Tetrahedron Letters,Vol.29,No.15,pp 1849-1852,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CHEMISTRY OF INSECT ANTIFEEDANTS FROM AZADIRACHTA INDICA (PART 1): CONVERSION FROM THE AZADIRACHTIN TO THE AZADIRACHTININ SKELETONS

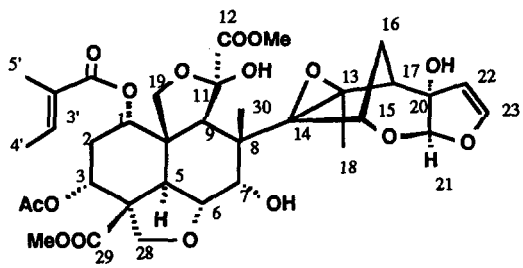
John N. Bilton, Philip S. Jones, Steven V. Ley*,
Nicholas G. Robinson, and Richard N. Sheppard

Department of Chemistry, Imperial College, London SW7 2AY, U.K.

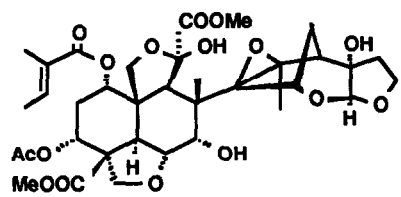
Summary: The conversion of azadirachtin derivatives to the corresponding azadirachtinin skeletons can be achieved in high yield under mild conditions.

The neem tree *Azadirachta indica* A. Juss is a source of compounds possessing several potent biological activities. However, recent attention has been centred around one compound, azadirachtin (**1**), which is a very strong insect antifeedant and ecdysis inhibitor. Its structure was only recently determined, requiring the careful application of modern n.m.r., x-ray crystallographic and mass spectral techniques by the groups of Ley,[1] Kraus[2] and Nakanishi.[3]

We remain interested in the chemistry of azadirachtin for several reasons. Most immediately we require a sound knowledge of its chemistry as an aid to the rational and flexible design of the later steps in our total synthesis of azadirachtin. Secondly, the production of modified azadirachtins is of use in biological studies on the mechanism of action of insect antifeedants. Finally, the understanding of the chemical reactivities and structure-activity relationships of azadirachtin derivatives, or simpler synthetic analogues,[4] is commercially important. In this letter we describe a series of rearrangement reactions involving opening of the C-13,14 epoxide. Other chemical and biological studies will be reported elsewhere.[5]



(1)



(2)

Most of our initial studies were carried out using the relatively stable dihydroazadirachtin (**2**). On attempted deoxygenation of the epoxide with a low valent tungsten reagent[6] a rearrangement occurred to give an inseparable 7:2 mixture of products as measured by ^{1}H n.m.r. spectroscopy in deuterochloroform solution (64%),(Scheme 1). These same products were formed in identical ratio when dihydroazadirachtin was treated with Amberlyst A15 and 4Å sieves in acetonitrile solution, and also when it was heated in toluene solution in the presence of triethylamine. When the product ratio was measured in hexadeuterobenzene solution it changed to 2:1, indicating that the two products were interconvertible.

The major product (**3a**) was readily identified by ^{1}H, ^{13}C n.m.r. and mass spectroscopy. There was a close similarity of most of the resonances with those reported for 1-tigloyl-3-acetyl-11-methoxy-azadirachtinin.[2] Strong downfield shifts of the C-13 and 14 resonances (94.19 and 94.03 p.p.m. respectively) were observed relative to those of azadirachtin, indicating that opening of the epoxide had taken place. The stereochemistry of this product was determined by nOe difference spectroscopy (Table 1) and the structure was further supported by the electron impact mass spectrum, which showed a strong peak at *m/z* 253 resulting from clevage of the C-6,7 and C-8,9 bonds. The corresponding peak for dihydroazadirachtin was much weaker, because this same fragmentation would first require a thermal opening of the epoxide.[1]

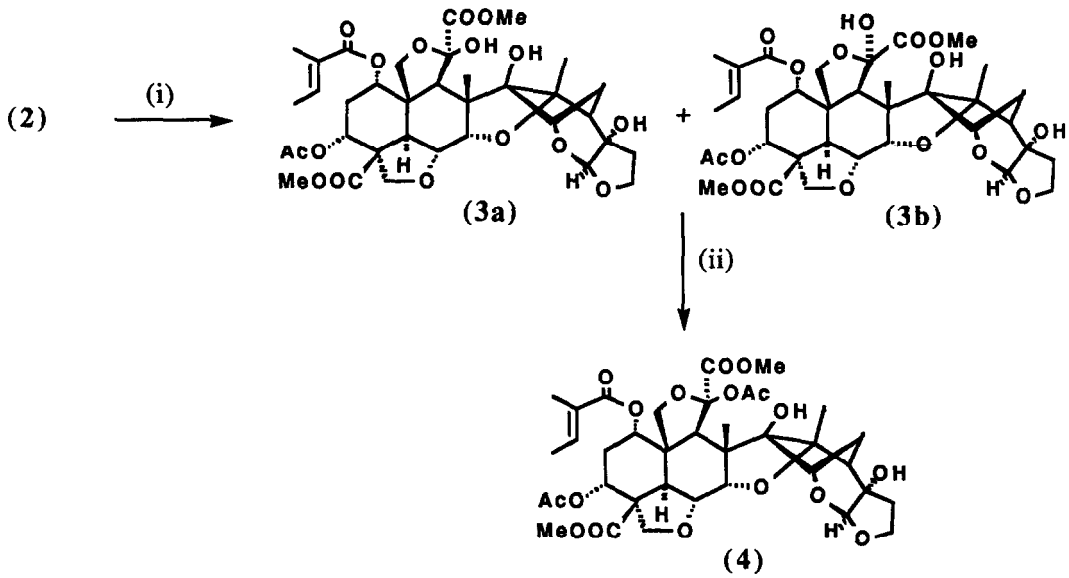
The minor rearrangement product gave almost identical ^{1}H nOe results (Table 1) except for an enhancement of the C-12 ester methyl group on irradiation at H-30. There were several substantial shifts in proton resonances relative to (**3a**); H-1 from 4.75 to 5.57, the ester methyl from 3.72 to 3.85, and H-30 from 1.68 to 1.27 p.p.m.. Thus the minor rearrangement product (**3b**) was epimeric at C-11 with (**3a**). This result is consistent with the recent isolation of 1-cinnamoyl-melianolone.[7]

Table 1. Nuclear Overhauser effects in the ^{1}H n.m.r. spectra (250 MHz, $CDCl_3$) of 1-tigloyl-3-acetyl-azadirachtinin (**3a**) and *11-epi*-1-tigloyl-3-acetyl-azadirachtinin (**3b**).

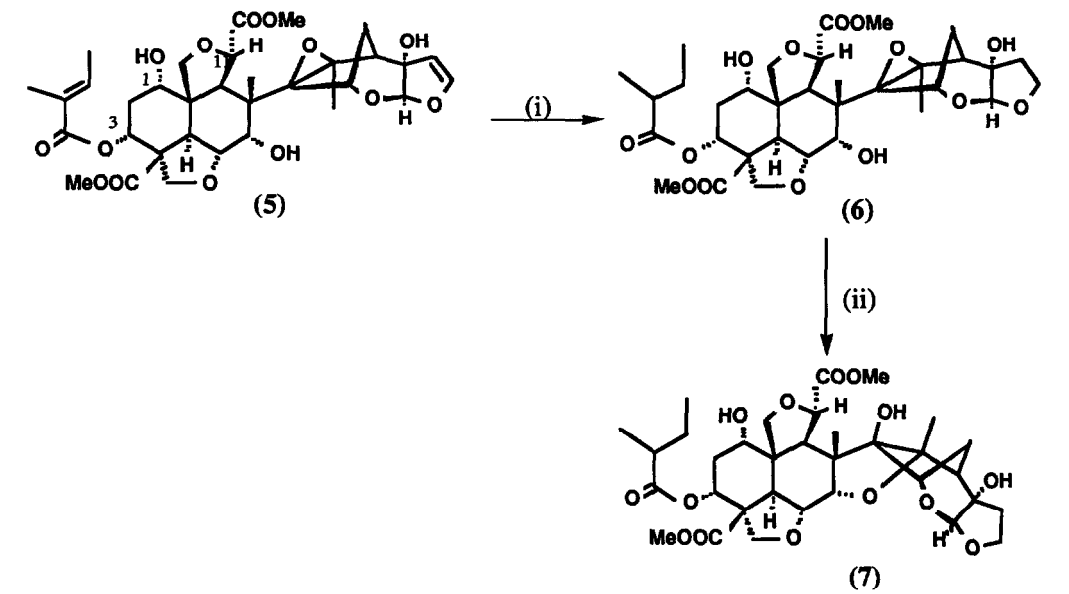
	(3a)	(3b)
Irradiated	Observed	Observed
7-H	30-H, 6-H, 21-H, 20-OH	30-H, 6-H, 21-H, 20-OH
9-H	18-H, 5-H, 14-OH	18-H, 5-H, 14-OH
15-H	14-OH, 30-H, 16-Ha	14-OH, 30-H, 16-Ha
18-H	17-H, 9-H, 16-Ha, 14-OH, 3'-H	17-H, 9-H, 16-Ha, 14-OH, 3'-H
21-H	20-OH, 7-H	20-OH, 7-H
30-H	15-H, 19-Ha, 6-H, 7-H, 14-OH	15-H, 19-Ha, 12-OMe, 6-H, 7-H, 14-OH

As chemical confirmation of the structures of the rearrangement products, they were converted to a single monoacetate (80%),(Scheme 1). The product was shown to be the 11-acetate, most probably (**4**), in accord with our experimental observations on the acetylation of azadirachtin and dihydroazadirachtin.

During further studies on the isolation of natural products from neem fruit two known compounds were isolated. The first was 1-tigloyl-3-acetyl-11-methoxy-azadirachtinin, previously isolated in low yield from the bark.[2] The second was 3-tigloylazadirachtol (**5**).[1,2,†] Hydrogenation of 3-tigloylazadirachtol was



Scheme 1 (i) *e.g.* Amberlyst A15, 4Å sieves, CH_3CN, RT, 24h. (ii) Ac_2O, cat. DMAP, Et_3N, RT, 48h.



Scheme 2 (i) H_2, cat. 10% Pd/C, MeOH, RT, 5h. (ii) Amberlyst A15, 4Å sieves, CH_3CN, RT, 4h.

not chemo- or stereospecific and gave tetrahydro derivative (**6**) as a 1:1 mixture of diastereomers (83%). Rearrangement of (**6**) was extremely facile, and even began to occur if the previous hydrogenation was allowed to proceed for too long. The reaction was completed by acid catalysis and gave a diastereomeric mixture (**7**) as sole product (92%),(Scheme 2).

Although similar rearrangements of azadirachtin and 3-tigloylazadirachtol were complicated by side reactions of the C-22,23 enol ether double bond, it is clear that the rearrangement process is important for all azadirachtin derivatives. Thus great care must continue to be exercised in the structural assignment of all products from neem.

Acknowledgements: *We thank the SERC and Rohm and Haas Company, Spring House, Pennsylvania, USA for financial support and Dr. David Morgan, University of Keele, for supplies of azadirachtin.*

Footnote

† We confirm that 3-tigloylazadirachtol and the materials previously described as 3-deacetyl-11-deoxyazadirachtin[1] and deacetylazadirachtinol[8] are all identical, and have structure (**5**). Our full nOe data is in accord with this structure. The optical rotation was concentration and solvent dependant, the same material giving $[\alpha]_D^{20}$ -40° c(0.36) $CHCl_3$ {lit.[1] -40.8°} and $[\alpha]_D^{20}$ -67° c(0.1) CH_2Cl_2 {lit.[2] -69°, solvent not stated}. Attempts at crystallisation always gave microcrystalline material, m.p. 150°C {lit.[1,8] 149-151°C}, and we never obtained the form reported by Kraus {lit.[2] 204-206°C}.

References

1. J.N.Bilton, H.B.Broughton, P.S.Jones, S.V.Ley, Z.Lidert, E.D.Morgan, H.S.Rzepa, R.N.Sheppard, A.M.Z.Slawin, and D.J.Williams, *Tetrahedron*, 1987, 43, 2805.
2. W.Kraus, M.Bokel, A.Bruhn, R.Cramer, I.Klaiber, A.Klenk, G.Nagl, H.Pohnl, H.Sadlo, and B.Vogler, *Tetrahedron*, 1987, 43, 2817.
3. C.J.Turner, M.S.Tempesta, R.B.Taylor, M.G.Zagorski, J.S.Termini, D.R.Schroeder, and K.Nakanishi, *Tetrahedron* 1987, 43, 2789.
4. S.V.Ley, D.Santafianos, W.M.Blaney, and M.S.J.Simmonds, *Tetrahedron Lett.*, 1987, 28, 221.
5. W.M.Blaney, S.V.Ley, M.S.J.Simmonds *et al.*, manuscripts in preparation.
6. K.B.Sharpless, M.A.Umbreit, M.T.Nieh, and T.C.Flood, *J.Am.Chem.Soc.*, 1972, 94, 6538.
7. S.M.Lee, J.A.Klocke, and M.F.Balandrin, *Tetrahedron Lett.*, 1987, 28, 3543.
8. I.Kubo, A.Matsumoto, T.Matsumoto, and J.A.Klocke, *Tetrahedron*, 1986, 42, 489.

(Received in UK 24 February 1988)