Long-Range Strategies in the LHASA Program: The Quinone Diels−Alder Transform

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The quinone Diels−Alder (QDA) reaction has considerable synthetic power in terms of introducing structural complexity. As a consequence, the corresponding transform is a worthwhile goal in retrosynthetic analysis and therefore has been implemented as a transform-goal, or long-range, strategy in the LHASA program. The implemented strategy allows LHASA to convert any suitable target containing the decalin ring system into a tetrahydronaphthoquinone to which the QDA transform can be directly applied. Illustrative examples of retrosynthetic sequences produced by the long-range transform are given.

INTRODUCTION

The LHASA System. Over the past three decades several computer programs have been developed to assist the chemist designing syntheses of complex organic molecules.[1−3] A major system in this field is the LHASA program.[4−6] The name is an acronym for "Logic and Heuristics Applied to Synthetic Analysis", which succinctly describes the aims and means of the program. LHASA was started as a research project to implement, in a computer program, E. J. Corey's approach to retrosynthetic analysis.[7−10] The program has been under development at Harvard University since the early 1970s and more recently also at Leeds University[11−14] and at the CAOS/CAMM Center.[15,16]

The LHASA system embodies a controlling program, written in FORTRAN and C, and a chemical knowledge base written in a "chemical English" language (CHMTRN). The knowledge base contains a large number of so-called transforms.[17] A transform is a program-type reaction description in which the scope and limitations of the reaction have been expressed in empirical rules written in CHMTRN. The special-purpose language CHMTRN includes many chemical terms as well as the usual programming constructions like block-ifs and subroutines, making it an excellent tool for the input of chemical knowledge.

The user communicates with the program *via* a graphical interface which is used for drawing structures, for selecting options, strategies, and precursors, and for displaying structures, retro-reactions, and the resulting retrosynthetic tree. The program operates in a rigorously retrosynthetic fashion. The user draws in a target structure and then selects a strategy for the retrosynthetic analysis; the program is able to assist the user in making a choice of a strategy. LHASA then searches its knowledge base for goal transforms, i.e., transforms which satisfy the strategy selected. The user can order the program to search deeper, i.e., to extend the search for applicable transforms by using so-called subgoal[18] transforms. Both goal and subgoal transforms are selected automatically by the program. The result is a retrosynthetic tree of alternative pathways, whose depth is dependent on the chosen strategy and the number of subgoal levels. Any precursor generated by the program can be processed again as the next target. Of course, the user may also choose to reprocess the original target using a different strategy. In this way, user and program interactively design a synthetic scheme.

A very useful guidance for retrosynthetic analysis can be provided by the application of a powerfully simplifying transform—corresponding to a reaction effecting a considerable increase in complexity. How is this guidance effected? Each reaction generates a characteristic structural element in the product. This substructure, called the *retron*,[19] must be present in a target to be able to apply the corresponding transform to that target. The retron is said to *key* the transform. When subgoal transforms are involved, not only exact retrons are considered but also so-called *partial retrons*.[9] A partial retron is derived from the exact or *full retron*[9] by a structure generalization. Very often the application of a powerfully simplifying transform is suggested by the presence of a (functionalized) ring of a specific size in the target molecule. Such a ring (e.g., a six-membered carbocycle in the case of the Diels−Alder transform) constitutes the partial retron for that goal transform. This retrosynthetic strategy, the key-reaction-based or transform-goal strategy, is a main strategy in the LHASA program. The desirable goal of such analyses warrants extended sequences of subgoal transforms to be explored and hence the strategy is often also called long-range. Several powerfully simplifying transforms have already been implemented as long-range transforms in the LHASA system, e.g., Diels−Alder,[20] Robinson annulation,[21] halolactonization,[22] and polyene cyclization.[15]

This paper describes a new long-range transform devoted to the quinone Diels−Alder reaction. It should be pointed out here that the authors of this paper did not in fact develop the quinone Diels−Alder long-range transform from scratch. Instead, they adopted an earlier design[23] which had not led to a successful implementation in the LHASA program. The techniques and constructs developed as a result of the earlier design were used at the time for other long-range transforms[21,22] and used again in the present implementation.

The Quinone Diels−Alder Reaction. In (total) synthesis, one of the most useful reactions for introducing structural complexity is the Diels−Alder reaction.[24,25] In this reaction, at least one new ring is formed, together with up to four new stereocenters, often with predictable regio- and stereoselectivity (Figure 1). The functionalized cyclohexene that is formed can easily be elaborated toward more complex structures. Many useful variations of the Diels−Alder

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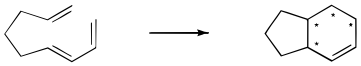

Figure 1. The Diels−Alder reaction.

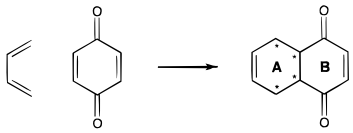

Figure 2. The quinone Diels−Alder reaction.

reaction exist, an important one of which is the quinone Diels−Alder (QDA) reaction (Figure 2). Although the reaction can be applied intramolecularly, the intermolecular version is more common, so generally one ring is formed, together with up to four stereocenters, as with the standard reaction. Diels−Alder reactions with quinones usually show excellent endo-selectivity, and when both the diene and the quinone are unsymmetrically substituted, regioselective cycloaddition is often possible. The high degree of functionalization of the initial adduct adds to the synthetic potential of the QDA reaction. The *cis*-decalin ring system contains at least four functional groups (where one or even both of the olefins can be part of an aromatic ring) which are excellent handholds for the attachment of new groups and side chains, often with good chemo-, regio-, and stereoselectivity. Regioselective elaboration is facilitated by the difference in electron density between the two olefins; often the B-ring ketones can also be discriminated, either because of electronic (with an unsymmetrically substituted B-ring olefin) or steric (by either A-ring, B-ring, or fusion substituents) effects. Stereoselective elaboration is facilitated by the bowl-shape of the *cis*-decalin ring system, which causes a prominent difference in steric accessibility between the two faces of the cycloadduct. It would appear that all these attractive properties make QDA adducts very suitable starting points for the synthesis of a wide variety of target molecules, many of which are highly functionalized. This is indeed the case; a representative selection is shown in Figure 3. A typical example of a total synthesis based on the QDA reaction is shown in Figure 4.

From the foregoing it is clear that a retrosynthetic strategy based on the quinone Diels−Alder transform as a goal transform can be very fruitful, but it is equally clear that such a strategy can at times be extremely difficult to apply. The full QDA retron is, of course, the *cis*-decalin of Figure 2. But what constitutes the partial retron for the QDA transform, the substructure used to *key* the long-range search? Taking into account the synthetic possibilities of the QDA adduct, it would seem that almost any substituted decalin could be made from it, functionalized or not, or even one containing an aromatic ring. Hence a decalin ring system could function as the partial retron. However, even a decalin substructure can be easily mapped onto only a few of the targets in figure 3, and then the possible pathways between target and QDA adduct still have to be identified. A major complication arises when one (or even both) of the rings is cleaved later in the synthesis route; the decalin is then hardly recognizable anymore in the final product. Most of the targets in Figure 3 do not contain the decalin ring system anymore. Of course, this mapping problem has repercussions for the implementation of the QDA goal transform strategy in the LHASA program. Note that in the remainder of this paper the terms "QDA goal transform search" and "QDA transform" (as in the title of this paper) are used interchangeably, although strictly speaking the latter is only the final step of the analysis.

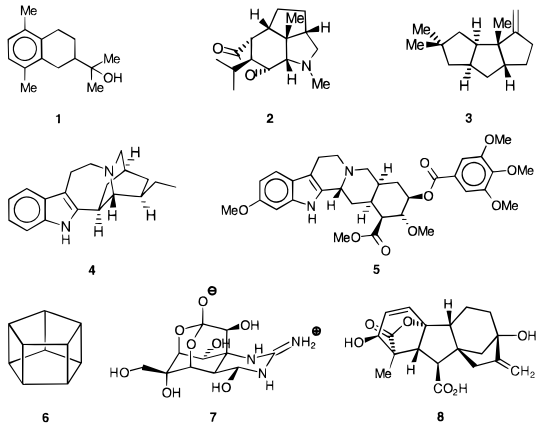

Figure 3. Target molecules whose synthesis has been based on the quinone Diels−Alder reaction: (1) occidol,[25] (2) dendrobine,[26] (3) hirsutene,[27] (4) ibogamine,[28] (5) reserpine,[29,30] (6) pentaprismane,[31] (7) tetrodotoxin,[32−35] and (8) gibberelic acid.[36,37]

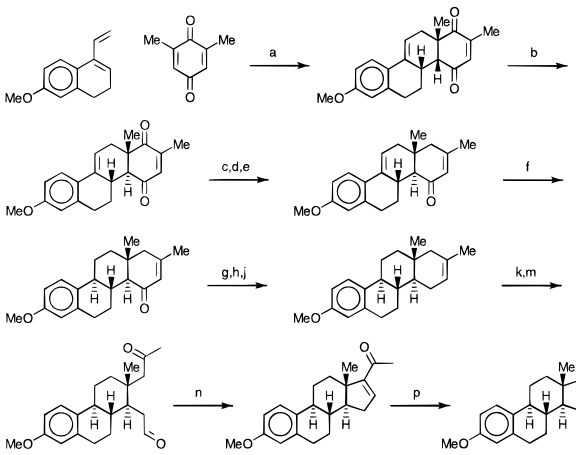

Figure 4. A synthesis of estrone methyl ether based on the quinone Diels−Alder reaction.[38] Reagents used: (a) $BF_3{\cdot}Et_2O$, (b) $NaHCO_3$/MeOH, (c) $LiAl(t\text{-}Bu)_3H$, (d) MsCl, (e) Zn/MeOH, (f) H_2/Pd, (g) Red-Al, (h) AcCl, (j) Li/NH_3/THF, (k) OsO_4/pyridine, (m) $Pb(OAc)_4$/THF, (n) HCl/THF, and (p) NH_2OH.

MAPPING THE QDA RETRON

As outlined in the introduction, recognition of the QDA retron becomes very difficult when the required decalin system is not present in the target molecule. Moreover, other transform-goal searches in the LHASA system[8,15,21,22] operate only on rings whose size correspond to the respective full retrons. In order to stay in line with these implementations, it is prudent to treat the QDA transform in the same way; that is, the partial retron is a carbocyclic bicyclo[4.4.0] ring system, and ring contraction, expansion, or cleavage transforms operating on this ring system are not considered as subgoals. Thus, the purpose of the retrosynthetic package for the QDA transform is to convert, by using subgoal transforms, any suitable decalin-containing target into a precursor containing the full retron for the QDA goal transform, which can then be applied (Figure 5). The goal of the analysis is, therefore, an SS-goal (substructure-goal), the substructure being the full QDA retron.

The QDA retron is depicted in Figure 6 with the atom, bond, ring, and face labeling used in this paper. The ring

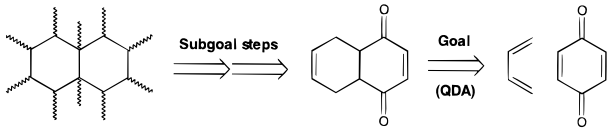

Figure 5. Overall operation of the quinone Diels−Alder package.

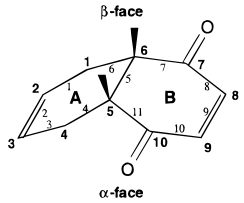

Figure 6. The retron for the quinone Diels−Alder transform with atom, bond, ring, and face labels.

derived from the reactant diene (the one formed by the cycloaddition) is called ring A, and the ring derived from the reactant quinone ring is called ring B. The concave face of the *cis*-decalin is called the α-face, and the convex face (the one initially containing the fusion substituents) is called the *β*-face. The precise structural characteristics of the full QDA retron—the substructure-goal—are the following (atom and bond numbering as in Figure 6):

- A cis-fused decalin, with fusion substituents in the *β*-face.
- sp^3-Hybridized atoms at atoms 1, 4, 5, and 6.
- Ketones at atoms 7 and 10.
- Double or aromatic bonds at bonds 2 and 9.
- No hydrogen-bearing hetero substituents at atoms 1, 2, 3, 4, 5, and 6.
- No donating groups on the decalin fusion (atoms 5 and 6), nor sterically demanding groups.
- The decalin is not bridged, except maybe for a bridge between atoms 1 and 4 in the *β*-face.
- The substituents on the decalin reflect the correct regioselectivity (quinone site and orientation) and stereoselectivity (endo) for the Diels−Alder reaction.

Clearly, the fact that there are so many potential synthetic targets for the QDA transform necessitates a careful design of the retrosynthetic package. A "divide and conquer" method is used. In a first-order approximation, subgoal transforms on ring A are treated independently from those on ring B, while any inter-ring transforms (e.g., haloetherification, halolactonization) and any transforms applied to the fusion substituents are treated as a disturbance on the overall structure of the package. The next issue is the order in which retrosynthetic operations should take place. Looking at the full retron, it should be noted that the functionality on ring B is more reactive than the functionality on ring A. Hence, from a synthetic point of view, reactions on the initial Diels−Alder adduct can best be carried out first on ring B. The ensuing reduction of reactivity will facilitate the subsequent synthetic operations. Therefore, from a retrosynthetic point of view, subgoal transforms should be carried out first on ring A of the target, which will then suffer less from reactive functional groups on ring B. Of course, very reactive functional groups in the target would have been removed first as part of the normal processing by LHASA, so these groups can be considered absent from the target as it is processed by the QDA transform.

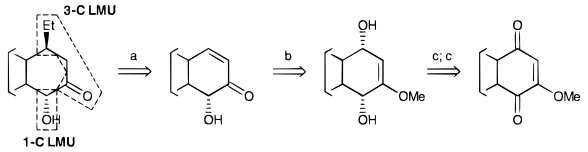

Figure 7. LMU assignments on a target and associated chemistry. Subgoal steps: (a) conjugate organometallic addition, (b) hydrolysis to enone, and (c) ketone reduction to alcohol.

The retrosynthetic analysis is guided by a matching process. A decalin ring system within the target is matched against the QDA retron, which can be done in two ways: either ring of the target decalin can become ring A (and the other one ring B). This corresponds to two different so-called *orientations*. Given one of these orientations, the target structure is mentally divided into three parts: the four nonfusion atoms of ring A (atoms 1−4, coming from the diene), the two fusion atoms (5 and 6), and the four nonfusion atoms of ring B (7−10). The task of matching the decalin against the QDA retron is now reduced to three smaller matching operations. The technique used to perform these matching operations for the A and B rings is identical to the one used in the Robinson Annulation[21] and Halolactonization[22] long-range transforms and is briefly described here again for convenience.

QDA PROCEDURES AND CHEMISTRY SUBROUTINES

Each of the A and B rings (usually without the decalin fusion atoms) is divided further into one or more subunits called *localized matching units* (LMUs).[21] An LMU consists of one to four carbon atoms and corresponds to specific retrosynthetic operations that can be performed at that subunit. The assignment of LMUs to particular substructures within the target is determined (or rather suggested) by functional groups and substitution patterns in the target and can generally be done in several ways. Figure 7 shows two LMU assignments, a one-carbon LMU and a three-carbon LMU, to the four nonfusion B-ring atoms of a target. These assignments constitute a complete LMU assignment for the B-ring part of the QDA retron. As can be seen from the example in Figure 7, an LMU assignment is closely connected to a particular sequence of transforms or sometimes to a number of related sequences. The one-carbon LMU should be convertible to a ketone, and the three-carbon LMU should be convertible to an enone which is subsequently "turned around" by a type of allylic oxygen shift. The subgoal transform sequence corresponding to a complete LMU assignment is called a *procedure*.[21]

For the QDA package, eight different procedures have been devised[40] for each of ring A (Figure 8) and ring B (Figure 9). Note that the first procedure of both lists is symmetrical with respect to the horizontal axis of the retron. The seven remaining procedures can be applied in two ways (top and bottom reversed), so there are actually 15 A-ring and 15 B-ring procedures. The combination of a particular orientation, a particular A-ring procedure, and a particular B-ring procedure is called a *QDA procedure*. The total number of possible QDA procedures is 450 (two orientations × 15 A-ring procedures × 15 B-ring procedures).

Sometimes an A or B procedure involves a fusion atom (see also Figures 8 and 9). But generally speaking, any operations required on the fusion atoms are postponed to a

later stage in the analysis when direct influences on the Diels−Alder regioselectivity is assessed (*vide infra*).

The application of a particular A-ring or B-ring procedure is in effect a "search" for a subgoal sequence or, stated differently, an attempt to perform the required subgoal transforms which constitute that procedure. In all these procedures, several subgoal steps and sequences occur repeatedly, such as olefin introduction, conjugate addition/alkylation, and allylic oxygen shift. For each of these retrosynthetic operations, a separate CHMTRN subroutine was created. Most of these so-called *chemistry subroutines*[21] had already been written for existing long-range transforms,[21,22] for example, GET_CO, GET_DB, GET_ENONE, and CLAISEN.

The following chemistry subroutines are used for steps (a)−(h) in Figures 8 and 9:

a: GET_DB: generates an olefin at a two-carbon LMU. One of the methods tried is the introduction of an epoxide using subroutine GET_EPOXIDE as it is often able to remove appendages.

b: CHECK_DIENE_TERMINAL: generates a type of substitution compatible with the Diels−Alder reaction at a one-carbon LMU which will become the diene terminus. This is a greatly expanded version of the CHECKFG subroutine written for the long-range Diels−Alder transform.[20] If there is a bridge, it must be in the β-face; otherwise at most one substituent is allowed which must be in the α-face. Heteroatom substituents cannot bear hydrogen atoms.

c: ALLYL_REARR: This "allylic rearrangement" is performed at a three-carbon LMU. Three types of substituents can be removed with concomitant shift of the olefin:[21] chloride (by allylic rearrangement with $SOCl_2$), sulfoxide (by 2,3-sigmatropic rearrangement of a sulfenate ester), and a carbonylmethyl appendage (by the Claisen rearrangement). The latter is done by the CLAISEN[41] subroutine.

d: SHIFT_OLEFIN: shifts an olefin to the desired position at bond 2 or bond 9, with concomitant 1,3-transposition or removal of oxygen functionality. Four ways of accomplishing this conversion have been devised. Usually several of these are tried, causing the analysis to branch:

1. A Wharton rearrangement transform (using the WHARTON subroutine) to go from an allylic alcohol back to the transposed enone.
2. A hydrolysis transform to go from an enone back to the transposed β-oxyenol ether.
3. An oxidative selenide elimination transform to go from an allylic alcohol back to an α-hydroxy selenide and thence to an epoxide and finally an olefin. The regioselectivity, originating from diaxial epoxide opening, is checked by applying empirical conformation rules.[42,43]
4. A haloetherification or halolactonization transform to go from an allylic alcohol back to the corresponding olefin using an appropriately placed group (alcohol, acid) on the other ring of the decalin. The intramolecular reaction ensures the regioselectivity of the olefin shift.

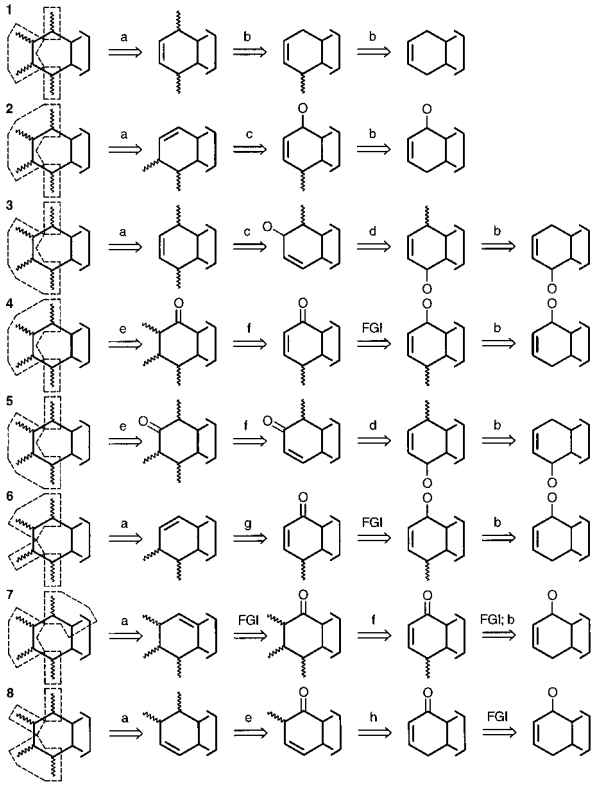

Figure 8. The eight A-ring procedures; boxes indicate LMU assignments. Subgoal steps: (a) olefin introduction, (b) "diene terminus" check, (c) allylic rearrangement, (d) allylic oxygen shift, (e) ketone introduction, (f) conjugate addition and alkylation, (g) conjugate addition and reduction, and (h) deconjugative alkylation.

The latter two methods are used only in the A-ring procedures; they even remove the oxygen functionality (not shown in Figure 8) and thus allow the symmetrization of the diene.

e: GET_CO: generates a ketone at a one-carbon LMU. A selection of the most important methods tried in this subroutine is shown in Figure 10.[21]

f: GET_ENONE: generates an enone at a three-carbon LMU, thereby removing appendages α and β to the ketone using a conjugate addition/alkylation transform. The ketone is introduced first by GET_CO.

g: GET_ENONE: also generates an enone at a three-carbon LMU, but this time using a conjugate addition transform to remove a β-appendage. Viewing the sequence synthetically, the intermediate enolate is not protonated or alkylated but trapped as an inorganic ester which is reduced to an olefin. Retrosynthetically, the olefin is introduced first by GET_DB.

h: DEALKYLATE: removes appendages α to a ketone using an alkylation transform. A deconjugative alkylation is used if there is an olefin on the other side, as in the case of the eighth A-ring procedure.

Examples are given for two of each of the A-ring (Figure 11) and B-ring (Figure 12) procedures. The majority of the B-ring procedures have a counterpart in a similar A-ring procedure. Of course, whereas in an A-ring procedure atoms a and 4 end up as a diene terminus, in a B-ring procedure atoms 7 and 10 should become ketones. A ketone (or enone,

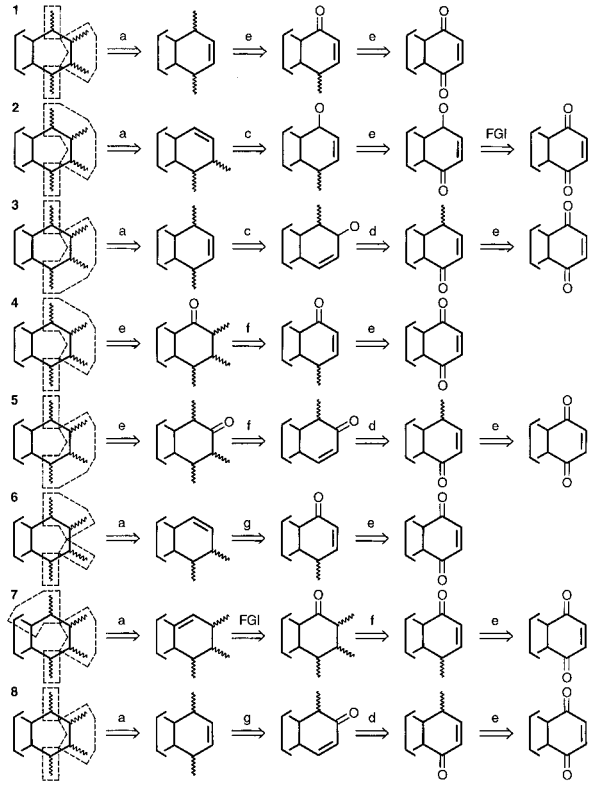

Figure 9. The eight B-ring procedures; boxes indicate LMU assignments. Subgoal steps: (a) olefin introduction, (c) allylic rearrangement, (d) allylic oxygen shift, (e) ketone introduction, (f) conjugate addition and alkylation, and (g) conjugate addition and reduction.

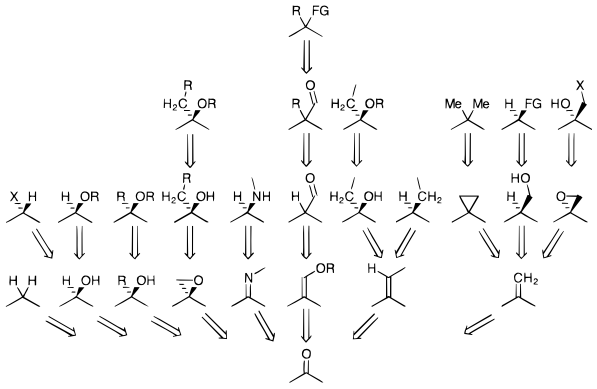

Figure 10. Sample subgoal sequences available to the GET_CO subroutine. R = alkyl or aryl, X = halogen, and FG = any functional group.

as there is an olefin at bond 9) gives a good handhold for synthetic elaboration, or, stated differently, it is fairly easy to steer retrosynthetic sequences in such a way as to end up with a ketone. In fact, several A-ring procedures can be seen to arrive at a ketone or enone at atoms 1 or 4 (see Figure 8), which then has to be removed or converted into a group more suitable as a diene terminus. In the B-ring procedures such sequences are used in a more direct way. Enone transposition, if needed, is also almost trivial (see procedure B5 in Figure 12). Viewing a B-ring procedure in the synthetic sense, the ketones at atoms 7 and 10 may make operations easier, but a few problems may come up as well.

The main problem would probably be that of regioselectivity. It is very difficult to assess the difference in reactivity between the two ketones of the QDA adduct and thence to offer guidelines to the user on how to effect regioselectivity.

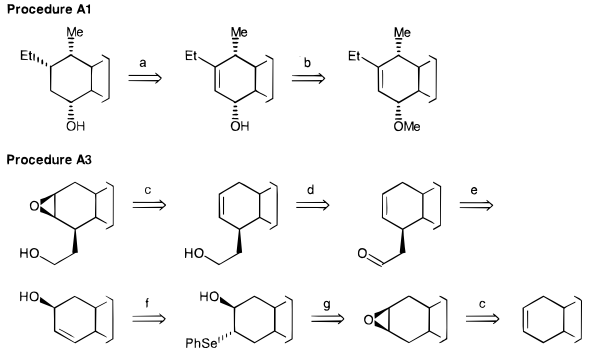

Figure 11. Two examples of A-ring procedure applications. Steps: (a) olefin reduction, (b) ether cleavage, (c) epoxidation, (d) carbonyl reduction to alcohol, (e) Claisen rearrangement, (f) selenide oxidation and elimination, and (g) epoxide opening by selenolate.

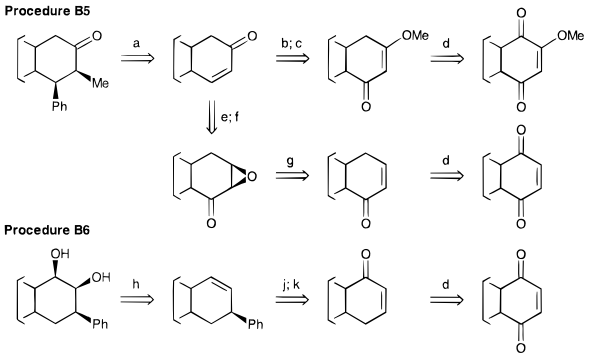

Figure 12. Two examples of B-ring procedure applications. Steps: (a) conjugate organometallic addition and alkylation, (b) hydrolysis to enone, (c) carbonyl reduction to alcohol, (d) ketone reduction, (e) alcohol oxidation, (f) Wharton rearrangement, (g) epoxidation, (h) cis-hydroxylation of olefin, (j) vinyl sulfonate reduction, and (k) conjugate organometallic addition and enolate trapping by sulfonyl halide.

If one ketone is much more reactive than the other, then selective transformation would be expected to be possible, or selective protection if the other ketone should react. This is a likely situation when the olefin at bond 9 has one ether substituent.[37] In other cases, subtle differences in the steric environment may be exploited;[29,34,44] remarkably, the sterically least hindered carbonyl is not always the more reactive one.[45] Because the information available is somewhat inconclusive and selectivity seems to be achievable in the majority of cases anyway, no attempt is made to assess the regioselectivity. The nonreacting carbonyl will usually be designated as "protected" by the program.

PRIOR PROCEDURE EVALUATION

The decalin that the long-range transform is operating on can have almost any substitution pattern. Thus, at the outset it is by no means obvious which subgoal transforms would be most appropriate. As not all procedures will be equally effective for a given target, an *a priori* assessment of their suitability is necessary in order to avoid lines of analysis leading to lengthy and cumbersome sequences. Without this assessment, LHASA would try all 450 QDA procedures. The method used to preselect the most promising QDA procedures is termed *Prior Procedure Evaluation* (PPE).

The PPE for the QDA package is adapted from those for the Robinson annulation[21] and Halolactonization[22] long-range transforms. Each procedure is a combination of a number of LMU assignments. The evaluation is done by examining

Table 1. Rating Calculation and Ordering of QDA Procedures[a]

A-Ring and B-Ring Procedure Ratings

orientation		1	2		1	2
	A1	5	100	B1	100	100
	A2	7	8	B2	7	8
	A3	3	2	B3	1	4

QDA Procedure Ratings

orientation	A proc.	B proc.	rating
1	A1	B2	12
1	A1	B3	6
1	A2	B2	14
1	A2	B3	8
1	A3	B2	10
1	A3	B3	4
2	A2	B2	16
2	A2	B3	12
2	A3	B2	10
2	A3	B3	6

QDA Procedures Grouped by Orientation/A Procedure

orientation	A proc.	B proc.	rating
1	A3	B3	4
1	A3	B2	10
1	A1	B3	6
1	A1	B2	12
2	A3	B3	6
2	A3	B2	10
1	A2	B3	8
1	A2	B2	14
2	A2	B3	12
2	A2	B2	16

[a] In this example, only three A-ring and three B-ring procedures are used.

those LMUs in turn and assessing how well the intended chemistry can be performed. "Performing chemistry" is nothing else than executing one or more chemistry subroutines; hence the *procedure rating* is expressed as a sum of *subroutine ratings*. Procedure and subroutine ratings are roughly equal to the number of synthetic steps required to introduce the desired functionality and then to execute the procedure/subroutine. A lower number (i.e., a shorter sequence) means a "higher" rating.

A Scheme such as in Figure 10 is used as a guideline to determine how far a given substitution pattern at an LMU is removed from the desired functionality. A "higher" level in Figure 10 represents a larger chemical distance to the carbonyl group. Depending on the substitution pattern in the target, the operation at a particular LMU is classified as "there", "easy", "moderate", "difficult", or "impossible", corresponding to a rating of 0, 1, 3, 5, or 100, respectively. This rating is more or less the expected number of steps. The subroutine ratings are then added to give a procedure rating. For a given target, the ratings for the A-ring and B-ring procedures are calculated for both orientations. Next, these ratings are combined to give overall QDA procedure ratings, as illustrated in the example of Table 1. Only the QDA procedures with a total rating of less than 100 are listed, as the other combinations are certain to fail. Only the best 15 QDA procedures will be attempted. For efficiency reasons, these 15 QDA procedures are subsequently reordered into groups which have the same orientation and A-ring procedure. The analysis for the different B-ring procedures can then be resumed from a common intermediate structure.

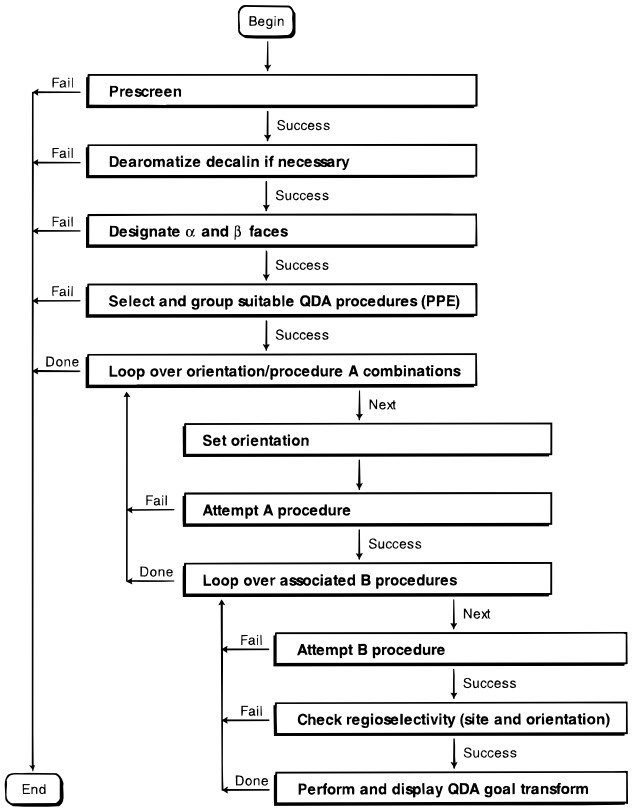

Figure 13. The QDA flowchart.

OVERALL OPERATION OF THE QDA PACKAGE

The overall operation of the QDA long-range search is depicted schematically as a flowchart in Figure 13. Several of the stages in the analysis have been already mentioned; hence most attention will be given here to the remaining issues.

The QDA analysis starts, as in most long-range transforms, with a definition of the partial retron and the way in which it can be "reoriented". Here, of course, the retron is a carbocyclic bicyclo[4.4.0] ring system and a reorientation can be done by exchanging the A-ring and B-ring assignments of the decalin system. The next step is a prescreen to exclude unsuitable targets. Several checks are performed here for features which would make the final QDA transform impossible, infeasible, or too cumbersome and which are not removed by the present subgoal capabilities. Such features include unsuitably placed fused, bridged, and/or aromatic rings, or an olefinic or unsuitably substituted decalin fusion. Aromatic targets are allowed, though. Since no separate procedures have been devised to handle aromatic targets, a dearomatization transform is attempted before anything else, e.g., a double acetate elimination.[46] The nonaromatic precursor can then be processed using the existing procedures.

If the target passes the prescreen and the dearomatization step, the α- and β-faces must be designated, i.e., it has to be determined which faces of the molecule should become the α- and β-faces. The faces are important to assess the diastereoselectivity of various transforms operating on the decalin and to steer the substituents at the diene termini into the α-face. The face designation is based on the substitution of the decalin fusion, but a decision problem occurs when the fusion is trans and unsubstituted. In that case the substitution pattern on the rest of the decalin is taken into consideration. Substituents can often end up on the α-face

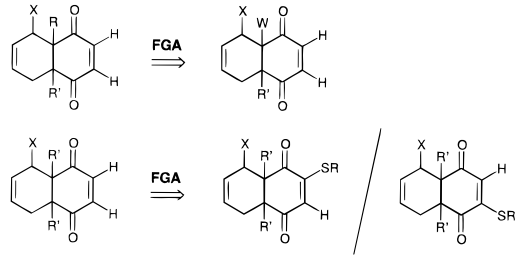

Figure 14. Correction of the site selectivity by FGA transforms. R = alkyl, R′ = H or alkyl, W = electron-withdrawing group, and X = any substituent (to indicate the orientational preference of the diene).

by reduction of an exocyclic double bond (olefin or carbonyl); this holds for both carbon and hetero substituents. On the other hand, carbon substituents are also often introduced by addition reactions, and these are likely to take place on the β-face. Hence hetero substituents are primarily used to choose the face designations when the fusion substitution does not provide a guideline.

The Prior Procedure Evaluation selects the QDA procedures to be attempted, as outlined in the preceding section. The QDA procedures are executed in two nested loops. The outer one loops over QDA procedures with a common orientation and A-ring procedure, the inner one over the B-ring procedures associated with a particular orientation/A-ring procedure. If an A-ring procedure fails, or if there are no more B-ring procedures, the next orientation/A-ring procedure is attempted. When a B-ring procedure has been successfully executed, the QDA goal transform can be performed, and the whole sequence is displayed to the user. The actual number of sequences generated can in fact be larger than the number of successful QDA procedures, because additional branching may occur in both the A-ring and B-ring procedures, e.g., in the SHIFT_OLEFIN subroutine discussed earlier.

THE QDA GOAL STEP—REGIOSELECTIVITY

One issue has not been discussed yet, i.e., the regioselectivity of the Diels−Alder reaction. Because the reaction involves a quinone, there are actually two types of regioselectivity. Firstly, the quinone has two dienophilic sites, giving rise to the issue of *site selectivity*. Secondly, as with all Diels−Alder reactions, the dienophile can add in two different ways to the diene (disregarding stereochemistry), producing *orientation selectivity* problems.

Site selectivity is assessed by considering the electronic and steric properties of the substituents on atoms 5, 6, 8, and 9 (see Figure 6). A simple numerical evaluation is applied, based on Hammett σ^+ [47,48] and Taft E_s [49,50] values. Hammett σ^+ values are used rather than σ values to express the marked effect of strongly electron-donating groups. The site-directing effect is expressed as $400 \times \sigma^+ + 100 \times E_s$ for each substituent, and these values are added for each dienophilic site. If the values of the two sites differ by more than 60 in favor of the 5,6-site, the site selectivity is considered to be satisfactory. Otherwise, subgoal transforms are attempted in order to improve the site selectivity. Two methods are tried, as shown in Figure 14. The electron density at the 5,6-site can be lowered by introducing an electron-withdrawing group at the fusion. Care is taken not to disturb the orientation selectivity (indicated schematically by introducing the group "ortho" to the directing group on the diene). Alternatively, the electron density at the 8,9-site can be increased by using a desulfurization transform.[51,52] Here the influence on the orientation selectivity is less severe and might operate either way (*vide infra*), so the sulfide can be introduced at either atom of the site. If the site selectivity cannot be corrected, the sequence will be abandoned.

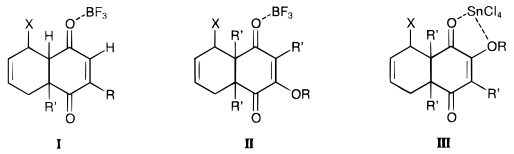

Figure 15. Correction of the orientation selectivity by Lewis acid catalysis. R = alkyl, R′ = H or alkyl, and X = any substituent (to indicate the orientational preference of the diene).

Orientation selectivity is treated in a similar way. However, here are some more substituents to be examined than with the site selectivity assessment. Interestingly enough, the influence of substituents with respect to orientation selectivity cannot be directly related to their electron-withdrawing or -donating properties.[53] The effect of substituents on the A ring is such that substituents on the diene (atoms 1, 2, 3, and 4) tend to end up "ortho" or "para" to a substituent on the fusion (atom 5 or 6).[54−56] A rough measure is used here to describe the directing effect of a group, e.g., hydrogen = 0, alkyl = 2, acetoxy = 3, sulfide = 4, and ester = 5. Note that all numbers are positive, simply reflecting the fact that no group on either diene or dienophile is known to exhibit a marked "meta"-directing effect. The substituent effect is larger with the positions next to the broken bonds (atoms 1, 4, 5, and 6).[53] For the directing effect of the more remote positions (atoms 2, 3, 8, and 9) a weighting factor of 0.25 is used in the calculation. The orientation selectivity is expressed as $(4 \times (E_1 - E_4) + E_3 - E_2) \times (4 \times (E_5 - E_6) + E_8 - E_9)$, where E_n is the directing effect of a substituent on atom n.

If the orientation selectivity is incorrect or insufficient, the effect of Lewis acid catalysis is examined. A Lewis acid catalyst such as boron trifluoride is known to reverse the orientation selectivity,[39,45,57−59] as with structures I and II in Figure 15. BF_3 is supposed to interact with the more basic and/or less sterically hindered carbonyl. On the other hand, tin tetrachloride has a different effect with quinones containing an ether group (structure III in Figure 15). The anomalous behavior of $SnCl_4$ has been attributed to a chelating effect,[60] although this explanation has been criticized.[59] Nonetheless, the effect of $SnCl_4$ is too useful to be ignored. LHASA will suggest an appropriate Lewis acid for the substitution patterns of Figure 15, and in other cases it will warn the user about a problem with the orientation selectivity.

THE QDA GOAL STEP—OTHER ISSUES

Two special situations may occur with the final step of the QDA analysis: A withdrawing group on the quinone and an *o*-xylylene-type structure as the diene.

Quinones with a withdrawing group may given somewhat less satisfactory results because of their high reactivity; they are better generated *in situ* by oxidation of the corresponding hydroquinone using silver oxide or manganese dioxide.[61−63] LHASA will show the hydroquinone precursor with an appropriate comment.

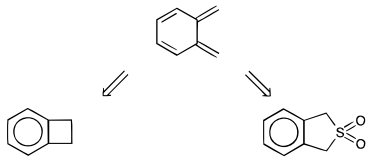

Figure 16. Retrosynthetic generation of stable precursors from *o*-xylylene-type dienes.

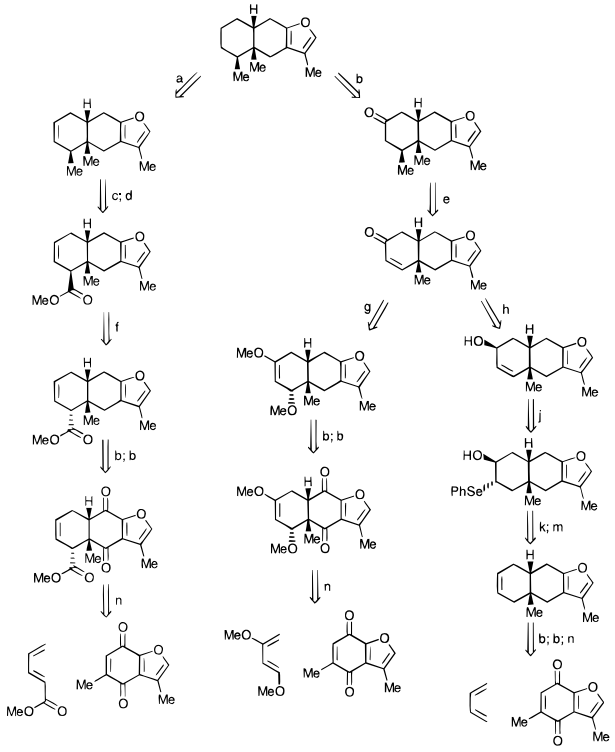

Figure 17. Sample retrosynthetic sequences from the quinone Diels−Alder analysis of a furanoeremophilane. Steps: (a) olefin reduction, (b) ketone reduction, (c) alcohol reduction, (d) ester reduction to primary alcohol, (e) conjugate organometallic addition, (f) epimerization, (g) hydrolysis to enone, (h) alcohol oxidation, (j) selenide oxidation and elimination, (k) epoxide opening by selenolate, (m) epoxidation, and (n) quinone Diels−Alder.

When bond 2 in the QDA adduct is aromatic, meaning that an aromatic ring is fused to the A ring, LHASA threatens to generate a diene with an *o*-xylylene-type structure. This is not a problem when the A ring is bridged by a lactone or another aromatic ring. In the first case, the precursor would have a benzopyranone-type structure which has been used as a diene;[64] in the second, the precursor would be an anthracene-type diene. In other cases, the intermediate is shown together with its generation from stable precursors. As with other Diels−Alder transforms in LHASA, two methods are used to generate the *o*-xylylene (Figure 16): (1) electrocyclic ring opening of a benzocyclobutene[65] and (2) extrusion of sulfur dioxide from a dihydroisobenzothiophene-dioxide.[66]

SAMPLE QDA ANALYSES

Three analyses are presented to demonstrate the capabilities and limitations of the QDA transform.

The first target is the furanoeremophilane of Figure 17. This compound (and similar ones) has been made using the QDA reaction.[67] The QDA analysis produced 21 sequences ranging in length from six to ten steps. In 13 of these sequences the ring fused to the furan ends up as the A ring, meaning that a furanobenzocyclobutene is used as the *in situ* source of the diene. In the remaining eight sequences, the other orientation is used, resulting in a furanobenzoquinone precursor. Three of the latter sequences are shown in Figure 17. The main problem with this target is the methyl group in the β-face of the A ring. Two solutions are offered: epimerization and disconnection. The epimerization (first sequence) requires an electron-withdrawing group, which is introduced on the side chain itself by an FGA transform. It should be noted that LHASA does not evaluate the epimerization step; this would require energy calculations which are presently not within the scope of an interactive program. A user interested in this sequence would have to assess this issue himself. Also, there is a serious risk that the olefin would shift into conjugation with the ester during the epimerization. This is actually no problem here, as the olefin reduction can easily be carried out in an earlier stage of the synthesis, for instance directly after the cycloaddition. The rest of the sequence is straightforward. The regioselectivity of the Diels−Alder addition is the expected one.[54] The second and third sequences both begin with an FGA transform to introduce a ketone and then a conjugate addition transform to disconnect the methyl group. The resulting enone is 1,3-transposed in two ways: a hydrolysis transform to a β-oxy enol ether and a sequence via an oxidative selenide elimination and epoxidation. The latter method allows the generation of a symmetrical diene precursor. The sequence is somewhat longer than the other two, however.

The method used by Bohlmann[67] to remove the methyl group was a ketone FGA on the α-position ("atom 3") to allow epimerization and alkylation transforms to operate. LHASA's failure to find this sequence can be attributed to a preference for removing side chains using conjugate additions rather than alkylations. In fact, alkylations are not explicitly taken into consideration in the procedures. The absence of strategies based on alkylation methodology is clearly a shortcoming, which can be overcome by adding alkylation methods to the existing procedures or by adding new procedures aimed at alkylations. Otherwise, the sequences that have been generated are quite satisfactory.

The second target is calaenene (Figure 18). Common to all sequences that were generated is the dearomatization step. A double acetate elimination is used, which allows the aromatic ring to be treated as either the A ring or the B ring. The first sequence exploits the relative stereochemistry of the alkyl substituents, which do not require further manipulation. The other sequences use the left-hand ring as the A ring, which does not need any modification at all. The methods applied are all based on conjugate addition to remove one alkyl group, and Wittig olefination followed by hydrogenation to remove the other one. The stereochemistry of the conjugate addition is apparently not assessed by the GET_ENONE subroutine. The alkyl group is much more likely to end up on the β-face, so all the sequences are stereochemically flawed in this respect. However, reordering the steps might improve the situation somewhat. For example, if in the synthesis the aromatization step is done earlier, the facial bias of the cis-decalin has disappeared, and only the relative stereochemistry of the alkyl groups has to be addressed.

All sequences have a major weak point at the very end: the orientation selectivity of the cycloadditions can be expected to be very poor, resulting in 1:1 mixtures of

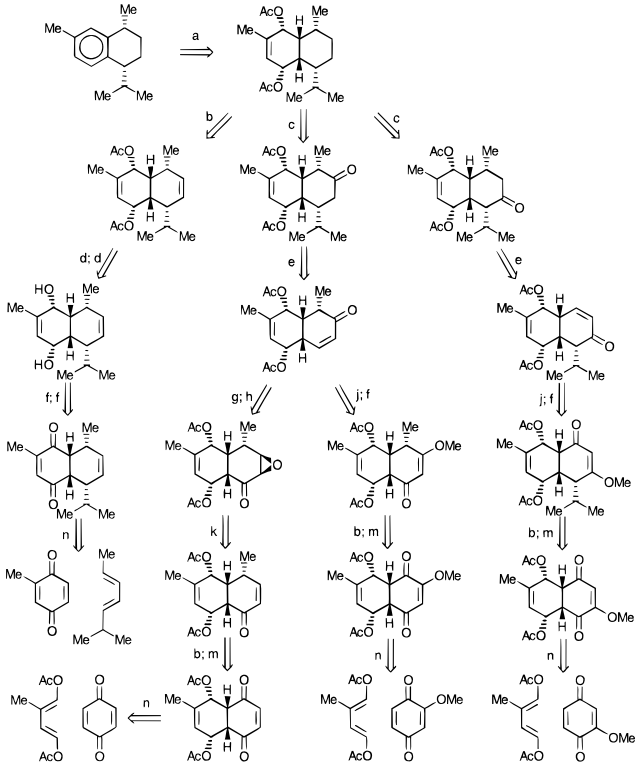

Figure 18. Sample retrosynthetic sequences from the quinone Diels−Alder analysis of calaenene. Steps: (a) aromatization by double elimination, (b) olefin reduction, (c) ketone reduction, (d) esterification, (e) conjugate organometallic addition, (f) carbonyl reduction to alcohol, (g) alcohol oxidation, (h) Wharton rearrangement, (j) hydrolysis to enone, (k) epoxidation, (m) Wittig olefination, and (n) quinone Diels−Alder.

regioisomeric cycloadducts. Only the second sequence has no regioselectivity problems, since it uses a symmetrical quinone. But there the problem is shifted to the regioselectivity of the Wittig reaction. Which carbonyl will react first, or can one perhaps be selectively protected? The influence of the remote methyl group seems to be too insignificant.

Summarizing, the QDA analysis of calaenene leaves something to be desired. One cause for the regioselectivity problems is the limited methodology for dearomatization transforms presently implemented. Other methods (e.g., carbon dioxide cycloelimination) might offer more opportunity for regiochemical bias in the diene.

The third and last sample target is forskolin (Figure 19). LHASA notices a masked olefin in the target, and a cis-glycolization transform can be applied to uncover it. The olefinic precursor is the actual target to which the QDA strategy is applied. Just one sequence is generated, which is shown in Figure 19. In the orientation chosen the A ring is the left-hand ring. The GET_CO subroutine removes the dimethyl group using steps (d)−(f). Obviously, the cyclopropane reduction can hardly be carried out at this stage, but an alternative could be provided by direct *gem*-dimethylation of the ketone. The ketone is subsequently taken back to an ether. Discrimination between the two ethers on the A ring can conceivably be achieved by internal protection, using the nearby ketone. The difference in steric accessibility of the two ethers is also quite large. The B ring requires some more work. The first step is a Wharton rearrangement, which also disconnects the pyranone ring (step (h)). This ether disconnection is done more or less implicitly by the Wharton transform; no stereoselectivity is

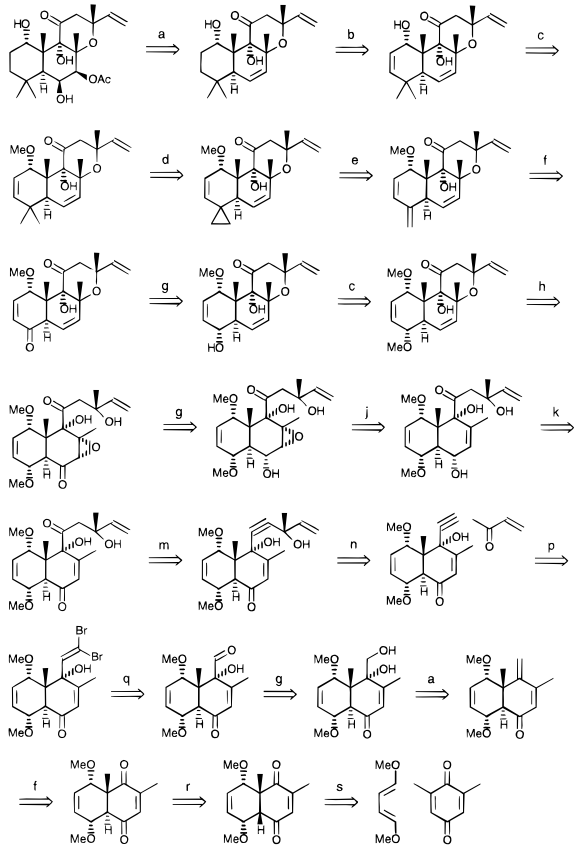

Figure 19. Sample retrosynthetic sequence from the quinone Diels−Alder analysis of forskolin. Steps: (a) cis-hydroxylation of olefin, (b) olefin reduction, (c) ether cleavage, (d) cyclopropane reduction, (e) cyclopropanation, (f) Wittig olefination, (g) alcohol oxidation, (h) Wharton rearrangement, (j) epoxidation, (k) carbonyl reduction to alcohol, (m) acetylene hydration, (n) acetylide addition to carbonyl, (p) reductive elimination to acetylene, (q) Wittig using CBr_4, (r) epimerization, and (s) quinone Diels−Alder.

assumed. The introduction of the second carbonyl (from step (m) onwards) is done by the GET_CO subroutine. The route is somewhat roundabout, because the intermediate GET_CO is aiming at is the α-hydroxy aldehyde; it applies a sequence of FGI transforms to get there. A shorter route is immediately obvious from the scheme: each of the acetylenes (the reactant and product of step (n)) could be made directly from the QDA adduct. Fortunately, there is a marked difference in steric accessibility between the two carbonyl groups. Also the regioselectivity of the cycloaddition is no problem as both reactants are symmetrical.

Interestingly, a total synthesis of forskolin based on the QDA reaction has in fact been considered in the literature, albeit using the other orientation.[63]

CONCLUSION

The development and implementation of the QDA package has resulted in a transform-based strategy which allows LHASA to generate retrosynthetic sequences of more than 20 steps in its search for the goal transform application. Although syntheses comprising tens of steps are not uncommon in the laboratory, it is quite unusual for a computer program to be able to produce such long sequences without any user interference. Moreover, usually 10−20 alternative routes are produced, giving the user ample opportunity to ponder over the synthetic possibilities of his target molecule offered by the QDA reaction alone.

The capabilities of the QDA package are quite impressive due to the various procedures that have been devised. An alternative subgoal mechanism would be an automatic one based on 2-D patterns;[68] while this mechanism would offer a much more general method to search for subgoal transforms, it is presently insufficient to generate subgoal sequences of a similar length. However, the technique of devising procedures is not the ultimate solution to the subgoal-search problem in a long-range transform either. The procedures form only a selection of all the possible chemistry that can be done, and often has been done, on the QDA adduct. The eternal trade-off between power and generality forces choices to be made. This can again be seen with the most recent addition to the QDA package, the capability to process aromatic targets (naphthalenes and tetralins). At present only a few methods to dearomatize the target are implemented; but the many methods available to obtain aromatic products from a wide variety of QDA adducts would result in a whole group of new substructure-goals to be considered. It is at this point that the limitation of the procedure-based approach is felt. If more targets were to be eligible for the QDA long-range transform, including targets in which one ring of the decalin has been cleaved, a better approach would probably be to devise a "decalin feeder" transform to convert a target to a nonaromatic decalin precursor. The decalin feeder would be a "super subgoal" transform dedicated to the QDA long-range transform and perhaps some of the other long-range transforms as well.

ACKNOWLEDGMENT

Use of the services and facilities of the Dutch CAOS/CAMM Center, under Grant No. SON 326-052, is gratefully acknowledged.

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