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SLIP : A PROGRAM TO SEARCH FOR LINEAR PRECURSORS. EXAMPLE OF STEROIDS.

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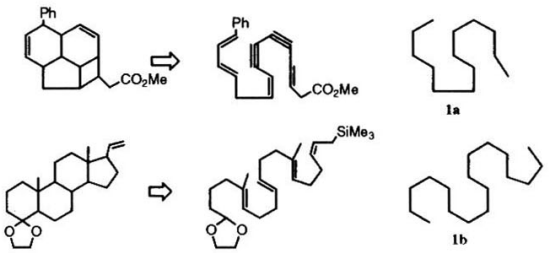
Abstract : We describe SLIP, a simple computer-aided organic synthesis program, whose aim is to generate all possible linear or acyclic precursors for any polycyclic structures described by their skeletons. SLIP was written with VisualBasic and is running on IBM/PC computer. Steroid skeleton was chosen as target molecule.

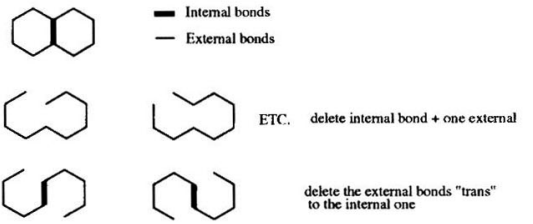
Introduction

We recently proposed the holosynthon concept[1] for designing syntheses in which several rings are build in one step. This concept overlaps with domino[2], tandem[3], cascade[4], sequential[5], multiple[6] reactions. Among these syntheses, the ones which involve a linear precursor are particularly spectacular. The synthesis of endiandric acid A by Nicolaou[7] or Jonhson's synthesis of the steroid skeleton[8] are perfect examples of such an approach (Scheme 1).



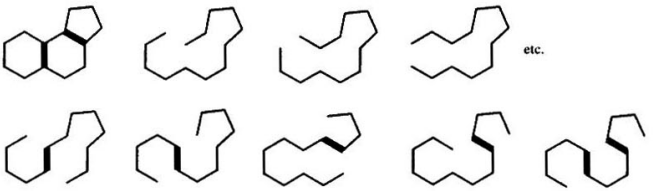
Scheme 1

The key steps shown in scheme 1 can be deducted from solutions **1a** and **1b**. For simple polycyclic structures the search for linear precursors, i.e. **1a** or **1b**, can be made by hand. Thus for the decalin skeleton, the linear precursors are found by i) deleting the internal bond and one of the external bonds and ii) deleting the external bonds which are "trans" to the internal one (See scheme 2).



Scheme 2

This "strategy" is valid for fused rings (See scheme 3).



Scheme 3

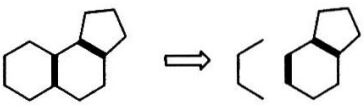
For fused linear systems the number of solutions is equal to the sum of the number of bonds of each ring. For decalin system there are 12 (2 x 6) possibilities. These correpond to the 10 external bonds plus the two cases depicted in scheme 2. For angular systems such as the one shown in scheme 3 the number of solutions is equal to 6 + 6 + 5 + 1 = 18. Seventeen solutions correspond to the case previously described and are partially displayed in scheme 3. The first line of this scheme corresponds to the deletion of the internal bonds and one external. The first four solutions of line 2 (scheme 3)

correspond to the deletion of "trans" bonds to one internal. Due to the angular position one more solution exists : the last of scheme 3.

For more complex structures however the systematic generation of all precursors cannot be made easily by hand. Therefore we wrote a program whose aim is to create all possible linear skeleton precursors for any polycyclic target. The chemist has then to imagine viable reactions which fit with the solutions. Several approaches already showed the interest to work at a skeletal level[6][9].

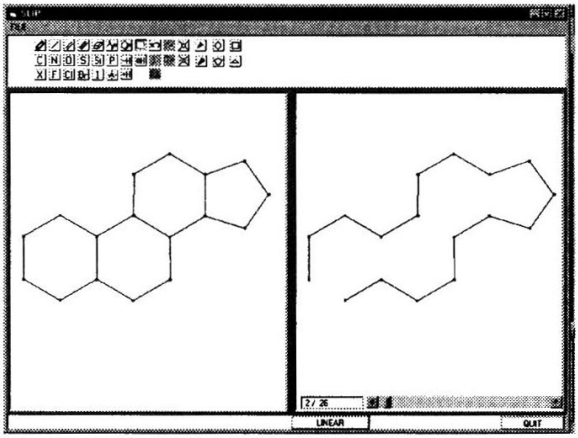
Program

SLIP (Search for LInear Precursors) is composed of two modules : one for the drawing of the target and one for the generation of all possible solutions. The generation of a linear precursor from a target of n rings necessitates to delete n bonds in the target. SLIP is a program which systematically deletes all possible combinations of n bonds (if there are three bonds to delete in a target of 12 bonds, SLIP will delete bonds 1, 2, 3, then 1, 2, 4, then 1, 2, 5, etc. to 1, 2, 12, then 1, 3, 4 ; 1, 3, 5 ... 1, 3, 12, then 1, 4, 5, etc). For each generated solution two tests are performed in order to check the validity of the precursor. The first test calculates the number of atoms with only one neighboor (hydrogen atoms are not counted) : these atoms are terminal of a chain. In a linear structure we must have two terminal atoms. The second test checks if the selected precursor contains only one structure. For example a solution may contain two terminal atoms but with two structures : it must be discarded (See scheme 4).

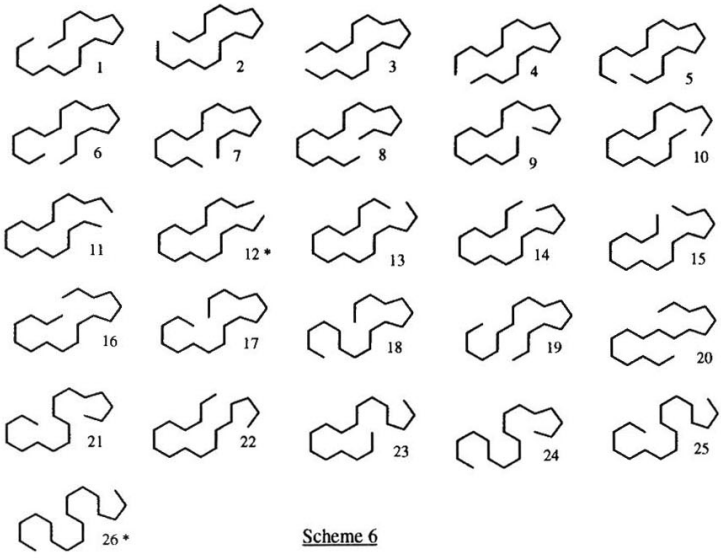


Scheme 4

Scheme 5 shows a view of the screen of SLIP. In the left window the user draws the target to analyse then he runs the LINEAR option and the solutions are displayed in the right window.



Scheme 5

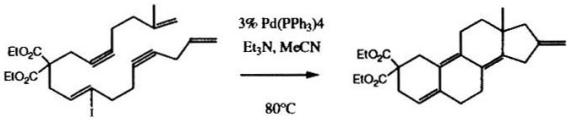


Scheme 6

Results

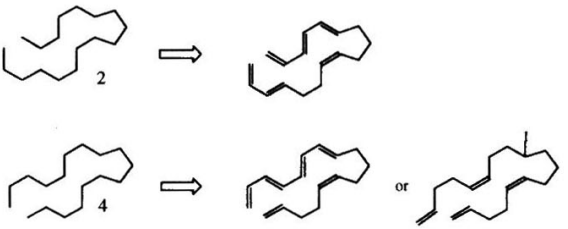
A steroid skeleton was selected as test molecule. SLIP generated 26 precursors (in 3 seconds on a 300 Mhz Gateway Personal Computer). They are shown in scheme 6. The seventeen first solutions are those which involve deletion of all internal bonds plus one external. Then solutions 18-23 correspond to the cases where one internal bond is left and its « trans » bonds are deleted. Three more solutions exist because of the angular position of the rings (solutions 24-26).

Solutions with a star (12, 26) correspond to known approaches. Solution 26 corresponds to Johnson's synthesis[8] and solution 12 involves a palladium catalyzed cascade sequence[10] (Scheme 7).



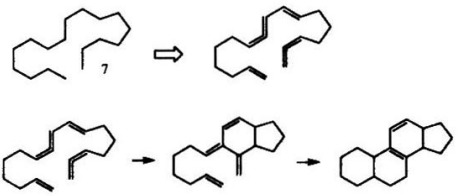
Scheme 7

Solutions 2 suggests tandem Diels-Alder reaction. Solution 4 suggests also Diels-Alder reaction or a palladium cascade sequence similar to the one of scheme 7 (scheme 8).



Scheme 8

Solution 7 suggests a Diels-Alder sequence from allenic precursor (scheme 9).

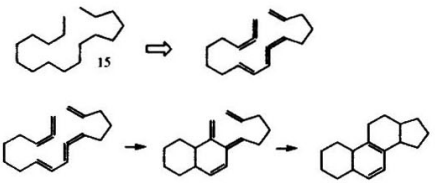


Scheme 9

This idea presents some analogy with Wang's synthesis[11] (scheme 10).

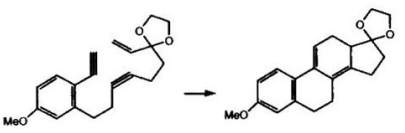
Scheme 10

Solution 15 suggests an idea similar to solution 7 (Scheme 11) :

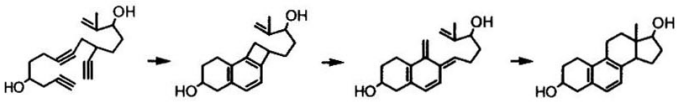


Scheme 11

Solutions 7 and 15 suggest also a [2+2+2] reaction as key step. This has been realized for structurally related precursors[12][13] (schemes 12, 13).



Scheme 12



Scheme 13

Solutions of schemes 10 and 13 can be discovered by SLIP with the acyclic option. When this option is selected the user has to indicate how many chains must be present in the solutions. In this case (schemes 10 and 13) this number is two, and 131 solutions are generated in 4 seconds. This option is less interesting because of the number of possibilities.

Conclusion

With our long term project of creating simple programs to help synthetic chemists, we described a new program whose aim is to show quickly the possible linear and acyclic precursors for any polycyclic target. This program works at the skeleton of the target and can dissect in few seconds any target. SLIP (Search for LInear Precursor) has been tested with steroid skeleton and provided original ideas. SLIP is written in VisualBasic and runs on standard IBM compatible computers with Windows interface. It can be obtained free upon request. (contact René Barone).

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