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CHEMISTRY OF INSECT ANTIFEEDANTS FROM *AZADIRACHTA INDICA* (PART 7)[1]: PREPARATION OF AN OPTICALLY PURE HYDROXYACETAL EPOXIDE RELATED TO AZADIRACHTIN.

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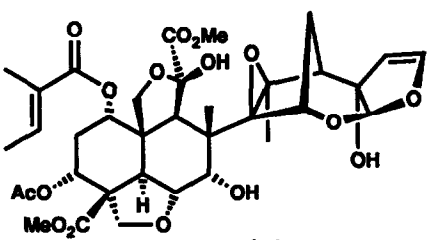
Summary: Preparation of an optically pure hydroxyacetal epoxide (2) as a model compound of the potent antifeedant azadirachtin (1) is reported.

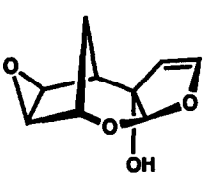
We wish to report new synthetic studies towards key structural fragments of the potent antifeedant and growth regulator agent azadirachtin (1)[2] isolated from the neem tree *Azadirachta Indica* A. Juss (Meliaceae).

In preliminary studies towards the total synthesis of (1) we have developed synthetic sequences to various components of this novel molecule including the substituted decalin unit[3] and a dihydrofuranyl acetal fragment.[1,4] Furthermore, we have shown that simple skeletal structures can mimic the antifeedant activity of the natural product.[4] These insect behavioural control substances have some advantages over conventional methods[5] and may well find future applications as part of integrated pest management control programmes.

Here we discuss the preparation of a hydroxytetracyclicacetal epoxide (2) as a species encompassing many of the structural elements found in (1). Additionally, preparation of this fragment defines synthetic procedures which may eventually be employed in the total synthesis of (1). The new sequence was developed as a necessary improvement to our previously described route[1] for the preparation of key fragments of (1) to provide multigramme quantities of suitable coupling material.



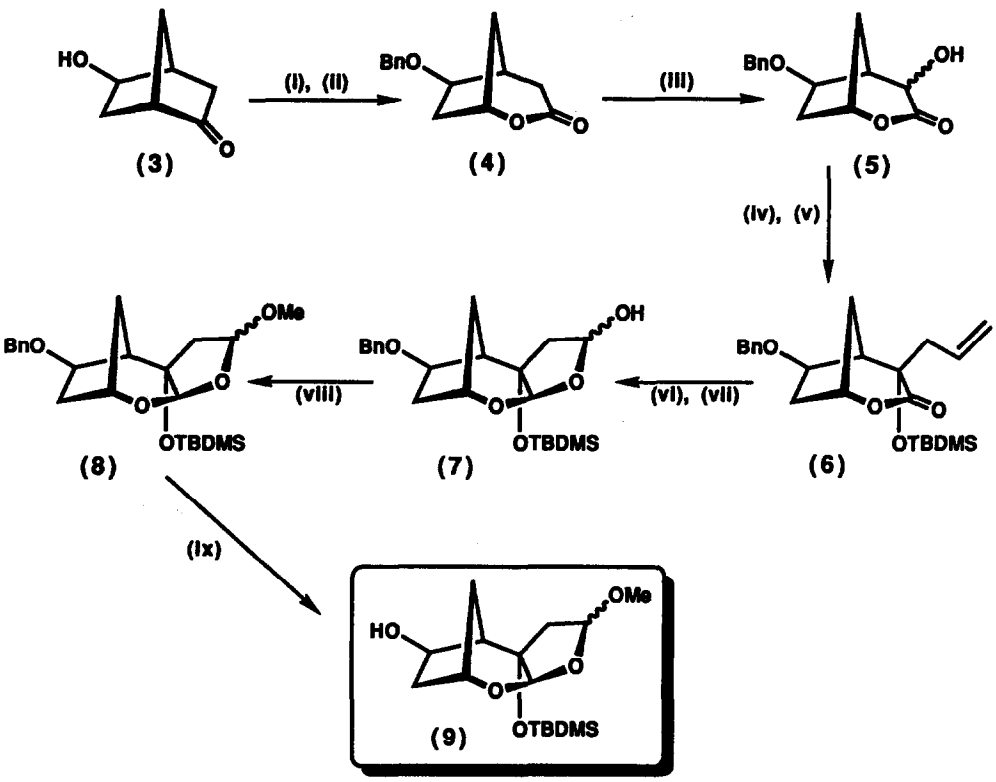
(1)



(2)

Reaction of the homochiral hydroxy bicyclic ketone (3)[6] with benzyl bromide followed by Baeyer Villiger oxidation with m-CPBA gave (4) in excellent overall yield (Scheme 1). Deprotonation and reaction with the new hydroxylating agent MoO_5.Py.DMPU (MoOPD)[7] gave the product (5). Following protection of (5) as its t-butyldimethylsilyl ether (81% overall), the enolate was prepared using KDA and stereoselectively quenched with allyl bromide to afford (6) (77%).

Scheme 1

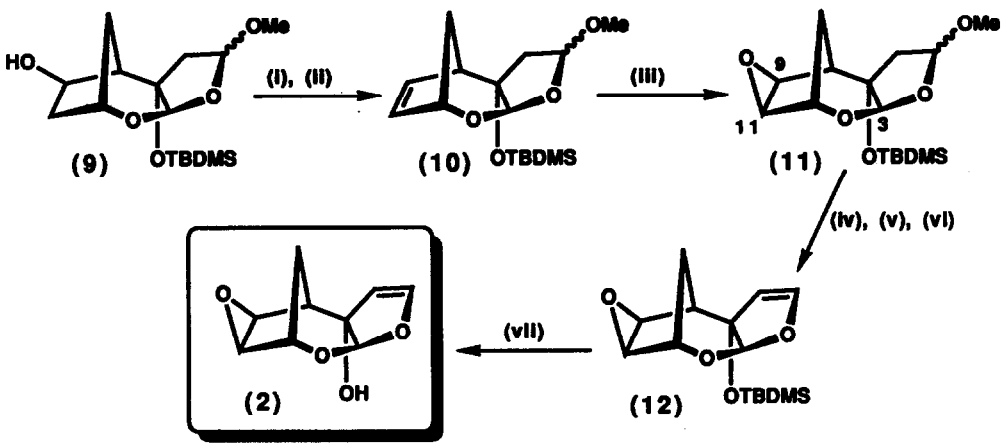


Reagents: (I) NaH, BnBr, $^{n}Bu_4NI$, THF, 0°C to RT. 3h. 98%; (II) m-CPBA, TsOH cat., DCM, RT. 3h. 91%; (III) LDA, THF, -78°C then MoOPD, -78°C to RT.; (Iv) $^{t}BuMe_2SiCl$, imidazole, DMF, RT. 14h. 81% overall; (v) KDA, THF, -78°C; HMPA; CH_2=$CHCH_2Br$, -78°C to 0°C. 77%; (VI) DIBAL, toluene, -78°C; (vII) O_3, DCM, -78°C then Ph_3P, RT. 14h. 75%. overall, α:β 1:4; (viii) Amberlyst 15, MeOH, 3 Å mol. sieves, MeCN, RT. 15min. 83%, α:β 1:3; (Ix) H_2,10% Pd/C, HCl cat., MeOH, RT. 98%.

This lactone, upon reduction with di-isobutylaluminiumhydride and ozonolysis, gave the hemiacetal (7). Protection of the hemiacetal (7), *via* anomeric exchange with methanol, afforded a crystalline compound (8), the structure of which was confirmed by X-ray crystallography.[8] Compound (8) was then readily converted to a pivotal intermediate (9)[9] by debenzylation with 10% Pd/C and hydrogen. This intermediate (9) will also be useful in the preparation of novel analogues difficult to obtain by other sequences.[10]

Dehydration of (9), *via* its mesylate with DBU, gave (10) in 95% overall yield. Stereoselective epoxidation of (10) with m-CPBA afforded the epoxide (11) (Scheme 2). The selectivity of this reaction was determined by detailed n.m.r. measurements including selected n.O.e. difference experiments. Irradiation of H3 (δ5.26, s) induced an enhancement of H9 (δ3.80, d, J 2.9 Hz; +1.9%) and H11 (δ3.50, br.d, J 2.5 Hz; +3.1%). The respective irradiation of H9 and H11 gave corresponding enhancements of H3 (+2.3% and +3.4%).

Scheme 2



Reagents: (I) MsCl, Et_3N, DCM, RT. 10 min.; (II) DBU, toluene, 120°C, 38h. 95% overall; (III) m-CPBA, DCM/satd. aq. $NaHCO_3$, 1:1, RT. 40h. 68%; (IV) Amberlyst 15, PhSH, 4Å sieves, RT. 21%; (V) m-CPBA, DCM, RT. 2 min.; (VI) Et_3N, toluene, 120°C, 10 min.; (VII) TBAF, THF, RT. 5 min. 73% overall.

The final stages in the synthesis followed our previously established route for the introduction of the enol ether double bond. Thus, treatment of (**11**) with benzene thiol in the presence of Amberlyst 15 ion exchange resin, followed by oxidation and *syn*-elimination, gave (**12**). Deprotection of (**12**) with tetra-n-butylammonium fluoride in the normal way gave (**2**).[11]

The above synthesis constitutes a new route to these interesting molecules which will be useful for the total synthesis of (**1**). This route will also provide a source of novel compounds for future biological evaluation as antifeedant materials.[12]

Acknowledgements: *We thank the S.E.R.C. and the ICI Strategic Research Fund for financial support.*

References and footnotes

1. For part 6 see Anderson, J.C.; Ley S.V. *Tetrahedron Lett.* **1990**, *31*, 431-432.
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5. For recent reviews see; van Beek, T.A.; de Groot, Ae. *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 513-527.; de Groot, Ae.; van Beek, T.A. *ibid.* **1987**, *106*, 1-18.

6. (1S, 4S, 5R)-5-Hydroxybicyclo[2.2.1]heptan-2-one (3): Clear oil; $[\alpha]_D^{20}$=-12.2° [c=2.81 (chloroform)]; υ_{max} (film) 3413, 2968, 1745, 1405, 1341, 1304, 1183, 1142, 1093, 1060, 1002, 959 and 908 cm^{-1}; δ(500 MHz, $CDCl_3$) 1.63 (1H, ddt, J 13.9, 4.2, 2.1 Hz, H6), 1.69 (1H, ddd, J 10.7, 2.2, 1.4 Hz, H7), 1.73 (1H, dd, J 17.9, 4.3 Hz, H3), 1.86 (1H, br.s, 5-OH), 1.98 (1H, ddd, J 13.9, 6.7, 2.3 Hz, H6), 2.02 (1H, dd, J 18.0, 5.9 Hz, H3), 2.03-2.06 (1H, m, H7), 2.57 (2H, m H1 and H4) and 4.08 (1H, br.d J 6.6 Hz, H5); m/z (EI+) 126 (M^+), 108 (M^+-H_2O), 82, 79, 67, 66, 57, 55, 41, 39, 27, 26; (Found: C, 66.44; H, 7.96. $C_7H_{10}O_2$ requires C, 66.65; H, 7.99%). All other compounds gave satisfactory n.m.r., i.r., Acc. Mass and/or micro analytical data.

7. Anderson, J.C.; Smith, S.C. *Synlett* **1990**, 107-108.

8. White needles: mp. 99-101°C (Recrystallised from Et_2O). We thank Dr D.J. Williams and A.M.Z. Slawin of this department for this result.

9. (1S, 3R, 5RS, 7S, 8R, 9R)-7-^{t}Butyldimethylsilyloxy-5-methoxy-2,4-dioxatricyclo[6.2.1.$0^{3,7}$] undecan-9-ol (9): Clear oil; υ_{max} (film) 3452, 2952, 2929, 2854, 1461, 1439, 1375, 1359, 1257, 1217, 1191, 1128, 1110, 1092, 1060, 1007, 967, 941 and 925 cm^{-1}; δ(500 MHz, $CDCl_3$) major diastereoisomer: 0.16 (3H, s, MeSi), 0.18 (3H, s, MeSi), 0.90 (9H, s, ^{t}BuSi), 1.43 (1H, br.s, 9-OH), 1.67 (1H, dddd, J 15.5, 5.2, 2.2, 1.0 Hz, $H10_{eq}$), 1.79 (1H, ddd, J 12.8, 5.1, 2.6 Hz, H11), 1.98 (1H, br.d, J 12.7 Hz, H11'), 2.19 (1H, dd, J 14.6, 5.9 Hz, H6), 2.29 (1H, dd, J 14.6, 5.3 Hz, H6), 2.40 (1H, br.d, J 4.9 Hz, H8), 2.45-2.50 (1H, m, $H10_{ax}$), 3.46 (3H, s, OMe), 4.46-4.48 (1H, m, H1). 4.69 (1H, br.d, J 6.0 Hz, H9), 4.69 (1H, s, H3), 5.28 (1H, t, J 5.6 Hz, H5); δ(500MHz, $CDCl_3$) minor diastereoisomer: 0.17 (3H, s, MeSi), 0.18 (3H, s, MeSi), 0.90 (9H, S, ^{t}BuSi),1.43 (1H, br.s, 9-OH), 1.64-1.69 (1H, m, $H10_{eq}$), 1.81 (2H, m, H11 and H11') 1.93 (1H, ddd, J 14.5, 2.6, 0.6 Hz, H6), 2.40 (1H, m, H8), 2.42-2.45 (1H, m, H6), 2.44-2.49 (1H, m, $H10_{ax}$), 3.39 (3H, s, OMe), 4.35-4.37 (1H, m, H1), 4.73 (1H, br.d, J 5.3 Hz, H9), 4.82 (1H, s, H3), 5.26 (1H, dd, J 6.6, 2.5 Hz, H5); m/z [CI+ (NH_3)] 348 (MNH_4^+), 316 (MNH_3-MeO^-), 299 (M^+-MeO^-), 241 (MNH_3-^{t}Bu-MeO^--H_2O), 201, 184, 167, 153, 123, 91; (Found: C, 57.87; H, 9.36. $C_{16}H_{30}O_5Si$ requires C, 58.15; H, 9.15%).

10. Nishikimi, Y.; Iimori, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3354-3359.

11. (1S, 3R, 7S, 8R, 9S, 11S)-2,4,10-Trioxatetracyclo[6.3.1.0.^{3,7}0^{9,11}]dodec-5-ene (2): Amorphous white solid; mp. 97-99°C; $[\alpha]_D^{20}$=-141.9° [c=0.16 (chloroform)]; υ_{max} (film) 3465, 3109, 3057, 2935, 1617, 1449, 1382, 1328, 1298, 1275, 1225, 1213, 1176, 1143, 1101, 1088, 1059, 1004 and 934 cm^{-1}; δ(500 MHz, $CDCl_3$) 1.36 (1H, d, J 13.1 Hz, H12'), 1.54 (1H, ddd, J 13.2, 5.5, 3.4 Hz, H12), 1.77 (1H, br.s 7-OH), 2.67 (1H, d, J 5.4 Hz, H8), 3.53 (1H, d, J 2.9 Hz, H11), 3.84 (1H, d, J 2.9 Hz, H9), 4.36 (1H, dt, J 3.4, 0.9 Hz, H1), 5.12 (1H, d, J 2.7 Hz, H6), 5.50 (1H, s, H3), 6.53 (1H, d, J 2.7 Hz, H5); m/z [CI+ (NH_3)] 200 (MNH_4^+), 183 (MH^+), 165 (M^+-OH), 153, 147 (MH^+-$2H_2O$), 137, 119, 109, 99, 84, 78; (Found: (MH^+), 183.0657. $C_9H_{10}O_4$ requires 183.0657).

12. The biological evaluation of compound (2) and more elaborate models will be reported at a later date.

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