Pure Appl. Chem., Vol. 77, No. 7, pp. 1115–1130, 2005.
DOI: 10.1351/pac200577071115

Development of methods suitable for natural product synthesis: The azadirachtin story*

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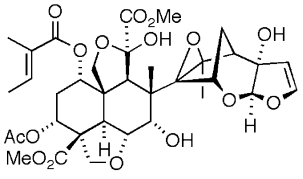
Abstract: Our synthesis work on the insect antifeedant azadirachtin is described. Particular emphasis is placed on the key coupling of a left-hand decalin fragment with a right-hand hydroxydihydrofuran acetal unit via a Claisen rearrangement reaction of an intermediate propargylic enol ether. New chemistry has been developed leading to control of an *endo*-selective intramolecular Diels–Alder reaction using silicon, which was essential for the construction of the appropriately functionalized decalin fragment. In order to install the five-ring hemiacetal of azadirachtin, we also developed a new ring contraction protocol via an intermediate six-ring cyano ester.

Keywords: natural product synthesis; azadirachtin; endo-selective intramolecular Diels–Alder; decalin; hydroxyfuranacetal.

INTRODUCTION

For many years, we have been interested in the synthesis and biology of plant-derived materials that deter predatory insects from feeding [1]. Current environmental pressures and the rapidly developing resistance to conventional pesticides provide the impetus to study new alternatives and more ecologically acceptable methods of insect population control, as part of integrated pest control management programs. Preeminent amongst these antifeedants for insects are those compounds derived from the Indian Neem tree, *Azadirachta indica* [2] and, in particular, the *seco*-limonoid azadirachtin (**1**) [3–5].



Azadirachtin **1**

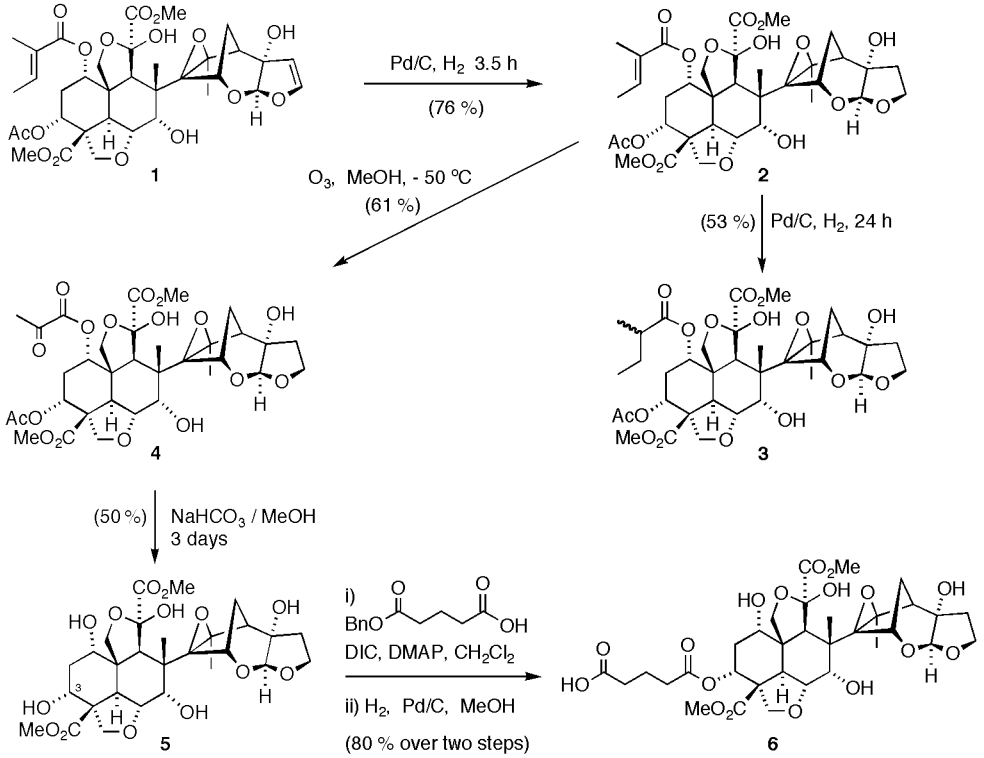
The biological effects of azadirachtin (**1**) have been extensively described, however, a particularly useful summary can be found in the review by Mordue [6]. Our own contributions in this area have been described in various articles over a number of years [7]. The complete structure determination of azadirachtin (**1**) was also a long-running saga and took many years to resolve [8–11]. It is pertinent also

Pure Appl. Chem.* **77, 1087–1296. An issue of reviews and research papers based on lectures presented at the 15th International Conference on Organic Synthesis (ICOS-15), held in Nagoya, Japan, 1–6 August 2004, on the theme of organic synthesis.

to comment on the general reactivity profile of azadirachtin (**1**) as these factors played a crucial role in developing our synthesis plans.

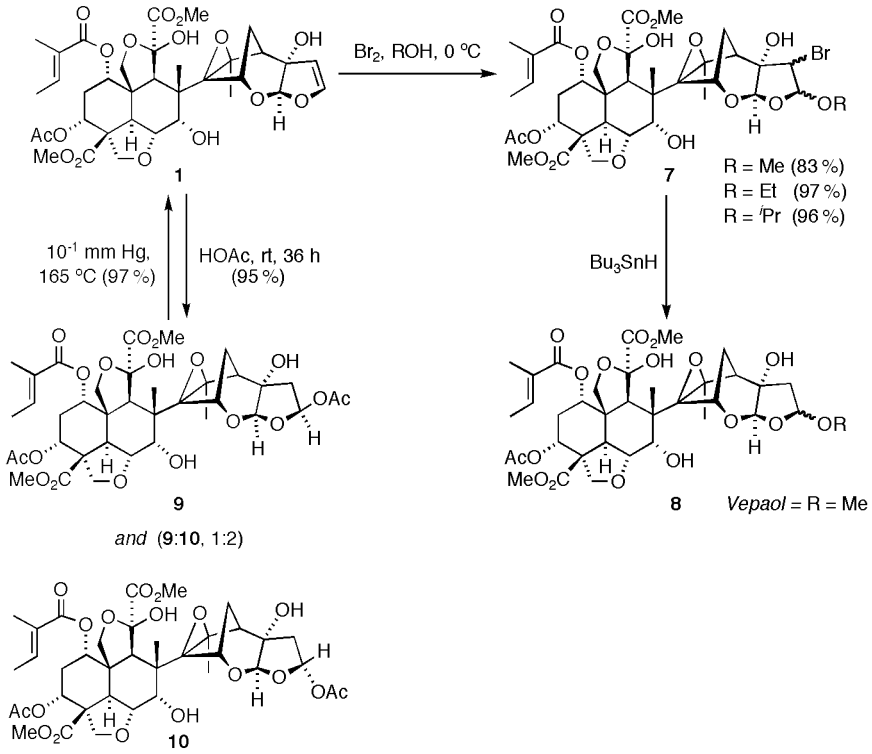
PRELIMINARY OBSERVATIONS

Early on in the program, we showed that we could selectively hydrogenate the enol ether double bond of azadirachtin (**1**) to give **2** (Scheme 1) [12]. This allowed us to either continue reduction to give the tetrahydro derivative **3** (which we showed to be equally active, but more stable than natural azadirachtin) or provide access by ozonolysis of the tigloyl side chain to give **4**, which was readily hydrolyzed to provide **5** [13]. These can be derivatized with various linker groups at the C-3 position of **5** to provide derivatives (such as **6**) that can be further coupled to fluorescent probes for biological studies, affinity columns, or protein conjugates [14].



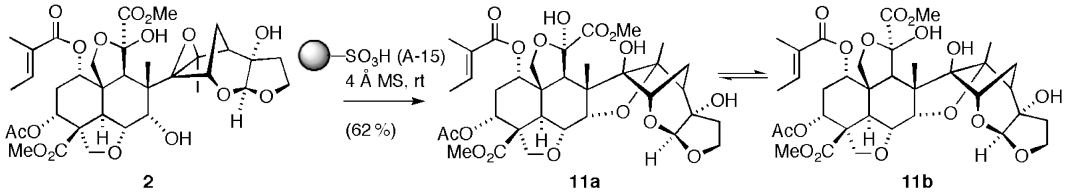
Scheme 1

During other studies, we showed that we could add alcohols to the electron-rich enol ether of **1** in the presence of electrophiles such as bromine to activate the anomeric position (Scheme 2). The products of these reactions, **7**, could be further reduced with tributyl tin hydride, and, in the case of the methoxy variant, provide supplies of natural products such as *vepaol* (**8**). This compound was not readily available from plant sources [15]. The enol ether double bond is also sensitive to addition of acetic acid to give epimeric acetates **9** and **10**. Remarkably, these can be used to recover azadirachtin (**1**) by thermolysis at 165 °C under vacuum [16]. This observation may prove useful for installation of the enol bond at a later stage in the synthesis of azadirachtin.

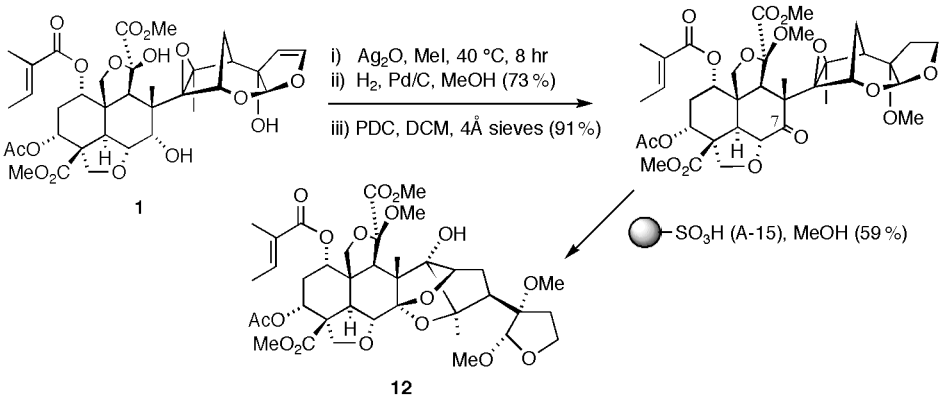


Scheme 2

We also demonstrated the acid sensitivity of the reduced azadirachtin derivative **2**. Treating **2** with Amberlyst A-15 sulfonic acid resin to give an equilibrating mixture of acetal isomers **11a** and **11b** (Scheme 3). Other derivatives obtained after methylation, hydrogenation, and C-7 oxidation underwent more complex rearrangements in the presence of acids, again involving ring-opening of the labile epoxide group, to provide the rearranged acetal **12** (Scheme 4) [16].

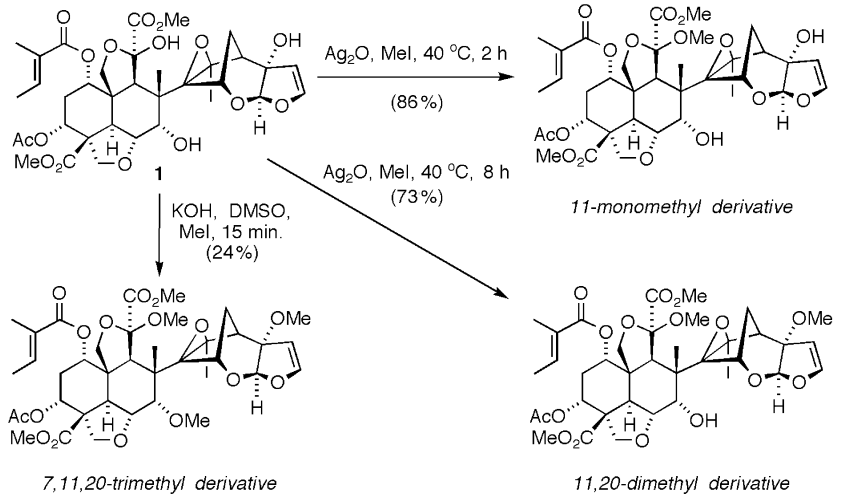


Scheme 3



Scheme 4

We have also reported on the base-catalyzed rearrangements of these molecules [16]. Finally, during experiments designed to probe the reactivity of the hydroxy groups, we showed that methylation occurs selectively and, therefore, we could exploit this observation in our synthesis planning (Scheme 5).

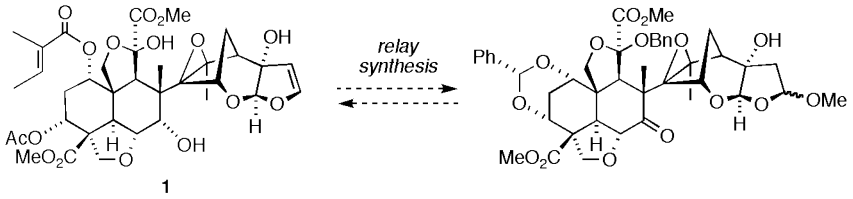


Scheme 5

SYNTHESIS

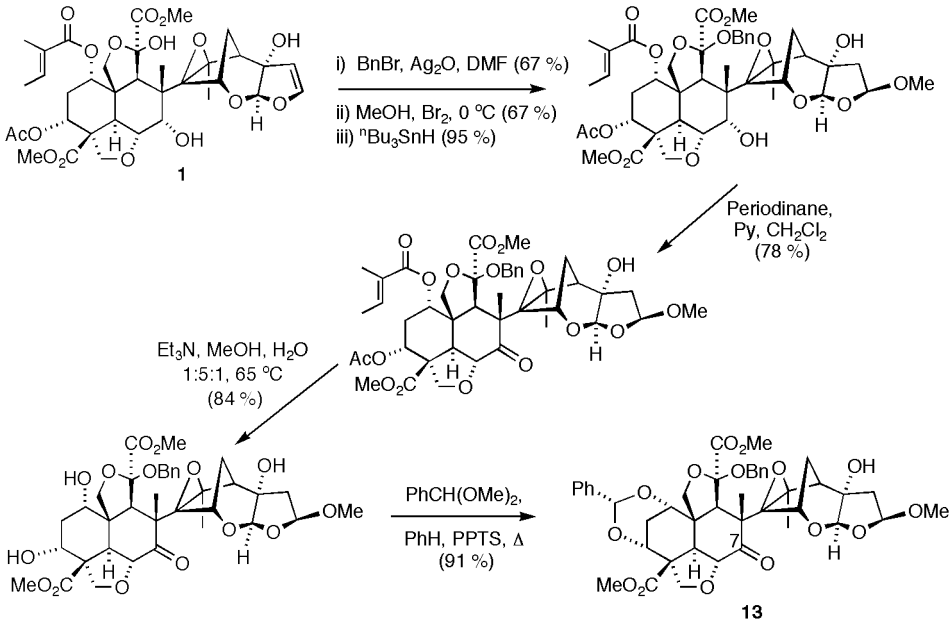
The synthesis of azadirachtin (**1**) itself presents a formidable challenge owing to its molecular complexity and its acid, base, and photosensitivity. It contains 16 stereogenic centers, of which 7 are tetrasubstituted, and it possesses a complex pattern of oxygen-containing functionalities. We have chosen to construct the molecule in a convergent manner by bringing together two fragments, each containing the required stereogenic centers and suitable functionality for conversion to the natural product [17]. While this makes good strategic sense, we recognize this particular bond construction, C-8 to C-14, will be one of the hardest bonds to form in the whole synthesis owing to its very hindered arrangement. However, before embarking on this ambitious pathway we wished to become more confident of the late functional group manipulation. We therefore devised a relay strategy that could lead from azadirachtin

to an advanced intermediate and back again to azadirachtin in a series of informative steps (Scheme 6) [18].



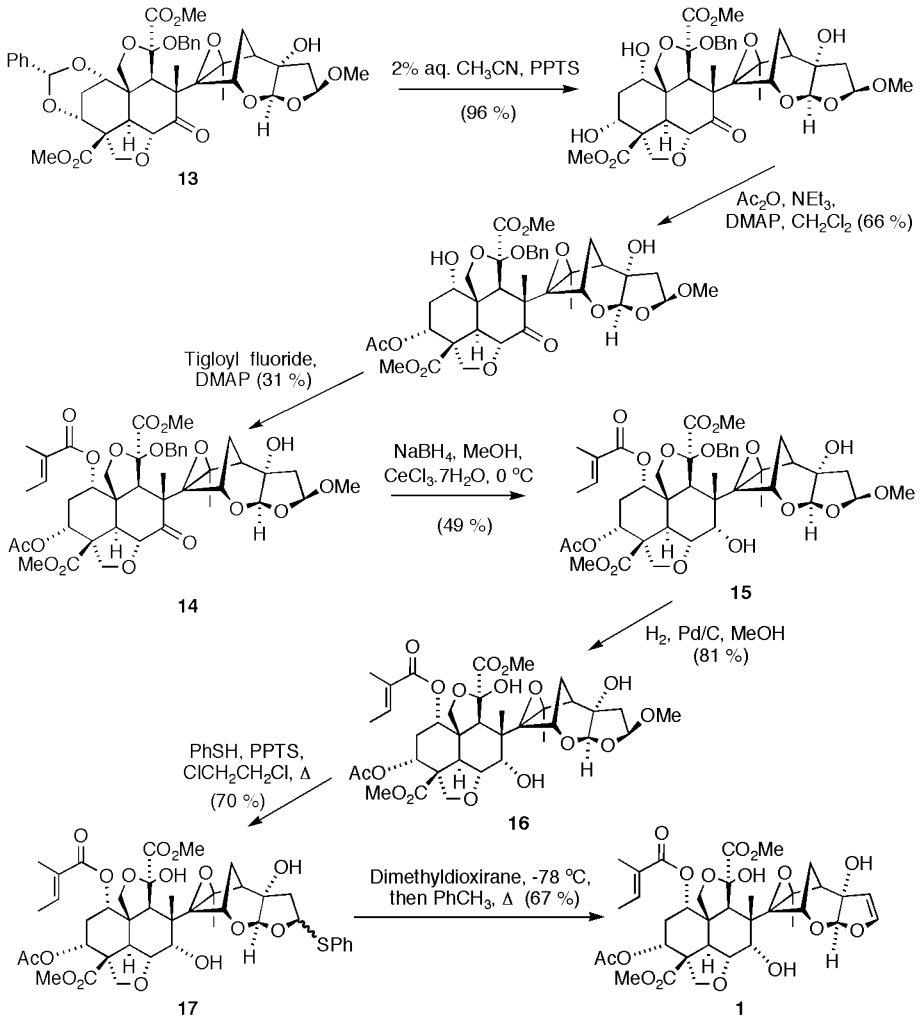
Scheme 6

We demonstrated the outward route to a potential target molecule that could serve as a relay point in the synthesis (Scheme 7). This compound, **13**, has the three key hydroxyl groups appropriately protected by benzyl and benzylidine units. It also contains a methoxy acetal, which we believed could be used to return the enol ether unit. Furthermore, a crucial C-7 carbonyl is present to facilitate the difficult fragment coupling as proposed earlier.



Scheme 7

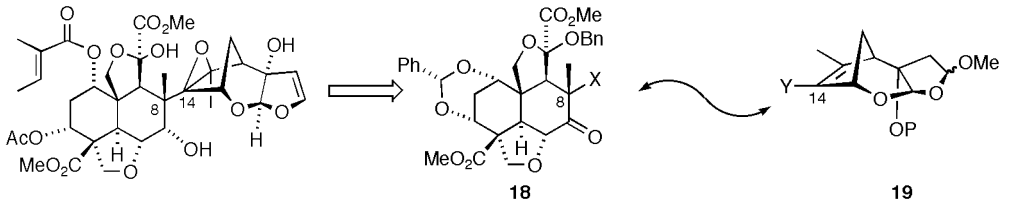
The return relay synthesis also progressed well in that we were able to return the relay compound (**13**) to azadirachtin (**1**) (Scheme 8). A number of interesting features of this route, however, deserve further comment. Namely, selective introduction of the C-3 acetate and C-1 tiglate could be achieved but not without some difficulty. Installation of the tiglate ester on the very hindered C-1 hydroxyl group required the use of the highly reactive tigloyl fluoride. Also of importance are the Luche reduction conditions ($NaBH_4$, $CeCl_3 \cdot H_2O$) to effect conversion of the C-7 ketone to the required 7α alcohol (**14**) in 49 % yield. The low yield of this reduction is due in part to the simultaneous formation of the 7β alcohol, which required separation by chromatography. The last steps in this relay route are important in that the benzyl protecting group on the anomeric position can be selectively removed in the presence of



Scheme 8

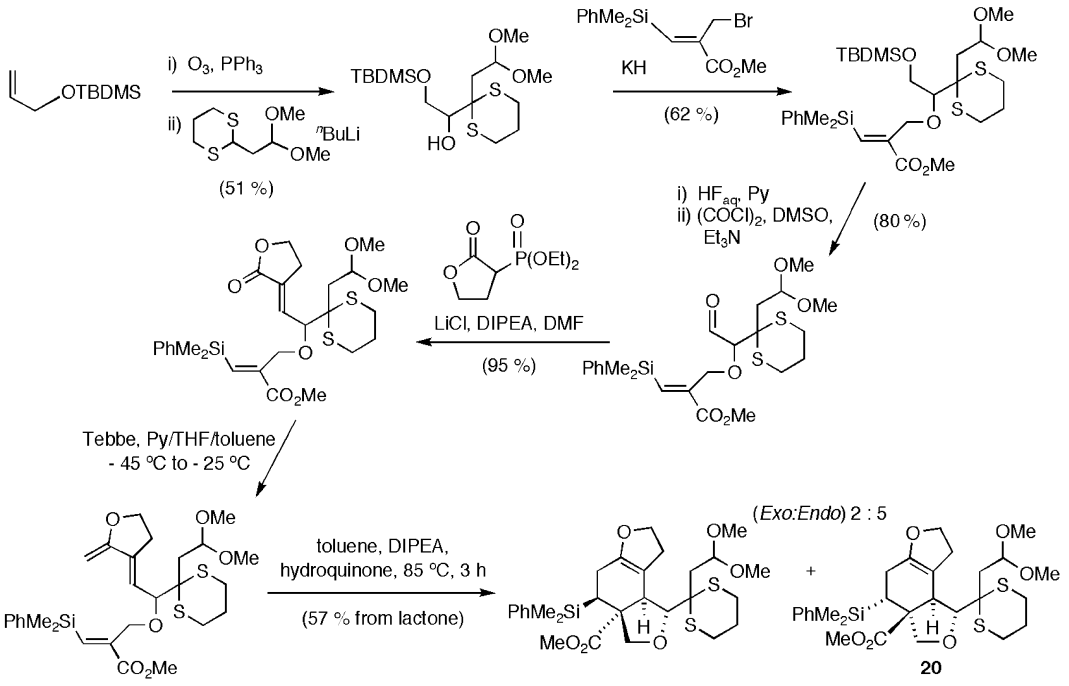
the unsaturated tigloyl group, namely, the conversion of **15** to **16**. This was anticipated based on the earlier selective hydrogenation experiments that we had carried out.

Finally, we were able to install the enol ether via selective acetal exchange with benzene thiol and pyridinium tosylate followed by oxidation of intermediate sulfide **17** with dimethyl dioxirane and *syn*-elimination of sulfinic acid. Again, these protocols have been well rehearsed on model systems [19]. The stage was now set to begin the total synthesis of azadirachtin itself given the success of these encouraging preliminary experiments. As discussed previously, we required routes to two key fragments, a left-hand decalin unit **18** [20] and an appropriately functionalized hydroxyfuranacetal portion **19** (Scheme 9).



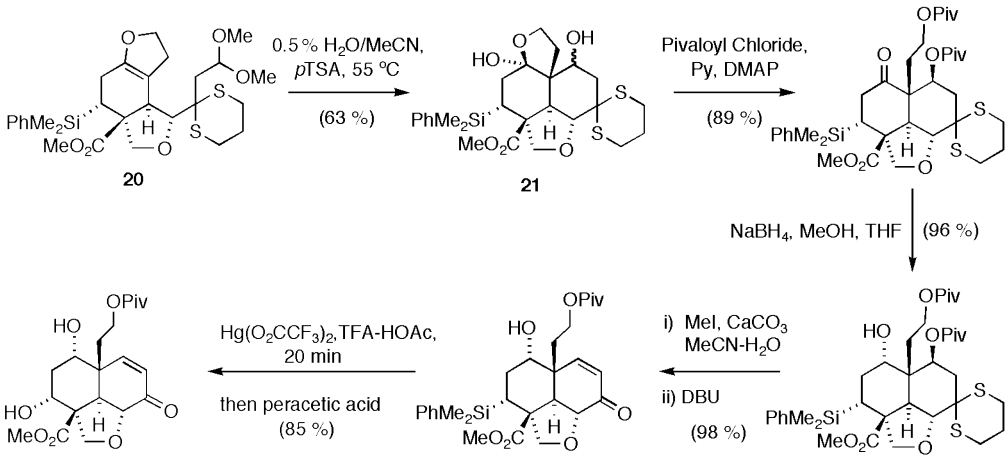
Scheme 9

Space here does not permit a full discussion of our routes to these fragments, nor can we comment in detail about the new chemistry that was necessary to achieve our goals. However, the route to the functionalized decalin unit is shown in Schemes 10–12.



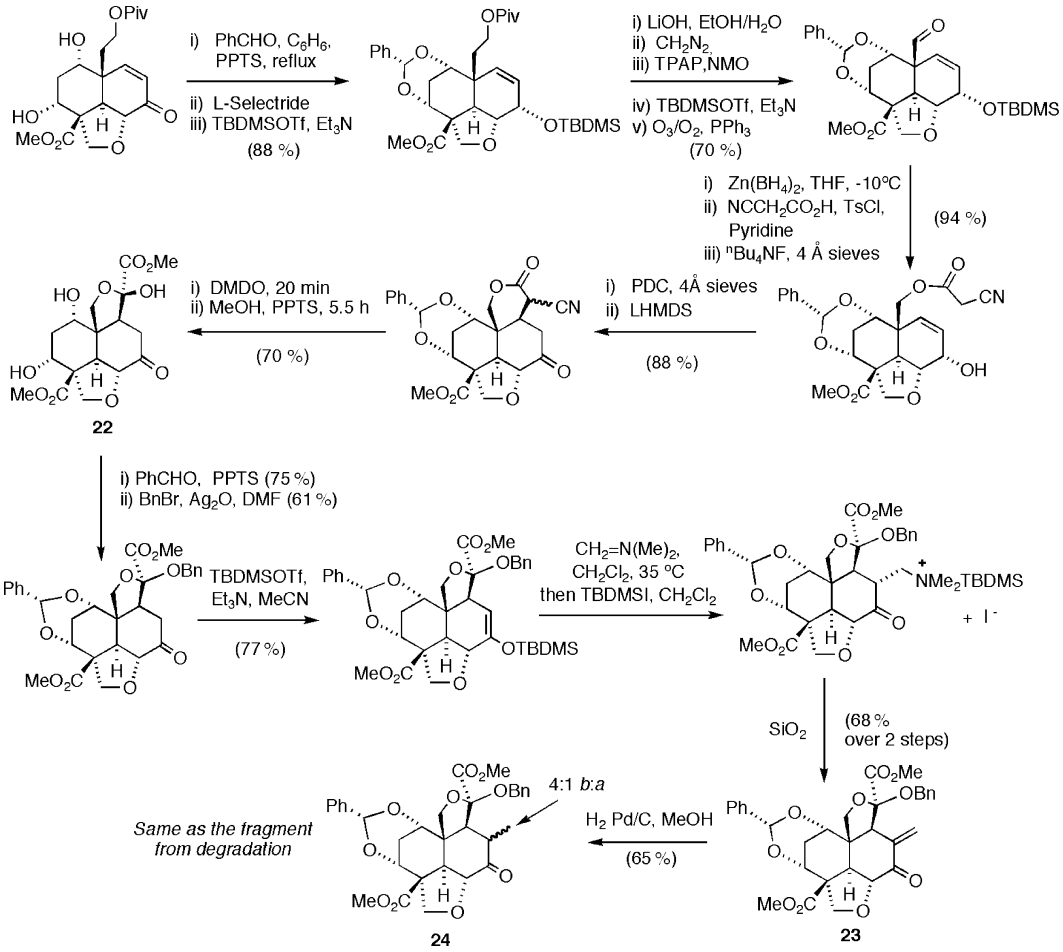
Scheme 10

Noteworthy in this synthesis is the deliberate use of a phenyldimethylsilyl substituent that was used to control the intramolecular Diels–Alder reaction in the required *endo*-mode. Without silicon present we had shown that only the *exo*-cycloadditon occurs [21]. The phenyldimethylsilyl group that finds its way to a C-3 axial position also controls C-1 carbonyl reduction stereochemistry at a later point. Finally silicon bows out of the synthesis upon Fleming oxidation to reveal the final C-3 hydroxyl group. The other feature important to this decalin fragment synthesis is the use we make of the fused enol ether **20**, which acts as an electron-rich component to effect decalin ring formation while simultaneously installing the correct C-1 oxidation pattern in compound **21** (Scheme 11) [22].



Scheme 11

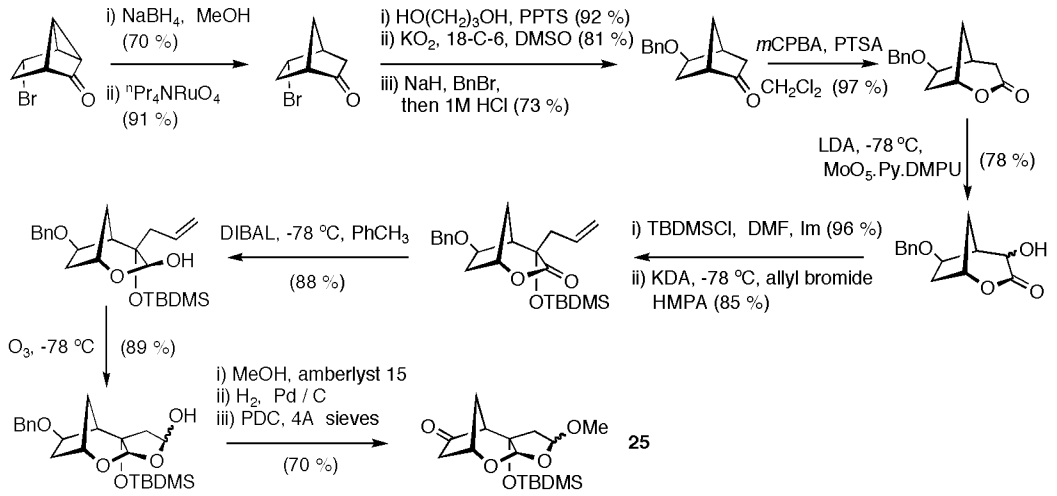
The last interesting solution to a difficult problem was the designed use of a cyanoester-mediated six-ring conjugate addition, which was then followed by dimethyldioxirane oxidation and methanolytic ring-opening and reclosure to give the five-ring hemiacetal (Scheme 12) [23]. In this one step, the last funtionalized ring of the decalin scaffold (**22**) was introduced in a very effective manner. Lastly, **22** was transformed through a series of steps through **23** to a methylated protected ketone unit (**24**) suitable for coupling. The choice of this unit was also governed by the fact that this fragment was available to us in multigram quantities by a specifically designed degradation sequence from the natural product [24].



Scheme 12

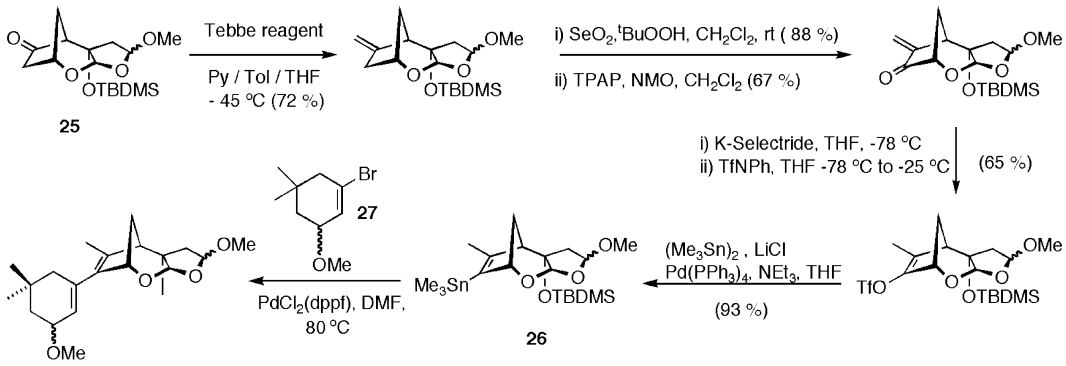
The next stage of the synthesis required chemistry that would afford a suitably functionalized right-hand hydroxyfuranacetal portion of the molecule. We have described several approaches to these types of units, however, Scheme 13 illustrates nicely some of the essential components of this work.

The final ketone **25** can be elaborated into many different potential right-hand coupling partners. We have also shown on other model systems how the epoxide and enol ether double bonds can be introduced at relevant stages. With the two fragments in hand, we could now begin the process of devising suitable coupling strategies, although this phase of the work was not without its frustrations.



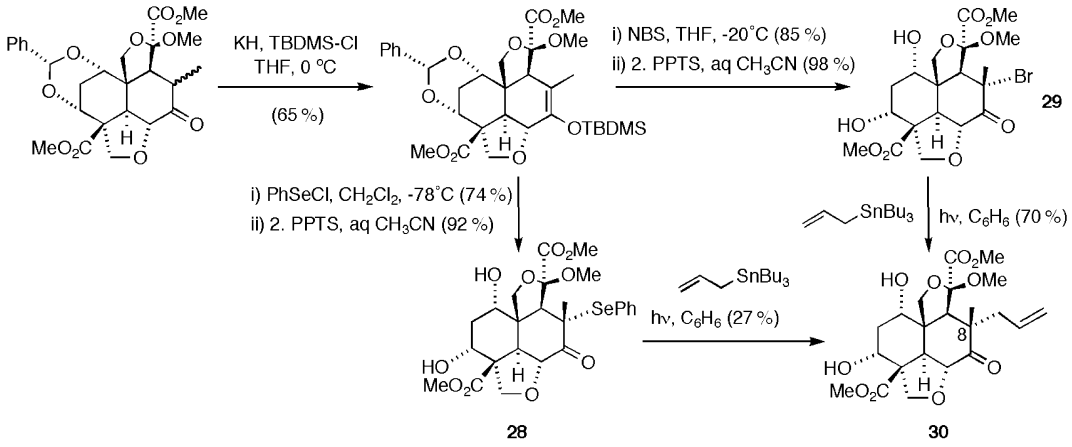
Scheme 13

In the first of these, we studied the possibility of a palladium-mediated cross-coupling of a suitably functionalized right-hand fragment stannane **26** with a model vinyl bromide **27** to afford a diene unit between the coupled partners (Scheme 14).



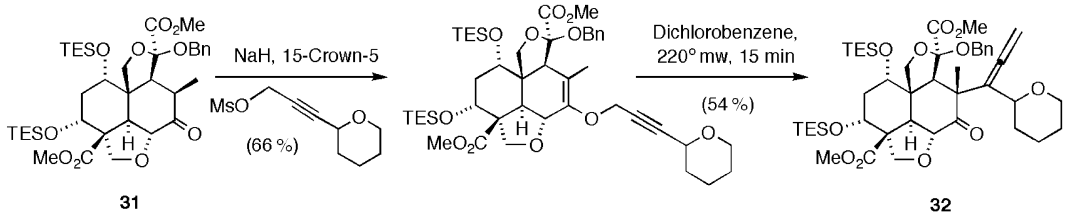
Scheme 14

While successful on the model, this approach failed when applied to the real system. Similarly attempts to couple via selenides **28** or bromo ketones **29** of the decalin fragment with allyl stannanes were successful with the parent allyl stannane to give compound **30**, but failed when the more functionalized right-hand unit stannane was investigated (Scheme 15).



Scheme 15

Many other tethered approaches were examined using silicon tethers, but in all cases were also unsuccessful. We eventually decided upon a Claisen strategy [25] since we knew our molecules tolerated high reaction temperatures. The first simple model approach employing an enol ether-propargylic Claisen rearrangement proceeded especially well to give an allene product **32** (Scheme 16).

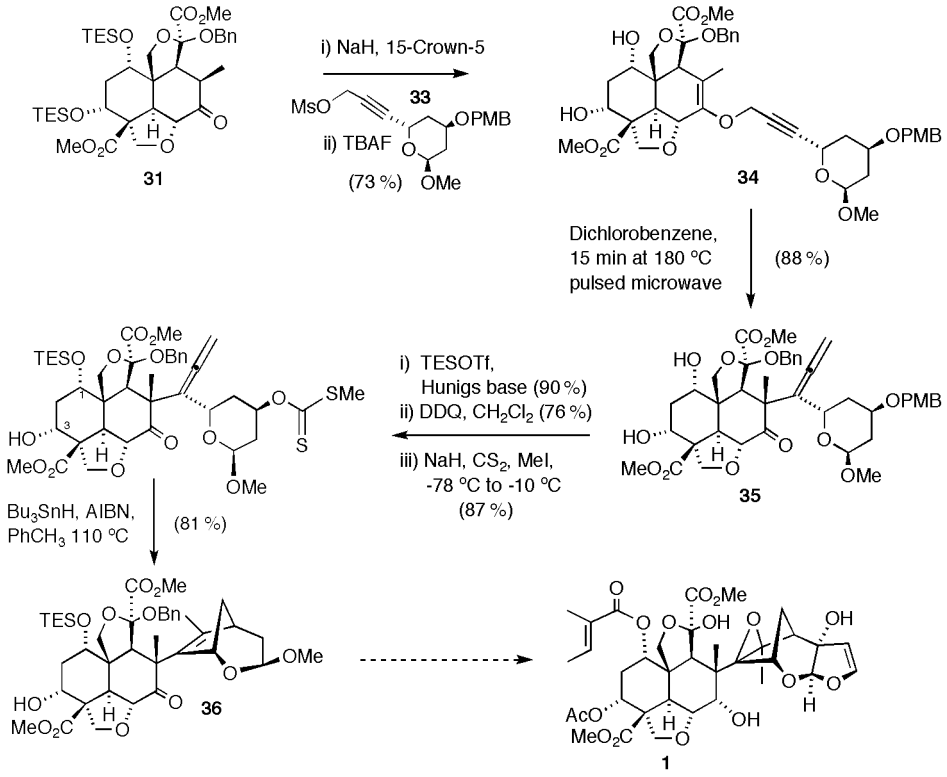


Scheme 16

The features of this process were the use of a suitably protected decalin ketone **31**, which via its enolate could be trapped with a substituted propargylic mesylate. On heating in a focused microwave unit at 220 °C for just 15 min, this gave a good yield of the corresponding rearranged allene product **32**.

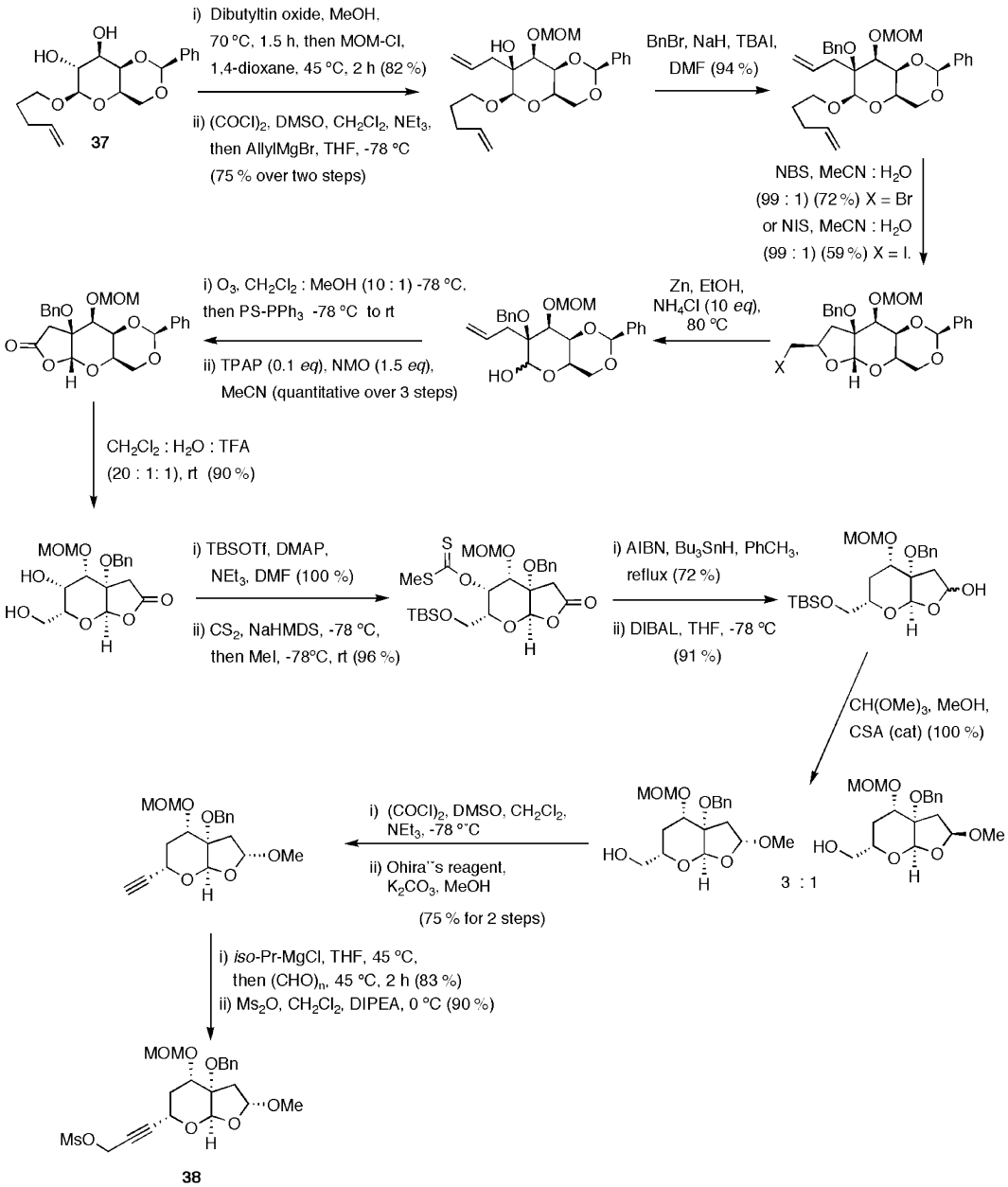
Normal thermal heating was shown to be far less efficient at affecting the formation of **32** than the microwave equivalent. This very promising result encouraged us to examine more elaborate coupling partners, as we had planned that the allene formed in these reactions would be an ideal trap for radicals that could be used in a later cyclization process. In this way, we envisaged that the required right-hand side unit could be assembled after the coupling process [26].

Accordingly, decalin **31** was coupled with a more chemically elaborate propargylic mesylate (**33**) and one that we believed could serve as a precursor to azadirachtin itself. The initial coupling of the enolate of **31** with **33** proceeded in a very acceptable 73 % yield for the desired *o*-alkylated product **34** (Scheme 17). This product underwent smooth microwave-promoted Claisen rearrangement at 180 °C in chlorobenzene in 88 % yield. Next, we showed that our planned radical cyclization procedure to the 3:2:1 bicyclic framework also worked nicely, and pleasingly it afforded only the *endo*-cyclized material **36**. Namely, the double bond was installed in the appropriate position for oxidation to the required epoxide of the azadirachtin skeleton. Clearly, product **36** could be progressed to azadirachtin, and this is approach is still underway. However, we decided on a bolder approach. This required us to construct a propargylic mesylate that when coupled with the decalin coupling partner would give a product containing *all* the carbons required for the natural product itself. This was not straightforward and required



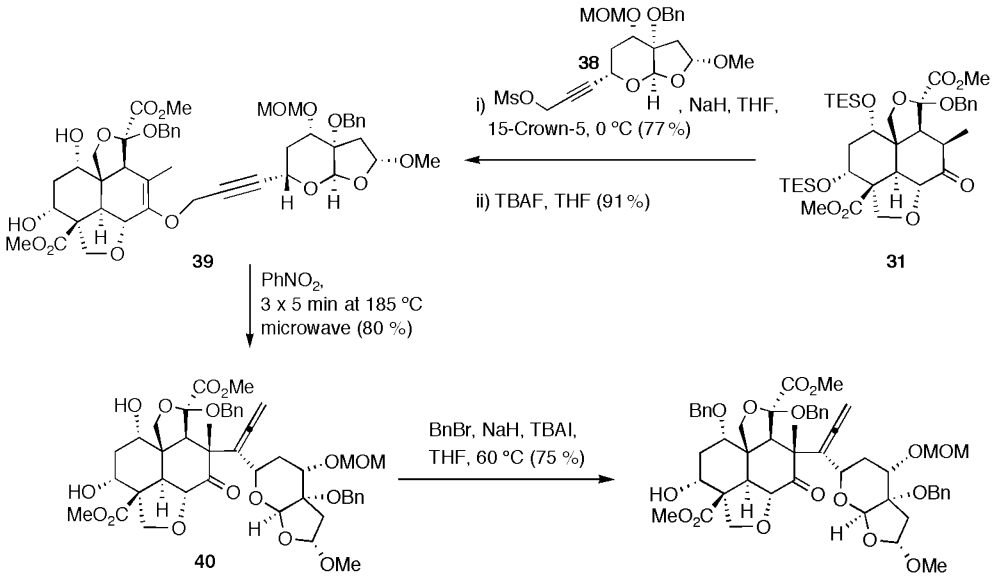
Scheme 17

considerable work to build a suitable coupling partner, but ultimately it was successful. The synthesis begins from a cheap and readily available carbohydrate source **37**. This was elaborated through a series of steps that we will not discuss in detail here, but the reader is referred to preliminary studies reported earlier in the year [27]. Needless to say, the route could be progressed, in quantity, to the MOM-benzyl protected bicylic propargylic mesylate **38** (Scheme 18).



Scheme 18

Pleasingly, propargylic mesylate **38** underwent enolate coupling with **31** to give the required material **39** for azadirachtin synthesis in excellent yield (Scheme 19). Although this coupled material suffers from considerable steric strain, **39** underwent the desired rearrangement in better than 80 % yield using nitrobenzene as the preferred solvent in the microwave-promoted Claisen reaction. Clearly, product **40** is on course for its elaboration to the natural product with azadirachtin (**1**) being only a few steps away from our previously prepared relay material.



Scheme 19

Much of the proposed chemistry, including the established relay sequence, is in place, and we anticipate completion of this program in the near future. The chemistry we have already reported toward the synthesis of azadirachtin demonstrates not only its challenge to synthetic chemists, but also the utility of its exquisite architecture as a platform to develop new chemical processes and methods for natural product synthesis [28].

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