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Chemistry of Insect Antifeedants from *Azadirachta Indica* (Part 10)[1]: Synthesis of a Highly Functionalised Decalin Fragment of Azadirachtin.

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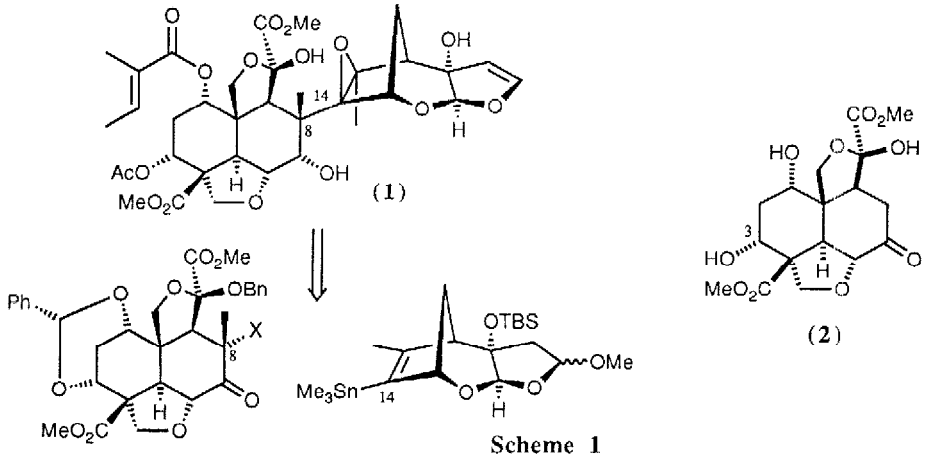
Summary: The synthesis of a highly functionalised decalin fragment (2) of the antifeedant azadirachtin (1) is described. A silyl group was employed to control the stereoselectivity of several key steps and to introduce C3 hydroxyl functionality. A novel ring contraction strategy afforded the inherent hemiketal unit.

Azadirachtin (1)[2], a potent antifeedant and growth disruptant isolated from the neem tree *Azadirachta Indica* A. Juss (Meliaceae)[3], has been the centre of much recent attention owing to its potential use in integrated insect pest control programmes.[4]

For our synthesis of (1) we envisaged coupling of an appropriately substituted decalin fragment with a suitably protected hydroxy acetal portion to form the linking C8-C14 bond (Scheme 1).

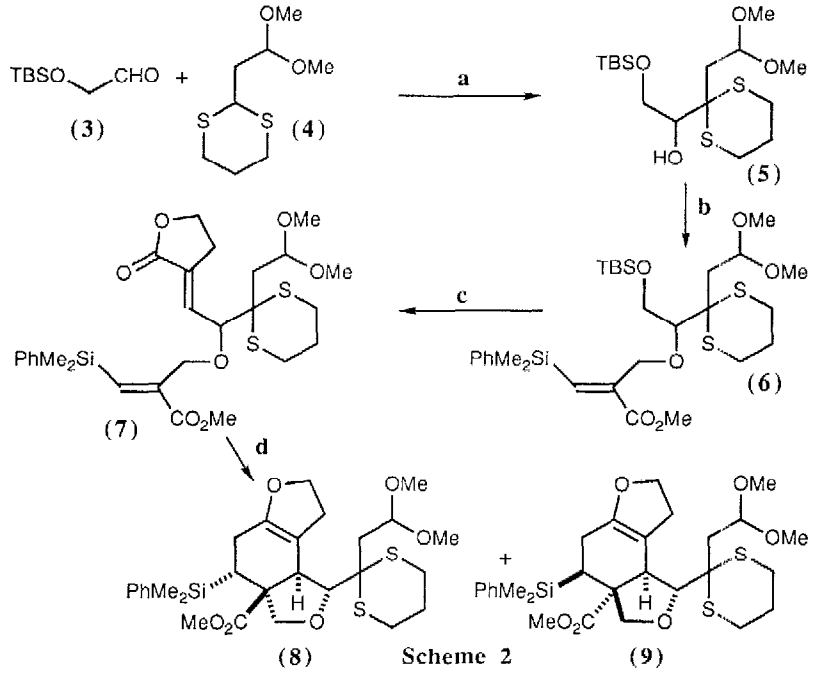


Scheme 1

Previous studies[5] by our group have established the viability of this general approach. These include syntheses of the required acetal fragments[6] and necessary functional group interconversions along with key degradation studies of the natural product to obtain the decalin unit.[1] Here we report the synthesis of a highly functionalised decalin derivative (2) central to the total synthesis of this challenging target molecule.

Key elements in this synthesis are the use of a phenyldimethylsilyl group both to set up many of the inherent stereogenic centres in (2) and, through a silyl Baeyer Villiger reaction, to provide the C3 hydroxyl substituent. A novel ring contraction reaction is employed to generate the five membered ring hemiketal portion of (2) which is present in azadirachtin itself.

Reaction of the aldehyde (3) with the anion from (4)[5] gave the secondary alcohol (5) (Scheme 2). This, on deprotonation with potassium hydride and alkylation with methyl (*E*)-2-(bromomethyl)-3-(dimethylphenylsilyl)propenoate[7] gave (6) following a similar protocol to our previous model studies.[5]



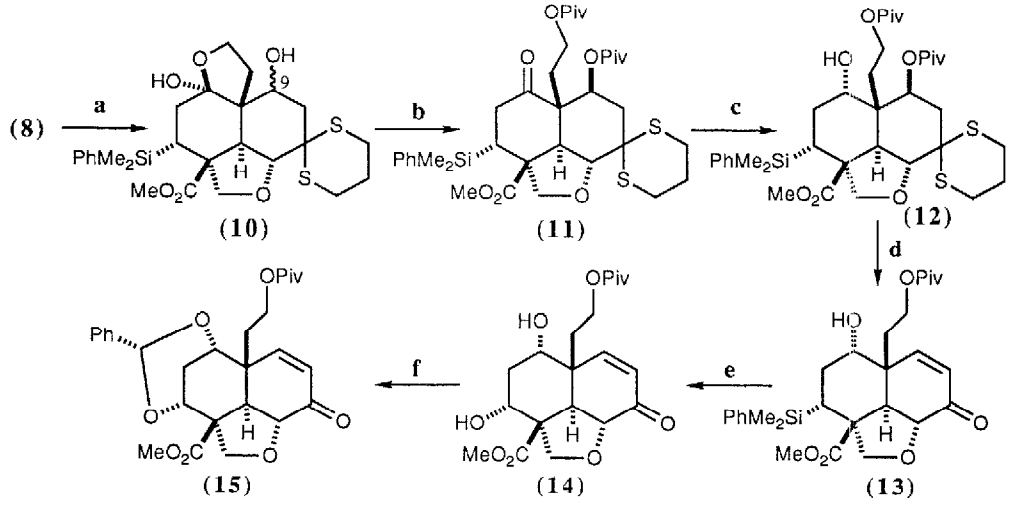
Scheme 2

a) ^{n}BuLi, TMEDA, 54 %. b) KH, Methyl *E*-2-(bromomethyl)-3-(dimethylphenylsilyl)propenoate, 60 %. c) i) HF_{aq}, Pyridine, 86 %; ii) $(COCl)_2$, DMSO, Et_3N, -78°C, 93 %; iii) LiCl, DIPEA, Diethylphosphonobutyrolactone, DMF, 95 %, *E*:*Z* 5:2. d) i) Tebbe Reagent, Pyridine, THF-Toluene, -40°C; ii) DIPEA (cat.), Hydroquinone (cat.), Toluene, 85°C, 2.5 h, 57 % over 2 steps.

Desilylation of the hydroxyl group with HF in pyridine and oxidation using oxalyl chloride/DMSO[8] gave an intermediate aldehyde which was reacted with 2-diethylphosphonobutyrolactone to give (7) as the major product accompanied by a small amount of the corresponding *Z*-isomer. The latter olefination reaction was most selective for the required *E* isomer, when carried out under modified Masamune-Roush conditions[9], where acetonitrile was replaced by the more polar DMF (*E*/*Z* ratio 5:2). Chemoselective methylenation of (7) at the lactone carbonyl group using the Tebbe reagent[10] gave an unstable dienol ether. Intramolecular Diels-Alder reaction was effected by warming in toluene at 85°C containing hydroquinone as antioxidant and DIPEA as proton scavenger, to give the required *endo* product (8) together with the *exo* compound (9) (ratio 5:2). The phenyldimethylsilyl group plays a key role in this reaction and was an important design element since the corresponding reaction with this group absent gave a 1:7 *endo* : *exo* selectivity.

The enol ether (8) was reacted in aqueous acetonitrile containing *p*-toluene sulphonic acid at 55°C to give the cyclised hemiketals (10) (ratio 12.3:1 C9 β:α) again in a similar fashion to our model studies[5] (Scheme 3). Reaction of the major β-isomer (10) with pivaloyl chloride afforded the ring opened keto dipivalate (11) in excellent yield. Reduction by $NaBH_4$ was again directed by the presence of the silicon control element to

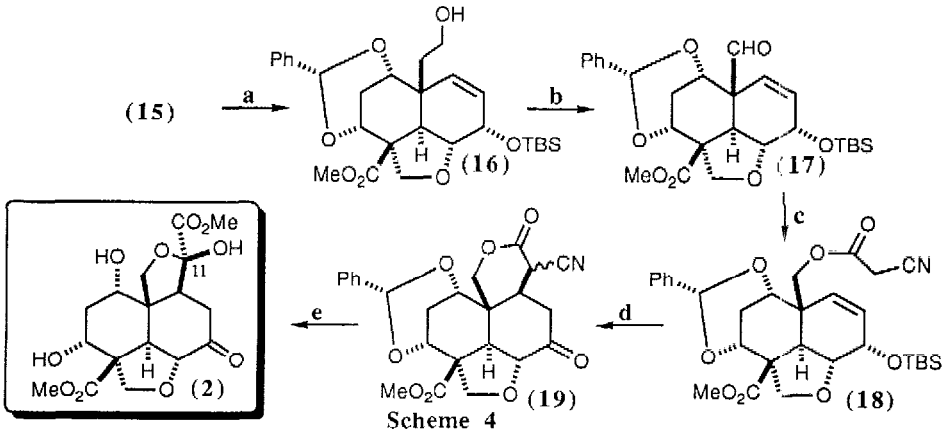
furnish exclusively the required axial C1 hydroxyl group. Removal of the dithiane in (12) and subsequent treatment with DBU effected β-elimination to afford the enone (13) in 92% overall yield. As the silicon moiety had served us well in controlling the stereoselectivity of the above reactions it was now time to exploit its final contribution, that of Baeyer-Villiger type[11] oxidation to an alcohol. This was best achieved using a slight modification of the Fleming conditions[12] whereby (13) was dissolved in HOAc and TFA containing mercury-(II)-trifluoroacetate followed by reaction with peracetic acid. In this way (13) gave the desired diol (14) in reliable yields around 85%. Finally, (14) was protected as the benzylidene acetal (15) in the usual way.



Scheme 3

a) *p*TSA (cat.), H_2O-MeCN, 55°C, 5.5 h, 63 %. b) Pivaloyl chloride, Pyridine, DMAP, 45°C, 89 %. c) $NaBH_4$, THF-MeOH, 96 %. d) i) MeI, MeCN, reflux, 100 %; ii) DBU (cat.), 92 %. e) $Hg(O_2CCF_3)_2$, TFA-HOAc, 10 min, then H_3CCO_3H, 85 %. f) PhCHO, PPTS, C_6H_6, reflux, 94 %.

For the last steps of the synthesis, (15) was stereoselectively reduced at C7 and the resulting allylic alcohol protected with *t*-butyl dimethylsilyl triflate. Hydrolysis with lithium hydroxide followed by diazomethane treatment gave the primary alcohol (16) in good overall yield (Scheme 4). The hydroxyethyl side chain in (16) was then elaborated to the aldehyde (17) in high yield by a sequence of reactions involving oxidation using periodinane reagent[13], silyl enol ether formation and ozonolysis. Treatment of (17) with zinc borohydride followed by *p*-toluenesulphonyl chloride and cyanoacetic acid gave ester (18) (95 %). Deprotection of (18) with TBAF and oxidation with PDC gave an intermediate enone which was subjected to an intramolecular conjugate addition reaction mediated by DBU to afford the lactone (19) (85%). Finally, this was transformed to the target decalin unit (2) in 45% overall yield using a novel ring contraction process. Thus, oxidation to the α-keto lactone with dimethyl dioxirane, ring-opening of the lactone and immediate reclosure to the lactol with methanol and triethylamine followed by acidic work-up gave (2)[14] readily separable from a small amount of the C11 epimer (ratio 7.5:1) by recrystallisation (Scheme 4). Optical resolution of an intermediate has also been achieved, full details of which will be reported later.



Scheme 4

a) i) L-Selectride®, THF, -78°C, 97 %; ii) TBSOTf, 2,6-Lutidine, 0°C; iii) LiOH, Ethanol-H_2O, 60°C; iv) CH_2N_2, 79 % over 4 steps. b) i) Periodinane, Pyridine; ii) TBSOTf, Et_3N, -10°C; iii) O_3/O_2, -78°C; iv) PPh_3, -78°C to rt, 74 % over 4 steps. c) i) $Zn(BH_4)_2$, -10°C; ii) $NCCH_2CO_2H$, *p*TosCl, Pyridine, 95 % over 2 steps. d) i) TBAF, 4 Å sieves, ii) PDC, 4 Å sieves; iii) DBU (cat.), MeCN; 85 % over 3 steps. e) i) Dimethyl dioxirane, 0°C, 30 min; ii) MeOH, Et_3N, 5 h; iii) CH_2N_2; iv) HCl (cat.), MeCN, 36 h, rt; 45 % over 4 steps.

In summary, we have devised a synthetic scheme[15] which provides the decalin skeletal component of azadirachtin in a form suitable for elaboration to the natural product itself. The synthesis provides materials which correspond to the relay studies reported in the preceeding communication.[1]

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14. The structure of (2) was confirmed by single crystal x-ray diffraction.
15. All new compounds gave satisfactory data including microanalysis and/or accurate mass measurement.

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