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New Computer-Based Approach for Seeking a Key Step in the Synthesis of Complex Structures. Application to Taxane and Crinipellin Diterpenoid Frameworks.

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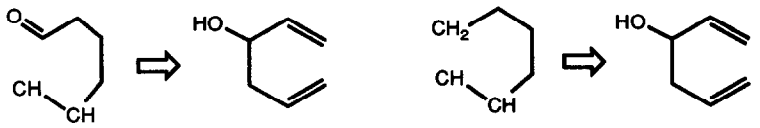
Abstract : *We describe a new approach to map the precursors of complex target structures, involving a key transform, employing a new version of our SOS program which works both backward and forward. In this approach target and reactions are coded on a skeleton model. Results obtained for two diterpenoid frameworks (taxane and crinipellin) of current interest are discussed.*

Introduction

We recently described a new version of our program SOS running on a Macintosh microcomputer [1]. This program can be conveniently used to rapidly scan the possible precursors of a target structure, employing a chosen key transform [2]. Since the key transform (oxy-Cope rearrangement, oxa-di-π-methane rearrangement, etc.) is always built-around some functional group(s), the location of the functionality on the target structure controls the options available for the carbocyclic ring construction. Thus, a predetermined position of the functionality on the target structure imposes restrictions on the number of precursors that can be generated by the program through a given transform. As the main emphasis and advantage of our approach [2] was to rapidly explore and generate access to complex carbocyclic skeletons through simpler and rapidly identifiable precursors, we sought to eliminate this limiting role of the functionality in mapping all the precursors of a target molecule.

To achieve this more general objective, we proposed to code the key reaction on a skeletal model. Thus, the oxy-Cope reaction could be coded as in scheme 1b instead of 1a.



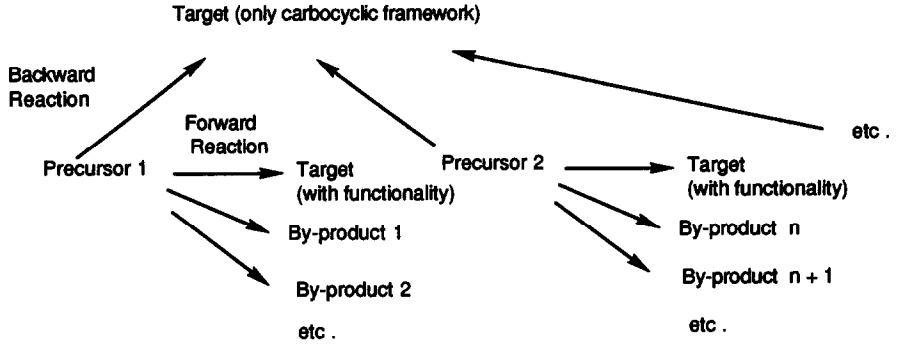
1a **1b**

Scheme 1

This simplification (skeleton reaction coding) can now generate many more, new and desirable options but without the functional group liability. However, in practice the user may find it difficult to perceive the site where the reaction takes place. To overcome this, we have modified the program by making it possible for it to work both backward and forward.

In fact, the reactions are coded in two steps : one for the retrosynthetic mode and one for the synthetic mode.

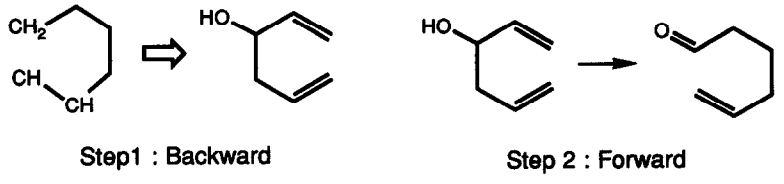
When the program proposes a precursor from the carbocyclic fragment of the target by applying a given transform, an option allows the computer to work forward also from this precursor, which now generates the functionality at the appropriate site. This option allows the computer to foresee all the possibilities of skeleton construction with diverse location of main functionalities (scheme 2) and in some cases, e.g., tandem cyclisation, intramolecular Michael additions, also provide entry into new structures (see by-products in scheme 2).



Scheme 2

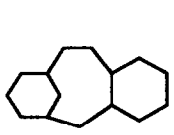
Results and Discussion :

In the skeleton reaction coding approach, a chosen transform is coded in two steps as shown for the oxy-Cope rearrangement [3] in scheme 3.

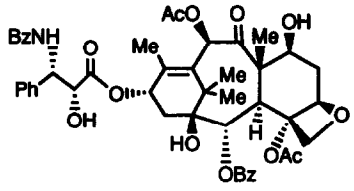


Scheme 3

This is followed by the input of the target molecule, which in the present context should preferably be the bare carbocyclic (or heterocyclic) framework. We selected the taxane skeleton 1 [4] which has aroused world-wide synthetic interest [5] because of the anti-cancer activity exhibited by a promising compound taxol 2 based on this framework.

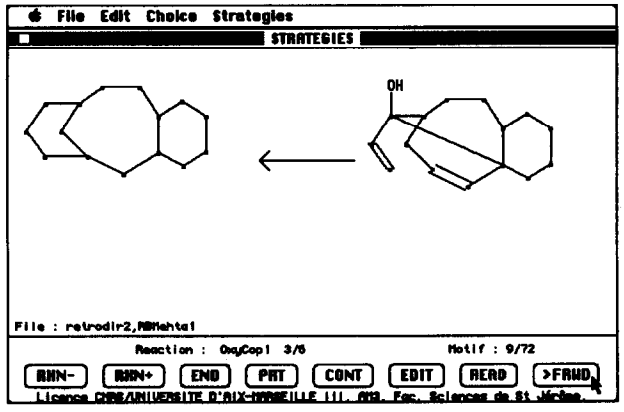


1



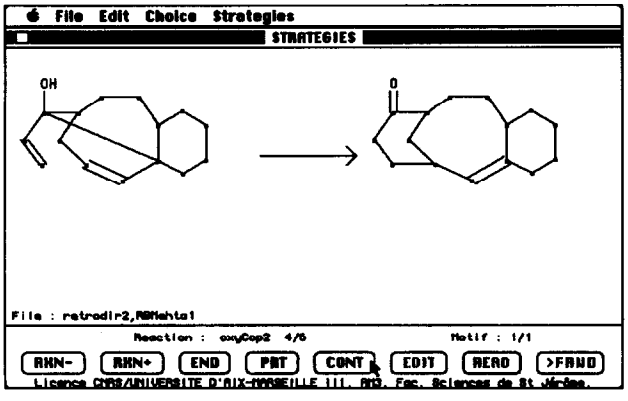
2

Scheme 4 shows the screen when the program proposes a precursor in response to the input of structure 1



Scheme 4

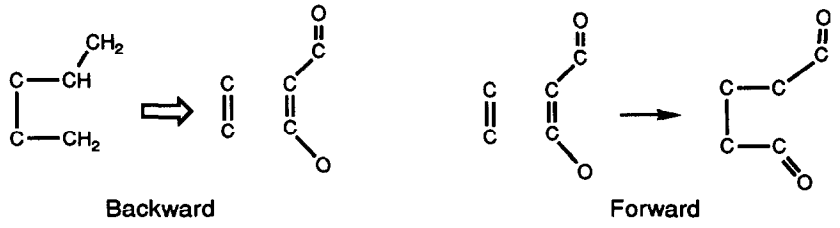
Next, when the FWRD option is clicked, the program displays the taxane framework with appropriately positioned functionalities (Scheme 5) :



Scheme 5

In all, the program generated 72 precursors. Some of the promising possibilities are shown in Table 1. Some of them have been proposed by the previous approach [2] such as the one marked by an asterisk. This solution has been experimentally checked by Zücker and Lupia [5c]. An advantage of the present approach is the location of the functionality.Thus, the derived target structures in Table 1 have a carbonyl functionality positioned in each of the three carbocyclic rings of the taxane framework 1. This advantage is particularly useful in the case of biologically active molecules because it offers suggestions for the synthetic design of many analogues.

We also explored the generation of taxane framework precursors through the intramolecular de Mayo reaction [6,7] , involving photochemical (2+2)-cycloaddition and cyclobutane fragmentation. The reaction was coded as shown in scheme 6.



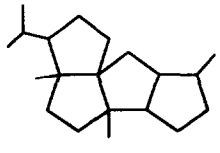
Scheme 6

The program generated 28 solutions and some of them are shown in Table 2 . Once again the derived target structures display a noteworthy dispersal of carbonyl functionalities on the taxane framework.

An additional utilitarian feature emerged from this search. Since there are two possible modes (head-to-head and head-to-tail) of intramolecular (2+2)-photocycloaddition, the program explores both these options and unravels products from both the pathways. Thus, besides the taxane-based derived targets, new carbocyclic structures of possible interest are also generated.

As another example of this approach, we coded the tandem-radical cyclisation reaction (scheme 7, X = precursor of radical) whose efficacy in multiple-carbocyclic ring construction has been recently demonstrated by Curran [8]. A tetracarbocyclic skeleton 3 based on the recently isolated tetraquinane antibiotics of crinipellin group 4 [9,10] was chosen as the input target.

Scheme 7



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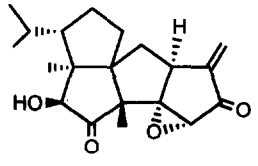

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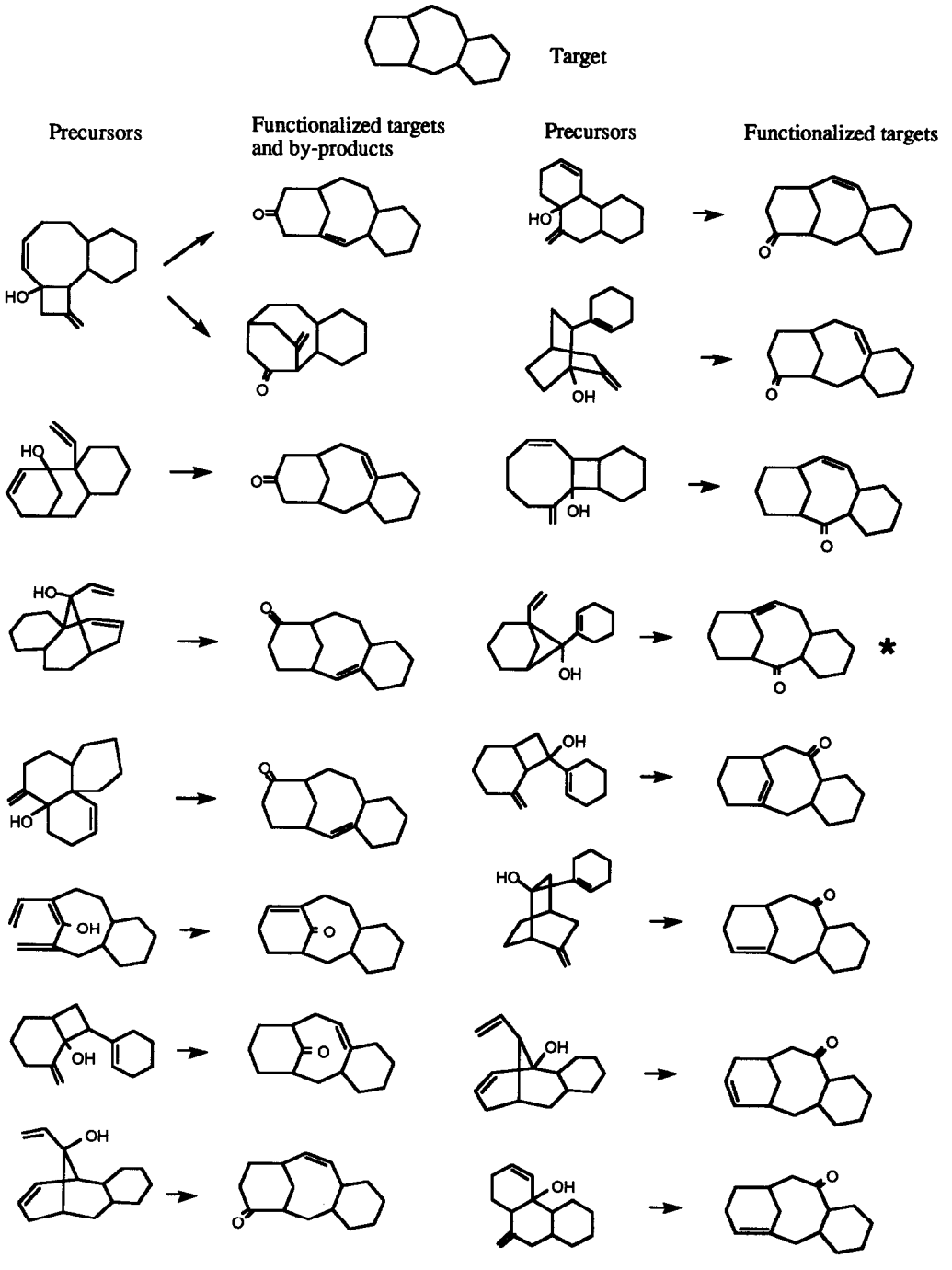


Table 1. Taxane skeleton analysis from oxy-Cope.

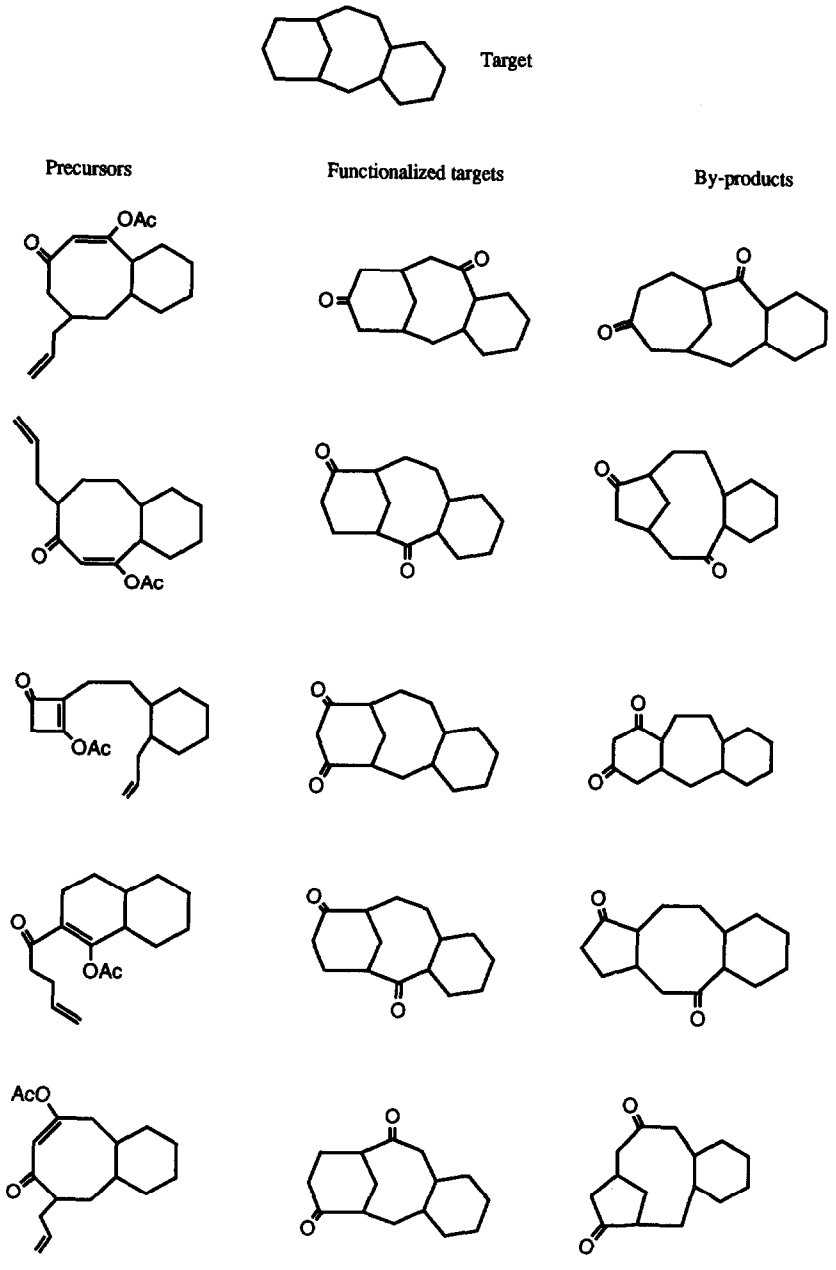


Table 2. Taxane skeleton analysis from de Mayo reaction

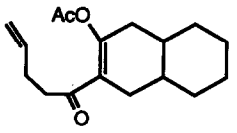
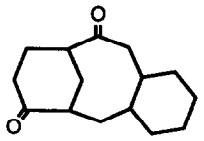
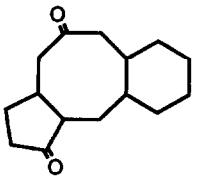
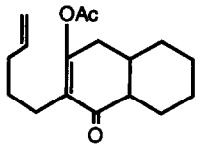
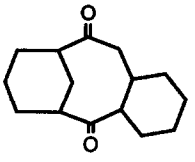
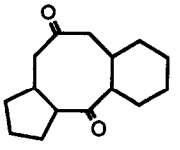
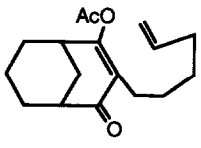
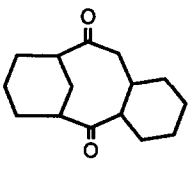
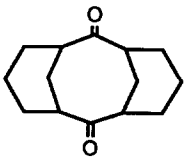
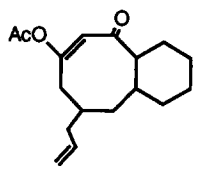
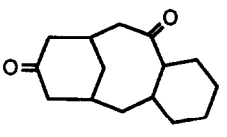
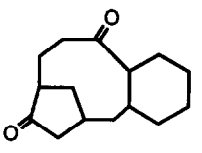
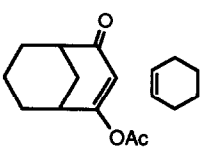
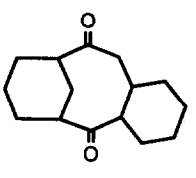
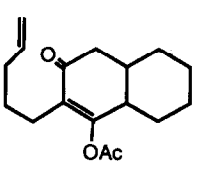
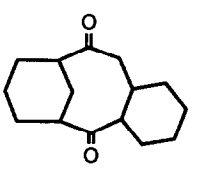
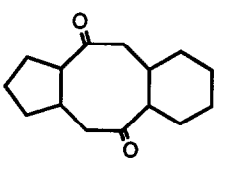
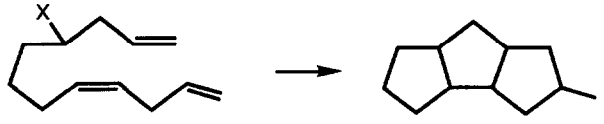
Precursors	Functionalized targets	By-products
		
		
		
		
		
		

Table 2. Continued

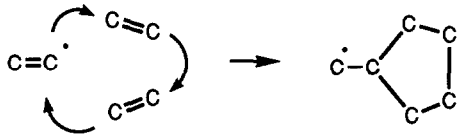
As many as 157 precursors were generated. Among them 79 have been rejected because they involve intermolecular addition or the formation of a ring of size greater than 6 in the first step. This leaves 77 valid solutions which fall into four main structural types : (a) cyclisations in bicyclo-[3.3.0]-octane (diquinane) precursors, (b) cyclisations in bicyclo-[5.3.0]-decane (5,8 fused) or 8-ring containing precursors, (c) cyclisations in precursors with two isolated five membered rings, (d) cyclisations in 11-ring precursors. Some of the interesting solutions are presented in Table 3. Solutions that involve intervention of allylic radicals and unfavourable cyclisations have been eliminated. Among the possible tandem cyclisations leading to a tetraquinane framework unraveled here and indicated in Table 3, a few have been experimentally performed, at least partly, in the construction of triquinane systems [11].

We have also analyzed the possibility of constructing three or four 5-membered rings at a time, through the formation of three or four bonds, in cascade. This is a typical case of holosynthon [12] or multiple cyclizations [13] . So we add a new reaction to form one bond : X-C-C-C <- C=C + C-X. The analysis of structures 5, 7, 9, 15 of Table 3 leads to structures 18 - 25 (Table 4) . Then the analysis of 19 leads to structures 26 and 27 (Table 4). That there exists an elegant possibility of constructing the tetracyclic crinipellin framework in one step, as indicated by the program is supported by the recent report on the construction of the triquinane system in one step from an acyclic precursor [14] (scheme 8).



Scheme 8

The analysis of the results of Table 4 showed an interesting possibility of cyclization (structures 21, 23, 26) described by the following scheme :



Such a cyclization demands specific spatial requirements of the partners but could lead to an unprecedented scheme of reaction.

Conclusion

The new modification (skeleton reaction coding) introduced into the SOS program enhances its utility and enables mapping of all precursors with wide variation in the location of functionality, employing a given transform. Thus, the program not only identifies the precursors to target structures but also provides clues for entry into analogues and in some cases to useful artefacts. The results with the two natural products 2 and 4 and many others have been quite encouraging and we feel that the approach proposed here will be a convenient and useful additional tool available to synthetic chemists.

This approach has been also developed in a program called STRAKS (STRAtegic Key Step) which runs on IBM 3090 and IBM/PC.

Acknowledgements : We thank A.N.R.T.(Association Nationale de la Recherche Scientifique) for a CIFRE grant (n° 543 / 88) attributed to one of us (P.A.)

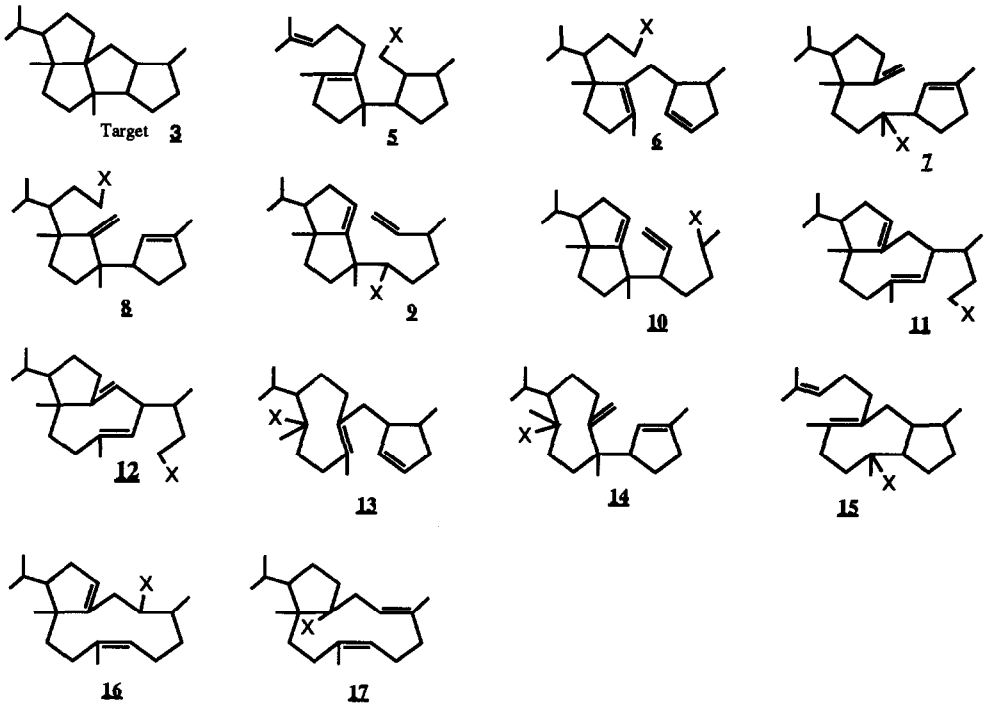


Table 3. Formation of crinipellin framework by tandem-radical cyclization.

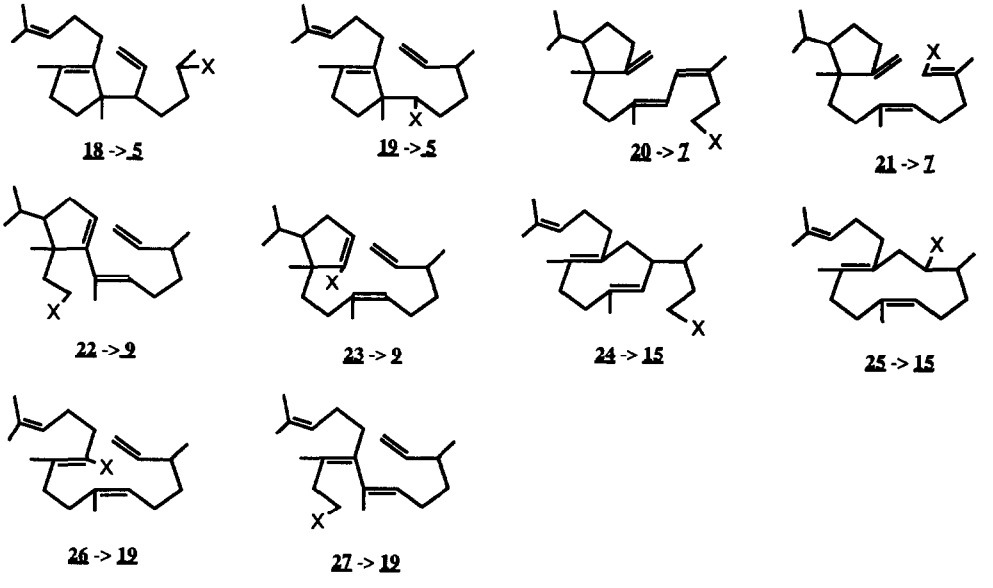


Table 4. Precursors of crinipellin skeleton involving the formation of 3 and 4 bonds.

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