CHAPTER ONE

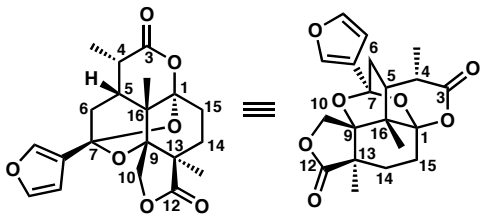
A Brief History of Saudin

1.1 Background and Introduction

1.1.1 Isolation and Proposed Biosynthesis

The caged diterpenoid saudin (**1**) was isolated in 1985 by Mossa and Cassady from the leaves of the *Clutia richardiana (L.)* family *Euphorbiaceae*, a toxic plant indigenous to the western and southern mountains of Saudi Arabia.[1] The complex polycyclic architecture was delineated by single crystal X-ray analysis and shown to be that depicted in Figure 1.1.1.

Figure 1.1.1



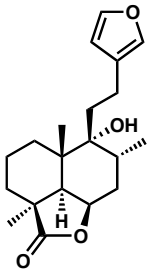
Saudin (1)

This unusual polycyclic natural product is presumably related to the labdane diterpenes (Figure 1.1.2). Within this family of natural products, saudin is a member of

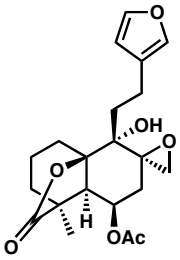
the furanoid labdanes (**2-4**), which may arise biosynthetically from the related pre-furanoid labdanes (**5-8**).

Figure 1.1.2

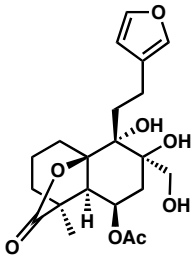
Furanoid Labdanes



Marrubiin (2)

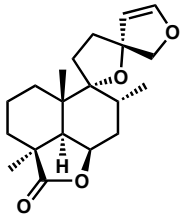


Nepetaefuran (3)

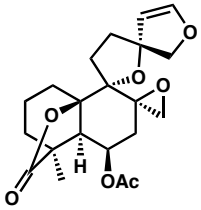


Nepetaefuranol (4)

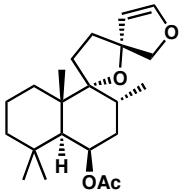
Pre-Furanoid Labdanes



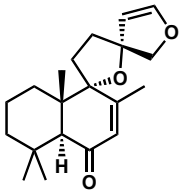
Premarrubiin (5)



Nepetaefolin (6)



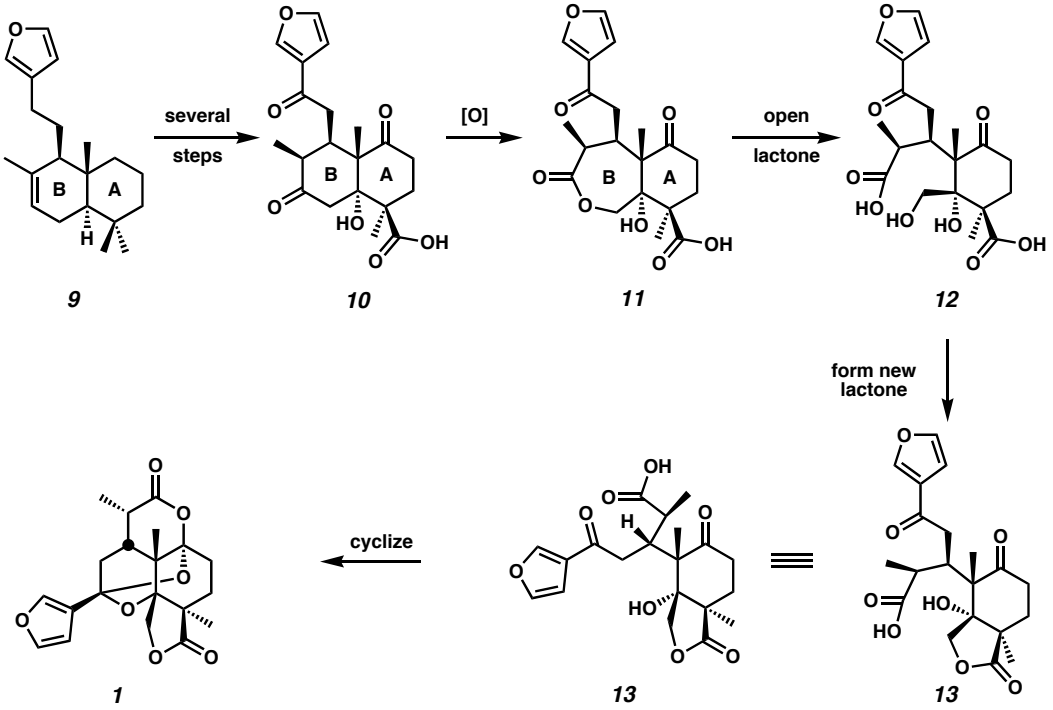
Prerotundifuran (7)



Presolidagenone (8)

In their original report on the isolation of saudin, Mossa and Cassady proposed a biosynthesis of the natural product based on its structural relationship to other labdane diterpenes (Scheme 1.1.1). Converstion of labdane precursor **9**[2] to triketone **10**, followed by oxidative expansion of the B ring, could lead to ε-lactone **11**. This intermediate could then undergo a series of hydrolysis and rearrangement steps to give the caged structure of saudin (**11→12→13→1**).

Scheme 1.1.1



1.1.2 Biological Activity

Three years after isolating and disclosing the structure of saudin (**1**), Mossa and co-workers reported the biological activity of this the novel caged diterpenoid.[3] Importantly, saudin was found to induce hypoglycemia in mice, both in vitro and in vivo. Given its potent hypoglycemic activity and oral bioavailability, saudin is an appealing lead structure for the development of new agents to treat diabetes mellitus. Unlike many other hypoglycemic agents, saudin's ability to reduce the glucose levels in mice and rats seems to be unrelated to the cellular pathways for insulin secretion. This unique mode of

action may provide a complementary form of treatment for diabetes mellitus, specifically in cases where other hypoglycemic agents have failed.

Diabetes mellitus, a group of diseases characterized by hyperglycemia, affects nearly 18.2 million people (6.3% of the population) and is the sixth leading cause of death in the United States (over 200,000 deaths per year).[4] In most cases it is the result of defective metabolism of insulin by the body. The disease is controllable in most patients using a regimen of diet, insulin injections, and oral hypoglycemic agents.[5]

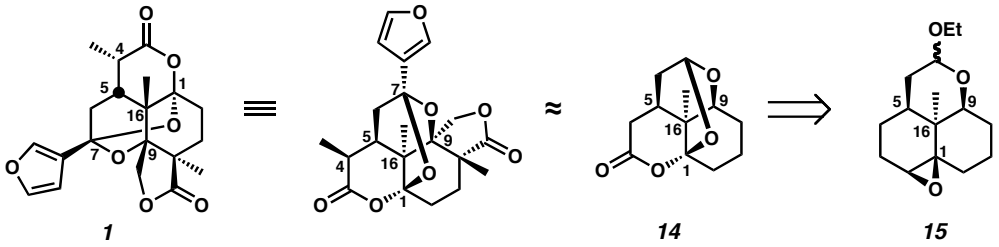
1.2 Synthetic Studies

In the twenty years since the isolation of saudin, a number of approaches to the synthesis of this natural product have been reported. Recently this effort resulted in the elegant syntheses of (±)-saudin by Winkler and (–)-saudin by Boeckman. These approaches, along with other incomplete synthetic efforts, are presented in this section.

1.2.1 González-Sierra's Approach[6]

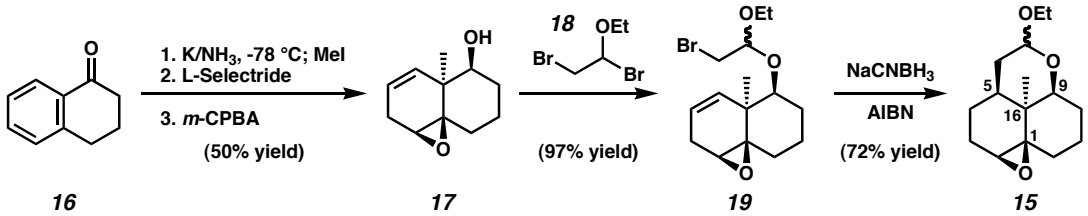
González-Sierra has developed an efficient strategy for generating the stereocenters at C(1), C(5), C(9), and C(16) of saudin (Scheme 1.2.1). His approach has focused on the construction of the polycyclic lactone **14**, which is a simplified model system for saudin. This intermediate may be accessed from epoxy-acetal **15**.

Scheme 1.2.1



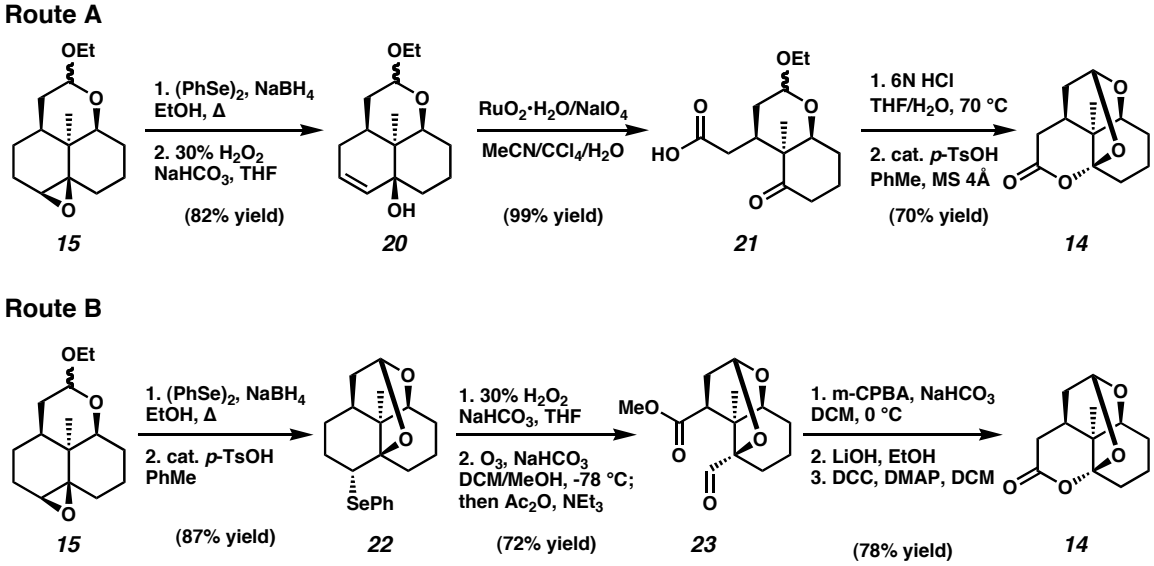
Epoxy-acetal **15** was synthesized rapidly from α-tetralone (**16**) via an intramolecular radical cyclization of bromoacetal **19** (Scheme 1.2.2). Importantly, this reaction sequence sets the correct relative stereochemistry at C(5), C(9), and C(16).

Scheme 1.2.2



With Epoxy-acetal **15** in hand, González-Sierra has developed two routes for the synthesis of lactone **14** (Scheme 1.2.3). In both cases, the decalin system was oxidatively degraded and recyclized to form the desired lactone functionality. The application of these strategies for the total synthesis of saudin is currently under investigation.

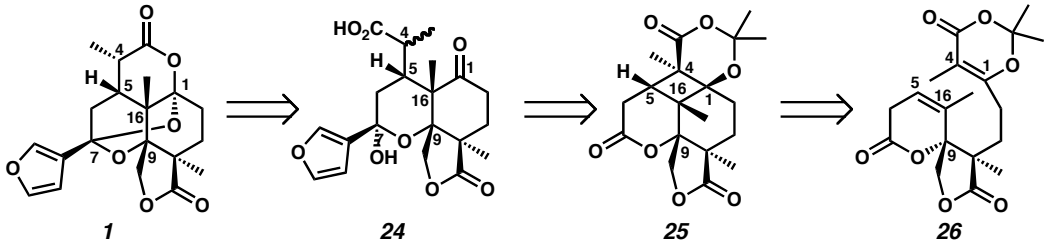
Scheme 1.2.3



1.2.2 Winkler's Approach[7]

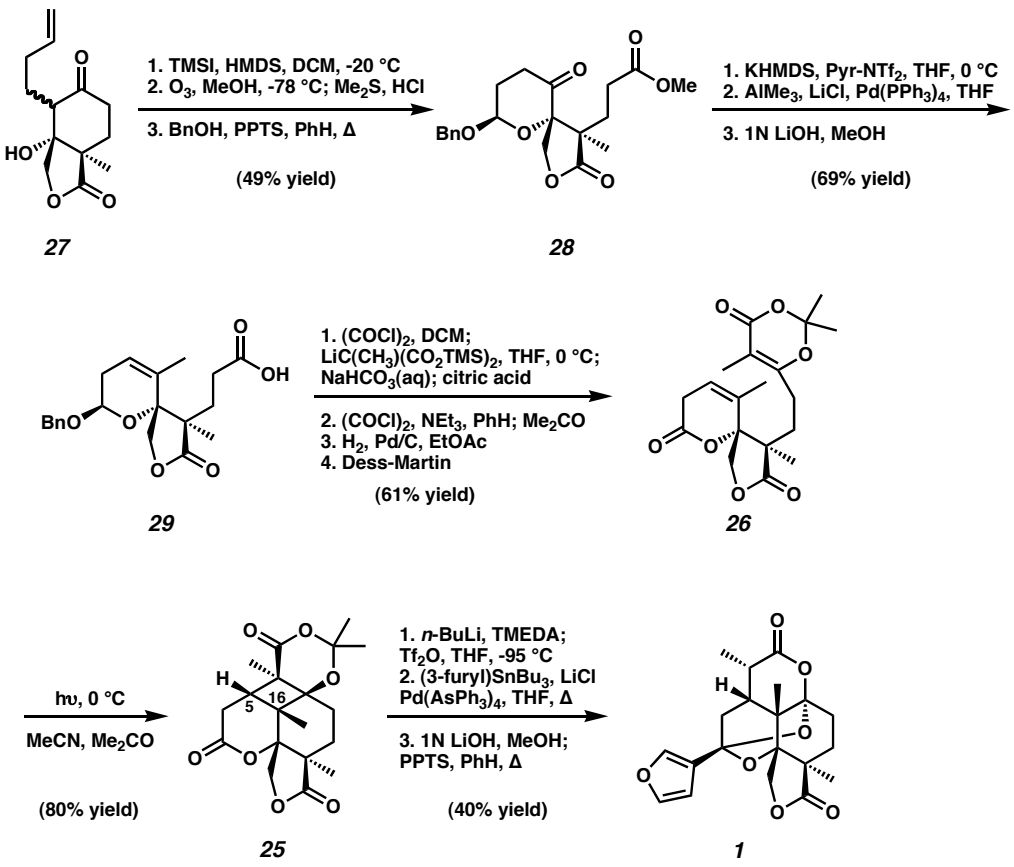
In 1999, Winkler reported the first total synthesis of (±)-saudin. The key step in this elegant strategy was an intramolecular [2+2] dioxenone photocycloaddition to generate the quaternary carbon center at C(16) (Scheme 1.2.4).

Scheme 1.2.4



Bicyclic ketone **27** was efficiently transformed into dioxenone **26** through a sequence that involved an oxidative cleavage of the six-membered ring structure in the starting material. Tricyclic dioxenone **26** underwent a highly diastereoselective [2+2] photocycloaddition to set the correct relative stereochemistry at C(5) and C(16) (Scheme 1.2.5). The cycloaddition product **25** was then easily converted to saudin following cyclobutane fragmentation and acetal constitution.

Scheme 1.2.5



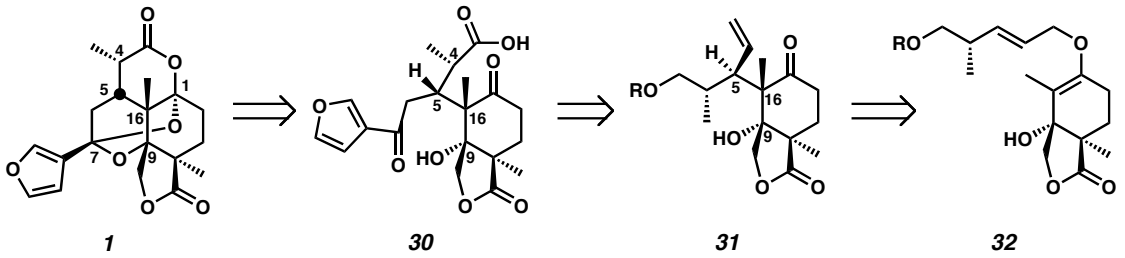
1.2.3 Boeckman's Approach[8,9]

Although Winkler was able to synthesize (±)-saudin, the absolute stereochemistry of the natural product was only established by Boeckman's total synthesis of (–)-saudin in 2002.

In his original strategy, Boeckman wanted to generate the correct relative stereochemistry at C(5) and C(16) via a Claisen rearrangement of enol ether **32** (Scheme

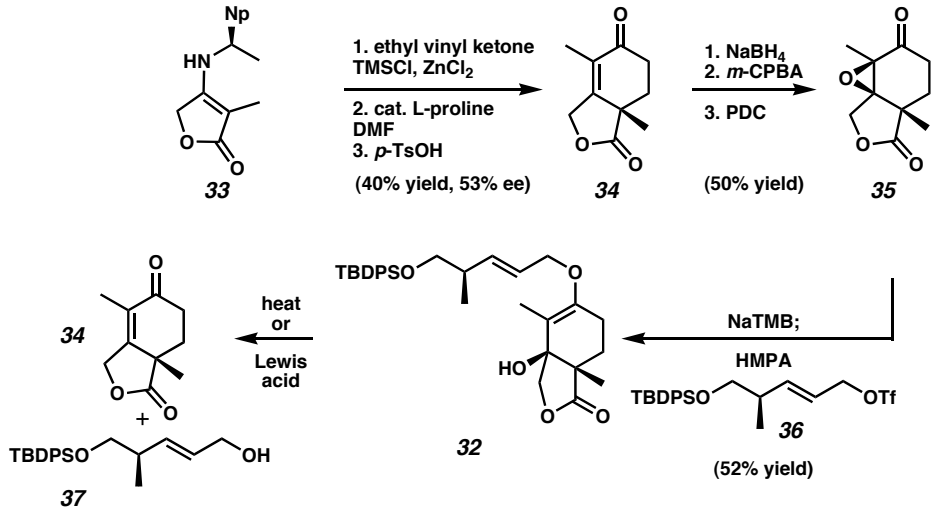
1.2.6). The diastereoselective formation of these two stereocenters proved to be a difficult task.

Scheme 1.2.6



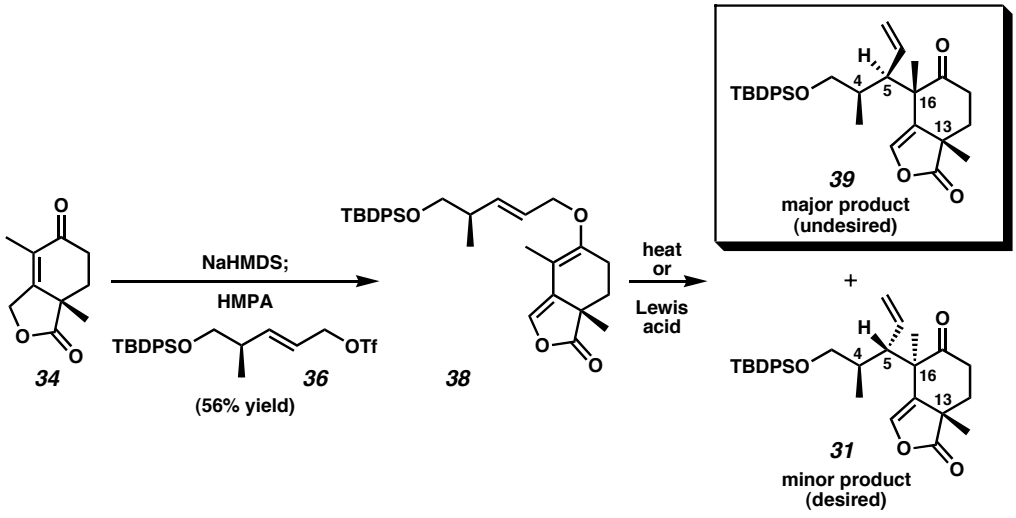
Although enol ether **32** was synthesized in 89% enantiomeric excess from chiral enamine **33**, the desired Claisen rearrangement was never realized under thermal or lewis acidic conditions (Scheme 1.2.7). In most cases the substrate for the Claisen rearrangement underwent hydrolytic decomposition to enone **34** and allylic alcohol **37**. This is presumably due to the susceptibility of enol ether **32** to β-hydroxy elimination.

Scheme 1.2.7



To address the instability of enol ether **32** to Claisen rearrangement conditions, an alternate Claisen strategy was explored. Enone **34** was converted to the extended enol ether **38**, which lacked the labile β-hydroxy functionality present in enol ether **32** (Scheme 1.2.8). Gratifyingly, this intermediate underwent a Claisen rearrangement. Unfortunately, the major product under both thermal and lewis acidic conditions was the undesired diastereomer **39**. Although the stereocenters at C(4) and C(5) could eventually be epimerized, the incorrect relative stereochemistry between the two quaternary carbon centers at C(13) and C(16) proved to be a fatal flaw in this synthetic strategy. It appeared that the bicyclic framework of enol ether **38** needed to be modified.

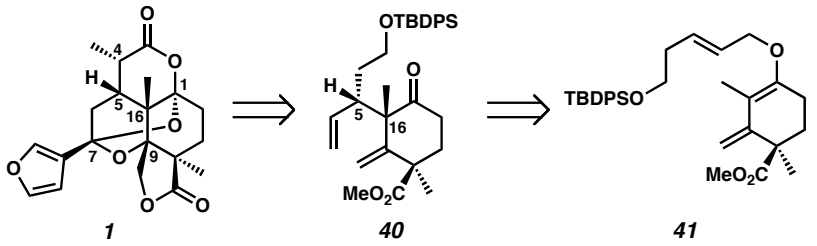
Scheme 1.2.8



Since the Claisen rearrangement approach did not provide the desired relative stereochemistry for the bicyclic enol ether class of substrates, Boeckman and co-workers

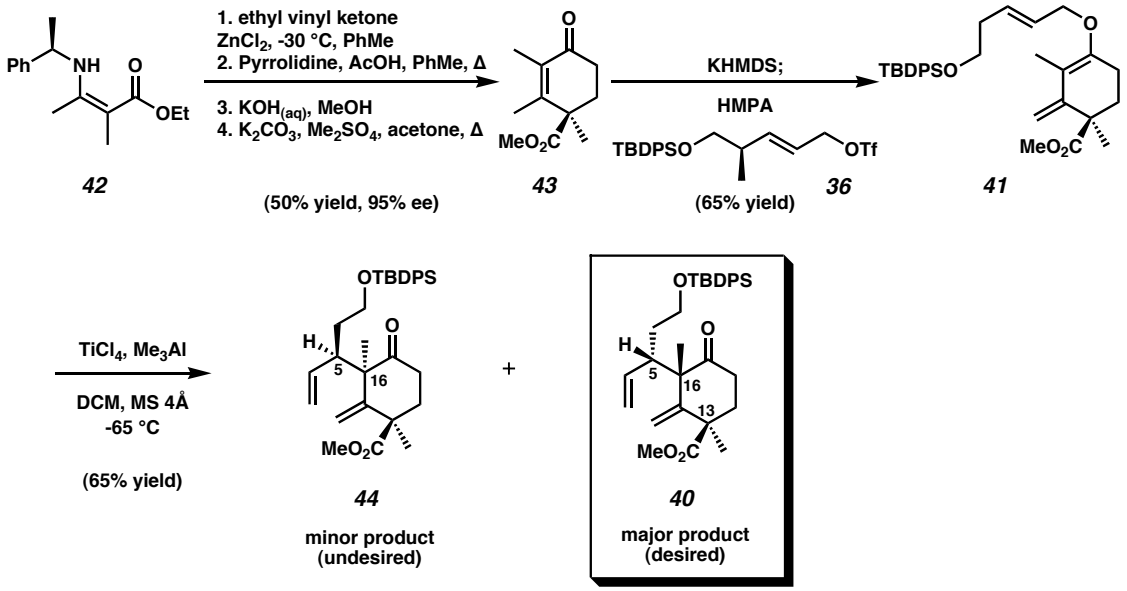
eventually made drastic modifications to the Claisen substrate (i.e., **41**, Scheme 1.2.9). In this new strategy, the lactone functionality would be installed later in the synthesis.

Scheme 1.2.9



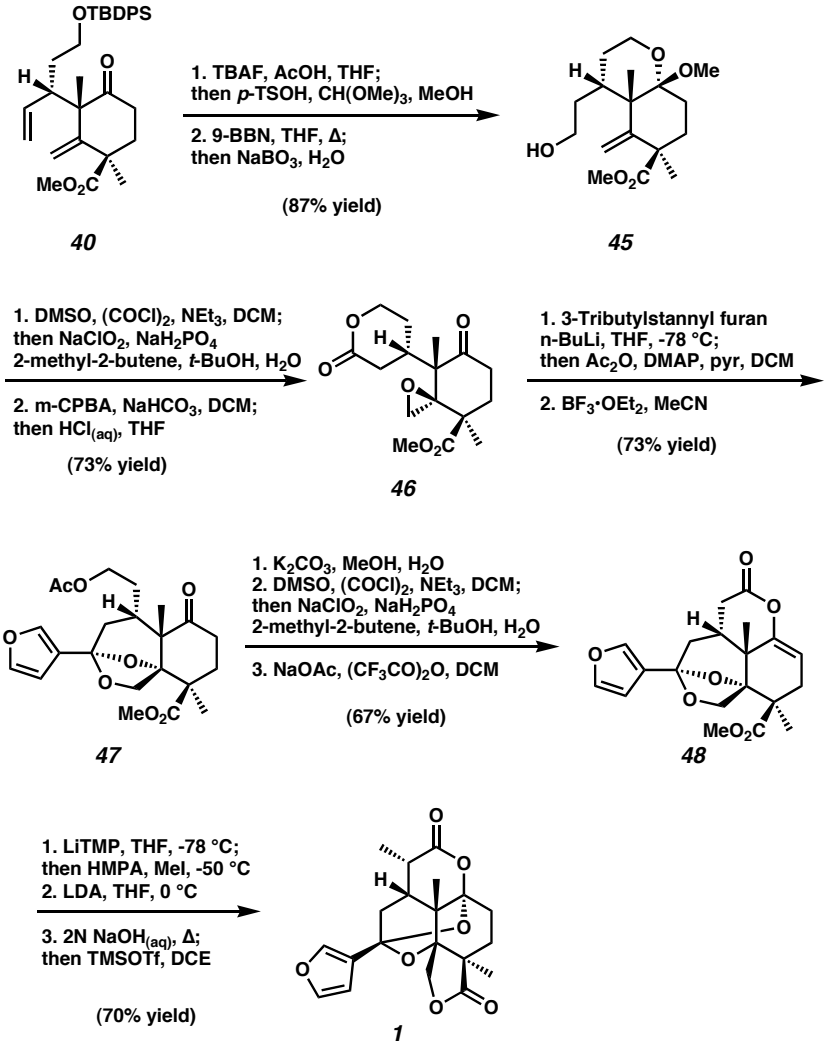
In analogy to the synthesis of bicyclic enol ether **38**, enol ether **41** was efficiently generated in high enantiomeric excess from chiral enamine **42** (Scheme 1.2.10). Gratifyingly, the lewis acid promoted Claisen rearrangement of this new enol ether yielded ketone **40** with the desired stereochemistry at C(5), C(13), and C(16).

Scheme 1.2.10



Claisen product **40** was then converted to (–)-saudin by a series of steps, which ultimately established the absolute stereochemistry of the natural product (Scheme 1.2.11).

Scheme 1.2.11



1.3 Conclusion

The caged diterpenoid saudin is a member of the furanoid labdane family of natural products. It has been shown to exhibit hypoglycemogenic bioactivity in mice and rats and is therefore a potential therapeutic agent for the treatment of diabetes mellitus. Considerable attention has been given to the synthesis of this natural product, which has culminated in two completed total synthesis by Winkler and Boeckman. In all of these aforementioned synthetic studies, saudin's unique structural complexity has served as the inspiration for the development of innovative chemistry. Although the strategies developed to construct saudin have been elegant, we were interested in developing a method that would build the core structure of the natural product in a more direct and convergent manner.

1.4 Notes and References

(1) Mossa, J. S.; Cassady, J. M.; Antoun, M. D.; Byrn, S. R.; McKenzie, A. T.; Kozlowski, J. F.; Main, P. *J. Org. Chem.* **1985**, *50*, 916-918.

(2) Although it may appear that labdane precursor **9** would lead to the non-natural enantiomers of the labdane diterpenes shown in Figure 1.1.2, in some cases both enantiomers of labdane diterpenes have been isolated. This suggests that both enantiomers of labdane precursor **9** may exist in nature. For recent examples of natural *ent*-labdane diterpenoids, see: (a) Matsud, T. Kuroyanagi, M.; Sugiyama, S.; Umehara, K.; Ueno, A.; Nishi, K. *Chem. Pharm. Bull.* **1994**, *42*, 1216-1225. (b) Fujita, T.; Fujitani, R.; Takeda, Y.; Takanishi, Y.; Yamada, T.; Kido, M. Miura, I. *Chem. Pharm. Bull.* **1984**, *32*, 2117-2125. (c) Jantan, I. Waterman, P. G. *Phytochemistry*, **1994**, *37*, 1477-1479. (d) Reddy, M. K.; Reddy, M. V. B.; Gunasekar, D.; Murthy, M. M.; Caux, C.; Bodo, B. *Phytochemistry*, **2003**, *62*, 1271-1275.

(3) Mossa, J. S.; El-Denshary, E. S. M.; Hindawi, R.; Ageel, A. M. *Int. J. Crude Drug Res.* **1988**, *26*, 81-87.

(4) Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2003. Rev

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(5) Davis, S. N.; Granner, D. K. Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Panceas. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*; Hardman, J. G., Limbard, L. E., Eds.; McGraw-Hill: New York, 1996; pp 1487-1517.

(6) (a) Labadie, G. R.; Cravero, R. M.; Gonzalez-Sierra, M. *Synth. Comm.* **1996**, *26*, 4671-4684. (b) Labadie, G. R.; Luna, L. E.; Gonzalez-Sierra, M.; Cravero, R. M. *Eur. J. Org. Chem.* **2003**, *17*, 3429-3434.

(7) Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425-7426.

(8) (a) Fang, Y. Studies Directed Toward the Total Synthesis of (–)-Saudin. Ph.D. Thesis, University of Rochester, Rochester, CA, 1991. (b) Neeb, M. J. Studies on the Total Synthesis of (–)-Saudin. Ph.D. Thesis, University of Rochester, Rochester, CA, 1995.

(9) Boeckman, R. K., Jr.; Ferreira, M. R. R.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190-191.