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STEREOSPECIFIC TOTAL SYNTHESIS OF AJUGARIN-IV

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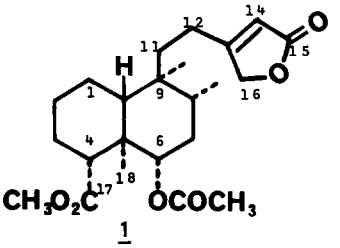
Summary A stereospecific sequence from the octalindione 2 leads in 21 steps to the new insecticide ajugarin-IV. Formation of the butenolide portion is conveniently achieved from acid 21 by successive use of the reagents tris(trimethylsiloxy)ethylene and ketenylidenetriphenylphosphorane.

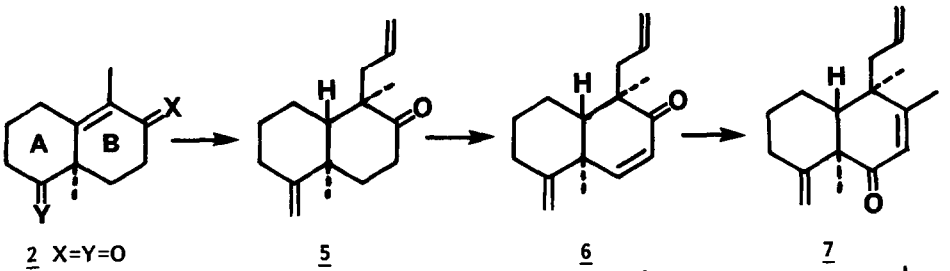
Current efforts toward the total synthesis of clerodane diterpenes[1] have been stimulated by the antifeedant and insecticidal properties noted for certain members of this class. Among the clerodane antifeedants recently isolated from the bitter leaves of the East African medicinal plant Ajuga remota (Labiatae) the trace component ajugarin-IV (1)[2] is unique in lacking both the C-4 epoxide and C-18 oxygen substituent characteristic of the previously described ajugarins.[3] We now describe a stereospecific total synthesis of ajugarin-IV by a route that comprises the first synthesis of any natural ajugarin insecticide. This sequence utilizes an interesting series of regio- and stereoselective transformations that could serve as prototypes for synthesis of the more highly oxygenated ajugarins.



1

Our starting material was the octalindione 2[4] which was selectively transformed (Scheme I) to the dithioketal 3.[5] This was converted by $Ph_3P{=}CH_2$ (4 eqt, DMSO, 90°, 12 hrs) followed by $HgCl_2$-$CdCO_3$ hydrolysis to the enone 4. Reductive allylation of 4 gave 70% of the AB trans methylene ketone 5, mp 47-49°.[6] To functionalize C-6 (ajugarin numbering), ketone 5 was converted to its Me_3Si enol ether followed by selective C-7 bromination (NBS, 0°) and dehydrobromination (LiBr-Li_2CO_3, DMF, reflux, 3 hrs). This gave the conjugated ketone 6 [IR 1670 cm^{-1}, NMR δ 7.12 (d, J=10Hz, 1H), 6.93 (d, J=10Hz, 1H), 4.63 (s, 1H), 4.60 (s, 1H), 90%]. The stage was now set for the two-step enone transposition developed by Dauben and Michno.[7] Thus the reaction of ketone 6 with MeLi gave a single tertiary alcohol in nearly quantitative yield.

Scheme I

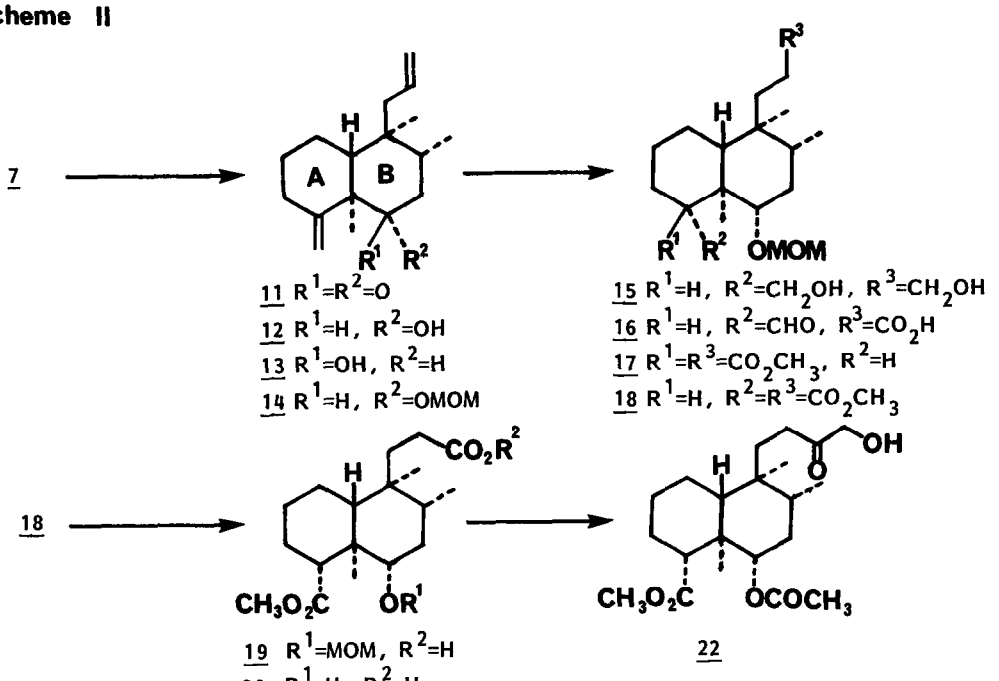


2 X=Y=O
3 X=S(CH$_2$)$_3$S, Y=O
4 X=O, Y=CH$_2$

5 6 7

8 9 10

Scheme II



11 R^1=R^2=O
12 R^1=H, R^2=OH
13 R^1=OH, R^2=H
14 R^1=H, R^2=OMOM

15 R^1=H, R^2=CH$_2$OH, R^3=CH$_2$OH
16 R^1=H, R^2=CHO, R^3=CO$_2$H
17 R^1=R^3=CO$_2$CH$_3$, R^2=H
18 R^1=H, R^2=R^3=CO$_2$CH$_3$

19 R^1=MOM, R^2=H
20 R^1=H, R^2=H
21 R^1=COCH$_3$, R^2=H

22

Unfortunately, treatment of this alcohol under standard Dauben-Michno conditions with pyridinium chlorochromate gave 20-30% of the undesired exo-methylene compound 8 together with 40% of the desired enone 7. This unexpected side reaction, not mentioned by other authors,[8] could be suppressed by use of the Collins reagent.[9] Under the latter conditions (6 eqt $CrO_3 \cdot 2$ py, CH_2Cl_2, 25°, 2 hrs) crystalline enone 7, mp 59-61° [IR 1660 cm^{-1}, NMR δ 5.92 (br s, 1H), 5.00 (s, 1H), 4.75 (s, 1H), 1.97 (br s, 3H)] was obtained in approximately 55% yield.

Dissolving metal reduction of enone 7 using standard conditions for direct conversion of enones to saturated alcohols (e.g., Li, NH_3, THF, EtOH)[10] afforded a nearly inseparable mixture of the desired alcohol 9 and the byproduct 10, in which the allyl group was reduced. When however the reduction was carried out in the complete absence of added proton source (10 eqt Li, NH_3, THF, -33°, 90 min), enone 7 was quantitatively transformed to a single saturated ketone, 11, in which the 8-methyl stereochemistry is assigned the expected equatorial configuration shown.[11] Reaction of this ketone with $LiAlH_4$ (4 eqt, Et_2O, -42°, 20 min) gave a 20 1 mixture of the equatorial alcohol 12 and the axial epimer 13. This mixture was readily separated (Si gel, 3 1 hexane-EtOAc, R_f for 12 = 0.15, R_f for 13 = 0.40) to give 83% of pure 12, mp 51-52° [NMR δ 3.89 (dd, J=4.5, 11Hz, 1H), 0.87 (d, J=7Hz, 3H)]. Alcohol 12 could be quantitatively converted to the MOM ether 14 with $ClCH_2OCH_3$ (2 eqt, 3 eqt iPr_2NEt, CH_2Cl_2, 25°, 2 da).

With the stereochemistry of the B-ring thus established, we examined the regio- and stereochemical problems of selective functionalization at the olefinic sites (Scheme II). An initial attempt to direct hydroboration of 14 at C-4 to yield the equatorial CH_2OH substituent by use of the bulky reagent disiamylborane (4 eqt Sia_2BH, THF, 0°→25°, 2 hrs, then alk. H_2O_2) gave in 80% yield a 1 1 mixture of diols epimeric at C-4. This diol mixture was oxidized to the diacids (6 eqt Jones rgt, Me_2CO, 0°→25°, 12 hrs, 30%) and esterified with CH_2N_2 to give the corresponding diester 17 and 18, R_f = 0.37 and 0.28 (Si gel, 3·1 hexane-EtOAc) respectively. The diester having R_f = 0.37 exhibited at 400 MHz a clean ^{1}H-nmr signal at δ 2.71 (dd, J=4.5, 2Hz, 1H) indicating an equatorial C-4 proton. The R_f = 0.28 isomer (18) was therefore assigned the desired equatorial C-4 $COOCH_3$ stereochemistry. With these assignments in hand, we explored the possibility of driving the hydroboration of the exocyclic C-4 vinyl group completely to the desired C-4 equatorial CH_2OH series by carrying out the disiamylborane reaction under equilibrating rather than kinetic conditions.[12] Indeed, when 14 was allowed to react with 5 eqt Sia_2BH in THF for 5 hours at reflux the sole product from H_2O_2 oxidation was a single diol assigned the structure 15. This was oxidized (7 eqt PDC, DMF, 25°, 12 hrs) to the aldehyde acid 16, then $NaClO_2$ oxidation (1.5 eqt, t-BuOH, 2-methyl-2-butene, 25°, pH 5, 24 hrs) and reaction with CH_2N_2 gave the single diester 18. By this stereospecific sequence the diolefin 14 was transformed to the desired diester stereoisomer 18 in 53% overall yield.

With correct stereochemistry in the alicyclic core now assured, the principal remaining problem was to construct the butenolide side chain. An interesting solution was developed through selective saponification of the unhindered ester (1.1 eqt KOH, CH_3OH, reflux, 24 hrs) to give 90% of the monoester 19, which was quantitatively hydrolyzed to the hydroxy ester 20 (6N HCl, aq THF, 25°, 12 h). Acetylation (3 eqt Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25°, 10 hr) followed by brief stirring with dilute aq HCO_3^- gave the acetate 21 in 95% yield. Conversion of 21 to ajugarin IV was accomplished in two steps. Reaction of 21 with excess ClCOCOCl (5 eqt, CH_2Cl_2, 25°, 2 hrs) followed by removal of all volatiles at reduced pressure and addition of 15 eqt of neat tris-

(trimethylsiloxy)ethylene,[13] then 12 hrs of heating at 90° followed by acid hydrolysis gave 56% of the crystalline hydroxy ketone 22, mp 128-131° [NMR. δ 4.27 (s, 2H), 2.30 (m, 1H), 2.15 (m, 1H)]. Reaction of this hydroxy ketone with ketenylidene triphenylphosphorane[14] (vastly superior to alternative reagents for our series)[15] for 1 hr at 25° gave in 86% yield crystalline (±)-ajugarin-IV (1), mp 175-176°.[16] Our racemic ajugarin IV had IR, UV, ^{1}H-NMR and MS identical to those of the natural product. Studies are in progress to convert our intermediate 14 into (±)-ajugarin-I by appropriate functionalization of the C-18 angular methyl group.[17]

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16. Natural ajugarin-IV [α_D] = -57.5°, had mp 119-120.5°C. All intermediates in our synthetic sequence had IR, MS or microanalysis and 400 MHz ^{1}H-NMR spectra in agreement with the assigned structures. Synthetic (±)-ajugarin-IV had mp 175-6°C, UV (CH_3OH) ν_{max} 212nm. ε 16,000. IR (CH_2Cl_2) 1785, 1750, 1730, 1635 cm^{-1}. 400 MHz ^{1}H-NMR ($CDCl_3$) δ 5.84 (br s, 1H), 4.74 (br s, 2H), 4.60 (dd, J=4.5, 11Hz, 1H), 1.97 (s, 3H), 1.21 (s, 3H), 0.82 (d, J=7Hz, 3H), 0 78 (s, 3H). Synthetic ajugarin-IV exhibited insecticidal activity against the silkworm, Bombyx mori, at 1500 ppm (LD_{95}), but only growth inhibitory activity against the pink bollworm, Pectinophora gossypiella at 1500 ppm (ED_{50}) with artificial diet feeding bio-assay. This activity is about one third of natural ajugarin-IV.

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