VIP Total Synthesis

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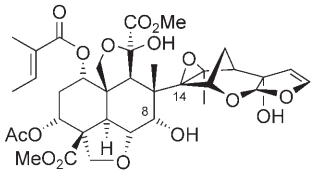
Synthesis of Azadirachtin: A Long but Successful Journey**

*Gemma E. Veitch, Edith Beckmann, Brenda J. Burke, Alistair Boyer, Sarah L. Maslen, and Steven V. Ley**

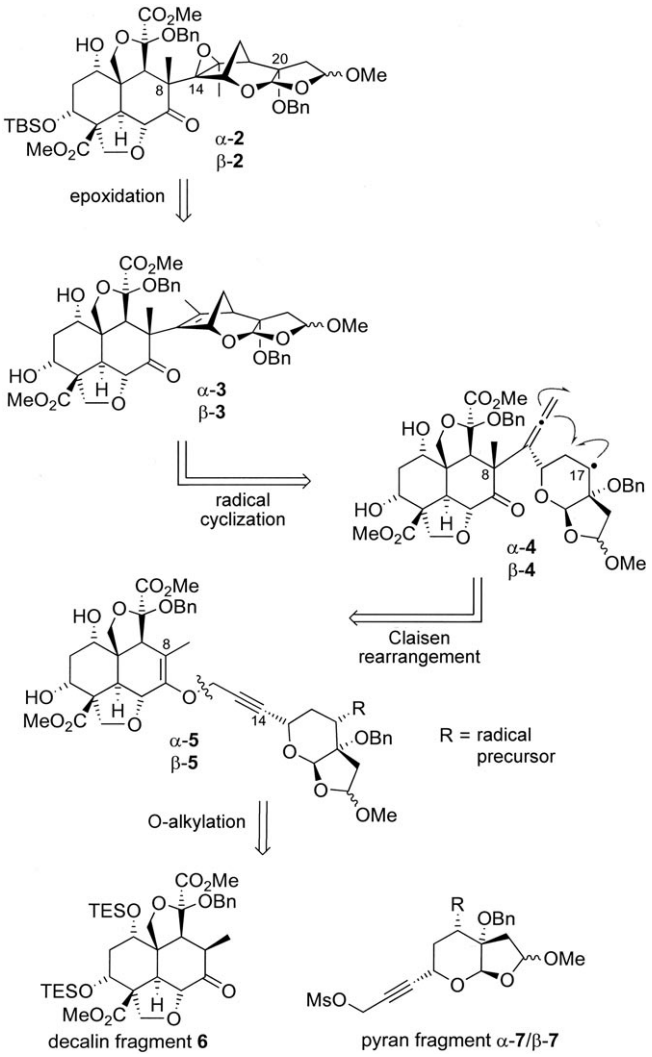
Azadirachtin (**1**)[1] is a complex natural product that has been at the center of structural,[2–5] biological,[6] and synthetic studies[7,8] ever since its isolation from the Indian neem tree *Azadirachta indica* in 1968.[9]



azadirachtin (**1**)

Despite enormous efforts within the synthetic community its synthesis has, until now, resisted all attempts. This is undoubtedly due to its complex molecular architecture, which comprises sixteen contiguous stereogenic centers, seven of which are tetrasubstituted carbon atoms. Azadirachtin possesses a diverse array of oxygenated functionalities in addition to a rigid conformation imposed by intramolecular hydrogen-bonding.[5] Furthermore its sensitivity to acid and base together with its photoinstability make it particularly prone to rearrangement[10] thereby frustrating many synthesis plans. Nevertheless we are pleased to report a successful outcome to our ambitions making use of both relay studies and prior work from our group.[11,12]

A degradative approach towards azadirachtin has been adopted in order to facilitate the investigation of end-game strategies, thereby rendering intermediate **2** the current target for total synthesis (Scheme 1).[11,12] The critical consideration in any approach towards azadirachtin is the construction of the sterically congested C8–C14 bond.[13] We originally envisioned a highly convergent strategy in which this central bond could be forged by the coupling of two fragments, which together contain all the requisite functionality for conversion



Scheme 1. Retrosynthetic analysis. Bn = benzyl, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

to the natural product. However, all attempts to directly install the C8–C14 linkage met with failure,[8,14] and an alternative was therefore sought. Our current approach was devised to maintain a high level of convergency whilst minimizing steric crowding in the fragment coupling process by selective O-alkylation of **6** with **7**.

Our new synthetic route relies on a late-stage, facially selective epoxidation to provide intermediate **2** from tetrasubstituted alkene **3**, which in turn is accessible from 5-*exo* cyclization of the C17 radical species **4**. In order to circumvent problems associated with intermolecular C8–C14 bond formation, it was envisaged that this central linkage be con-

[*] G. E. Veitch, Dr. E. Beckmann, Dr. B. J. Burke, A. Boyer, S. L. Maslen, 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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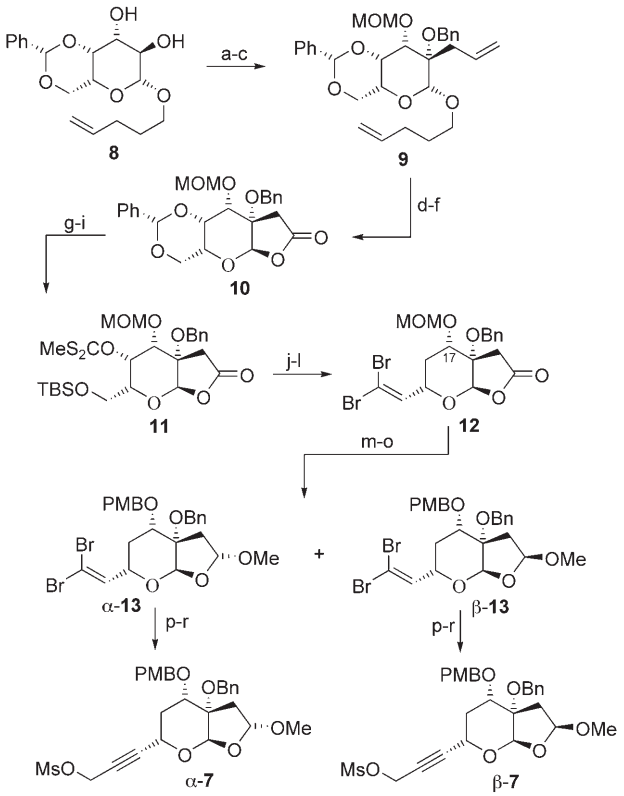
structed by Claisen rearrangement of propargylic enol ether **5**. Intermediate **5** could then derive from O-alkylation of decalin **6** with propargylic mesylate **7**. Decalin fragment **6** was available both by total synthesis, published previously within our group,[15] and also by degradation of the natural product.[16]

The synthesis of pyran coupling partner **7** commenced from known diol **8**, available in three steps from β-D-galactose pentaacetate (Scheme 2).[17] Standard protecting-group manipulation and an oxidation/Grignard-addition sequence led to differentially protected carbohydrate **9** as the only observed diastereoisomer.[18] The requisite tetrahydrofuran



Scheme 2. Synthesis of propargylic mesylates **7**. Reagents and conditions: a) Bu_2SnO, MeOH, reflux, then MOMCl, 1,4-dioxane, RT, 82%; b) 1. SO_3·py, DMSO, *i*Pr_2NEt,CH_2Cl_2, 0°C; 2. AllylMgCl, THF, −78°C, 85%; c) BnBr, NaH, DMF, RT, 87%; d) NBS, MeCN/H_2O (9:1), pH 7, RT, 60%; e) Zn, EtOH, NH_4Cl, 80°C, 99%; f) 1. O_3, CH_2Cl_2, −78°C, then PS-PPh_3, RT; 2. TPAP, NMO, CH_3CN, RT, 95%; g) CH_2Cl_2/TFA/H_2O (20:1:1), RT, 99%; h) TBSCl, DMAP, DMF, NEt_3, RT, 90%; i) CS_2, NaHMDS, −78°C, then MeI, −78°C, 99%; j) AIBN, *n*Bu_3SnH, toluene, 110°C, 70%; k) CH_2Cl_2/TFA/H_2O (20:1:1), RT, 80%; l) 1. SO_3·py, DMSO, *i*Pr_2NEt, CH_2Cl_2, 0°C; 2. *t*BuOK, Ph_3PCHBr_2·Br, THF, RT, 80%; m) TMSBr, CH_2Cl_2, 0°C, 82%; n) PMBTCA, $La(OTf)_3$, THF, RT, 90%; o) 1. DIBAL-H, CH_2Cl_2, hexane, −78°C; 2. Amberlyst15, MeOH, RT, 70%; p) MeLi·LiBr, THF, −78°C–0°C, 80%; q) *i*PrMgCl, $(CH_2O)_n$, THF, 45°C, 80%; r) Ms_2O, *i*Pr_2NEt, CH_2Cl_2, 0°C, 90%. AIBN = azobisisobutyronitrile, DIBAL-H = diisobutylaluminium hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethyl formamide, DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazanide, MOMCl = chloromethyl methyl ether, NBS = *N*-bromosuccinimide, NMO = *N*-methyl morpholine-*N*-oxide, PMBTCA = *p*-methoxybenzyl trichloroacetimidate, PS = polymer support, py = pyridine, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethane sulfonyl, TFA = trifluoroacetic acid, TPAP = tetrapropylammonium perruthenate.

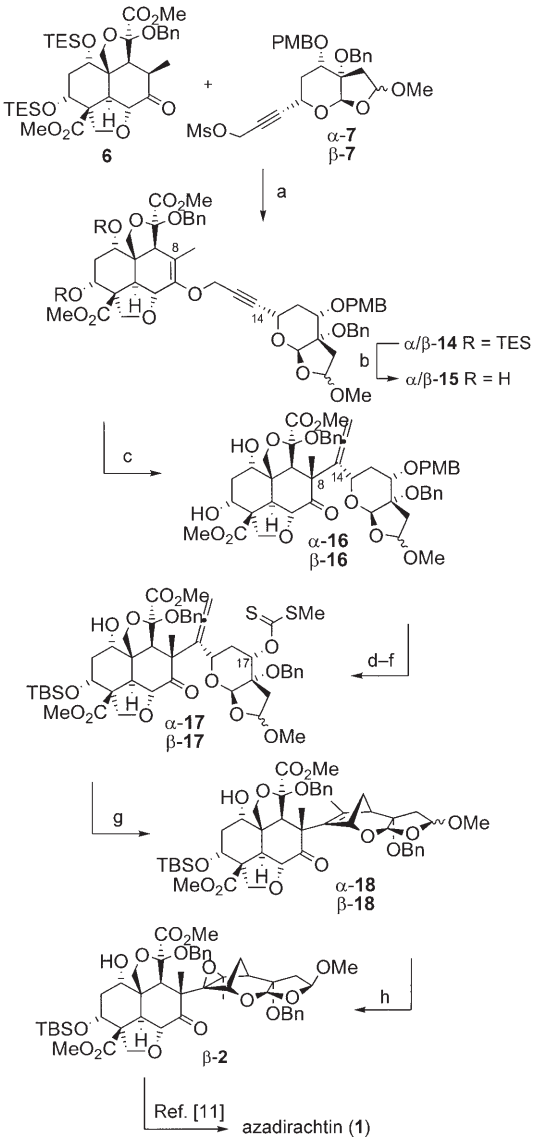
ring was constructed by deglycosidation[19] and ozonolysis of allyl tetrahydropyran **9** followed by oxidation of the resulting lactol to lactone **10**.[20] Transformation of **10** to xanthate **11** was followed by Barton–McCombie deoxygenation[21] and an oxidation/Wittig protocol to yield dibromoolefin **12**. At this stage it was necessary to use an alternative protecting group at C17 as preliminary studies had shown that the MOM ether could not be removed selectively at a more advanced stage of the synthesis.[8,22]

The MOM ether of **12** was therefore cleaved and replaced with a PMB ether, and a reduction/acetalization sequence was then performed to yield a 1:1 mixture of the two diastereomers α-**13** and β-**13**, which could be separated by column chromatography. The two epimers of **13** were then independently subjected to Corey–Fuchs alkynylation conditions and further homologated with *para*-formaldehyde, and the resulting propargylic alcohols were treated with methanesulfonic anhydride to furnish the desired propargylic mesylates α-**7** and β-**7** ready for coupling with decalin fragment **6**. At this stage we had made no firm decisions as to whether one or both of these diastereomers would be brought forward to the natural product. In the end both served as viable precursors.[23]

With the fully functionalized fragments α-**7**/β-**7** and **6** in hand, it was finally possible to effect the crucial coupling reaction (Scheme 3). Preliminary studies indicated that a tenfold excess of decalin **6** was required for complete conversion to propargylic enol ether **14**,[24,25] which subsequently underwent TBAF-mediated desilylation to afford diol **15**. Claisen rearrangement[26] of propargylic enol ether **15** under thermal or gold(I)-catalyzed conditions was then employed both to construct the key C8–C14 bond whilst simultaneously installing the requisite allene for the ensuing radical cyclization leading to **16**. Following protecting-group manipulations, the desired C17 radical precursor **17** was formed in anticipation of the pivotal cyclization event. As expected from model studies,[25] treatment of **17** with tributyltin hydride and AIBN in refluxing toluene initiated 5-*exo* cyclization to smoothly furnish alkene **18**.

Selective epoxidation of tetrasubstituted alkene **18**, the only remaining step in the synthesis, presented the greatest synthetic challenge. Following extensive optimization, we were finally rewarded when prolonged heating of **18** with magnesium monoperoxyphthalate[27] in the presence of a radical inhibitor resulted in the formation of relay intermediate **2** for the first time (Scheme 3). Interestingly, epoxidation of both α- and β-**18** yielded the β diastereomer of our relay target (β-**2**), implying an epimerization of alkene α-**18** to its β form prior to epoxidation. This assumption is also supported by the lower yield from the transformation of α-**18**. Epoxide β-**2** was identical in all respects to material derived from our relay studies[11] and therefore constitutes the final step in the synthesis of azadirachtin (**1**).

The work reported herein represents the conclusion of a 22-year synthesis journey leading to the first successful preparation of the insect antifeedant azadirachtin. While only a fragment of the total synthesis effort is reported here, the challenge has, over the years, generated new chemistry and elucidated a wealth of information concerning the



Scheme 3. Fragment coupling and completion of the synthesis. Reagents and conditions: a) NaH, [15]crown-5, THF, 0 °C, α: 81 %, β: 76 %; b) TBAF, THF, 0 °C, α: 90 %, β: 95 %; c) Microwave, 1,2-dichlorobenzene, 185 °C, 80 % or $[(Ph_3PAu)_3O]BF_4$, CH_2Cl_2, RT, 80 %; d) TBS-imidazole, DMF, 100 °C, α: 70 %, β: 90 %; e) DDQ, CH_2Cl_2, H_2O, RT, 85 %; f) CS_2, NaHMDS, THF, −78 °C, then MeI, −78 °C 60 % over two steps; g) Bu_3SnH, AIBN, toluene, 100 °C, high dilution, 80 %; h) MMPP·H_2O, 5-*tert*-butyl-4-hydroxy-2-methyl-phenyl-sulfide, $NaHCO_3$, MeOH, 105 °C, sealed tube, 7 d, α:20 % (85 % based on recovered starting material) β: 50 % (85 % based on recovered starting material). DDQ = dichlorodicyanoquinone, MMPP = magnesium monoperoxyphthalic acid, TBAF = tetra-*N*-butylammonium fluoride.

biological properties of this fascinating molecule. We can only anticipate that this will be the start of other research programs, which one day may lead to alternative compounds for insect pest control.

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[23] This route provided a total of 0.8 g of propargylic mesylates **7**, which was subsequently coupled with decalin fragment **6**.

[24] While we do see mixtures of O- and C-alkylation products in experiments with simplified models of both fragments, pleasingly exclusive O-alkylation is observed in the real system, which we believe to be due to fortuitous steric factors.

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