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CHEMISTRY OF INSECT ANTIFEEDANTS FROM *AZADIRACHTA INDICA* (PART 6)[1]: SYNTHESIS OF AN OPTICALLY PURE ACETAL INTERMEDIATE FOR POTENTIAL USE IN THE SYNTHESIS OF AZADIRACHTIN AND NOVEL ANTIFEEDANTS.

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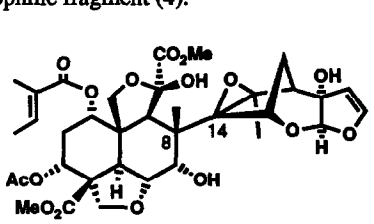
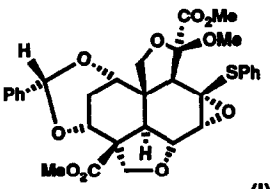
Summary: For potential use in a synthesis of the antifeedant azadirachtin (1) and novel antifeedants, a key tricyclic acetal intermediate (2) has been prepared in optically pure form in 12 steps from the known (-)-3-endo-bromotricyclo[3.2.0.0^{2,7}]heptan-6-one (3).

Azadirachtin (1) is a highly oxygenated tetranortriterpenoid isolated from the neem tree *Azadirachta Indica* A. Juss (Meliaceae)[2]. Its extremely potent biological activity as an antifeedant and growth regulatory agent[3,4] have prompted synthetic studies in order to understand the structure activity relationships[1] and to prepare simpler compounds that display comparable biological behaviour[5].

In view of recent studies by Shibasaki[6] we wish to report related work on the preparation of a key optically pure cyclic acetal fragment (2) which may serve as a potential intermediate in the total synthesis of (1). For our synthesis we anticipate coupling of (2), following oxidation and enol ether formation, with a suitable electrophilic fragment (4).



(1)



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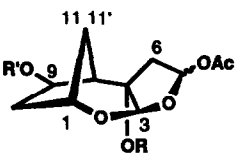
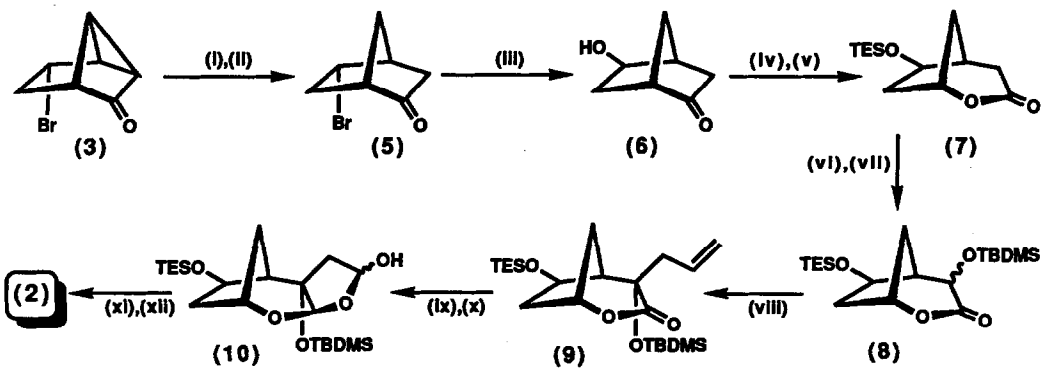


(i),(ii) (2) R=TBDMS, R'=OH
(11) R=OH, R'=TBDMS

(i) $^{t}BuMe_2SiCl$, Imidazole, DMF, RT.16h. 69%; (ii) $^{n}Bu_4NF$, THF, RT. 45 min. 97%.

The choice of the acetate in (2) was deliberate in that we have already shown that it is possible to recover the sensitive 22,23-enol ether double bond at a late stage by thermal elimination[7]. Preparation of the fragment (4) has already reached an advanced intermediate[8]. Synthesis of (2) was achieved from the known bromide[9] (3) which in turn was obtained from (-)-bicyclo[3.2.0]hept-2-en-6-one prepared *via* an enzymatic reduction[10] or by resolution.

Homoconjugate reduction of (3) with sodium borohydride followed by oxidation with tetra-n-propylammoniumperruthenate[11] (TPAP) gave the bromide[12] (5) 62%. Treatment of (5) with silver trifluoroacetate and water in the dark gave an excellent yield of the ketoalcohol (6). This underwent smooth Baeyer Villiger oxidation and protection of the hydroxyl group with triethylsilyl chloride to afford (7). Oxidation of (7) *via* the enolate using LDA / molybdenum peroxide reagent MoO_5.pyridine.HMPA (MoOPH)[13] and silylation with ^{t}butyldimethylsilyl chloride afforded the bis-protected lactone (8).This on deprotonation using KDA in THF / HMPA at -78°C followed by alkylation with allyl bromide gave a complex mixture of products from which the major product (9) could be isolated by flash chromatography in 42% yield.



Reagents: (I) $NaBH_4$, MeOH. 70%; (II) TPAP, NMO, 4Å ground sieves, MeCN, 30 min. 89%; (III) CF_3CO_2Ag, acetone/H_2O, 3:1, 60°C, dark, 60h. 98%; (IV) mCPBA, TsOH cat., DCM, RT. 30 min. 82%; (V) Et_3SiCl, Et_3N, DMAP, DCM, RT. 1h. 77%; (VI) LDA, THF -78°C then MoOPH, -78°C to RT. 42%; (VII) $^tBuMe_2SiCl$, imidazole, DMF, RT. 4h. 89%; (VIII) KDA, THF, -78°C ; HMPA ; CH_2=$CHCH_2Br$, -78°C to RT. 42%; (IX) DIBAL, toluene, -78°C. 89%; (X) O_3, DCM, -78°C then Ph_3P, RT. 12h. 90%; (XI) Ac_2O, Et_3N, DMAP, DCM, RT. 2h. 98%; (XII) AcOH / H_2O / THF, 3:3:1, RT. 1h. 85%.

The final steps of the synthesis proceeded according to our previously established sequence[5]. Diisobutylaluminium hydride reduction of (9) to the bicyclic lactol followed by ozonolysis in CH_2Cl_2 with triphenylphosphine work up gave the required tricyclic lactol (10) in 80% overall yield. This was finally elaborated to (2) by acetylation and selective deprotection with aqueous acetic acid at room temperature. The ^1H nmr spectrum of compound (11), readily derived from (2), was sufficiently resolved to allow some n.O.e. studies in order to determine its relative stereochemistry. The respective irradiation of H6β (δ2.46, dd, J 14.8, 4.8 Hz) and H9 (δ4.61, s) induced an enhancement of H11' (δ1.92, br.dd, J 12.7, 1.0 Hz; +8.0%) and H3 (δ4.80, s; +5.1%). These results are consistent with the relative stereochemistry assigned to (11) and hence compound (2).The above route constitutes a short and efficient route to (2). This fragment is the pivotal intermediate for coupling studies to (1) and for elaboration to a number of novel antifeedants, details of which will be reported at a later date.

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