1

PROBLEM ANALYSIS IN ORGANIC REACTION MECHANISM

1.1 OVERVIEW

Uncertain questions, in general, need to be recognized as true problems from the very beginning. This is not trivial considering that a given chemical reaction can be explained readily (not a problem, just an exercise in spite of a few unknowns), whereas another may not have any solution in sight (a true problem).

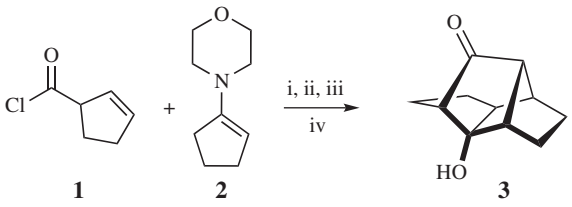
Problems are there for learning, not for troubling. One misses most of their instructive value and fun by rushing through them without first analyzing the real chemistry behind the scene. Pondering options, examining routes of action, taking decisions, and drawing a successful plan constitute a most rewarding and enjoyable experience: a game with complex rules.

This is what problem analysis (PA) is all about. This chapter focuses on the basic steps that will extract the most of each mechanistic riddle with the aid of a number of embedded mechanistic problems for you to try and then compare your solution with the one provided here. In so doing, you will begin your training as a problem solver in organic reaction mechanism from the first pages.

1.2 INTRODUCTION

Perhaps the *educated guess* to postulate a reaction mechanism is the most popular procedure among dilettante problem solvers. Starting materials and reagents are

The Art of Problem Solving in Organic Chemistry, Second Edition. Miguel E. Alonso-Amelot.



1 **2** **3**

i: Et_3N, then H_3O^+
ii: AcCl, pyridine
iii: UV (254 nm), cyclohexane
iv: KOH, dioxane, H_2O

SCHEME I.1 Adapted from Reference 1. Copyright © 1978 American Chemical Society, by permission.

treated using familiar reactions to approach products. This task usually turns into a stop-and-go stepwise protocol toward the goal. Frequently enough, however, neither starting materials nor reagents look familiar enough and progress comes to a frustrating standstill.

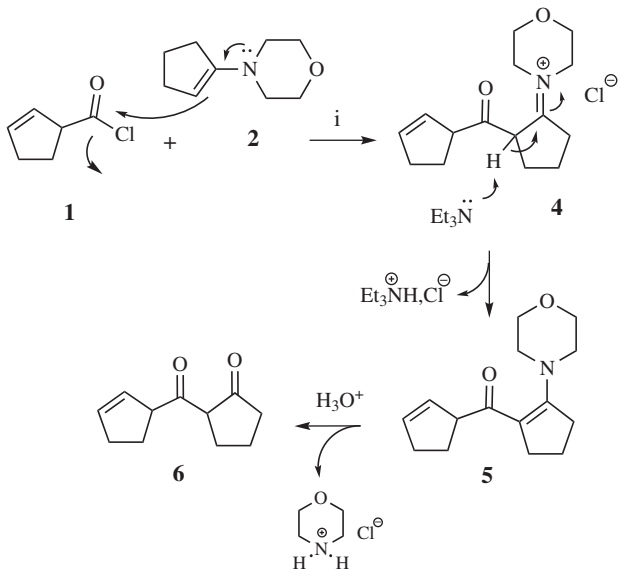
As this is a workbook, let us put to test the previous assertion with a working example. Take the reaction of Scheme I.1, extracted from a now classical transformation [1] and try to propose a reasonable mechanism. Do not be discouraged if you cannot.

This set of reagents does not involve fancy components, extravagant catalysts, or extreme reaction conditions. A good strategy at the onset is to focus your attention on the molecular hot spots: the highly active functions. Then, work your way through, supported by the chemistry you presently know. After producing an answer, compare your reactions with the *belabored* (on purpose) solution described below. It may look a bit lengthy, but keep in mind the point we want to make here: the awkwardness of this honest, exhaustive, stop-and-go educated guess approach. So please be patient if you want to learn and enjoy.

1.2.1 "Pushing Forward" a Solution in Formal and Exhaustive Terms

We shall resort to *educated guesses* in strict abidance to the rules of organic mechanism and *thoroughness* to leave no loose ends. This is not the best recommendation to proceed but good enough for what we want to demonstrate: Paying too much attention to detail is unproductive, pathway branching, and confusing.

A fast look at Scheme I.1 reveals that compound **3** appears to have many more carbon atoms than **1** or **2** taken individually, whereas the morpholine segment has disappeared. Also there are lots of new C–C connections in **3**, suggesting that bonding the starting materials is a good idea. Additional C–C bonds may be built from there as needed.



SCHEME I.2

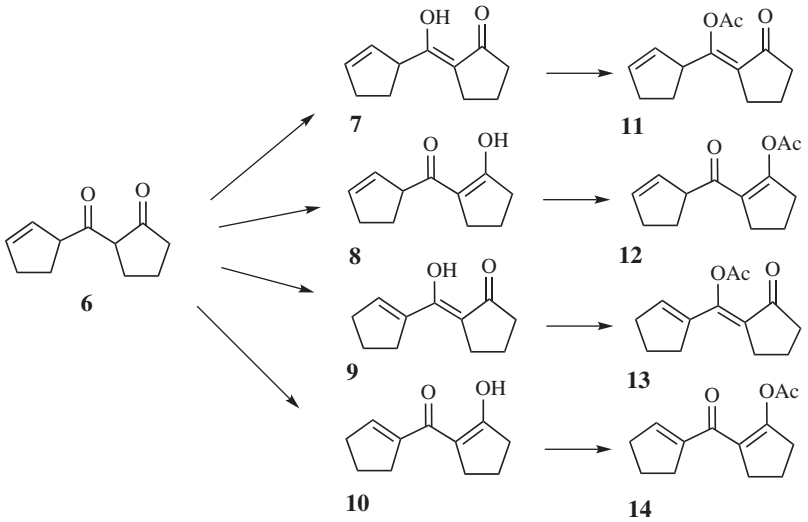
To that end, one makes use of the electronically active carbons in the starting materials: Cl–C=O in **1** and the enamine in **2**, a familiar electrophile–nucleophile combination. Expectedly, β-diketone **6** is spawn effortlessly via **5** after aqueous acid workup (Scheme I.2). Triethylamine mops up the HCl produced (leaving it alone would have blocked the enamine as the pH decreased).

Take note that there are as many carbon and oxygen atoms in **6** as in target compound **3**, so no additional moles of **1** or **2** are required. The rest of the sequence seems accessible enough, requiring only a few connections and disconnections here and there in **6.**

Well, let us see if this is so simple: Please go back to Scheme I.1 and observe the reaction conditions of Step ii. Clearly, this is a standard acetylation. Or is it really? There is no OH in sight to acylate, but one can create this OH easily by enolization of **6**. There are two firsthand enols **7** and **8** that, after acylation, will furnish enol acetates **11** and **12**. In fact, enol acetates **13** and **14** are also conceivable by C=C isomerization to the thermodynamically more stable conjugated acetates. Now we have four reaction products to submit to the next step. Our educated guess has led us to an irritating ramification of the reaction scheme (Scheme I.3).

Worse comes to worst: At this point one cannot conjecture a priori which is the most likely enol acetate, except for the stability of the conjugated systems. Hence, more educated suppositions are in order and all potential intermediates need to be considered in the next step.

Step iii: Activation comes from UV light of a high pressure Hg lamp (254 nm). Usually, this entails [2 + 2] coupling of C=C bonds located at accessible distances to



SCHEME I.3

give a cyclobutane derivative after photoexcitation of the C=C–C=O unit (denoted *). Woodward–Hoffmann rules dictate that only the suprafacial–suprafacial approach of the two π bonds would be allowed for a concerted reaction. But none of dienes **11–14** can attain this conformation (try your own Dreiding models or visit Suppl I # 1 in http://tapsoc.yolasite.com/), acquiring chiefly the supra-antarafacial configuration. This argument would have serious consequences for the stereochemistry of the resulting cyclobutanes, but not in our present case.

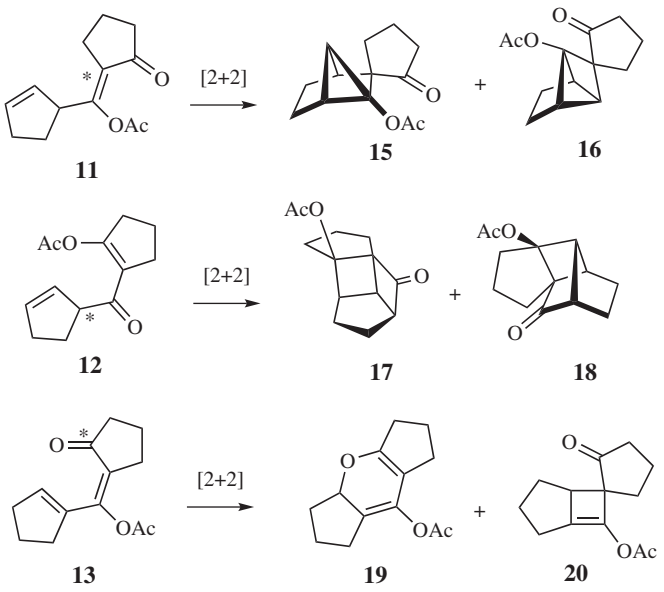
Two C–C bonds are formed in the [2 + 2] photocycloaddition, taking us closer (but we do not yet know how) to target **3**. We are driven to this blind conclusion by the increase in scaffold complexity. Rewriting enol acetates **11–14** to better observe the photoexcited $\pi-\pi^*$ interactions, one may postulate not one but *two intramolecular* [2 + 2] *cycloaddition products for each diene* (Scheme I.4). This means that our brainchild has tragically branched out into *eight* different compounds (**15–22)**, while product **3** is still as elusive as ever (none of them resembles it).

Things are getting a bit out of hand, so some clean up is due. One may discard a priori some of the photo adducts of Scheme I.4 on the basis of two criteria without resorting to Procrustean methods[1]:

(a) Resemblance to product **3** backbone, if any, and

(b) Structural incongruence.

[1] *Procrustes, a barbaric bandit in Greek mythology, forced his victims to fit the length of his bed by either stretching savagely their bodies with ropes if too short or amputating their limbs if too tall. So, to place an argument on the bed of Procrustes is adapting it to circumstance through arm twisting or irrational means.*



SCHEME I.4

(a) *Resemblance*: By comparing the [2.2.1] bicyclic portion of **3** with photo products **15–20**, (with some concession to additional rearrangements still to come), structures **19** and **20** may be put aside momentarily to be retaken only if exploitation of the rest does not furnish the target.

(b) *Incongruence*: While there are limits to scaffold construction of carbon [0.0.x.y . . .](multi)cyclic structures, organic synthesis has been able to produce incredibly strained compounds [2]. Therefore, it is not that simple to filter off apparently implausible structures. Besides, reaction conditions are mild (0°C) and strained compounds may survive.

In terms of intuitive (*eye-assessed*) relative probability of occurrence based on the *anticipated* relative ΔH of each compound, I would propose the following order: **18** > **15** > **17** > **16**. Do you have a different opinion? Table I.1 may help to dissipate any

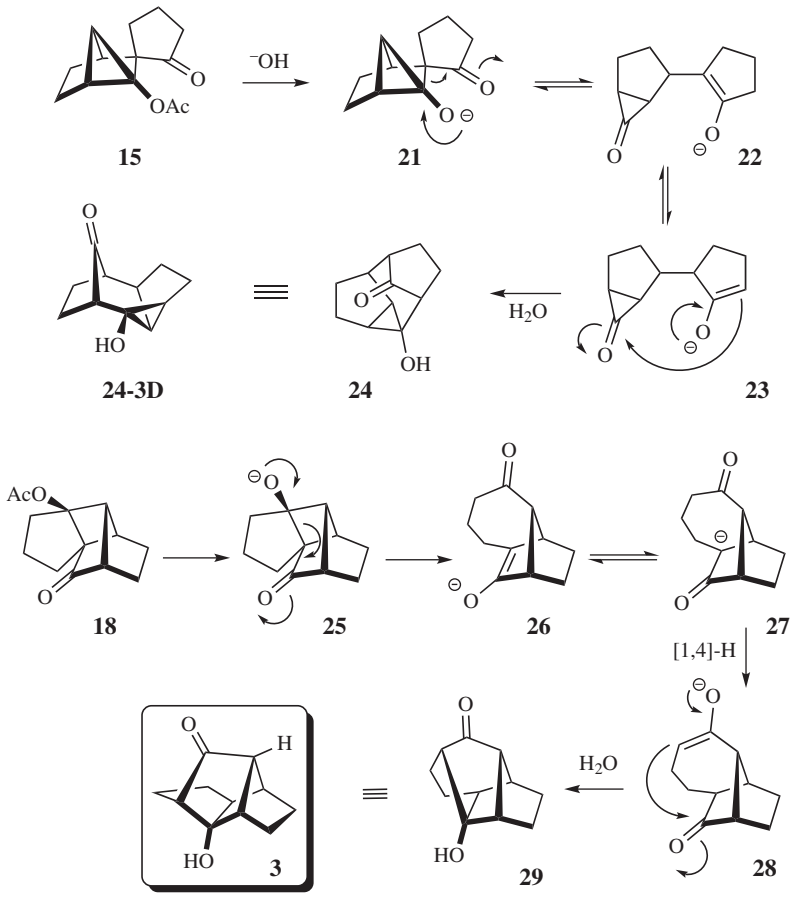
TABLE I.1 Total Strain Energy (kcal/mol) Relative to Cubane of Photo Adducts 15–18 **of Scheme I.4 (Calculated by Molecular Mechanics Methods (ChemBioDraw (CambridgeSoft) MM2 Interface)**

Compound #	*E* (kcal/mol)
15	−109.3
16	−54.5
17	−42.5
18	−49.6

handweaving controversy by revealing, after some molecular mechanics calculations, that my prediction was completely wrong. Was yours too? Mind that the more negative strain energy values imply a more stable compound. The order of stability suggested by molecular mechanics, hence the probability of the dominant photolysis, is now **15** > **16** > **18** > **17**. This order holds if we assume product-like transition states, as cyclization to such strained scaffolds are endothermic.

Although one should not take blindfolded the dictates of molecular mechanics calculations, the strain energy difference of compound **15** relative to the rest is so large that not considering it first for the next reaction would be an unpardonable gaffe. Regrettably though, basic hydrolysis and retro-aldol bond breakage followed by the reverse reaction on odd cyclopropenone **22** leads to a carbon scaffold (**24**) unrelated to target **3**. (Scheme I.5).

Acetate **17** would be next in line for scrutiny. In light of the previous discussion, it is clear that the other enolate would also give a bicyclo-cyclopropane far removed from



SCHEME I.5

3. Neither would **16** (try to convince yourself of this). All our hopes are seemingly pinned on compound **18**. Scheme I.5 describes the retro-aldol disconnection and reconnection applied to it.

At the end of the day we finally succeeded with this last minute basket, and yet it is not possible to clearly justify the chain of events leading to **18** as the most favorable conduit. It is of reassuring interest that this reaction can be stopped at the stage of diketone **27** by replacing acetate with benzyl ether, which is then removed by hydrogenolysis after UV irradiation [1]. While allowing the retro-aldol condensation, the neutral medium prevents further enolate recoupling (**27** → **29**).

1.2.2 Lessons from this Example

Although we were able to come up with an acceptable solution after treading through so many possibilities and letting our sketch reach almost unmanageable proportions, there is this residual sense of unwise application of our chemical knowledge. Exhaustiveness is not necessarily a formula for success in mechanism design and many other endeavors of professional life. Albert Einstein was once quoted as saying: "*Any intelligent fool can make things bigger, more complex, and more violent. It takes a touch of genius and a lot of courage to move in the opposite direction.*"

I dare say that you are among those who wish to move in this "opposite direction." But you will never walk this road by *pushing forward starting materials towards products without previous analysis of the problem and drawing a clever plan from it to* ***select*** *sound options and discard others*, no matter if you are well intentioned and supported by sound chemistry. As will be shown in Chapter 3, working the other way around (understanding the product rather than starting materials) may be much more creative, practical, and productive.

1.3 AVOIDING THE QUAGMIRE

A much more constructive and effective approach to reaction mechanism develops if, before throwing ourselves to scribble structures and curly arrows to convert starting materials into products, we take time first *to focus our attention on precise issues* regarding associations between all compounds, starting materials, products, and reagents in an organized way. This is so obvious, you might say, but not many people do this.

This planning begins with PA. An introductory review of PA as applied to organic chemistry reactions is the subject of the rest of this chapter. Subsequent chapters will deal with specific techniques in the search of valid solutions.

PA may be focused in many ways as the abundance of references dealing with this topic leads one to believe. In essence:

> *Problem analysis is an exercise in asking the right questions to clear the way toward the right solutions (notice the plural here).*

This assertion is probably too simplistic, but it is a good launching pad as we allow this idea to grow from this uncomplicated start. Problem solutions generally emerge *after* pondering options stemming from meticulous questioning and analysis.

1.4 THE BASIC STEPS OF PROBLEM ANALYSIS

There are three steps that may be applied not only to organic chemistry problems but to almost any situation requiring PA.

1. Recognize whether the reaction (or issue) under scrutiny is a true problem.
2. Analyze the problem by asking the right questions, discarding the irrelevant.
3. Drawing a first sketch for guidance in developing the definite answer.

These steps are now described in detail with more embedded problems for you to work out as you read.

1.4.1 Recognizing the Problem

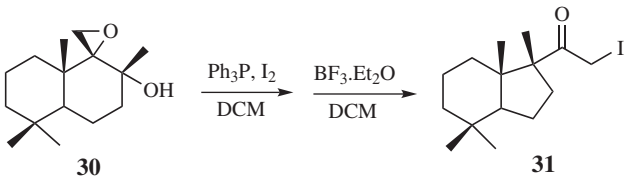
What is a problem is our first question. This is not as dumb as it sounds because many students, no matter how advanced, confuse exercises with genuine problems. A key question solves this doubt: *After a first bird's eye view, do I recognize a feasible solution right away?* If the answer is yes, then the problem does not exist; the reaction is just an exercise. A problem-example illustrates this point.

Suppose you are faced with the reaction of Scheme I.6, which I extracted from a recent synthesis sequence of (+)−austrodoral, a natural sesquiterpene [3]. We shall treat this reaction along the elementary lines described above.

Queries at the onset, once you have a superficial evaluation:

(a) Is this *really* a problem?
(b) Is it worth the effort solving it?
(c) Will I learn anything by devising and testing a mechanism?

Answers will vary depending on each one's background and attitude. Scheme I.6 may constitute a challenging problem with lots to learn from for sophomore



30 **31**

SCHEME I.6

undergraduates but quite accessible for a hardened veteran of the graduate school, who may recognize familiar signs for a likely solution.

The implication is clear: The magnitude of the problem depends on the observer: his/her knowledge store, readiness to use it, and a shed of audacity. Try your wits now and then carry on with our PA below.

Our solution through PA The knowledgeable reader may have examined the reaction in the following argument string.

(a) *Which is the main reaction here*? Ring contraction of a carbinol while a ketone ends up in the side chain of product **31.** This has the flavor of a pinacol-type rearrangement.

(b) If (a) is correct, a carbenium ion is in order as pinacol rearrangements are generally preceded by a C^+ or equivalent next to a *sec*- or *tert*-carbinol like the C–OH in **30**.

(c) Where to find this C^+? Epoxide and *tert*-carbinol in **30** are perfectly positioned for this once we bring powerful Lewis acid ($BF_3.Et_2O$) on the scene.

(d) But what do we make of the triphenylphosphine–iodine mixture? Having no other source of iodine, it should be responsible somehow for the α-iodoketone in **31**.

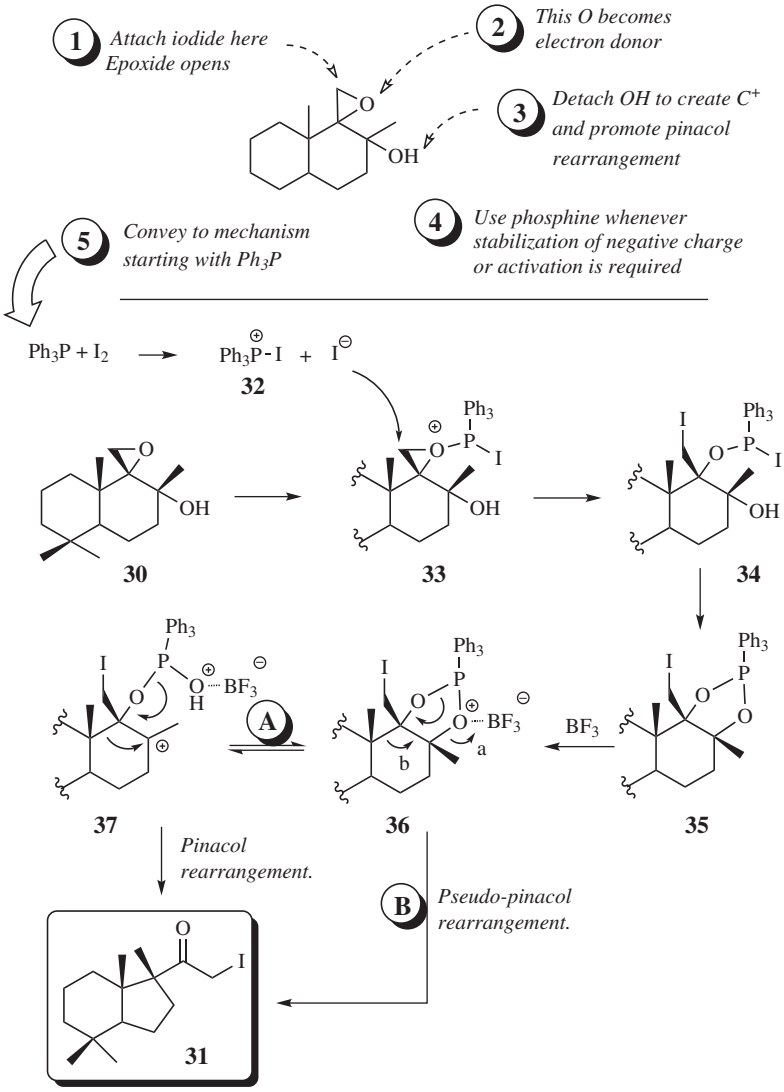
(e) A literature search tells us that, among other applications, triphenylphosphine–iodine is useful for the mild elimination of *tert*-alcohols to give the thermodynamic alkene, but here . . . it would stop any pinacol rearrangement on its tracks if this ever occurred on tertiary alcohol in **30**. Road blocked here.

(f) One needs to operate first with Ph_3P and I_2 on the epoxide in a different manner and then see where to go from there, pursuing to create the desired C^+ for the pinacol rearrangement. From this first analysis a working sketch can be devised at this stage (Scheme I.7, top).

Based on this first plan, a reasonable sequence may be put together beginning with active iodide as nucleophile. At **36** the sequence splits. While path **A** follows the classical pinacol rearrangement through a full carbenium ion, route **B** entails a concerted redeployment of valence electrons reminiscent of the Wittig reaction. The latter would be more akin with the observed *cis*- dimethyl arrangement in product **31.**

The mechanism is solved and ceases to be a problem for those of you who thought it was indeed problematic. For other more advanced individuals it may not have been really a problem, just a moderately demanding exercise.

Now, compare this relatively accessible sequence with the **38** → **39** transmogrification (Scheme I.8, top). Because the answer is not immediately apparent, this reaction looks as if we have a veritable problem here. The overwhelming effect of complex product **39** may discourage more than one reader although it is simpler to solve than it seems (see Problem 28 for a feasible solution).

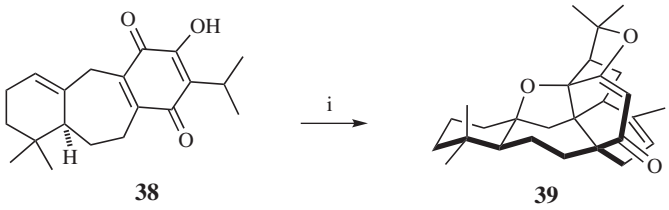


SCHEME I.7

Therefore it may be safe to contend that *a problem is any situation requiring a solution not in sight after a first appraisal*.

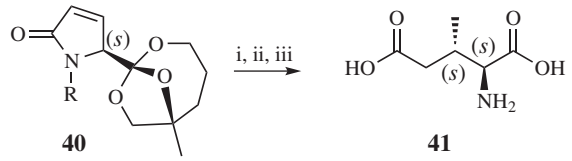
Corollary: *Any situation with a detectable, accessible, and correct solution is not a problem, but an exercise in cognitive management*.

Dull jobs have a lot to do with this corollary; creative ones deal with fresh and authentic, lively problems all the time.



38 **39**

i: $BF_3.Et_2O$; E-α-ocimene; 0ºC (1.5 h) to 50ºC (10 h), CH_2Cl_2



40 **41**

R = boc = 

i: MeLi, THF; ii: 6N HCl; iii: EtOH

SCHEME I.8

1.4.2 Analyzing Problems by Asking the Right Questions, Discarding the Irrelevant

The number of irrelevant questions asked in group discussions is astonishing. One must be clear about what is a right question that will open the way rather than drive attention away with immaterial prattle. Take, for example, **40** → **41** (Scheme I.8, bottom), a simple one to analyze for someone reasonably familiar with alkylation and hydrolysis [4]. Now, compare the two following sets of questions and ponder their relevance to constructive solutions. These were construed randomly on purpose and stem from a real-life group discussion.

1. Is it run under argon?
2. Is it useful for my thesis?
3. Does the product retain functional groups of the starting material unchanged?
4. Which ones?
5. Does this reaction have a name? And the source journal... Does it come from a Max Plank Institute lab or a university in Thailand? (no offense)
6. Does it produce toxic fumes?
7. Does stereochemistry matter?
8. Why didn't they use dioxane instead of THF?

Let us cut it short momentarily to weigh their impact on our specific aim: proposing a reasonable mechanism.

Irrelevant questions: 1, 2, 5, and 8, as they do not lend support to clarify the problem. As far as question 5, many nonmainstream universities produce excellent research. Question 6 is also beside the point if you do not plan to run this reaction on your bench or recommend it to someone else. However, it may contain useful mechanistic information only if you knew which toxic substance was being evolved for element balance and so forth.

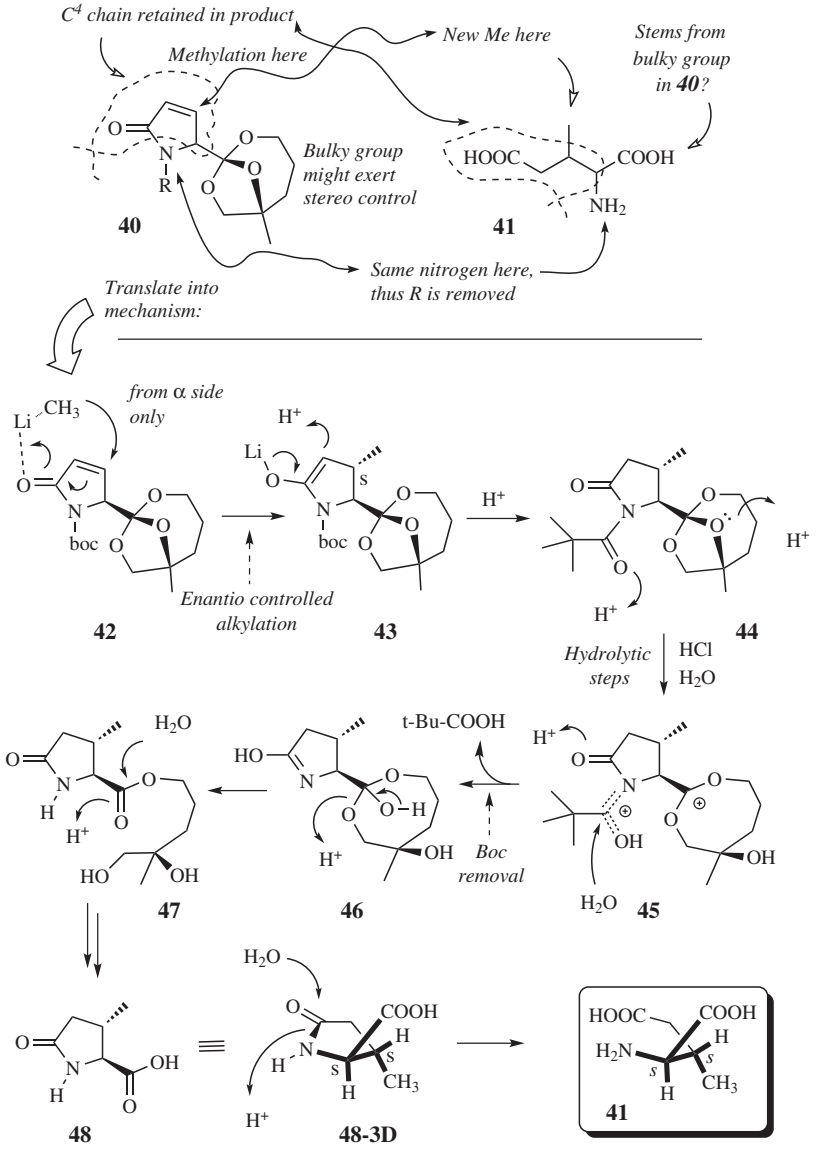
Here is a second set of more focused issues.

9. As the lactam backbone contains four carbon atoms in line, is it likely that these atoms end up as the four carbon chain of α-aminosuccinate **41**?
10. If so, the lactam ring must be fractured at some stage. At which stage? Does this make a difference? Are there lactam ring-opening reagents in the mixture?
11. By chance is MeLi the source of the extra methyl on C^3 of my target or does it operate just as a strong base?
12. In case MeLi contributes to the carbon backbone as a nucleophile, which electrophilic carbons are available in **40** for docking this methyl?
13. Is this site C^4 of lactam **40** in view of the vicinity to the C–N bond, given that a $C(CH_3)$–$C(NH_2)$ occurs in **41**? Any other site available?
14. On the other hand, what does one do with the trioxabicyclooctane group (the bulky thing to the right of **40**)? Why was this orthoester placed there in the first place? Is it just protecting a group, possibly of the second carboxylate in succinate in view of its abundance of oxygen atoms, or perhaps a stereochemical auxiliary to control the enantioselectivity?
15. Is the absolute configuration of product **40** of any significance to mechanism?
16. Is it worth the trouble to draw a 3D rendering to understand the stereochemistry?

In this second analysis round, *all questions seem relevant*. These thoughts are chained sequentially: One question drives your ideas to other queries that were not in your mind at the beginning.

1.4.3 Drawing a First Outline for Guidance

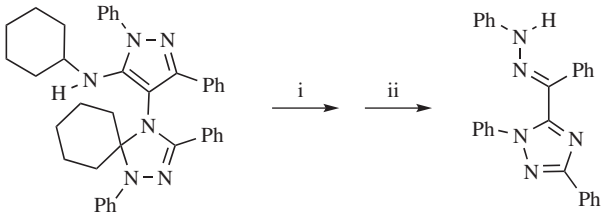
Sketching ideas in one single drawing is always helpful to see them in perspective, organize hypotheses, and discuss them with yourself and fellow mates. A well-supported mechanistic sequence can then be proposed with stereochemical features included (Scheme I.9). Hopefully, you have tried your own and will be delighted to check that your solution was correct. This reaction is much more modest than Scheme I.9 leads one to believe since all it took was (1) 1,4 Michael addition and (2) extensive hydrolysis. Details in the latter became necessary to emphasize the origin of the (*s,s*) configuration in target **41**.



SCHEME I.9

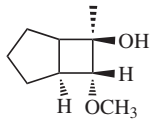
1.4.4 Asking the Right Questions and Proposing the Right Answers . . . is enough?

In simple situations like the preceding example it may suffice. But more complex problems demand additional considerations because *even the right questions will not crop up easily*. Read again the previous sentence and then consider the reaction



49 **50**

i: H_3O^+; ii: Standing in EtOH solution for 2 weeks



$\xrightarrow[\text{Pyridine}]{POCl_3}$ $C_{10}H_{16}O$

51 **52**

^{1}H NMR: d 5.37 ppm, J = 6.2 Hz (1H)

SCHEME I.10

49 → 50 (Scheme I.10, top) for a few minutes [5]. A few obvious questions would quickly find large roadblocks.

(a) Main reaction here? Well, not sure . . . .
(b) If unable to answer, at least give a clue of what is happening? Hmm, two cyclohexyl units seem to walk off, heterocycles get busted and rearrange crazily; definitely messy (increasingly gross language of an ever more anxious student). Who dared to report this oddball?

And then, what relevant question comes next? Options are cut short; thus the answer remains in an obscure corner. As the first few assumptions and questions failed, this reaction becomes *a problem* that demands systematic analysis and perhaps some outside help. Because you may need more training as a problem solver (read on and you will get it) before tackling this reaction, let us postpone its discussion until Problem 49 later on.

1.5 INTUITION AND PROBLEM SOLVING

According to modern psychology, people face and interpret reality through two parallel channels: the intuitive (System I) and the rational (System II). System I is of more animal nature, whereas System II is exclusively human, or so we are led to believe. As anybody else, scientists use both systems most of the time every day of their lives with mixed emphasis and results. System I gets the upper hand when solving problems *with insufficient data,* a very common predicament.

The subject of the intuitive versus the rational in scientific endeavor has been discussed extensively and continues to be a matter of debate. The consensus is that science cannot rely on intuition alone to achieve anything really valid. Intuition entries, which are humanly unavoidable, should be given some room only in the first stages of analysis of a problem without fully processed evidence. After its many success stories in science, intuition is welcome as a jump start but only to be substantiated after careful rational analyses and experiments, and then approved or discarded.

For example, consider the **51** → **52** reaction (Scheme I.10, bottom) [6]. In providing you with only scant evidence of product **52**, I have perturbed deeply (and hopefully) the basic way of reasoning chemical problems to force a change in your mind setting towards System I, especially during the first stages of assessment. Later on I will pour in more evidence to substantiate the case and let your wits drift toward System II.

What does your intuition tell you? This is what I would predict: After scanning your eyes swiftly across structure **51** and the empirical formula of **52**, *you know* that one oxygen atom was lost (intuition fingers OH). Also the ^{1}HNMR fingerprint of a vinyl proton in **52** calls for a trivial *cis*- elimination of water at the heart of the mechanism. Intuition will also articulate that, as the malicious educator you assume I am, I should be asking for something more substantial than elementary elimination of water to explain **52.** In the absence of alternatives, your inklings are more inclined to fracture the carbon backbone in **51** to make of this reaction something of substance. After all, your chemist "chi" *feels* that cyclobutanols fused to other carbocycles are prone to shattering by $POCl_3$ to dispose of all that ring strain. Not bad for intuition alone, aided with a drop or two of educated guesses.

Next, let me throw in a bit of hard information to shove your mind toward System II's rational thinking: ^{1}H and ^{13}C NMR spectra of product **52** (Figure I.1).

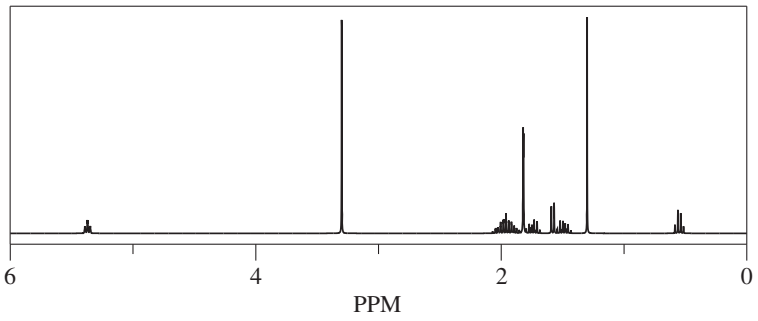
Analysis: The ^{1}H NMR data shows three methyl groups in **52**, $R_3C–CH_3$, $=C–CH_3$, and OCH_3. ^{13}C chemical shifts support this picture adding the C=C and $C–O–CH_3$ carbons. Also, no terminal $=CH_2$ is there, which would have meant a simple water elimination in **51** in the direction of the carbinol methyl. If so, there is no alternative pathway but this one: Cyclobutane must be unraveled to accommodate the vinyl system. To this end, a C^+ should be established without the β-elimination, likely through loss of OH encouraged by $POCl_3$.

Solid spectral evidence and our previous knowledge of $POCl_3$ actuation on carbinols and likely outcomes supplemented intuition in drawing Scheme I.11 without much hesitation. Regardless of the two divergent routes **A** and **B**, both NMR spectra discard **55a** as an option. Also, the high field *dd* signal at δ 0.6 ppm is decisive evidence in favor of the cyclopropyl structure. Compound **55b** was indeed the $C_{10}H_{16}O$ product observed experimentally [6].

While the intervention of intuitive thinking is almost unavoidable and even pleasing, indulging in instinctive contemplations for too long becomes a high risk attitude in science. In the next chapters we will deal with the rational systematic approach to PA in organic reaction mechanism, appealing chiefly to thinking System II. And yet, forfeiting System I altogether would not be possible, as half-animals we still are.

For more on intuition in science, visit Suppl I # 2 in http://tapsoc.yolasite.com/.

^{1}H NMR spectrum



^{13}C NMR spectrum

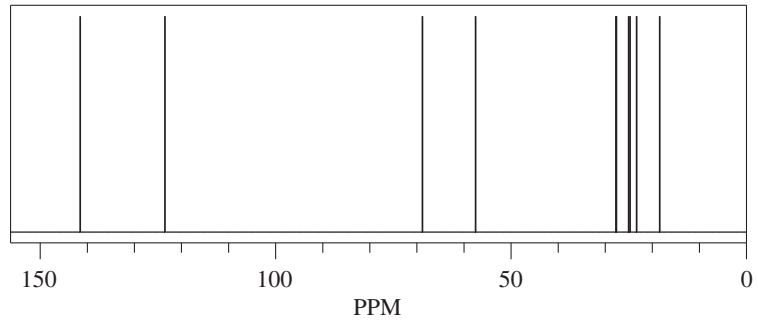
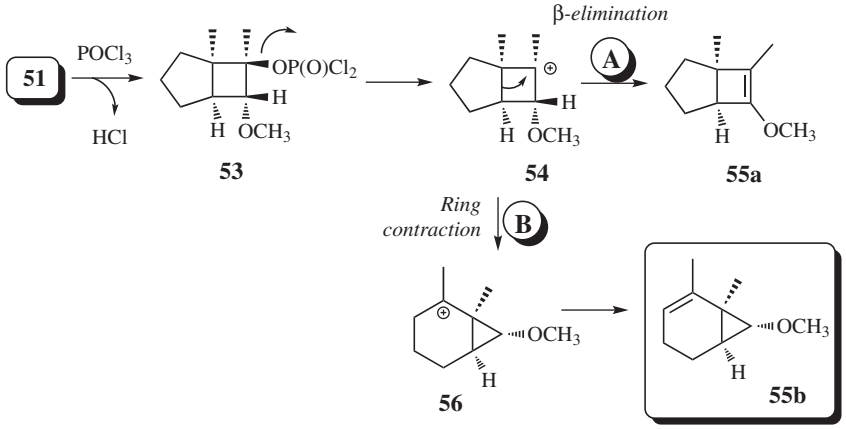


FIGURE I.1 Simulated NMR spectra of compound **52**.



SCHEME I.11

1.6 SUMMING UP

1. Solving problems of organic reaction mechanism puts all your capacities at work: accumulated knowledge, mind responsiveness, imagination, logic reasoning, and a shed of courage to dare think out of the box occasionally.
2. All this high power cerebral commotion is aimed at a single highly focused objective: elucidating the reaction mechanism reasonably well, so it demands well organized and constructive thinking aided by the toolkit of strategies offered in this book.
3. Pushing forward starting materials with assistance from reagents to get closer to products as your only line of attack is not such a good idea. Planning ahead is much more productive.
4. Mind boggling, distraction, and stumbling into dead ends, common and frustrating by-products of problem solving, can be avoided effectively by following an orderly plan based on the application of those basic concepts most advanced students and practitioners have dropped behind long ago as too elementary, in addition to a healthy dosage of advanced concepts and a hefty measure of practice and focused perseverance.
5. Problems need to be identified as such and analyzed carefully by asking relevant questions. Proposed solutions need to be explored and assessed against good chemistry grounds. A single sketch encompassing preliminary ideas brings an integrated view for fresh options to show up. The amount of information uptaken by eye-scanning over a plot, figure, or sketch is enormous. Exploit it!
6. Although intuition is a valuable tool in interpreting our world and facing many daily situations, it is of limited use in problem analysis in the hard sciences but useful when evidence is scant. Solutions to mechanistic problems should never be left entirely to intuition, as bad chemistry will show its ugly head.
7. Ultimately, problem solving as part of a profession is a game, no matter how challenging, for which, in time, one develops an irresistible taste.

It is all about orderly thinking up there in the brain. This organ, weighing no more than 2% of your body weight, swallows up 20% of the total oxygen you inhale while burning 25% of your daily glucose storage. There has got to be a jolly good evolutionary reason for this and the brain's PA capacity stands as a most likely and powerful driving force. It is never a bad idea to put it to work for the good reasons.

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