VIP Total Synthesis

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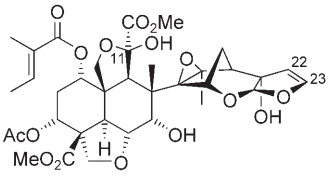
A Relay Route for the Synthesis of Azadirachtin**

*Gemma E. Veitch, Edith Beckmann, Brenda J. Burke, Alistair Boyer, Carles Ayats, and Steven V. Ley**

The study of a plant's natural defence mechanisms against predatory insect attack often leads to the discovery of novel molecules that have important biological effects. Such is the case with azadirachtin (**1**), a fascinating natural product first



azadirachtin (**1**)

isolated from the Indian neem tree *Azadiracta indica (A. Juss)*, in 1968.[1] Azadirachtin exhibits potent antifeedant and growth-disruptant properties against a broad spectrum of insect species yet displays very low mammalian toxicity (LD_{50}(rat) $> 5\ g\,kg^{-1}$) and appears to cause little disruption to beneficial species such as pollinating bees and ladybirds.[2]

The structure of this complex natural product was finally elucidated following many years of intense research[1,3–11] culminating in the publication of three back-to-back full papers in 1987.[7–9] Likewise, understanding of the precise mode of action of azadirachtin continues to evolve. Detailed studies have revealed an elaborate set of interactive pathways, the full discussion of which is beyond the scope of this short communication.[12]

In preparation for the total synthesis and to define the structure–activity relationships of azadirachtin,[13–17] we have been engaged in an extensive investigation of its reactivity pattern,[18] in particular its propensity for rearrangement under acidic[19] basic[13] and photolytic[20] conditions. Based on our cumulated experience in this regard,[21,22] we have devised a new relay route that has proved instrumental for the synthesis of azadirachtin.[23,24]

[*] G. E. Veitch, Dr. E. Beckmann, Dr. B. J. Burke, A. Boyer, Dr. C. Ayats, Prof. Dr. S. V. Ley
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge, CB2 1EW (UK)
Fax: (+44) 1223-336-442
E-mail: svl1000@cam.ac.uk
Homepage: http://leygroup.ch.cam.ac.uk

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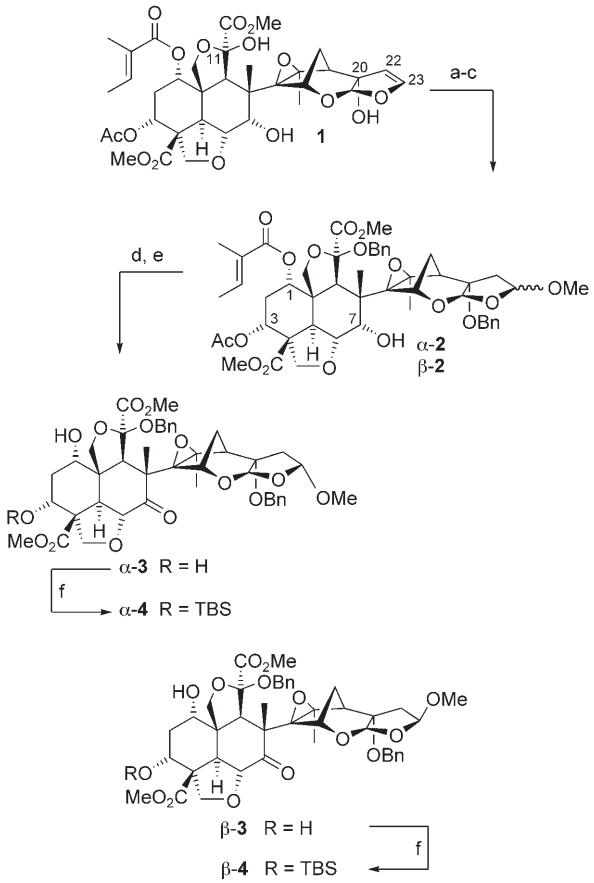
Azadirachtin (**1**) represents an exceptionally challenging synthetic target by virtue of its sixteen contiguous stereogenic centers and complex pattern of oxygen-containing functionalities. The conformation and reactivity of azadirachtin are strongly influenced by the presence of intramolecular hydrogen-bonding interactions, evident from X-ray crystallographic studies.[6,25] In addition, both the hemiacetal at C11 and the C22–C23 enol ether are sensitive functionalities and are therefore important considerations in the design of any total synthesis.

Potential strategies for the masking of the C22–C23 enol ether had been investigated previously,[21,22] where it was found that a C23 methyl acetal was particularly stable in subsequent transformations. Although this derivative was accessed as an epimeric mixture, further studies[21] employed only the β-C23 epimer. We anticipated that this might present a severe disadvantage in our forward synthesis, as it could be difficult to control this stereogenic center. Work reported herein addresses this problem by providing a new relay route that can utilize both epimeric forms (Scheme 1).

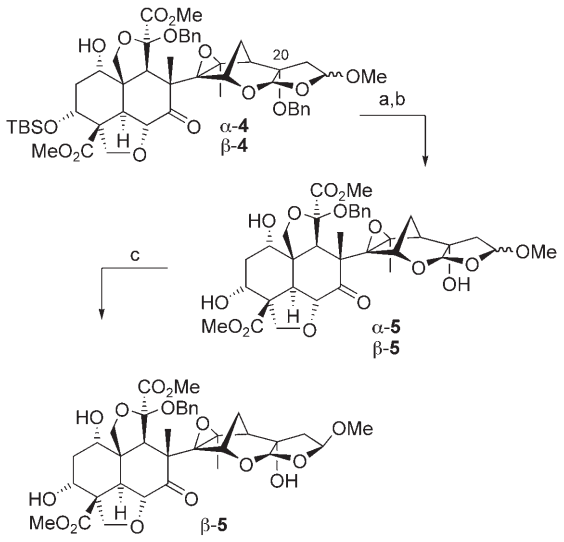
Accordingly, preparation of relay target **4** commenced with a methoxybromination/reduction protocol, thus converting the reactive enol ether present in **1** to a 1:1 mixture of its C23 α and β methyl acetals. Silver oxide mediated alkylation then permitted selective protection of the C11 and C20 hydroxy groups providing dibenzyl ether **2**.[26] Oxidation of the remaining C7 hydroxy group present in **2**, followed by saponification of the C1 2-methylcrotonoyl (tigloyl) and C3 acetyl esters afforded intermediate **3**. At this stage the C23 diastereomers were separated and the individual epimers converted to their C3 silyl ethers (α-**4** and β-**4**).[27]

Attention was then turned towards the synthesis of azadirachtin from α-**4** and β-**4**, in order to establish these silyl ethers as our new targets for total synthesis (Scheme 2). TBAF-mediated desilylation of α-**4** and β-**4** followed by selective hydrogenolysis of the C20 benzyl ether generated triols α-**5** and β-**5** in excellent yield.[28] As the C23 β epimer of intermediate **5** had been converted to azadirachtin in a first-generation relay approach,[21] it was desirable to epimerize the C23 α epimer in order to link our new route to these previous relay studies. Consequently, the α epimer (α-**5**) was treated with Amberlyst 15 and methanol in acetonitrile resulting in a 1:1 mixture of diastereomers, from which the desired epimer (β-**5**) could be isolated cleanly.

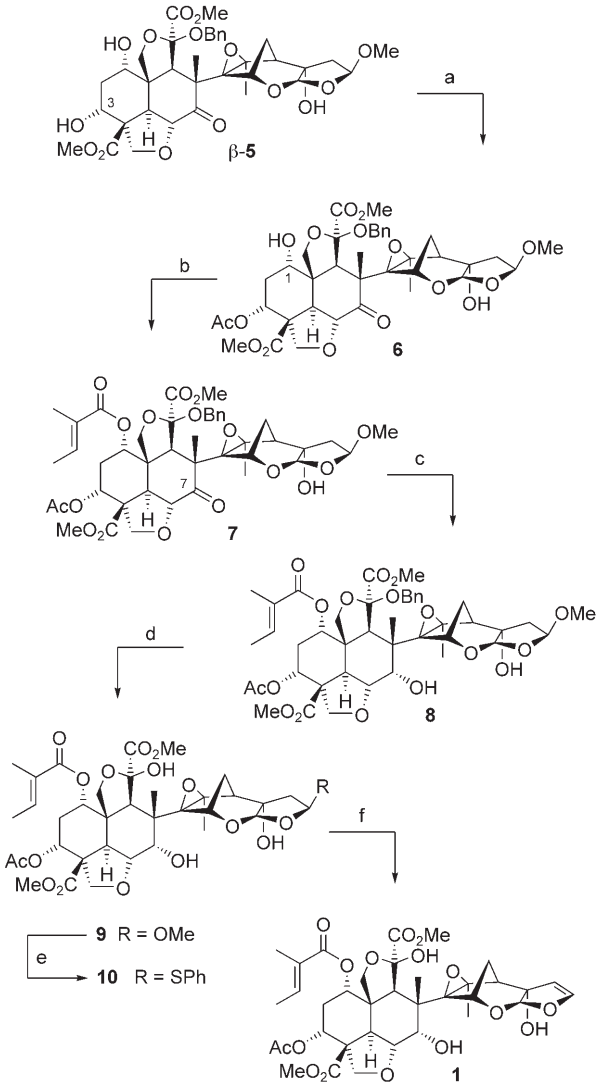
Selective acetylation at the C3 position of triol β-**5** was then achieved under standard conditions to provide acetate **6** in good yield (Scheme 3). However, esterification of the hindered C1 hydroxy group proved more problematic. A wide variety of reagents were screened for this pivotal transformation, most of which proved unsuccessful. Our previously



Scheme 1. Degradation of azadiractin (**1**) to relay target **4**. Reagents and conditions: a) NBS, MeOH, RT, quant.; b) Bu_3SnH, AIBN, toluene, reflux, 91%; c) BnBr, Ag_2O, DMF, RT, 60%; d) DMP, CH_2Cl_2, RT, 99% e) Et_3N/MeOH/H_2O (1:5:1), 65 °C, 99%; f) TBSOTf, *i*Pr_2NEt, CH_2Cl_2, −78 °C, 90%. AIBN = azobis*iso*butyronitrile, Bn = benzyl, DMP = Dess–Martin periodinane, MS = molecular sieves, NBS = *N*-bromosuccinimide, TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate.



Scheme 2. Return of α-**4** and β-**4** to azadirachtin (**1**). Reagents and conditions: a) TBAF, THF, 0 °C, α: quant., β: quant.; b) Pd/C, 10 bar H_2, MeOH, RT, α: 99%, β: 85%; c) Amberlyst 15, 3 Å MS, MeOH, MeCN, RT, 49%. TBAF = tetra-*n*-butylammonium fluoride.



Scheme 3. Return of **5** to azadirachtin (**1**). Reagents and conditions: a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 74%; b)$CH_3CH(CH_3)(CO)O(CO)C_6H_2Cl_3$, Cs_2CO_3, toluene, reflux, 6 d, 50% (80% based on recovered starting material); c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 49%; d) Pd/C, H_2, MeOH, RT, 81%; e) PhSH, PPTS, CH_2ClCH_2Cl, 80 °C, 70%; f) DMDO, CH_2Cl_2, −78 °C–RT, then toluene, reflux, 67%. DMAP = 4-dimethylaminopyridine, DMDO = dimethyldioxirane, PPTS = pyridinium toluene-*p*-sulfonic acid.

described relay route utilized the highly reactive tigloyl fluoride to effect formation of **7**, albeit in poor yield (19%).[21] Following extensive optimization studies, we are now able to obtain tiglate **7** in 50% yield by treatment of **6** with a tiglic acid/Yamaguchi mixed anhydride[29] and Cs_2CO_3 in refluxing toluene. Pleasingly, unreacted starting material can be recovered from this reaction and further converted to the desired product.

The next hurdle in our synthesis was the stereoselective reduction of the C7 ketone present in **7** to provide the requisite axial alcohol found in the natural product. Owing to the high degree of steric hindrance about this C7 center, it was not possible to employ bulky reducing reagents such as L-Selectride. Matters were complicated further by the presence

of the C1 tigloyl ester, which was also susceptible to conjugate reduction. Finally, it was found that Luche[30] conditions cleanly reduced the C7 ketone, although a 1:1 mixture of diastereomers was obtained.[21] The unwanted equatorial alcohol could, after separation, be reoxidized and subsequently reduced, to give yields of **8** up to 75% after one recycle. Cleavage of the benzyl ether of **8** then proceeded smoothly to furnish C11 lactol **9** in excellent yield, with no concomitant reduction of the tiglate functionality.

At the conclusion of the relay synthesis, the sensitive C22–C23 enol ether was unmasked by first converting methyl acetal **9** to phenyl sulfide **10** upon treatment with thiophenol and catalytic PPTS in toluene. Oxidation of **11** with DMDO, followed by pyrolysis, reinstalled the enol ether, thereby completing the relay sequence between azadirachtin (**1**) and **5**.[21]

The work reported herein defines key intermediates that, through a series of selective transformations, can be converted to the natural product azadirachtin (**1**), a potent insect antifeedant and growth-disrupting agent. This study sets the stage for the effective total synthesis of this elusive molecule, the details of which are disclosed in the following communication.[23]

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[24] The availabilty of azadirachtin has permitted its use in this relay approach, however, it can only be obtained commercially as crude neem extract (30% azadirachtin), which requires extensive purification prior to use.
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[26] The C11,C20 dibenzylated compound was the major product, but it was accompanied by small quantities of mixed-alkylation products, the ratios of which were dependent on the reaction conditions.
[27] C1 reactivity during alkylation reactions was in all examples lower than at any other position, presumbaly owing to steric constraints imposed by the molecule's conformation.
[28] Selectivity in the debenzylation was obtained by careful experimentation and solvent screening.
[29] The tiglic acid/Yamaguchi mixed anhydride was purified prior to use, for details see M. Ball, S. P. Andrews, F. Wierschem, E. Cleator, M. Smith, S. V. Ley, *Org. Lett.* **2007**, *9*, 663–666.
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