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CHEMISTRY OF INSECT ANTIFEEDANTS FROM AZADIRACHTA INDICA (PART 2): SYNTHESIS OF A POLYOXYGENATED DECALIN WITH LIMONOID STRUCTURAL HOMOLOGY.

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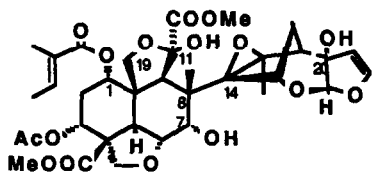
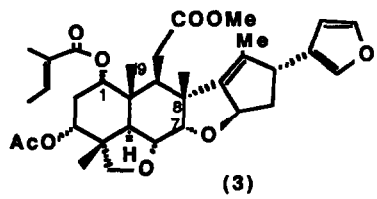
Abstract: *The synthesis of a polyoxygenated decalin (2) with limonoid structural homology, common to salannin and azadirachtin, has been completed using an efficient intramolecular Diels- Alder cycloaddition.*

Azadirachtin (1)[1] is a naturally occurring tetranortriterpene isolated from the neem tree *Azadirachta indica* (A. juss). There is considerable interest in this and a number of related compounds as potentially novel pest control agents due to their extremely potent antifeedant and ecdysis inhibiting properties.[2] We recently reported the synthesis of a fragment of azadirachtin which shows similar antifeedant properties.[3] As a continuation of our studies in this area we now report a convergent route to the polyoxygenated decalin (2) which shows considerable structural homology with members of the limonoid series, such as azadirachtin (1) and salannin (3).



(1)



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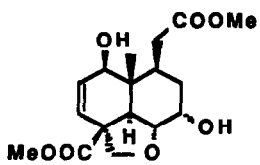

(2)

The synthetic strategy utilised incorporated an intramolecular Diels-Alder reaction and a stereocontrolled ring-closure to give exclusively the *trans* decalin.

Aldehyde (4) was prepared from 2,3-butanedione in 56% yield over four steps. This was then coupled to fragment (5) prepared from commercially available 1,3-dithiane and bromoacetaldehyde dimethylacetal, using n-butyllithium in the presence of tetramethylethylenediamine. An excess of the dithiane (5) was required due to substantial intramolecular coordination of the lithio anion. The product alcohol was formed in good yield (93%) and was then converted to the potassium salt and alkylated with methyl-2-(bromomethyl)prop-2-enoate (6) (prepared in two steps from commercially available materials).[4] Protecting group manipulation and enol etherification then allowed rapid access to the triene (7) which underwent a Diels-Alder cycloaddition upon heating at 135 °C for 45min. in anhydrous DMSO. This reaction proceeded in excellent yield to give only two of the four possible diastereomeric products in an *endo* (8):*exo* (9) ratio of 2.5:1 . Clearly the presence of a sterically demanding substituent allylic to the diene in (7) exerted a considerable stereocontrolling influence since both *trans*-(*endo*) and *cis*-(*exo*) fused products were formed as single diastereomers. Also worthy of note is the selectivity, albeit modest, for the *trans*-fused product. Concerted, asynchronous[5] intramolecular cycloaddition leading to bicyclo[4.3.0] systems where peripheral bond formation is at a more advanced stage in the transition state, usually gives more of the *cis*-fused isomer. This is normally attributed to the greater stability (lower energy) of a *cis*-skewed pseudo-nine-membered transition state geometry, although more elaborate explanations have been advanced.[6] The structures of (8) and (9) were confirmed by high field ^{1}H-NMR data in comparison with literature precedents[7] and examples from our own laboratory. Also, the product of *exo* addition (9), was converted to a crystalline derivative which was amenable to X-ray crystallographic analysis. Thus three important chiral centres had been established with the correct relative stereochemistry in one synthetic step.

Attempts to form a naphthofuran from (8) by an intramolecular Mukaiyama[8] reaction of the acetal with the newly-formed tetrasubstituted enol ether were unsuccessful. However, simultaneous removal of the silicon and dioxane protecting groups (AcOH/THF/H_2O 65 °C; 73%) gave an aldehyde (10) which was treated with dimethyl malonate under Knoevenagel conditions (piperidine/AcOH; 90%) to give the unsaturated ester (11). This compound, when stirred with sodium methoxide in methanol at room temperature, underwent smooth cyclisation to give exclusively the *trans*-fused cyclisation product (12) which contained the methylene diester substituent in the β-equatorial configuration. This remarkable selectivity in a reaction which defined the stereochemistry at a further two centres was attributable to the restraining influence of the tetrahydrofuran ring prohibiting access to the transition state leading to the *cis*-product and to the steric effect of the dithiane protecting group.

Decarboxylation of (12) (DMSO/H_2O/NaCl) with a diazomethane work-up gave (13) in 81% yield. Double bond formation to give enone (14) proceeded via α–selenylation and oxidative elimination (i;LDA/NPSP ii;3-(*p*-nitrophenyl)-2-(phenylsulphonyl)oxaziridine[9], DCM/$NaHCO_3$) in 62% over two steps. Removal of the dithiane group (MeI/$CaCO_3$; 70%) gave a diketone (15) which was prone to epimerisation α to the newly unmasked carbonyl. However, with care a single isomer could be obtained and this underwent reduction in the presence of $NaBH_4$ and $CeCl_3.7H_2O$ to give diol (2).

This compound represents an advanced intermediate which displays considerable homology with the natural products azadirachtin and salannin. In particular, the correct relative stereochemistry has been established at six chiral centres.Work is currently in hand to further elaborate this intermediate towards our goal of a total synthesis of a limonoid insect antifeedant.

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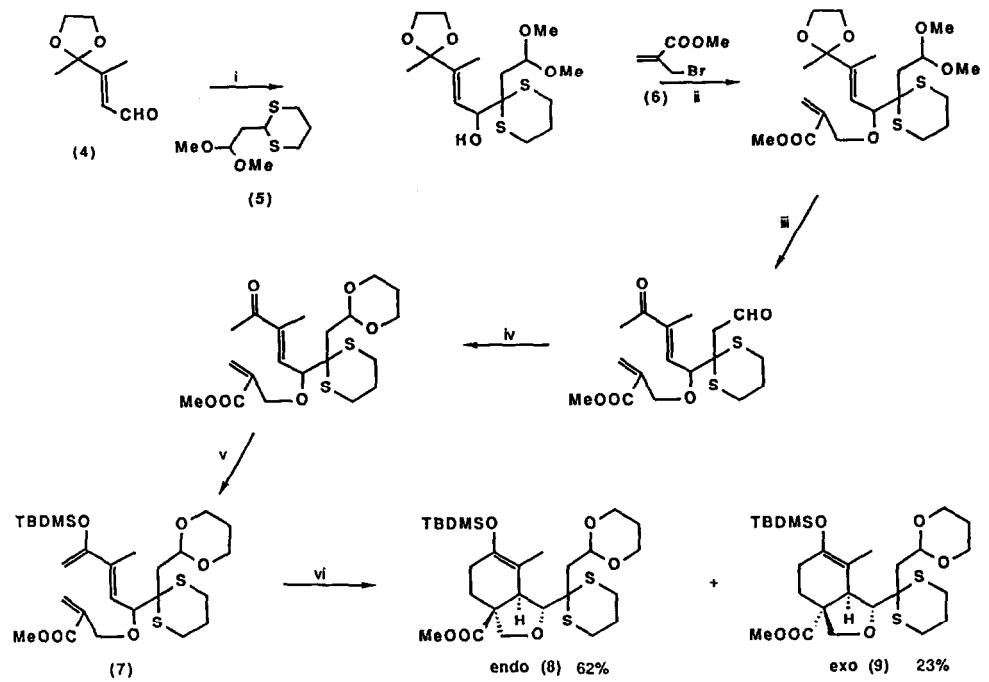
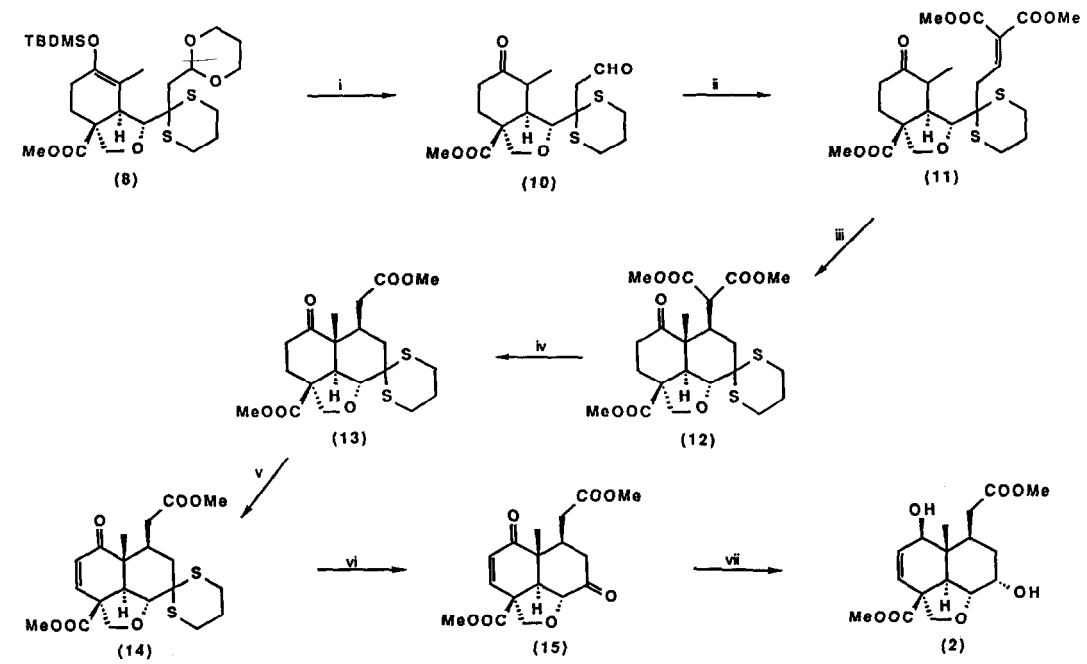
Scheme 1



i) BuLi, TMEDA. 93%. ii) KH, TMEDA. 80%. iii)PPTS, Acetone/H_2O. 94%. iv)Propane-1,3-diol, PPTS. 79%. v)TBDMSOTf, Et_3N. 87%. vi)DMSO, 135 °C

Scheme 2



i)AcOH/THF/H_2O, 65 °C. 73%. ii)Dimethyl malonate, piperidine, AcOH, 80 °C. 90%. iii)NaOMe, MeOH, r.t. 60%. iv)a. DMSO,NaCl,H_2O, 160 °C; b. CH_2N_2. 81% v)a. LDA, NPSP. b. 3-(p-nitrophenyl)-2-(phenylsulphonyl)oxaziridine, $NaHCO_3$/DCM. 62% overall.vi)MeI, CH_3CN/H_2O. 70%. vii)$NaBH_4$, $CeCl_3.7H_2O$. 95%.

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Footnotes

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