DOI: 10.1002/anie.200802675

Natural Product Synthesis

The Azadirachtin Story

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Keywords:
antifeedants · Claisen rearrangement · epoxidation · natural products · radical cyclization

Azadirachtin has been the subject of intensive research within the scientific community ever since its isolation from the neem tree in 1968. There are now over 1000 publications relating to this natural product which cover all aspects of structural, biological and synthetic studies. Herein, we describe the worldwide synthesis efforts towards this fascinating molecule.

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1. Introduction

The neem tree, *Azadirachta indica* (A. Juss 1830), is a large evergreen tree that has been known and revered within the Indian sub-continent for over 2000 years (Figure 1). In ancient Sanskrit writings it is referred to as Arishtha, "reliever of sickness", owing to its wide-spread application in Ayurvedic and Unani medical treatments:[1,2] leaf extracts have been used therapeutically against leprosy and malaria whilst the bark has served to relieve pain and combat fever.[3] However, perhaps the most impressive property of neem reported to date is its ability to repel insect pests. Although this property had been exploited in India for generations,[4] it was not until 1959 that Heinrich Schmutterer brought neem to the attention of the Western world. During an invasion of locusts in the Sudan, he observed that the neem tree was the only plant which remained relatively undamaged while all other vegetation was consumed. Though swarms of locusts settled on the tree, all left without feeding or causing significant damage to this potential food source.[1]

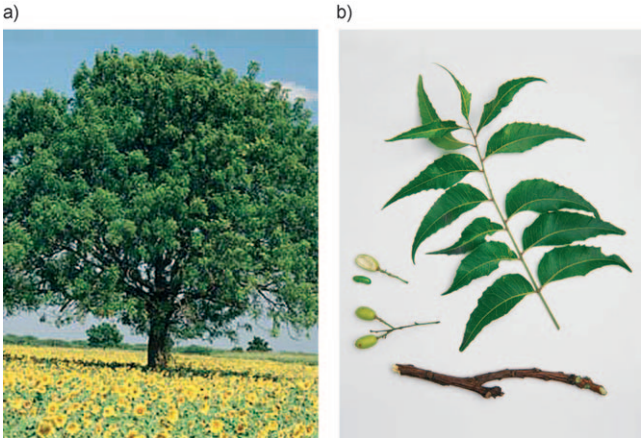

Figure 1. a) The neem tree. b) Leaves, twigs and seeds from the neem tree.

Following a systematic search, a new compound was isolated from seed kernels of the neem tree which suppressed feeding in the desert locust *Schistocerca gregaria*.[5] This substance was named azadirachtin and preliminary structural studies revealed several of the molecular fragments present: a decalin core, a dihydrofuran acetal unit and three distinct ester groups (Figure 2).[6] In the absence of modern spectroscopic techniques, no further refinement was possible at the time.

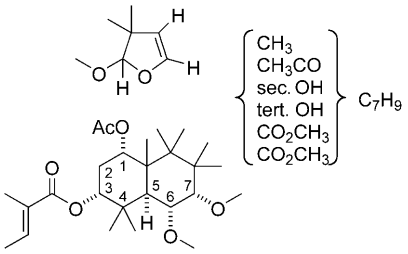

Figure 2. Early molecular fragments proposed for azadirachtin.[6]

The azadirachtin molecule was soon shown to be effective systemically in plants[7] and to possess wide-ranging growth disruptant properties as well as phenomenal antifeedant activity.[8] In spite of this, more than seven years passed before the first complete structural proposal for azadirachtin was presented by Nakanishi and co-workers (**1**, Figure 3).[9] Their interpretations employed both partially relaxed Fourier transform ^{13}C NMR spectroscopy and the hypothetical rela-

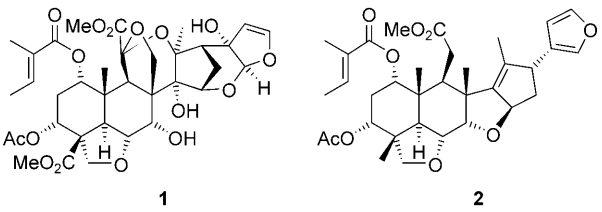

Figure 3. Nakanishi's azadirachtin **1**[9] and salannin **2**.[10]

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tionship of azadirachtin to known terpenoids such as salannin **2**.[10]

Nakanishi's azadirachtin **1** silenced the synthetic community and no further studies were published until 1984 when Kubo reported the isolation and structural elucidation of an azadirachtin congener.[11] This molecule was named desacetylazadirachtinol and assigned structure **3** (Figure 4), largely based upon the Nakanishi structure.

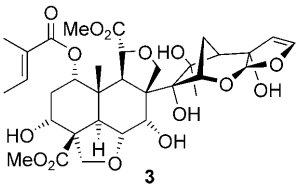

Figure 4. Kubo's desacetylazadirachtinol **3**.[11]

Although the structure of azadirachtin (as **1**) had been widely accepted for ten years, when we came to devise a synthesis route to this molecule we had occasion to re-examine the NMR data and became doubtful of the published structure.[12] Based on further NOE studies, we proposed an alternative structure for azadirachtin in early 1985, which revised a number of aspects, particularly those relating to the decalin framework (**4**, Figure 5).

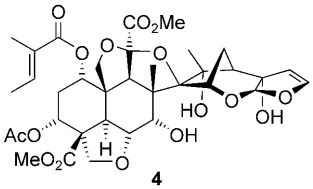

Figure 5. Ley's first structural reappraisal of azadirachtin.[12]

However, later in the same year we were able to grow crystals suitable for X-ray diffraction of an azadirachtin derivative **6**, which led us to unequivocally[13] identify **5** as the correct constitution for the natural product (Figure 6).[14] A preliminary communication, which detailed these findings

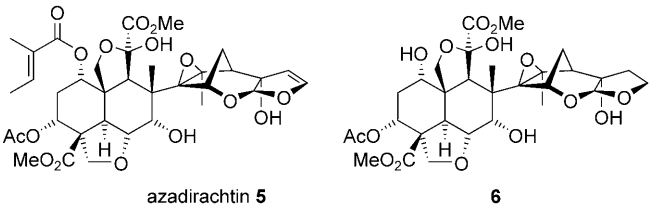

Figure 6. Azadirachtin **5** and a crystalline derivative **6**.[15,18]

was received by the Journal of the Chemical Society on the 17th September 1985.[15]

Following our correct reassignment of the decalin portion of azadirachtin,[12] Kraus et al. expressed similar doubts about the Nakanishi structure and, based upon more detailed NMR data, were able to independently discern the epoxide feature in **5**.[16] These results brought to an end a saga which tested the very limits of structural analysis at the time and paved the way for the real challenge: the synthesis of this fascinating molecule.[17–19]

2. The Chemistry of Azadirachtin

2.1. Derivatisation and Structure–Activity Relationships

At the outset, we chose to investigate the chemical reactivity profile of azadirachtin both to establish the functional groups responsible for activity and to aid the development of a viable synthesis plan. Early on in the program it was demonstrated that the enol ether double bond in **5** could be selectively hydrogenated to give **7** (Scheme 1).[18] Further hydrogenation of **7** then provided the tetrahydro-derivative **8**.[20] These studies proved to be important as the resulting compounds **7** and **8** were considerably more stable than azadirachtin to acidic and photo-oxidative conditions, yet retained potent antifeedant activity.[20]

Selective functionalisation of the C22–C23 enol ether present in azadirachtin (**5**) was also explored. Clean addition reactions occurred either with acetic acid alone or with alcohols in the presence of bromine (Scheme 2).[20,21] The resulting adducts (**9** and **10**) were of value to our on-going structure–activity studies, indicating that an increase in steric

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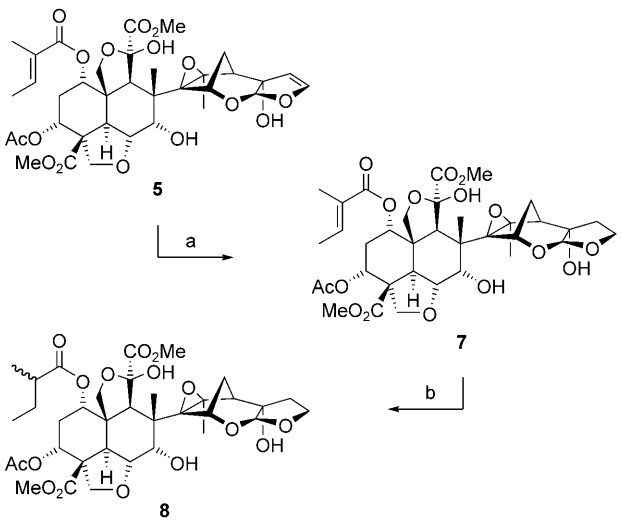
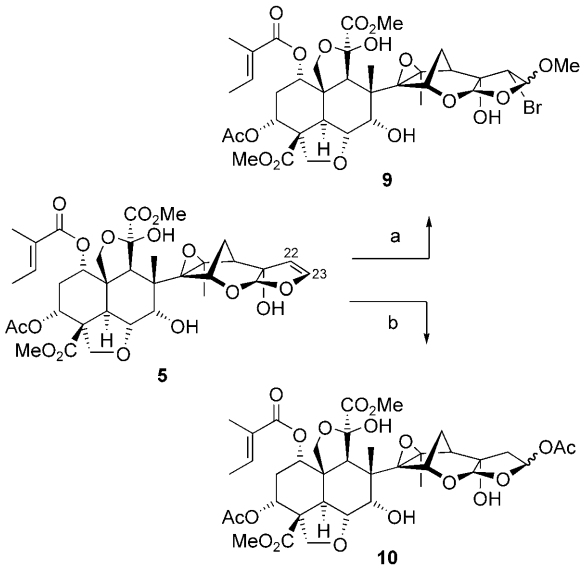
Alistair Boyer, originally from Warrington (UK), studied Natural Sciences at the University of Cambridge (2000–2004). He completed a MSci project with Professor Andrew B. Holmes and is currently a Ph.D. student in Professor Ley's research group working towards a second-generation synthesis of azadirachtin.



Scheme 1. Hydrogenation of azadirachtin.[18,20] Reagents and conditions: a) Pd/C, H_2, MeOH, RT, 3.5 h, 76%; b) Pd/C, H_2, MeOH, RT, 24 h, 53%.



Scheme 2. Functionalisation of the enol ether double bond in **5**.[20,21] Reagents and conditions: a) Br_2, MeOH, RT, 96%; b) AcOH, RT, 3 d, 95%.

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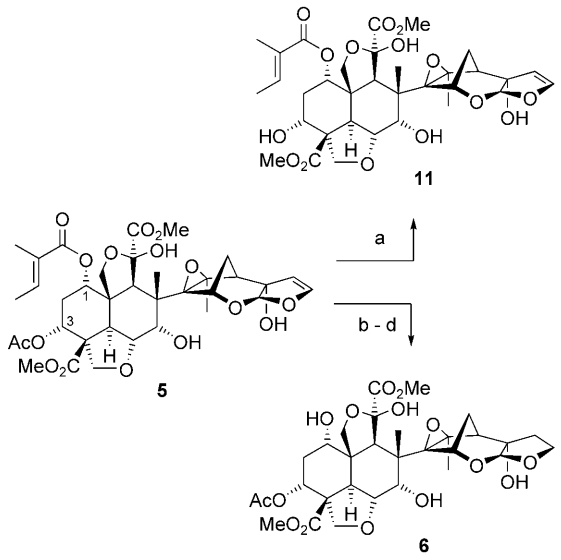
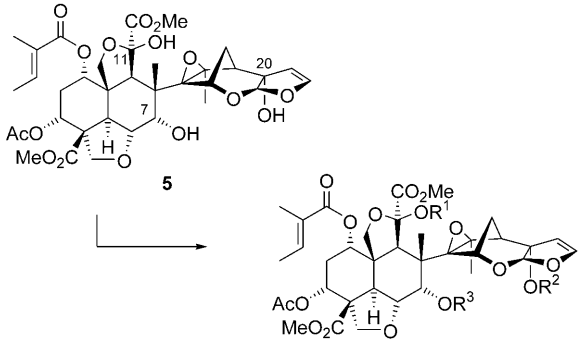
bulk in this region of the molecule generally resulted in decreased antifeedant activity.[20]

Saponification of the ester groups, present in **5**, was first accomplished by Morgan,[6] who observed that the C3 acetate could be rapidly removed upon basic hydrolysis to afford **11** (Scheme 3). Following hydrogenation of the enol ether double bond in **5**, the C1 tigloyl ester could also be removed selectively in an oxidation/hydrolysis sequence to give **6**. Interestingly, both compounds **6** and **11** retained biological activity equivalent to azadirachtin itself.[20]



Scheme 3. Hydrolysis reactions of azadirachtin.[6] Reagents and conditions: a) aq. KOH, MeOH, RT, 1 h, then CH_2N_2, $CHCl_3$, 13%; b) PtO_2, H_2, EtOAc, 50 lb in^{-2}, RT, 1 h, 60%; c) $NaIO_4$, $KMnO_4$, *t*BuOH, water, RT, 75 min, 22%; d) $NaHCO_3$, MeOH, RT, 70 min, 37%.

Significantly, alkylation of the three hydroxy groups in azadirachtin could also be achieved in a highly selective fashion (Scheme 4).[22] Treatment of **5** with methyl iodide and silver(I) oxide for only 2 h at 40 °C provided the 11-

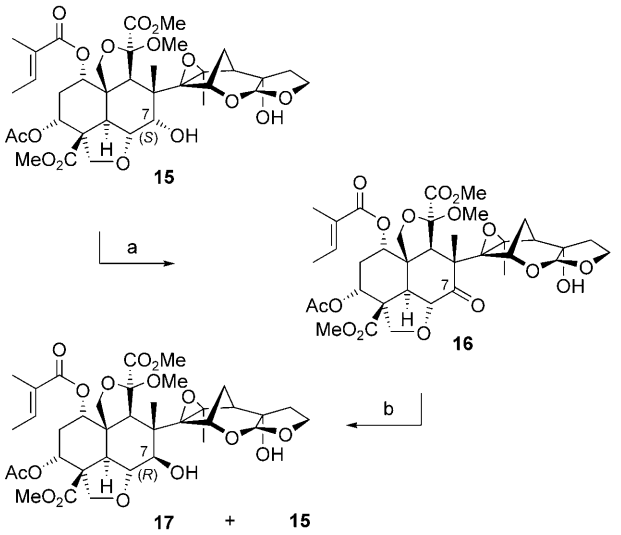


route a: **12** R^1 = Me, R^2 = R^3 =H
route b: **13** R^1 = R^2 = Me, R^3 =H
route c: **14** R^1 = R^2 = R^3 = Me

Scheme 4. Alkylation reactions of azadirachtin.[17,23,24] Reagents and conditions: a) Ag_2O, MeI, 40 °C, 2 h, 86%; b) Ag_2O, MeI, 40 °C, 8 h, 73%; c) KOH, MeI, DMSO, 15 min, 24%.

monomethyl derivative **12** exclusively,[23] whilst the 11,20-dimethyl derivative **13** was obtained as the major product when the reaction time was increased to 8 h. More forcing conditions still were required to effect formation of 7,11,20-trimethyl derivative **14**,[17] which in turn led to a decrease in its isolated yield. On screening these derivatives for biological activity, both **12** and **13** displayed comparable antifeedant activity to the natural product against *Spodoptera littoralis*.[24] However, the trimethyl derivative **14** was only weakly active suggesting that the C7 substituent plays a key role in orientation and binding to a putative biological target.

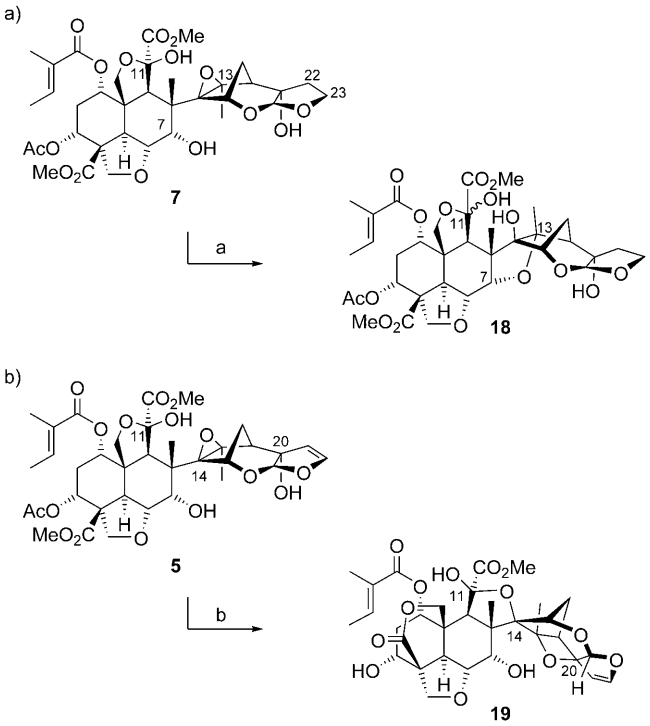
In order to probe the influence of the C7 hydroxy group in more detail, three further analogues were prepared (**15**–**17**, Scheme 5).[25] The first of these, **15**, was derived from azadirachtin in two steps and displayed comparable activity to the natural product. However, oxidation of **15** at the C7 position gave a compound with considerably reduced activity (**16**). The non-natural C7 epimer (**17**) was then prepared by Luche reduction[26] of **16** and shown to be completely devoid of antifeedant activity thereby confirming the importance of the *S*-configuration at C7.[25] These results illustrate that simple changes, particularly those that affect the conformation of azadirachtin, can have a dramatic effect on biological activity. This may be attributed to the disruption of a complex hydrogen bonding network within the natural product.[27]



Scheme 5. Oxidation of an azadirachtin derivative.[25] Reagents and conditions: a) Dess–Martin periodinane, CH_2Cl_2, 35 °C, 5 d, 86%; b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, **15**: 44%, **17**: 34%.

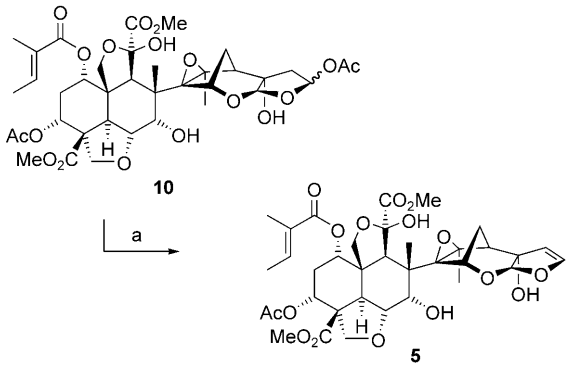
2.2. Stability Studies

Azadirachtin **5** is highly unstable to acidic conditions owing to the presence of its labile enol ether. Moreover, reduction of the C22–C23 double bond in **5** fails to fully stabilize the molecule due to the reactivity of its tetra-substituted epoxide. Thus, treatment of 22,23-dihydroazadirachtin (**7**) with Amberlyst-15, an acidic resin, afforded **18**, through intramolecular ring-opening of the epoxide at C13 and concomitant equilibration of the C11 hemiacetal (Scheme 6a).[20] Studies also revealed that azadirachtin was highly unstable to basic conditions (Scheme 6b): when **5** was subjected to sodium methoxide in methanol, a complex skeletal rearrangement occurred to generate **19** as the major isolable product.[25]



Scheme 6. Acid[20] (a) and base[25] (b) mediated rearrangement of the azadirachtin skeleton. Reagents and conditions: a) Amberlyst-15, sieves 4 Å, MeCN, RT, 3 d, 51%; b) NaOMe, MeOH, RT, 2.5 h, 23%.

In contrast, the azadirachtin skeleton proved remarkably stable to elevated temperatures, an observation which was ultimately of benefit to our synthetic strategy: pyrolysis of acetic acid adduct **10** at 170 °C in vacuo cleanly returned azadirachtin **5** in quantitative yield (Scheme 7).[21]

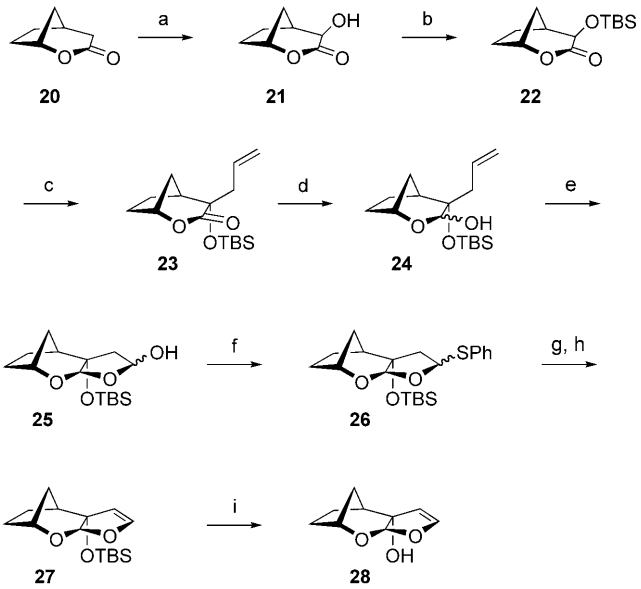


Scheme 7. Pyrolysis of acetic acid adduct **10**.[21] Conditions: a) 170 °C, 1.3×10^{-3} mm Hg, 5 min, 99%.

3. Synthesis of Azadirachtin Hydroxyfuran Acetal Fragments

3.1. Our Early Work

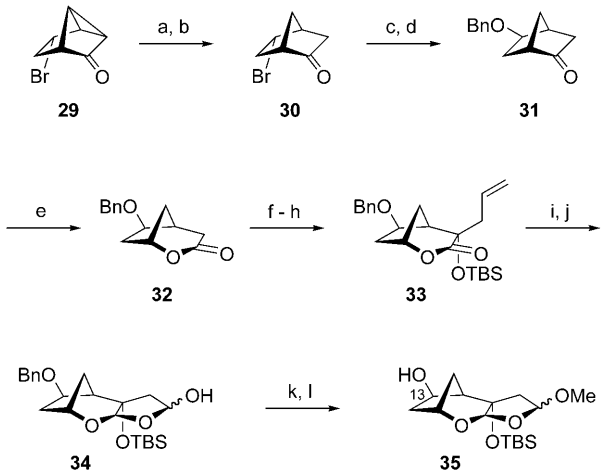
We began serious studies towards the synthesis of azadirachtin in 1987 and chose initially to prepare a simple model compound **28** based on the dihydrofuran acetal unit present in the natural product (Scheme 8).[28] It was anticipated that **28** might also possess insect-repellant activity given our previous work on the clerodane family of antifeedants which had illustrated that fragment synthesis could indeed afford active compounds.[29]



Scheme 8. Synthesis of hydroxy dihydrofuranacetal **28**.[28] Reagents and conditions: a) LDA, THF, −78 °C, then MoOPH, −78 °C to 0 °C, 67%; b) TBS-Cl, imidazole, DMF, RT, 94%; c) KDA, THF, −78 °C, then allyl bromide, −78 °C, 87%; d) DIBAL-H, toluene, −78 °C, 67% brsm; e) O_3, CH_2Cl_2, −78 °C, then PPh_3, RT, 93%; f) PhSH, Amberlyst-15, sieves 4 Å, MeCN, 82%; g) *m*CPBA, CH_2Cl_2, RT, 83%; h) toluene, reflux, 92%; i) TBAF, THF, RT, 84%.

The route to **28** began from optically pure lactone **20**, which is readily available on a large scale from norborneol.[30] Oxidation of the lithium enolate of **20** with MoOPH complex[31] at −78 °C provided **21**, which was subsequently converted to the corresponding silyl ether (**22**). A facially selective allylation reaction was then employed (**22**→**23**) to install the necessary carbon atoms for construction of the dihydrofuran ring in **28**. Reduction of **23** proceeded smoothly to afford lactol **24**, after which an ozonolysis reaction generated intermediate **25** with the complete tricyclic framework in place. Next, we chose to exploit the thermal stability of azadirachtin (cf. Scheme 7) to effect elimination of water from **25**. This was successfully achieved through a three-step sequence: namely conversion of lactol **25** to the sulfide (**26**), oxidation to an intermediate sulfoxide and pyrolysis to give compound **27**. Finally, cleavage of the silyl ether present in **27** provided the dihydrofuran acetal target **28**. Interestingly, while **28** showed significant antifeedant activity against *Spodoptera littoralis* it did not display the growth development effects of azadirachtin itself.[28]

The next task was to prepare a substituted hydroxyfuran acetal fragment that could ultimately be used in the synthesis of azadirachtin. We therefore selected **35** as a versatile intermediate possessing reactive functionality at the C13 position for later manipulation (Scheme 9).[32] In pursuit of **35**,



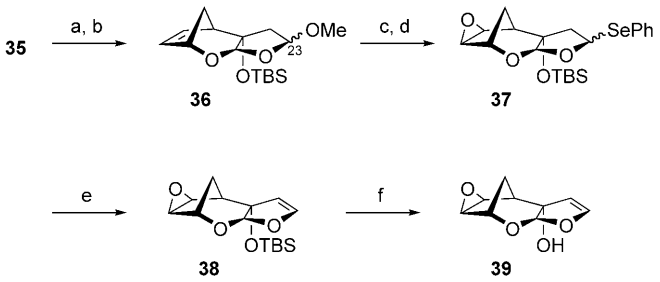
Scheme 9. Synthesis of an enantiomerically pure acetal intermediate for potential use in the synthesis of azadirachtin.[32] Reagents and conditions: a) $NaBH_4$, MeOH, 70%; b) TPAP, NMO, sieves 4 Å, MeCN, 30 min, 91%; c) CF_3CO_2Ag, acetone-H_2O (3:1), 60 °C, 60 h, 98%; d) NaH, BnBr, THF, 98%; e) *m*CPBA, CH_2Cl_2, RT, 97%; f) LDA, −78 °C, then MoO_5·pyridine·DMPU, 78%; g) TBS-Cl, imidazole, DMF, RT, 14 h, 96%; h) KDA, allyl bromide, −78 °C, 85%; i) DIBAL-H, toluene, −78 °C, 88%; j) O_3, CH_2Cl_2, −78 °C, then PPh_3, RT, 89%; k) Amberlyst-15, MeOH; l) H_2, Pd/C, MeOH, 73% over 2 steps.

enantiopure ketone **29** was first prepared according to the literature procedure[33] and subjected to a homoconjugate reduction/oxidation sequence to provide **30**.[34] Displacement of bromide ion from **30** was then achieved with silver trifluoroacetate in aqueous acetone and the resulting alcohol protected as the corresponding benzyl ether (**31**). Following Baeyer–Villiger oxidation[35] (**31**→**32**), we were able to arrive at compound **34** using analogous chemistry to that developed in the synthesis of **28** (cf. Scheme 8). Methanolysis and debenzylation of **34** then furnished **35** as an epimeric mixture of methyl acetals in good overall yield and in sufficient quantities to allow further study.[32]

From compound **35**, a range of potential coupling partners for the total synthesis of azadirachtin was prepared.[32] In so doing, two important concepts were demonstrated, namely the installation of the enol ether functionality (**36**→**38**) and the diastereoselective epoxidation of **36** (Scheme 10).

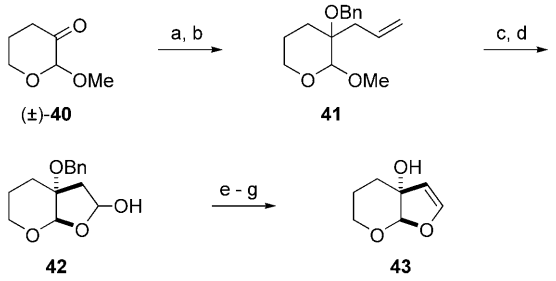
3.2. The Muckensturm Approach

At around the same time as our studies, Muckensturm et al. developed a sequence of reactions to install the enol ether functionality of the natural product.[36] The requisite



Scheme 10. Model epoxidation studies and enol ether installation.[32] Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, RT, 10 min; b) DBU, toluene, 110 °C, 38 h, 95% over 2 steps; c) DMDO, acetone-CH_2Cl_2 (1:1), RT, 98%; d) Amberlyst 15, PhSeH, sieves 4 Å, MeCN, RT, 44%; e) 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine, pyridine, CH_2Cl_2, RT, 10 min, 57%; f) TBAF, THF, RT, 5 min, 95%.

carbon atoms were introduced by allyl Grignard addition to a ketone (**40**, Scheme 11). Then, hydrolysis of the methyl acetal in **41** and oxidative cleavage of the alkene resulted in hemiacetal **42**. Finally acetylation and vacuum pyrolysis at 550 °C completed the fragment synthesis. Several intermediates from these studies were tested for antifeedant activity but all were inactive, even at high concentrations.[36]

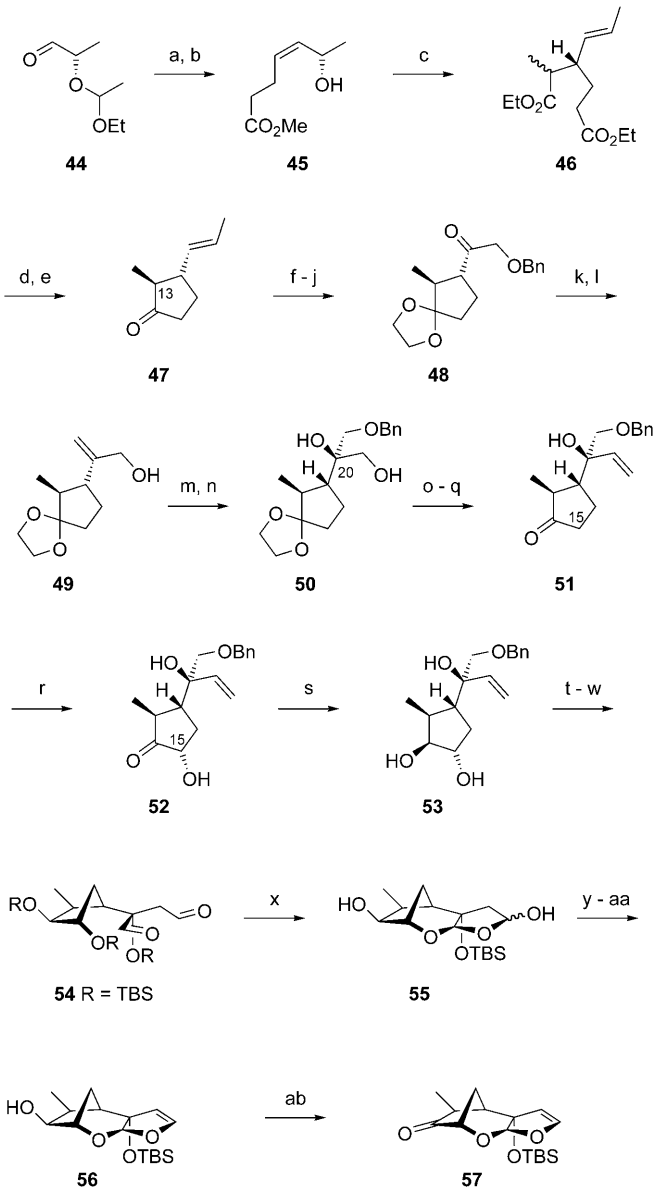


Scheme 11. Muckensturm's simplified furanacetal synthesis.[36] Reagents and conditions: a) allylMgBr, Et_2O, 84%; b) BnBr, NaH, TBAI, THF, LDA, THF, 89%; c) HCl, 90 °C, 100%; d) $NaIO_4$, OsO_4, 35%; e) Ac_2O, pyridine, DMAP, 93%; f) H_2, Pd/C, 80%; g) 0.2 mm Hg, 550 °C, 30%.

3.3. The Shibasaki Approach

Others soon entered the arena and in 1989, Shibasaki et al. reported the stereoselective assembly of an alternative hydroxyfuran acetal unit **57**, which was designed as a potential intermediate for the synthesis of azadirachtin (Scheme 12).[37]

In order to access **57** in an efficient manner, a novel cascade sequence was designed whereby the tricyclic furan acetal framework would be generated in a single step from functionalised cyclopentane **54**. The synthesis of this key building block began from chiral aldehyde **44**[38] which was converted to (*Z*)-alkene **45** with excellent selectivity. Johnson–Claisen rearrangement[39] of **45** then provided diester **46**, which could be progressed to **47** using a Dieckmann condensation[40] followed by Krapcho decarboxylation.[41] Under the reaction conditions for the Dieckmann process, epimerisation at C13 also occurred, providing the thermodynamically favoured *trans* product. Next, a seven step sequence converted **47** to allylic alcohol **49**, at which point the requisite C20 quaternary stereocentre was established. This was accomplished by epoxidation of **49** under Sharpless condi-

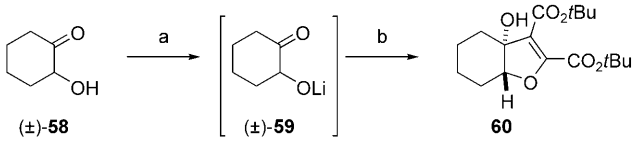


Scheme 12. The Shibasaki approach to hydroxyfuran acetal **57**.[37] Reagents and conditions: a) $Br^-Ph_3P^+(CH_2)_3CO_2Et$, *t*BuOK, THF, −78 °C to RT, 94%; b) AcOH-H_2O-THF (3:1:1), 100%; c) $EtC(OEt)_3$, $EtCO_2H$, xylene, 140 °C, 91%; d) KH, THF, 89%; e) NaCl, H_2O, DMSO, 130 °C, 100%; f) $HOCH_2CH_2OH$, TsOH, benzene, reflux, 84%; g) OsO_4, NMO, 99%; h) $NaIO_4$, 95%; i) $BnOCH_2SnBu_3$, *n*BuLi, −78 °C, 83%; j) CrO_3, pyridine, sieves 4 Å, 94%; k) H_2, Pd/C; l) $Br^-Ph_3P^+Me$, *t*BuOK, 78% over 2 steps; m) TBHP, (−)-DET, $Ti(OiPr)_4$, sieves 4 Å, CH_2Cl_2, −20 °C, 96%; n) BnOH, KH, THF, 91%; o) SO_3·pyridine, DMSO, Et_3N, 93%; p) $Br^-Ph_3P^+Me$, *t*BuOK, 50 °C, 89%; q) $FeCl_3$·SiO_2, acetone, 100%; r) LDA, THF, −78 °C, then MoOPH, −30 °C, 40%; s) $Me_4NBH(OAc)_3$, AcOH, MeCN, RT, 83%; t) TBS-OTf, 2,6-lutidine, 50 °C, 91%; u) BH_3·THF, then Me_3NO, diglyme, 61%; v) H_2, Pd/C, 90%; w) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, RT; x) AcOH-H_2O-THF (3:3:1), 60 °C, 60% over 2 steps; y) PhSH, BF_3·Et_2O, 83%; z) *m*CPBA, $NaHCO_3$; aa) toluene, reflux, 38% over 2 steps; ab) PDC, DMF, 40 °C, 98%.

tions[42] followed by a regioselective ring opening with potassium benzyloxide to generate diol **50** as a single diastereomer. Further manipulations, including a substrate controlled oxidation at C15, afforded dialdehyde **54**, an appropriate precursor for the pivotal cyclisation. Fortunately, as predicted, treatment of **54** with aqueous acid promoted a cascade of events, during which the necessary tricyclic furanacetal framework of **55** was put in place. The final steps in the Shibasaki synthesis utilised chemistry developed for our synthesis of **28** to arrive at the fully functionalised azadirachtin fragment (**57**).

3.4. The Jauch Approach

In 1991, Jauch and Schurig reported studies towards the synthesis of model compounds related to the dihydrofuran acetal fragment of azadirachtin (Scheme 13).[43] This work



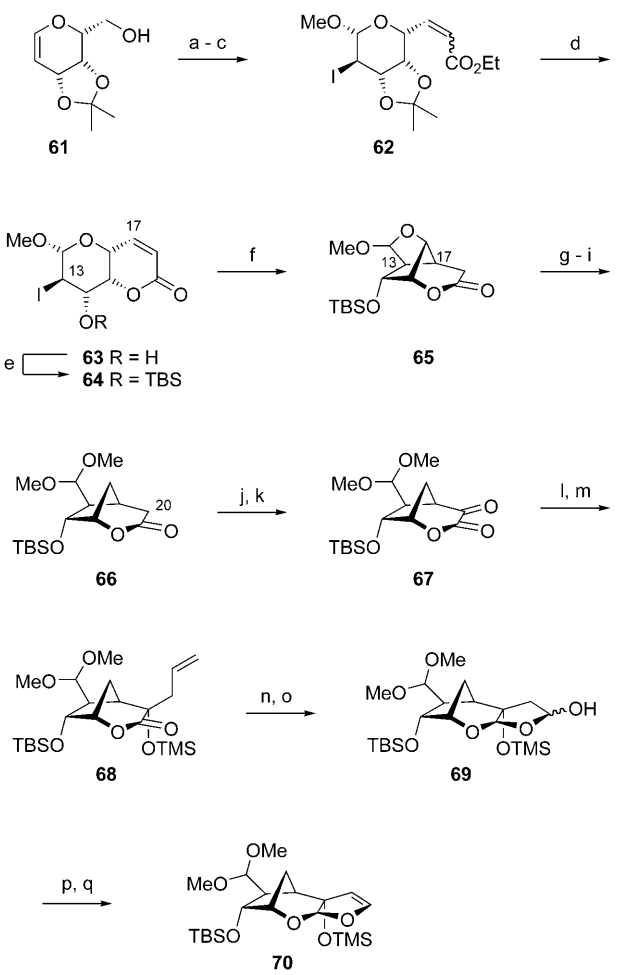
Scheme 13. Jauch's procedure for the preparation of racemic 4-hydroxy-4,5-dihydrofurans.[43] Reagents and conditions: a) MeLi, −80 °C; b) (*t*BuOOC)CC(COO*t*Bu), LiBr, Et_2O, −60 °C to −30 °C, 69% over 2 steps.

describes a highly diastereoselective procedure for the preparation of substituted 4-hydroxy-4,5-dihydrofurans (**60**). Unfortunately, the diastereoselectivity obtained in the key reaction did not correspond to the necessary *cis*-ring junction of the natural product, nonetheless, this represents an interesting approach to hydroxy dihydrofuran scaffolds.

3.5. The Fraser-Reid Approach

An attractive approach to the tricyclic dihydrofuran acetal fragment of azadirachtin was reported in 1994 by Fraser-Reid and Henry in which a transannular radical cyclisation was employed as the key step (Scheme 14).[44] The starting point for this synthesis was 3,4-*O*-isopropylidenegalactal (**61**)[45] which was prepared from D-galactal through modification of a known procedure.[46] Intermediate **61** then underwent iodomethoxylation, oxidation and Wittig olefination to provide iodide **62** in modest yield. After acetonide hydrolysis and lactonisation (**62**→**63**) everything was in place for the principal carbon–carbon bond forming event. Thus, **64** was subjected to tributyltin hydride and AIBN, which cleanly effected the desired cyclisation to tricyclic lactone **65**. Further manipulations gave the bicyclic [3.2.1]lactone **66** in a total of eight steps and 24% yield from monoacetone galactal **61**.

To introduce the angular C20 hydroxy group, present in azadirachtin (**5**), a different strategy was employed to that seen in the previous approaches. In this instance, hydroxylation of the potassium enolate of **66** with the Davis oxaziridine,[47] followed by oxidation of the intermediate

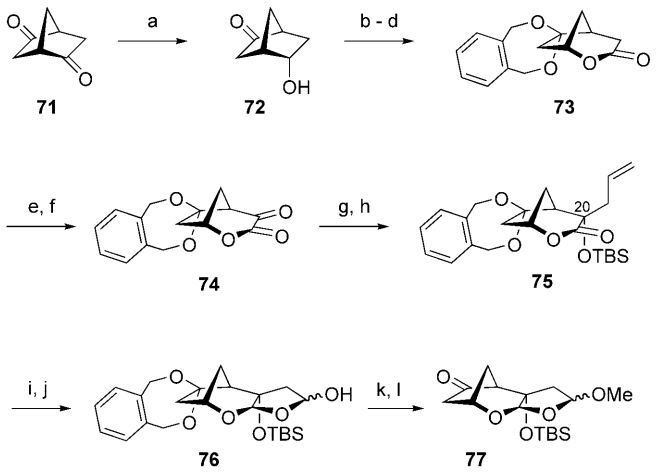


Scheme 14. Fraser-Reid's synthesis of the tricyclic dihydrofuran fragment of azadirachtin.[44] Reagents and conditions: a) NIS, MeOH, MeCN; b) PCC, sieves 4 Å, CH_2Cl_2; c) Ph_3PCHCO_2Et, MeOH, 60% over 3 steps; d) TFA, H_2O, toluene; e) TBS-OTf, 2,6-lutidine, THF, DMF, 71%; f) nBu_3SnH, AIBN, toluene, reflux, 87%; g) PPTS, MeOH, 78%; h) $ClC(S)OC_6H_4F$, Et_3N, DMAP, CH_2Cl_2; i) nBu_3SnH, AIBN, benzene, reflux, 75% over 2 steps; j) KHMDS, Davis 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine; k) PCC, CH_2Cl_2, 70% over 2 steps; l) nBu_3Sn-allyl, $LiClO_4$, Et_2O; m) TMS-imidazole, $ClCH_2CH_2Cl$, 60 °C, 83% over 2 steps; n) DIBAL-H, toluene, −78 °C; o) O_3, CH_2Cl_2, Ph_3P; p) $ClCOC_6H_4NO_2$, Et_3N, DMAP, 71% over 3 steps; q) collidine, *o*-$C_6H_4Cl_2$, reflux, 40 min, 76%.

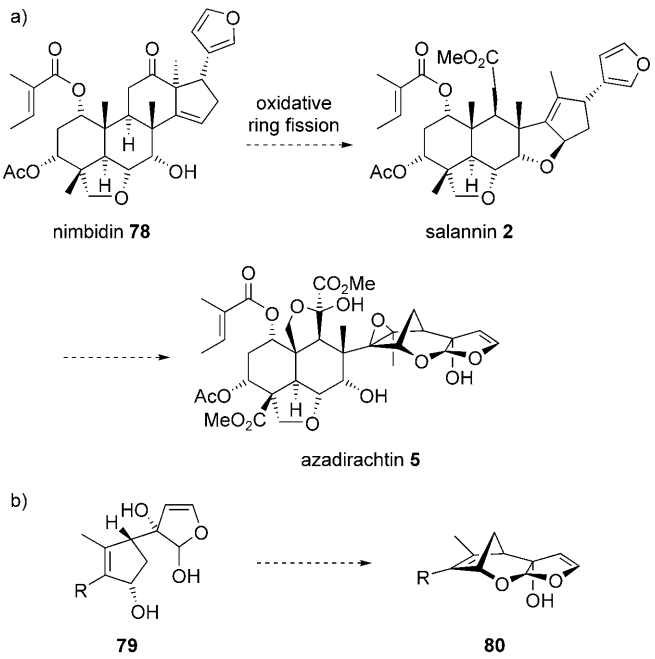
alcohol, furnished the reactive dicarbonyl **67**. A lithium perchlorate mediated[48] allyl addition to **67** then installed the remaining carbons required for the dihydrofuran acetal unit of **70**. Finally, reduction of lactone **68** was immediately followed by ozonolysis to afford an epimeric mixture of lactols (**69**), which were cleanly converted to the target dihydrofuran acetal **70**.

3.6. The Watanabe Approach

In 1996, Watanabe et al. reported an efficient and enantioselective route to hydroxyfuran acetal fragment **77** (Scheme 15).[49] The starting point in this approach was chiral alcohol **72**, prepared by kinetic resolution of diketone **71**[50]



Scheme 15. Watanabe's synthesis of hydroxyfuran acetal fragment.[49] Reagents and conditions: a) baker's yeast, Celite, H_2O, hexane, RT, 20 h, 21–28% (73–78% *ee*); b) 1,2-benzenedimethanol, TsOH, benzene, reflux, 81%; c) $(COCl)_2$, DMSO, CH_2Cl_2, −70°C, then Et_3N, −70°C to RT, 94%; d) 1. *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0°C to RT; 2. 5×recrystallisation, 57% (97% *ee*); e) LDA, THF, MoOPH, −78°C to 20°C, 86%; f) $(COCl)_2$, DMSO, CH_2Cl_2, −70°C, then Et_3N, −70°C to RT, 81%; g) allyl lithium, THF, −78°C, 79%; h) 1. TBS-OTf, 2,6-lutidine, CH_2Cl_2, reflux, 48 h; 2. recrystallisation, 93%, >99% *ee*; i) DIBAL-H, TMS-Cl, toluene, −78°C, 12 h, 84%; j) O_3, $NaHCO_3$, CH_2Cl_2, −78°C, then Ph_3P, −78°C to RT, 99%; k) MeI, Ag_2O, MeCN, 30 h, 93%; l) H_2, Pd/C, EtOAc, 30 min, 91%.



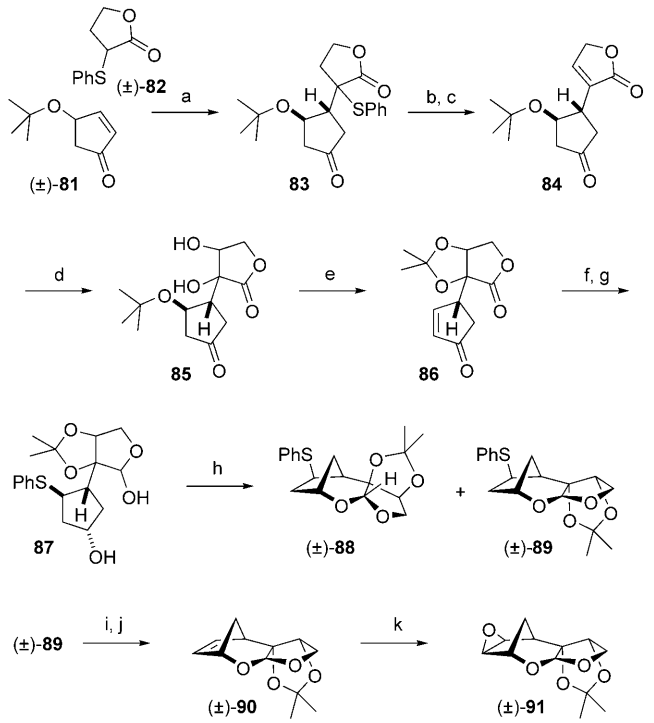
Scheme 16. Proposed biosynthesis of azadirachtin (a) and application to fragment synthesis (b).[54,55]

with baker's yeast.[51–53] The carbonyl group of **72** was then protected as its *O*-xylidenedioxy acetal and the resulting compound subjected to Swern oxidation conditions. Next, Baeyer–Villiger reaction and a two step oxidation protocol gave dicarbonyl **74**, a similar intermediate to that prepared by Fraser-Reid (cf. Scheme 14). As before, allyl addition generated the tetrasubstituted stereocentre at C20, after which installation of the tetrahydrofuran ring was achieved in an analogous manner to our previously reported protocol (cf. Scheme 8). Overall, this route delivered compound **77** in excellent yield and in only twelve synthetic steps.

3.7. The Winterfeldt Approach

A biomimetic approach towards the hydroxyfuranacetal fragment of azadirachtin was delineated by Winterfeldt and Schlesiger in 1997.[54,55] Based on the structural similarity of azadirachtin (**5**) to other natural products, nimbidin **78** and salannin **2**, it was proposed that these three compounds share a common biosynthetic pathway (Scheme 16a).[56] With this pathway in mind, it was envisaged that a suitable hydroxyfuran acetal fragment (**80**) could derive from a hemiacetal such as **79** (Scheme 16b).

Accordingly intermediate **87** was prepared in seven steps from *rac*-**81** as a 3:1 mixture of diastereoisomers (Scheme 17). Acid-mediated transacetalisation of **87** then promoted the biomimetic ring-closing event, affording the target [3.2.1]bicycle **89** in modest yield. Finally, oxidation and elimination furnished the alkene **90**, which underwent epox-



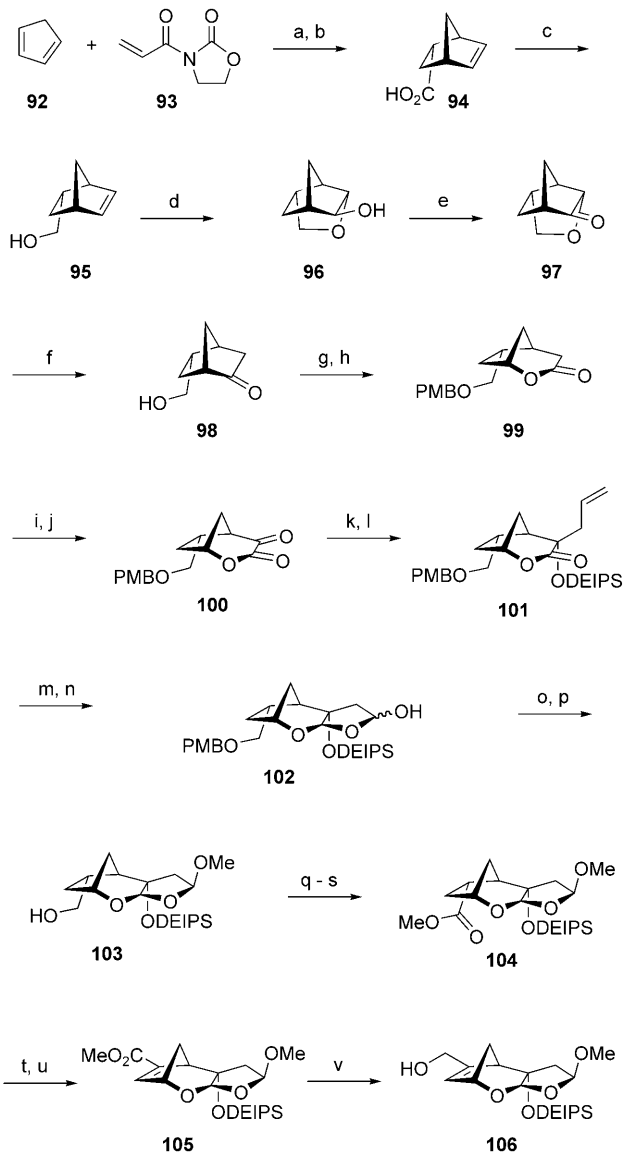
Scheme 17. Biomimetic approach to a racemic hydroxyfuranacetal fragment **91**.[54,55] Reagents and conditions: a) LiHMDS, THF, DMPU, −78°C, 65%; b) *m*CPBA, CH_2Cl_2, −78°C; c) Et_3N, CH_2Cl_2, 71% over 2 steps; d) $NaIO_4$, $RuCl_3$, 0°C, 4 min, 93% (3:1 mixture of stereoisomers); e) PPTS, acetone, dimethoxypropane, reflux, 57% (3:1 mixture of stereoisomers); f) PhSH, DBU, MeOH, 0°C, 95% (3:1 **89**:**88** mixture of stereoisomers); g) DIBAL-H, CH_2Cl_2, −78°C, 94%; h) TFA, acetone, **88**: 51%, **89**: 17%; i) MeOH, MTBE, H_2O, $NaIO_4$, RT, 18 h; j) Et_3N, toluene, reflux, 24 h, 69%; k) DMDO, acetone, 99%.

idation with exquisite facial selectivity to form an analogue of the furan acetal portion of azadirachtin (**91**).

3.8. The Murai Approach

Murai et al. have also reported studies towards the total synthesis of azadirachtin in which hydroxyfuran acetal **106** was prepared as a key building block (Scheme 18).[57]

In order to generate intermediate **106** in an enantiopure fashion, an asymmetric Diels–Alder reaction of cyclopentadiene **92** and acryloyl derivative **93**[58] was employed. This cycloaddition proceeded in excellent yield and enantioselectivity using Evans' method[59,60] and the resulting cycloadduct was subjected to LiOOH[61] to afford carboxylic acid **94**. Following reduction of **94** to the corresponding alcohol (**95**), treatment with *m*CPBA promoted an epoxidation/cyclisation sequence to give cyclic ether **96**. Oxidation of **96** then allowed cleavage of the cyclic ether present in **97** with SmI_2 at −78 °C to provide **98**. Baeyer–Villiger oxidation[35] was again used to install the lactone present in **99** and the tetrahydrofuran ring in **102** was constructed using previously reported methods (cf. Schemes 9, 14 and 19). Standard chemical manipulations allowed access to primary alcohol **106** which was an important intermediate for fragment coupling studies (see Section 5).



Scheme 18. The Murai synthesis of the azadirachtin [3.2.1]bicycle fragment **106**. Reagents and conditions: a) (4*S*,4′*S*)-2,2′-(propane-2,2-diyl)-bis(4-*tert*-butyl-4,5-dihydrooxazole), $Cu(OTf)_2$, −78 °C, 23 h, 97% (99% *ee*); b) LiOH, H_2O_2, THF, H_2O, 0 °C, 40 min, 94%; c) $LiAlH_4$, Et_2O, 0 °C, 1.5 h, 97%; d) *m*CPBA, CH_2Cl_2, −10 °C to RT, 1.5 h, 91%; e) Dess–Martin periodinane, CH_2Cl_2, RT, 99%; f) SmI_2, THF, MeOH, −78 °C, 40 min, 98%; g) PMB-Cl, NaH, TBAI, DMF, RT, 2.5 h, 92%; h) MMPP, EtOH, H_2O, RT, 2 h, 95%; i) KHMDS, THF, −78 °C, 1.5 h, then MoO_5·pyridine·DMPU, −78 °C, 6 h, 86%; j) Dess–Martin periodinane, CH_2Cl_2, RT, 18 h, 100%; k) nBu_3Sn-allyl, $LiClO_4$, Et_2O, RT, 22 h, 98%; l) DEIPS-OTf, iPr_2NEt, CH_2Cl_2, RT, 6.5 h, 89%; m) DIBAL-H, TMS-Cl, CH_2Cl_2, −95 °C, 0.5 h, 98%; n) O_3, CH_2Cl_2, −78 °C, 2 min, then Ph_3P, 86%; o) NaH, MeI, THF, RT, 1.5 h, 96%; p) DDQ, CH_2Cl_2, H_2O, RT, 4 h, 100%; q) Dess–Martin periodinane, CH_2Cl_2, RT, 16 h; r) $NaClO_2$, 2-methyl-2-butene, *t*BuOH, H_2O, NaH_2PO_4, RT, 16 h, 83% over 2 steps; s) CH_2N_2, Et_2O, 5 min, 90%; t) KHMDS, THF, −78 °C, 0.5 h, then PhSeCl, 5 min, 94%; u) H_2O_2, pyridine, CH_2Cl_2, 0 °C, 15 min, 100%; v) DIBAL-H, Et_2O, −78 °C, 3 h, 86%.

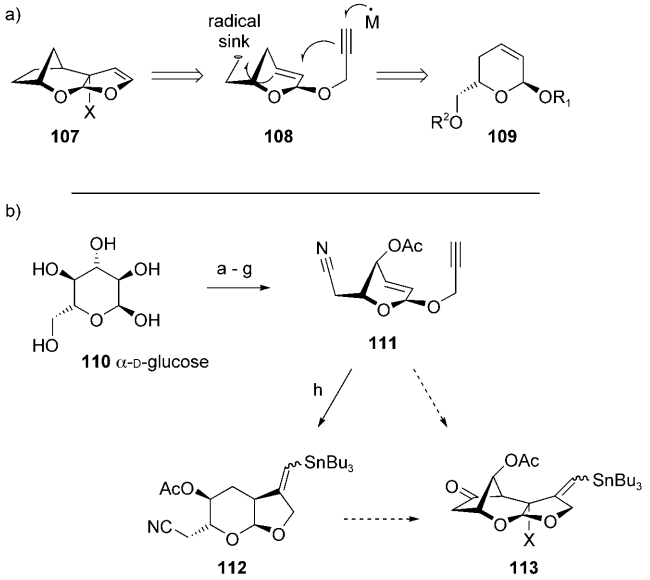
3.9. The Raina Approach

A model synthetic approach towards the hydroxyfuran-acetal fragment present in azadirachtin has recently been described.[62] This study aimed to use a tandem radical cyclisation process, in which the tricyclic framework of **107** would be built up in a single step (Scheme 19a). It was envisaged that the cyclisation precursor **109** could ultimately derive from a readily available carbohydrate source. Accordingly, α-D-glucose (**110**) was converted to the test substrate **111** in seven steps and 18% overall yield by a standard sequence of transformations (Scheme 19b). The critical cyclisation reaction was then performed and, whilst the transformation of **111** to vinyl stannane **112** was successfully realised, this intermediate unfortunately did not undergo further reaction to the desired tricyclic system (**113**).

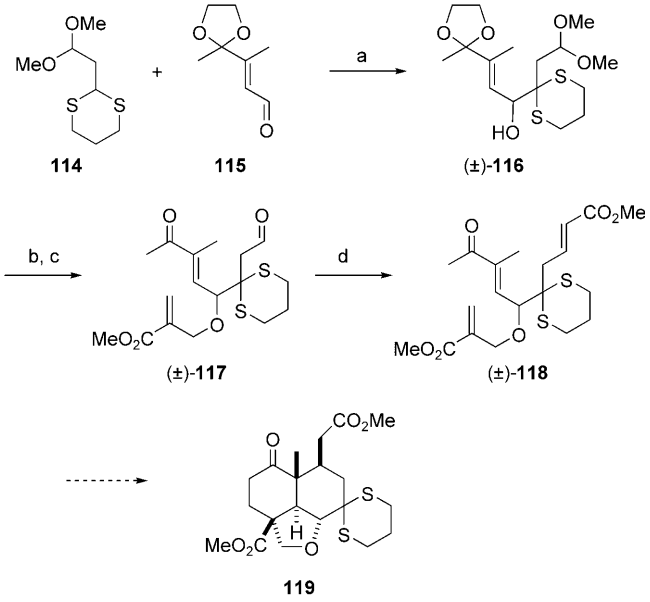
4. Synthesis of Azadirachtin Decalin Fragments

4.1. Our Approach

The first studies towards the synthesis of the densely functionalised decalin core of azadirachtin were published by our group in 1988.[63,64] We initially envisaged that a triple Michael addition cascade might be employed to construct the required *trans* decalin unit and consequently the preparation of a suitable substrate was investigated (**118**, Scheme 20). The anionic coupling of dithiane **114** and aldehyde **115** proceeded smoothly to afford allylic alcohol **116**, after which alkylation, acetal hydrolysis and Wittig olefination generated the chosen precursor **118**, possessing three distinct Michael acceptors. Disappointingly and despite extensive studies, conditions could not be found to effect the desired cascade process and we were forced to re-evaluate our approach.

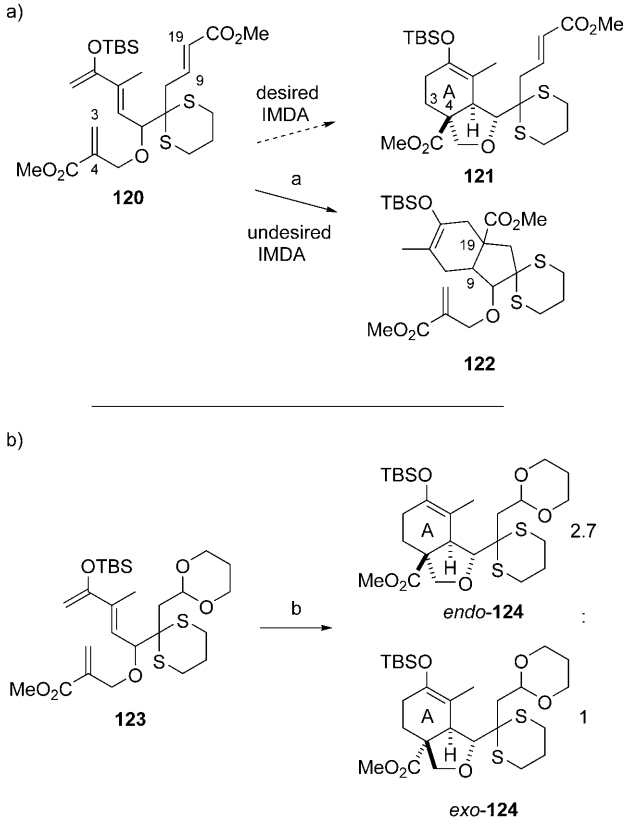


Scheme 19. Retrosynthetic analysis employed by Raina et al. (a) and studies towards the tandem radical cyclisation reaction (b).[62] Reagents and conditions: a) Ac_2O, $HClO_4$, P(red), Br_2, 15 °C; b) AcOH, NaOAc, Zn, $CuSO_4$, −10 °C, 4 h, 40% over 2 steps; c) NaOMe (cat.), MeOH, RT, 2 d, 95%; d) *p*-TsCl, pyridine, −20 °C, 15 h, then Ac_2O, RT, 12 h, 80%; e) $HC{\equiv}CCH_2OH$, $BF_3{\cdot}Et_2O$, $CHCl_3$, 10 °C, 5 min, 90%; f) NaCN, DMSO, 60 °C, 3 h, 70%; g) Ac_2O, pyridine, CH_2Cl_2, RT, 12 h, 92%; h) $n$$Bu_3SnH$, AIBN, benzene, reflux, 5 h, 56%.



Scheme 20. Triple Michael cascade for the synthesis of the decalin core of **5**.[64] Reagents and conditions: a) nBuLi, TMEDA, THF, −92 °C, 93%; b) KH, methyl-2-bromomethylprop-2-enoate, benzene, RT, 80%; c) PPTS, acetone, H_2O, reflux, 94%; d) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, RT, 88%.

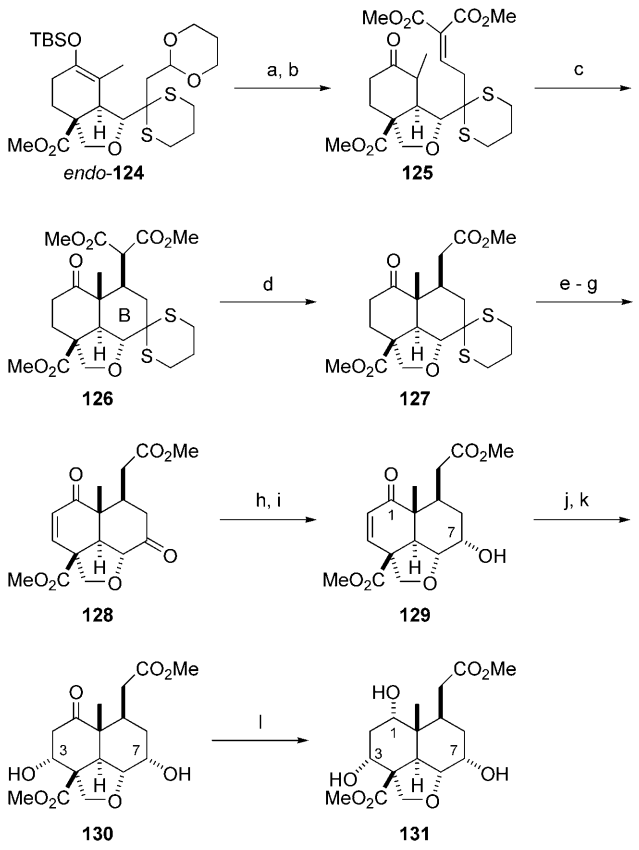
Next, we examined an intramolecular Diels–Alder (IMDA) approach to construct the A-ring present in azadirachtin and accordingly, ketone **118** was converted to the corresponding silyl enol ether, **120**. However, heating in toluene did not provide the desired product **121**, owing to competitive, preferential reactivity of the second dienophile present in **120** (Scheme 21a). Nevertheless, we went on to prepare an alternative Diels–Alder precursor, **123**, from aldehyde **117**, in which there would be no such competing process. Pleasingly, **123** underwent thermal IMDA reaction with a reasonable degree of selectivity for formation of the desired *endo* adduct (Scheme 21b).



Scheme 21. Preliminary studies towards an IMDA reaction.[63] Conditions: a) toluene, 135 °C; b) DMSO, 135 °C, *endo*-**124** 61%, *exo*-**124** 23%.

With the A-ring of azadirachtin in place, we focussed on construction of the B-ring (Scheme 22). When *endo*-**124** was treated with acetic acid, cleavage of both silyl ether and dioxolane protecting groups occurred, to reveal ketone and aldehyde functionalities respectively. Condensation of the aldehyde with dimethylmalonate then yielded triester **125**, which successfully underwent a diastereoselective intramolecular Michael reaction upon treatment with sodium methoxide to provide *trans* decalin **126**. Decarboxylation then proceeded without incident to give compound **127** in 80% yield.

Following a sequence of steps, we next established the correct oxidation level at C1, C3 and C7 (**127**→**131**). Ketone **127** was first transformed to the corresponding enone and, as the planned introduction of the C3 hydroxy group involved an oxidation, it was also necessary to remove the oxidatively labile dithiane protecting group to give **128**. Treatment of **128** with $NaBH_4$ generated the correct configuration at C7, but also effected untimely reduction at C1. However, the desired



Scheme 22. Towards the synthesis of the decalin fragment of azadirachtin. Reagents and conditions: a) AcOH, THF, H_2O, 65 °C, 73%; b) dimethylmalonate, piperidine, AcOH, 80 °C, 90%; c) NaOMe, MeOH, RT, 60%; d) 1. DMSO, NaCl, H_2O, 160 °C; 2. CH_2N_2, 80%; e) LDA, *N*-PSP, THF, −78 °C, 90%; f) 3-(*p*-nitrophenyl)-2-(phenylsulfonyl)oxaziridine, $NaHCO_3$, CH_2Cl_2, 68%; g) MeI, MeCN, H_2O, 95%; h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, RT, 78%; i) MnO_2, CH_2Cl_2, RT, 60%; j) H_2O_2, K_2CO_3, MeOH, 0 °C, 95%; k) Al/Hg, $NaHCO_3$, EtOH, RT, 95%; l) $NaBH_4$, $MgBr_2$, $NaHCO_3$, THF, 80%.

enone **129** could be accessed following selective re-oxidation at C1 using manganese dioxide. Epoxidation of enone **129** then occurred exclusively from the α-face and reductive ring-opening of the resulting oxirane generated the C3 hydroxy group (**130**). Finally, the C1 hydroxy group was installed following a chelation-controlled reduction of ketone **130** using $NaBH_4$ in combination with $MgBr_2$.

We had planned to transform **131** into a fully functionalised decalin fragment by the incorporation of an oxygen bridge between the C19 and C11 positions (Figure 7). Indeed, the formation of tetrahydrofuran rings by intramolecular hydrogen abstraction with an oxy-radical was well documented.[65] In this particular case, however, remote oxidation could not be realised despite extensive studies and we were again forced to re-evaluate our strategy.[24]

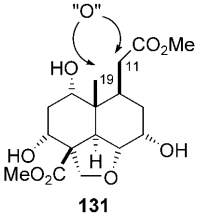
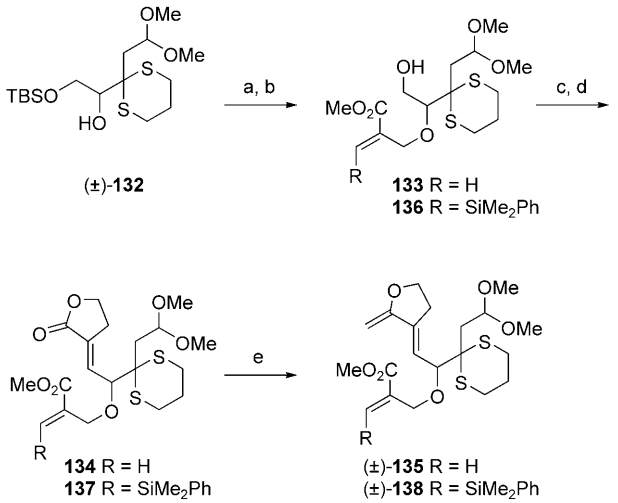


Figure 7. Remote oxidation approach.

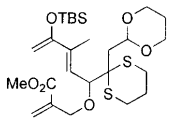
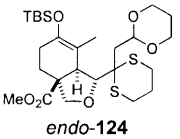
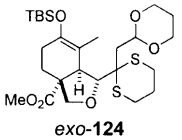
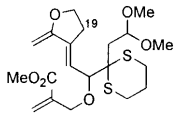
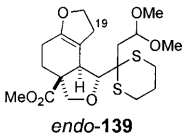
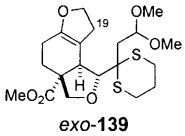
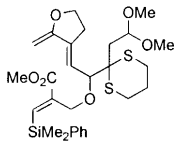
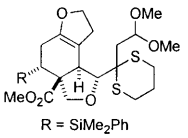
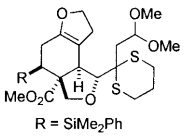
Based on the knowledge gained from these failed attempts, we decided to introduce oxygenation at the C19 position at an earlier stage in the synthesis. By analogy with the previous work, it was anticipated that a related intramolecular Diels–Alder strategy could be used to construct the A-ring in azadirachtin (**5**): therefore the constrained triene **135** was prepared in five steps from an accessible precursor, **132** (Scheme 23).[66,67]



Scheme 23. Synthesis of IMDA precursors **135** and **138**.[71] Reagents and conditions: a) KH, THF, 17 min, then methyl 2-(bromomethyl) propenoate or (*Z*)-methyl 2-bromomethyl-3-dimethylphenyl-silylpropenoate, 88% (R = H), 60% (R = $SiMe_2Ph$); b) HF·pyridine, MeCN, 16 h, 77% (R = H), 85% (R = $SiMe_2Ph$); c) DMSO, $(COCl)_2$, THF, −35 °C, 20 min, then Et_3N, −78 °C to 21 °C, 70% (R = H), 93% (R = $SiMe_2Ph$); d) α-diethoxyphosphonyl-butyrolactone, LiCl, iPr_2NEt, MeCN, 55% (R = H), 34% (R = $SiMe_2Ph$); e) Tebbe reagent, pyridine, THF-toluene (2:1), −50 °C to −35 °C.

Although we had observed selectively for the *endo*-adduct during the course of our previous studies (Table 1, Entry 1), we were mindful of the fact that the undesired *exo* product might predominate in the IMDA reaction of **135** if peripheral bond formation were to occur significantly in advance of internal bond formation.[68–70] Indeed, this proved to be the case and in the cycloaddition reaction of **135**, the *exo*-product dominated over the required *endo* product (8:1, Table 1, Entry 2). However, by detailed analysis of potential transition states, taking into account allylic strain, transannular effects and the possibility of asynchronicity in the reaction transition state, we reasoned that a large phenyldimethylsilyl group, strategically placed on the dienophile component, would disfavour the undesired IMDA pathway. In the event, we were pleased to find that the appropriately modified substrate **138** formed *endo*-**140** preferentially over the undesired *exo* compound with a selectivity of 5:2 (Table 1, Entry 3). This was an important observation as it pointed out the key role that substituents such as the dimethylphenylsilyl group have in overturning the inherent stereochemical bias for this type of IMDA reaction. Moreover, in our case, it also placed the silyl

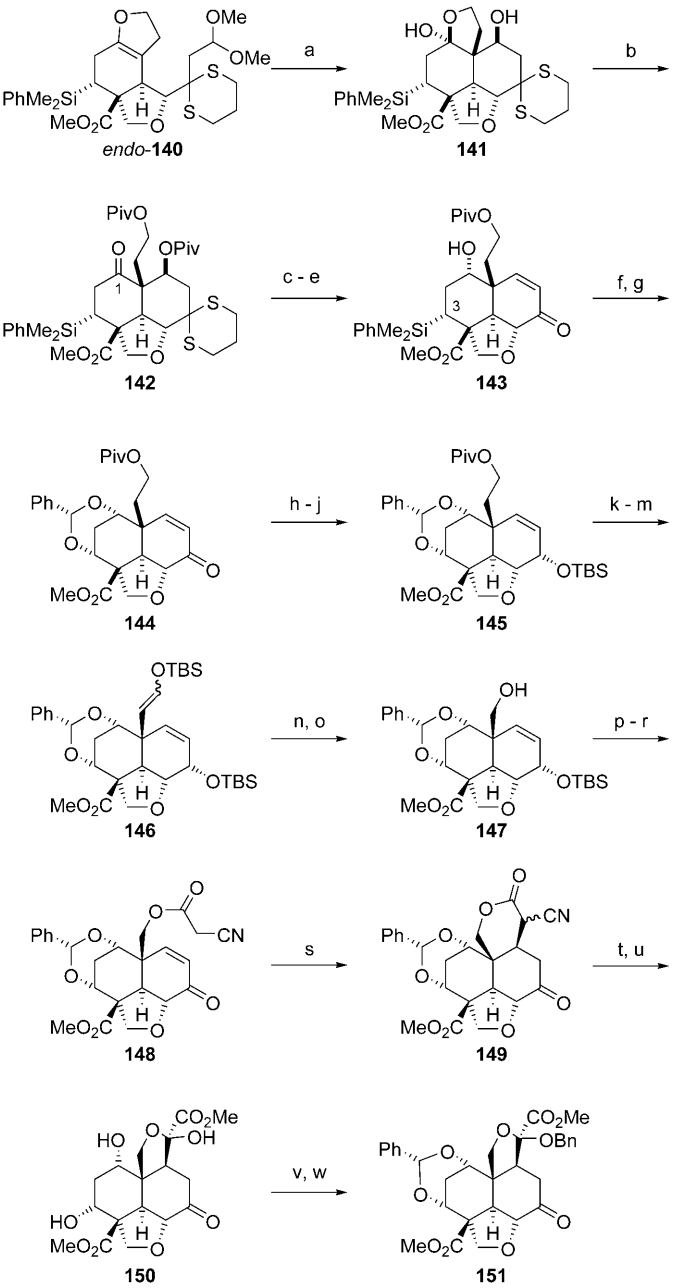
Table 1: Diels–Alder studies.[71]

Entry	Substrate	Product *endo*	Product *exo*
1[a]	 (±)-**123**	 *endo*-**124** 2.7	 *exo*-**124** 1
2[b]	 (±)-**135**	 *endo*-**139** 1	 *exo*-**139** 8
3[c]	 (±)-**138**	 R = $SiMe_2Ph$ *endo*-**140** 2.4	 R = $SiMe_2Ph$ *exo*-**140** 1

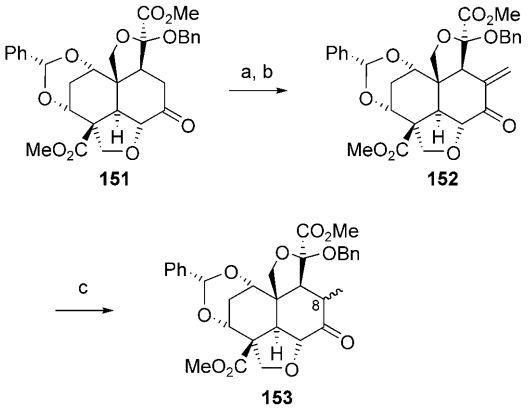
Conditions: [a] DMSO, 135 °C, 0.75 h; [b] toluene, 60 °C, 5 h; [c] toluene, 85 °C, 4 h, 21 % (*endo*-**140**), 25 % recovered **138** over 2 steps.

substituent in the axial position required for later transformation to the C3 hydroxy group of azadirachtin.

The silicon group also acted to control several other key events in our synthesis of the decalin fragment **151** (Scheme 24). Along with the constraining effect of the saturated furan ring, it enabled a facile and stereoselective acid-catalysed ring closure of *endo*-**140** to give the required *trans* decalin **141** as the only product. Next bis-pivaloylation of **141** afforded ketone **142** which then required stereoselective reduction of the C1 carbonyl group to give an axial hydroxy group as in the natural product **5**. Once again, the steric bulk of the C3 dimethylphenylsilyl silyl group came into play and dominated the facial selectivity of the reduction process, negating the need for chelation control (cf. Scheme 22). Following formation of enone **143**, the C3 silyl group finally bowed out of the synthesis through a modified Fleming–Tamao oxidation[72] and the resulting 1,3-diol was capped as its benzylidene acetal (**144**). A sequence of straightforward steps then excised one carbon from the pendant side-chain of **144** and gave the malononitrile ester **148** which was deliberately chosen to facilitate the subsequent six-ring Michael addition process (**148**→**149**). In the presence of DMDO, the nitrile in **149** encouraged rapid oxidation to a carbonyl group that, following methanolysis, ring-opening and reclosure, lead to the desired δ-lactol **150** in a single step. This reaction sequence was carefully designed to solve the difficult problem of installing the δ-lactol into the eventual decalin coupling partner **153**, which itself was obtained in a series of straightforward steps (Scheme 25).[73]



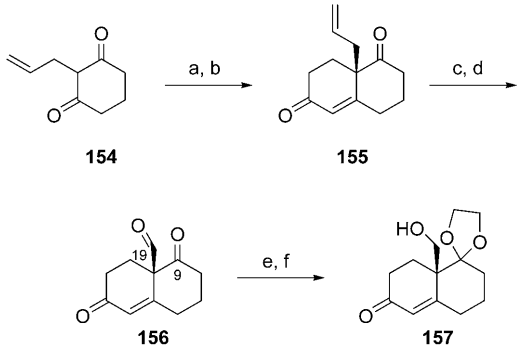
Scheme 24. Synthesis of decalin **151**.[66,67] Reagents and conditions: a) PTSA, H_2O, MeCN, 55 °C, 5.5 h, then H_2O, MeCN, RT, 2 h, 45 %; b) Piv-Cl, pyridine, DMAP, CH_2Cl_2, 45 °C, 72 h, 81 %; c) $NaBH_4$, MeOH, THF, RT, 90 min, 82 %; d) MeI, $CaCO_3$, water, MeCN, 55 °C, 7 h, 98 %; e) DBU, CH_2Cl_2, RT, 135 min, 100 %; f) $Hg(O_2CCF_3)_2$, AcOH, TFA, RT, 10 min, then AcOOH, 10 °C to RT, 2 h, 85 %; g) PhCHO, PPTS, benzene, reflux, 83 %; h) Li[sBu_3BH], THF, −78 °C; i) resolution via the 1*S*,4*R*-(−)-camphanic esters, 44 %; j) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 25 min, 96 %; k) LiOH·H_2O, EtOH, 60 °C, 5 h, then CH_2N_2, RT, 91 %; l) Dess–Martin periodinane, pyridine, CH_2Cl_2, 13 °C to RT, 25 min, 90 %; m) TBS-OTf, Et_3N, CH_2Cl_2, −15 °C to −5 °C, 2.5 h, 52 % recovered, recycled once; n) O_3, Sudan Red 7B, CH_2Cl_2, −78 °C, 1 h then PPh_3, −78 °C to RT, 12 h, 85 % over 2 steps; o) $Zn(BH_4)_2$, Et_2O, THF, −10 °C, 3 h; p) cyanoacetic acid, toluene *p*-TsCl, pyridine, CH_2Cl_2, RT, 20 min, 98 % over 2 steps; q) TBAF, sieves 4 Å, THF, RT, 4 h, 93 %; r) PDC, sieves 4 Å, CH_2Cl_2, RT, 2.75 h, 88 %; s) LiHMDS, THF, 0 °C to RT, 70 min, 100 %; t) DMDO, acetone, 0 °C, 22 min; u) PPTS, MeOH, 5.5 h, 70 % over 2 steps; v) benzaldehyde, PPTS, benzene, reflux, 4.6 h, 74 %; w) BnBr, Ag_2O, DMF, RT, 3.5 h, 61 %.



Scheme 25. Methylation of the decalin fragment at C8.[73] Reagents and conditions: a) TBS-OTf, Et_3N, MeCN, 77%; b) $CH_2{=}N(Me_2)^+I^-$, CH_2Cl_2, 35 °C, then SiO_2, CH_2Cl_2, 68%; c) H_2, Pd/C, MeOH, 60% (1:4 C8-α:β).

4.2. The Nicolaou Approach

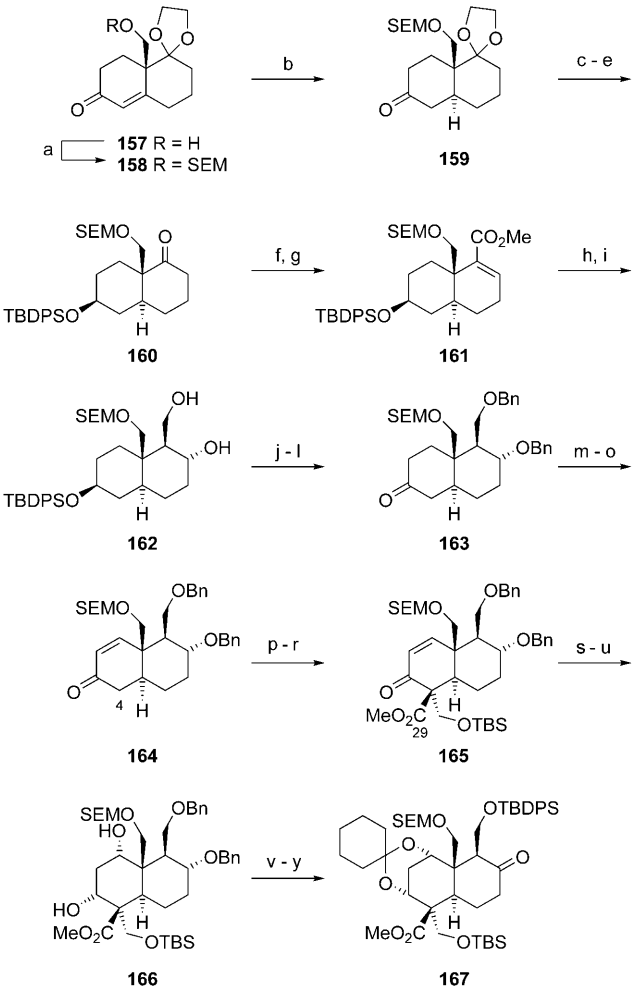
Nicolaou's approach towards the highly functionalised decalin core present in azadirachtin (**5**) employed an intermediate first described by Benn and Hanselmann (**157**).[74] Construction of **157** relied upon a Hajos–Parrish–Eder–Sauer–Wiechert reaction,[75,76] which allowed access to **155** as a single enantiomer (Scheme 26). Rhodium-mediated



Scheme 26. Synthesis of the enantiopure decalin **157**.[74] Reagents and conditions: a) methyl vinyl ketone, 80% aq. MeOH, NaOH, reflux; b) L-proline, DMSO, RT, 59% over 2 steps, 99% *ee*; c) $RhCl_3$, 2-propanol, HCl, reflux, 70%; d) O_3, EtOH, −78 °C; e) $NaBH_4$, MeOH-CH_2Cl_2 (1:1), −78 °C, 96% over 2 steps; f) 2-ethyl-2-methyl-1,3-dioxolane, TsOH, ethylene glycol, RT, 75%.

isomerisation[77] was then followed by ozonolytic cleavage to effect functionalisation at C19 (**155**→**156**). Selective reduction of the aldehyde present in **156** and protection of the ketone at C9 afforded decalin **157** in a good yield over the six steps (30%).

In order to establish the *trans* geometry at the decalin ring junction, a dissolving metal reduction was performed (**158**→**159**, Scheme 27), after which standard manipulations gave intermediate **164**. At this point the C4 quaternary centre was generated in a stereoselective fashion by treatment of **164** under Mander's[78] conditions to effect installation of the C29

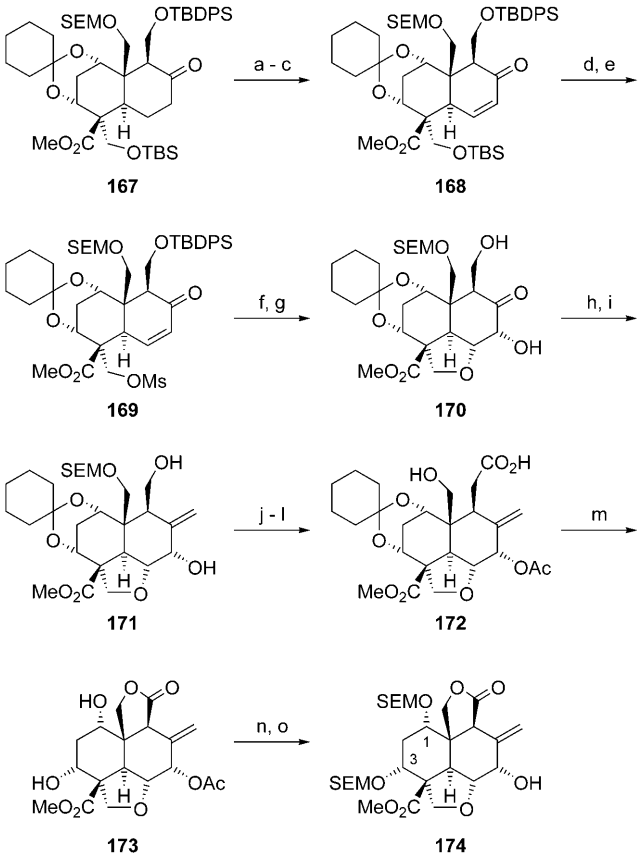


Scheme 27. Nicolaou's approach to a decalin fragment.[106–108] Reagents and conditions: a) SEMCl, iPr_2NEt, CH_2Cl_2, 25 °C, 85%; b) Li, NH_3, −78 °C, 80%; c) $NaBH_4$, THF-EtOH (1:1), −78 to 25 °C, 99%; d) TBDPS-Cl, imidazole, DMAP, DMF, 25 °C, 80%; e) PPTS, acetone, 65 °C; f) KHMDS, 5-chloro-2-bistriflylamino-pyridine, THF, −78 °C, 72% over 2 steps; g) $Pd(OAc)_2$, PPh_3, CO, iPr_2NEt, MeOH, DMF, 60 °C, 89%; h) DIBAL-H, CH_2Cl_2, −78 °C, 95%; i) BH_3·THF, THF, 0 °C, then H_2O_2, NaOH, 65%; j) NaH, BnBr, TBAI, THF-DMF (3:1), 25 °C; k) TBAF, THF, 25 °C, 91% over 2 steps; l) $(COCl)_2$, DMSO, −78 °C, then Et_3N, −78 °C to 25 °C, CH_2Cl_2, 89%; m) KHMDS, TES-Cl, THF, −78 °C; n) PhSeCl, CH_2Cl_2, −78 °C; o) H_2O_2, THF, 25 °C, 80% over 3 steps; p) LiHMDS, $NCCO_2Me$, THF, −78 °C, 93%; q) $(CH_2O)_n$, Yb(OTf)$_3$, THF, 2 h; r) TBS-OTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 74% over 2 steps; s) [$BnNMe_3$]Br, TBHP, THF, H_2O, 25 °C, 87%; t) $(PhSe)_2$, $NaBH_4$, EtOH, 25 °C, 91%; u) $NaBH_4$, MeOH-CH_2Cl_2 (1:15), 25 °C, 63%; v) 1,1-dimethoxy-cyclohexane, PPTS, benzene, 80 °C, 74%; w) 10% Pd/C, $NaHCO_3$, H_2, EtOAc, 25 °C, 91%; x) TBDPS-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 94%; y) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 91%.

ester group. Further C4 alkylation then proceeded exclusively from the α-face to yield **165**, following standard formation of the silyl ether.

To introduce the 1,3-oxygenation pattern present in the target compound, **174**, a three step sequence was carried out: epoxidation of the enone in **165** was followed by regioselective ring-opening of the resulting oxirane with PhSeNa.[79]

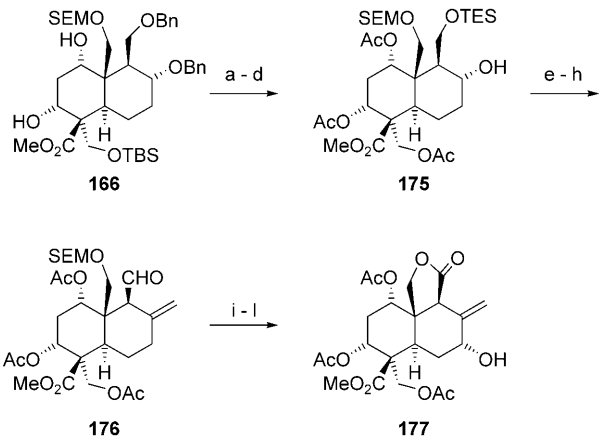
Finally, stereoselective reduction of the hydroxyketone thus formed, provided the expected diol **166**. Next, the installation of the tetrahydrofuran ring in **174** was addressed and consequently **166** was converted to mesylate **169** (Schemes 27 and 28). Dihydroxylation of **169** then occurred from the least



Scheme 28. Synthesis of decalin **174**.[107] Reagents and conditions: a) KHMDS, TES-Cl, THF, −78 °C; b) PhSeCl, CH_2Cl_2, −78 °C; c) H_2O_2, THF, 25 °C, 95% over 3 steps; d) TBAF, THF, 25 °C, 94%; e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; f) OsO_4, NMO, *t*BuOH-THF-H_2O 5:5:1, 25 °C, 95% over two steps; g) TBAF, THF, 25 °C, 96%; h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 95%; i) 1. Ph_3PCH_2, Et_2O, 25 °C, 93%; 2. K_2CO_3, MeOH, 25 °C, 92%; j) TEMPO, PS-bromite, CH_2Cl_2, 0 °C, 75%; k) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 92%; l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF-*t*BuOH-H_2O (2:4:1), 25 °C; m) HCl, EtOH-Et_2O (1:1), 25 °C, 75% over 2 steps; n) SEM-Cl, *i*Pr_2NEt, TBAI, $CHCl_3$, 61 °C, 89%; o) K_2CO_3, MeOH, 25 °C, 99%.

hindered face and was accompanied by an intramolecular displacement reaction to generate **170** after desilylation. Ultimately, a lactonisation reaction of compound **172** gave **173** which was progressed to the potential coupling partner **174**.

Although decalin **174** represents the principal coupling partner that Nicolaou and co-workers have employed in studies towards the total synthesis of azadirachtin, an alternative fragment has also been reported (**177**, Scheme 29). However, this fragment would require a number of difficult and selective late-stage transformations to be of real use in the synthesis of azadirachtin.



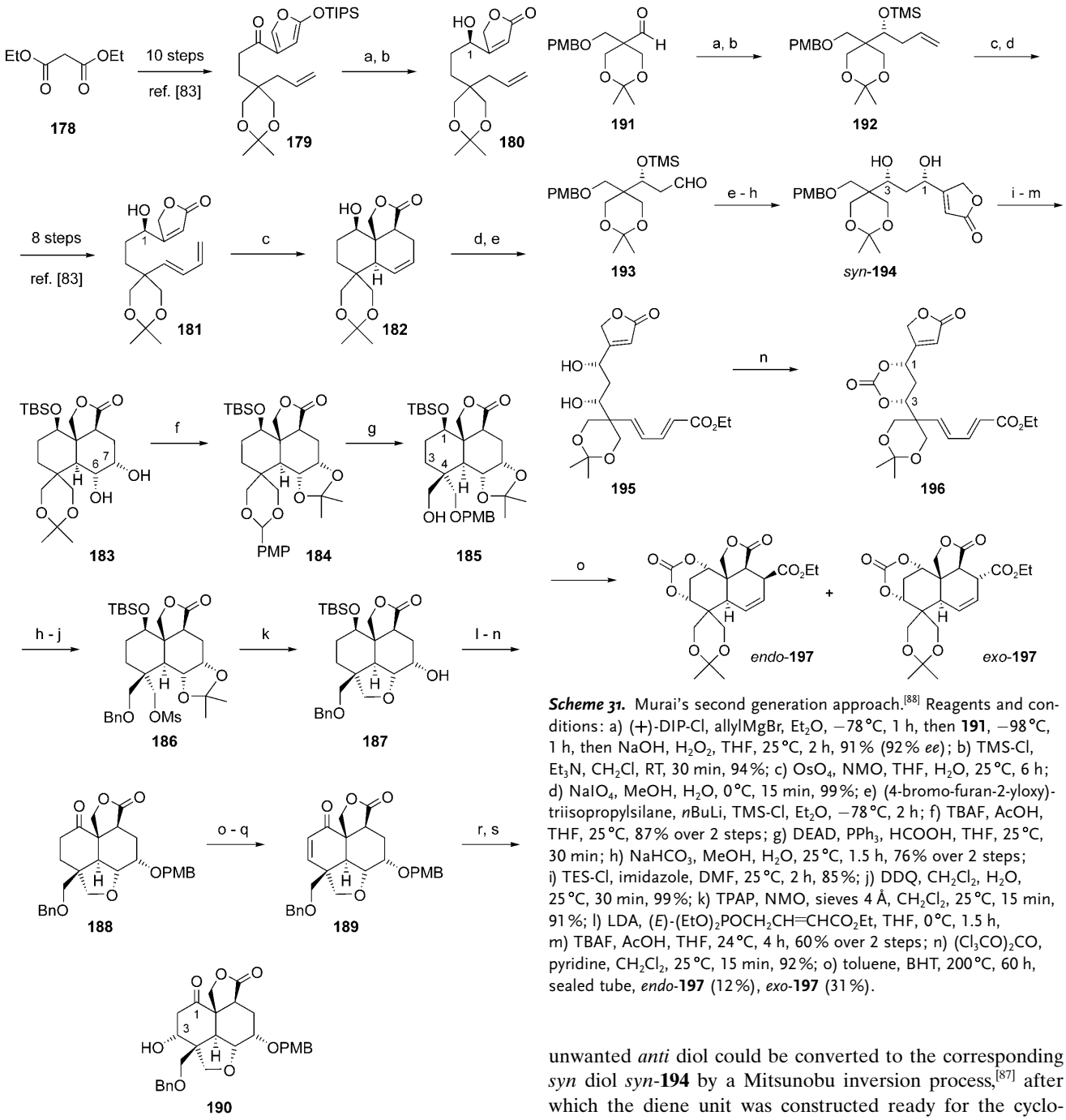
Scheme 29. Synthesis of decalin **177**.[108] Reagents and conditions: a) TBAF, THF, 25 °C; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 92% over 2 steps; c) 10% Pd/C, H_2, EtOH, 25 °C, 98%; d) TES-Cl, Et_3N, CH_2Cl_2, 25 °C, 82%; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 91%; f) Ph_3PCH_2, Et_2O, 25 °C, 80%; g) DDQ, THF-H_2O (9:1), 25 °C, 97%; h) Dess–Martin periodinane, CH_2Cl_2, 25 °C, 92%; i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF-*t*BuOH-H_2O (2:4:1), 25 °C; j) HCl, EtOH-Et_2O (1:1), 25 °C; k) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 6 h, 94% over 3 steps; l) SeO_2, TBHP, CH_2Cl_2, 25 °C, 51%.

4.3. The Murai Approach

Murai's first generation route also employed an IMDA reaction to construct the decalin core in azadirachtin (Scheme 30).[80,81] Early studies indicated the requirement of the *R* configuration at C1 to control the diastereoselectivity in this process (**181**→**182**) and this critical centre was therefore installed through CBS-reduction[82] of ketone **179**.[83] The necessary triene was then accessed following an eight-step sequence (**180**→**181**) after which the desired cycloaddition proceeded in good yield and selectivity to afford **182**.

Next, dihydroxylation of **182** served to install both 6*R* and 7*S* centres present in the natural product and later enabled an intramolecular displacement process to construct the tetrahydrofuran ring in **187**. The quaternary stereocentre at C4 was established from PMP acetal **184**, which could be opened in a selective manner with sodium cyanoborohydride to give **185**. In order to set up the 1,3-oxygenation pattern found in azadirachtin, it was then necessary to invert the stereocentre at C1 and to introduce functionality at C3. After conversion of **188** to the intermediate enone (**189**), epoxidation and regioselective ring opening provided the requisite C3 hydroxy group. However, all attempts to selectively reduce the C1 ketone present in **190** met with failure and, as a consequence, this strategy was abandoned.

In a second generation approach, Murai et al. used an alternative Diels–Alder precursor **196**, in which the critical stereocentres at C1 and C3 were already installed (Scheme 31).[84] In the synthesis of **196**, aldehyde **191**[85] first underwent asymmetric allylation[86] with (+)-DIP-Cl and allyl magnesium bromide to give **192** following protection. Coupling of **193** with a lithiated furan derivative was then followed by silyl-group removal to afford a 2:1 *anti*:*syn* mixture of diols (**194**) in excellent yield. Fortunately, the



Scheme 30. Murai's first generation approach.[81,83,84] Reagents and conditions: a) (*S*)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-*c*]-[1,3,2]oxazaborole, $BH_3{\cdot}SMe_2$, THF, −10 °C; b) TBAF, THF, 0 °C, 99% over 2 steps, 97% *ee*; c) BHT, toluene, 210 °C, autoclave, 2 d, 40-48%; d) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 93%; e) OsO_4, NMO, THF-H_2O-*t*BuOH (2:1:2), RT, 73%; f) PPTS, benzene, reflux, then *p*-anisaldehyde, 79%; g) $NaCNBH_3$, TfOH, sieves 3 Å, DMF, RT, 80% of a 6:1 mixture; h) BnBr, NaH, TBAI, THF, RT, 93%; i) DDQ, CH_2Cl_2-H_2O (20:1), RT, 85%; j) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; k) PPTS, ethylene glycol-THF (1:20), 50 °C, 83%; l) PMB-TCA, TfOH, Et_2O, RT, 70%; m) TBAF, THF, 0 °C to 25 °C, 95%; n) PDC, sieves 3 Å, CH_2Cl_2, RT, 82%; o) LDA, THF, −78 °C then TMS-OTf, 66%; p) *N*-PSP, TMS-OTf, THF, 0 °C to RT; q) $NaIO_4$, MeOH-H_2O (4:1), RT, 44% over 2 steps; r) TBHP, TBAF, DMSO, RT; s) $Na[PhSeB(OEt)_3]$, AcOH, EtOH, RT, 30% over 2 steps.

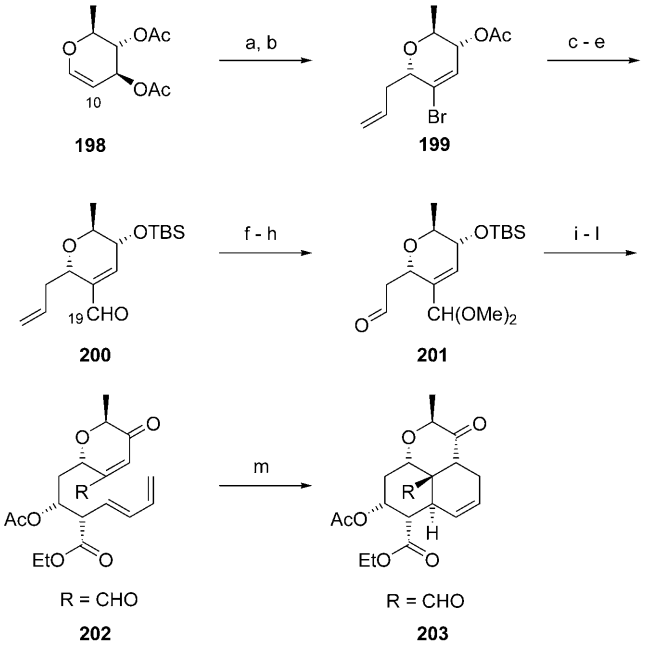
Scheme 31. Murai's second generation approach.[88] Reagents and conditions: a) (+)-DIP-Cl, allylMgBr, Et_2O, −78 °C, 1 h, then **191**, −98 °C, 1 h, then NaOH, H_2O_2, THF, 25 °C, 2 h, 91% (92% *ee*); b) TMS-Cl, Et_3N, CH_2Cl, RT, 30 min, 94%; c) OsO_4, NMO, THF, H_2O, 25 °C, 6 h; d) $NaIO_4$, MeOH, H_2O, 0 °C, 15 min, 99%; e) (4-bromo-furan-2-yloxy)-triisopropylsilane, *n*BuLi, TMS-Cl, Et_2O, −78 °C, 2 h; f) TBAF, AcOH, THF, 25 °C, 87% over 2 steps; g) DEAD, PPh_3, HCOOH, THF, 25 °C, 30 min; h) $NaHCO_3$, MeOH, H_2O, 25 °C, 1.5 h, 76% over 2 steps; i) TES-Cl, imidazole, DMF, 25 °C, 2 h, 85%; j) DDQ, CH_2Cl_2, H_2O, 25 °C, 30 min, 99%; k) TPAP, NMO, sieves 4 Å, CH_2Cl_2, 25 °C, 15 min, 91%; l) LDA, (*E*)-$(EtO)_2POCH_2CH{=}CHCO_2Et$, THF, 0 °C, 1.5 h, m) TBAF, AcOH, THF, 24 °C, 4 h, 60% over 2 steps; n) $(Cl_3CO)_2CO$, pyridine, CH_2Cl_2, 25 °C, 15 min, 92%; o) toluene, BHT, 200 °C, 60 h, sealed tube, *endo*-**197** (12%), *exo*-**197** (31%).

unwanted *anti* diol could be converted to the corresponding *syn* diol *syn*-**194** by a Mitsunobu inversion process,[87] after which the diene unit was constructed ready for the cycloaddition reaction (*syn*-**194**→**195**). It was speculated that a free 1,3-diol **195** would provide undesired products during the planned IMDA reaction[88] and a rigidifying cyclic carbonate, **196**, was employed to solve this problem. The IMDA of **196** then proceeded without incident to give decalins *endo*-**197** and *exo*-**197**, both of which represent viable precursors for the synthesis of azadirachtin.

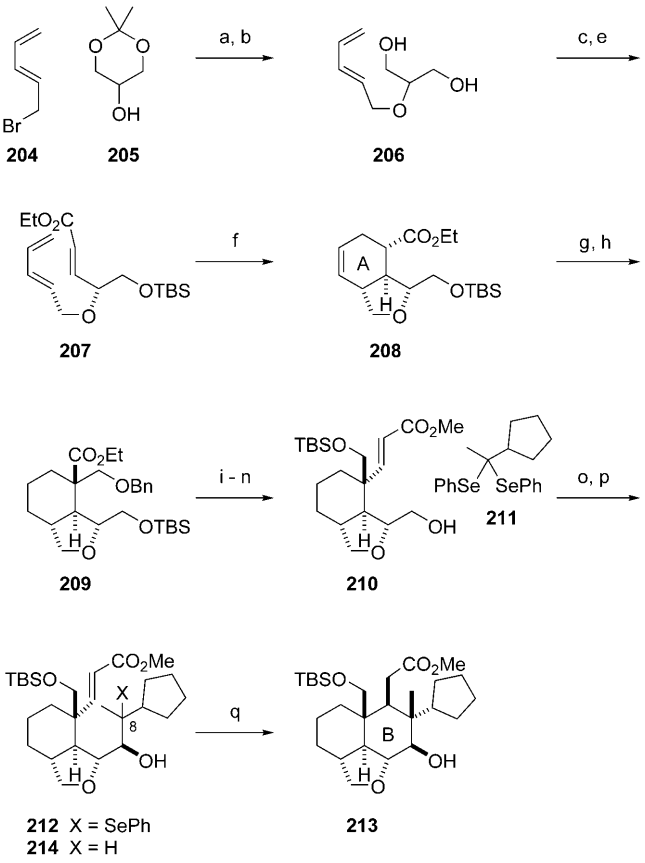
4.4. The Fraser-Reid Approach

Fraser-Reid implemented another version of an IMDA strategy to assemble the decalin core present in azadirachtin but in this instance the inherent chirality of a sugar (L-

rhamnal) was used to control the stereochemical outcome of the process (Scheme 32).[89] The commercially available sugar **198** was first selectively brominated at C10 and a Ferrier rearrangement[90] then permitted efficient chirality transfer to



Scheme 32. Fraser-Reid's approach to the decalin fragment.[89] Reagents and conditions: a) Br_2, CH_2Cl, then DBU, 76%; b) nBu_3Sn-allyl, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C to RT, 76%; c) NaOMe, MeOH; d) NaH, TBS-Cl, THF, 99% over two steps; e) THF, DMF, −78°C, then *t*BuLi, 97%; f) CSA, $Me_2C(OMe)_2$, reflux, 94%; g) NMO, 1% OsO_4, THF, H_2O; h) $NaIO_4$, THF, H_2O, 85% over 2 steps; i) ethyl sorbate, Bu_2BOTf, CH_2Cl_2, −78°C, 58%; j) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0°C to RT; k) HF·pyridine, THF, RT; l) PCC, SiO_2, CH_2Cl_2, RT, 76% over 3 steps; m) toluene, reflux, 70%.



Scheme 33. Watanabe's approach to a decalin fragment.[91] Reagents and conditions: a) KH, 88%; b) TsOH, MeOH, 90%; c) *n*BuLi, TBS-Cl, 79%; d) $(COCl)_2$, DMSO, then Et_3N; e) triethyl phosphonoacetate, NaI, 93% over two steps; f) $EtAlCl_2$, CH_2Cl_2, −78°C to 0°C, 67%; g) H_2, PtO_2, 98%; h) LDA, BOM-Cl, TMEDA, 61%; i) $LiAlH_4$, 78%; j) TBS-Cl, imidazole, 98%; k) H_2, $Pd(OH)_2/C$, 97%; l) $(COCl)_2$, DMSO, then Et_3N; m) $Ph_3P{=}C(H)CO_2Me$, 76% over 2 steps; n) AcOH-H_2O-THF (2:1:2), RT, 93%; o) $(COCl)_2$, DMSO, −78°C, then Et_3N, −78°C to 0°C, 98%; p) **211**, *n*BuLi, THF, −110 to 5°C, 32% (42% recovery of **210**), q) nBu_3SnH, AIBN, toluene, reflux, **213**: 28%, **214**: 60%.

provide **199**. Standard manipulations led to installation of the C19 aldehyde (**199**→**200**), which ultimately served to activate the dienophile present in **202** towards Diels–Alder reaction. The addition of ethyl sorbate to aldehyde **201** later installed the remaining stereocentres present in **202** with good control. Finally, triene **202** was heated under reflux to provide decalin **203** as a single diastereomer, containing much of the functionality required for conversion to the natural product.

4.5. The Watanabe Approach

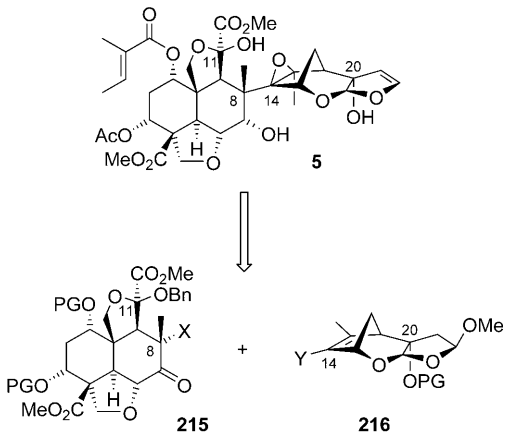
By analogy to our earlier studies, Watanabe also chose an IMDA reaction to build both the A-ring and the tetrahydrofuran unit present in the natural product in a single operation (**207**→**208**, Scheme 33).[91] Another noteworthy feature of this synthesis was the use of a radical cyclisation reaction to construct the B-ring required for azadirachtin. To achieve this, an appropriate precursor, **212**, was prepared from **210** in two steps, namely oxidation and addition of the organolithium derived from **211**. In the event, the expected radical reaction proved problematic; whilst the desired cyclisation occurred to some extent, the major product isolated was that resulting from direct reduction of the C8 centred radical (**214**). Whilst this seemingly negative result was disappointing, it prompted Watanabe to design a much improved second-generation synthesis (see Section 5).

5. Attempts at Azadirachtin Fragment Union

For some time, azadirachtin syntheses were obsessively focused upon the synthesis and union of fully functionalized fragments of the natural product (see Sections 3 and 4). This was due in part to the structural complexity of **5** but also to the attractive possibility of a late stage fragment coupling process. Unfortunately, this approach proved more challenging than one might have imagined and a total of 22 years elapsed between the precise structural elucidation of azadirachtin and its first successful synthesis.[92–94]

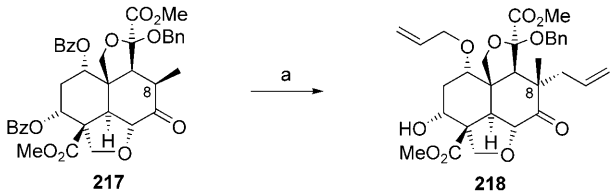
5.1. Our Early Coupling Studies

Initially, we envisioned a highly convergent approach in which two fragments of similar size and complexity could be directly united to forge the central C8–C14 bond present in the natural product (Scheme 34).[95] Whilst this disconnection made excellent strategic sense, it was chemically naïve, owing to the lack of appropriate methodology to effect the formation of such a sterically congested linkage.



Scheme 34. Original synthesis plan.

While many of the methods that we first chose to investigate proved successful during model studies, they could not be realised with more complex substrates. For example, all attempts to generate and subsequently quench an enolate at the C8 position of **217** and related intermediates, were met with disappointing results (Scheme 35).[96]

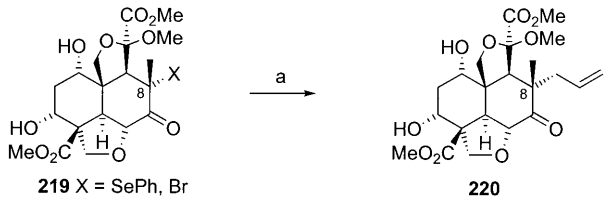


Scheme 35. Attempted direct C8 functionalisation of **217**. Reagents and conditions: a) NaH, allyl bromide, THF, RT, 29%.

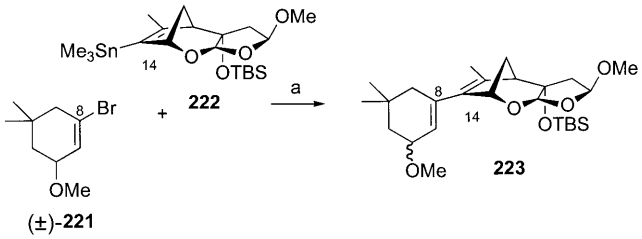
Nevertheless, one observation which initially gave encouragement was that C8-centred radicals, generated from the corresponding selenide or bromide precursors **219**, reacted with allyltributylstannane under irradiation to give the corresponding C8-allyl derivatives **220** (Scheme 36).[97,98] Whilst this worked in the case of simple stannanes, we were never able to effect coupling with more elaborate partners.

Alternatively, we examined a palladium-mediated approach (Scheme 37). Again, while model fragments **221** and **222** could be united, the real systems failed, despite extensive experimentation and effort.

The possibility of promoting intramolecular fragment coupling by exploiting a tether was also investigated



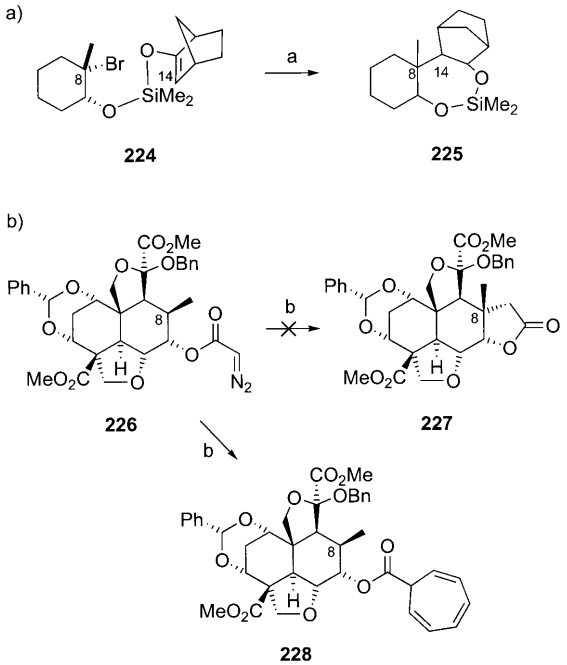
Scheme 36. Radical C8–C14 bond formation. Reagents and conditions: a) nBu$_3$Sn-allyl, $h\nu$, benzene, RT, 70% (X = Br), 27% (X = SePh).



Scheme 37. Palladium-mediated C8–C14 bond formation. Reagents and conditions: a) [PdCl$_2$(dppf)], DMF, 100 °C, 6 h, 35%.

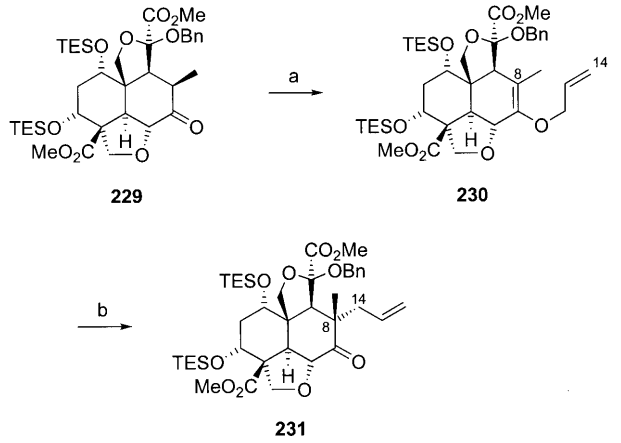
(Scheme 38). Once again, in the case of a radical-mediated process, the results obtained using simple analogues were encouraging but, frustratingly, more advanced architectures were less accommodating and failed to deliver the key carbon–carbon bond (Scheme 38a). A tethered C–H insertion approach to effect functionalisation at C8 was similarly unsuccessful (Scheme 38b).[96]

Ultimately, we selected a Claisen rearrangement to install the hindered C8–C14 bond in azadirachtin as this process is well suited to the formation of carbon–carbon bonds between



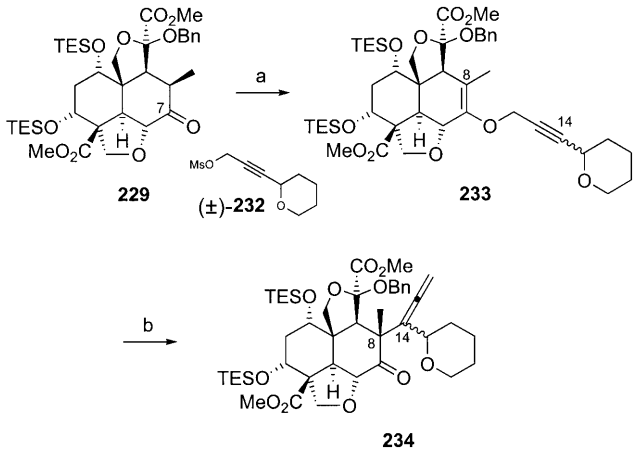
Scheme 38. Use of a tether to promote C8–C14 bond formation. Reagents and conditions: a) nBu$_3$SnH, AIBN, benzene, reflux, 50% (mixture of 4 diastereoisomers); b) Rh$_2$(OAc)$_4$, benzene, reflux, 43%.

highly substituted centres.[99,100] Our initial studies in this area were very promising: following selective *O*-alkylation at C7 (**229**→**230**, Scheme 39),[101] allyl vinyl ether **230** underwent the desired sigmatropic rearrangement to provide **231** in good yield and as a single diastereoisomer.



Scheme 39. Functionalisation at C8 by *O*-alkylation/allylic Claisen rearrangement. Reagents and conditions: a) NaH, [15]crown-5, allyl bromide, THF, 0 °C, 2 h, 66%; b) xylene, reflux, 43 h, 71%.

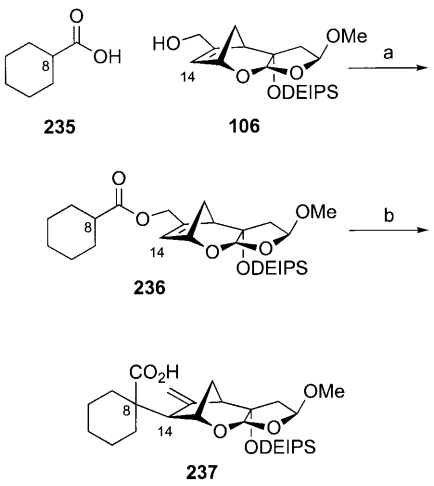
More elaborate examples were investigated and proved equally successful: for example, the enolate of **229** underwent selective *O*-alkylation with mesylate **232**, followed by a microwave-induced Claisen rearrangement to provide the allene **234** (Scheme 40). This concept was eventually employed in the synthesis of azadirachtin itself (see Section 6).



Scheme 40. Intramolecular C8–C14 bond formation by propargyl Claisen rearrangement. Reagents and conditions: a) NaH, **232**, [15]crown-5, THF, 0 °C, 2 h, 66%; b) 1,2-dichlorobenzene, microwave irradiation, 180 °C, 15 min, then 220 °C, 15 min, 53%.

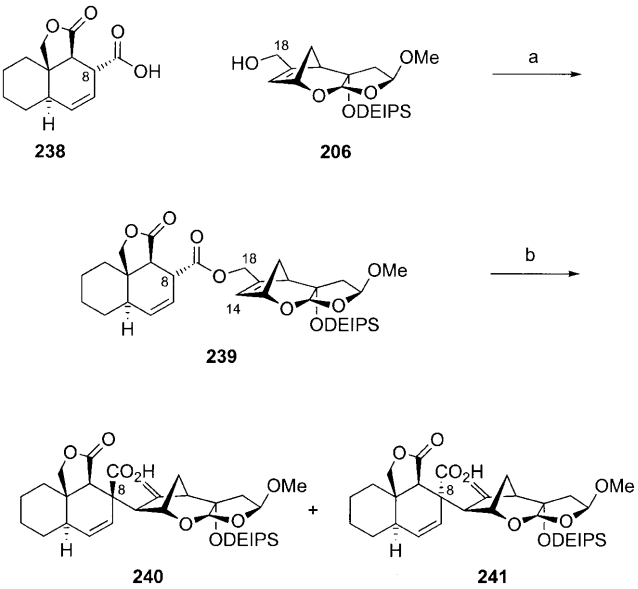
5.2. The Murai Approach

At a similar time, Murai et al. published a related Claisen approach to construct the central C8–C14 bond present in azadirachtin.[102] This process was first investigated using a decalin surrogate, **235**, to establish suitable reaction conditions (Scheme 41). Following esterification of **235** with tricyclic furanacetal fragment **106**, Ireland–Claisen rearrangement proceeded in excellent yield to afford **237** as an appropriate model for C8–C14 bond formation.



Scheme 41. Studies towards C8–C14 bond formation with achiral decalin surrogate **235**.[103] Reagents and conditions: a) EDCI, DMAP, CH_2Cl_2, RT, 2 h, 72%; b) KHMDS, TMS-Cl, Et_3N, toluene, −78 °C to 70 °C, 12 h, 87%.

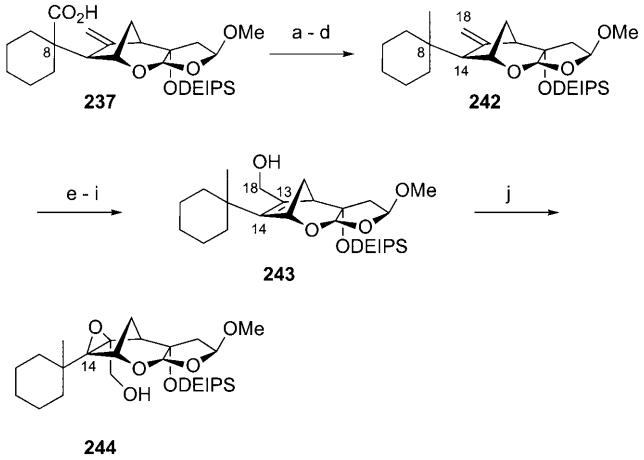
The optimised reaction conditions were applied to a more complex substrate **238** and the rearranged products, **240** and **241**, were obtained as a 1:3 mixture of diastereomers (Scheme 42). Unfortunately, the major diastereomer was that with the incorrect configuration at C8. Nonetheless, further study of the reaction parameters proved fruitful and modification of both base and silylating agent led to a



Scheme 42. Murai's approach to C8–C14 bond formation.[103] Reagents and conditions: a) EDCI, DMAP, CH_2Cl_2, RT, 72%; b) $SiMe_2Cl_2$, Et_3N, toluene, LiHMDS, −78 °C to 70 °C, 87%, (4:1) **240**:**241**.

synthetically useful 4:1 d.r. in favour of the required isomer (**240**), but again only on a model system.

In order to demonstrate the viability of this Ireland–Claisen strategy for the synthesis of azadirachtin, it was necessary to fully reduce the carboxy group at the C8 position. This was achieved in a high-yielding four-step sequence (**237**→**242**, Scheme 43). Model studies were also employed to

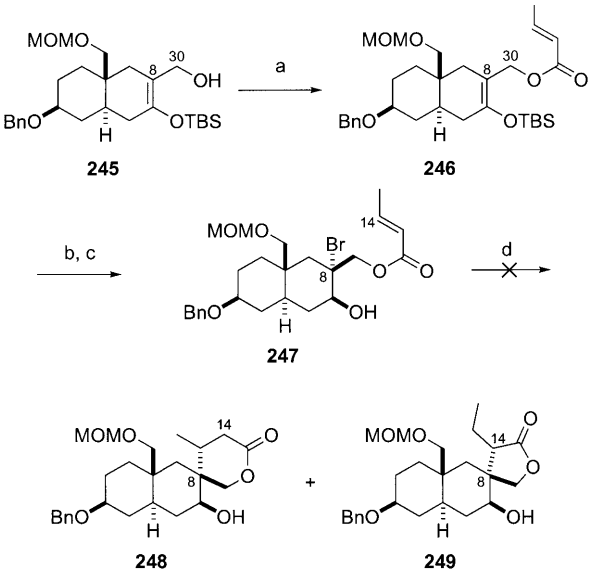


Scheme 43. Tether removal and model epoxidation studies.[103] Reagents and conditions: a) CH_2N_2, Et_2O, 0 °C; b) DIBAL-H, CH_2Cl_2, −78 °C, 99% over 2 steps; c) imidazole, PPh_3, I_2, benzene, RT, 93%; d) $NaBH_4$, DMSO, 100 °C, 87%; e) *m*CPBA, $NaHCO_3$, CH_2Cl_2, RT, 90%; f) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −55 °C, 7 h, 78%; g) KHMDS, HMPA, THF, −55 °C, *then* NBS, 71%; h) LiBr, Li_2CO_3, DMF, 125 °C, 99%; i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 78%; j) $[VO(acac)_2]$, TBHP, CH_2Cl_2, RT, 99%.

examine the installation of the sterically congested C13–C14 epoxide in **5**.[103] Standard manipulations permitted the transformation of *exo* olefin **242** to a suitable epoxidation precursor **243**. Intermediate **243** then smoothly underwent directed epoxidation upon treatment with vanadyl acetoacetonate and *tert*-butyl hydroperoxide to provide **244** as the sole product of the reaction.

5.3. The Nicolaou Approach

Nicolaou and co-workers have studied a number of strategies for the construction of the central C8–C14 bond within azadirachtin (**5**). In a similar approach to Murai, initial efforts were focussed on an intramolecular C8–C14 bond forming process using an ester linker at C30 to tether the two molecules.[104] The key difference in this approach lies in the carbon–carbon bond forming event in which a radical cyclisation was deemed to be the method of choice.[105] Accordingly, an appropriate decalin precursor, **245**, was prepared and coupled with a simple surrogate for the dihydrofuranacetal unit in **5** (Scheme 44). Bromination and reduction installed a radical precursor at C8 (**247**) but unfortunately, conditions could not be found to effect the desired cyclisation and therefore an alternative strategy was examined.



Scheme 44. Nicolaou's initial approach to C8–C14 bond formation.[104] Reagents and conditions: a) (*E*)-but-2-enoyl chloride, pyridine, CH_2Cl_2, RT, 99%; b) NBS, CH_2Cl_2, −78 °C; c) $NaBH_4$, CH_2Cl_2, MeOH, −78 °C, 53% over 2 steps; d) Ph_3SnH, AIBN, toluene, reflux, 0%.

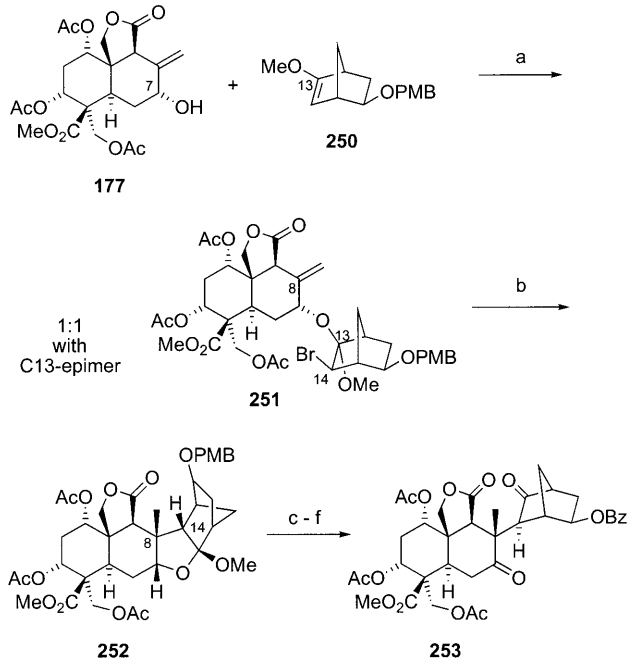
The second approach developed by Nicolaou et al. also employed an intramolecular radical cyclisation reaction to effect C8–C14 bond formation.[106–108] However, owing to the difficulties encountered previously, a different method was employed for fragment union. Bicycle **250** was treated with bromine to generate an active electrophile, which was then trapped by the C7 hydroxy group in **177** to afford **251** as a mixture of C13 diastereoisomers (Scheme 45). Both of these diastereoisomers represented valid precursors for the synthesis of azadirachtin.

The radical cyclisation of **251** proceeded without incident to furnish **252** in good yield and it was then necessary to cleave the temporary bridge that had enabled the key C8–C14 bond formation. A short high-yielding sequence of reactions established the viability of this approach (**252**→**253**) and clearly the product of this process contains many, but certainly not all, of the features necessary for a synthesis of azadirachtin.[108]

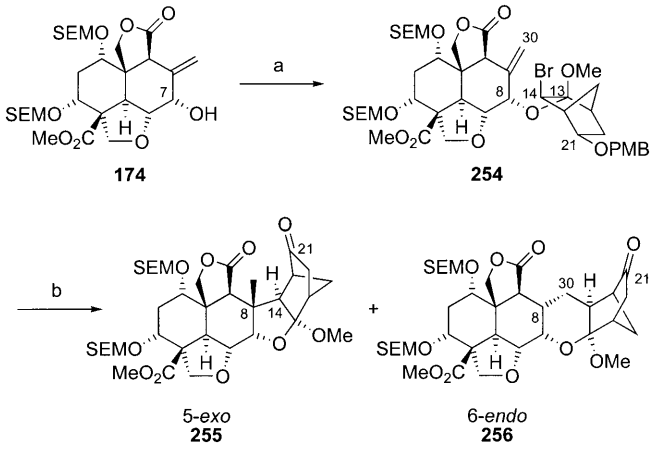
A similar series of reactions were carried out using a more functionalised fragment **174**, however significant differences in reactivity were observed (Scheme 46).[107] The fragment coupling process afforded **254** as a single C13 diastereoisomer (cf. Scheme 45). Even more surprising was the outcome of the radical cyclisation reaction. Previously, the product obtained was that resulting from 5-*exo* cyclisation of **254**, yet in this instance a mixture of both 5-*exo* and 6-*endo* products was observed. It is important to note that of the two intermediates **255** and **256**, only the former has the potential for productive development towards azadirachtin.

5.4. The Watanabe Approach

Watanabe's most recent work[109] demonstrates a refreshing alternative towards azadirachtin synthesis and benefits

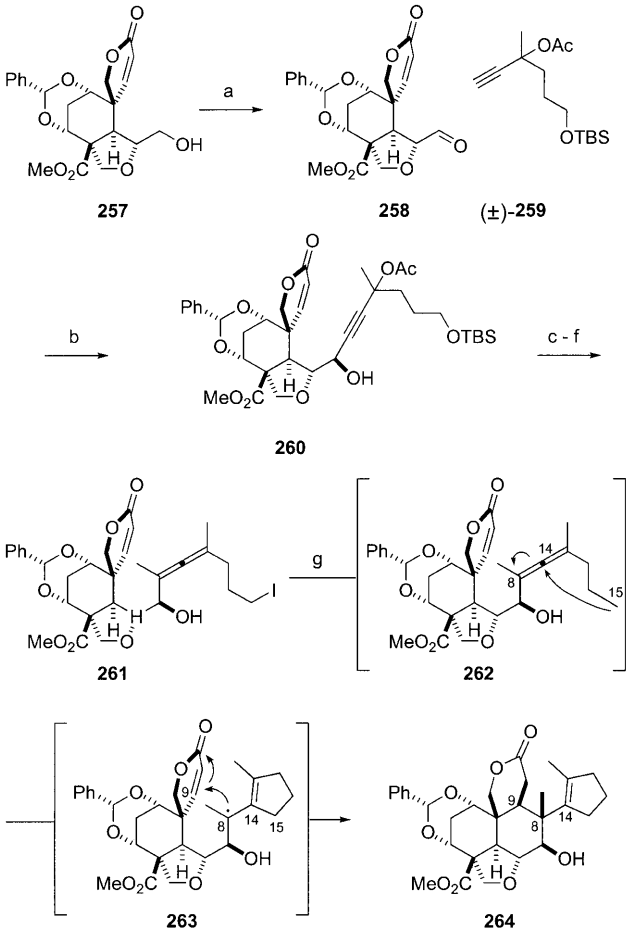


Scheme 45. Nicolaou's successful approach to C8–C14 bond formation.[108] Reagents and conditions: a) Br_2, *N*,*N*-dimethylaniline, K_2CO_3, CH_2Cl_2, −78 °C to 0 °C; b) $(Me_3Si)_3SiH$, AIBN, toluene, reflux, 80%; c) $Pd(OH)_2/C$, H_2, EtOH, RT; d) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT; e) H_2O-TFA (1:9), 65 °C, 75% over 3 steps; f) PCC, 1,2-dichloroethane, 65 °C, 80%.



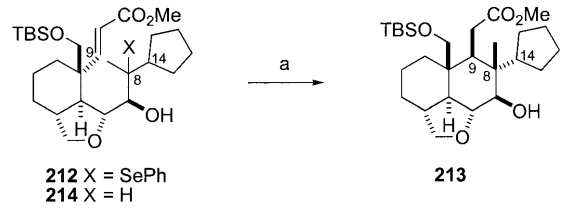
Scheme 46. Nicolaou's successful approach to C8–C14 bond formation.[107] Reagents and conditions: a) Br_2, **250**, *N*,*N*-dimethylaniline, K_2CO_3, CH_2Cl_2, −78 °C to 0 °C, 76%; b) $(Me_3Si)_3SiH$, AIBN, toluene, reflux, **255** (32%), **256** (42%).

from the knowledge acquired during earlier reported studies. Most approaches share a common strategy whereby *O*-alkylation/acylation is immediately followed by the critical C8–C14 bond forming process but, by way of contrast, Watanabe chose to construct the C8–C9 bond in **5** at a late stage with the C8–C14 linkage in place (Scheme 47). The precursor for this reaction was constructed by the addition of acetylene **259** to aldehyde **258**. An allene moiety was then installed by S_N2' addition of methyl magnesium bromide to alkyne **260** and standard manipulations furnished the iodide



Scheme 47. The Watanabe radical cascade to azadirachtin.[109] Reagents and conditions: a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; b) **259**, LiHMDS, THF, −78 °C, 23% over 2 steps; c) MeMgBr, CuI, LiBr, THF, 0 °C, 78%; d) TBAF, THF, 0 °C to RT, 97%; e) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT, 90%; f) NaI, $NaHCO_3$, DMF, RT, 94%; g) $n$$Bu_3SnH$, AIBN, toluene, reflux, 90%.

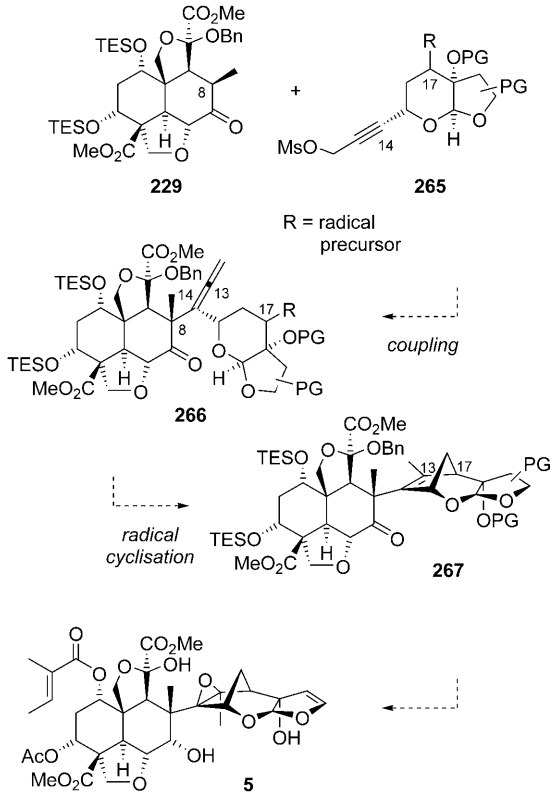
261. Previous attempts at radical C8–C9 bond formation were hampered by the formation of **214** (Scheme 48), but when **261** was subjected to radical cyclization conditions, the desired cascade occurred to give decalin **264**. Although the addition of **259** to **258** only proceeded in 23% yield, the excellent yield for the radical cyclisation of **261** proves the validity of Watanabe's approach. We look forward to seeing this strategy applied to compounds which contain all the functionality required for azadirachtin (**5**).



Scheme 48. Early studies towards azadirachtin.[91] Reagents and conditions: a) $n$$Bu_3SnH$, AIBN, toluene, reflux, **213**: 28%, **214**: 60%.

6. The Synthesis of Azadirachtin

Finally, given our earlier extensive model studies, we felt confident that many of the fundamental problems in our synthesis had now been resolved.[94] We reasoned that the exceptionally hindered C8–C14 bond found in azadirachtin was best constructed by *O*-alkylation of an enolate precursor followed by Claisen rearrangement of the resulting propargyl enol ether (see Section 5). This route would make use of the best of our decalin syntheses but would necessitate the synthesis of a new propargylic mesylate, **265** (Scheme 49).



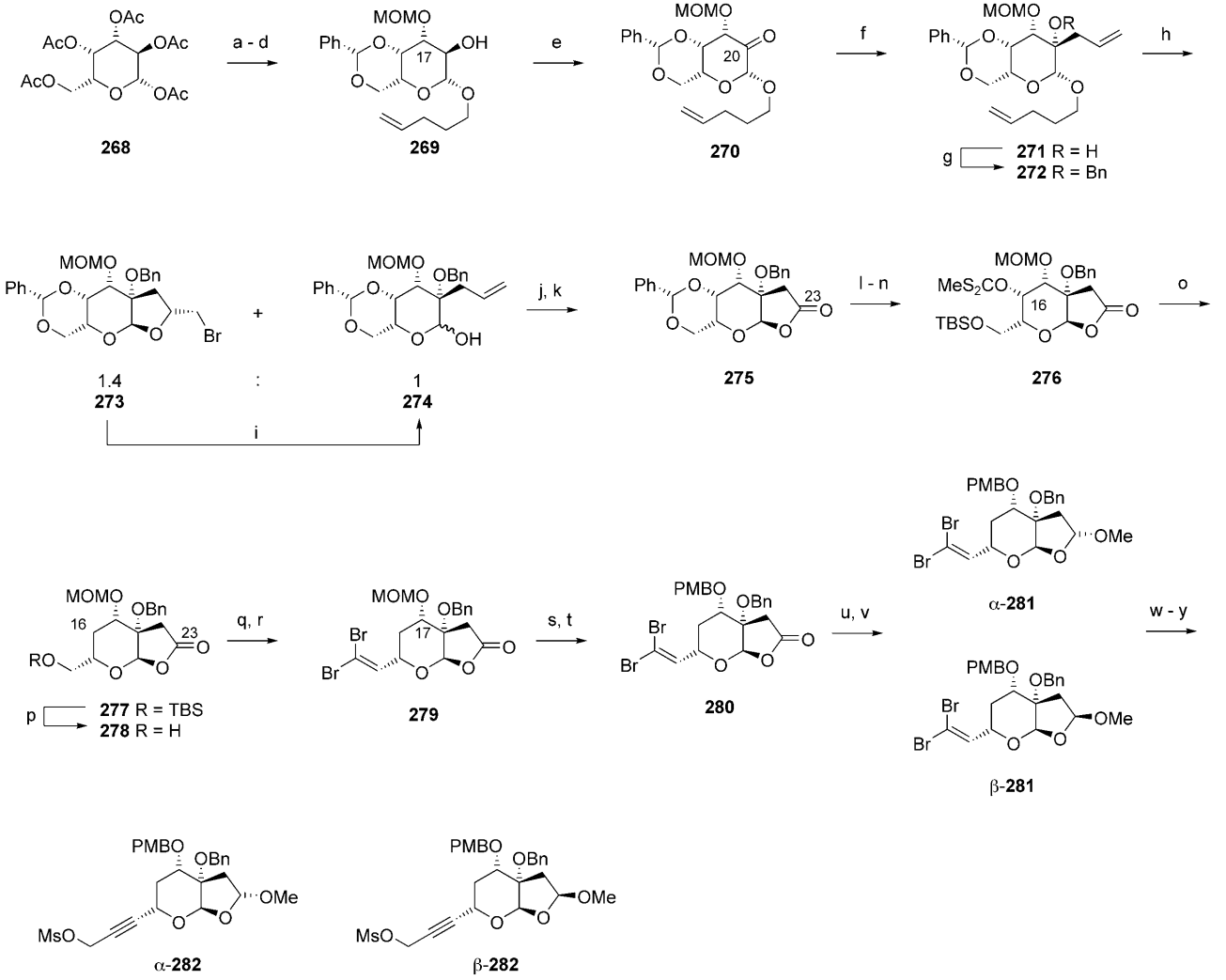
Scheme 49. Proposed route to azadirachtin (**5**).

This new coupling partner **265** was designed to meet a number of criteria. It contained all the carbon atoms required for the complete azadirachtin framework and was therefore expected to provide a fully functionalised allene, **266**, following the previously developed coupling strategy. However, the essential component of the new fragment **265** was a radical precursor at the C17 position. This was important as we anticipated that a C17 centred radical could undergo a highly selective cyclisation reaction onto the nearby allene and in so doing, construct the [3.2.1]bicyclic system present in azadirachtin in a single operation (**266**→**267**).

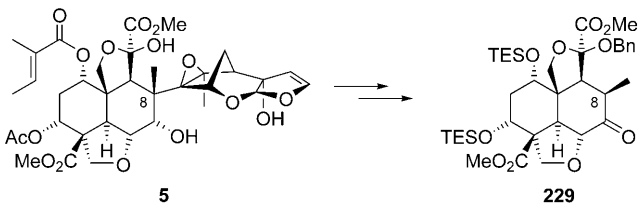
We therefore chose propargylic mesylate **282** as an appropriate target, possessing sufficient functionality for conversion to the natural product (Scheme 50). At the outset, the protecting-group strategy was not fully defined but was meant to be flexible so as to accommodate any necessary changes in the evolution of the final route. The synthesis of **282** began from a cheap, commercially available carbohydrate derivative **268**, in which much of the stereochemistry we would require was already in place (Scheme 50).[110] First, **268** was progressed to **269** using standard protecting group manipulations and, whilst these proceeded without incident, it is important to note the choice of a C17-MOM protecting group at this stage. With **269** in hand, we set about studying the nucleophilic addition of an allyl Grignard reagent to the corresponding C20-ketone **270**. It was quickly concluded that facial selectivity in the reaction was exquisite and furthermore that the Grignard reagent could be added directly to the crude oxidation reaction mixture.[111] With the C20-allyl group installed, we could then attempt to form the necessary tetrahydrofuran ring using similar chemistry developed over the course of our earlier work (cf. Schemes 8 and 9). Accordingly, the pentenyl glycoside **272** was treated with NBS with the aim of forming the corresponding hemiacetal **274**. Disappointingly, the allyl group showed competitive reactivity to the pentenyl moiety and a major by-product, **273**, was isolated which was the result of a cascade of bromination reactions. Extensive investigations revealed that this was unavoidable, but that the desired product could be readily accessed following Boord reaction[112] of the bromoether **273**. Ozonolysis and TPAP-mediated oxidation[113] then proceeded smoothly to generate lactone **275**. Deoxygenation at C16 was the next objective and, following standard procedures, xanthate **276** readily underwent Barton–McCombie[114] reaction to give **277**. The principal remaining task in our synthesis of the fully functionalised azadirachtin fragment was the introduction of the propargylic mesylate group. Thus, silyl ether **277** was cleaved to the corresponding primary alcohol **278** which could be routinely transformed to the dibromoolefin **279**. It was at this point that we opted to perform any remaining protecting group manipulations as part of our route.

While the C17-MOM ether had performed well in the synthesis thus far, it was not compatible with the projected final steps and thus it was replaced with the C17-PMB ether **280**. Also, the C23-lactone **280** was transformed into the more familiar methyl acetal **281**. It is important to note that although an epimeric mixture at C23 was obtained, both intermediates were viable precursors for the furan acetal portion of the natural product, so following separation, both were advanced side-by-side. The corresponding terminal alkyne was accessed by Corey–Fuchs elimination and the homologation/mesylation sequence then proceeded without incident to give the fully functionalised azadirachtin coupling partner **282**.

After the successful preparation of propargylic mesylate **282** we next investigated the critical fragment coupling process. Early studies with a simplified system had indicated that the *O*-alkylation of decalin ketone **229** was not a trivial process, requiring forcing conditions to effect complete conversion.[115] Most notably, these early studies employed a five-fold excess of a propargylic mesylate fragment, a luxury that we could scarcely afford given the 26-step synthesis route from which the new mesylate **282** derived. We were fortunate however that we had a ready supply of the decalin coupling partner **229**, which was available from azadirachtin in a short degradative sequence (Scheme 51).[23,116,117]



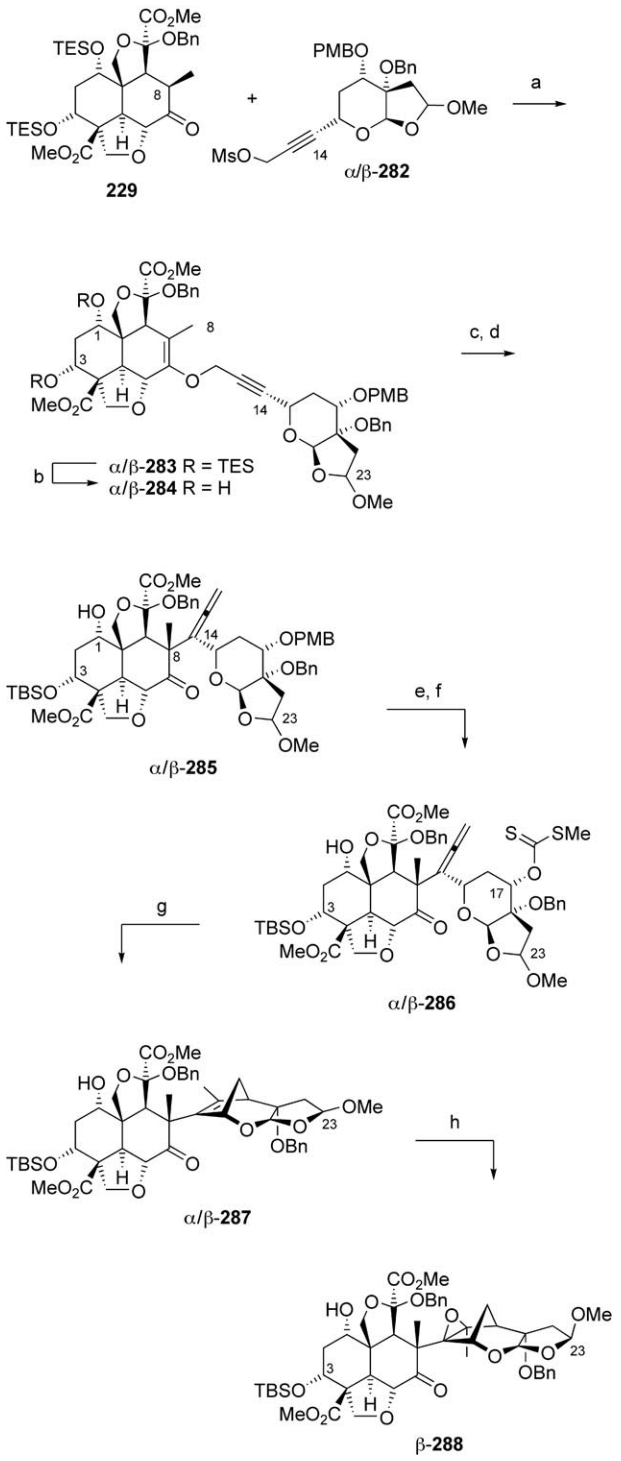
Scheme 50. Synthesis of propargylic mesylates **282**. Reagents and conditions: a) 4-penten-1-ol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT; b) NaOMe, MeOH, RT; c) PhCHO, CSA, $CHCl_3$, 30% over 3 steps; d) nBu_2SnO, MeOH, reflux, then MOM-Cl, 1,4-dioxane, RT, 93% over 2 steps; e) $SO_3{\cdot}$pyridine, DMSO, iPr_2NEt, CH_2Cl_2, 0°C; f) allylMgCl, THF, −78°C, 85%; g) BnBr, NaH, DMF, RT, 92%; h) NBS, MeCN-H_2O (9:1), pH 7, RT, 58% 1.4:1 mix of **273**:**274**; i) Zn, EtOH, NH_4Cl, 80°C; j) O_3, CH_2Cl_2, −78°C, then PS-PPh_3, RT; k) TPAP, NMO, MeCN, RT, 76% over 3 steps; l) CH_2Cl_2-TFA-H_2O (20:1:1), RT, 97%; m) TBS-Cl, DMAP, DMF, Et_3N, RT, 71%; n) CS_2, NaHMDS, −78°C, then MeI, −78°C, 92%; o) AIBN, nBu_3SnH, toluene, 110°C, 99%; p) CH_2Cl_2-TFA-H_2O (20:1:1), RT, 81%; q) $SO_3{\cdot}$pyridine, DMSO, iPr_2NEt, CH_2Cl_2, 0°C; r) *t*BuOK, $Ph_3PCHBr_2{\cdot}$Br, THF, RT, 78% over 2 steps; s) TMS-Br, CH_2Cl_2, 0°C, 99%; t) PMB-TCA, $La(OTf)_3$, THF, RT, 90%; u) DIBAL-H, CH_2Cl_2, hexane, −78°C; v) Amberlyst 15, MeOH, RT, 74% over 2 steps; w) MeLi·LiBr, THF, −78°C to 0°C, α: 97%, β: 93%; x) *i*PrMgCl, $(CH_2O)_n$, THF, 45°C, α: 89%, β: 78%; y) Ms_2O, iPr_2NEt, CH_2Cl_2, 0°C, α: 90%, β: 90%.



Scheme 51. Degradation of azadirachtin to the decalin fragment **229**.[116]

As a consequence, we chose to re-examine the conditions required to promote the coupling reaction of **229** and **282** to establish whether the reaction would in fact proceed using an excess of the decalin ketone **229**. Pleasingly, it was found that treatment of the enolate of **229** (5 equiv) with propargylic mesylate **282** (1 equiv) in the presence of [15]crown-5 afforded excellent yields of the desired propargylic enol ether **283** (Scheme 52). Although intermediate **283** was highly unstable, desilylation with TBAF occurred rapidly and the resulting diol **284** proved to be somewhat less prone to decomposition. It is important to note that, whilst preliminary model studies achieved the *O*-alkylation/Claisen sequence in the presence of TES protecting groups at C1 and C3, more advanced studies demonstrated that removal of these was a prerequisite for the Claisen rearrangement.[115]

Since the propargylic Claisen reaction had been performed many times before on a wide variety of azadirachtin-related substrates we anticipated that this should be one of the few transformations in the route which would proceed



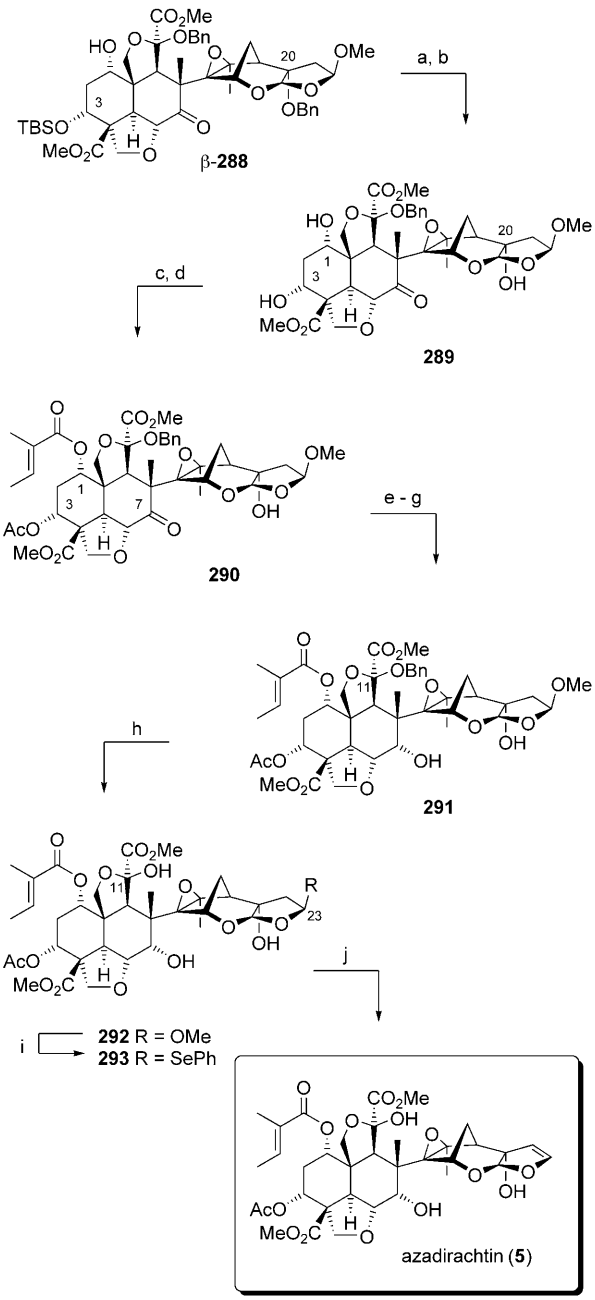
Scheme 52. Fragment coupling, formation of the [3.2.1]bicycle and epoxidation. Reagents and conditions: a) NaH, [15]crown-5, THF, 0 °C, α: 82 %, β: 74 %; b) TBAF, THF, 0 °C, α: 90 %, β: 99 %; c) microwave irradiation, 1,2-dichlorobenzene, 185 °C, α: 86 %, β: 83 %; d) TBS-imidazole, DMF, 100 °C, α: 91 %, β: 86 %; e) DDQ, CH_2Cl_2, H_2O, RT, α: 91 %, β: 95 %; f) CS_2, NaHMDS, THF, −78 °C, then MeI, −78 °C, α: 86 % over 2 steps, β: 57 % (75 % brsm) over 2 steps; g) nBu$_3$SnH, AIBN, toluene, 100 °C, high dilution, α: 90 %, β: 91 %; h) MMPP·6 H_2O, 5-*tert*-butyl-4-hydroxy-2-methyl-phenylsulfide, $NaHCO_3$, MeOH, 105 °C, sealed tube, 7 d, α:22 % (85 % brsm), β: 65 % (85 % brsm).

"without incident". Imagine our dismay when the first attempt to convert **284** to **285** gave a multitude of compounds! Furthermore, the yield obtained in the course of these first studies was so miserable (< 5 %) that unambiguous characterisation of what was thought to be the allene could not be accomplished. We proceeded to screen the conditions used in the Claisen rearrangement and rapidly discovered that a change in solvent had a phenomenal effect on the reaction. The use of 1,2-dichlorobenzene in place of nitrobenzene resulted in a dramatic increase of yield from < 5 % to 80 %. This suggested that nitrobenzene may well behave as an oxidizing agent at the elevated temperatures employed in the rearrangement.

With this hurdle overcome, we next turned our attention to the installation of a radical precursor at the C17 position. It was first necessary to reprotect the hydroxy groups at C1 and C3, a transformation which appeared deceptively simple. However, despite enormous effort, we were unable to protect *both* alcohol groups owing to the unreactive nature of the hindered C1 hydroxy group. Unperturbed, we continued with the synthesis in the hope that the lack of reactivity at C1 would also preclude any reaction at this site in the subsequent xanthate-forming step. Pleasingly, when the bulky TBS group was used to protect the C3 hydroxy, good selectivity was observed for the formation of the desired C17 xanthate. Everything was now in place to attempt the radical cyclisation of **286** which, after some optimisation, proceeded in excellent yield to afford **287** as a single isomer, which possesses the carbon framework of the natural product itself.

The next major challenge was the epoxidation of the tetrasubstituted olefin present in **287** and, as is often the case in complex natural product synthesis, material was scarce. Nevertheless, we were fortunate to have access to both 23α and 23β epimers of the product epoxide **288**[93] and we were therefore able to perform initial epoxidation reactions on a very small scale, using NMR to determine whether any of the desired product was present. Since alkene **287** contains many potentially reactive functional groups, we were concerned that other undesired oxidative reaction pathways might complicate identification of the reaction product. However, after extensive experimentation, it was found that magnesium monoperoxyphthalate[118] was able to cleanly effect the epoxidation of compound **287**, albeit with modest conversion. Interestingly, both 23α and 23β epimers afforded an identical product, β-**288**. Presumably the α-epimer is not reactive under the epoxidation conditions and instead slowly epimerises to give the β-epimer which then undergoes the epoxidation process.

Following this very important epoxidation step, we could begin the task of unveiling the remaining functionality present in the natural product (Scheme 53). Firstly, the protecting groups at C3 and C20 were removed under standard conditions (β-**288**→**289**) and regioselective monoacetylation of the resulting triol was achieved using acetic anhydride. Although the esterification at C3 was relatively straightforward, the corresponding increase in steric bulk rendered the formation of the requisite C1 tigloyl ester much more challenging. Several highly reactive tigloylation reagents were investigated for this transformation,[119] how-



Scheme 53. Final steps in the synthesis of azadirachtin.[93,119,121] Reagents and conditions: a) TBAF, THF, RT, 95%; b) H_2, Pd/C, EtOH, RT, 3 h, 95%; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 76%; d) $CH_3CHC(CH_3)(CO)O(CO)C_6H_2Cl_3$, Cs_2CO_3, toluene, reflux, 6 d, 50% (95% brsm); e) Et_3N, MeOH, H_2O, RT, 93%; f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, RT, 91%; g) Ac_2O, Et_3N, DMAP, CH_2C_{l2}, RT, 87%; h) Pd/C, H_2, THF, RT, 14 h, 89%; i) PhSeH, PPTS, $ClCH_2CH_2Cl$, reflux; j) H_2O_2, pyridine, 0°C, 85% over 2 steps.

ever, by far the best was a Yamaguchi-type activated ester.[120] Whilst this gave a 50% yield of **290**, the remainder of the reaction mixture comprised only unreacted starting material which could be readily recovered and recycled.

The next challenge in the synthesis was the stereoselective reduction of the C7 ketone to give the axial alcohol found in the natural product. Unfortunately, optimised conditions for direct reduction of **290** gave only a 1:1 mixture of C7 epimers. However, basic hydrolysis of the C3 acetate, Luche[26] reduction and acetate reintroduction afforded the desired alcohol, **291**, as a single diastereoisomer in 80% yield over the three-step sequence.[121,122] The acid-labile C11-hemiacetal was then obtained following hydrogenolysis without any reduction of the tigloyl ester (**291**→**292**). The final task in the synthesis was the conversion of the C23-methyl acetal to the corresponding enol ether. The groundwork for this process was already in place from our earlier studies (cf. Scheme 10) and following this precedent we were able to synthesise the intermediate selenoacetal **293**. Following mild oxidation, spontaneous elimination of benzeneselenenic acid occurred to, at last, give the natural product, azadirachtin (**5**), in excellent yield, identical in all respects to an authentic sample.[121]

7. Summary and Outlook

Although this epic journey has spanned some 22 years, we are pleased by the synthesis discoveries that have been made along the way. All the synthetic intermediates en route to azadirachtin have provided important structural activity information and allowed for the functional groups responsible for biological activity to be probed.[123–139] Given this knowledge, we feel that azadirachtin (**5**) is still an attractive target for commercial development. With the putative biological targets now being defined, we can anticipate renewed interest in azadirachtin: specifically the design of analogues and alternative small molecule mimetics.

List of Abbreviations

[15]crown-5	1,4,7,10,13-pentaoxacyclopentadecane
acac	acetylacetonate
AIBN	azobisisobutyronitrile
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
BOM	benzyloxymethyl
brsm	based on recovered starting material
Bz	benzoyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DEIPS	diethyl isopropylsilyl
DET	diethyl tartrate
DIBAL-H	diisobutyl aluminium hydride
DIP	di-isopinocamphenyl borane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMAP	*N*,*N*-dimethylamino pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene

EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
KDA	potassium diisopropylamide
LDA	lithium diisopropylamide
*m*CPBA	*meta*-chloroperbenzoic acid
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
MoOPH	MoO_5·pyridine·HMPA
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium *para*-toluene sulfonate
PS	polymer supported
PSP	phenylselenophthalimide
PTSA	*para*-toluene sulfonic acid
SAR	structure–activity relationship
SEM	trimethylsilylethoxymethyl
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetimidate
TEMPO	2,2,6,6-tetramethyl-piperidin-1-oxyl radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tigloyl	(*E*)-2-methylbut-2-enoyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine
TMS	trimethylsilyl
TPAP	tetra-*n*-propyl ammonium perruthenate
Ts	toluenesulfonyl

We gratefully acknowledge the EPSRC (G.E.V and A.B), Pfizer Global R + D and Merck for fundingas well as Dr. Matt O'Brien for providing the frontispiece artwork for this article.

Received: June 6, 2008

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