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HOLOWin : a Fast Way to Search for Tandem Reactions with Computer. Application to the Taxane Framework.

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Abstract. We describe the HOLOWin program whose aim is to search for tandem reactions in synthetic strategies. Targets and reactions are coded at a skeletal level. The program runs on an IBM/PC and takes advantage of the facilities offered by the Windows interface to have a better analysis of the target through several windows. Copyright © 1996 Elsevier Science Ltd

Introduction.

In 1986 we suggested to use the importance of Holosynthons and Holotransforms in synthetic strategies. Such strategies are centered on reactions with one pot formation of several bonds[1]. The prefix holo (from the Greek holos : whole) draws the attention to the fact that, for such transformations, the chemist has to look at the target as a whole in contrast to the majority of synthetic reactions in which only one bond is formed at a time. A holosynthon is therefore a structural entity whose reactivity makes possible major changes in complexity and/or similarity (that is the degree of resemblance between two molecules) in one pot. Such a holosynthon appears clearly in Bertz-type diagrams summarizing synthetic strategies when the change is expressed in terms of complexity[2]. Much remains to be done in the direction of obtaining a consistent representation mapping simultaneously complexity and similarity changes. This concept overlaps with tandem reactions[3], cascade reactions[4], sequential transformations[5], domino reactions[6], one-pot multibond formations[7], multibond forming processes[8], composite reactions[9], multiple constructions[10]. This field is of growing interest as indicated by recent reviews[11,12].

In the field of computer-aided organic synthesis, we have been involved for some time in the search for the key step of a synthesis[13] to build the skeleton of the target. In the Syngen program, Hendrickson showed the importance of the construction of the target skeleton[14]. In our approach target and reactions are coded at a skeletal level. For example if we search for the synthesis of taxol 1a (scheme 1), the target submitted to the computer is structure 1b or 1c.

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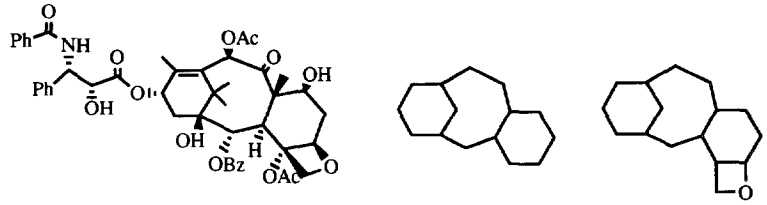
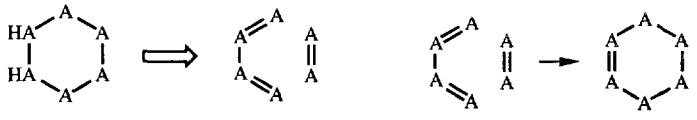


1a **1b** **1c**

Scheme 1

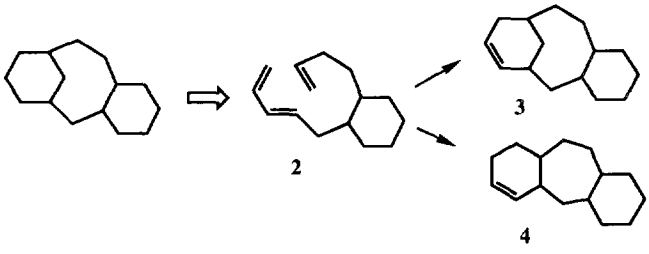
Reactions are coded by two transforms : backward and forward. The backward transform generates functionalized precursors from the skeleton, and the forward transform builds the corresponding functionalized target. Let us take the classical Diels-Alder reaction to show how the reactions are coded in this approach (Scheme 2).



Backward Forward

Scheme 2

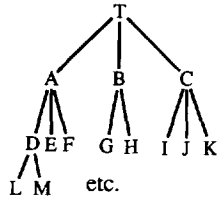
The letter A stands for any atom, in order to generalize the reaction. So, if we submit the skeleton of taxol to the program, it generates 12 precursors. Among them precursor 2 (scheme 3) seems an attractive possibility. Then, applying the forward Diels-Alder transform to this precursor the program generates products 3 and 4 (scheme 3) which could be formed. At this stage, the program is not able to predict which structure is favored and relies on a critical examination by the user. The main idea beeing to show where the functions will be located in the target and, if they exist, all the possible by-products.



Scheme 3

We developed this approach for Macintosh[13a,b] and IBM/PC[13c] (STRAKS program). The results were encouraging : for taxol, a key step proposed by the program[13a] in 1989 was independently realized by another group of researchers[15] and a strategy to build triquinane by radical cyclization[13b] was successfully tested by Prof. D. P. Curran[16]. This approach focused

attention on the search for one key step. The search for tandem reactions, which concentrates two or three steps to build the key step, was done by a breadth analysis of the synthetic tree (see scheme 4) : T beeing the target, the program generated precursors A, B, C, it was necessary to save them on disk and then to analyse them in a second stage. For example, to generate the sequence T, A, D, L, the program generated A, B, C, then analysis of A generated D, E, F, and then analysis of D generated L. In order to improve this analysis we decided to develop a new version using the advantages of multiple windows allowed by the Windows interface in order to perform also a depth analysis of the synthetic tree, that is the direct generation of the sequence T, A, D, L.



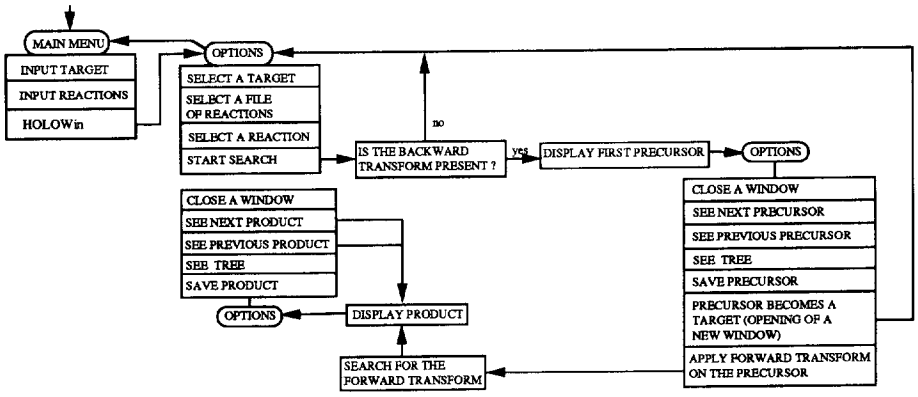
Scheme 4

HOLOWin

The concept of this new program, called HOLOWin (from Holosynthon and Windows), is similar to STRAKS. A simplified flow-chart is displayed in Scheme 5. Improvements have been carried out for the input of the target and the reactions. The use of menus, buttons, icons allows a user-friendly interface. Figure 1 shows the screen during the input of a reaction : the chemist first draws the forward transform, the backward reaction is automatically drawn at the bottom of the screen, then he has only to modify the backward substructure. Presently about forty reactions among the most important for the formation of carbon-carbon bonds, and used in tandem reactions[3-12], have been coded. The user can add his own reactions.

Figures 2-4 show how the program runs during the search of tandem reactions for taxol. First, the chemist loads the target, then he selects a reaction. Here the Diels-Alder reaction was chosen. Clicking in the retrosynthesis arrow starts the search of the substructure. When all the substructures have been found, the program builds and displays the first precursor. The user then has the possibility to select the option which applies the forward reaction to the precursor. Precursors are displayed in the central part of the window and the possible products in the right part. By clicking in the right and left arrow icons the chemist may visualize the different precursors and/or products. When an interesting precursor is displayed on the screen the user may save it for further analysis, as in STRAKS[13c]. Another option is offered by HOLOWin, allowing the in-depth analysis as described above : the user can click in the target icon and a new window appears in which the precursor is now the target. In this new window, again, the chemist selects a reaction and the new target is analyzed. Here, the precursor generated by Diels-Alder reaction was analyzed by Michael reaction. Again a new window could be opened to analyze the new precursor, and so on. Then the chemist may return to the previous window and continue the analysis.

This multiple windows analysis allows the chemist an in-depth analysis of the target aimed at a direct search for tandem reactions. Figures 5 and 6 show some suggestions given by



Scheme 5

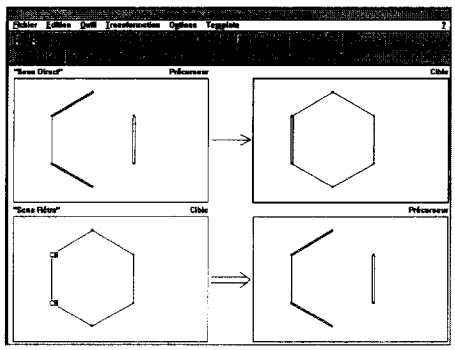


Figure 1. Input of a reaction.

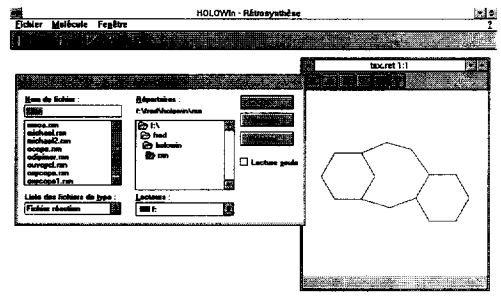


Figure 2. Selection of a reaction file.

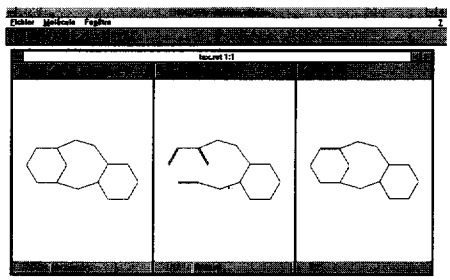


Figure 3. Target, precursor and product from Diels-Alder reaction.

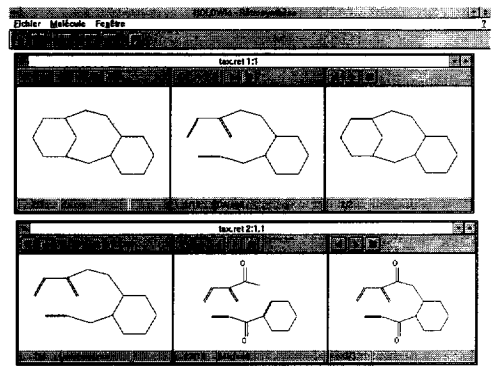


Figure 4. Analysis of the previous precursor in a new window.

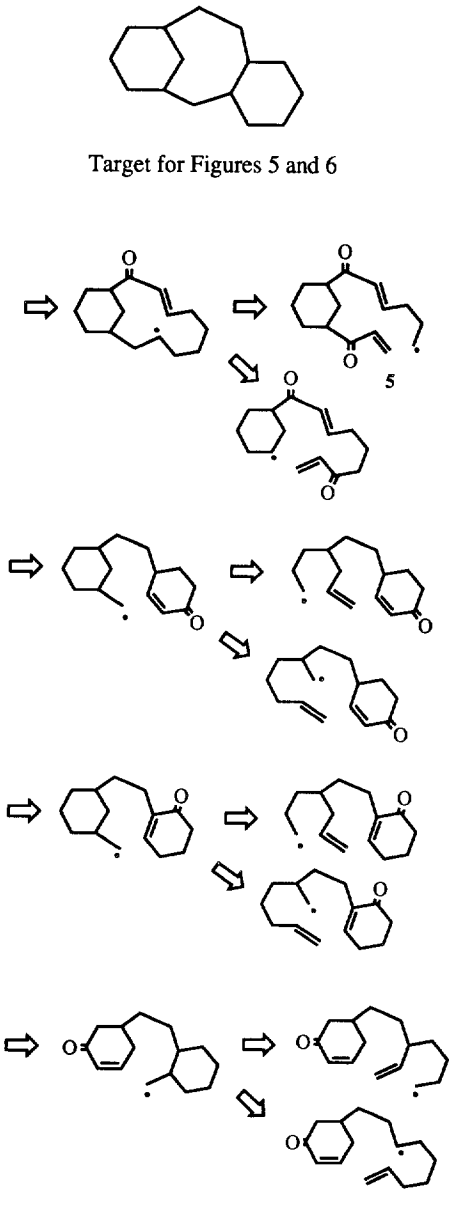


Figure 5 : Some radical tandem reactions suggested by HOLOWin for the synthesis of taxol skeleton.

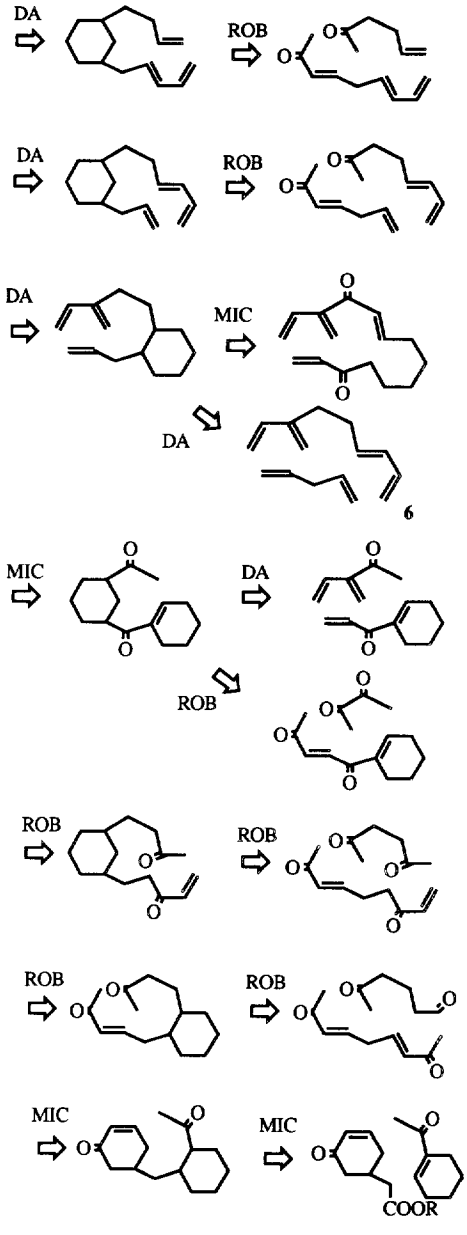


Figure 6 : Some tandem reactions suggested by HOLOWin by Robinson, Diels-Alder and Michael reactions.

the program using tandem reactions to build the taxol skeleton from Diels-Alder, Robinson, Michael and radical reactions. Tandem Michael-Robinson reactions and tandem radical reactions have been described, whereas tandem Diels-Alder-Robinson reactions have not been described[2-12]; so, for this tandem reaction a special adaptation would have to be designed. The program reproduced the tandem radical macrocyclisation-radical transannulation strategy used by Pattenden[17] (solution 5, Fig. 5) and the two consecutive Diels-Alder reactions described by Winkler[18] (solution 6, Fig. 6).

Conclusion

We developed HOLOWin, a new program to search for tandem reactions by a simple and fast approach using multiple windows. By few clicks of the mouse the chemist can dissect the target from any reaction to search for general strategies in contrast to the "classical" retrosynthetic approach where a retrosynthetic tree, as exhaustive as possible, is generated[1]. This approach allows the chemist to quickly generates ideas and in the case of rearrangements it proposes easily solutions which, sometimes, are not obvious to perceive. Solutions suggested for the taxol skeleton show the potential of such an approach.

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