck down by a heart attack and passed away. Simply, I was not prepared to face the reality of his death. After having given a memorial speech for Bob Woodward at the Twelfth International Symposium on the Chemistry of Natural Products in Tenerife, Spain, I visited Professor Yoshimasa Hirata, my PhD mentor at Nagoya, Japan, on my way back to Cambridge. Obviously, Professor Hirata understood my emotional pains and saw that I was at a critical stage in my career. However, he did not rely on standard words of sympathy but rather showed me the proposed gross-structure of the marine natural product palytoxin.[10–12] At *that* moment, my mind was back to the chemistry with full curiosity and excitement.

By then, I had developed deep interest in molecules with many stereogenic centers. With an increase in stereogenic centers, the total number of stereoisomers possible for a given molecule increases exponentially. For instance, in principle 1024 stereoisomers are possible for a molecule with 10 stereogenic centers, whereas 1,048,576 stereoisomers are possible for a molecule with 20 stereogenic centers. Our curiosities and interests were, and still are, primarily two-fold: how to establish the stereochemistry, static and dynamic, of a molecule with many stereogenic centers and how to synthesize such a molecule. The marine natural product palytoxin is, I felt, a marvelous vehicle to address these issues. In addition to 4 *trans*- and 3 *cis*-olefinic bonds, there are 63 stereogenic centers present in palytoxin. Twenty-nine of them are in the acyclic portions, and the configurations of 27 of them were unknown. Our first concern was how to establish their relative and absolute configurations. One would suggest an X-ray analysis to be an obvious method to solve this problem. However, it should be noted that, in spite of extensive efforts by Professor Hirata and others, neither palytoxin nor its direct derivative has ever, even now, been crystallized.

We then considered the possibility of using NMR spectroscopy for this purpose. Needless to mention, NMR spectroscopy is one of the most powerful and reliable methods to deduce the relative configuration of substituents on an usual ring-system. However, the situation is different for an acyclic system. Using the case of 1,2-disubstituted acyclic compounds as an example, we analyzed the potential issues associated with this approach. It is widely recognized that the vicinal $^1H/^1H$ spin-coupling constant for *threo*-isomers is smaller than that of the corresponding *erythro*-isomers. This phenomenon is explained in terms of the conformation preferentially adopted by the carbon backbone of an acyclic compound. With the extended conformation of the carbon backbone, the two protons are in the *anti*-orientation for the *erythro*-isomer, whereas the two protons are in the *gauche*-orientation for the *threo*-isomer. However, in order to apply this generally recognized trend for stereochemical assignment, one has to be sure that there is no exception to this observation. In this context, the NMR study on 2,3-diacetoxybutanes by Bothner-By in 1962 is instructive.[13]

Having given some thought to X-ray- and NMR-based approaches, we opted to rely on organic synthesis. Use of organic synthesis to solve structural problems was one of our research themes. As a matter of fact, my first independent research was concerned with establishing the geometric stereochemistry of the enol formate present in *Latia* luciferin by organic synthesis.[14] Our research plan for the palytoxin project is summarized as follows:

1. Synthesize all the possible stereoisomers for a degradation product of palytoxin from a chiral starting material with known absolute configuration.
2. Confirm that all the stereoisomers can be distinguished by spectroscopic and/or chromatographic methods.
3. Find which stereoisomer matches the degradation product.
4. Repeat the same procedure for other degradation products.
5. Establish the complete structure of palytoxin, by combining all this information.

Given this unmanageably large problem, we naturally considered the possibility of dissecting it into a collection of smaller problems, solving each of these smaller problems, and then assembling them to solve the original problem. We paid attention to the eight major degradation products but soon realized that there were still too many stereoisomers possible for four out of the eight. Therefore, we needed to dissect them further into a collection of even smaller problems which could be tackled in a realistic time span.

On the basis of extensive efforts for two years, we were able to elucidate the complete structure of palytoxin (Fig. 5).[15,16] The stereochemical assignment via organic synthesis provided the foundation for our chemical investigations on palytoxin. Under the given circumstances, we could not imagine that any other method might give us an equally unambiguous conclusion. However, we also recognized that this work was possible only with enormous efforts by many co-workers. We then began wondering how one might be able to decrease the amount of manpower efforts but still gain an equally unambiguous conclusion. Eventually, this curiosity led us to the universal NMR database concept (vide infra).

With the complete structure of palytoxin, we began its total synthesis. By the summer of 1985, we developed the syntheses of the eight key building blocks. Each synthesis was improved and polished up to a level satisfactory in terms of overall efficiency and practicability. For example, before the final route was developed, the C8–C22 segment had been synthesized by four different routes. Each of the syntheses had provided numerous opportunities to discover exciting and intriguing new chemistry, which was, in our view, worth pursuing in its own right. However, we also appreciated the fact that the progress beyond this stage critically depended on the availability of these building

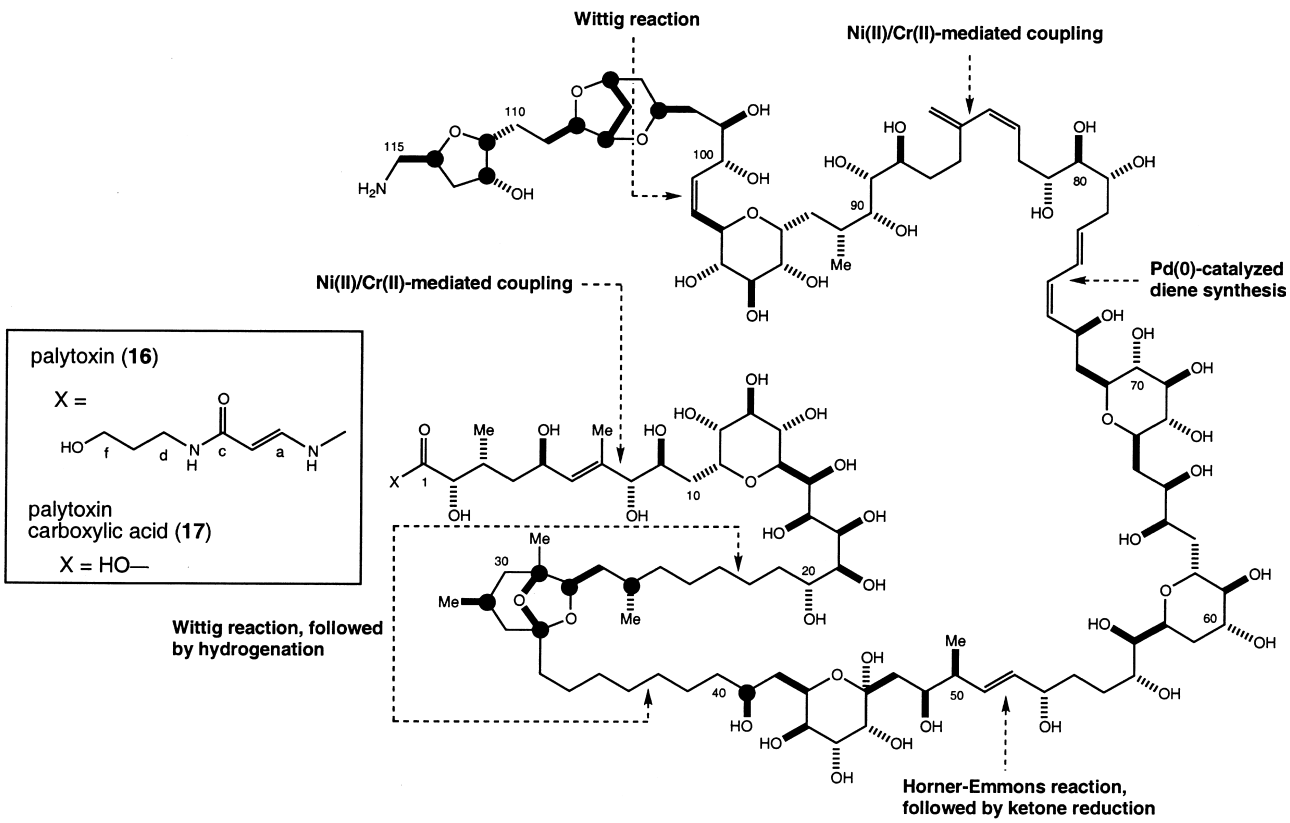


Figure 5. The relative and absolute configuration of the stereogenic center marked by • was known. The eight major degradation products are the segments containing C1–C6, C7–C19, C18–C51, C47–C56, C52–C74, C77–C83, C84–C98, and C99–C115 carbons, respectively. A broken arrow indicates the C–C bond-forming reaction and site for the final assembly.

blocks. In this context, we should note that each of these building blocks were available in multi-gram quantities.

With a practical synthetic route to all the key building blocks, we were able to address the question of how we could couple them together. Some of the couplings could be carried out in a relatively straightforward manner, whereas others turned out to be much more challenging. One of the more challenging couplings was the C7–C8 bond-formation. Using suitable model systems, we evaluated the feasibility and applicability of various bond-forming reactions and found the Ni(II)/Cr(II)-mediated coupling reaction to be the best, by far, for this purpose. A brief review on how this coupling reaction was developed through the palytoxin project is in order.

In connection with the synthesis of C8–C22 segment, we were faced with the task of transforming aldehyde **18** into allylic alcohol **20**, which seemed possible through routine synthesis operations. However, we soon found that standard

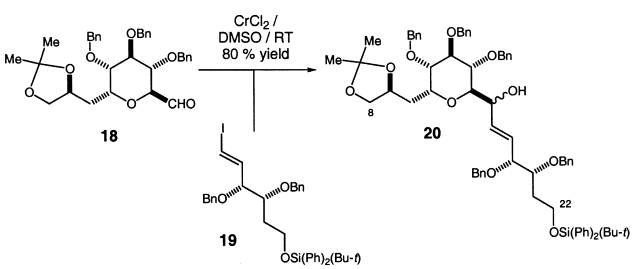


Figure 6.

approaches involving Wittig and aldol reactions were not as effective as we had hoped. The clue to the solution came from the timely work of Nozaki and co-workers on the Cr(II)-mediated addition of alkenyl halides to aldehydes.[17] After much trial-and-error experimentation, we were able to accomplish the required coupling by adding $CrCl_2$ to a DMSO solution of aldehyde **18** and *trans*-iodoolefin **19** at room temperature in the absence of oxygen (Fig. 6).

The Cr(II)-mediated coupling reaction provided an excellent solution to our problem except for one technical difficulty we had yet to overcome. Unlike the Cr(II)-mediated coupling of allyl halides with aldehydes, the success of this coupling mysteriously depended on the source and batch of $CrCl_2$. This fact reminded me of the first research I was ever engaged in, *The Catalytic Action of Metal Salts on the Borohydride Reduction of α-Bromoketone*, through which I experienced the excitement associated with original research activities.[18] We naturally speculated that the success of Cr(II)-mediated coupling might depend on some unknown contaminant in $CrCl_2$. Therefore, we tested the effect of transition metals on the Cr(II)-mediated coupling reaction, which led us to the discovery that a trace amount of $NiCl_2$ had a dramatic effect when added to the reaction medium.

The Ni(II)/Cr(II)-mediated coupling allows a carbon–carbon bond formation between alkenyl halides and aldehydes, which can usually be achieved by traditional organometallic reagents such as Grignard, lithium, or cuprate. However, there are several unique characteristics

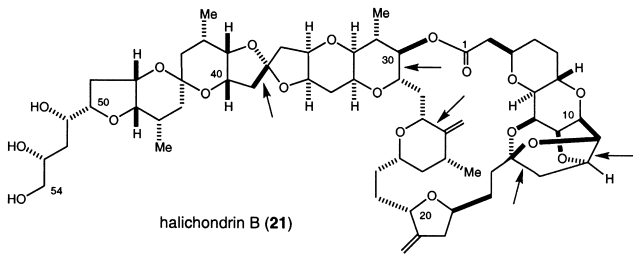


Figure 7. An arrow indicates the C–C bond formation by a Ni(II)/Cr(II)-mediated coupling.

of this reaction. In our view, this coupling reaction demonstrates its uniqueness most, when applied to polyfunctional substrates for which conventional organometallic reagents are difficult to apply. The coupling reaction of the C1–C7 segment with the C8–C51 segment best illustrates this point; the Ni(II)/Cr(II)-mediated coupling reaction using 2 equiv. of vinyliodide yielded a 5:1 mixture of the desired product and its C8 diastereomer in 75% yield.[19,20]

To study further its scope and limitations, we had purposely chosen to use the Ni(II)/Cr(II)-mediated coupling reaction as the key bond-forming step for the synthesis of various natural and non-natural products.[21] Among them, the synthesis of halichondrins, a class of polyether macrolides isolated from the marine sponge *Halichondria okadai*, deserves special comment.[22] Halichondrins exhibit extraordinary in vitro and in vivo antitumor activity. However, the very limited supply of halichondrins from natural sources has prevented further evaluation of their potential clinical application. Coupled with this fact, their intriguing and challenging structural features encouraged us to undertake a synthesis project for this class of natural products. In practice, we planned, and successfully executed the assembly of halichondrin B using the five Ni(II)/Cr(II)-mediated coupling reactions (Fig. 7).[23]

Perhaps, the most interesting discovery on the biological activity of halichondrin B was made by chance. Upon the completion of synthesis, we asked Dr Bruce Littlefield at Eisai Research Institute (ERI) to evaluate the in vitro and in vivo antitumor activities of the totally synthetic halichondrin B as well as several synthetic intermediates. The results were sensational: the antitumor activity of halichondrin B resides in the right portion of the molecule.[24] Based on this exciting discovery, ERI undertook the massive drug discovery efforts, through which two exceptional drug candidates have emerged.[25]

Obviously, the structural complexity of the right half of halichondrin B and ERI's drug candidates, exceeds by far any synthetic drug which is found on the market. However, we believe that contemporary synthetic organic chemistry has the capacity of developing an economically feasible synthesis of these molecules.

As mentioned, the Ni(II)/Cr(II)-mediated coupling reaction demonstrates its unique potential most when applied to a polyfunctional molecule. In other words, this reaction shows its power at a late-stage in a multiple-step synthesis where scalability and practicability are not necessarily the top priority. However, in order to use the Ni(II)/Cr(II)-mediated

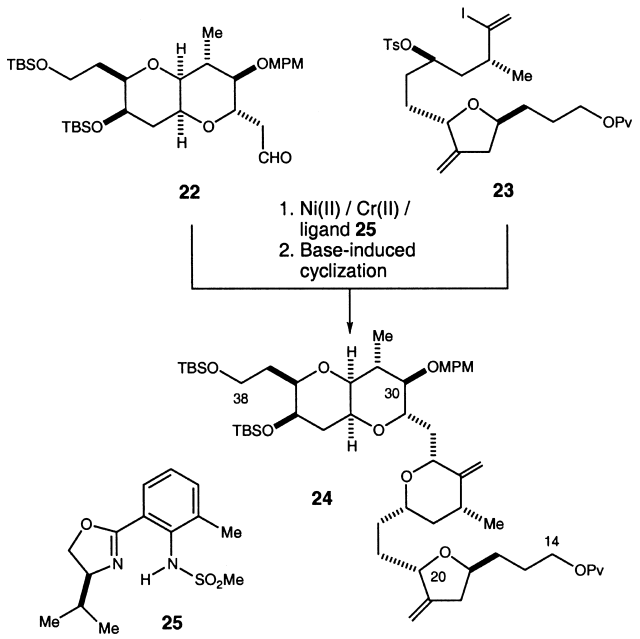


Figure 8.

coupling reaction for practical purposes, we must pay attention to two specific issues. First, since this coupling reaction is typically carried out in the presence of 3–4 equiv. of $CrCl_2$, it is highly desirable to develop a method to decrease the amount of Cr-salt. Second, it is also desirable to develop an asymmetric process to control the stereochemical outcome. In this context, we should add our recent progress. In the presence of the chiral ligand **25**, the C26–C27 bond-formation is now possible in a stereoselective manner under both stoichiometric and catalytic conditions. Although some improvements are still required to perfect the process, this will certainly provide an added value to the Ni(II)/Cr(II)-mediated coupling reaction (Fig. 8).[26]

Using the seven coupling reactions summarized in Fig. 5, the eight building blocks were assembled to afford the fully protected palytoxin carboxylic acid bearing eight different and 43 total protecting groups. All the protecting groups were successfully removed by five synthetic operations to furnish the totally synthetic palytoxin carboxylic acid (**17**) in 35% overall yield. Although the overall yield of deprotection was not high in a direct sense, the average yield per each deprotection exceeded 97.5%. In order to carry out the synthesis selectively and efficiently, we needed to protect the alcohols, amine, ketone, and carboxylic acid. Provided with the chemical reactions that allow us a selective and efficient transformation of one compound to the other without help of protecting groups, we could dramatically improve the overall efficiency of synthesis. From time to time, we have made, and continue to make, some attempts toward this goal. In this connection, we should note that the transformation of palytoxin carboxylic acid (**17**) to palytoxin (**16**) was realized without using protecting groups. The key for this success relied on the observation that, upon aqueous acetic acid treatment, the C1 carboxylic acid readily forms the δ-lactone which, then, smoothly reacts with an amine.[27–29]

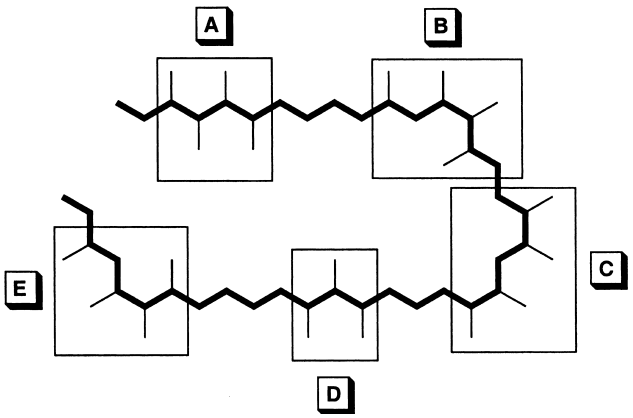
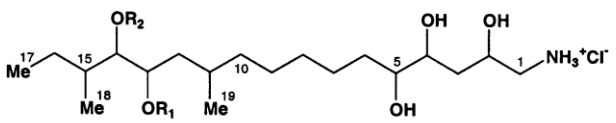


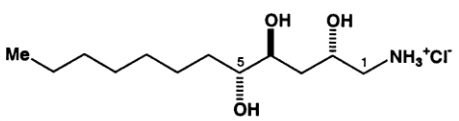
Figure 9.

The program of stereochemical assignment via organic synthesis has gradually evolved from the approach adopted for palytoxin, to the method tested in AAL toxins/fumonisins and also maitotoxin, and finally to the concept of the universal NMR database approach. Our primary research goal has been to advance and develop the concept and logic for reducing the amount of synthetic efforts. In this context, the universal NMR database approach has, we believe, progressed to the level where the relative and absolute configuration of an unknown compound can be determined without degradation and/or derivatization work.

Using a generalized molecule, we will outline the concept and logic used in the universal NMR database approach.



26a : AAL Toxin T_{A1} : R_1 = tricarballylic acid, R_2 = H
26b : AAL Toxin T_{A2} : R_1 = H, R_2 = tricarballylic acid
27 : AAL Toxin T_A backbone : $R_1 = R_2 = H$



28 : Right-Half Model of the backbone of AAL Toxin T_A
5α,4β,2α-diastereomer

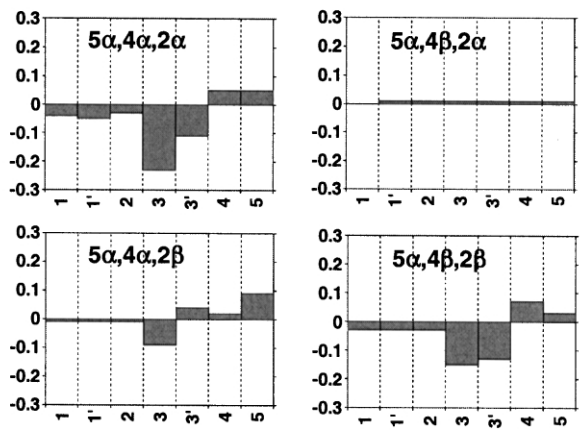


Figure 10. Comparison of ^1H chemical shifts ($\delta_{AAL\ toxin} - \delta_{SYN}$ in ppm).

Given an unmanageably complex structure such as the one in Fig. 9, one would seek a way of breaking it into a collection of smaller molecules, solving their structures and assembling them to solve the structure of the original molecule. On the other hand, as evident from the palytoxin case, this approach would require extensive synthetic and degradative work.

The generalized molecule is composed of structural clusters **A**–**E**, which are connected with a varying number of methylene bridges. We assumed: (1) the structural properties of these clusters are inherent to the specific stereochemical arrangement of the (small) substituents on the carbon backbone and (2) the structural properties of these clusters are independent from the rest of molecule, when they are sufficiently separated from each other. To test these hypotheses experimentally, we noticed that the AAL/fumonisin class of natural products provided an ideal testing ground. For an illustration of this, the right half of AAL toxin T_A is used. The model **28** was chosen, and the relevant ^1H chemical shifts of each diastereomer were compared with those of the right half of the natural product. Through this exercise, as well as the same exercise on the left half, it became evident that all the possible diastereomers exhibit differing and distinct spectroscopic behavior from each other and that the structural characteristics of only one diastereomer matches beautifully with those of the right half of the natural product (Fig. 10).[30]

Separated with a five-methylene bridge, the two clusters present in the backbone of AAL toxin T_A could be treated independently. The study on the marine natural product maitotoxin gave valuable information on the minimum chain-length required for this operation (Fig. 11). For assignment of the relative configuration of its C1–C15 portion, we independently treated the C1–C9 and C12–C15 clusters and demonstrated that the two-methylene bridge functions as an insulator that almost completely shuts down the chemical communication between them.[31,32]

The AAL toxin and maitotoxin studies provided us with the guidelines for selecting imaginary sites to dissect a given large molecule to a collection of smaller clusters (Fig. 12).

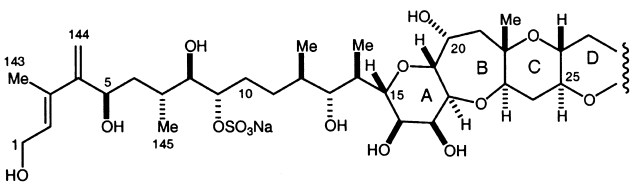
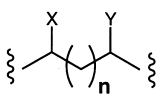


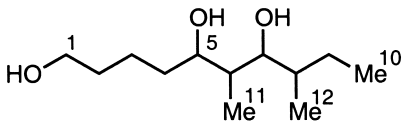
Figure 11. C1–C-27 Portion of maitoxin (**29**). For the complete structure of maitotoxin, see Refs. 31,32.



n = 0 or 1:
Primary steric and/or stereoelectronic interactions.

n ≥ 2:
No primary steric and/or stereoelectronic interactions.

Figure 12.



	C.5	C.6	C.7	C.8		C.5	C.6	C.7	C.8
30a	α	α	β	β	**30e**	β	α	β	β
30b	α	α	α	α	**30f**	β	α	α	α
30c	α	α	β	α	**30g**	β	α	β	α
30d	α	α	α	β	**30h**	β	α	α	β

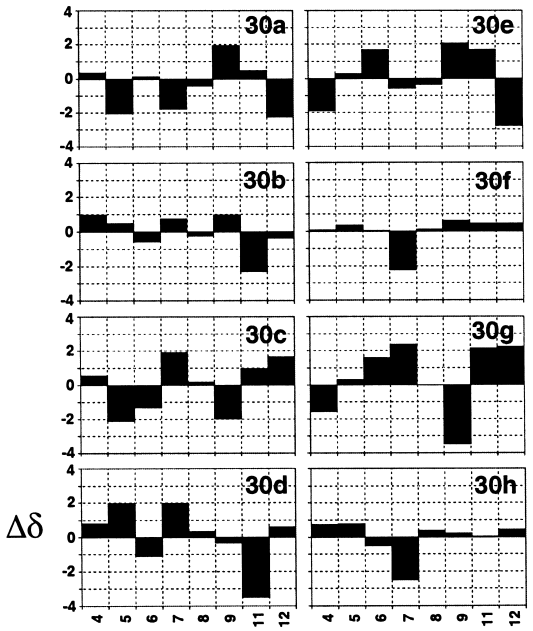


Figure 13. ^{13}C NMR profiles of **30a**–**h**. $\Delta\delta=\delta_{diastereomer}-\delta_{average}$ in CD_3OD.

For a case of $n\geq 2$, primary steric and/or stereoelectronic interactions between functional groups X and Y can, at least at the first approximation, be ignored and therefore the structural moieties containing X and Y can be treated as independent clusters. On the other hand, as primary steric and/or stereoelectronic interactions between X and Y are significant for a case of $n=0$ or 1, the structural moiety containing X and Y needs to be treated as one cluster.[33]

For the cases of AAL toxin and maitotoxin, the order of events was that we first identified a specific target molecule and then selected the models suitable for the specific target molecule. Naturally, we wondered how we might be able to apply the structural characteristics collected from these models to structural analysis of general cases, leading us to the development of a universal NMR database. The concept of this approach was first tested with the contiguous dipropionate case. This structural unit is widely found in a large number of the so-called polyketide natural products, and, once the concept and logic are verified, this class of natural products should offer us an excellent opportunity for testing the reliability and usefulness of this approach.[34]

Model **30** was chosen for describing the structural profile of each diastereomer possible for the contiguous dipropionate moiety. One could use various parameters including ^1H chemical shifts and $^1H/^1H$ vicinal spin-coupling constants in NMR spectroscopy to portray the structural profile for each diastereomer, but we chose the ^{13}C chemical shifts first to demonstrate the feasibility of this approach. In the cases of AAL toxin and maitotoxin, we compared the chemical shifts of synthetic model-diastereomers with the chemical shifts of the natural product and used a degree of chemical shift deviation as the indicator for match/mismatch judgments. For the universal NMR database purpose, we used a deviation of chemical shift from the average value of the eight synthetic diastereomers as the reference point. In order to correlate the NMR data of a future unknown compound with a universal database, we need to estimate the effects on chemical shifts due to additional functional groups present in the unknown compound. The left-side chain in **30** should allow us to install representative functional groups on the backbone and determine their effects on the database.

With the eight synthetic diastereomers possible for **30**, the contiguous dipropionate ^{13}C NMR database was created, which demonstrated that each diastereomer exhibits distinct and differing ^{13}C NMR profiles (Fig. 13). The ^{13}C NMR profiles were determined in three commonly used NMR solvents, CD_3OD, $(CD_3)_2SO$, and $CDCl_3$. It is important to note that, upon changing the solvent from CD_3OD to $(CD_3)_2SO$, each nucleus of the eight diastereomers was found to exhibit approximately the same magnitude of solvent effects, and therefore the overall ^{13}C NMR profile in CD_3OD and $(CD_3)_2SO$ became virtually identical. On the other hand, upon changing the solvent from CD_3OD to $CDCl_3$, each nucleus of the eight diastereomers was found to exhibit a different magnitude of the solvent effects. These observations indicate that an intramolecular hydrogen-bonding array does not play a major role in determining the overall structural characteristics of these diastereomers in CD_3OD and $(CD_3)_2SO$, whereas it does play a role in $CDCl_3$. Thus, the solvent of choice is CD_3OD or $(CD_3)_2SO$. In addition, the concentration-dependency of the ^{13}C NMR profile was found to be negligible, if any.

To determine chemical shift increments on the ^{13}C NMR database due to the presence of additional functional groups, the C1 terminus was used to prepare two series of derivatives. The ^{13}C chemical shift increments were experimentally determined, which were found to compare well with those predicted by the program developed by Renate Buergin Schaller.[35] This exercise showed that, using this program, the adjustment(s) necessary to the ^{13}C NMR database due to presence of a new array of functional groups can be secured.

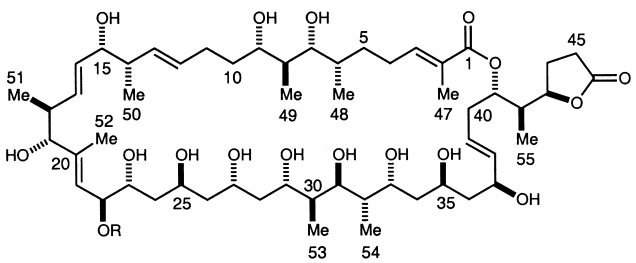


Figure 14. Complete structure of oasomycins A and B. **30a**: oasomycin A (R=H) **30b**: oasomycin B (R=α-D-mannosyl).

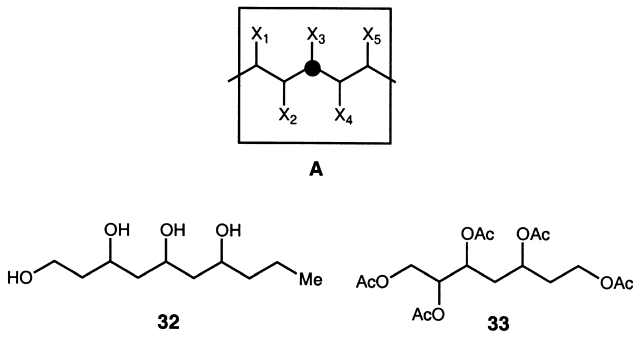


Figure 15.

In order to test its reliability and usefulness, the contiguous dipropionate ^{13}C NMR database was first applied to predict the relative configuration for the C5–C10 portion of the desertomycin/oasomycin class of natural products. The predicted stereochemistry was then confirmed through the synthesis of the C3–C12 degradation product (Fig. 14).[34]

Based on the guidelines for dissecting a given molecule (Fig. 12), the C21–C38 portion should be treated as one cluster. With 11 stereogenic centers, there are 1024 diastereomers possible for this portion of the molecule, immediately raising a few concerns about this approach. Obviously, creation of the NMR database for such a large cluster requires extensive synthetic efforts. The more serious concern is: if one had to create an NMR database specifically for each given case, it would defeat the concept of the approach itself. Therefore, we wished to test whether a small NMR database such as **30** might be useful for a stereochemical analysis of a small portion within a large cluster. With the guidelines applied to a five-carbon system such as **A** (Fig. 15), the chemical shift of the central carbon marked by •, or the proton attached to it, are expected to be: (1) dependent on the stereochemistry of the functional groups present on the next and one-farther carbons, cf. the boxed portion in **A**, but (2) independent of the rest of the functional groups present in the cluster. In other words, these NMR databases possess a self-contained nature; namely, the NMR characteristics of the • carbon are determined only by the functional groups present within the box.[36] The important consequence derived from this recognition is that small universal databases can independently be applied to relevant structural moieties to predict the relative stereochemistry of a large cluster. Indeed, only three, small NMR databases **30**, **32**, and **33** were sufficient to predict the correct relative configuration of the C21–C38 portion of oasomycin A.[37]

Thus far, the universal NMR database has been created by using acyclic compounds. With the assumption that the macrocyclic lactone ring does not (significantly) affect their NMR properties, we applied these databases to the stereochemical assignment of the desertomycin/oasomycin class of natural products. In this context, the 32-membered polyene macrolide antibiotic mycoticin A, also known as flavofungin, provided valuable insight. We noticed a small but noticeable deviation in the ^{13}C chemical shift found in the 1,3,5-triol system in mycoticin A from that in the acyclic 1,3,5-triol ^{13}C NMR database. Interestingly, this deviation becomes more significant in the 28-membered polyene macrolide antibiotic filipin III. In our view, there are at least two probable reasons for the observed deviations. First, it is well documented that the polyene and 1,3-polyol chains interact with each other transannularly, and an anisotropic effect from the polyene chain on the 1,3-polyol chain may result in a deviation of the chemical shifts. Second, mycoticin A and filipin III are known to be relatively conformationally rigid. The universal NMR databases contain configurational as well as conformational information for a given system, and the observed deviations may thus be due to a difference in the population of conformers.[33]

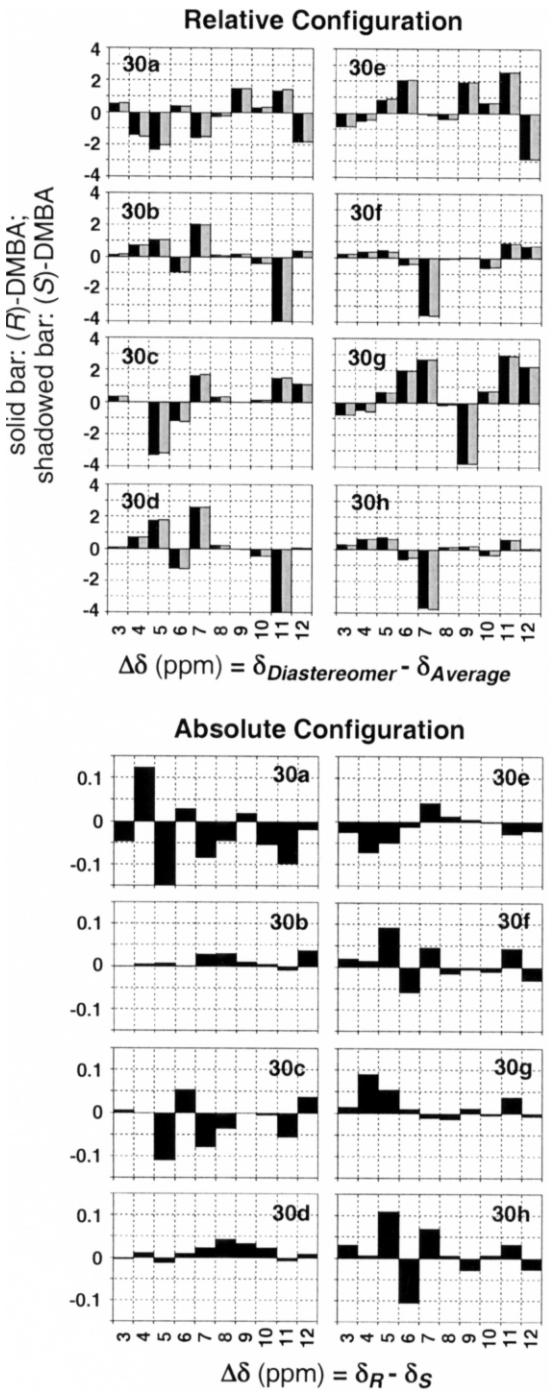


Figure 16. ^{13}C NMR profiles of **30a**–**h** in (*R*)- and (*S*)-DMBA.

With only two additional NMR databases, we were able to determine the relative configuration for all the clusters present in the desertomycin/oasomycin class of natural products.[38] Through these studies, it has become evident that the universal NMR database approach allows us to predict the relative stereochemistry of each cluster without degradation/derivatization work. However, in order to establish the complete stereochemistry of an unknown compound, it is required to know the stereochemistry of one cluster relative to others and the absolute configuration of at least one stereogenic center. Provided with the absolute configuration of each cluster, this problem is automatically solved.[39] In this context, we have recognized the possibility that the absolute, as well as relative configuration of a given cluster could be predicted through an NMR database approach in a *chiral* solvent.

Through an extensive search, (*R*)- and (*S*)-*N*,α-dimethylbenzylamines (PhCH(Me)NHMe, DMBA) have emerged as chiral NMR solvents suitable for our purposes. For illustration, the contiguous dipropionate database **30** is again used (Fig. 16). Each diastereomer of **30** exhibits a distinct and differing NMR profile, demonstrating that this database can be used for prediction of the relative stereochemistry of a structural cluster in an intact form. On the other hand, the ^{13}C chemical shift differences observed in (*R*)- and (*S*)-DMBAs well exceed the limit of measurement for every diastereomer, demonstrating that these databases can be used for prediction of the absolute configuration of each cluster in an intact form. In addition, we have recently developed a new chiral NMR solvent which allows us to establish the absolute configuration of an isolated alcohol.[40,41]

With the information on both the relative and absolute configuration for each cluster, one can assemble all the clusters and establish the complete structure. As mentioned before, we have first focused on the ^{13}C NMR chemical shifts to portray the structural profile of a given structural cluster. Of course, some other parameters such as ^{1}H NMR chemical shifts and $^{1}H/^{1}H$ vicinal spin-coupling constants can be used for this purpose. It should be added that NMR databases using ^{1}H chemical shift profiles have been found to be complementary to NMR databases using ^{13}C chemical shift profiles.[42,43]

We have successfully applied the universal NMR databases to elucidate the complete structure of several natural products. It is our belief that this newly advanced concept offers enormous potential and will add a new dimension to the discipline of structural chemistry. We would note again that the universal databases contain both static and dynamic stereochemical information. Thus, we believe that the NMR database concept can be extended beyond stereochemical assignment. For example, it could be applied to the design of molecular architecture and selective chemical transformations.

As major parts of the palytoxin structure could be viewed as *C*-oligosaccharides, we became interested in comparing the conformational characteristics of *C*-glycosides with that of corresponding *O*-glycosides. The modern era of conformational analysis on carbohydrates began with the recognition of anomeric and *exo*-anomeric effects. The term *exo*-anomeric effect was introduced by Lemieux to describe the observed, preferred glycosidic conformation of sugars.[44] Of the three staggered rotamers around the glycosidic bond of an α-(axial)-carbohydrate, the conformation **34**-**A** is preferred over **34**-**B** and **34**-**C** (Fig. 17). This holds true for both oligosaccharides and simple *O*-alkyl glycosides. This conformational preference has been attributed to a combination of (a) steric preference (**34**-**A** > **34**-**B** > **34**-**C**) and (b) electronic stabilization (**34**-**A** = **34**-**C** > **34**-**B**). The same conformational preference is true for the glycosidic bond of a β-(equatorial)-carbohydrate. Substantial controversy remained as to the relative importance of steric and electronic factors in aqueous or methanolic solution. No experiment directly addressed the relative importance of the steric and electronic components of the *exo*-anomeric effect.

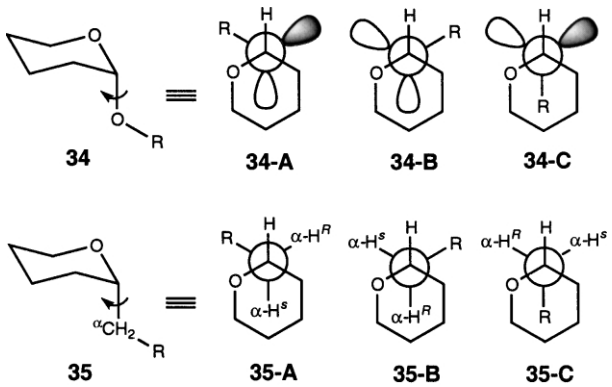


Figure 17.

C-Glycosides **35** represent a possible model for investigating the steric interactions around the glycosidic bonds of carbohydrates in the absence of electronic stabilization (Fig. 17). The conformation of the carbon analogs can be determined experimentally from the vicinal $^{1}H/^{1}H$ spin-coupling constants between the C1 and the Cα protons. This conformation can be compared with that of the parent oxygen compound, and the importance of the electronic interaction can be estimated on that basis. The perturbation caused by the *O*→*C*-substitution is expected to be minimal due to the offsetting bond angle (C–C–C: 109° vs C–O–C 116°) and bond length (C–C: 1.54 Å vs C–O: 1.43 Å).

We began with simple *C*-monoglycosides, thereby observing a strong preference of *exo*-anomeric conformation for the *C*-glycosidic bonds. Variable temperature NMR experiments indicated that they exist as a mixture of staggered conformers rather than a single twisted conformer. The single conformer obtained from the modified Karplus equation was regarded as a time-averaged conformation, yielding the approximate dihedral angles of 55° for the axial *C*-glycosides and −80° for the equatorial *C*-glycosides, which are in good agreement with the value of 55° for methyl α-D-glucopyranoside and −70° for methyl β-D-glucopyranoside. Although the presence of stereoelectronic stabilization cannot be excluded in the oxygen case, the conformational behavior of *O*-glycosides can be accounted for by steric effects at the first approximation.[45]

We then proceeded to the conformational analysis of

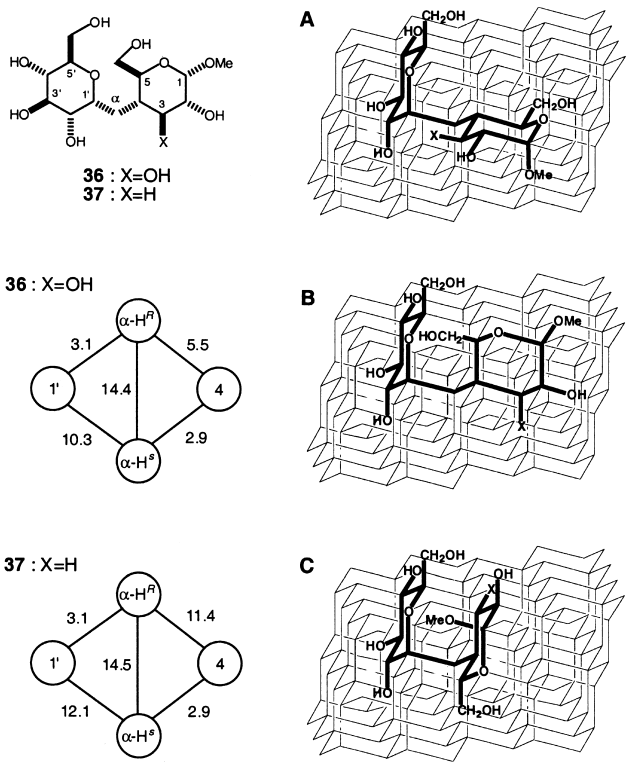


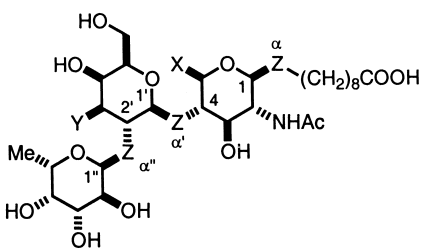
Figure 18. Structure of *C*-disaccharides, diamond-lattice analysis, and $^{1}H/^{1}H$ spin-coupling constant diagrams.

C-disaccharides. The ^{1}H NMR spectrum clearly showed that all the *C*-disaccharides studied predominantly adopt the *exo*-anomeric conformation around the *C*-glycosidic bond. In order to clearly evaluate and present through-space steric interactions, we introduced a diamond lattice analysis. For illustration, methyl *C*-maltoside (**36**: X=OH) is used (Fig. 18). Since the conformational preference of the *C*-glycosidic bond is now well established, only the three staggered conformers around the *C*-aglycosidic bond, **A**, **B**, and **C**, are considered. An inspection of the three conformers on the diamond lattice shows that none of them is free of 1,3-diaxial-like steric destabilization, although conformer **A** seems to be least sterically destabilized. This analysis is nicely reflected in the experimental vicinal $^{1}H/^{1}H$ spin-coupling constants in the ^{1}H NMR spectrum. Importantly, the exact same behavior is known for the corresponding *O*-dissacharides, i.e. steric hindrance results in distortion predominantly around the aglycosidic bond, again indicating the conformational similarity between the two classes of compounds.

Examining the conformation on the diamond lattice, one can recognize that removal of the C3 hydroxyl group or inversion of its configuration should eliminate the 1,3-diaxial-like steric interaction present in the conformer **A**, and this conformer is expected to become dominant. Indeed, a dramatic conformational change due to this simple structural modification was shown experimentally—note the $^{1}H/^{1}H$ spin-coupling constant diagrams for **36** vs **37** in Fig. 18.[46]

Through these studies, it has become evident that the conformational characteristics of *O*-glycosides are duplicated by the carbon analogs, from which two important ramifications emerge. First, the specific conformation of an oligosaccharide can be estimated from the experimentally determined conformation of its carbon analog. Second, the conformational analysis of *O*-oligosaccharides can be performed based on the principles developed for the *C*-disaccharides. We then decided to prepare the carbon analog of a biologically significant substrate and demonstrate three issues on the basis of this analysis. We wished: (1) to show that the conformational properties of this compound can be predicted and that the prediction can be experimentally tested, (2) to demonstrate that the compound can be induced to adopt different yet predictable and well-defined conformations as a result of specific, rationally designed structural modifications, and (3) to examine their effect(s) on the biological behaviors in comparison to the corresponding parent *O*-glycosides. The Type II O(H) blood group determinant trisaccharide **38a** and its carbon analog **39a** are ideally suited for this purpose (Fig. 19).

The conformational analysis of the blood group determinant *C*- and *O*-trisaccharides was conducted independently on two disaccharide-sites, namely the one containing the galactosyl-glucosamine moiety and the other containing the fucosyl-galactose moiety. This exercise allowed us to identify the strategic groups that should effectively modulate the conformational properties. To test this prediction experimentally, we developed a flexible synthesis of this class of *C*-trisaccharides **39a**–**d**. Vicinal coupling constants from ^{1}H NMR spectroscopy and 2D NOESY spectroscopy demonstrated that structural modifications in the *C*-trisaccharides result in large changes in their conformational preferences consistent with the prediction made from the diamond lattice analysis. To test the impact of solution conformation on receptor-ligand recognition, the affinities of compounds **38a**–**d** and **39a**–**d** toward the lectin I of *Ulex europaeus* (UEA-I) were studied, thereby showing that the binding affinities of the H-type II trisaccharide **38a** and the corresponding carbon analog **39a** are virtually identical. The activities of the structurally modified *C*-trisaccharides **39b**–**d** were found to decrease sharply relative to the unmodified *C*-trisaccharide **39a**, correlating conformation to binding affinity. A parallel gradient in binding affinity was observed for the *O*-trisaccharides **38a**–**d**. The selectivity of UEA-I for epitopes **38a**–**d** and **39a**–**d** validated the assumption that its receptor site largely defines a bound conformation for the substrates,



38a: X=CH_2OH, Y=OH, Z=O
38b: X=CH_2OH, Y=H, Z=O
38c: X=H, Y=OH, Z=O
38d: X=Y=H, Z=O

39a: X=CH_2OH, Y=OH, Z=CH_2
39b: X=CH_2OH, Y=H, Z=CH_2
39c: X=H, Y=OH, Z=CH_2
39d: X=Y=H, Z=CH_2

Figure 19. Structure of *O*- and *C*-human blood determinant trisaccharides and their analogs.

and established that the conformational behavior of *O*-glycosides such as **38a–d** is similar to that of *C*-glycosides such as **39a–d**.[47]

A number of groups are actively engaged in studying the conformational analysis of *O*- and *C*-glycosides. It is generally agreed that the conformational characteristics of *C*-glycosidic bonds compare well with those of the corresponding *O*-glycosidic bonds; namely, both *O*- and *C*-glycosides distinctly adopt the *exo*-anomeric conformation. However, there is a discrepancy of whether the conformational characteristics of *C*-aglycosidic bonds parallel those of the corresponding *O*-aglycosidic bonds. In this context, it is worthwhile adding that, through X-ray analysis, the conformation of *C*-lactose bound to peanut lectin was shown to be practically identical to the conformation of its parent *O*-lactose bound to the same protein, and also that both on- and off-rates of *C*-lactose to peanut lectin are practically identical to those of *O*-lactose.[48]

On the basis of extensive ^{1}H NMR studies in aqueous methanol, palytoxin has been shown to adopt one predominant conformation. The conformational analysis on palytoxin was first conducted through the ^{1}H NMR analysis of the eleven smaller segments. These segments were chosen, and synthesized, in such a way that the each segment has an overlapping structural portion with the next segment. The ^{1}H NMR characteristics of these segments were found to be remarkably well compared to those of the corresponding structural portion of palytoxin. Interestingly, all the *C*-glycosidic bonds present in these segments, as well as palytoxin itself, distinctly adopt the *exo*-anomeric conformation.[49,50]

Combining the conformational preferences of these small segments yielded the preferred global conformation of palytoxin itself. In this preferred global conformation, the distance between the C- and N-terminals was estimated to be 31 Å. In order to provide experimental support for the predicted global conformation, we developed a chemical ruler based on conformationally well-defined 3_{10}-helical oligopeptides and estimated the distance between the C- and N-terminals to be 30 Å through fluorescence energy transfer experiments.[49]

The conformational studies on *C*- and *O*-glycosides have been extended to a new program, synthetic 3-*O*-methyl-D-mannose-containing polysaccharides (sMMP) and synthetic 6-*O*-methyl-D-glucose-containing polysaccharides (sMGP) (Fig. 20). 3-*O*-Methyl-D-mannose-containing polysaccharides (MMP) and 6-*O*-methyl-D-glucose-containing (lipo)-polysaccharides (MG(L)P), isolated from *Mycobacterium smegmatis*, are known to profoundly affect fatty acid biosynthesis, including an increase in the overall rate of fatty acid biosynthesis and change of product distribution. Both MMP and MGP are shown to exhibit an interesting host/guest chemistry with C_{16}- or longer acylCoA in water.[51] In our view, these extraordinary chemical and biochemical properties warrant further investigations on these classes of naturally occurring polysaccharides. Unfortunately, however, the polysaccharides from natural sources are known to be a complex mixture of structurally

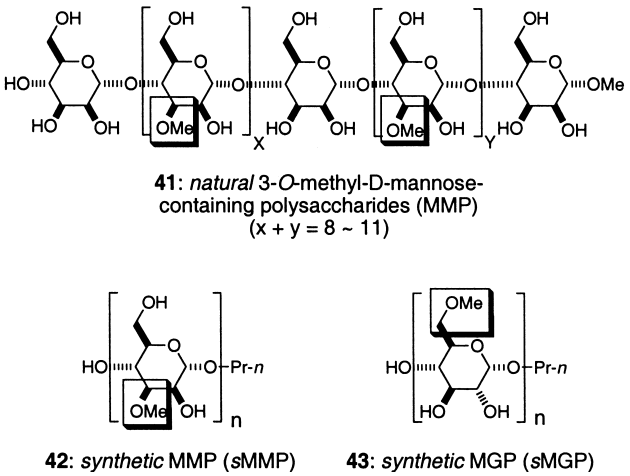


Figure 20. Structure of *natural* MMP, *synthetic* MMP, and *synthetic* MGP.

closely related polysaccharides. To overcome this difficulty, we have designed, and developed a highly convergent synthesis of sMMP (**42**) and sMGP (**43**). To our delight, both sMMP and sMGP exhibit the host/guest chemistry exactly as we hoped for. For instance, both sMMP ($n=16$) and sMGP ($n=16$) form a 1:1 host/guest complex with C-20 fatty acid in water even at 5×10^{-7} M. With chemically homogeneous sMMP and sMGP, we hope to learn about the fundamental chemistry and biochemistry of how MMP and MGP modulate the biosynthesis in *M. smegmatis*.[52]

The CH_2-bridged *C*-glycoside chemistry has recently led to one additional twist—a covalently cross-linked Watson–Crick base-pair model. The concept of covalently linked cross-sections with molecular architecture similar to Watson–Crick hydrogen-bonded base pairs was introduced by Nelson Leonard in the mid-1980s.[53] Since then, several types of covalently linked systems have been developed. However, these systems are generated from preformed double helices as seen in the seminal work of Verdine.[54] The Leonard system may offer unique opportunities to address questions regarding the chemistry of DNA and RNA. Being encouraged with our successful experience with the CH_2-bridge *C*-glycosides, we have recognized the possibility that CH_2-bridged base-pair models may be uniquely suited to the chemical exploration of covalently cross-linked nucleosides/nucleotides. In addition to added chemical stability, these base-pair models should adopt only Watson–Crick or reverse Watson–Crick base-pairings while maintaining conformational flexibility along the CH_2-bridge. We have developed an efficient synthesis of two types of base-pair models, type-I base pair **44** and type-II base pair **45**, and then shown that both base-pair models can effectively be incorporated in anti-parallel or parallel *n*-, *h*-, and *H*-types of DNA/RNA-oligomers. CD and NMR spectroscopic studies have demonstrated that these DNA-oligomers bearing a covalently cross-linked Watson–Crick base-pair model beautifully mimic the conformational properties found in the corresponding native duplexes. These studies form a foundation for using them as the mimics of native DNA/RNA, and it is our hope that their added stability due to the CH_2-bridge will offer unique opportunities to learn about the DNA/RNA chemistry (Fig. 21).[55]

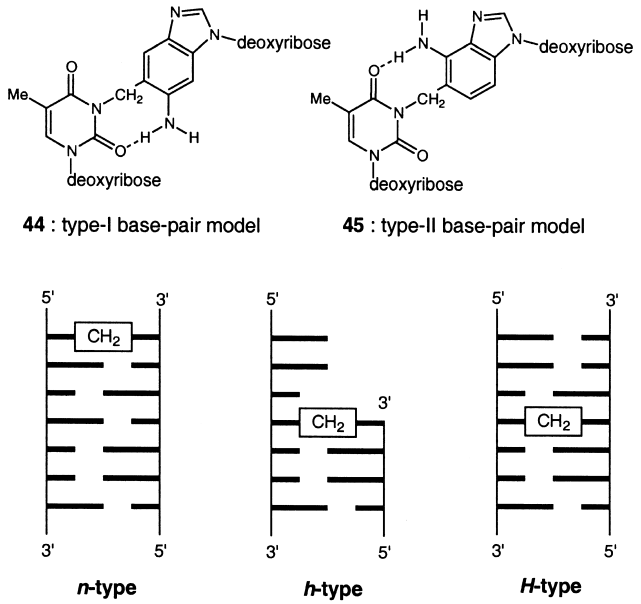


Figure 21. Structure of type-I and II CH_2-bridged base-pair models and generalized structure of *n*-, *h*-, and *H*-type DNA/RNA-oligomers.

I have focused on my personal perspective in our research activities on the marine natural product palytoxin. As a result, literature quotations on the work by others may not be as thorough as they should be. Nevertheless, I hope that our excitement and appreciation for palytoxin are conveyed in a fair manner. Over the past two decades, palytoxin has been an inexhaustible source of inspiration, and I am greatly indebted to the late Professor Hirata for introducing me to this extraordinary natural product.

Acknowledgments

I would like to express my sincere appreciation to a remarkable group of former and present co-workers. Their creativity, dedication, determination, and spirit have made it possible for us to have these extraordinarily challenging, exciting, and rewarding chemical adventures. Financial support from the National Institute of Health (NS-12108 and CA-22215) and the National Science Foundation is gratefully acknowledged.

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