A Total Synthesis of the Guaiane Furanosesquiterpene (±)-Gnididione, a Metabolite of *Gnidia latifolia*

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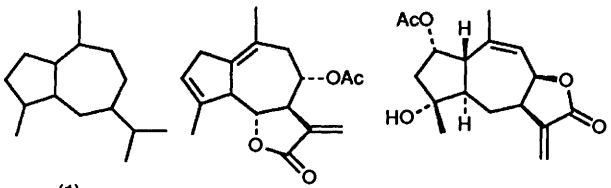
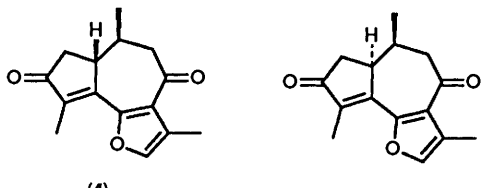
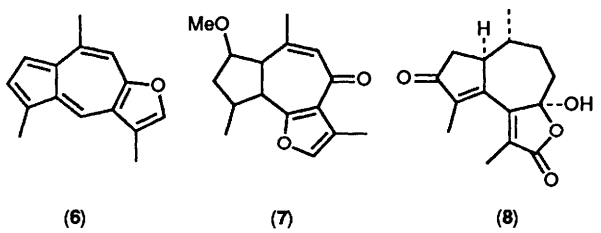
Various approaches to the furanosesquiterpene (±)-gnididione (**4**) are described, all of which feature the furancarboxylic acid dianion (**14**) as a key intermediate. The eventually successful route using the disconnection (**10**) ⟶ (**11**) + (**12**) + (**13**) proceeded *via* condensation of dianion (**14**) with 3-methylglutaric anhydride (**44**). Protection of the derived keto-diester (**45a**) as the corresponding *N,N*-dimethylhydrazone (**45b**) and Dieckmann cyclisation led to the diketo-ester (**46b**) after deprotection. Following stereospecific incorporation of the appropriate butanone side chain by double deprotonation of ester (**46b**) and alkylation using the bromo-ketone (**47**), the resulting dione (**48**) was subjected to intramolecular aldol ring closure using potassium t-butoxide as base. Saponification and decarboxylation of the aldol product (**49**) then gave (±)-gnididione (**4**).

Sesquiterpenes based on the guaiane skeleton (**1**) form one of the largest groups of terpenoid natural products and are often encountered as α-methylenebutyrolactones, usually referred to as guaianolides, in which the lactone ring is formally obtained by joining the oxidised isopropyl side chain to either C-6 [as in zuurbergenin (**2**)] or to C-8 [as in neo-gaillardin (**3**)] of the central perhydroazulene ring system.[1] Gnididione (**4**) is a very unusual example of a guaiane sesquiterpene because of the presence of a furan ring in place of the much more common lactone function. The compound was isolated from anti-leukaemic fractions of the plant *Gnidia latifolia* Gilg. (Thymelaeaceae) during Kupchan's extensive search for tumour inhibitors and the structure (**4**) (or its enantiomer)

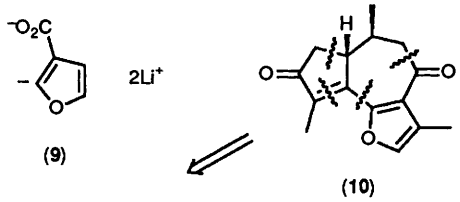


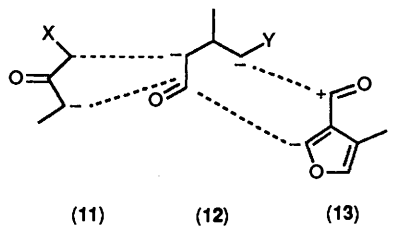




assigned on the basis of spectroscopic and microanalytical data together with some chemical transformations. These included acid-catalysed epimerisation of the relatively uncommon *cis*-geometry between H-1 and Me-10 to give the *trans*-epimer, isognididione (**5**).[2] Two other members of this rare class are the furanoguaiazulene linderazulene (**6**),[3] isolated from a deep-sea gorgonian (*Placogorgia* or *Paramuricea* spp.) and the furanoguaianone (**7**), of unknown stereochemistry, which occurs in myrrh essential oil.[4] A most unusual sesquiterpene, melicophyllone B (**8**), has recently been found in the root bark of *Melicope triphylla* (Lam.) Merr. in which the carbon skeleton differs from the guaianes in that the isopropyl side chain is attached to C-6 rather than C-7.[5] However, the hydroxy-lactone present in this compound perhaps represents the closest biosynthetic partner to the corresponding, as yet unknown, furanosesquiterpene.

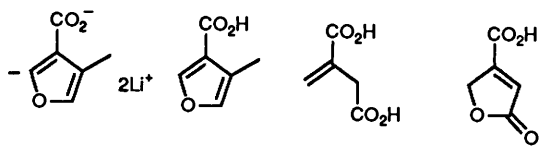
The basis of our strategies for the total synthesis of gnididione (**4**) was the observation that furan-3-carboxylic acid could be doubly deprotonated to give the dianion (**9**), which was known to condense extremely efficiently with aldehydes and ketones.[6] Under normal reactivity conditions, the carboxylate residue in dianion (**9**) would provide an electrophilic carbonyl centre. Thus, the four key carbon–carbon bond forming reactions indicated in formula (**10**) were envisaged, whereby Dieckmann and aldol condensations or equivalents thereof could be used to establish the seven- and five-membered rings respectively. We therefore required the doubly functionalised four- and six-



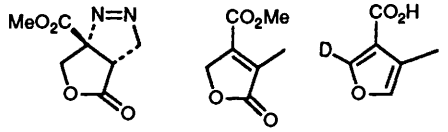


carbon fragments (**11**) and (**12**) and the dianion (**14**) derived from 4-methylfuran-3-carboxylic acid (**15**) [*cf.* (**9**)] which would provide overall the synthon (**13**). At this stage, the two main considerations were the optimum order of these bond-forming

reactions and whether or not the desired dianion (**14**) could be obtained from the corresponding free acid. This latter crucial feature of the synthesis was our starting point.



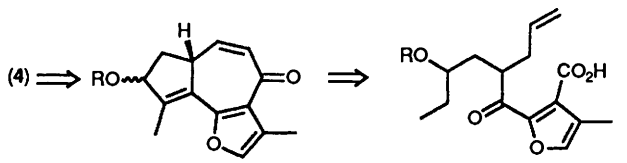
(**14**) (**15**) (**16**) (**17**)



(**18**) (**19**) (**20**)

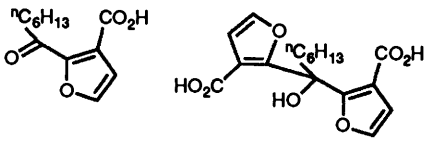
While it is certainly possible to metallate methyl groups adjacent to carboxylate functions in heteroaromatic acids, this usually only occurs in the absence of free vinylic positions α- to the heteroatom(s) or when the methyl group itself is in such a position.[7] We therefore felt confident that deprotonation of 4-methylfuran-3-carboxylic acid (**15**) would occur only at the desired 2-position.[6] Two routes were used to prepare the acid (**15**) in quantity. The first approach featured a Diels–Alder cycloaddition between 4-phenyloxazole[8] and methyl tetrolate followed by an *in situ* elimination of benzonitrile *via* a retro-Diels–Alder reaction.[8,9] This procedure was, in our hands, less satisfactory than a slight modification of the approach developed by Pelletier and his co-workers, starting from itaconic acid (**16**),[10] despite the requirement in this latter procedure of relatively large quantities of ethereal diazomethane. Thus, bromination of acid (**16**) followed by neutralisation using aqueous sodium carbonate and acidification (HCl) gave aconic acid (**17**).[11] Treatment of this material with two equivalents of ethereal diazomethane smoothly generated the crystalline pyrazoline lactone (**18**) in excellent overall yield. [All attempts to esterify acid (**17**), in order to decrease the amount of diazomethane required, failed; these included Me_2SO_4–K_2CO_3, EtI–Ag^+, MeOH–H^+ (toluene-*p*-sulphonic acid, pyridinium toluene-*p*-sulphonate), and mixed anhydride alcoholysis]. Pyrolysis of the pyrazoline (**18**) could only be carried out on a 2–3 g scale as recommended by Pelletier.[10] At best, larger-scale runs resulted in considerable loss of product (**19**) which was swept out of the apparatus during the *extremely violent* evolution of nitrogen; at worst, a violent detonation occurred. However, it was found that pyrolysis of 2–3 g batches in xylene stirred and maintained at 140 °C in an oil bath proceeded smoothly and much less vigorously, the elimination taking *ca.* 3 min. In this way, a 30 g batch could be processed in a single flask in *ca.* 0.75 h apparently safely. The final di-isobutylaluminium hydride reduction of the lactone (**19**) and subsequent dehydration and saponification then gave the required acid (**15**) as previously described.[10] That the required dianion (**14**) could indeed be obtained was proven by deprotonation of acid (**15**) using the previously described conditions[6] followed by quenching with deuterium oxide. Only the 2-deuterio derivative (**20**) was obtained in essentially quantitative yield.

With a view to introducing the 10-methyl group stereoselectively at a very late stage, our first retro-synthetic analysis proceeded *via* the cycloheptenone (**21**) and thence to the furyl ketones (**22**), on the assumption that an aldol cyclisation would provide the cyclopentenone function and that the allyl side chain could be oxidised to a methoxycarbonylethyl residue suitable for Dieckmann ring closure to the corresponding

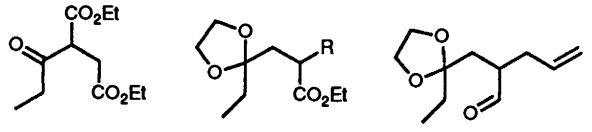


(**21**) (**22**)

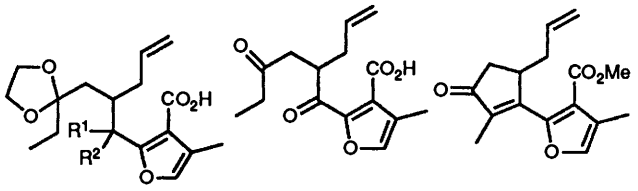
cycloheptanone. However, model furyl ketones were found to be formed in only low yields in condensations between dianions (**9**) or (**14**) and carboxylic acid esters or acid chlorides.[6] For example, addition of dianion (**9**) to ethyl heptanoate gave a 22% yield of the ketone (**23**) along with the double addition product (**24**) in a similar yield, the remaining product present in the acidic fraction being the starting acid. The reactions of dianion (**9**) with aldehydes and ketones are fast enough to allow selective condensations; thus, addition of dianion (**9**) to one equivalent each of n-heptanal and ethyl heptanoate at −78 °C resulted in exclusive attack on the aldehyde. We were therefore led to use a condensation with an appropriate aldehyde and then oxidise the initial product to the required ketone (**22**). We chose to use the dioxolane (**27**) which was readily prepared in six steps



(**23**) (**24**)



(**25**) (**26**) **a**; R = H **b**; R = $CH_2CH{:}CH_2$ (**27**)



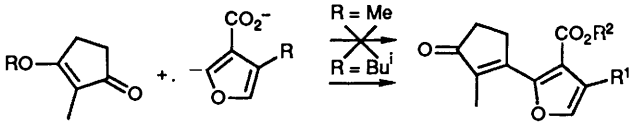
(**28**) **a**; R^1 = OH; R^2 = H **b**; R^1, R^2 = O (**29**) (**30**)

from dimethyl maleate. Radical Michael addition[12] of propanal to diethyl maleate gave the keto-diester (**25**) which was subsequently decarboxylated by heating in moist dimethyl sulphoxide[13] and protected as the dioxolane (**26a**). Enolisation and trapping using allyl bromide[14] in the presence of DMPU [1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)one][15] afforded the homologue (**26b**) which was finally converted to the aldehyde (**27**) by sequential lithium aluminium hydride reduction and oxidation using pyridinium chlorochromate (PCC) on alumina.[16]

Condensation of dianion (**14**) with aldehyde (**27**) afforded an excellent yield of the desired acid (**28a**) which was oxidised to the corresponding ketone (**28b**) using the Swern method.[17] Furfuryl alcohols are notoriously difficult to oxidise to the corresponding ketones owing to the ease with which they decompose or rearrange, especially to cyclopentenone derivatives.[18] The problem was somewhat compounded in our case

as we decided to leave the carboxylic acid residue unprotected because a corresponding ester function could interfere with the subsequent intramolecular aldol condensation. Many methods failed, including MnO_2–CH_2Cl_2 (presumably the free acid group caused the substrate to be irreversibly absorbed by the reagent), $BaMnO_4$–CH_2Cl_2, PCC, pyridinium dichromate (PDC), and Jones reagent. The successful Swern oxidation had the additional complication that some of the product was converted to the corresponding methylthiomethyl ester, necessitating the inclusion of an alkaline hydrolysis step. Deprotection to give the diketone (**29**) was effected using warm aqueous formic acid (stronger acids caused destruction of the furan ring), and the final, key, intramolecular aldol condensation was performed by prolonged treatment of the diketone with 1.5M aqueous potassium hydroxide. After esterification using diazomethane and column chromatography, the furyl cyclopentenone (**30**) was isolated in at best *ca.* 27% overall yield based on the starting furancarboxylic acid (**15**).

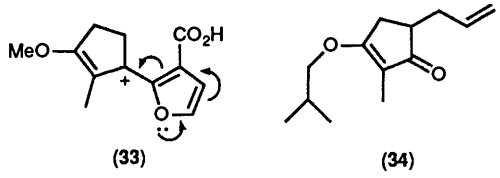
At this stage, we were able to shorten this rather lengthy sequence by taking advantage of the established route to 3-substituted cyclopentenones consisting of condensations between a nucleophile and a 3-alkoxycyclopentenone followed by acid-catalysed hydrolysis and dehydration. We were discouraged from using this route by the observation[6,19] that the dianion (**9**), while appearing to react with the methoxy



(**31**) **a**; R = Me
b; R = Bu^i

(**9**); R = H
(**14**); R = Me

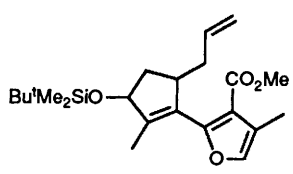
(**32**) **a**; $R^1 = R^2 = H$
b; R^1 = Me; R^2 = H
c; $R^1 = R^2$ = Me



(**33**) (**34**)

cyclopentenone (**31a**), gave none of the expected product (**32a**) upon acidic work-up under a variety of conditions. Extensive destruction of the furan ring occurred, presumably owing to preferential involvement of the furan oxygen lone pair in stabilising the intermediate cyclopentyl carbonium ion (**33**) and hence leaving the furan ring open to nucleophilic attack. By a simple but crucial change to the corresponding isobutyl derivative (**31b**),[20] a trial reaction succeeded in producing a good yield of the model cyclopentenone (**32b**) when the reaction mixture was worked up using aqueous citric acid; the facile loss of the isobutyl group as isobutene presumably accounts for this. The parent 2-furyl-lithium is also known to react similarly with the cyclopentenone (**31b**).[21] The substituted vinylogous ester (**34**) was therefore required; this was readily obtained in excellent yield by kinetic deprotonation and alkylation using allyl bromide of the cyclopentenone (**31b**). Subsequent condensation with dianion (**14**), acidification, esterification (CH_2N_2) and purification by column chromatography gave a much improved yield of 62% of the desired furyl cyclopentenone (**30**).

Protection of the ketone function in the cyclopentenone (**30**), prior to hydroboration–oxidation of the allyl side chain, proved difficult. Attempts using standard acid-catalysed methods in combination with ethylene glycol or propane-1,3-dithiol led to destruction of the furan ring while only very poor yields of the desired dioxolane were obtained using milder methods [*e.g.* 1,2-bis(trimethylsilyloxy)ethane, trimethylsilyl trifluoromethanesulphonate catalyst].[22] We therefore elected to reduce the ketone to the corresponding alcohol and protect this function as the t-butyldimethylsilyl ether (**35**). Hydroboration of the ether (**35**) and direct oxidation of the intermediate trialkylborane species using either PDC[23] or PCC[24] gave, respectively, a low (*ca.* 10%) yield of the corresponding acid (**36c**) and none of the expected aldehyde (**36b**). That the problem was associated with the oxidation step was evident from the realisation of an 84% yield of the alcohol (**36a**) by hydroboration of the ether (**35**) using bis(1,2-dimethylpropyl)borane.[25] Both PDC and PCC oxidations of the alcohol (**36a**) caused destruction of the furan ring. After a number of trials, the best sequence leading to diester (**36d**) found was a two-step oxidation firstly using Fetizon's reagent[26] to give the aldehyde (**36b**) and then brief treatment with ice-cold Jones reagent[27] followed by diazomethane. The overall yield was, however, only 21% and this was complicated by the unexpected lability of diester (**36d**). A small



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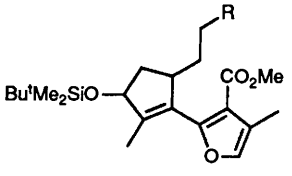
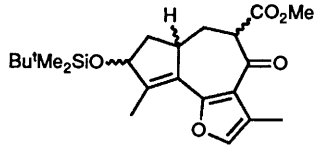


(**36**) **a**; R = CH_2OH
b; R = CHO
c; R = CO_2H
d; R = CO_2Me



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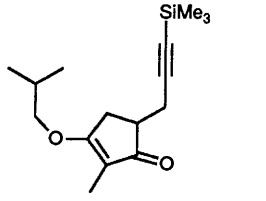
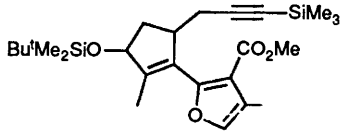


(**38**)

(**39**)

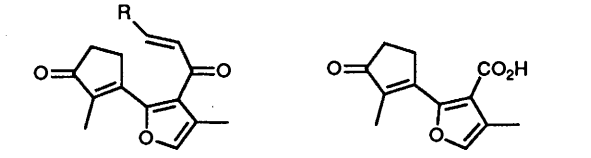


(**40**)

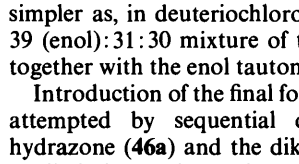
sample of the latter was successfully cyclised [lithium diisopropylamide (LDA) in tetrahydrofuran (THF); −78 °C; reflux, 5 h] to give the keto-ester (**37**) in moderate yield, thus indicating the viability of the Dieckmann step. However, the latter low yields together with sensitivity of some of the intermediates caused us to abandon this route.

An attempt to circumvent these oxidation steps was made using the more highly functionalised cyclopentenone (**38**) readily prepared from the isobutyl enol ether (**31b**) and the propynyl bromide (**39**)[28] using exactly the same conditions as for the synthesis of the allyl analogue (**34**). Hydroboration–oxidation using dicyclohexylborane–$H_2O_2/^-OH$[29] of the dianion adduct (**40**) was expected to lead directly to the required acid (**36c**). However, condensations between dianion (**14**) and enol ether (**38**) gave only traces of the expected adduct [*cf.* (**30**)], the major reaction apparently being deprotonation of the electrophile by the dianion, possibly α- to the acetylene function. In any event, a good yield of the starting acid (**15**) was recovered.

The ease with which the enol ether adducts (**30**) and (**32**) could be obtained prompted us to examine an alternative method of constructing the cycloheptanone residue by adding the extra two carbons required to the carboxylic acid function, rather than to the cyclopentenone, in the form of the vinyl ketones (**41**). These then could undergo an intramolecular aldol condensation by attack of C-4 of the cyclopentenone. We hoped that such a condensation would be guided by steric and electronic constraints to give directly gnididione (**4**) from (**41b**). Against these factors were the expected kinetic enolisation of C-5, cyclisation of which would lead to a rather strained bicyclo[5.2.1] system, whereas the thermodynamic enolate formed from the enone function would be expected to react at C-2 to give the deconjugated enone. We hoped, in the case of the dione (**41b**) at least, that cyclisation involving this centre would be disfavoured by the presence in the product of vicinal methyl groups. In the event, both vinyl ketones were obtained in excellent yields from the acid chloride derived from the acid (**42**) by palladium(0)-catalysed coupling with tetravinyltin and tetra-(prop-1-enyl)tin respectively.[30] However, attempts to cyclise these substrates using a variety of acids or bases, both weak and strong, led either to no cyclised materials or low to moderate yields (10–30%) of the C-2 cyclised products (**43**). At best, only traces of products with the required skeleton were detected.



(**41**) **a**; R = H
b; R = Me



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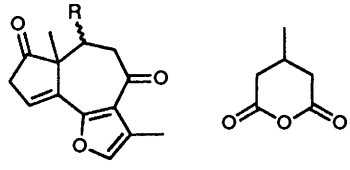
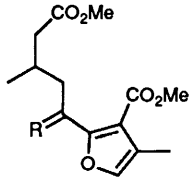
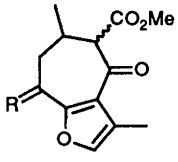


(**43**) **a**; R = H
b; R = Me

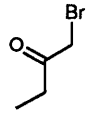
(**44**)



(**45**) **a**; R = O
b; R = $NNMe_2$



(**46**) **a**; R = $NNMe_2$
b; R = O



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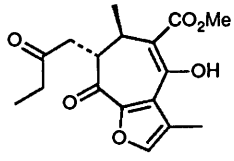
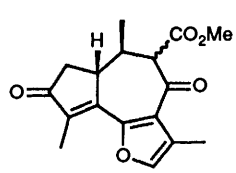


(**48**)

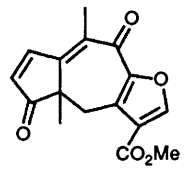
We therefore turned to a strategy wherein the cycloheptanone function was elaborated first [*i.e.* (**12**) + (**13**) followed by (**11**)]. In this, we were greatly aided by the observation made by Gammill and Hyde[31] that dianion (**9**) condensed cleanly with cyclic anhydrides to give furyl ketones directly. Hence, we were pleased to find that condensation of dianion (**14**) with 3-methylglutaric anhydride (**44**) followed by esterification of the crude product and column chromatography gave routinely a *ca.* 56% yield of the required diester (**45a**) along with *ca.* 20% recovered methyl 4-methylfuran-3-carboxylate. Attempts directly to cyclise keto-diester (**45a**) gave, rather than the required cycloheptanone, moderate yields of what appeared to be a furanocyclopentanedione resulting from attack of the ketone enolate onto the furano-carboxylate. Reduction of the keto-diester (**45a**) to the corresponding hydroxy-diester followed by silylation of the new hydroxy function gave a sensitive diester which underwent Dieckmann cyclisation in moderate yields only. In order to avoid the need for such a reduction–oxidation sequence and perhaps the low-yielding Dieckmann step, we decided to try alternatives for protecting the ketone function in keto-diester (**45a**) directly. From previous experience (*vide supra*) we knew that it was unlikely that this could be achieved using strongly acidic conditions. After a number of trials, the requirement for mild conditions led us to the dimethylhydrazone derivative (**45b**) which was formed in good yield as a mixture of (*Z*)- and (*E*)-isomers by heating the keto-diester (**45a**) with 1,1-dimethylhydrazine in ethanol containing a trace of glacial acetic acid. The key Dieckmann cyclisation was also effected in good yield using sodium bis-(trimethylsilyl)amide in ether at reflux, a reportedly optimum set of conditions for such intramolecular condensations.[32] Deprotection of the initial product (**46a**) using methyl iodide in moist ethanol at reflux then provided the rather sensitive diketo-ester (**46b**). [Deprotection using $Cu(OAc)_2$ failed.] Analysis of the spectral data exhibited by the β-keto-ester (**46a**) was complicated by the presence both of (*Z*)- and (*E*)-hydrazone isomers, diastereoisomerism about the ester and methyl substituents, and *ca.* 25% of the corresponding enol tautomer. Proton NMR analysis of diketo-ester (**46b**) was somewhat simpler as, in deuteriochloroform, the compound existed as a 39 (enol):31:30 mixture of the two possible diastereoisomers together with the enol tautomer.

Introduction of the final four-carbon unit [*viz.* (**11**)] was then attempted by sequential double deprotonations of both hydrazone (**46a**) and the diketo-ester (**46b**) followed by direct *C*-alkylation using 1-bromobutan-2-one (**47**) and various protected derivatives. It seemed likely that the two most acidic sites in these substrates would be those adjacent to the C=X functions on the cycloheptane ring and not the α-furyl position, and further that the enolised β-keto-ester function should be relatively unreactive. Whereas double deprotonations of the hydrazone (**46a**) proved fruitless, treatment of diketo-ester (**46b**) with LDA (2.2 equiv.) in THF at −78 °C followed by the bromo-ketone (**47**) and hexamethylphosphoric triamide (HMPA) led directly to a good yield of the desired homologue (**48**). In contrast to the keto-ester (**46b**), this material existed in the enol form (**48**) to an extent of 85% in $CDCl_3$. Analysis of the 250 MHz proton NMR spectrum showed this enol tautomer to be essentially a single diastereoisomer which was assigned the *trans*-stereochemistry shown on the assumption that the electrophile (**47**) approached the rather flat dianion derived from diketo-ester (**46b**) on the opposite face to the substituent methyl group. Two diastereoisomeric forms of the keto tautomer of enol (**48**) in a ratio of 3:1 accounted for the bulk of the remaining resonances and these were assigned to the two epimers about the methoxycarbonyl function. Only a very minor amount (<4%) of material appeared to be epimeric at the butanone side chain.

The final aldol cyclisation was first attempted using aqueous potassium hydroxide in THF in the hope that saponification and decarboxylation of the methoxycarbonyl group would also occur under these conditions. However, only a low yield of isognididione (**5**) along with many other products was isolated. In contrast, treatment of dione (**48**) with potassium t-butoxide in THF–t-butyl alcohol[33] gave, in 67% isolated yield, the cyclopentenone (**49**) which, in contrast to the precursor (**48**), existed entirely in the keto form in deuteriochloroform as a 71:29 mixture of epimers about the ester function. Finally, saponification and decarboxylation using 1M aqueous potassium carbonate gave only (±)-gnididione (**4**), m.p. 102–103 °C, which was identical in all respects except rotation (IR, UV, ^1H



(49)



(50)

NMR, mass spectra) with the natural material.[2] In line with the foregoing aldol condensation attempt, when the final saponification was effected using aqueous potassium hydroxide, a poorer yield of diketonic material was obtained which consisted of a 1:4 mixture of gnididione (**4**) and isognididione (**5**). Isolation of the latter by column chromatography gave material which was identical according to ^{1}H NMR and mass spectroscopy with the naturally derived compound.[2]

During the latter stages of this work, the first total synthesis of racemic gnididione was reported by Jacobi and Selnick.[34,35] This route featured an elegant application of an (oxy-Cope)–(Diels–Alder)–(retro-Diels–Alder) sequence both to form the furan ring and to establish the complete ring system of the natural product. The close biosynthetic relationship between the furan function and the much more common α-methylenebutyrolactone group in the guaianes has also been exemplified in synthetic approaches to examples of the latter group which feature the use of furanoid intermediates [*e.g.* (**50**) and reduction products thereof].[36] As in the synthesis reported herein, the furan ring is used as a template to build up the remaining ring systems but in addition also as a masked form of the sensitive lactone function. This present route to gnididione should therefore also be adaptable to the elaboration of guaiane α-methylenebutyrolactones.

Experimental

General Details.—M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. Unless otherwise stated, UV spectra were obtained using ethanol solutions and a Pye-Unicam SP 800 spectrometer and IR spectra obtained from thin films on sodium chloride plates using a Perkin-Elmer 710B spectrometer. ^{1}H NMR spectra were usually obtained using dilute solutions in deuteriochloroform and a Perkin-Elmer R32 instrument operating at 90 MHz or in some cases [δ_H(250)] using a Bruker WM-250 PFT instrument operating at 250 MHz. In all spectra, tetramethylsilane was used as the internal standard and line separations (J) are expressed in Hz. ^{13}C NMR spectra were also recorded using $CDCl_3$ solutions and the latter instrument at 62.8 MHz. Molecular weights were determined from mass spectra measured using either an A.E.I. MS 902 or a VG 7070 spectrometer, both operating in the electron impact mode at 70 eV.

All reactions were performed under an atmosphere of dry nitrogen where possible. Benzene, xylene, and ether were dried over sodium wire; dichloromethane, DMPU, HMPA, dimethyl sulphoxide (DMSO), di-isopropylamine, and triethylamine were all dried by distillation from calcium hydride and stored under nitrogen over freshly activated molecular sieves. THF was purified by distillation from benzophenone ketyl under nitrogen and the alcohols (MeOH, EtOH) by distillation from the corresponding magnesium alkoxides. All organic solutions were dried using magnesium sulphate. Light petroleum refers to the fraction of b.p. 60–80 °C unless otherwise noted.

Ethereal diazomethane was prepared from *N*-methyl-*N*-nitrosourea in the usual way. Unless otherwise stated, chromatography was carried out using columns of silica gel (Merck grade 9385) eluted with freshly distilled solvents.

4-Methylfuran-3-carboxylic Acid (**15**).—In our hands, the Diels–Alder reaction[8,9] between 4-phenyloxazole[8] and methyl tetrolate provided poorer overall yields of more difficult to purify methyl 4-methylfuran-3-carboxylate than a modification of the route described by Pelletier and co-workers.[10] Thus, itaconic acid (**16**) (130 g) was converted into aconic acid (**17**) as described by Campbell and Hunt.[11] Aconic acid (**17**) showed m.p. 157–159 °C (lit.,[11] m.p. 156 °C); δ_H[$CDCl_3$ + 10% $(CD_3)_2CO$] 5.21 (2 H, d, J 2, CH_2), 6.77 (1 H, t, J 2, C=CH_2), and 7.20 (1 H, br s, CO_2H). The overall yield was 44%.

The pyrazoline lactone (**18**) was prepared in 85–90% yield as previously described from aconic acid and ethereal diazomethane and showed m.p. 72–73 °C (ether) (lit.,[10] m.p. 69–70 °C); δ_H 3.38 (2 H, dd, J 9 and 2, CH_2N), 3.80 (3 H, s, CO_2CH_3), 4.93 (2 H, dd, J 5 and 2, CH_2O), and 5.00–5.40 (1 H, m, CH).

The pyrazoline lactone (**18**) (2–3 g portions) was added to dry xylene (15 ml), stirred and heated using an oil bath maintained at 140 °C. After nitrogen evolution had subsided (3–4 min), similar portions were added up to a total of 30 g. The cooled solution was vacuum distilled to give the furanone (**19**) (20.35 g, 80%), b.p. 75–80 °C at 0.25 mmHg (lit.,[10] b.p. 145–147 °C at 25 mmHg); δ_H 2.18 (3 H, t, J 2, :CCH_3), 3.90 (3 H, s, CO_2CH_3), and 4.91 (2 H, q, J 2, CH_2O).

The foregoing lactone (**19**) was reduced using di-isobutylaluminium hydride (1M in toluene) in THF solution as previously described[10] to provide methyl 4-methylfuran-3-carboxylate (>90% yield on a 5–10 g scale), b.p. 70–80 °C at 15 mmHg (lit.,[10] b.p. 64–66 °C at 12 mmHg); δ_H 2.24 (3 H, br s, 4-CH_3), 3.88 (3 H, s, CO_2CH_3), 7.29 (1 H, br q, J *ca.* 1.5, 5-H), and 7.90 (1 H, m, 2-H).

Methyl 4-methylfuran-3-carboxylate (3.08 g, 22 mmol) and aqueous potassium hydroxide [1.36 g in water (12 ml)] were stirred together for 18 h at 20 °C. The resulting solution was diluted with water (20 ml) and washed with ether (20 ml) then cooled in ice and acidified with 2M hydrochloric acid. The mixture was extracted with ether (3 × 30 ml) and the combined extracts were washed with water (20 ml) then dried and evaporated. Crystallisation of the residue from toluene–light petroleum (1:3 v/v) gave 4-methylfuran-3-carboxylic acid (**15**) (2.50 g, 90%) as a colourless powder, m.p. 136–137 °C (lit.,[10] m.p. 138–139 °C); δ_H 2.24 (3 H, d, J *ca.* 1.5, 4-CH_3), 7.33 (1 H, br q, J *ca.* 1.5, 5-H), and 8.10 (1 H, m, 2-H).

2-Deuterio-4-methylfuran-3-carboxylic Acid (**20**).—n-Butyllithium (1.22 ml of a 1.8M solution in hexanes, 2.2 mmol) was added to dry di-isopropylamine (0.3 ml, 2.2 mmol) stirred at −10 °C under nitrogen. After 0.25 h, the mixture was cooled in a dry ice–acetone bath, diluted with dry THF (2.5 ml), and treated dropwise *via* a syringe with a solution of 4-methylfuran-3-carboxylic acid (0.162 g, 1 mmol) in THF (1.5 ml).[6] After 0.5 h at this temperature, deuterium oxide (1 ml) was added and the mixture allowed to warm to ambient temperature during 0.5 h. The resulting solution was acidified with 2M hydrochloric acid and extracted with ether (3 × 10 ml). The combined extracts were washed with water (10 ml) and saturated brine (10 ml) then dried and evaporated to leave the deuteriated acid (**20**) (0.126 g, 99%), m.p. 136–138 °C; δ_H 2.21 (3 H, br s, 4-CH_3) and 7.33 (1 H, m, 5-H), m/z 127 (M^+, 100%), 110 (49), 81 (28), and 57 (24).

Less than 5% of undeuteriated material was detected by ^{1}H NMR spectroscopy (δ_H 8.10, 2-H).

Ethyl 3-(2-Ethyl-1,3-dioxolane-2-yl)propanoate (**26a**).—A solution of diethyl 2-(1-oxopropyl)butanedioate (**25**)[12] (85 g), dimethyl sulphoxide (600 ml), and water (7 ml)[13] was refluxed for 4 h, then cooled and continuously extracted with n-hexane for 24 h. The hexane extract was washed with water (100 ml),

dried, and evaporated. Distillation of the residue then gave ethyl 4-oxohexanoate (112.6 g, 95%), b.p. 105–110 °C at 16 mmHg (lit.,[12] b.p. 109–112 °C at 18 mmHg); δ_H 1.08 (3 H, t, *J* 7, 6-CH_3), 1.26 (3 H, t, *J* 7, OCH_3), 2.53 (2 H, q, *J* 7, 5-CH_2), 2.65 (2 H, t, *J* 5, CH_2CO), 2.70 (2 H, t, *J* 5, CH_2CO), and 4.15 (2 H, q, *J* 7, OCH_2CH_3).

A solution of ethyl 4-oxohexanoate (37.3 g, 240 mmol), ethylene glycol (27 ml, 480 mmol) and toluene-*p*-sulphonic acid monohydrate (0.02 g, 0.1 mmol) in benzene (250 ml) was refluxed under a Dean and Stark water separator for 24 h. The cooled solution was poured into 1M aqueous potassium hydroxide (100 ml), the organic layer separated, and the aqueous layer extracted with benzene (2 × 50 ml). The combined benzene solutions were washed with water (100 ml) and saturated brine (100 ml), then dried and evaporated, and the residue distilled to give the *dioxolane* (**26a**) (36.7 g, 76%) as a colourless oil, b.p. 75–76 °C at 0.1 mmHg, which showed ν_{max} 1 730 cm^{-1}; δ_H 1.08 (3 H, t, *J* 7, CCH_2CH_3), 1.26 (3 H, t, *J* 7, OCH_2CH_3), 2.40–2.81 (6 H, m, 3 × CH_2), 3.98 (4 H, m, 2 × CH_2O), and 4.15 (2 H, q, *J* 7, OCH_2CH_3); *m/z* 202 (M^+, 40%) and 173 (100) (Found: C, 59.5; H, 9.1. $C_{10}H_{18}O_4$ requires C, 59.4; H, 8.9%).

Ethyl 2-(2-*Ethyl*-1,3-*dioxolan*-2-*ylmethyl*)*but*-3-*enoate* (**26b**).—Lithium di-isopropylamide [from n-butyl-lithium (46.9 ml of 1.6M solution in hexanes) and di-isopropylamine (10.2 ml), 75 mmol] in THF (75 ml) was prepared as described above. The solution was cooled in dry ice–acetone and treated dropwise with a solution of the foregoing ester (**26a**) (15.15 g, 75 mmol) in THF (25 ml).[14] After 0.5 h at this temperature, allyl bromide (7.9 ml, 90 mmol) and DMPU (0.96 ml, 75 mmol)[15] were added simultaneously. After a further 0.5 h at < −70 °C, the solution was poured into saturated aqueous ammonium chloride (250 ml) and the resulting mixture extracted with ether (3 × 100 ml). The combined extracts were washed with water (100 ml) then dried and evaporated. A ^1H NMR spectrum of the residue indicated > 80% conversion to the desired product. Careful distillation employing a Vigreux column gave, following a forerun of the starting ester (**26a**) (1.8 g), the *allyl derivative* (**26b**) (13.07 g, 72%), as a colourless oil, b.p. 88–90 °C at 0.4 mmHg; ν_{max} 1 723 and 1 640 cm^{-1}; δ_H 0.90 (3 H, t, *J* 7, CCH_2CH_3), 1.26 (3 H, t, *J* 7, OCH_2CH_3), 1.50–2.75 (7 H, m), 3.95 (4 H, s, 2 × CH_2O), 4.16 (2 H, q, *J* 7, OCH_2CH_3), 4.95–5.22 (2 H, m, :CH_2), and 5.55–6.03 (1 H, m, :CH) (Found: C, 64.1; H, 8.9; M^+, 242.1510. $C_{13}H_{22}O_4$ requires C, 64.5; H, 9.1%; *M*, 242.1518).

2-(2-*Ethyl*-1,3-*dioxolan*-2-*ylmethyl*)*pent*-4-*enal* (**27**).—The foregoing ester (**26b**) (4.57 g, 18.9 mmol) in dry ether (10 ml) was added dropwise to a vigorously stirred suspension of lithium aluminium hydride (0.79 g, 20.8 mmol) in dry ether. After 10 min, saturated aqueous amonium chloride (100 ml) was carefully added and the ether layer separated. The aqueous layer was extracted with fresh ether (2 × 50 ml) and the combined ether solutions were washed with water (100 ml) then dried and evaporated, and the residue distilled to give 2-*ethyl*-1,3-*dioxolan*-2-*ylmethylpent*-4-*en*-1-*ol* (3.4 g, 90%) as a colourless oil, b.p. 83–84 °C at 0.3 mmHg; ν_{max} 3 450 and 1 640 cm^{-1}; δ_H 0.91 (3 H, t, *J* 7, CCH_2CH_3), 1.53–2.22 (6 H, m, 3 × CH_2), 3.08–3.26 (1 H, m, $CHCH_2OH$), 3.46–3.73 (2 H, m, CH_2OH), 4.02 (4 H, s, 2 × CH_2O), 4.95–5.21 (2 H, m, :CH_2), and 5.61–6.01 (1 H, m, :CH) (Found: C, 66.1; H, 10.1. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.0%).

The foregoing alcohol (1.0 g, 5 mmol) was stirred with pyridinium chlorochromate on alumina (12.6 g, 10 mmol)[16] in dry benzene (15 ml) at ambient temperature for 24 h. The suspension was filtered, the solid washed with dry ether (3 × 20 ml), and the combined filtrates were evaporated. Distillation of the residue gave the aldehyde (**27**) (0.85 g, 86%) as a colourless oil, b.p. 70–75 °C at 0.6 mmHg; ν_{max} 1 715 and 1 640 cm^{-1}; δ_H 0.91 (3 H, t, *J* 7, CCH_2CH_3), 1.53–2.22 (6 H, m, 3 × CH_2), 3.22–3.40 (1 H, m, $CHCHO$), 4.02 (4 H, s, 2 × CH_2O), 4.95–5.21 (2 H, m, :CH_2), 5.61–6.01 (1 H, m, :CH), and 9.57 (1 H, d, *J* 3, CHO). The sample appeared to be >95% pure according to the ^1H NMR spectrum and was used immediately in the next step.

2-[2-(2-*Ethyl*-1,3-*dioxolan*-2-*ylmethyl*)-1-*hydroxypent*-4-*enyl*]-4-*methylfuran*-3-*carboxylate* (**28a**).—n-Butyl-lithium (1.99M in hexane; 1.16 ml, 2.3 mmol) was added dropwise to di-isopropylamine (0.32 ml, 2.3 mmol) stirred at −10 °C under nitrogen. After 0.25 h, THF (1 ml) was added and the solution cooled in a dry ice–acetone bath. 4-Methylfuran-3-carboxylic acid (**15**) (0.126 g, 1 mmol) in THF (2.5 ml) was added dropwise followed by, after 0.5 h, a solution of the aldehyde (**27**) (0.2 g, 1.01 mmol) in THF (1 ml). The solution was immediately decolourised. The cooling bath was removed and after 1 h, the mixture was acidified with dilute aqueous citric acid (10 ml) and extracted using ether (3 × 15 ml). The combined extracts were washed with water (15 ml), dried, and evaporated to give the acid (**28a**) (0.305 g, 94%) which was adjudged to be sufficiently pure for use in the next step.

An analytical sample was obtained by treatment of the crude acid (0.19 g) with excess of ethereal diazomethane at ambient temperature for 1 h. Evaporation of the resulting solution followed by column chromatography over silica gel with ethyl acetate–light petroleum (3:7 v/v) gave the corresponding *methyl ester* (0.17 g) as a colourless oil and mixture of diastereoisomers, ν_{max} 3 500, 1 720, and 1 640 cm^{-1}; δ_H 0.90 (3 H, t, *J* 7, CCH_2CH_3), 1.10–2.61 (7 H, m), 2.23 (3 H, br s, CH_3), 3.87 (3 H, s, CO_2CH_3), 3.92–4.03 (1 H, m, $CHOH$), 3.99 (4 H, s, 2 × CH_2O), 4.90–5.25 (2 H, m, :CH_2), 5.53–6.08 (1 H, m, :CH), and 7.21 (1 H, br s, furyl-5-H); *m/z* 338 (M^+, 100%) and 323 ($M - CH_3$, 88) (Found: C, 64.2; H, 7.8. $C_{18}H_{26}O_6$ requires C, 63.9; H, 7.7%).

Methyl 4-*Methyl*-2-(2-*methyl*-3-*oxo*-5-*prop*-2-*enylcyclopent*-1-*enyl*)*furan*-3-*carboxylate* (**30**).—(*a*) To a stirred solution of oxalyl chloride (0.2 ml, 2.18 mmol) in dry dichloromethane (10 ml) stirred at −60 °C under nitrogen was added dropwise dry dimethyl sulphoxide (0.34 ml, 4.75 mmol) in dichloromethane (2 ml).[17] After 5 min, the unpurified hydroxy-acid (**28a**) (0.32 g, 0.99 mmol) in dichloromethane (2 ml) was added dropwise followed, after 0.25 h, by triethylamine (0.67 ml, 4.95 mmol). After a further 5 min, the cooling bath was removed and the mixture allowed to warm to ambient temperature. Water (10 ml) was added, the dichloromethane layer separated, and the aqueous layer extracted with dichloromethane (2 × 10 ml). The combined organic solutions were washed successively with 10 ml aliquots each of 2M hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, water, and saturated brine, then dried and evaporated. The residue was stirred with aqueous potassium hydroxide [0.5 g in water (20 ml)] at ambient temperature for 12 h; after washing with ether (10 ml), the solution was acidified using 2M hydrochloric acid and extracted with ether (3 × 15 ml). The combined extracts were washed with water (10 ml) then dried and evaporated to leave the crude ketone (**28b**) (0.21 g), δ_H 0.88 (3 H, t, *J* 7, CCH_2CH_3), 1.61 (2 H, q, *J* 7, CH_2CH_3), 1.80 (2 H, dd, *J* 7 and 2, CH_2CH:), 2.02–2.62 (3 H, m, $CHCH_2$), 2.36 (3 H, br s, CH_3), 3.82 (4 H, s, 2 × CH_2O), 4.98–5.25 (2 H, m, :CH_2), 5.50–6.00 (1 H, m, :CH), and 7.53 (1 H, m, furyl-5-H); *m/z* 322 (M^+, 100%).

The ketone (**28b**) (25 g), formic acid (10 ml), water (10 ml), and THF (30 ml) were stirred together and heated to 50 °C (oil bath) for 3 h. After removal of most of the THF by rotary evaporation, the cooled residue was partitioned between water (100 ml) and ether (100 ml). The separated aqueous layer was

extracted with fresh ether (2 × 50 ml) and the combined extract washed with water (100 ml), dried, and evaporated to give the crude diketone (**29**) (2.0 g); δ_H 1.03 (3 H, t, *J* 7, CH_2CH_3), 2.30–2.70 (2 H, m), 2.36 (3 H, br s, furyl-4-CH_3), 2.37 (2 H, q, *J* 7, $COCH_2CH_3$), 2.85 (2 H, d, *J* 4, $COCH_2CH$), 3.00–3.11 (1 H, m), 4.96–5.25 (2 H, m, :CH_2), 5.50–6.00 (1 H, m, :CH), and 7.55 (1 H, m, furyl-5-H).

The diketone (**29**) (2.0 g) was stirred with 1.5M aqueous potassium hydroxide (50 ml) at ambient temperature under nitrogen for 5 days. After washing with ether (20 ml), the mixture was acidified with 2M hydrochloric acid and extracted with ether (3 × 20 ml). The combined extracts were washed with water (20 ml) then dried and treated with an excess of ethereal diazomethane for 1 h at ambient temperature. After evaporation, the residue was chromatographed over silica gel, with ethyl acetate–light petroleum (3:7 v/v) as eluant to give the *cyclopentenone* (**30**) [0.90 g; 29% from the hydroxy-acid (**28a**)] (R_f 0.5) as a pale yellow oil, λ_{max} 244, 308, and 328 (infl.) nm; ν_{max} 1 700 and 1 640 cm^{-1}; δ_H 1.86 (3 H, d, *J* 2, $CH_3CC{=}O$), 2.31 (3 H, d, *J ca.* 2, furyl-4-CH_3), 2.43 (2 H, app. dd, *J* 2 and 1.5, CH_2CH:), 2.65 (2 H, d, *J* 7, CH_2CO), 3.58–3.74 (1 H, m, $CHCH_2$), 3.95 (3 H, s, CO_2CH_3), 4.98–5.28 (2 H, m, :CH_2), 5.56–6.02 (1 H, m, :CH), and 7.53 (1 H, q, *J* 2, furyl-5-H); *m/z* 274 (M^+, 17%), 259 (5, *M* − CH_3), 247 (58), 233 (9, *M* − $CH_2CH{=}CH_2$), 215 (27, *M* − CO_2CH_3), 135 (52), 105 (21), 91 (46), and 67 (100) (Found: C, 69.8; H, 6.8. $C_{16}H_{18}O_4$ requires C, 70.1; H, 6.6%).

(*b*) 4-Methylfuran-3-carboxylic acid (**15**) (0.25 g, 2 mmol) was converted to the dianion (**14**) exactly as described above [(**28a**)] and to this was added the enol ether (**34**) (see below) (0.42 g, 2.02 mmol) in THF (1 ml). The cooling bath was removed and after 1 h, the mixture was diluted with water (10 ml) containing a few drops of 2M aqueous potassium hydroxide and washed with ether (10 ml). Acidification using solid citric acid was followed by extraction with ether (3 × 10 ml). The combined extracts were washed with water (20 ml) and saturated brine (10 ml) then dried, esterified, and purified as described in (*a*) to yield the cyclopentenone (**30**) (0.48 g, 62%) identical in all respects with material prepared using route (*a*).

Methyl 4-*Methyl*-2-(2-*methyl*-3-*oxocyclopent*-1-*enyl*)*furan*-3-*carboxylate* (**32c**).—Using exactly the same procedure described in (*b*) above for the preparation of the cyclopentenone (**30**), condensation between the dianion (**14**) (2 mmol) and the enol ether (**31b**) (2.05 mmol) gave the acid (**32b**) (0.31 g, 71%) as a viscous oil, sufficiently pure for the next steps (*vide infra*), which showed δ_H 1.93 (3 H, dd, *J ca.* 2.5 and 1, cyclopentenyl-2-CH_3), 2.36 (3 H, d, *J ca.* 2, furyl-4-CH_3), 2.49–2.62 (2 H, m), 2.93–3.14 (2 H, m), and 7.56 (1 H, q, *J* 2, furyl-5-H). An analytical sample was secured by esterification using ethereal diazomethane followed by chromatography over silica gel with ethyl acetate–light petroleum (1:2 v/v) as eluant to give the *ester* (**32c**) (93%) as a pale yellow oil, ν_{max} 1 697 cm^{-1}; δ_H 1.90 (3 H, dd, *J ca.* 2.5 and 1, cyclopentenyl-2-CH_3), 2.20 (3 H, d, *J ca.* 2, furyl-4-CH_3), 2.46–2.62 (2 H, m), 2.86–3.06 (2 H, m), 3.91 (3 H, s, CO_2CH_3), and 7.46 (1 H, q, *J* 2, furyl-5-H); *m/z* 234 (M^+, 20%), 203 (21), 175 (37), 135 (10), 105 (26), and 67 (100) (Found: C, 66.9; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.6; H, 6.0%).

2-*Methyl*-3-(2-*methylpropoxy*)-5-(*prop*-2-*enyl*)*cyclopent*-2-*en*-1-*one* (**34**).—Lithium di-isopropylamide [from Bu^nLi (2.0 ml of a 1.65M solution in hexanes, 3.3 mmol) and di-isopropylamine (0.45 ml, 3.3 mmol)] in THF (5 ml) was maintained under nitrogen in a dry ice–acetone bath while a solution of the isobutyloxy enol ether (**31b**)[20] (0.5 g, 3 mmol) in THF (5 ml) was added dropwise. The resulting orange solution was stirred at this temperature for 0.5 h, then treated with allyl bromide (0.28 ml, 3.3 mmol) and HMPA (0.52 ml, 3 mmol).[14] After a further 0.5 h, the solution was poured into saturated aqueous ammonium chloride (20 ml) and the resulting mixture extracted with ether (3 × 15 ml). The combined extracts were washed with water (2 × 10 ml) and saturated brine (10 ml), then dried and evaporated. Distillation of the residue gave the *ether* (**34**) (0.59 g, 95%), as a colourless oil, b.p. 130–131 °C at 0.5 mmHg; λ_{max} 252 nm; ν_{max}(CCl_4) 1 690 and 1 630 br cm^{-1}; δ_H 1.01 [6 H, d, *J* 7, $(CH_3)_2CH$], 1.62 (3 H, t, *J* 1, 2-CH_3), 1.80–3.00 (6 H, m), 3.97 (2 H, d, *J* 7, CH_2O), 4.97–5.26 (2 H, m, :CH_2), and 5.56–6.04 (1 H, m, :CH); *m/z* 208 (M^+, 34%), 152 (57), 137 (13), 124 (13), 112 (36), 83 (24), and 57 (100) (Found: C, 74.7; 9.8. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.6%).

Methyl 2-[3-(*Dimethyl*-*t*-*butylsilyloxy*)-2-*methyl*-5-*prop*-2-*enylcyclopent*-1-*enyl*]-4-*methylfuran*-3-*carboxylate* (**35**).—The ketone (**30**) (1.26 g, 4.6 mmol) in methanol (25 ml) was treated with sodium borohydride (0.15 g) until TLC indicated completion of the reduction (*ca.* 0.5 h). The methanol was evaporated off and the residue partitioned between ice–cold 2M hydrochloric acid (15 ml) and ether (30 ml). The separated aqueous layer was extracted with ether (2 × 20 ml) and the combined organic solutions were washed with water (20 ml) then dried and evaporated to give the expected alcohol (1.16 g, 91%) as an unstable oil, and mixture of diastereoisomers, R_f 0.35 [EtOAc–light petroleum (3:7)]; δ_H 1.75 (3 H, d, *J* 2, cyclopentenyl-2-CH_3), 1.84–2.80 (4 H, m, cyclopentenyl-CH_2 and CH_2CH:), 2.20 (3 H, d, *J ca.* 2, furyl-4-CH_3), 3.45–3.59 (1 H, m, cyclopentenyl-5-CH), 3.84 (3 H, s, CO_2CH_3), 4.50–4.79 (1 H, CHOH), 4.85–5.21 (2 H, m, :CH_2), 5.47–6.03 (1 H, m, :CH), and 7.26 (1 H, q, *J ca.* 2, furyl-5-H).

The foregoing alcohol (1.13 g, 4.1 mmol), triethylamine (0.63 ml, 4.51 mmol), chlorodimethyl-t-butylsilane (0.68 g, 4.51 mmol), and *N*,*N*-dimethylaminopyridine (10 mg) were stirred together in dry dichloromethane at ambient temperature for 12 h. Evaporation and chromatography of the residue over silica gel with ethyl acetate–light petroleum (1:4 v/v) as eluant gave the silyl ether (**35**) (1.28 g, 80%) as a colourless oil, R_f 0.75, and as a 3:1 mixture of diastereoisomers. The mixture showed λ_{max} 278 nm and ν_{max} 1 710 cm^{-1} while the major diastereoisomer showed δ_H (250) 0.09 (3 H, s, CH_3Si), 0.11 (3 H, s, CH_3Si), 0.92 (9 H, s, Bu^tCSi), 1.46 (1 H, dd, *J* 13 and 7, 4′-H), 1.65 (3 H, m, 2′-CH_3), 1.91–2.20 (2 H, m, CH_2CH:), 2.01–2.30 (1 H, m, 5′-H), 2.17 (3 H, d, *J* 1.2, 4-CH_3), 2.47 (1 H, dd, *J* 13 and 7.5, 4′-H), 3.78 (3 H, s, OCH_3), 4.66 (1 H, br t, *J* 6, 3′-CH), 4.89–4.98 (2 H, m, :CH_2), 5.62–5.73 (1 H, m, :CH), and 7.16 (1 H, q, *J* 1.2, 5-H) (primes refer to the cyclopentenyl unit); δ_C −4.71 (CH_3Si), −4.37 (CH_3Si), 9.85 (q), 13.2 (q), 18.17 ($SiCMe_3$), 25.91 ($SiCMe_3$), 39.02 (t), 39.61 (t), 44.17 (5′-C), 51.02 (OCH_3), 79.55 (3′-CO), 115.50 (s), 115.60 (:CH_2), 121.48 (s), 130.95 (s), 136.83 (d), 139.09 (d), 145.97 (s), 156.35 (s), and 164.59 (C=O). The isomer ratio was determined by integration of the cyclopentenyl-3′-CH resonances at δ 4.66 and δ 4.80 (minor). The mixture also exhibited *m/z* 390 (M^+, 24%), 375 (21), 349 (100), 333 (58), 259 (31), 227 (45), 75 (47), and 73 (81) (Found: C, 67.9; H, 8.5. $C_{22}H_{34}O_4Si$ requires C, 67.7; H, 8.7%).

Methyl 2-[3-(*Dimethyl*-*t*-*butylsilyloxy*)-5-(3-*hydroxypropyl*)-2-*methylcyclopent*-1-*enyl*]-4-*methylfuran*-3-*carboxylate* (**36a**).—Bis(1,2-dimethylpropyl)borane (0.22 ml of a 1.92M solution in ether)[25] was added dropwise *via* a syringe to a solution of the unsaturated ester (**35**) (0.17 g, 0.43 mmol) in ether (0.5 ml) maintained at 0 °C under nitrogen. After 2 h at this temperature, the solvent was evaporated off and the residue dissolved in ice–cold methanol (2 ml). Following the addition of cold 3M aqueous sodium hydroxide (0.2 ml), hydrogen peroxide (30%; 0.2 ml) and additional sodium hydroxide (0.2 ml) were added. The resulting mixture was extracted with ether (3 × 10 ml) and the combined extracts were washed with water (20 ml)

then dried and evaporated to give the *alcohol* (**36a**) (0.15 g, 84%), as a colourless oil, b.p. 120–130 °C at 0.1 mmHg; λ_{max} 278 nm; ν_{max} 3 500 and 1 700 cm^{-1}; δ_H 0.07 (3 H, s, CH_3Si), 0.09 (3 H, s, CH_3Si), 0.91 (9 H, s, $SiCMe_3$), 1.30–1.59 (4 H, m), 1.64 (3 H, m, 2′-CH_3), 1.95–2.07 (1 H, m), 2.14 (3 H, d, *J* 1.2, 4-CH_3), 2.99–3.05 (1 H, br s, OH), 3.50 (2 H, dt, *J* 13 and 7, CH_2CH_2O), 3.50–3.56 (2 H, m, CH_2O), 3.79 (3 H, s, OCH_3), 4.65 (1 H, br t, *J* 7, 3′-H), and 7.15 (1 H, q, *J* 1.2, 5-H) (primes refer to the cyclopentenyl unit) (major diastereoisomer); *m/z* 408 (M^+, 13%), 393 (20), 349 (44), 276 (9), 259 (11), 245 (24), 227 (41), 199 (26), and 75 (100) (Found: C, 64.9; H, 8.9. $C_{22}H_{36}O_5Si$ requires C, 64.7; H, 8.8%).

Methyl 2-{3-(*Dimethyl-t-butylsilyloxy*)-5-[2-(*methoxycarbonyl*)*ethyl*]-2-*methylcyclopent*-1-*enyl*}-4-*methylfuran*-3-*carboxylate* (**36d**).—The alcohol (**36a**) (0.15 g, 0.36 mmol) was refluxed with Fetizon's reagent (2.06 g, 3.62 mmol)[26] in benzene (10 ml) for 12 h. The cooled mixture was filtered and the solid washed with benzene (2 × 20 ml). The combined filtrates were evaporated and the residue chromatographed over silica gel with ethyl acetate–light petroleum (3:7 v/v) as eluant to give the *aldehyde* (**36b**) (0.045 g, 30%), R_f 0.90; λ_{max} 278 nm; ν_{max} 1 700br and 1 600 cm^{-1}; δ_H 0.09 (3 H, s, CH_3Si), 0.07 (3 H, s, CH_3Si), 0.91 (9 H, s, $SiCMe_3$), 1.30–1.59 (4 H, m), 1.64 (3 H, m, 2′-CH_3), 1.95–2.07 (1 H, m), 2.14 (3 H, d, *J* 1.2, 4-CH_3), 3.50–3.55 (2 H, m), 3.79 (3 H, s, OCH_3), 4.65 (1 H, br t, *J* 7, 3′-H), 7.15 (1 H, q, *J* 1.2, 5-H), and 9.65 (1 H, br t, *J ca.* 2, CHO); *m/z* 406 (M^+, 24%), 349 (29), 293 (21), 199 (49), 131 (61), 91 (11), 75 (100), and 73 (76). A quantity of the starting alcohol (0.030 g, 20%) was also recovered.

Jones reagent[27] was added dropwise to a stirred solution of the foregoing aldehyde (**36b**) (0.1 g, 0.25 mmol) in acetone (3 ml) at 0 °C. As soon as a permanent orange colour appeared, the solution was partitioned between water (10 ml) and chloroform (5 ml). After separation, the aqueous layer was extracted with fresh chloroform (2 × 5 ml) and the combined organic solutions were dried and evaporated. The residue was treated with excess of ethereal diazomethane (1 h; 0 °C) and the material isolated after evaporation chromatographed over silica gel with ethyl acetate–light petroleum (1:4 v/v) as eluant to give the *diester* (**36d**) (0.074 g, 69%), R_f 0.41; λ_{max} 275 nm; ν_{max} 1 710br cm^{-1}; δ_H 0.09 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.86 (9 H, s, $SiCMe_3$), 1.30–1.59 (3 H, m), 1.60 (3 H, m, 2′-CH_3), 1.95–2.07 (1 H, m), 2.14 (3 H, m, 4-CH_3), 2.30–2.56 (3 H, m), 3.59 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 4.63 (1 H, br t, *J* 7, 3′-H), and 7.18 (1 H, m, 5-H) (Found: M^+, 436.2287. $C_{23}H_{36}O_6Si$ requires *M*, 436.2281).

Methyl 2-[4-(*Methoxycarbonyl*)-3-*methyl*-1-*oxobutyl*]-4-*methylfuran*-3-*carboxylate* (**45a**).—A solution of lithium di-isopropylamide [from n-butyl-lithium (41.6 ml of a 1.6M solution in hexanes; 66.6 mmol) and di-isopropylamine (9.39 ml, 67 mmol)] in THF (125 ml) was stirred under nitrogen and cooled in a dry ice–acetone bath while a solution of 4-methylfuran-3-carboxylic acid (**15**) (3.86 g, 30.6 mmol) in THF (25 ml) was added dropwise. The resulting yellow solution was stirred at this temperature for 40 min, then treated with a solution of 3-methylglutaric anhydride (**44**) [4.63 g, 36 mmol; freshly prepared from 3-methylglutaric acid (Aldrich) following treatment with acetic anhydride (reflux; 16 h), distillation (b.p. 120 °C at 1.0 mmHg), and crystallisation from ether] in THF (5 ml) during 5 min. The resulting darker mixture was stirred (with some difficulty) at the same temperature for 1.75 h then warmed to ambient temperature during 40 min and poured into a mixture of 1M hydrochloric acid (150 ml) and ether (70 ml). The separated aqueous phase was extracted with ether (2 × 100 ml) and the combined organic solutions were washed with saturated brine (150 ml) then dried and evaporated. The residual viscous oil was dissolved in dry methanol (250 ml) to which acetyl chloride (3 ml) had been added and the resulting yellow solution refluxed for 15 h then cooled and concentrated *in vacuo*. The residue was dissolved in ether (250 ml) and the resulting solution washed with saturated brine (2 × 60 ml) then dried and evaporated. The residue was chromatographed over silica gel with ethyl acetate–light petroleum (b.p. 40–60 °C) (30:70) as eluant to give the *diester* (**45a**) (4.8 g, 56%), as a pale yellow oil, λ_{max} 284.3 nm; ν_{max} 1 727 and 1 715 cm^{-1}; δ_H (250) 1.04 (3 H, d, *J* 6.7, CH_2CHCH_3), 2.10 (3 H, d, *J* 1.0, 4-CH_3), 2.26 (1 H, dd, *J* 15.2 and 7.5, $MeO_2CCH_AH_B$), 2.43 (1 H, dd, *J* 15.2 and 6.1, $MeO_2CCH_AH_B$), 2.62 (1 H, br octet, *J ca.* 6.8, CH_2CHCH_3), 2.80 (1 H, dd, *J* 16.5 and 7.1, $O{=}CCH_AH_B$), 2.94 (1 H, dd, *J* 16.5 and 6.4, $O{=}CCH_AH_B$), 3.66 (3 H, s, $CH_2CO_2CH_3$), 3.92 (3 H, s, 3-CO_2CH_3), and 7.30 (1 H, q, *J* 1.0, 5-H); *m/z* 282 (M^+, 5%), 251 (9), 222 (9), 209 (11), 182 (96), 177 (51), 167 (100), 150 (77), 143 (72), 137 (25), 115 (22), 109 (29), and 69 (79) (Found: C, 59.5; H, 6.5. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4%).

The final esterification step could equally well be carried out using ethereal diazomethane (0–20 °C; 1 h). Between 20 and 25% yields of methyl 4-methylfuran-3-carboxylate could be recovered either by chromatography or by vacuum distillation (*ca.* 60–80 °C at 1 mmHg) into a cold trap. Small samples of the diester (**45a**) were also purified by Kugelrohr distillation [b.p. 230 °C (oven temp.) at 0.8mmHg].

Methyl 2-[1-(*Dimethylhydrazono*)-4-(*methoxycarbonyl*)-3-*methylbutyl*]-4-*methylfuran*-3-*carboxylate* (**45b**).—A solution of the keto-diester (**45a**) (4.40 g, 15.6 mmol), 1,1-dimethylhydrazine (1.48 g, 24.6 mmol), and glacial acetic acid (5 drops) in dry ethanol (25 ml) was refluxed for a total of 6.5 h; after 1.5, 3, and 4.5 h additional aliquots of the hydrazine (0.84 g, 14 mmol) were added. The cooled solution was concentrated *in vacuo* and the residue purified by chromatography over neutral alumina (Grade II) with ethyl acetate–light petroleum (b.p. 40–60 °C) (15:85) as eluant to give the hydrazones (**45b**) (4.25 g, 84%) as a *ca.* 4:3 mixture of (*Z*)- and (*E*)-isomers, λ_{max} 272 and 293 (infl.) nm; ν_{max} 1 725br and 1 635 cm^{-1}; δ_H 0.93 and 1.00 (3:4 ratio of d, *J ca.* 6, CH_2CHCH_3), 2.12–2.22 (m, 4-CH_3), 2.46 and 2.56 (4:3 ratio of s, NMe_2), 3.66 (3 H, s, $CH_2CO_2CH_3$), 3.82 (3 H, s, 3-CO_2CH_3), and 7.22 and 7.25 (3:4 ratio of q, *J ca.* 1, 5-H); *m/z* 324 (M^+, 100%), 293 (20), 280 (77), 251 (26), 216 (40), 208 (29), 181 (20), 176 (27), 148 (27), 144 (54), 143 (31), 134 (29), and 59 (37) (Found: M^+, 324.1669. $C_{16}H_{24}N_2O_5$ requires *M*, 324.1685).

Methyl 3,6-*Dimethyl*-4,8-*dioxo*-5,6,7,8-*tetrahydro*-4H-*cyclohepta*[b]*furan*-5-*carboxylate* (**46b**).—A solution of the hydrazones (**45b**) (6.76 g, 20.9 mmol) in dry ether (45 ml) was added dropwise during 0.75 h to a stirred suspension of sodium bis(trimethylsilyl)amide (11.51 g, 62.9 mmol) in dry ether (1 000 ml) at reflux under nitrogen. The resulting orange-brown suspension was stirred and refluxed for a further 1.75 h then cooled in ice, treated with glacial acetic acid (30 ml), and washed with saturated brine (3 × 100 ml). The clear ether solution was dried and evaporated to give a red oil which was chromatographed over Grade III neutral alumina with ethyl acetate–light petroleum (b.p. 40–60 °C) (15:85) as eluant to give the hydrazones (**46a**) (3.78 g, 62%) as an orange oil containing a mixture of (*Z*)- and (*E*)-isomers (*ca.* 4:3), each of which existed in the enol form to an extent of *ca.* 25%, and of diastereoisomers of the keto forms. Spectroscopic features included λ_{max} 240, 256 (infl.), 293, 304, and 342 nm; ν_{max} 1 735 and 1 632 cm^{-1}; δ_H 0.80–1.37 (3 H, m, 6-CH_3), 2.05–2.20 (3 H, m, 3-CH_3), 2.53–2.62 (6 H, m, $N(Me_2)$), 3.59, 3.66, 3.76, and 3.78 (3 H, all s, CO_2CH_3), 7.20–7.28 (1 H, m, 2-H), and 13.24 (enolic OH); *m/z* 292 (M^+, 100%), 260 (17), 233 (11), 203 (9),

190 (14), 188 (13), 149 (12), 143 (12), 134 (12), 113 (12), 69 (21), and 51 (33) (Found: M^+, 292.1426. $C_{15}H_{20}N_2O_4$ requires M, 292.1423).

A solution of the foregoing hydrazones (0.28 g, 0.96 mmol) and iodomethane (3 ml) in 95% ethanol (2 ml) was refluxed for 8 h then cooled and evaporated *in vacuo*. Chromatography of the residue over silica gel with ethyl acetate–light petroleum (b.p. 40–60 °C) (25:75) as eluant gave the dione (**46b**) (0.157 g, 65%) as a yellow oil and a mixture of the enol form and two diastereoisomeric keto tautomers, λ_{max} 246, 249 (infl.), 294 (infl.), 309, and 342 (infl.) nm; $\nu_{max}(CHCl_3)$ 3 320br, 1 735, 1 665br, and 1 610 cm^{-1}; δ_H (250) 0.98 (1.17 H, d, J 7.4, 6-CH_3), 1.11 (0.90 H, d, J 6.9, 6-CH_3), 1.21 (0.93 H, d, J 7.1, 6-CH_3), 2.15 (0.93 H, d, J 1.08, 3-CH_3), 2.17 (0.90 H, d, J 1.11, 3-CH_3), 2.20 (1.17 H, d, J 0.99, 3-CH_3), 2.66–3.03 (3 H, m), 3.36 (0.39 H, dqd, J 13.8, 7.4, and 2.7, 6-H, enol), 3.64 (0.31 H, d, J 8.0, 5-H), 3.68 (0.93 H, s, OCH_3), 3.69 (0.90 H, s, OCH_3), 3.79 (1.17 H, s, OCH_3), 3.81 (0.30 H, d, J 2.2, 5-H), 7.37–7.39 (1 H, m, 2-H), and 13.30 (0.39 H, s, enol OH); m/z 250 (M^+, 100%), 235 (28), 219 (21), 218 (25), 203 (58), 191 (45), 190 (20), 180 (37), 177 (15), 176 (16), 175 (42), 162 (32), 150 (56), 122 (32), 109 (42), 94 (27), 91 (22), and 69 (53) (Found: M^+, 250.0829. $C_{13}H_{14}O_5$ requires M 250.0841). The ratios [39(enol):31:30] were determined by careful integration of the various first-order signals in the proton NMR spectrum.

Methyl trans-4-Hydroxy-3,6-dimethyl-8-oxo-7-(2-oxobutyl)-7,8-dihydro-6H-cyclohepta[b]furan-5-carboxylate (**48**).—The dione (**46b**) (0.50 g, 2.0 mmol) in dry THF (2 ml) was added dropwise *via* a syringe during 5 min to a stirred solution of lithium di-isopropylamide [from n-butyl-lithium (2.75 ml of a 1.6M solution in hexanes, 4.40 mmol) and di-isopropylamine (0.62 ml, 4.42 mmol)] in THF (12 ml) under nitrogen and cooled in a dry ice–acetone bath. The resulting orange solution was stirred at this temperature for 0.75 h by which time a heavy precipitate had formed. To this was added 1-bromobutan-2-one (**47**) (0.23 ml, 2.25 mmol) in THF (0.5 ml) dropwise during 5 min followed after a further 5 min by HMPA (2 ml). The now orange solution was stirred at the same temperature for 1.5 h then allowed to warm to ambient temperature during 0.5 h. The solution was diluted with ether (15 ml) and poured into 1M hydrochloric acid (15 ml). The phases were separated and the aqueous phase was extracted with ether (2 × 20 ml). The combined organic solutions were washed with water (2 × 15 ml) and saturated brine (2 × 15 ml) then dried and evaporated. Chromatography of the residue over silica gel with ethyl acetate–light petroleum (b.p. 40–60 °C) (10:90) as eluant gave the homologue (**48**) (0.35 g, 55%) as a yellow oil which in chloroform solution existed largely (85%) as the enol tautomer and which showed λ_{max} 246, 249 (infl.), 295 (infl.), 312.5, and 345 (infl.) nm; ν_{max} 3 100–2 700br, 1 714, 1 656br, and 1 610 cm^{-1}; δ_H (250) (enol) 1.02 (3 H, t, J 7.3, CH_3CH_2), 1.08 (3 H, d, J 7.4, 6-CH_3), 2.28 (3 H, d, J 1.1, 3-CH_3), 2.30–2.41 (2 H, m, CH_3CH_2), 2.50 (1 H, dd, J 16.7 and 4.6 O=CCH_AH$_B$), 2.69 (1 H, dd, J 16.7 and 10.1, O=CCH$_A$H$_B$), 3.24 (1 H, ddd, J 10.1, 5.4, and 4.6, 7-H), 3.45 (1 H, qd, J 7.4 and 5.4, 6-H), 3.82 (3 H, s, OCH_3), 7.46 (1 H, q, J 1.1, 2-H), and 13.47 (1 H, s, 4-OH); m/z 320 (M^+, 16%), 302 (16), 291 (21), 273 (15), 261 (41), 251 (14), 250 (16), 249 (50), 243 (26), 231 (27), 219 (26), 218 (16), 217 (100), 216 (20), 205 (12), 191 (15), 188 (23), 177 (28), 163 (27), 133 (12), 117 (19), 116 (16), 109 (21), 91 (14), 69 (34), 57 (58), and 55 (38) (Found: M^+, 320.1251. $C_{17}H_{20}O_6$ requires M, 320.1260).

The two diastereoisomers (*ca.* 3:1 ratio) of the *trans*-keto-ester tautomer gave resonances at δ_H 2.25 [d, J 1.1, (minor), 3-CH_3] and δ_H 2.27 [d, J 1.1, (major), 3-CH_3] together with δ_H 7.39 [q, J 1.1 (major), 2-H) and δ_H 7.44 [q, J 1.1 (minor), 2-H]. Traces (<4%) of what could be the corresponding *cis*-isomer (enol?) showed δ_H 2.17 and 2.18 (both d, J 1.1, 3-CH_3).

Methyl 3,6,9-Trimethyl-4,8-dioxo-4,5,6,6a,7,8-hexahydroazuleno[4,5-b]furan-5-carboxylate (**49**).—A suspension of potassium t-butoxide (0.0194 g, 0.173 mmol) in THF (6 ml) containing t-butyl alcohol (0.3 ml) was stirred under nitrogen at ambient temperature and treated with a solution of the dione-ester (**48**) (0.0184 g, 57.6 μmmol) in THF (1 ml) during 1 min. The resulting orange suspension was then stirred at 40 °C for 1.25 h, cooled in ice, and acidified using glacial acetic acid (1 ml). The yellow solution was diluted with ether (10 ml), washed with water (4 ml), and saturated brine (2 × 4 ml), then dried and evaporated. The residue was chromatographed over silica gel eluted with ethyl acetate–light petroleum (b.p. 40–60 °C) (15:85) to give the cyclopentenone (**49**) (0.012 g, 67%) as a yellow oil and a 71:29 mixture of epimers at the ester function, λ_{max} 234 (infl.), 241, 256, 259, 324 (infl.), 332 (infl.), 339, and 346 (infl.) nm; $\nu_{max}(CHCl_3)$ 1 737, 1 688br, and 1 582 cm^{-1}; δ_H (250) 1.19 (2.13 H, d, J 6.9, 6-CH_3), 1.26 (0.87 H, d, J 7.3, 6-CH_3), 2.09 (0.87 H, d, J 1.7, 9-CH_3), 2.11 (2.13 H, d, J 0.9, 9-CH_3), 2.17 (2.13 H, br s, 3-CH_3), 2.22 (0.87 H, br s, 3-CH_3), 2.35–2.61 (*ca.* 3.8 H, m), 2.75 (0.71 H, d, J 6.7), 2.79 (0.71 H, d, J 5.0), 2.85–2.96 (0.71 H, m), 3.60 (0.71 H, d, J 6.4, 5-H), 3.65 (2.13 H, s, OCH_3), 3.75 (0.87 H, s, OCH_3), 3.83 (0.29 H, d, J 3, 5-H), and 7.35–7.41 (1 H, m, 2-H); m/z 302 (M^+, 10%), 243 (100), 201 (36) and 174 (43) (Found: M^+, 302.1149. $C_{17}H_{18}O_5$ requires M, 302.1154).

cis-(+)-3,6,9-*Trimethyl-5,6,6a,7-tetrahydroazuleno*[4,5,b]-*furan-4,8-dione* [(+)-*Gnididione*] (**4**).—1M Potassium carbonate (0.2 ml) was added dropwise to a solution of the foregoing β-keto-ester (**49**) (0.020 g) in methanol (1.5 ml) and the resulting orange solution stirred at ambient temperature for 4 h then evaporated. Following the addition of saturated brine (10 ml) and acidfication to pH 1 using 2M hydrochloric acid, the product was extracted into ethyl acetate (3 × 8 ml). The combined extracts were dried and evaporated to give a residue, the proton NMR spectrum of which showed the presence of gnididione (**4**) [δ_H 1.12 (d, J 6.7, 6-CH_3] but not of isognididione (**5**) [δ_H 0.80 (d, J 6.8, 6-CH_3].[2] The crude product was chromatographed over silica gel with ethyl acetate–light petroleum (b.p. 40–60 °C) (10:90) as eluant to give, after crystallisation from aqueous methanol, (±)-gnididione (**4**) (0.013 g, 80%) as colourless solid, m.p. 102–103 °C [lit.,[2] m.p. for (+)-(**4**), 110–111 °C] which exhibited spectral data (UV, IR, ^1H NMR, and mass spectrum) identical with those reported for the natural material.[2] The sample was a single (>98%) diastereoisomer according to both ^1H and ^{13}C NMR spectra, the latter showing δ_H 9.80 (CH_3), 10.15 (CH_3), 21.35 (CH_3), 33.01 (CH), 40.86 (CH_2), 46.60 (CH), 54.14 (CH_2), 123.52 (C), 126.74 (C), 138.13 (C), 142.25 (2-CH), 153.65 (C), 154.24 (C), 195.94 (C=O), and 206.41 (C=O).

When the β-keto-ester (**49**) (0.06 g) was stirred with potassium hydroxide (0.017 g) in 90% aqueous methanol (0.3 ml) at ambient temperature for 16 h, work-up as described above gave a crude product which, according to its proton NMR spectrum contained a *ca.* 1:4 mixture of gnididione (**4**) and isognididione (**5**). Column chromatography as above gave isognididione (**5**) (0.012 g, 25%) as a gum (lit.,[2] amorphous solid) which showed spectral data (^1H NMR and mass) identical to those reported for naturally derived material.[2]

Acknowledgements

We thank the SERC for financial support.

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Paper 9/04947I
Received 20*th November* 1989
Accepted 12*th December* 1989