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SYNTHESIS OF A LIMONOID, AZADIRADIONE

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Summary: Azadiradione **1** has been synthesized stereoselectively from *trans, trans*-farnesol.

Since the elucidation of the structure of limonin in 1960,[1] a large number of naturally occurring substances of the limonoid family have been isolated and characterized structurally. Described herein is a synthesis of azadiradione **1**, a tetracarbocyclic member of the limonoid group isolated from the neem plant, *Azadirachta indica*.[2,3] Because numerous tetracyclic limonoids have been prepared from **1** chemically,[4] the synthesis of azadiradione constitutes a formal synthesis of many members of the group.

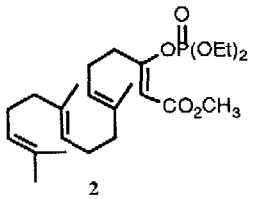
trans,trans-Farnesol (98% Aldrich) was converted to the corresponding bromide by mesylation with 1.1 equiv of methanesulfonyl chloride and 1.3 equiv of triethylamine in CH_2Cl_2 at -20°C for 30 min followed by treatment with 2 equiv of lithium bromide in THF at -20°C for 2 h (96% yield). The enol phosphate **2** was obtained in 80% yield by the reaction of farnesyl bromide with the sodio and lithio derivative of methyl acetoacetate (1.2 equiv, -78°C, 2 h, THF)[5,6] followed by phosphorylation with diethyl chlorophosphate (1.3 equiv at -78°C initially and -20°C for 3 h). Slow addition of **2** (over 1.5 h) in dry nitromethane solution (0.1 *M*) to a solution of mercuric trifluoroacetate (0.08 *M* in nitromethane) at 0°C and further reaction for 1 h at 0°C afforded, after stirring with aqueous sodium chloride and isolation, the tricyclic organomercurial β-keto ester **3** (27% yield) as a crystalline solid,[7] mp 201-202°C. At this stage the stereochemical assignments were based solely on precedent with related polyene cyclization reactions. Later in the synthesis it was possible to assign all the ring junctions as *trans* using NOE studies and by direct comparison of synthetic intermediates with authentic samples derived from neem oil.

The replacement of mercury by oxygen[8] was accomplished as follows. The organomercurial **3** was suspended in DMF and added slowly to a solution of sodium borohydride (3 equiv in DMF at 23°C) which was maintained at saturation with oxygen by rapid bubbling of O_2 through a glass dispersion tube. The

mixture was filtered through Celite and treated with 1 *N* sulfuric acid at 10°C to hydrolyze borate esters. Extractive isolation gave a mixture of alcohols in 91% yield which was oxidized in acetone with 8 *N* Jones reagent (aq CrO_3, sulfuric acid) at 0°C to give diketone **4** (86% yield). Deprotonation using sodium hydride in THF at reflux for 1 h followed by reaction with 1.1 equiv of diethyl chlorophosphate at 0°C for 10 min provided the corresponding enol phosphate which was ketalized with ethylene glycol (*p*-toluenesulfonic acid, benzene, Dean-Stark trap) to furnish ketal **5** (87% yield). Reduction of **5** with diisobutylaluminum hydride in toluene at -20°C for 30 min, followed by quenching with 30 : 1 methanol and 1 *N* aqueous HCl, gave the allylic alcohol **6** (90% yield). Conversion of **6** to the nitrite ester **7** was accomplished with 5 equiv of HO_3SONO in pyridine at 0°C for 30 min followed by quenching with methanol and extractive isolation. Photolysis of **7** (sunlamp, CH_2Cl_2, 50°C) afforded the Barton reaction product,[9] oxime **8**, in 28% yield along with the aldehyde corresponding to **6** which could be recycled. Treatment of oxime **8** with 1 *N* HCl and acetaldehyde at 23°C for 12 h provided the hemiketal **9** which could be selectively reduced to the 7α-hydroxyl compound **10** with tetramethylammonium triacetoxyborohydride[10] in acetone-acetic acid at -78°C for 20 min.

The alcohol **10** was elaborated to triketone **11** (90% yield) in one flask by using a combination of Michael and Nef reactions according to the following process: (1) slow addition over 20 min of an ethanolic solution of **10** to an ethanolic solution of the the sodium salt of 3-(2-nitroethyl)furan at reflux and (2) cooling to 10°C and rapid addition of the mixture to 12 *N* HCl-ethanol (1 : 3) at 10°C.[7] Exposure of **11** to 1 *M* sodium ethoxide in ethanol at 70°C for 45 min effected aldol cyclization to tetracyclic enone in 92% yield. The hindered 7α-hydroxyl group of this enone was protected as the methoxymethyl ether using forcing conditions to provide **12** (methoxymethyl bromide and tetrabutylammonium iodide with diisopropylethylamine in acetonitrile at 70°C for 7 h, 92% yield).

The attachment of an α–oriented methyl group at the C/D ring was accomplished in several steps using the hydroxyl-directed Simmons-Smith cyclopropanation reaction. Reduction of diketone **12** (lithium tri-*sec*-butylborohydride in THF at -78°C for 30 min) gave stereospecifically diol **13** which was subjected to selective Mitsunobu inversion[12] at C(16) using benzoic acid, diethyl azodicarboxylate and triphenylphosphine in THF at 23°C for 3 h to give benzoate **14**. This ester was hydrolyzed (NaOH-ethanol at 23°C for 12 h) to give the inverted diol **15** in 50% overall yield. Reaction of diol **15** and ethereal Simmons-Smith reagent (prepared from methylene iodide and Zn-Ag couple)[11] at 0°C left the A-ring unaffected and provided the cyclopropyl carbinol **16** in 61% yield. Oxidation of both hydroxyl groups was performed with the



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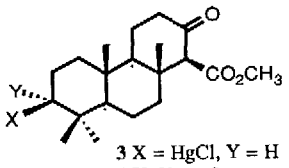
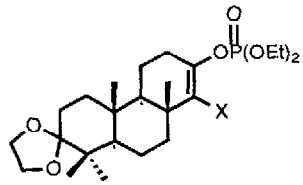
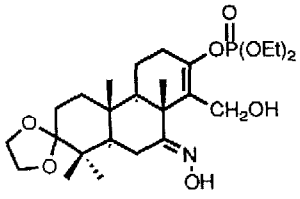


3 X = HgCl, Y = H
4 X, Y= =O



5 X = CO_2CH_3
6 X = CH_2OH
7 X = CH_2ONO



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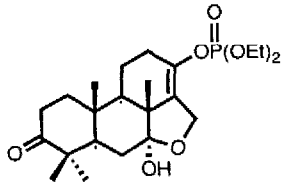

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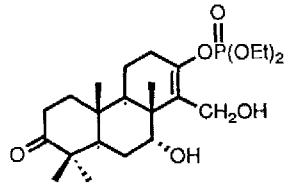

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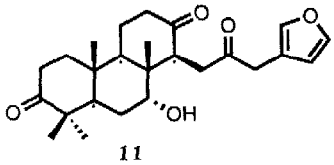

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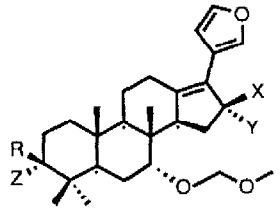
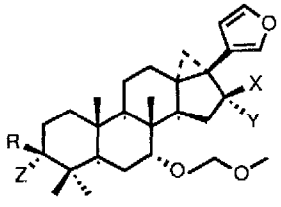
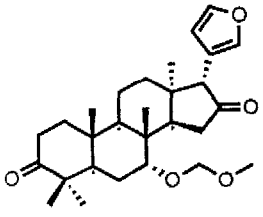


12 X, Y = =O; R,Z = =O
13 X = OH, Y = H; R = H, Z = OH
14 X = H, Y = OCOPh; R = H, Z = OH
15 X = H, Y = OH; R = H, Z = OH



16 X = H, Y = OH; R = H, Z = OH
17 X , Y = =O; R, Z = =O



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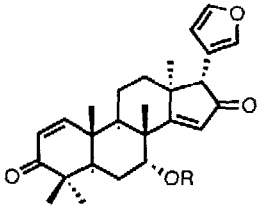
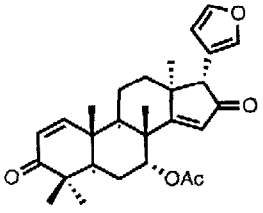


19 R = CH_2OCH_3
20 R = H



1 Azadiradione

Dess-Martin[13] reagent (CH_2Cl_2, 23°C for 10 min) which gave the diketone **17** in quantitative yield. Reduction of cyclopropyl ketone **17** with lithium in ammonia-THF solution followed by oxidation of the reaction product with the Dess-Martin reagent, produced diketone **18** in 92% overall yield. This material was identical by spectroscopic and TLC chromatographic comparison with the methoxymethyl ether of tetrahydroazadiradione, obtained from the natural product in low yield by reduction with lithium in ammonia-THF and quenching with acetic acid. Diketone **18** was converted to dione **19** by sequential reaction with three equivalents of LDA (-78°C in THF for 3 min) followed by excess phenylselenyl bromide, oxidation (30% H_2O_2 in H_2O-pyridine) and selenoxide elimination. The dienone **19** so obtained was identical with the methoxymethyl ether of azadiradione by 500 MHz ^1H NMR, MS (DCI-isobutane), IR and TLC comparison. Removal of the protective group could be accomplished using trimethylsilyl bromide in methylene chloride at -20°C for 17 h giving **20** in 91% yield. Acylation with acetic anhydride and dimethylaminopyridine in THF at 23°C for 17 h generated azadiradione **1**.[14]

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