Natural Product Synthesis

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Second-Generation Synthesis of Azadirachtin: A Concise Preparation of the Propargylic Mesylate Fragment**

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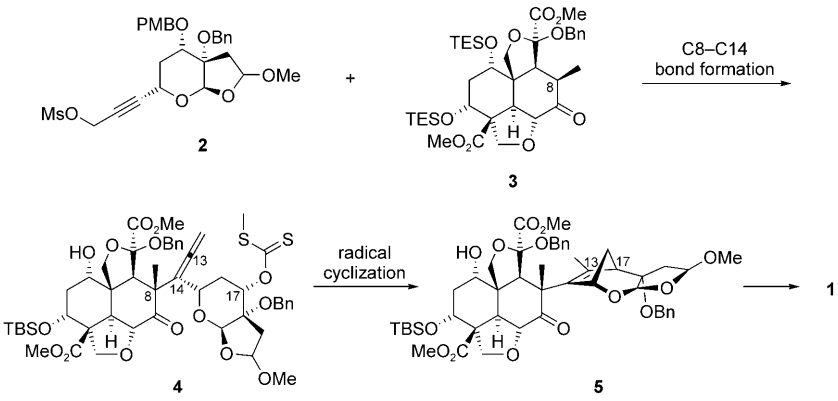
Azadirachtin (**1**) is a complex natural product which was first isolated from the Indian neem tree in 1968 (Figure 1).[1] It is a potent insect antifeedant and growth inhibitor;[2] and this, combined with its challenging architecture, has generated great interest in its chemical synthesis.[3–5]

Recently,[4] we reported the first synthesis of azadirachtin by using an approach which evolved over several iterations (Scheme 1).[7] The most significant consideration in our approach was the formation of the C8–C14 bond: it was demonstrated that the O-alkylation of decalin ketone **3** with a propargylic mesylate **2** and subsequent Claisen rearrangement can form this hindered central linkage. The resulting allene then served as the terminus for a C17-centered radical, thus allowing rapid access to the desired tricyclic framework (**4**→**5**) and ultimately the natural product **1**.



Scheme 1. Strategy for the synthesis of azadirachtin (**1**).[3,4,7] Bn = benzyl, Ms = methanesulfonyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = trimethylsilyl.

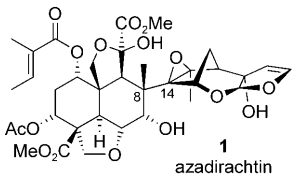
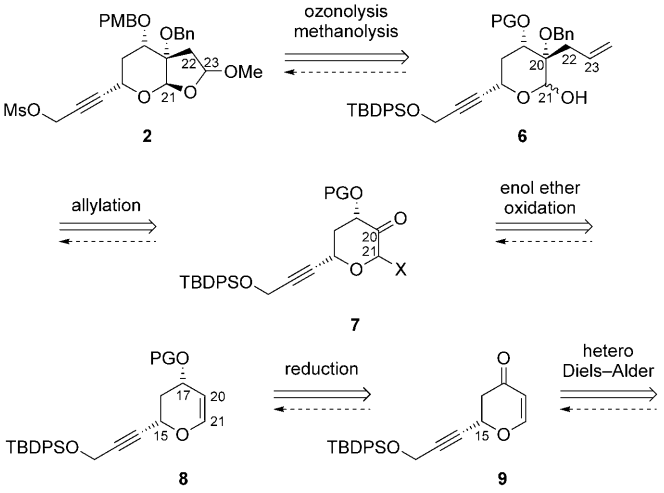


Figure 1. Structure of azadirachtin (**1**).[6]

Although the original route provided sufficient quantities of the propargylic mesylate **2** to complete the synthesis, the route was unnecessarily long. Herein, we describe a concise second-generation approach by building on the knowledge gained during earlier studies.

It was envisaged that the tetrahydrofuran ring present in **2** could be formed by the selective ozonolysis and methanolysis of a hemiacetal **6** (Scheme 2).[8] The requisite allyl group could be introduced by the allylation of a ketone **7**, which in turn could arise through an oxidative sequence from the enol ether **8**. The stereogenic center at C17 could be formed by the diastereoselective reduction of the dihydropyranone **9**, which should be available from an enantioselective hetero Diels–Alder reaction.[9]

Firstly, we investigated the hetero Diels–Alder reaction, for which the aldehyde component **12** was synthesized from readily available 2-propyn-1,4-diol (Scheme 3).[10] However, there are few examples of alkynal derivatives used as substrates in the hetero Diels–Alder reaction,[11] and furthermore the aldehyde **12** was highly unstable. As a result, many catalysts used in hetero Diels–Alder reactions were unsuitable for this transformation and gave either low yield or poor



Scheme 2. Second-generation synthesis plan. PG = protecting group, TBDPS = *tert*-butyldiphenylsilyl.

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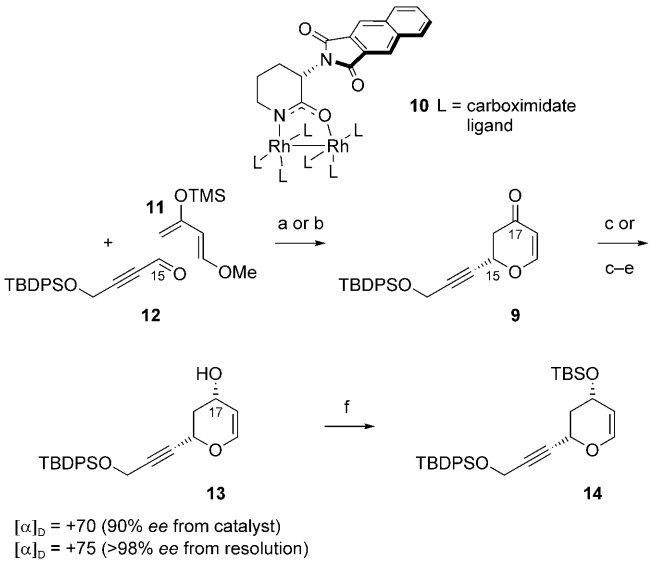
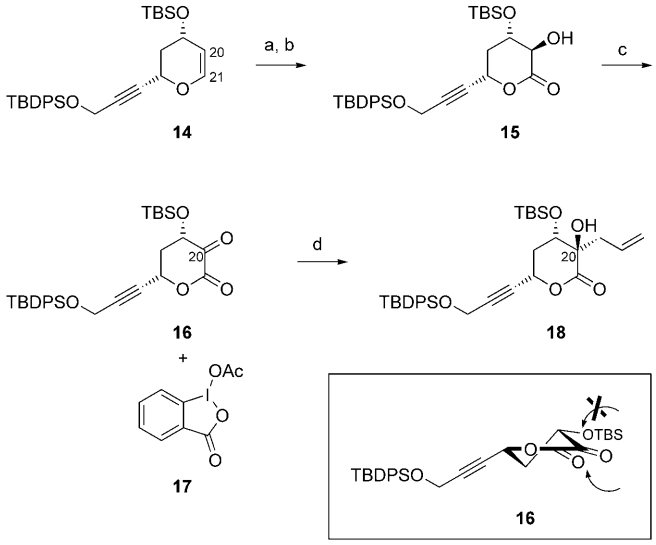


Scheme 3. Preparation of enol ether **14**. a) **10** (2.5 mol%), CH_2Cl_2, −60°C; then TFA, RT, 90% *ee*, 77% (over 2 steps); b) $ZnCl_2$, CH_2Cl_2, 0°C to RT, 86% (over 2 steps); c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, EtOH, −115 to −90°C, 83%; d) Ac_2O, NEt_3, CH_2Cl_2, RT, 96%; e) PS "Amano" lipase (*Burklodleria cepacia*), aqueous pH 7 buffer/acetone (9:1), RT, 43% (45% recovered acetate); f) TBSCl, imidazole, CH_2Cl_2, RT, 95%. TMS = trimethylsilyl, TFA = trifluoroacetic acid.



Scheme 4. Undesired stereochemical outcome in the allylation of the α-keto lactone **16**: a) OsO_4, *N*-methylmorpholine *N*-oxide, *t*BuOH/H_2O (9:1), RT, 98%; b) TEMPO, nBu_4NCl, KBr, NaOCl, CH_2Cl_2/water/brine (2:1:1), 0°C, 71%; c) Dess–Martin periodinane, CH_2Cl_2, RT; then toluene, concentrate in vacuo; d) (allyl)nBu_3Sn, $ZnCl_2$, CH_2Cl_2, RT, 54% (over 2 steps). TEMPO = 2,2,6,6-tetramethyl-piperidin-1-oxyl.

enantiodiscrimination. After considerable experimentation, Hashimoto's dirhodium carboximidate catalyst **10**[11b]—a catalyst specifically optimized for the hetero Diels–Alder reaction of propargylic aldehydes—was able to promote the desired cycloaddition, and gave 90% *ee* and 77% yield over the two steps. Although this approach represents a highly efficient preparation of the hetero Diels–Alder adduct **9**, the cost of the catalyst and time-consuming nature of its preparation encouraged us to prepare **9** as a racemate with the aim of resolving the two enantiomers at a later stage in the synthesis.

With sufficient quantities of the dihydropyranone **9** now available, we next examined the reduction of the ketone at C17. Under Luche conditions[12] at −78°C the desired *syn* geometry (**13**) was formed with an 8:1 preference, but by simply lowering the temperature to −115°C this ratio increased to 11:1. Pleasingly, the undesired epimer could be readily separated and recycled to give the starting ketone **9** by oxidation with TPAP.[13] It was at this stage that we opted to resolve the racemic intermediate and thus the allylic alcohol *rac*-**13** was converted into the corresponding acetate. We found that the PS "Amano" lipase worked rapidly and selectively,[14] and gave the product **13** as a single enantiomer. It was anticipated that the secondary alcohol **13** could be readily protected as its PMB ether (see **2**), but all attempts to install the PMB protecting group met with failure. Instead, protection of **13** as its TBS ether proved straightforward and gave the enol ether **14**.

At this stage we faced a number of possibilities with which to introduce the tetrahydrofuran ring in **2** and we initially targeted the α-keto lactone **16** (Scheme 4). Dihydroxylation of the enol ether **14** proceeded smoothly, but attempts to directly oxidize the corresponding diol to the dicarbonyl **16** proved fruitless. Instead, a stepwise sequence was used in which first, oxidation with TEMPO led to the α-hydroxy lactone **15**. The second oxidation, to generate the dicarbonyl **16**, proved much more challenging. Analysis of the reaction mixture indicated that treatment of the alcohol **15** with Dess–Martin periodinane[15] generated the desired product **16**, but attempts to isolate it by using the standard work-up protocol resulted in decomposition. Attempts to effect in situ allylation of dicarbonyl **16** were similarly unsuccessful. After these disappointing results, we tried to find a method of isolating the fragile product **16**, but both direct concentration of the reaction mixture and attempts to neutralize the reaction mixture resulted in decomposition of the labile product. Eventually, we were able to access the desired dicarbonyl **16** (as a mixture with the oxidant by-product: benziodoxolone **17**) by adding toluene to the crude reaction mixture and removing the acid by-product as a toluene/acetic acid azeotrope.[16] With the dicarbonyl **16** in hand, the allylation was readily achieved using allyl tri-*n*-butyl stannane and zinc(II) chloride.[17] Although the problem of creating and handling the sensitive dicarbonyl **16** had been solved, the selectivity of the allylation reaction gave exclusively the undesired C20-epimer **18**! To explain this result, we propose that the molecule adopts a half-chair conformation in which axial attack promotes delivery of the allyl group from the same side as all of the other substituents on the ring.

However, the enol ether **14** offered several alternatives for the installation of the remaining functionality in the mesylate **2** and we next investigated an acetal unit at C21 (**19**; Scheme 5). Treatment of the enol ether **14** with DMDO rapidly and selectively generated the glycal oxide which, in methanol, underwent ring opening to provide the methyl

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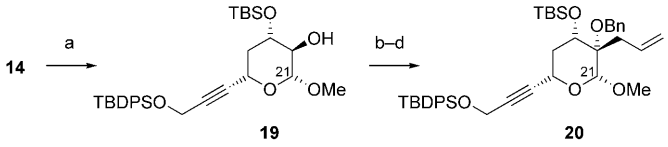
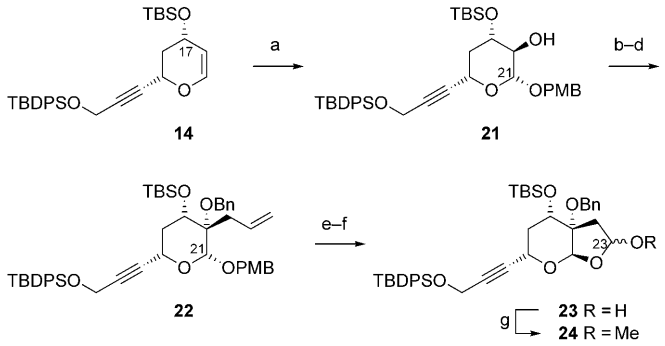


Scheme 5. Preparation of methyl acetal **20** for the synthesis of **2**: a) DMDO, acetone/CH_2Cl_2 (1:1), 0 °C; then MeOH, 82%; b) Dess–Martin periodinane, CH_2Cl_2, RT; c) (allyl)MgBr, THF, −78 °C, 78% (over 2 steps); d) NaH, BnBr, DMF, 0 °C to RT, 62%. DMDO = dimethyldioxirane, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

acetal **19**. Standard manipulations then led to the intermediate **20**, which possesses much of the functionality required to complete the synthesis. Nevertheless, reaction conditions to selectively cleave the methyl acetal at C21 in **20** could not be found.[18]

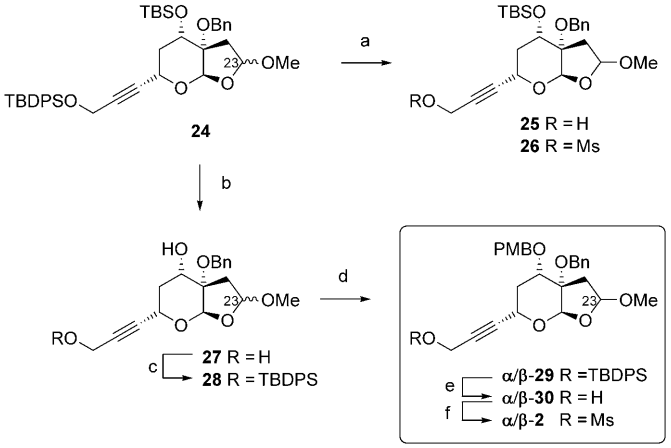
Therefore, we chose an alternative acetal derivative. The glycal oxide (from **14**) was treated with PMB alcohol and zinc(II) chloride to form the PMB-protected acetal **21** (Scheme 6). The nonpolar nature of the molecule allowed



Scheme 6. Completion of the core for propargylic mesylate **2**: a) DMDO, acetone/CH_2Cl_2 (1:1), 0 °C; then PMBOH, $ZnCl_2$, CH_2Cl_2, 0 °C to RT, 86%; b) Dess–Martin periodinane, CH_2Cl_2, RT; c) (allyl)MgBr, THF, −110 °C; d) NaH, BnBr, DMF, 0 °C to RT, 52% (over 3 steps); e) O_3, CH_2Cl_2, −78 °C; then PS–PPh_3, RT; f) CH_2Cl_2 (90 ppm water)/TFA (9:1), RT; g) Amberlyst A-15, molecular sieves (3 Å), MeOH/MeCN (1:10), RT, 1:1 to 1:5 (α/β) mixture of C23-epimers. PS = polystyrene supported.

the excess PMB alcohol to be removed simply by aqueous extraction. Oxidation with the Dess–Martin reagent[15] proceeded smoothly to access the ketone at C20. Then, addition of allyl Grignard reagent at −110 °C generated the desired configuration at C20 with excellent selectivity, and the resulting tertiary alcohol was protected as its benzyl ether **22**—as required for the synthesis of **2**. When we attempted to prepare the hemiacetal (see **6**; Scheme 2), extensive decomposition of the substrate **22** was observed upon treatment with DDQ. The use of trifluoroacetic acid solved this problem[19] and promoted the desired cleavage of the acetal unit to give the δ-lactol. However, we observed an improvement in the overall yield if the sequence of events was altered. Ozonolysis of **22** smoothly generated the aldehyde, which was treated with TFA to effect cleavage of the PMB acetal and resulted in the hemiacetal **23**. Then, the lactol was transformed into the desired methyl acetal **24** (as a mixture of epimers at C23) after acidic methanolysis. It turned out to be serendipitous that earlier attempts to introduce a PMB ether group at C17 were unsuccessful, as its use to protect the hemiacetal unit at C21 was key in the synthesis of the core of mesylate **2**.

With the carbon framework of the mesylate **2** in place, all that remained was manipulation of the protecting groups (Scheme 7). Treatment of the bis(silyl ether) **24** with one



Scheme 7. Final steps in the second-generation synthesis of propargylic mesylate fragments **2** and **26**: a) TBAF, THF, RT, 39% (over 4 steps); b) TBAF, THF, RT, 39% (over 4 steps); c) TBDPSCl, imidazole, CH_2Cl_2, RT, 87%; d) NaH, PMBBr, nBu_4NI, DMF, 0 °C to RT, 26% α-**29**, 52% β-**29**; e) TBAF, THF, RT, 96% α-**30**; 84% β-**30**; f) Ms_2O, iPr_2NEt, CH_2Cl_2, 0 °C, 90%. TBAF = tetra-*n*-butylammonium fluoride.

equivalent of either HF·pyridine or TBAF resulted in highly selective formation of the propargyl alcohol **25**. The corresponding propargylic mesylate **26** represents a potential intermediate for a second-generation synthesis of azadirachtin; however, the fragment **2** that was used previously in the synthesis of azadirachtin contained a PMB ether at C17. Consequently, the bis(silyl ether) **24** was treated with an excess of TBAF to effect complete desilylation. Reprotection of the less hindered primary alcohol **27** allowed access to the secondary alcohol **28** which could then be transformed into the corresponding PMB ether **29** using PMB bromide and sodium hydride in the presence of nBu_4NI. At this stage the C23 epimers **29** were separated by column chromatography and, as both represent precursors to the natural product,[4a] TBAF was used to effect removal of the TBDPS protecting group to give the corresponding propargylic alcohols α-**30**/β-**30**, which were identical in all respects to those prepared previously[7] (see the Supporting Information).

In summary, by generating and using the α-keto lactone **16** we have discovered a highly selective method of introducing substitution in a δ-lactone and have devised a convenient work-up procedure for the isolation of sensitive Dess–Martin oxidation products. After extensive experimentation, it was found that the PMB-substituted acetal **22** could be elaborated to complete a second-generation synthesis of propargylic mesylate **2**. Notably, all of the stereogenic centers in the

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molecule were selectively installed using the single stereocenter at C15, which was set by a highly effective enantioselective hetero Diels–Alder reaction. Overall, this route represents a highly efficient preparation of the azadirachtin coupling partner **2**, and proceeded in only 17 steps (compared to 26 steps for the original route). Studies are currently underway towards a second-generation synthesis of the decalin portion **3** of this ever-fascinating molecule azadirachtin (**1**).

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