# Computer-Assisted Synthetic Analysis. Selection of Protective Groups for Multistep Organic Syntheses

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A crucial problem in planning a synthesis is the selection of protective groups for reactive functionality which would interfere with one or more steps in the sequence. This paper describes computer programs designed to assist the chemist in selection of protective groups. PROTECT is a stand-alone program which accesses a database of reactivities of 228 protective groups vs. 108 prototype reaction conditions. Also described is an enhancement to the LHASA program for computer-assisted synthetic analysis which allows LHASA to post-process sequences it has generated, suggesting protective groups for functional groups found to be interfering to the reaction conditions for one or more steps in the synthetic scheme. Examples of the operation of both programs are included.

## I. Introduction

In an ideal chemical synthesis, functionality created in a particular step never interferes with succeeding steps. In practice, it is often impossible to carry out one or more of the succeeding steps directly because of incompatibility between existing functional groups and the reagents required for these succeeding transformations. Occasionally, reordering the steps in the synthesis and/or changing the reagents will remove such problems of incompatibility, but often the chemist must resort to protection and subsequent deprotection of the interfering functionality.

Some of the most elegant examples of functional group protection are those in which a group can be masked by reaction with another functional group in the molecule. However, this so-called "internal protection"[1] process is less common than "external protection", in which the protective group is derived from the protecting reagent rather than from the reactant itself. The science of devising external protection has advanced considerably in recent years, and two very useful compilations of protective groups for a variety of functional group types exist.[2]

A number of factors must be taken into account in devising a plan for functional group protection.[3] The protective group should be easy to put on selectively at the desired site in high yield. It must withstand the reaction conditions for all the steps in which the functional group is not affected and it must withstand the protection and deprotection reactions performed on other functional groups. It must not interfere itself as a reactant with other functional groups. Finally, it must be easy to remove selectively in high yield. A general discussion of functional group protection has been published previously.[4]

## II. Manual Selection of Protective Groups

The process of selecting a protective group involves a number of discrete steps. First, the proposed scheme is summarized, with reactants, reaction conditions, and products delineated for each synthetic step. Next, the relative reactivities of the functional groups in each reactant and product are evaluated, and potentially interfering groups are identified. For each such interfering group, a number of possible protective groups are considered. Each candidate protective group is attached hypothetically, and its reactivity toward the reaction conditions for successive steps is evaluated. If the proposed protective group is not stable toward all these reaction conditions, it is rejected.

A number of other factors must also be taken into consideration. Candidate protective groups must stand up not only to reaction conditions for the succeeding steps in the synthesis but also to the conditions for addition and removal of other protective groups. In addition, the reactivity of each candidate protective group as a reagent itself must be considered, not only toward unprotected functionality but also toward other protective groups which would be in the reactants at each step. The optimum stage for addition and removal of each protective group must be chosen, with the possibility that a single protective group may, if carried through several steps, serve to protect a functional group in two or more steps in which that functional group is expected to be interfering. Often the initially chosen set of protective groups for a synthesis will be changed to allow for simultaneous protection of more than one functional group or for simultaneous removal of more than one protective group. Finally, it may be possible to minimize the number of protective groups necessary or to make use of certain desirable protective groups possible by reordering the steps in the original synthetic scheme.

## III. Functional Group and Protective Group Reactivities

Clearly, accurate evaluation of the reactivity of functionality and of protective groups for that functionality toward a wide variety of reaction conditions is central to the process of choosing protective groups. One approach to making this task easier for the chemist is to tabulate reactivities of a representative number of functional groups and protective groups toward a chosen set of "prototype" reaction conditions. Collaborative efforts in our laboratories have resulted in two such tabulations, one for functional groups and one for protective groups. The functional group vs. reaction condition database has now been expanded from 112 × 60, as first described,[4] to 112 × 138.[5] The 112 figure includes 46 functional group types whose reactivity is considered to be relatively independent of chemical environment and 18 group types which are "subclassified" according to chemical environment. In this latter category, reactivities toward the 138 prototype reagents are assigned to each of 66 functional group sub-

(1) The "internal protection" module in the LHASA program for computer-assisted synthetic analysis will be described in a later paper.
(2) (a) McOmie, J. F. W., Ed. "Protective Groups in Organic Chemistry"; Plenum: New York and London, 1973. (b) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981.
(3) See: Greene, T. W., ref 2b, p 1.
(4) Corey, E. J.; Orf, H. W.; Pensak, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 210.
(5) The new reactivity tables are included as an appendix to Joncas, L. J. Ph.D. Thesis, Tufts University, 1980.

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```
$ R TBLEDIT

     TBLEDIT allows examination and/or modification of reactivity
   levels of FGs towards LHASA conditions.

   Would you like a dump of the reactivity tables (Y or N)? N
   Would you like to examine or modify the tables (Y or N)? Y

                        FUNCTIONAL GROUPS LIST

 1  KETONE           17 DIAZO            33 SULFONE         49 TRIHALIDE
 2  ALDEHYDE         18 HALOAMINE        34 C*SULFONATE     50 ACETYLENE
 3  ACID             19 HYDRAZONE        35 LACTAM          51 OLEFIN
 4  ESTER            20 OXIME            36 PHOSPHINE       52 VIC*DIHALIDE
 5  AMIDE*1          21 IMINE            37 PHOSPHONATE     53 HALOHYDRIN
 6  AMIDE*2          22 THIOCYANATE      38 EPOXIDE         54 GLYCOL
 7  AMIDE*3          23 ISOCYANIDE       39 ETHER           55 HEMIACETAL
 8  CARBONIUM        24 NITRILE          40 PEROXIDE        56 ACETAL
 9  ISOCYANATE       25 AZO              41 ALCOHOL         57 AZIDE
10  ACID*HALIDE      26 HYDROXYLAMINE    42 ENOL*ETHER      58 DISULFIDE
11  THIOESTER        27 NITRO            43 O*SULFONATE     59 ALLENE
12  AMINE*3          28 ENAMINE          44 FLUORIDE        60 LACTONE
13  AZIRIDINE        29 THIOL            45 CHLORIDE        61 VINYLW
14  AMINE*2          30 EPISULFIDE       46 BROMIDE         62 VINYLD
15  AMINE*1          31 SULFIDE          47 IODIDE          63 ESTERX
16  NITROSO          32 SULFOXIDE        48 GEM*DIHALIDE    64 AMIDZ

   Enter a functional group number: 1
   Enter a condition number (To list type 0): 45

   KETONE has the following reactivities towards condition  45 (Wittig):

        SUBCLASS  REACTIVITY     SUBCLASS DESCRIPTOR

            1          H         Strained, cyclic
            2          H         Alpha CH2, cyclic, enolizable
            3          M         Alpha CH, cyclic, enolizable
            4          H         Alpha CH3 or CH2, acyclic, enolizable
            5          H         2 Alpha CH, acyclic, enolizable
            6          M         1 Alpha CH, acyclic, enolizable
            7          L         Enolizable, alpha W-group assisting
            8          M         Enolizable, alpha W-group other side
            9          H         Enolizable, beta C=C or leaving group
           10          H         Alpha dicarbonyl
           11          M         Alpha W-group, non-enolizable
           12          M         Other non-enolizable

   Would you like to change the reactivity data (Y or N)? N
   Would you like to examine or change another FG reactivity (Y or N)? N
   Would you like to write out new tables (Y or N)? N
$
```

**Figure 1.** Example of the use of TBLEDIT for retrieval of information from the functional group reactivity (FG/RGNT) database. VINYLW is a vinyl-extended withdrawing group. VINYLD is a vinyl-extended donating group. ESTERX is the singly bonded oxygen end of an ester. AMIDZ is the nitrogen end (or ends) of a secondary (AMIDE*2) or tertiary (AMIDE*3) amide. User responses are underlined.

classes. The protective group database[2b] contains reactivities of some 228 protective groups toward 108 prototype conditions.[6] Both of these databases are structured around a relatively rough three-level (high (H), medium (M), or low (L) reactivity scheme. (The protective group database also has a reactive (R) level for situations in which the reagent not only removes the protective group but also alters the original functional group in the process.)

## IV. Access to Reactivity Databases

While it is possible to obtain information from the two databases mentioned above by simply looking through them, we have found it more convenient to write computer programs for this purpose. The TBLEDIT program was originally written to allow easy modification of the functional group vs. reaction condition (FG/RGNT) tables but can also be used to extract information from them. A sample dialog is shown in Figure 1.

The PROTECT program for obtaining information from the protective group vs. reagent (PG/RGNT) database is considerably more complicated than TBLEDIT, mostly because it can be used not only for database retrieval but also for analyzing an entire synthetic sequence, as described in the next section. In database retrieval mode, PROTECT has three submodes of operation. Submode 1 shows the chemist the protective groups at each level of reactivity for a specified functional group type in a particular prototype reaction condition. Submode 2 shows the chemist the reactivity of a particular protective group for a specified functional group type in a particular prototype reaction condition. Submode 3 lists the prototype reaction conditions in which a particular protective group has each of the four different levels of reactivity (H, M, L, or R). Sample output from submode 2 is shown in Figure 2.

(6) A correspondence between the 108 reaction conditions in the protective group database and the 138 prototype conditions in the LHASA functional group reactivity database has been established, allowing LHASA to use both databases.

```
$ R PROTECT

   ************************************************************
   * HARVARD PROTECTIVE GROUP INFORMATION RETRIEVAL PROGRAM *
   ************************************************************

      This program has two modes of operation. In the first mode
   the user may retrieve information about the behavior of protective
   groups in a variety of reaction conditions. In the second mode
   the program can assist the chemist in selecting protective groups
   for a sequence of reactions.

   Do you want mode 1 or mode 2? 1

      The program has information on protective groups for seven
   different types of functional groups:

      1) ALCOHOL                        4) ALDEHYDE OR KETONE
      2) 1,2 or 1,3 GLYCOL              5) ACID
      3) PHENOL OR CATECHOL             6) THIOL
                                        7) AMINE

   Which type of functional group would you like protected? 4

   You now have a choice among 3 different sub-modes of operation:

(1)   You may choose a specific reaction condition and have the
      program suggest all protective groups at each level of
      reactivity towards that condition.

(2)   You may specify a particular protective group and a specific
      reaction condition and find out the reactivity of that group
      towards that condition.

(3)   You may choose a specific protective group and have the program
      list the reaction conditions which the protective group could
      withstand at a given level of reactivity.

   Which sub-mode would you like? 2

   Protective group  (<CR> to list, X to exit this mode): 5.5
   Reaction condition(<CR> to list, X to exit this mode): 45


 Protective group 1,3-Dioxanes
 has LOW reactivity towards Wittig
 For more information see

 Greene, T., PROTECTIVE GROUPS IN ORGANIC SYNTHESIS,
          New York, Wiley, 1981, p.122


   Protective group (<CR> to list, X to exit this mode): X
   Do you have another functional group to protect? N
$
```

**Figure 2.** Example of the use of the database retrieval mode (mode 1) of operation of PROTECT. User responses are underlined.

## V. Protection Analysis of Multistep Sequences

The major objective in writing PROTECT was to provide the chemist with a program for performing a complete functional group protection analysis on a synthetic sequence. PROTECT is a stand-alone program, requiring no graphical input or output devices, currently implemented on Digital Equipment Corporation VAX-series minicomputers running the VMS operating system. PROTECT can be used for database retrieval, as described above, or for analyzing an entire synthetic sequence, as follows: First, the chemist sketches out the proposed synthetic sequence, showing all functional groups, intermediates, and reaction conditions, and numbering all of the structures. Next, he runs the PROTECT program, selects multistep analysis mode, and responds to a question concerning the number of steps in the sequence. For each step, PROTECT asks how many structures make up the reactants for the step and then elicits information about each reactant, including the types of all functional groups and the reaction conditions to which the reactant is exposed. While the functional groups must be unambiguous for each structure, the chemist is allowed to input alternative sets of reagents and have PROTECT select the "best" set by minimizing the amount of anticipated functional group interference. Reagents and functional group types are coded by number. Complete lists of these codes can be displayed on the screen if the chemist so desires. The dialog proceeds with a number of questions which allow the program to subclassify (see section III) those functional groups whose chemical reactivity has been found to depend on molecular environment. Similar information is elicited for each succeeding step, with the exception that the functional

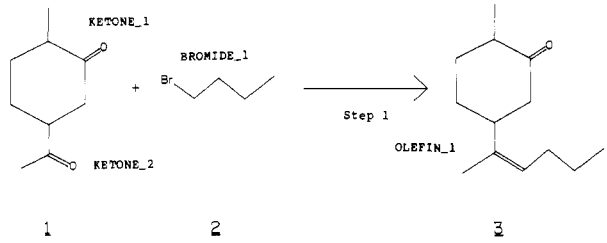



**Figure 3.** The Wittig reaction used for demonstration of the synthetic analysis mode (mode 2) of PROTECT.

group dialog is slightly altered. PROTECT keeps track of which functional groups are changed in a step and which are unchanged by asking the user to describe each new structure as a combination of old and new functional groups. If a functional group is carried over from one structure to another, PROTECT asks whether the subclassification of that group has changed (if the group type is subclassified). For new groups and old ones whose subclassification has changed, the subclassification dialog is conducted as described above. Finally, the user is allowed to designate certain functional groups as "participating" in one or more of the reaction steps. These participating groups are ones which are apparently unchanged but which are actually involved in the chemistry (e.g., the ketone in a 1,4 addition to an unsaturated ketone) and would certainly not need protection. Sample input for the one-step "sequence" in Figure 3 is shown in Figure 4.

After all the chemical information has been input, the chemist answers a few procedural questions and the analysis is performed. The input information may be saved in a disk file for later modifications and subsequent analysis. These modifications are controlled by subroutine PGEDIT, which allows changes to functional group subclassification, changes to "participating" functional groups, changes to reagents, and addition of further steps to the sequence.

PROTECT can display its results on the terminal, store them in a disk file, or both. The format is the same in all cases and consists of a step-by-step summary of the functional groups in each structure in each step, showing

```
$ R PROTECT

    ************************************************************
    * HARVARD PROTECTIVE GROUP INFORMATION RETRIEVAL PROGRAM *
    ************************************************************

        This program has two modes of operation. In the first mode
    the user may retrieve information about the behavior of protective
    groups in a variety of reaction conditions. In the second mode
    the program can assist the chemist in selecting protective groups
    for a sequence of reactions.

    Do you want mode 1 or mode 2? 2
    Do you want to edit a reaction sequence in a file? N
    How many steps are in the reaction sequence? 1

                              ***********
                              * STEP  1 *
                              ***********

    How many structures make up the reactants in step  1? 2

                          **********************
                          * FGs IN STRUCTURE 1 *
                          **********************

    Enter FG numbers ending each with an <ESC>
    Enter 99 to list FGs
    Enter 0  to terminate input

       FG_1   :1$     |  KETONE_1
       FG_2   :1$     |  KETONE_2
       FG_3   :

                     *******************************
                     * REAGENTS FOR STRUCTURE  1   *
                     *******************************

    Enter alternative sets of reagents separated by <CR>s.
       Each set must be a list of reagent numbers separated by commas.
       PROTECT will select the optimum set of reagents for this structure.

    Enter L to see the list of reagents
    Enter <CR> to end reagent input

       Set  1: 45
       Set  2:

                      ****************************
                      * SUBCLASSES FOR KETONE_1 *
                      ****************************

    Enter subclasses separated by commas
    Enter L to see the list of subclasses

    Subclasses: L

              1          Strained, cyclic
              2          Alpha CH2, cyclic, enolizable
              3          Alpha CH, cyclic, enolizable
              4          Alpha CH3 or CH2, acyclic, enolizable
              5          2 Alpha CH, acyclic, enolizable
              6          1 Alpha CH, acyclic, enolizable
              7          Enolizable, alpha W-group assisting
              8          Enolizable, alpha W-group other side
              9          Enolizable, beta C=C or leaving group
             10          Alpha dicarbonyl
             11          Alpha W-group, non-enolizable
             12          Other non-enolizable

    Subclasses: 2

                      ****************************
                      * SUBCLASSES FOR KETONE_2 *
                      ****************************

    Enter subclasses separated by commas
    Enter L to see the list of subclasses

    Subclasses: 4
```

```
                          **********************
                          * FGs IN STRUCTURE 2 *
                          **********************

    Enter FG numbers ending each with an <ESC>
    Enter 0 to terminate input

       FG_1   :46$    |  BROMIDE_1
       FG_2   :

                     *******************************
                     * REAGENTS FOR STRUCTURE  2   *
                     *******************************

    Enter alternative sets of reagents separated by <CR>s.
       Each set must be a list of reagent numbers separated by commas.
       PROTECT will select the optimum set of reagents for this structure.

    Enter L to see the list of reagents
    Enter <CR> to end reagent input

    Set  1: 22,39,45
    Set  2:

                      ****************************
                      * SUBCLASSES FOR BROMIDE_1 *
                      ****************************

    Enter subclasses separated by commas
    Enter L to see the list of subclasses

    Subclasses: L

              1          Vinyl
              2          Aromatic
              3          Tertiary, benzylic, or alpha D-group
              4          Alpha W-group
              5          Allylic
              6          Other

    Subclasses: 6

                          ******************
                          * FINAL STRUCTURE *
                          ******************

    How are Structure  1 functional groups changed in Structure  3?

     Enter U<ESC> for no change
     Enter R<ESC> for removal
     Enter L<ESC> to list FGs
     Enter new FG number(s)<ESC> to change to new FG(s)

       KETONE_1       :U$    |  KETONE_1
       KETONE_2       :51$   |  OLEFIN_1

    How are Structure  2 functional groups changed in Structure  3?

       BROMIDE_1      :R$

    List any other new functional groups (End = 0)

       NEWFG_ :

    Has KETONE_1 subclassification changed from structure  1? N

    Do the following FGs participate in step  1 (Answer Y or N)?

    KETONE_1       :N

    Please enter an identifier for the analysis: WITTIG
    Do you want to save your reaction sequence? Y

                          ******************
                          * OUTPUT OPTIONS *
                          ******************

                F Output to a file
                S Output to screen
                B Output to both screen and a file

    Which option would you like? F
    Saved sequence is in file: WITTIG.DAT
    Results of analysis are in file: WITTIG.TXT
    Do you have another synthesis to analyze? N
$
```

**Figure 4.** Input dialog for protective group analysis of the Wittig reaction in Figure 3. User responses are underlined.

```
**********************************
* PROTECTION ANALYSIS OF WITTIG *
**********************************

           ***********
           * STEP  1 *
           ***********

STRUCTURE  1   CONDITIONS: > Wittig

 FG           Level   Participate? Protect? Subclasses

KETONE_1       High       no          yes         2
KETONE_2       High       yes         no          4

STRUCTURE  2   CONDITIONS: > Ph3P, RLi, Wittig

BROMIDE_1      High       yes         no          6

          ****************************************
          * FUNCTIONAL GROUPS NEEDING PROTECTION *
          ****************************************

KETONE_1
Needs protection in steps   1

Protective groups for KETONE_1 for step  1

ID              PROTECTIVE GROUP                    PAGE NUMBER

 5.1     Dimethyl Acetal/Ketals                        117
 5.5     1,3-Dioxanes                                  122
 5.6     5-Methylene-1,3-dioxanes                      123
 5.8     1,3-Dioxolanes                                124
 5.9     4-Bromomethyl-1,3-dioxolanes                  128
 5.10    4-o-Nitrophenyl-1,3-dioxolanes                128
 5.11    S,S'-Dimethyl Acetal/Ketals                   129
 5.19    1,3-Dithianes                                 133
 5.20    1,3-Dithiolanes                               133
 5.24    1,3-Oxathiolanes                              139
 5.29    N,N-Dimethylhydrazones                        142
 5.33    o-Phenylthiomethyl oximes                     146
 5.43    Bismethylenedioxy derivatives                 150
```

**Figure 5.** Output from PROTECT analysis of the Wittig reaction in Figure 3. Page numbers refer to "Protective Groups in Organic Synthesis".[2a]

their reactivities to the conditions, whether or not they participate in the reaction (either by virtue of being changed in the step or from having been so designated by the chemist), whether or not they need protection if they are not participating, and their subclass(es) (if appropriate). Next, for each functional group needing protection, PROTECT outputs a list of suggested protective groups with page number references to "Protective Groups in Organic Synthesis".[2b] (Sample output corresponding to the example in Figure 3 and the input in Figure 4 is shown in Figure 5.) Protective groups selected from the database are those whose reactivities toward the prototype conditions for a step are lower than the reactivity of the least reactive participating group. For example, the participating groups in the Wittig reaction in Figure 3 (KETONE_2 and BROMIDE_1) both have high reactivity toward their respective reagents, so the protective groups listed for the interfering ketone (KETONE_1) are those whose reactivities toward the Wittig prototype condition are low or medium. It should also be noted that any protective group which might itself act as an interfering reagent toward one or more functional groups contained in the reactant(s) for a particular step (e.g., a sulfur-containing protective group in the presence of a displaceable leaving group) is removed from consideration.

Finally, for multistep sequences, PROTECT attempts to find protective groups which will protect an interfering group over all the steps in which it interferes. If a group needs protection only in steps 1 and 2 of a sequence, the program will simply AND the sets of appropriate protective groups for each step, obtaining a resultant set which it outputs to the chemist. If the group needs protection in steps 1 and 3, PROTECT will look for protective groups capable of withstanding the reaction conditions not only for steps 1 and 3 but also for step 2.

## VI. Evaluation of Functional Group Interference in LHASA

Although the "off-line" version of PROTECT described above is useful as an information source, the primary motivation for writing software to take advantage of the database of protective groups[2b] was to enhance the capabilities of the LHASA program for computer-assisted synthetic analysis.[7] LHASA has for several years been capable of identifying situations in which the reaction conditions for a transformation would also cause changes to nonparticipating groups in the reactant.[4] The program recognizes 64 different types of functional groups[8] and, as mentioned in section III above, subclassifies 18 of these types according to molecular environment in order to better assess their reactivities toward certain reaction conditions. Using the FG/RGNT tables of functional group and functional group subclass vs. reagent reactivities described above, LHASA can assign a low, medium, or high reactivity to any FG–reagent combination.

Specification of reaction conditions to LHASA is carried out by inclusion of CONDITIONS statements in the transform (retroreaction) entries which make up its chemical database. Each of the 138 prototype reaction conditions is assigned to a word, or "specifier", in the CHMTRN chemical English language in which the database is written. For example, the Grignard Addition to Carbonyl transform would include the line CONDITIONS RMgX, where RMgX refers to the 40th of the 138 prototype reagents. In the event that two reacting partners are exposed to different reagents, the conditions can be specified appropriately. For example, conditions for the Wittig transform are CONDITIONS Wittig AND IN FRAGMENT*2 Ph3P AND RLi. LHASA is also equipped to choose from among any number of alternative sets of conditions for a transform and to handle specification of conditions in a particular order. For example, the block of conditions statements in the Oxidative Cleavage of Terminal Methylene transform looks like

```
CONDITIONS OsO4 FOLLOWED BY HIO4
CONDITIONS OsO4 FOLLOWED BY Pb[IV]/25
CONDITIONS Peracid/50 AND pH2:4 FOLLOWED
  BY HIO4
CONDITIONS Peracid/50 AND pH2:4 FOLLOWED
  BY Pb[IV]/25
CONDITIONS Ozone/MINUS*50.
```

Using as input the information on functional groups from the functional group recognition module and the information on reaction conditions from the transform entries in the database, LHASA can choose an optimum set of conditions for a particular transformation. This process is controlled by subroutine EVLFGR (for EVaLuate Functional Group Reactivity). First, the functional groups in the reactant(s) are classified as participating or nonparticipating (a participating group is one which is modified in the reaction, one which contributed positively to the "transform rating" during transform evaluation, e.g., by a CHMTRN line such as ADD 15 IF THERE IS A WITHDRAWING GROUP ON ALPHA TO ATOM*2 OFFPATH, or one which is explicitly designated as participating in the transform entry, e.g., by a CHMTRN line such as DESIGNATE THE KETONE ON ATOM*1 AS PARTICIPATING). Next, the reactivities of the participating groups toward all the reagents in each set of alternative prototype reaction conditions are assessed. A variable MINLEVEL is assigned the lowest of these values for each set of conditions. Next, the reactivities of the nonparticipating groups are assessed for each set of conditions, and any group whose reactivity is equal to or

(7) Long, A. K.; Rubenstein, S. D.; Joncas, L. J. *Chem. Eng. News* **1983**, *61* (19), 22 and references cited therein.

(8) The current method for recognizing functional groups in LHASA is documented in Orf, H. W., Ph.D. Thesis, Harvard University, 1976, Chapter 4. LHASA has recently been modified in collaboration with Prof. A. P. Johnson's group at Leeds University to allow it to recognize an unlimited number of different functional group types.

greater than MINLEVEL is assumed to be interfering. Finally, interferences for each alternative set of conditions are summed, and the set engendering the least interference from the nonparticipating groups is chosen as the "best" set of conditions for the transform. This best set of conditions is displayed to the chemist on the LHASA precursor display[7] under the name of the transform.

LHASA also displays the interfering groups to the chemist by drawing boxes around them on the precursor display. Groups deemed "protectable" are enclosed in solid boxes, while those for which no protective groups exist are displayed with dashed boxes. In addition, LHASA decrements the "transform rating" by a certain amount for each interfering group, using a larger decrement for unprotectable groups than for protectable ones.

## VII. Functional Group Protection in LHASA

Selection of protective groups for interfering functionality in LHASA is handled by program module PGEXEC (for Protective Group EXECutive). PGEXEC and its associated routines are much simpler to use than the offline protective group program PROTECT, since all the information about the reaction sequence, including steps, structures, functional groups, subclassification, participation, and prototype reagents, is already in memory and does not have to be input by the chemist. The process of finding protective groups using LHASA is of course further facilitated by the graphical interface. First, the chemist generates a synthesis tree[7] using LHASA. The tree display now includes a PROTECT button, which may be selected with the graphical input device (magnetic stylus, light pen, mouse, crosshair, etc.). Next, the chemist points to the bottom node, or structure, of the desired retrosynthetic sequence, and PGEXEC performs the analysis for protective groups, writes the results to a file on the disk, and returns control to the tree display. The chemist is then free to choose another sequence for a protective group analysis, to select a node for further retrosynthetic analysis, to return to the sketch pad to draw in another structure, etc.

PGEXEC functions in much the same fashion as PROTECT, described above. When the chemist selects a terminal node from the synthesis tree, a sequence in the synthetic direction is grown to the top of the tree (the original target structure). Next, the reactivities of all the functional groups in each step of the sequence are assessed and stored. Protective groups for all nonparticipating groups which did not contribute positively to the transform rating for a given step are obtained from the PG/RGNT tables, using the criterion that the reactivity of a candidate protective group must be lower than MINLEVEL, the minimum reactivity of the participating groups toward the least reactive of the prototype reaction conditions for the step in question. Next, protective groups which would themselves be reactive toward nonparticipating groups in the reactant(s) for a particular step are eliminated from consideration. (For example, the nucleophilic sulfur of a thiomethyl protective group might be incompatible with a halide in the same molecule.) At this stage, a step-by-step summary of the protective group analysis, identical with the one described above for the PROTECT program, is output. Next, sets of protective groups for functional groups needing protection in more than one step of the sequence are ANDed together in the manner described above for PROTECT, and the results are written to the output file.

## VIII. Sample Protective Group Analysis Using LHASA

A retrosynthetic sequence for the synthesis of brefeldin A (1) is shown in Figure 6. This sequence, generated using LHASA, duplicates as closely as possible the route published in the literature.[9] The two key organometallic condensations (steps 1 and 5), the oxidation in step 6, and the lactonization (step 7) require that protection be arranged for all the hydroxyl groups in the synthesis at one time or another. As mentioned above, LHASA flags these interfering functional groups at the sequence-generation stage by drawing boxes around them when the appropriate retrosynthetic precursors are displayed to the chemist. After the full protective group analysis by PGEXEC, these interfering groups appear in the output (Figure 7) as nonparticipating (Participating? = "no") or as having a reactivity (level) equal to or higher than the least reactive participating group and thus as needing protection (Protect? = "yes"). For example, the step-by-step summary in Figure 7 shows that ALCOHOL_1 needs protection in step 1, that ALCOHOL_1, ALCOHOL_2, and ALCOHOL_3 need protection in step 5, etc.[10] The "FG origin" column in Figure 7 gives the LHASA atom number labels of the carbon origins of each functional group for the convenience of the chemist (see structure 1, Figure 6). It should also be noted that all of the optional sets of prototype reaction conditions extracted from the transform entry in the chemistry database for LHASA are displayed to the chemist in this output. The preferred set, chosen by minimizing the number of nonparticipating interfering functional groups, is marked with a ">".

Protective groups suggested by PGEXEC are shown under "Functional Groups Needing Protection" in Figure 7. The program found all of the protective groups used in the actual synthesis (*tert*-butyldimethylsilyl ether (TBDMS) for ALCOHOL_1, (2-methoxyethoxy)methyl ether (MEM) for ALCOHOL_2, (methylthio)methyl ether (MTM) for ALCOHOL_3, and tetrahydropyranyl ether (THP) for ALCOHOL_4) in addition to a number of others. As is apparent from the case of ALCOHOL_1, the constraint that candidate protective groups be able to withstand the reaction conditions for all the intervening steps between those in which a group is actually interfering severely limits the number of protective groups suggested by the program.

## IX. Conclusion and Future Plans

The PROTECT program and the PGEXEC module in LHASA have been designed as tools to assist the chemist in the analysis of synthetic problems. However, certain crucial decisions must still be made by the chemist, some of them in the planning stages and others during the actual execution of the synthetic plan. As we mentioned in section II above, the process of selecting protective groups is complex. Additional decisions must be made concerning the timing of protection and deprotection steps, the possibility of using a single protective group to protect more than one functional group or even more than one group type, the chance that reordering steps in the original synthetic scheme may eliminate the need for one or more instances of functional group protection, and the possibility of using masked functionality or internal protection to avoid functional group interference problems.

One area in which an expanded database of chemical information might be able to assist the chemist further is

(9) Corey, E. J.; Wollenberg, R. W.; Williams, D. R. *Tetrahedron Lett.* **1977**, 2243 and references cited therein.

(10) The enedione system in structure **2**, shown to need protection toward $NaBH_4$ conditions in step 9 (VINYLW_3 and OLEFIN_3), was not found to be interfering in the actual synthesis. It is possible that the enedione system is not susceptible to reduction in this case because of an inability to achieve a planar conformation in the 13-membered lactone ring.

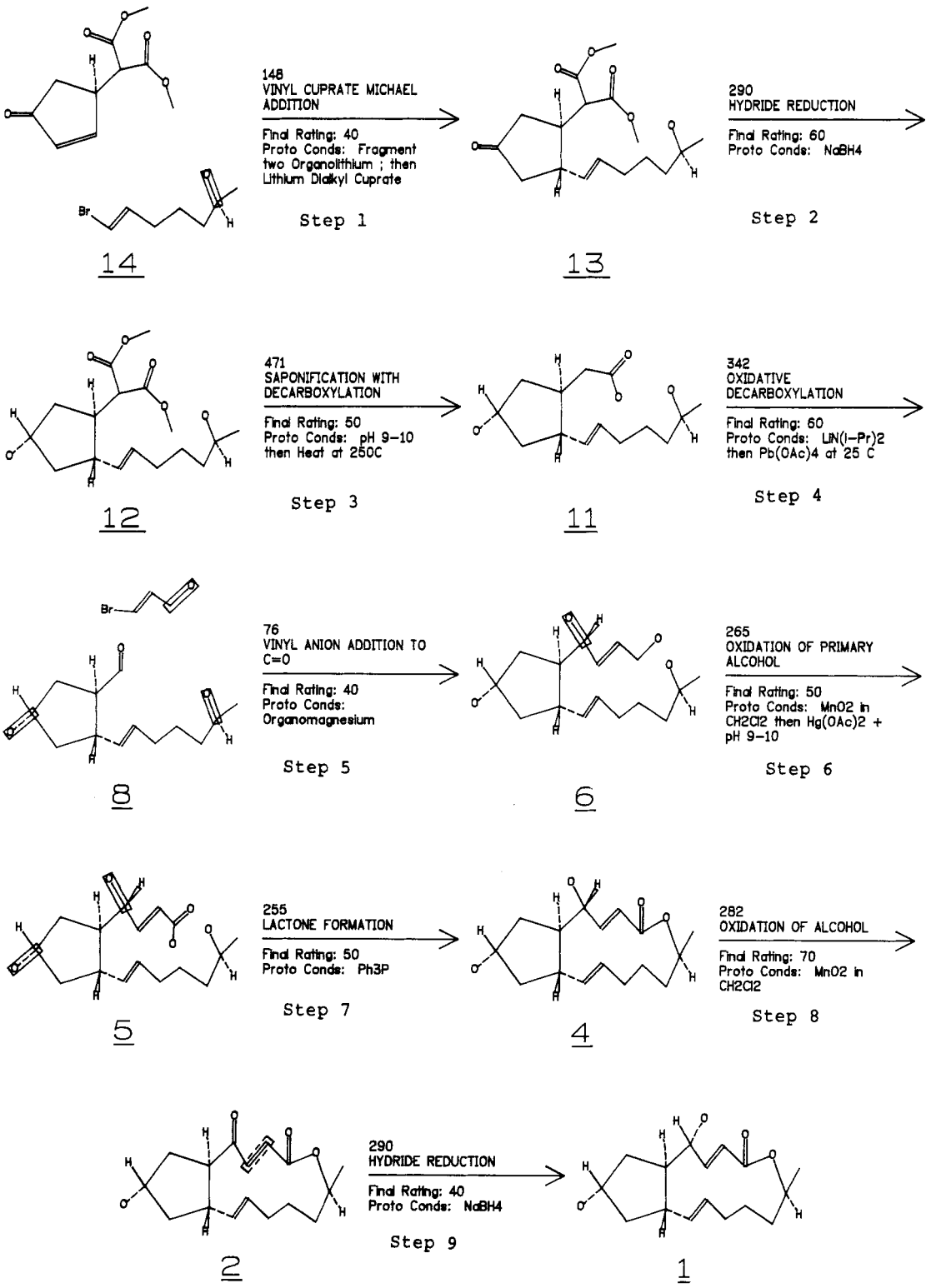
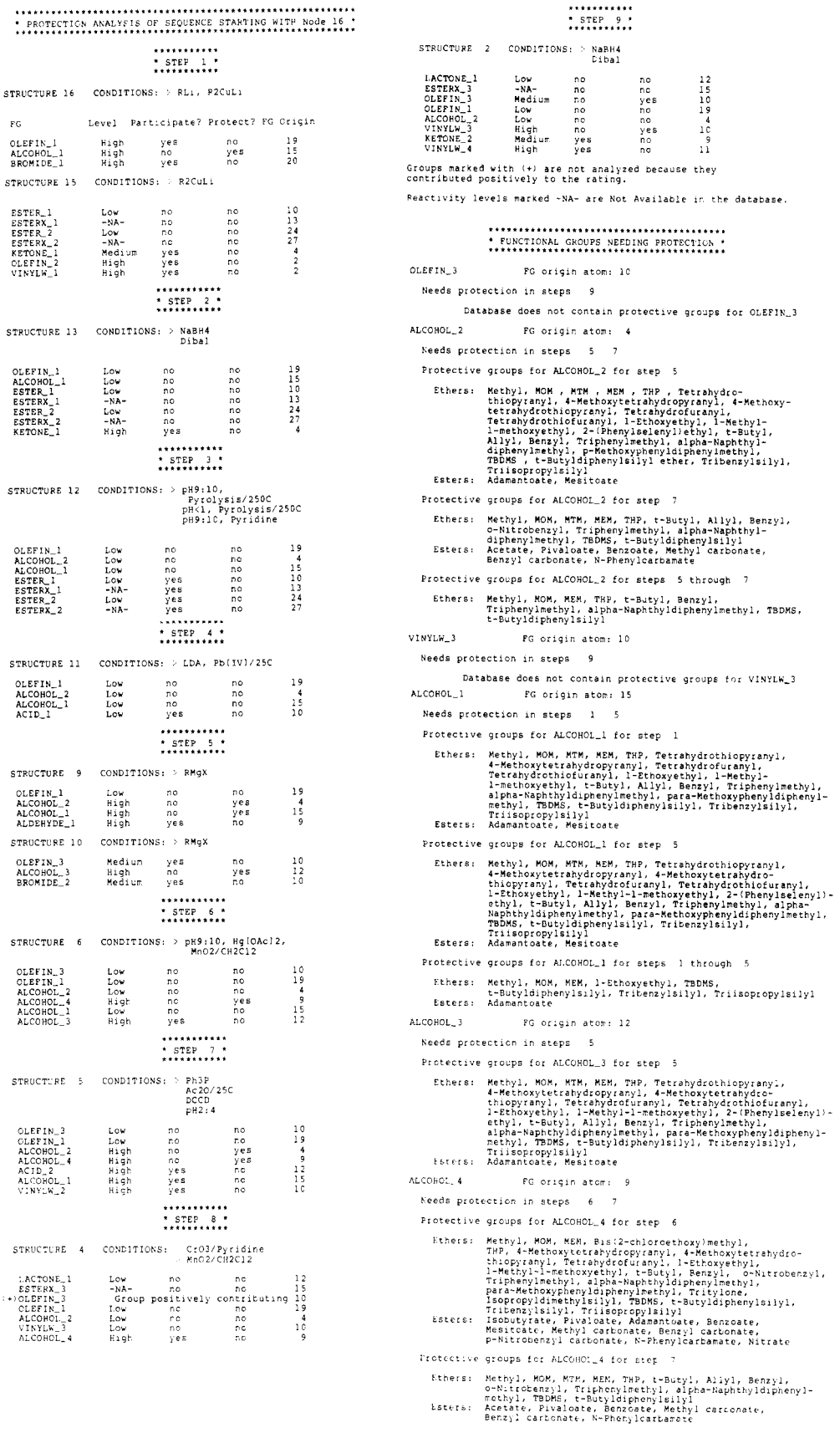



**Figure 6.** Retrosynthetic sequence for brefeldin A. LHASA draws a box around each functional group needing protection. A solid box indicates a group for which protective groups are available. A dashed box indicates that the database does not contain protective groups for that functional group.

that of protection/deprotection. Currently, PROTECT and PGEXEC have no access to information about the reaction conditions necessary to add and remove protective groups. If this information were incorporated into a database, further refinements to the suggested sets of protective groups could readily be made. Certain protective groups might have to be eliminated from consideration because the conditions necessary to add them or remove them were not compatible with other protective groups or unprotected functional groups in the molecule. Unfortunately, the volume of data necessary to encompass the variety of very finely tuned methods for selective removal of protective groups makes the task of assembling a database for this purpose a large one.

Perhaps an easier task would be the assembly of more specialized databases of protective groups for particular classes of compounds. In particular, the science of functional group protection has been taken to quite a high level in the syntheses of polypeptides, oligonucleotides, and sugars. Here again it is possible that a finer reactivity scale



```
**********************************************************
* PROTECTION ANALYSIS OF SEQUENCE STARTING WITH Node 16 *
**********************************************************

                    **********
                    * STEP  1 *
                    **********

STRUCTURE 16   CONDITIONS: > RLi, R2CuLi

 FG             Level  Participate? Protect? FG Origin

 OLEFIN_1       High       yes         no        19
 ALCOHOL_1      High       no          yes       15
 BROMIDE_1      High       yes         no        20

STRUCTURE 15   CONDITIONS: > R2CuLi

 ESTER_1        Low        no          no        10
 ESTERX_1       -NA-       no          no        13
 ESTER_2        Low        no          no        24
 ESTERX_2       -NA-       no          no        27
 KETONE_1       Medium     yes         no         4
 OLEFIN_2       High       yes         no         2
 VINYLW_1       High       yes         no         2

                    **********
                    * STEP  2 *
                    **********

STRUCTURE 13   CONDITIONS: > NaBH4
                             Dibal

 OLEFIN_1       Low        no          no        19
 ALCOHOL_1      Low        no          no        15
 ESTER_1        Low        no          no        10
 ESTERX_1       -NA-       no          no        13
 ESTER_2        Low        no          no        24
 ESTERX_2       -NA-       no          no        27
 KETONE_1       High       yes         no         4

                    **********
                    * STEP  3 *
                    **********

STRUCTURE 12   CONDITIONS: > pH9:10,
                             Pyrolysis/250C
                             pH<1, Pyrolysis/250C
                             pH9:10, Pyridine

 OLEFIN_1       Low        no          no        19
 ALCOHOL_2      Low        no          no         4
 ALCOHOL_1      Low        no          no        15
 ESTER_1        Low        yes         no        10
 ESTERX_1       -NA-       yes         no        13
 ESTER_2        Low        yes         no        24
 ESTERX_2       -NA-       yes         no        27

                    **********
                    * STEP  4 *
                    **********

STRUCTURE 11   CONDITIONS: > LDA, Pb(IV)/25C

 OLEFIN_1       Low        no          no        19
 ALCOHOL_2      Low        no          no         4
 ALCOHOL_1      Low        no          no        15
 ACID_1         Low        yes         no        10

                    **********
                    * STEP  5 *
                    **********

STRUCTURE  9   CONDITIONS: > RMgX

 OLEFIN_1       Low        no          no        19
 ALCOHOL_2      High       no          yes        4
 ALCOHOL_1      High       no          yes       15
 ALDEHYDE_1     High       yes         no         9

STRUCTURE 10   CONDITIONS: > RMgX

 OLEFIN_3       Medium     yes         no        10
 ALCOHOL_3      High       no          yes       12
 BROMIDE_2      Medium     yes         no        10

                    **********
                    * STEP  6 *
                    **********

STRUCTURE  6   CONDITIONS: > pH9:10, Hg[OAc]2,
                             MnO2/CH2Cl2

 OLEFIN_3       Low        no          no        10
 OLEFIN_1       Low        no          no        19
 ALCOHOL_2      Low        no          no         4
 ALCOHOL_4      High       no          yes        9
 ALCOHOL_1      Low        no          no        15
 ALCOHOL_3      High       yes         no        12

                    **********
                    * STEP  7 *
                    **********

STRUCTURE  5   CONDITIONS: > Ph3P
                             Ac2O/25C
                             DCCD
                             pH2:4

 OLEFIN_3       Low        no          no        10
 OLEFIN_1       Low        no          no        19
 ALCOHOL_2      High       no          yes        4
 ALCOHOL_4      High       no          yes        9
 ACID_2         High       yes         no        12
 ALCOHOL_1      High       yes         no        15
 VINYLW_2       High       yes         no        10

                    **********
                    * STEP  8 *
                    **********

STRUCTURE  4   CONDITIONS:   CrO3/Pyridine
                           > MnO2/CH2Cl2

 LACTONE_1      Low        no          no        12
 ESTERX_3       -NA-       no          no        15
(+)OLEFIN_3      Group positively contributing  10
 OLEFIN_1       Low        no          no        19
 ALCOHOL_2      Low        no          no         4
 VINYLW_3       Low        no          no        10
 ALCOHOL_4      High       yes         no         9

                    **********
                    * STEP  9 *
                    **********

STRUCTURE  2   CONDITIONS: > NaBH4
                             Dibal

 LACTONE_1      Low        no          no        12
 ESTERX_3       -NA-       no          no        15
 OLEFIN_3       Medium     no          yes       10
 OLEFIN_1       Low        no          no        19
 ALCOHOL_2      Low        no          no         4
 VINYLW_3       High       no          yes       10
 KETONE_2       Medium     yes         no         9
 VINYLW_4       High       yes         no        11

Groups marked with (+) are not analyzed because they
contributed positively to the rating.

Reactivity levels marked -NA- are Not Available in the database.

                    ****************************************
                    * FUNCTIONAL GROUPS NEEDING PROTECTION *
                    ****************************************

OLEFIN_3          FG origin atom: 10

  Needs protection in steps   9

        Database does not contain protective groups for OLEFIN_3

ALCOHOL_2         FG origin atom:  4

  Needs protection in steps   5   7

  Protective groups for ALCOHOL_2 for step  5

    Ethers:  Methyl, MOM , MTM , MEM , THP , Tetrahydro-
             thiopyranyl, 4-Methoxytetrahydropyranyl, 4-Methoxy-
             tetrahydrothiopyranyl, Tetrahydrofuranyl,
             Tetrahydrothiofuranyl, 1-Ethoxyethyl, 1-Methyl-
             1-methoxyethyl, 2-(Phenylselenyl)ethyl, t-Butyl,
             Allyl, Benzyl, Triphenylmethyl, alpha-Naphthyl-
             diphenylmethyl, p-Methoxyphenyldiphenylmethyl,
             TBDMS , t-Butyldiphenylsilyl ether, Tribenzylsilyl,
             Triisopropylsilyl
    Esters:  Adamantoate, Mesitoate

  Protective groups for ALCOHOL_2 for step  7

    Ethers:  Methyl, MOM, MTM, MEM, THP, t-Butyl, Allyl, Benzyl,
             o-Nitrobenzyl, Triphenylmethyl, alpha-Naphthyl-
             diphenylmethyl, TBDMS, t-Butyldiphenylsilyl
    Esters:  Acetate, Pivaloate, Benzoate, Methyl carbonate,
             Benzyl carbonate, N-Phenylcarbamate

  Protective groups for ALCOHOL_2 for steps  5 through  7

    Ethers:  Methyl, MOM, MEM, THP, t-Butyl, Benzyl,
             Triphenylmethyl, alpha-Naphthyldiphenylmethyl, TBDMS,
             t-Butyldiphenylsilyl

VINYLW_3          FG origin atom: 10

  Needs protection in steps   9

        Database does not contain protective groups for VINYLW_3

ALCOHOL_1         FG origin atom: 15

  Needs protection in steps   1   5

  Protective groups for ALCOHOL_1 for step  1

    Ethers:  Methyl, MOM, MTM, MEM, THP, Tetrahydrothiopyranyl,
             4-Methoxytetrahydropyranyl, Tetrahydrofuranyl,
             Tetrahydrothiofuranyl, 1-Ethoxyethyl, 1-Methyl-
             1-methoxyethyl, t-Butyl, Allyl, Benzyl, Triphenylmethyl,
             alpha-Naphthyldiphenylmethyl, para-Methoxyphenyldiphenyl-
             methyl, TBDMS, t-Butyldiphenylsilyl, Tribenzylsilyl,
             Triisopropylsilyl
    Esters:  Adamantoate, Mesitoate

  Protective groups for ALCOHOL_1 for step  5

    Ethers:  Methyl, MOM, MTM, MEM, THP, Tetrahydrothiopyranyl,
             4-Methoxytetrahydropyranyl, 4-Methoxytetrahydro-
             thiopyranyl, Tetrahydrofuranyl, Tetrahydrothiofuranyl,
             1-Ethoxyethyl, 1-Methyl-1-methoxyethyl, 2-(Phenylselenyl)-
             ethyl, t-Butyl, Allyl, Benzyl, Triphenylmethyl, alpha-
             Naphthyldiphenylmethyl, para-Methoxyphenyldiphenylmethyl,
             TBDMS, t-Butyldiphenylsilyl, Tribenzylsilyl,
             Triisopropylsilyl
    Esters:  Adamantoate, Mesitoate

  Protective groups for ALCOHOL_1 for steps  1 through  5

    Ethers:  Methyl, MOM, MEM, 1-Ethoxyethyl, TBDMS,
             t-Butyldiphenylsilyl, Tribenzylsilyl, Triisopropylsilyl
    Esters:  Adamantoate

ALCOHOL_3         FG origin atom: 12

  Needs protection in steps   5

  Protective groups for ALCOHOL_3 for step  5

    Ethers:  Methyl, MOM, MTM, MEM, THP, Tetrahydrothiopyranyl,
             4-Methoxytetrahydropyranyl, 4-Methoxytetrahydro-
             thiopyranyl, Tetrahydrofuranyl, Tetrahydrothiofuranyl,
             1-Ethoxyethyl, 1-Methyl-1-methoxyethyl, 2-(Phenylselenyl)-
             ethyl, t-Butyl, Allyl, Benzyl, Triphenylmethyl,
             alpha-Naphthyldiphenylmethyl, para-Methoxyphenyldiphenyl-
             methyl, TBDMS, t-Butyldiphenylsilyl, Tribenzylsilyl,
             Triisopropylsilyl
    Esters:  Adamantoate, Mesitoate

ALCOHOL_4         FG origin atom:  9

  Needs protection in steps   6   7

  Protective groups for ALCOHOL_4 for step  6

    Ethers:  Methyl, MOM, MEM, Bis(2-chloroethoxy)methyl,
             THP, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydro-
             thiopyranyl, Tetrahydrofuranyl, 1-Ethoxyethyl,
             1-Methyl-1-methoxyethyl, t-Butyl, Benzyl, o-Nitrobenzyl,
             Triphenylmethyl, alpha-Naphthyldiphenylmethyl,
             para-Methoxyphenyldiphenylmethyl, Tritylone,
             Isopropyldimethylsilyl, TBDMS, t-Butyldiphenylsilyl,
             Tribenzylsilyl, Triisopropylsilyl
    Esters:  Isobutyrate, Pivaloate, Adamantoate, Benzoate,
             Mesitoate, Methyl carbonate, Benzyl carbonate,
             p-Nitrobenzyl carbonate, N-Phenylcarbamate, Nitrate

  Protective groups for ALCOHOL_4 for step  7

    Ethers:  Methyl, MOM, MTM, MEM, THP, t-Butyl, Allyl, Benzyl,
             o-Nitrobenzyl, Triphenylmethyl, alpha-Naphthyldiphenyl-
             methyl, TBDMS, t-Butyldiphenylsilyl
    Esters:  Acetate, Pivaloate, Benzoate, Methyl carbonate,
             Benzyl carbonate, N-Phenylcarbamate
```

**Figure 7.** LHASA protective group analysis for the synthesis of brefeldin A (1) in Figure 6. Structures **15** and **16** are the two fragments making up structure **14** in Figure 6. Similarly, structures **9** and **10** are the fragments in structure **8**. Note that the actual output is in the format shown in Figure 5. The format used here is designed only to save space. MOM = methoxymethyl. MTM = (methylthio)methyl. MEM = (2-methoxyethoxy)methyl. THP = tetrahydropyranyl. TBDMS = *tert*-butyldimethylsilyl.

than the rough high, medium, and low system described above might have to be devised.

Another particularly intriguing area for future research is the design of algorithms for reordering steps in a previously generated synthetic sequence. Minimization of functional group interference is of course only one of a

number of possible motivations for reordering the steps in a synthesis. The rewards of a successful reordering analysis are potentially great, however, in that elimination of pairs of protection/deprotection steps can greatly enhance the overall efficiency and elegance of a synthetic plan.

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# Zinc-Modified Cyanoborohydride as a Selective Reducing Agent

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Zinc-modified cyanoborohydride generated from sodium cyanoborohydride and zinc chloride in a 2:1 molar ratio is found to be a selective and versatile reducing agent. The reagent in diethyl ether reduces aldehydes, ketones, and acid chlorides to the corresponding alcohols but does not reduce acid anhydrides, acids, esters, and tertiary amides. The reagent in methanol is very useful for reduction of enamines, reductive amination of aldehydes and ketones, reductive methylation of amines, and deoxygenation of aldehydes and ketones.

The combination of sodium borohydride with various metal halides has attracted a great deal of attention as selective and versatile reducing agents in the past decade.[1-10] In general, they modify the usual reducing ability of sodium borohydride and often reduce several functional groups which are inert to sodium borohydride alone. For instance, the reductions of acid chlorides to aldehydes,[2] alkenes to saturated hydrocarbons,[3] and alkenes to alcohols[4] can be achieved by use of the combination of sodium borohydride with Cu(I), Co(II), and Sn(IV), respectively, while such conversions can not be achieved with sodium borohydride alone.

Although the reducing properties of the combination of sodium borohydride with metal halides have been intensively investigated, there are relatively few reports in the literature on the use of the combination of sodium cyanoborohydride with metal halides. It has been reported by Hutchins that the combination of sodium cyanoborohydride with Cu(II) and triphenylphosphine,[11] Pd(0),[12] and boron trifluoride etherate[13] are capable of reducing acid chlorides to aldehydes, allylic acetates to alkenes, and epoxides to alcohols in a regio- and stereoselective manner, respectively.

As our continuous efforts toward the development of new hydride reducing agents,[14] we have reported that zinc-modified cyanoborohydride in diethyl ether reduces tertiary, allyl, and benzyl halides but it is inert toward primary alkyl, secondary alkyl, vinyl, and aryl halides.[15] This paper describes general reducing properties of zinc-modified cyanoborohydride in the reduction of selected carbonyl compounds, reduction of enamines, reductive amination of aldehydes and ketones, reductive methylation of amines, and deoxygenation of aldehydes and ketones via the intermediacy of tosylhydrazones.

## Results and Discussion

**Nature and Stability of Zinc-Modified Cyanoborohydride.** Zinc-modified cyanoborohydride utilized in this study was prepared by mixing sodium cyanoborohydride and anhydrous zinc chloride in a 2:1 molar ratio at room temperature in several solvents such as diethyl ether, tetrahydrofuran, and methanol. When a 2:1 molar mixture of sodium cyanoborohydride and zinc chloride in diethyl ether was stirred at room temperature for 1 h, a white slurry appeared at the bottom of the flask. The white slurry contained almost all the active hydroborate species and metal chlorides, while the ether solution did not contain an appreciable amount of the hydroborate species and chloride ion. Iodometric titration revealed that the white slurry contained approximately 90% of the reducing power, while the ether solution contained only 2% of the reducing power, indicating that the present reagent is very slightly soluble in diethyl ether. However, it was found

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