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HOW TO SEARCH ORIGINAL KEY STEPS IN A SYNTHESIS OF COMPLEX STRUCTURES BY USING A MICROCOMPUTER AS A CHEMICAL POCKET-LIKE CALCULATOR

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ABSTRACT

The need for a computer-based protocol is considered to rapidly map the precursors of complex carbocyclic target structures, employing a key transform. A utilisation of our SOS program towards this end is described. Examples are given of several carbocyclic skeletons present in natural products of current interest.

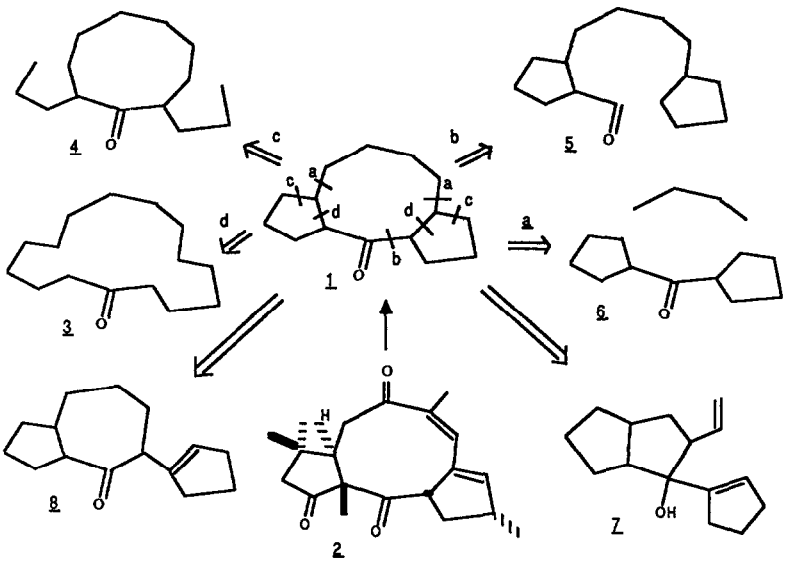
INTRODUCTION

While conceptualisation and solution of synthetic problems still continues to be dominated by individual creativity, intuition and the ability to efficiently orchestrate the knowledge and understanding of chemical reactions towards a certain goal, the past two decades have witnessed definitive attempts to systematise synthetic design from a logical base using the computer [1]. Presently, more than twenty programs have been described for computer assisted organic synthesis (CAOS) [1]. Most of these work backwards (retrosynthetically) from the target and the main focus of early approaches was the construction of a synthetic tree. This inevitably led to a combinatorial explosion and in order to limit and overcome it, new tactics

and strategies were then devised. These include an extension of the LHASA program in which synthetic pathways incorporating specific ring forming transforms, e.g., Diels-Alder reaction, Robinson annulation, etc., to the target can be explored with a depth of search corresponding to as many as 15 steps [2]. PASCOP allows the user to define his own strategies by means of a special language [3]. SYNGEN automatically finds the shortest convergent synthesis best suited to a good synthetic design [4]. REKEST uses a particular coding of reactions for seeking the key steps of a synthesis [5]. A more recent innovation has been a protocol for mapping all possible fragmentation and rearrangement reactions leading to a target molecule [6]. Notwithstanding these fine tactical improvisations, use of CAOS in simplifying and/or solving complex synthetic problems has not become commonplace. One of the main reasons seems to be that the programs run on mini or main frame computers with prices of software which are often dissuasive.

Recognizing that the major concern in the synthesis of a complex molecule is the assembly of its carbocyclic (or heterocyclic) framework, we addressed ourselves to the limited but fundamentally important question of selecting the key reaction to generate the gross skeleton of the target molecule with the aid of a computer. The choice of this key step or reaction in setting-up the requisite carbon skeleton is generally not obvious when one is dealing with polycyclic and bridged ring systems composed of one or many uncommon rings like 4, 5, 7, 8, 9 etc. Retrosynthetic analysis based on strategic bond disconnections to locate the precursor does not substantially simplify the problem in such substrates. However, proper identification of key transforms can and does provide some short and simple solutions for the construction of the bridged and polycyclic molecules. Let us illustrate this through the retrosynthetic analysis of the 5-9-5 fused skeleton 1 present in the anti-tumor diterpenoid jatrophatrione 2 [7]. Some of the precursors 3-6 of 1 through bond disconnection approach are shown in scheme 1.

While some simplification of the 5-9-5 fused skeleton is quite apparent, there is no obvious solution to the central issue of the construction of the 9-ring from readily recognised precursors. On the other hand, retrosynthetic analysis of 1 based on two key transforms, the thermal anionic oxy-Cope rearrangement [8] and the photochemical oxa-di π-methane rearrangement [9], generates precursors 7 and 8 respectively. Both of these precursors correspond to familiar ring systems and provide a definitive way to the construction of the 5-9-5 skeleton.



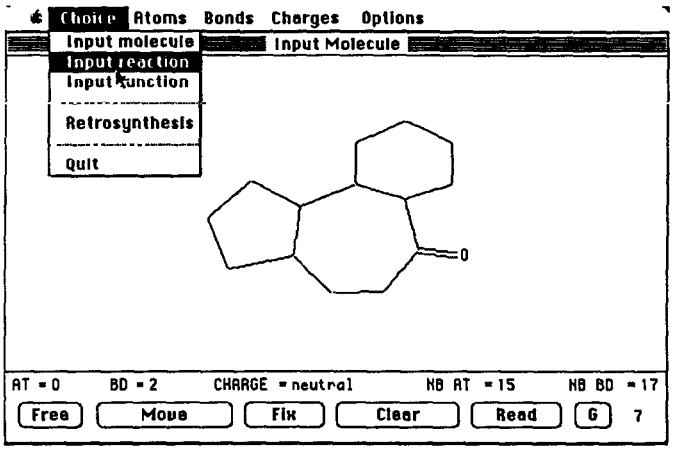
Scheme 1

While such transforms based on retrosynthetic analysis can be carried out by the synthetic chemist using paper and pencil, the exercise can be tedious and time-consuming, and certain interesting possibilities may easily be missed. We present here a simple way of using our SOS (Simulated Organic Synthesis) software [10] to rapidly scan all potential precursors of a complex target employing a chosen key transform [11]. We propose a new tool to synthetic chemists, which could make their search for new strategies easier and more systematic.

PROGRAM

The first version of SOS was developed in 1973 on an IBM 1130 with a memory of 32 Kb [12]. A second version, very similar to the first one, was developed for an Apple II microcomputer [13]. Recently we developed a new version for the Macintosh microcomputer. This version is described in another paper [10] and we summarize here only the main improvements of this software :

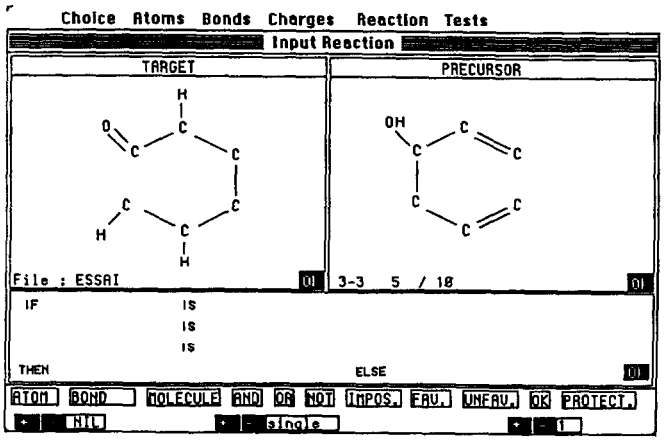
- The program is user friendly thanks to the mouse and scrolling windows.
- The input of the target is easily done by drawing it on the screen by means of the mouse. (Scheme 2) .



Scheme 2

- The perception module of the program which seeks for the main features of the target is open to the user who may add the substructures that he wants.

- The input of reactions (or transforms if we use a terminology from the field of CAOS) is mainly graphic. The user draws the transforms on the screen, ie, the substructures which describe the reaction retrosynthetically . Scheme 3 displays this module for the oxy-Cope rearrangement.



Scheme 3

- Two possibilities are available for the evaluation of a solution :

(i) by alphanumerical tests which have the following form :

if atom (or bond) No1 is "function1" and/or "function2" and /or "function3"
and/or if atom (or bond) No2 is "function4" and/or "function5" and /or "function6"
and/or if atom (or bond) No3 is "function7" and/or "function8" and /or "function9"
then Action1 else Action2

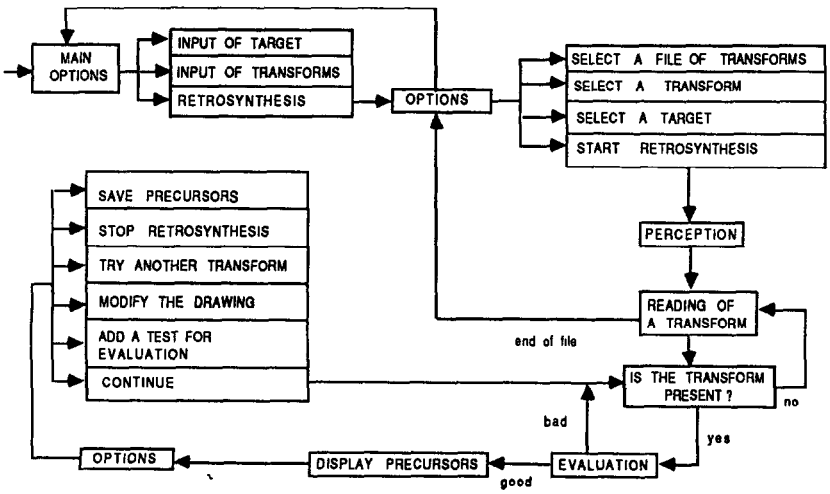
No1, No2, No3 are the number of atoms (or bonds) which are tested.

Function i is a substructure found during the perception module.

Action may be : the reaction is possible, impossible, favoured, unfavoured or the group must be protected.

(ii) by graphical tests : the user draws the substructures which may influence the reaction and indicates the actions to perform if the substructures are present in the target.

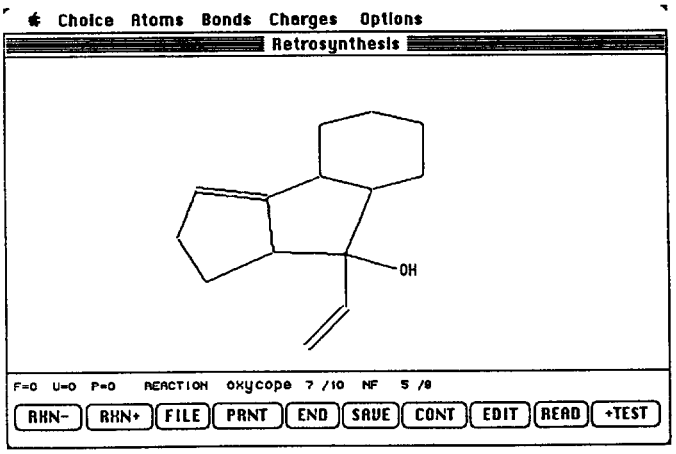
- All the tests are independent; therefore one may enter the knowledge in bulk. This feature allows one to modify the evaluation tests during the retrosynthesis.



Scheme 4

As in the previous versions , the program is interactive. Thanks to features above the chemist may enter a compound and a reaction very easily. These interactive features allow one to use the microcomputer as a chemical pocket-like calculator and check quickly if a given transform may be thought to be a key reaction to construct the skeleton of the target. Scheme 4 shows the flow chart of the program.

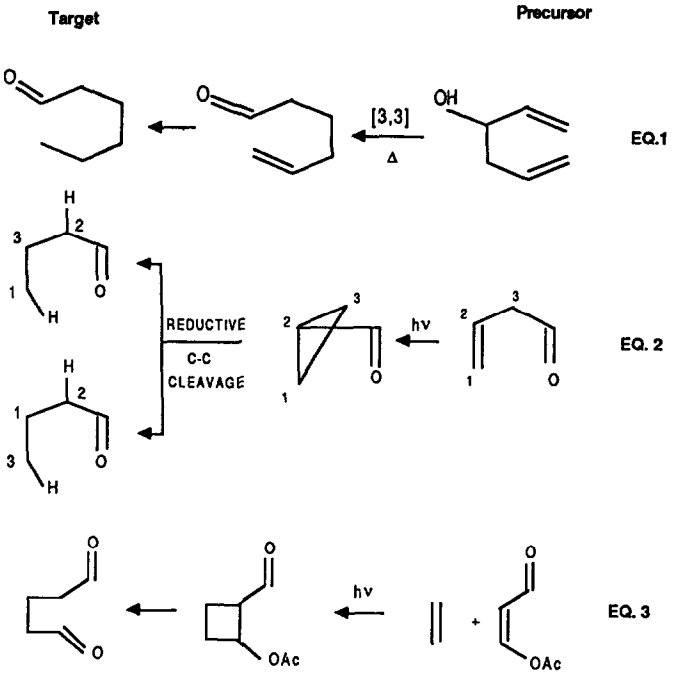
The simple way to use it is to enter the transform then the target. The program then generates all the possible precursors. It is also possible to have several transforms and several targets and the program checks all the possibilities. Scheme 5 shows a potential precursor of the target of scheme 2 by application of the transform shown in scheme 3.



Scheme 5

RESULTS

To illustrate the use of SOS software, three key transforms, i) anionic oxy-Cope rearrangement [8], ii) photochemical oxa-di-π-methane rearrangement-reductive cyclopropane cleavage [9], iii) intramolecular de Mayo reaction (2+2-photocycloaddition - fragmentation) [14], which are currently popular with synthetic chemists were selected. They were coded in the recognition forms indicated in eq. 1-3, respectively, for placement on any chosen target skeleton to map all precursor structures. Stereochemical aspects were not included but all regioisomers were considered.



Several carbocyclic skeletons corresponding to anti-tumour taxane diterpenes 9-12[15], the sphaerane class of marine diterpenes 13 [16], linear triquinanes of the hirsutene-coriolin-capnellene type 14 [17], angular triquinanes of the isocomene-pentelenene-silphenene type 15 [18] and the sesquiterpene hydrocarbon longifolene 16 [19] were chosen to generate the precursors through the transforms presented in eq. 1-3. The results are summarised in Table 1. The placement of functionality on the skeletons 9-16 is not entirely arbitrary but was dictated by considerations of the functionalisation present in the target natural product. However, relocation of the carbonyl groups on the carbon framework could be used to generate more precursors.

All the precursors for target skeletons 9-16 were examined and those involving strained bridgehead double bonds, cyclopropanol or cyclopropene moities and many small rings were eliminated. Only those solutions which appeared 'non-obvious' to us and which to our knowledge have not been attempted previously for the construction of the skeletons 9-16 are indicated in Table 1.

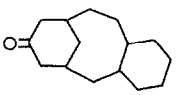
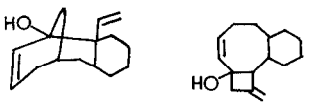
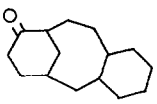
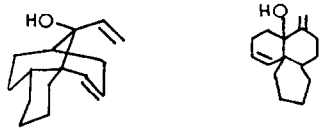
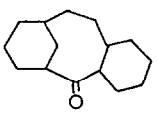
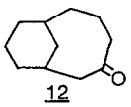
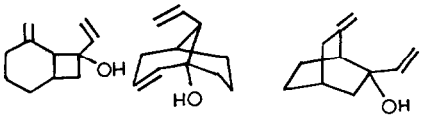
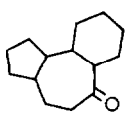
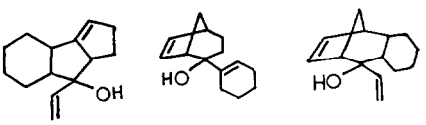
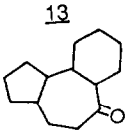
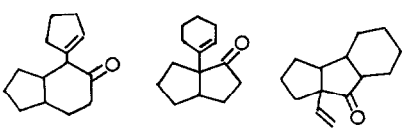
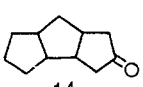
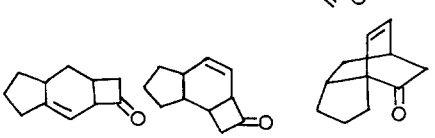
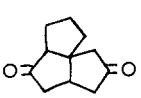
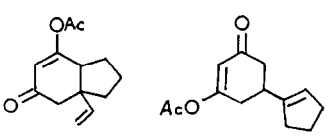
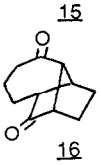
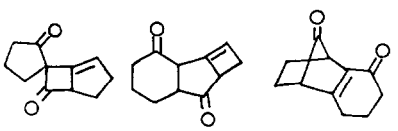
Sl No	Target Skeleton	Key Transform	Total No. of Precursors revealed	Some of the promising precursors
1	 9	Oxy-Cope	7	
2.	 10	Oxy-Cope	6	
3.	 11	Oxy-Cope	6	
4	 12	Oxy-Cope	5	
5	 13	Oxy-Cope	8	
6	 13	ODPM rearrangement & reductive C-C cleavage	8	
7	 14	ODPM rearrangement & reductive C-C cleavage	8	
8	 15	de Mayo Reaction	4	
9	 16	ODPM rearrangement & reductive C-C cleavage	18	

TABLE 1 Examples of solutions given by the program.

CONCLUSION

We describe in this paper a new way to use our SOS software. Instead of constructing a complete synthetic tree, the chemist selects some specific reactions that he feels are specifically adapted to the desired targets, then the program applies the transforms to each target and displays all the precursors which are predicted. Therefore, the chemist can check quickly his ideas for strategies for the synthesis of the different targets.

This approach provides a new tool offered to the organic chemist. This new tool may help him by delegating the tedious task of generating precursors to the microcomputer which can be seen as a chemical pocket-like calculator. This pocket-like calculator not only saves time but also systematizes the chemist's creative ideas.

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11 Such capability was available in CAOS programs but, surprisingly, had never been described specifically. The advent of easily accessible microcomputers gives the possibility for every laboratory to use this approch.

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