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Chemistry of Insect Antifeedants from *Azadirachta Indica* (Part 9)[1]: Oxidative Reactions of Azadirachtin Derivatives Leading to C8-C14 Bond Cleavage.

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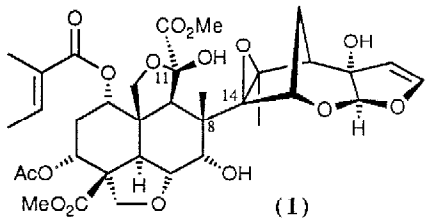
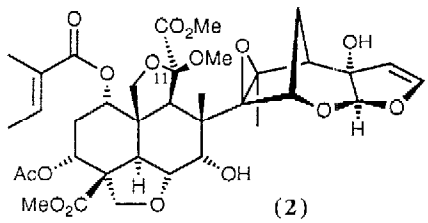
Summary: A novel macrocyclic carbonate (4) was obtained by pyridinum chlorochromate oxidation of an azadirachtin derivative (3). This underwent efficient C8-C14 bond cleavage *via* a retro-Aldol reaction to give a highly functionalised decalin derivative (5) with potential for use in relay synthesis of azadirachtin.

For several years we have been studying the structure,[2] synthesis[3] and biological activity[4] of the potent insect antifeedant and growth disruption agents such as azadirachtin (1) and related compounds *eg* (2).[5] These materials have potential as novel environmentally acceptable pest control agents. In addition we can use these compounds to probe fundamental feeding and host plant recognition processes in insect species. This work has led to extensive structure activity studies[6] and the preparation of simple analogues which display antifeedancy properties.[1] Furthermore we have observed rearrangement reactions of these compounds which have implications for synthetic planning and for biological evaluation.[7]



(1)

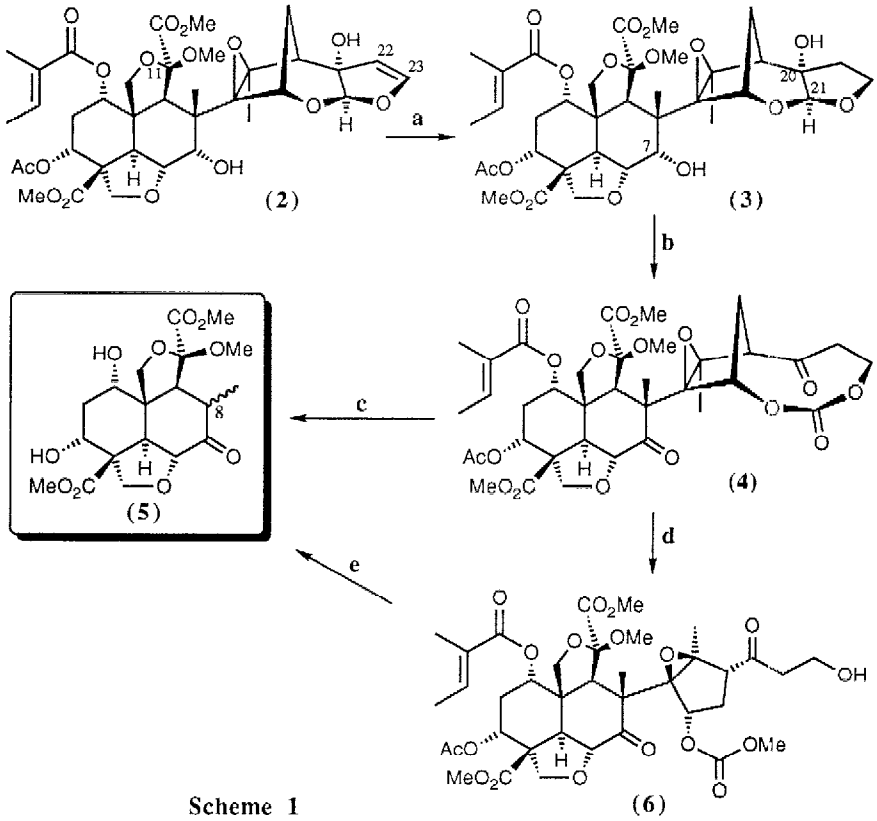


(2)

Here we describe some new oxidation reactions of azadirachtin derivatives which provide materials suitable for degradation studies and in particular, by employing a novel retro-Aldol reaction, afford the decalin portion of these molecules by C8-C14 bond cleavage. This key reaction gives important compounds for synthetic studies and generates fragments necessary for further biological evaluations.

In order to prepare the retro-Aldol precursor, azadirachtin (1) was selectively methylated at the C-11 hydroxyl group, using iodomethane and silver (I) oxide, to give (2) in 86% yield. This reaction was a modification of the original Klocke procedure which gave (2) in only 50% yield.[5] By methylating at this position we removed the binding hydrogen bond to the neighbouring epoxide group and thereby facilitated conformational mobility which assisted in later reactions, notably oxidation at C7.[8] Selective hydrogenation of (2), with palladium on charcoal as catalyst in methanol, removed the sensitive C22-C23 enol double bond to give (3)[9] (Scheme 1). This reaction coupled with C11-methylation, greatly improved stability without loss

of biological activity.[7] Oxidation of (3) with excess pyridinium chlorochromate (PCC)[10] (10 equiv) in dichloromethane containing 4Å molecular sieves gave the novel diketocarbonate (4) in an excellent 72% yield, the product being fully characterised by single crystal x-ray diffraction.[11] This reaction was also accompanied by a small amount (12%) of the C7 oxidised product where the C20-C21 bond had not been cleaved. By reacting (4) with sodium methoxide in methanol for 24hr a series of reactions took place to give the required decalin fragment (5)[12] in 92% yield!

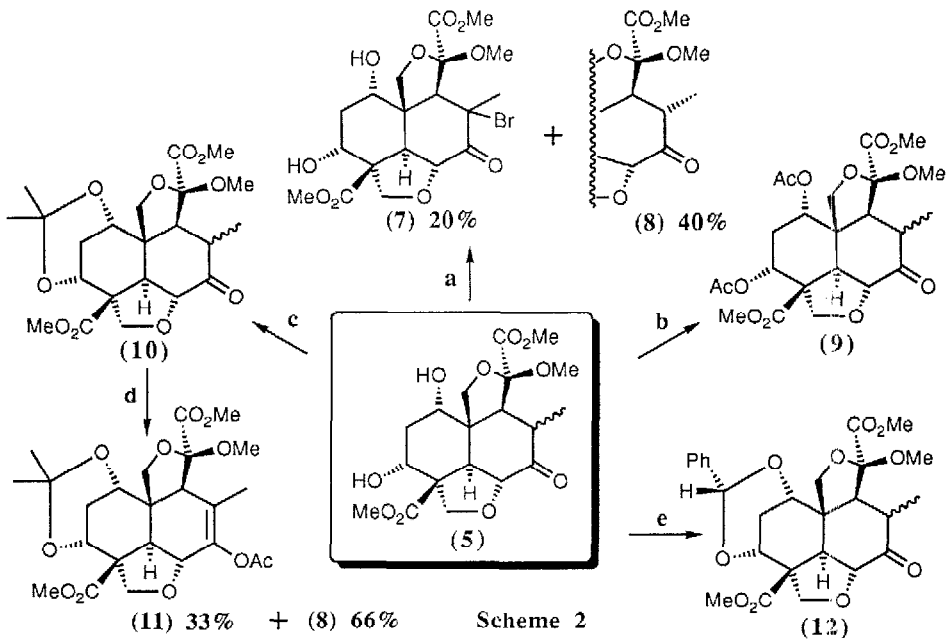


Scheme 1

a) H_2 (1atm), 10% Pd/C, MeOH, 20min, 82%. b) PCC, 4Å sieves, DCM, RT, 48hr, 72%. c) NaOMe, MeOH, RT, 24hr, 92%. d) MeOH, RT, 1hr, 85%. e) NaOMe, MeOH, RT, 24hr, 82%.

We believe this process involved macrocyclic ring opening of the carbonate which then left the C20 carbonyl group in a position suitable for base catalysed β-elimination and ring opening of the epoxide. The resulting alcoholate then underwent a facile retro-Aldol reaction to cleave the C8-C14 bond and finally the base also effected saponification of the esters at C1 and C3 to afford (5) as a 2:1 α:β mixture of C8 epimers. In accord with this proposal (4) reacted with methanol over 1hr to to give (6). Treatment with methoxide as before gave the fragmented material (5) in 82% yield (Scheme 1). Obviously (5) is an excellent compound for further synthetic and biological studies. Other bases could also be used to achieve the retro-Aldol process of which potassium carbonate in methanol was the best giving (5) in 90% yield after only 5 hr.

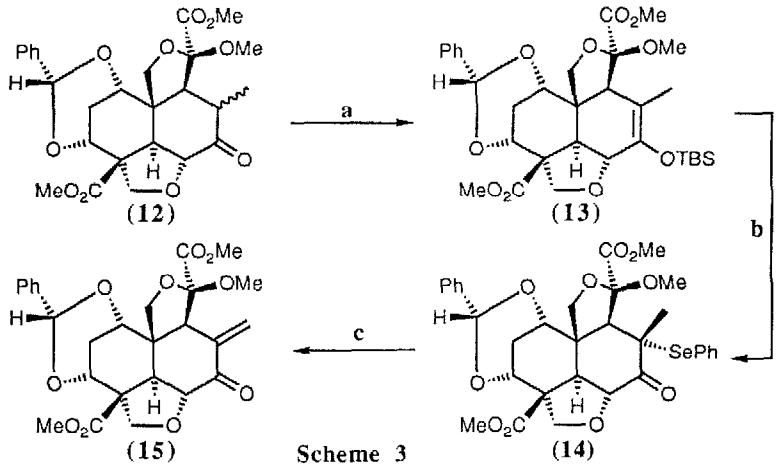
With (5) now readily available we have investigated further reactions to give compounds for coupling studies and to match related derivatives obtained by total synthesis[13] (Scheme 2). We believe these building blocks will prove crucial in establishing relay sequences to the natural products. For example (5) could be brominated at the C8 position using pyridinium bromide perbromide[14] to give (7) albeit in a rather modest 20% yield owing to unreactivity of the α-isomer (8) under these particular reaction conditions. Acetylation with acetic anhydride, triethylamine and *N,N*-dimethylaminopyridine gave the diacetate (9). The 1,3-diol group in (5) could also be protected as its corresponding acetonides (10) using 2-methoxypropene and PPTS in dichloromethane. The enolacetate (11) was cleanly made from the β-isomer of (5) using sodium acetate in acetic anhydride, with the α-isomer recovered. Reaction of (5) with benzaldehyde and pyridinium *p*-toluenesulphonate (PPTS) under Dean - Stark conditions gave the benzylidene acetals (12) as a separable 2:1 α:β mixture of C8 methyl isomers.



a) $PyHBr_3$, AcOH, 90°C. b) Ac_2O, Et_3N, DMAP, DCM, 0°C, 2hr, 86%. c) 2-Methoxypropene, PPTS, DCM, RT, 24hr, 79%. d) NaOAc, Ac_2O, RT. e) PhCHO, PPTS, benzene, reflux, 1hr, 80%.

Several reactions of the benzylidene compounds (12) were also carried out (Scheme 3). The silylenol ether (13) was prepared *via* deprotonation of (12) with potassium hydride. Selenenation with phenylselenenyl chloride gave a moderate 57% yield of the α-selenide (14). Subsequent oxidation and elimination exclusively gave the *exo* olefin (15) in quantitative yield.

The above degradation and synthetic studies are crucial to our total synthesis of (1) and additionally provide key compounds for coupling reactions and biological assessment.



Scheme 3

a) KH, TBSCl, THF, 0°C to RT, 70%. b) PhSeCl, DCM, -78°C, 57%. c) Davis oxaziridine, $CHCl_3$, RT, 15min, 100%.

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References and footnotes:

1. For part 8, see Anderson, J.C.; Ley, S.V.; Santafianos, D.; Sheppard, R.N. *Tetrahedron* in press. For part 7, see Anderson, J.C.; Ley, S.V. *Tetrahedron Lett.*, **1990**, *31*, 3437.
2. Bilton, J.N.; Broughton, H.B.; Jones, P.S.; Ley, S.V.; Lidert, Z.; Morgan, E.D.; Rzepa, H.S.; Sheppard, R.N.; Slawin, A.M.Z.; Williams, D.J. *Tetrahedron*, **1987**, *43*, 2805.
3. Ley, S.V. 'Synthesis of Antifeedants for Insects: Novel Behaviour Modifying Chemicals From Plants', in 'Bioactive Compounds From Plants', Ciba Foundation Symposium 154, John Wiley and Sons, **1990**, p80-98.
4. Blaney, W.M.; Simmonds, M.S.J.; Ley, S.V.; Anderson, J.C.; Toogood, P.L. *Entomol. Exp. Appl.* **1990**, *55*, 149.
5. Yamasaki, R.B.; Klocke, J.A. *J. Agric. Food Chem.*, **1987**, *35*, 467.
6. Blaney, W.M.; Simmonds, M.S.J.; Ley, S.V.; Anderson, J.C.; Toogood, P.L. *Entomol. Exp. Appl.* **1990**, *55*, 169.
7. Anderson, J.C.; Ley, S.V.; Smith, S.C. Manuscript in preparation.
8. Anderson, J.C. PhD Thesis University of London, 1990.
9. All new compounds gave satisfactory data including microanalysis and/or accurate mass measurement.
10. Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.*, **1975**, *16*, 2647.
11. We thank Dr D.J.Williams of this department for this determination.
12. Data for (5) : υ_{max} (film) 3438, 2953, 1722, 1435, 1288, 1240, 1089, 912 and 733cm^{-1}; ^1H δ (500MHz, $CDCl_3$, natural prod. numbering) for α isomer: 1.25 (3H, d, J 6.7, H-30), 1.95 (1H, dt, J 15.8, 2.7, H-2), 2.28 (1H, dt, J 15.8, 3.1, H-2), 2.71 (1H, d, J 14.2, H-5), 2.85 (1H, d, J 8.1, H-9), 3.06-3.08 (1H, m, H-8), 3.35 (3H, s, C11-OMe), 3.43 (1H, d, J 6.5, OH), 3.57 (1H, d, J 9.8, H-19), 3.74 (1H, d, J 7.4, OH), 3.76 (3H, s, CO_2Me), 3.82 (3H, s, CO_2Me), 4.11-4.17 (4H, m, H-1, H-19 and 2xH-28), 4.49-4.52 (1H, m, H-3) and 4.77 (1H, dd, J 14.2, 1.2, H-6); and for β isomer 1.15 (3H, s, H-30), 2.25-2.33 (2H, m, 2xH-2), 2.75 (1H, quint, J 6.5, H-8), 3.06-3.11 (3H, m, OH, H-5 and H-9), 3.29 (3H, s, C11-OMe), 3.61 (1H, d, J 9.5, H-19), 3.66 (1H, br, s, OH), 3.69 (1H, d, J 9.8, H-19), 3.77 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 4.02 (1H, m, H-1), 4.07 (1H, d, J 8.4, H-28), 4.13 (1H, d, J 8.4, H-28), 4.42 (1H, d, J 14.0, H-6) and 4.50 (1H, m, H-3); m/z (CI, NH_3) 432 ($M+NH_4^+$), 414 (M^+), 400 ($M+NH_4^+$-MeOH), 383 (M^+-OMe), 355 (M^+-CO_2Me), 291, 274, 195 and 178; Found (M^+) 414.1526. $C_{19}H_{26}O_{10}$ requires 414.1526.
13. See following paper: Part 10 in the series.
14. Djerassi, C.; Scholz, C.R. *J. Am. Chem. Soc.*, **1948**, *70*, 417.

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