

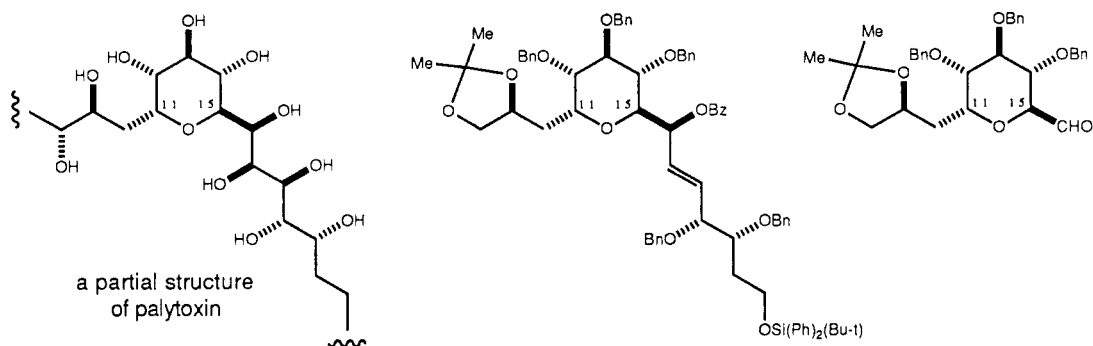
Applications of Ni(II)/Cr(II)-mediated coupling reactions to natural products syntheses

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ABSTRACT - This paper presents a brief review on the history of the development of Ni(II)/Cr(II)-mediated coupling reaction and its application to natural products syntheses.

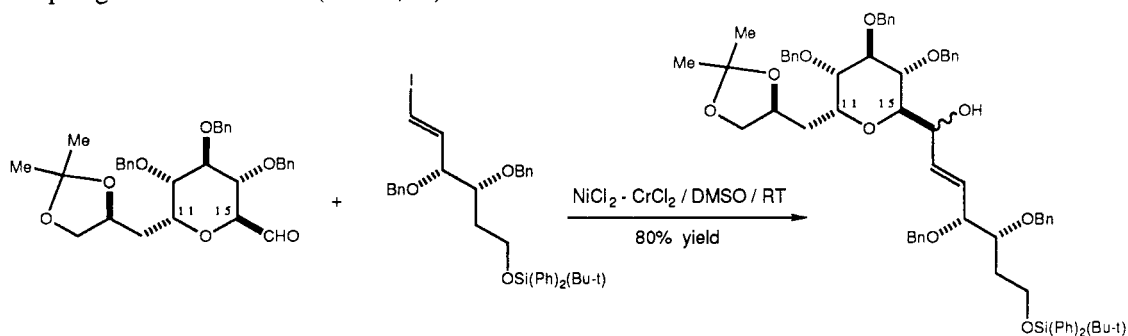
During the synthetic studies on the marine natural product palytoxin, we recognized the *trans*-allylic benzyloxy benzoate to be the key intermediate for the synthesis of the C.8-C.22 segment (ref. 1-4). We had planned to synthesize this substance from the aldehyde or its synthetic equivalent, which seemed possible through routine synthetic operations. However, we soon realized that standard synthetic routes such as Wittig and aldol approaches were not as practical as we had hoped. Among the many possibilities attempted, a coupling reaction utilizing organocuprates gave, at least in the model series, very promising results. However, in spite of extensive efforts, we were unable to generate the desired organocuprate reagent from the *trans*-iodoolefin.



The clue to the solution came from the timely work of Professor Nozaki and co-workers on the Cr(II)-mediated addition of alkenyl halides to aldehydes (ref. 5). After much trial-and-error, we were able to realize the required coupling by adding CrCl₂ to a DMSO solution of aldehyde and iodoolefin at room temperature in the absence of oxygen. This reaction warrants several comments. First, we examined a large number of highly-oxygenated substrates, and found the coupling to be remarkably effective even for polyfunctional cases, including α -oxygenated aldehydes with iodoolefins or β -iodoenones. Second, the stereochemistry of *trans*- as well as *cis*-iodoolefins is retained at least in the cases of disubstituted iodoolefins and trisubstituted *trans*-iodoolefins. Third, with respect to the newly introduced chiral center, this process produces a mixture of two possible diastereomers with a moderate-to-good preference for one

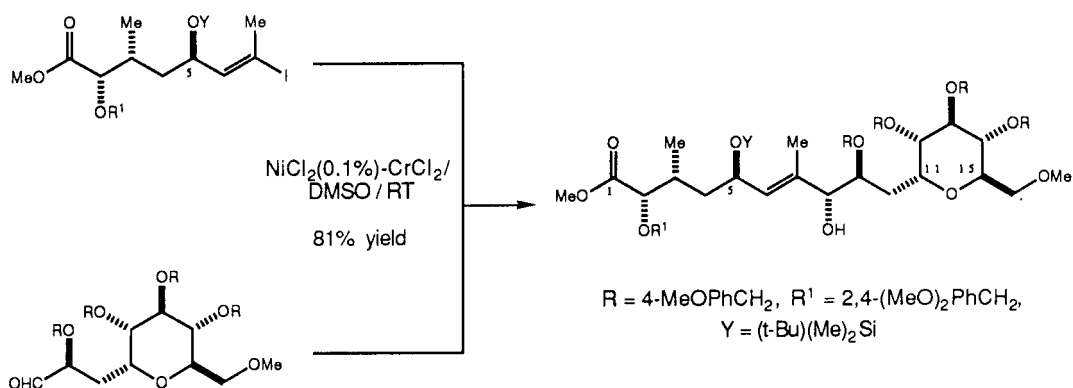
stereoisomer. It is worth mentioning that the major products produced from α -alkoxy and α,β -bisalkoxy aldehydes have the stereochemistry opposite to cuprate or Grignard products.

The Cr(II)-mediated coupling reaction provided an excellent solution to our problem except for one technical difficulty. Unlike the Cr(II)-mediated coupling of allyl halides with aldehydes (ref. 6), the success of this coupling mysteriously depended on the source and batch of CrCl₂. We also tested a home-made Cr(II)-reagent without success. These facts naturally suggested an intriguing possibility that the success of this coupling might depend on some unknown contaminant in CrCl₂. For this reason, we examined the effect of transition metals on the Cr(II)-mediated coupling reaction and found that NiCl₂, when added to the reaction medium, has a dramatic effect. Although we did not establish whether the effectiveness of the commercially available CrCl₂ sample was because of Ni salt or some other metal contaminant, it is now possible to achieve the coupling using CrCl₂ from any source with excellent reproducibility. It is important to keep the NiCl₂ content in CrCl₂ low [about 0.01%~1% (w/w)] to avoid formation of dienes from iodoolefins by homocoupling. Reactions are fast in DMF, THF, or a mixture of DMF and THF, which is usually the choice of solvent for coupling of iodoenones. Reactions are slower in DMSO but this often gives much cleaner results for the coupling of iodoolefins (ref. 7, 8).

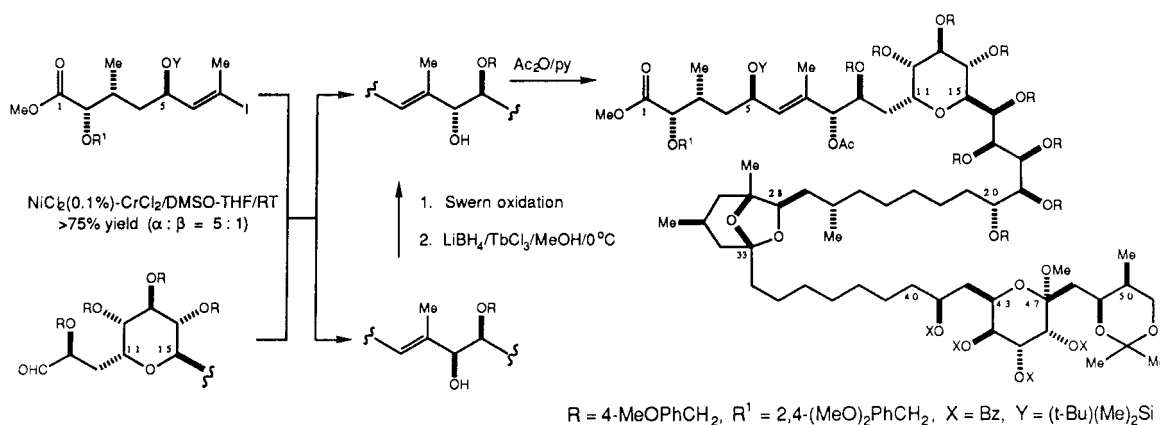


With respect to the possible mechanism for the activation of an alkenyl iodide, this process may involve an initial reduction of Ni(II) into Ni(I) or Ni(0) by Cr(II), oxidative addition of an alkenyl iodide to Ni(I) or Ni(0), and then transmetalation with Cr(II) or Cr(III), to generate the organometallic reagent which then couples with an aldehyde. On the other hand, Ni(II) is regenerated and completes the cycle.

It became obvious that the Ni(II)/Cr(II)-mediated coupling would provide a unique solution to the C.7-C.8 bond formation for the palytoxin synthesis, if we could overcome one additional technical difficulty. Namely, it was important to use an excess of vinyl iodide to achieve the Ni(II)/Cr(II)-mediated coupling reaction efficiently, which was not a serious problem as long as the vinyl iodides were inexpensive. Unfortunately, the vinyl iodide required for the C.7-C.8 bond formation was not cheap by any means, forcing us to search for a method to increase the efficiency of the catalytic cycle. For this reason, we studied the effect of C.5 protecting group on the coupling reaction using a model system. The results were dramatic; with a silyl protecting group at the C.5 position, the coupling reaction could be achieved in excellent yield even with 2 equivalents of the vinyl iodide (ref. 9). Although the reason(s) for the dramatic improvement in the efficiency of the catalytic cycle still remains unclear, this observation, i.e. a high efficiency on the substrate with a silyl protecting group(s), is quite general. We found one additional bonus from this model study. The C.8-stereoselectivity was improved up to the level of 10:1, favoring the desired diastereomer.



The 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 of this reaction. Experimentally, activation of a carbon-iodine bond in the presence of an aldehyde offers an attractive convenience for many cases. In our view, this coupling reaction has demonstrated its potential and uniqueness for polyfunctional substrates, for which conventional organometallic reagents are difficult to apply. The coupling reaction of the C.1-C.7 segment with the C.8-C.51 segment best illustrates this point; the Ni(II)/Cr(II)-mediated coupling reaction under standard conditions using 2 equivalents of the vinyl iodide yielded the expected product in 75% yield as a 5:1 mixture of the C.8 diastereomers, favoring the desired product (ref. 7). The minor undesired stereoisomer was converted into the desired stereoisomer via an oxidation-reduction process. After acetylation, hydrolysis of the acetonide group under mild acidic conditions furnished the complete left half of palytoxin.

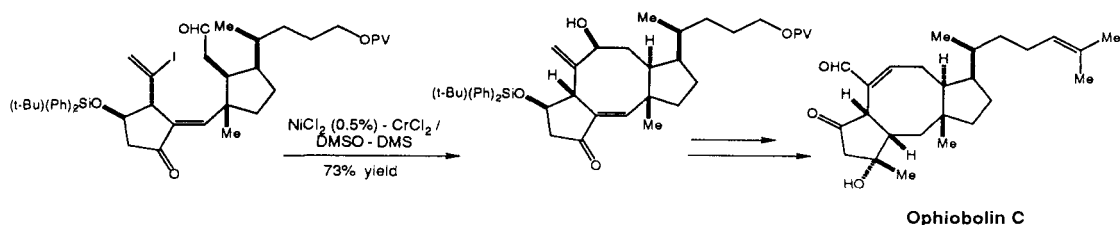


Functional groups stable under the coupling conditions :

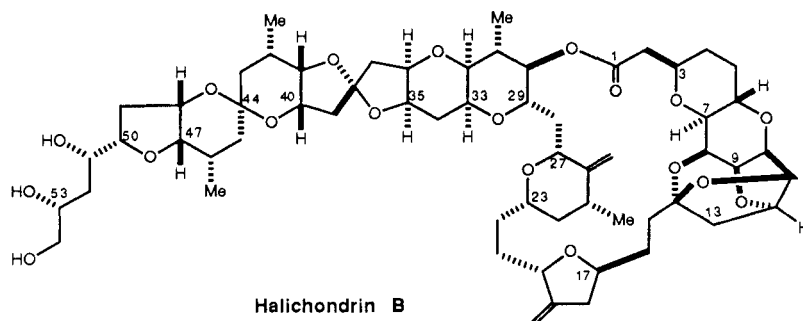
esters, amides, nitriles, ketones, acyls, acetals, ketals, ethers, silyl ethers, alcohols, olefins. . . .

We have used the Ni(II)/Cr(II)-mediated coupling reaction as the key bond-forming step for the synthesis of various natural and non-natural products. Among them, the synthesis of ophiobolin C deserves comment (ref. 10). This work demonstrates the usefulness of the Ni(II)/Cr(II)-mediated coupling reaction for ring formation, even for medium ring formation; construction of the highly functionalized eight-membered ring was effectively accomplished by treatment of the vinyl iodide aldehyde with CrCl_2 containing NiCl_2 (0.5%) in a mixture of DMSO

and dimethyl sulfide (1% v/v) at room temperature for 2 hours. It is worth noting that a single stereoisomer was formed in this cyclization, and its stereochemistry was found to be the one anticipated on the basis of steric considerations.



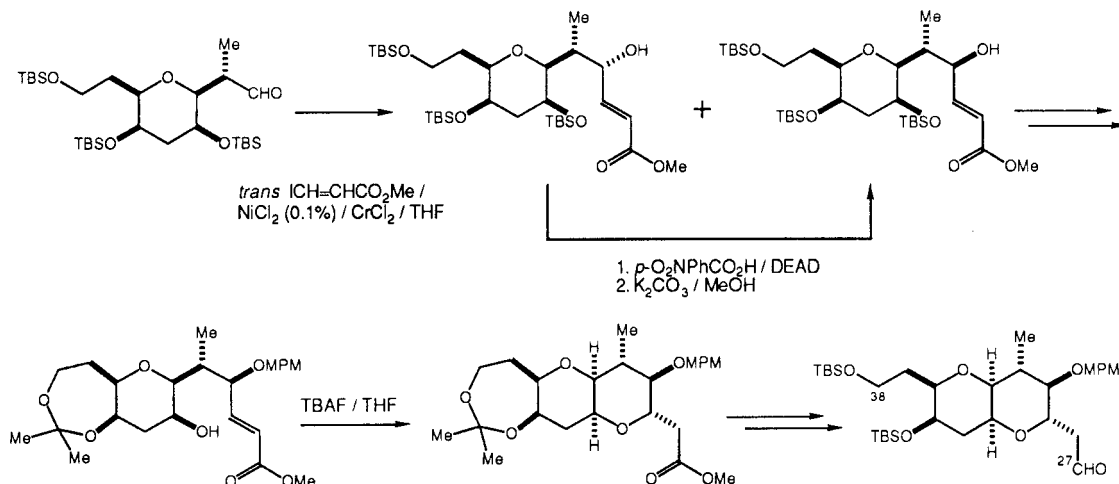
In order to further illustrate the scope and limitation of the Ni(II)/Cr(II)-mediated coupling reaction, we now outline the five carbon-carbon bond forming steps used in the synthesis of halichondrins, a class of polyether macrolides isolated from the marine sponge *Halichondria okadae* (ref. 11). Halichondrins, especially halichondrin B and homohalichondrin B, exhibit an extraordinary in-vitro and in-vivo antitumor activity (ref. 11). However, the very limited supply of halichondrins from natural sources has prevented further evaluation for their potential clinical application thus far. Their intriguing and challenging structural features, coupled with this fact, have encouraged us to undertake synthetic efforts toward this class of natural products (ref. 12, 13).



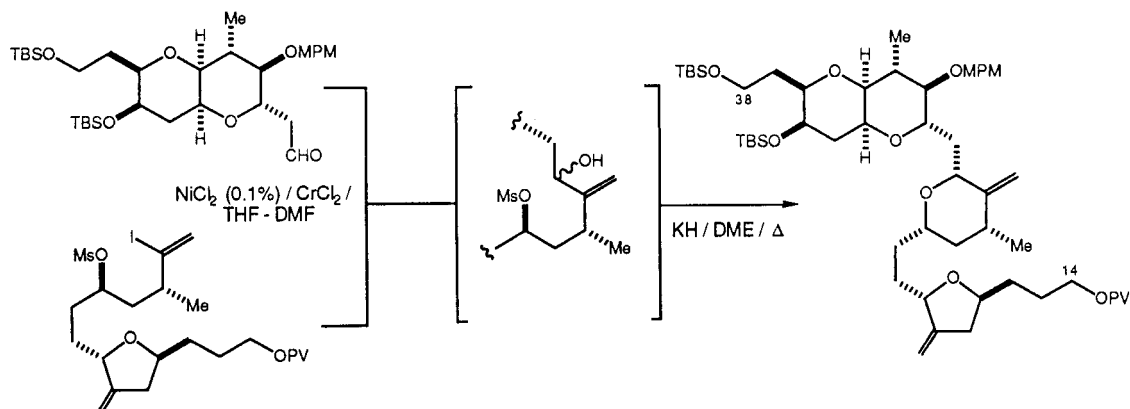
The first Ni(II)/Cr(II)-mediated coupling reaction used in this work is depicted below. It allowed an efficient carbon-carbon bond formation between the aldehyde and the β -position of acrylate to form a γ -hydroxy-*trans*-acrylate in 90-95% yield. This example once again demonstrates the uniqueness of this coupling reaction. However, it also shows its limitation; namely, the product formed was approximately a 2:1 mixture of the two possible diastereomers, favoring the desired stereoisomer. The minor, undesired alcohol was subjected to the Mitsunobu procedure (ref. 14) to invert the stereochemistry. There is a distinct possibility that the stereochemical outcome of this type of coupling reaction could be dictated by using a suitable chiral ligand. We have made some efforts along this line, but have met with only limited success thus far. Undoubtedly, some device of controlling the stereochemical course should give additional versatility to this process.

After protection of the allylic alcohol as an MPM group, deprotection of the silyl groups, and protection of the two-out-of-three resultant alcohols as an acetonide, the Ni(II)/Cr(II)-coupling product was subjected to a Michael reaction in the presence of commercially available tetrabutylammonium fluoride in THF at room

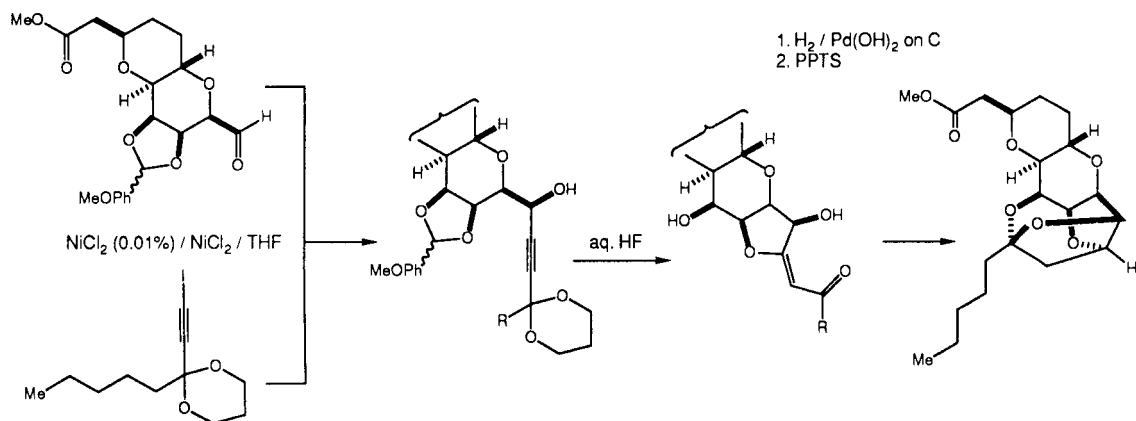
temperature, to furnish the desired cyclized product with an excellent stereoselectivity (>20:1). Using routine synthetic reactions, this Michael product was transformed into the C.27-C.38 segment.



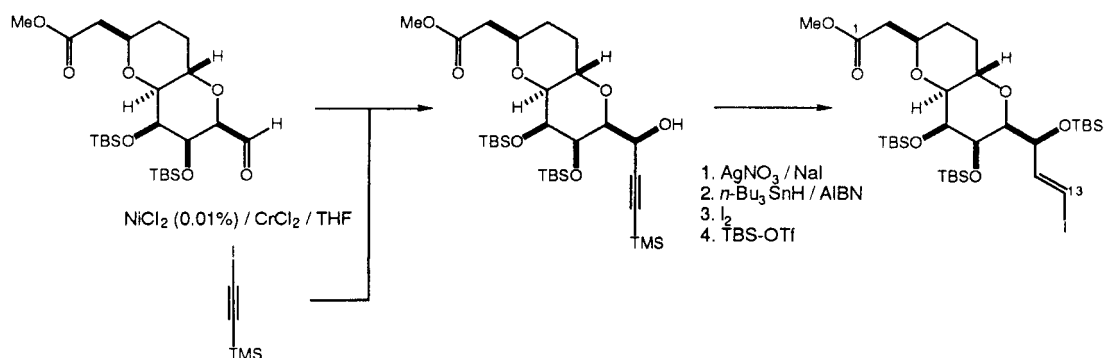
The second Ni(II)/Cr(II)-mediated coupling reaction used in the synthesis of halichondrins is shown below. This reaction allowed us to couple the two segments with the fragile functional groups and to complete a highly convergent synthesis of the C.14-C.38 portion. The overall yield for this process was 50-60%, and the stereoselectivity was approximately 6:1 favoring the desired product.



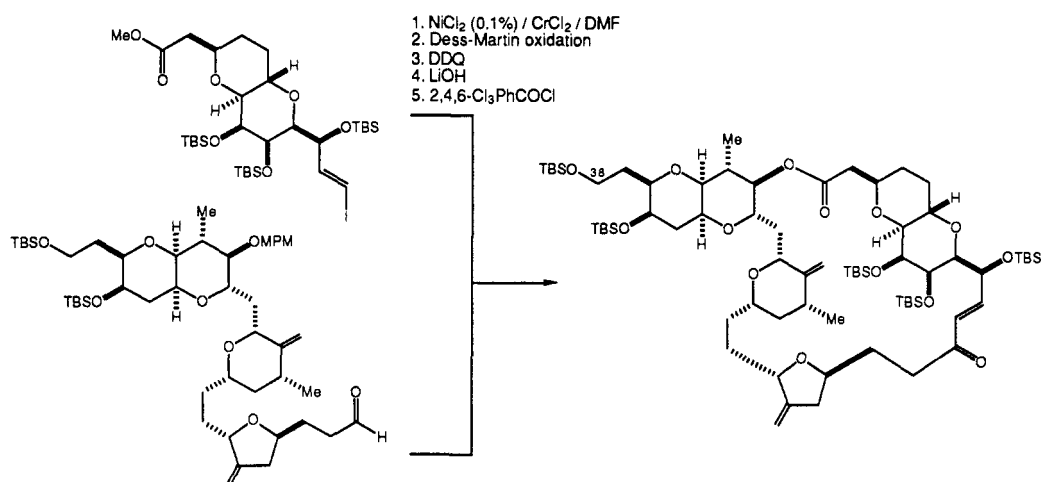
We recognized the possibility to construct the intriguing polycyclic ring system around the C.1-C.15 moiety by using the Ni(II)/Cr(II)-mediated coupling reaction, and studied its feasibility first in the model series. The aldehyde was subjected to the Ni(II)/Cr(II)-mediated coupling reaction with the iodoacetylene (1.4 equivalents), to yield the expected, desired propargyl alcohol in excellent yield. This coupling reaction warrants several comments. First, as described before, this process is exceptionally well suited for cases where the aldehyde is labile. In this case, the aldehyde can potentially give problems associated with enolization such as epimerization and dehydration. However, under the Ni(II)/Cr(II)-mediated coupling conditions, we observed no complications. Second, the stereoselectivity was slightly over 8:1, favoring the desired product, which was anticipated on the basis of steric considerations. Third, the NiCl₂ content in CrCl₂ needs to be much lower for iodoacetylenes than for iodoolefins.



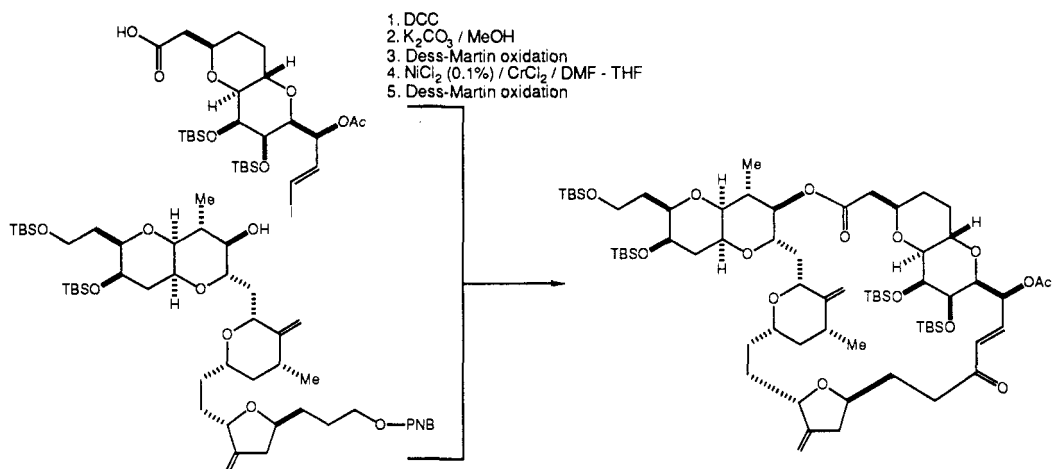
The propargyl alcohol thus obtained was subjected to acid treatment to form the vinylogous ester, hydrogenation, then mild acid treatment, to furnish the desired polycyclic compound in excellent overall yield. This model study yielded a solution for the synthesis of the polycyclic system around the C.1-C.15 moiety. However, we realized that some modification on this approach should be considered for two major reasons. First, the Ni(II)/Cr(II)-mediated coupling reaction is most effectively accomplished with a slight excess, typically 1.5-2.0 equivalents, of iodoolefins or iodoacetylenes. We had planned to use the C.12-C.38 segment as the iodoacetylene component in the real system. Not surprisingly, the synthesis of the C.12-C.38 segment required more effort than the synthesis of the C.1-C.11 segment. Second, hydrogenation was needed stereospecifically to introduce the C.12 chiral center, but the intact C.12-C.38 segment contains two exocyclic olefinic bonds. In order to overcome these potential difficulties, we decided to modify the original plan slightly. Namely, the aldehyde and trimethylsilyliodoacetylene were first subjected to the Ni(II)/Cr(II)-mediated coupling reaction, to yield the expected TMS-acetylene in over 90% yield (stereoselectivity=8:1), which was then converted to the *trans*-iodoolefin by using routine synthetic reactions.



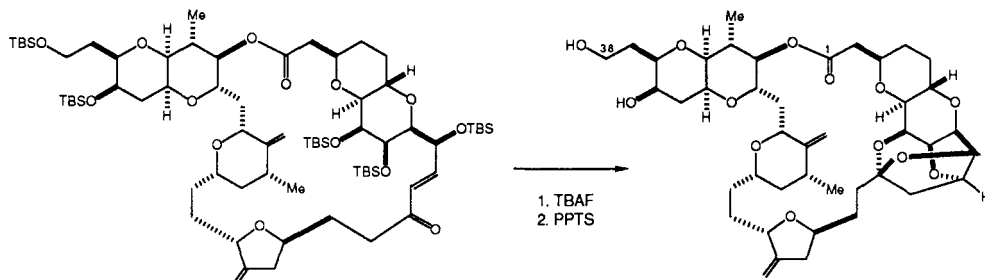
This *trans*-iodoolefin provided the opportunity of using the Ni(II)/Cr(II)-mediated coupling reaction to assemble the entire C.1-C.38 backbone. Obviously, this process could be used intermolecularly or intramolecularly to achieve the goal. We tested the intermolecular approach first; under standard conditions with two equivalents of vinyl iodide, the expected coupling product was isolated in 70-80% yield. After oxidation with Dess-Martin reagent (ref. 15), MPM deprotection with DDQ (ref. 16), and ester hydrolysis with lithium hydroxide, this product was subjected to the Yamaguchi macrolactonization conditions (ref. 17), to furnish the C.1-C.38 enone in excellent overall yield.



As demonstrated in the synthesis of ophiobolin C, the Ni(II)/Cr(II)-mediated coupling reaction could be used in an intramolecular fashion. Indeed, we found the Ni(II)/Cr(II)-mediated macrocyclization to be amazingly effective, particularly for the substrate with an acyl group at the C.11 position. With respect to overall efficiency, however, the intermolecular version was found to be slightly better than the intramolecular version.



The C.1-C.38 enone thus obtained was subjected to deprotection of the TBS groups with tetrabutylammonium fluoride (neutral) in THF at room temperature. In addition to the expected deprotection of the TBS groups, the resultant C.9 alcohol was added to the enone in a Michael fashion under these conditions. A brief acid treatment of the crude product facilitated the intramolecular ketalization, to furnish the complete right half of halichondrins in excellent overall yield.



In concluding this presentation, we are pleased to note that the complete right half of halichondrins has recently been transformed into norhalichondrin B.

Acknowledgement I would like to express my warmest appreciation to the co-workers whose spirit, dedication, stamina, and skill have enabled us to bring this stimulating, exciting, challenging, and rewarding venture to its successful conclusion. The co-workers who have energetically and enthusiastically participated in the projects outlined are acknowledged in the references. Financial assistance for the palytoxin, ophiobolin C, and halichondrin programs is provided from the National Institutes of Health (NS 12108), the National Science Foundation (CHE 89-09762), and the National Institutes of Health (CA 22215), respectively.

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