The Total Synthesis of the Clerodane Diterpene Insect Antifeedant Ajugarin I

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The first total synthesis of the polyoxygenated diterpene insect antifeedant ajugarin I (**1**) has been achieved by a route which involves a new method for the construction of 3-substituted-Δ^2-butenolides.

As a result of an observation that *Ajuga remota* (*Labiatae*) plants were not eaten by various insect species, subsequent isolation studies afforded three new polyoxygenated clerodane diterpene antifeedants,[1] the major component being assigned the structure ajugarin I (**1**). These antifeedant compounds immediately attracted the attention of synthetic chemists and resulted in the extensive model studies[2] and one total synthesis[3] of a related less functionalised insecticide, ajugarin IV (**2**).

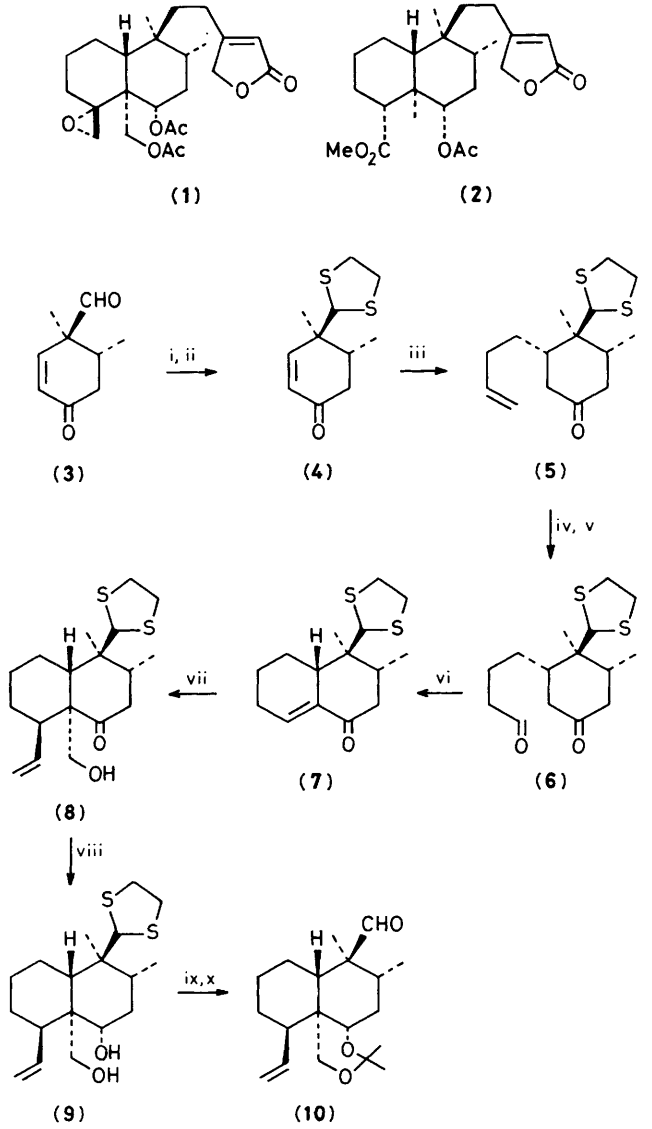
Here we report the first total synthesis of ajugarin I (**1**) using a strategy previously developed in these laboratories to construct appropriately functionalised *trans*-decalin ring systems.[2d]

The Diels–Alder reaction, at 120 °C over 24 h, of 1-methoxy-3-trimethylsilyloxybutadiene,[4] (Danishefsky's diene) with *E*-2-methylbut-2-enal afforded an adduct which upon treatment with aqueous hydrochloric acid in tetrahydrofuran (THF) gave the enone (**3**)† in 50% overall yield.‡ Conversion of (**3**) into the monodithiolane (**4**) was achieved in 55% yield by a sequence of reactions which involved initial diprotection

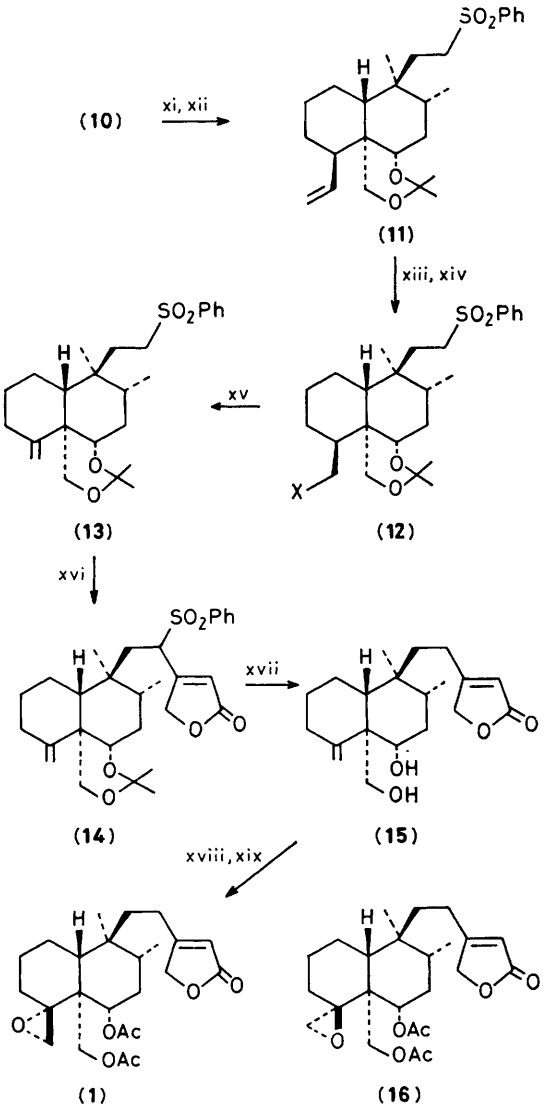
† All new compounds were fully characterised by spectroscopic, elemental microanalysis, and/or accurate mass methods.

‡ The mass balance in this reaction was partly made up by the other major product of cycloaddition of the diene to the aldehyde carbonyl group; for other examples of this process see S. Danishefsky, N. Kato, D. Askin, and J. F. Kerwin, Jr., *J. Am. Chem. Soc.*, 1982, **104**, 360.

followed by specific removal of the more labile enone dithiolane group. The introduced dithiolane moiety in (**4**) acted as an excellent stereocontrol unit during the copper mediated addition of but-3-enylmagnesium bromide to afford (**5**) as the only detectable product in 93% yield.§ Compound (**5**) was treated with an excess of borane methyl sulphide to yield an intermediate diol (95%), which, without purification was converted by oxidation [using pyridine(py)·SO_3, Me_2SO[5]] into the keto-aldehyde (**6**) in 72% yield. Aldol condensation of (**6**) in the presence of camphor sulphonic acid gave the enone (**7**) in a useful 80% yield. Introduction of the requisite *trans*-hydroxymethyl substituent was guaranteed in the next step by vinyl cuprate addition to (**7**) from the least hindered side, followed by quenching of the resulting regiospecific enolate with formaldehyde at −40 °C to give (**8**) (52%). Stereospecific conversion of (**8**) into the diol (**9**) required prior formation of the diphenylbutylsilyl ether, to remove the reduction directing properties of the hydroxy group, followed by treatment with lithium aluminium hydride to give (**9**) in 69% yield upon work-up. Alternatively, (**9**) could be obtained directly from (**7**) in 44% overall yield without full purification of intermediates. Protection of (**9**) as the acetonide was trivial (95%); however the regeneration of the aldehyde group from the



Scheme 1. *Reagents:* i, $(CH_2SH)_2$, benzene, toluene-*p*-sulphonic acid, 12 h; ii, $CdCO_3$, $Hg(OAc)_2$, benzene–ether–H_2O (5:4:1), 24 h; iii, $(CH_2{=}CHCH_2CH_2)_2CuMgBr$ (2.2 equiv.), Et_2O, −40 °C, 1 h; iv, borane methyl sulphide, THF at room temp.; then H_2O_2–NaOH; v, py·SO_3 (6 equiv.), Me_2SO, CH_2Cl_2 at room temp.; vi, camphorsulphonic acid, benzene, reflux, 1 h; vii, $(CH_2{=}CH)_2$-CuLi (2.2 equiv.), THF, −40 °C, then CH_2O in THF at −40 °C; viii, Ph_2Bu^tSiCl, imidazole, dimethylformamide, then $LiAlH_4$, Et_2O, room temp.; ix, acetone, anhydrous $CuSO_4$, 12 h; x, $Tl(OCOCF_3)_3$ (1.8 equiv.), THF, room temp., and Na_2HPO_4 buffer (10 equiv.), 30 min.



Scheme 2. *Reagents:* xi, $(Me_3\bar{S}iCHSO_2Ph)Li^+$ (1.05 equiv.), −78 °C, THF followed by Ac_2O, py, 4-*N*,*N*-dimethylaminopyridine, then Bu^n_4NF, THF, room temp., 2 h; xii, $LiEt_3BH$, THF, room temp., 4 h; xiii, O_3, EtOH, 0 °C, then an excess of $NaBH_4$, 1 h; xiv, *N*-phenylselenophthalimide–Bu^n_3P (3.5 equiv.), THF, room temp., 12 h; xv, O_3, −78 °C, 10 min, then in CCl_4, Et_2NH, at reflux; xvi, Bu^nLi, THF–hexamethylphosphoramide (5:1), −78 °C, 15 min, then Bu^tMe_2SiO–CH_2–C≡C–CO_2Et followed by an excess of Bu^n_4NF, THF, room temp., 2 h; xvi, Na–Hg, MeOH, Na_2HPO_4 buffer, −20 °C, 2 h, then trifluoroacetic acid, H_2O, MeCN, room temp., 30 min; xvii, excess of *m*-chloroperbenzoic acid, CH_2Cl_2, Na_2HPO_4, room temp., 10 min; xix, Ac_2O, py, 4-*N*,*N*-dimethylaminopyridine, 2 h.

§ In order to achieve complete stereocontrol during the conjugate addition reaction, extensive experimental investigation was necessary, a full discussion of which will be presented at a later date.

dithiolane could only usefully be achieved by treatment with thallium(III) trifluoroacetate[6] to give (**10**) (69%) (m.p. 92—94 °C, ν_{max} 1710 cm^{-1}) (Scheme 1).

The incorporation of an homologated sulphone moiety was then necessary in order to facilitate later introduction of the butenolide group. Reaction of (**10**) with the lithio-anion of phenylsulphonyl(trimethylsilyl)methane followed by acetylation and treatment with tetra-n-butylammonium fluoride gave an intermediate vinyl sulphone (96%) (m.p. 181—183 °C). This was conjugatively reduced with $LiEt_3BH$, again in 96% yield, to afford (**11**) (m.p. 173—174 °C). Conversion of the vinyl side chain in (**11**) into the desired *exo*-methylene group required ozonolysis and borohydride reductive work-up to give (**12**, X = OH) (100%), followed by formation of the selenide (**12**, X = SePh) using *N*-phenylselenophthalimide–Bu^n_3P[7] (75%) and *syn*-elimination of the corresponding selenoxide to give (**13**) (86%)[^{1}H n.m.r. (250 MHz), δ 5.03 (1H, br. s), 4.87 (1H, br. s), 4.13 (1H, d, *J* 12.1 Hz), 3.85 (1H, dd, *J* 1 and 12.1 Hz), and 3.95 (1H, ddd, *J* 1, 5, and 12.1 Hz)]. The anion of (**13**) was treated with the novel butenolide synthon $Bu^tMe_2SiOCH_2$–C≡C–CO_2Et (prepared in two steps from prop-2-ynyl alcohol by reaction with t-butylmethylsilyl chloride–pyridine followed by magnesium acetylide formation and quenching with ethyl chloroformate). This gave an adduct which was immediately treated with tetra-n-butylammonium fluoride to effect deprotection and concomitant cyclization to the butenolide (**14**) in 45% overall yield, (m.p. 98—100 °C).¶ Reductive removal of the phenylsulphone group in (**14**) with sodium amalgam[8] and deprotection of the acetonide afforded the key *exo*-methylene diol (**15**) in 75% yield overall for the two steps [^{1}H n.m.r. (250 MHz) δ 5.83 (1H, m) 5.15 (1H, br. s), 5.02 (1H, br. s), and 4.73 (2H, m)].

Final elaboration to the natural product required epoxidation of (**15**) with *m*-chloroperbenzoic acid** in CH_2Cl_2 at room temperature and diacetylation with acetic anhydride in the presence of 4-*N*,*N*-dimethylaminopyridine to give ajugarin I (**1**) and 4-*epi*-ajugarin I (**16**) in 20 and 62% yields respectively (Scheme 2).

The synthetic material was identical in all respects to an authentic sample of the natural product. The 4-*epi*-isomer (**16**) gave spectral parameters identical to the previously synthesised compound[2e] and showed many similar features to a related model decalin system.[2d]

The synthetic strategy discussed above is clearly applicable to the preparation of many other clerodane related natural insect antifeedants.

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¶ Further examples of this new method for construction of butenolide derivatives will be reported separately.

** *m*-Chloroperbenzoic acid was used since planned epoxidation[2d] of (**15**) using $VO(acac)_2$–Bu^tOOH (Hacac = acetylacetone) led to substantial decomposition of the butenolide.

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