A Brief, Stereoselective Total Synthesis of the Guaiane Sesquiterpene (±)-Gnididione

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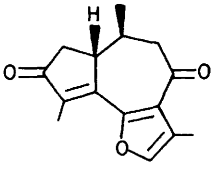
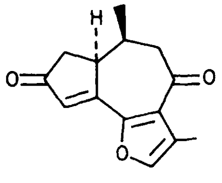
A total synthesis of the guaiane sesquiterpene (±)-gnididione (**1**) has been achieved using carbanion chemistry at each key stage.

Examples of guaiane and pseudoguaiane sesquiterpenes abound in Nature, the largest subgroup being those in which the isopropyl group attached to the central perhydroazulene ring system is present as part of a fused lactone ring, most often having an α-methylene substituent.[1] Gnididione (**1**)[2] is a unique member of the guaianes as it contains a furan function in place of the more common lactone ring. The compound was isolated from the plant *Gnidia latifolia* during Kupchan's extensive search for tumour inhibitors and the structure (**1**) (or its enantiomer) was proposed on the basis of spectral data and some chemical transformations, which included acid-catalysed epimerisation to isognididione (**2**). Subsequently, one other example of a guaiane furanosesquiterpene has been reported, linderazulene (**3**), which occurs in some deep-sea corals.[3] The validities of structures (**1**) and (**2**) have been confirmed by elegant total syntheses involving an (oxy-Cope)–(Diels–Alder)–(retro-Diels–Alder) sequence.[4] Herein, we report a rather brief alternative approach to both gnididione (**1**) and its epimer (**2**) in which all the key carbon–carbon bond formations were effected using carbanion chemistry. The basic strategy is indicated in Scheme 1. We envisaged that the dianion (**4**), derived[5] from the corresponding furoic acid, could be coupled to a six-carbon fragment which would eventually be used to elaborate the central cycloheptanone ring by a Dieckmann cyclisation onto the 3-carboxylate function of the furan. A four-carbon unit could be incorporated before or after coupling with the dianion (**4**) and used to form the cyclopentenone ring by an intramolecular aldol condensation. In the successful sequence outlined below, stereoselection was achieved by late introduction of this four-carbon fragment onto a furanocycloheptanedione.

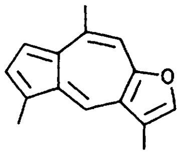
Our starting point was the preparation of 4-methyl-3-furoic



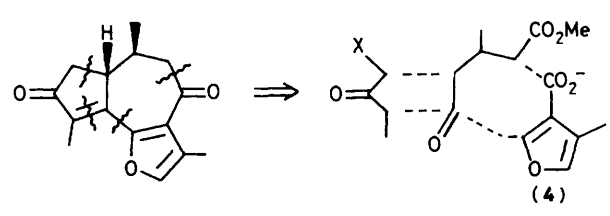
(**1**)



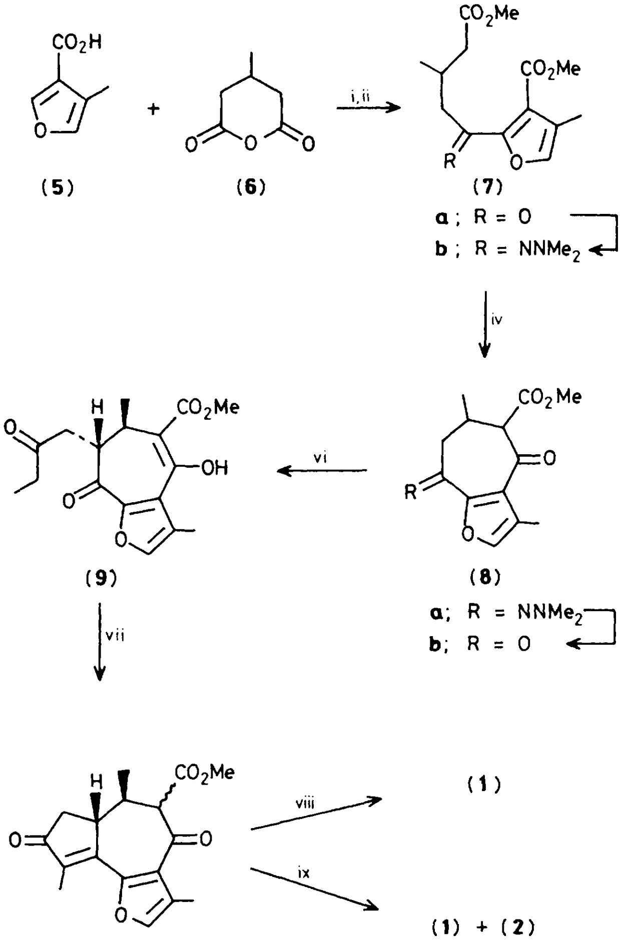
(**2**)



(**3**)



Scheme 1



Scheme 2. *Reagents:* i, 2 equiv. LDA, THF, −78 °C, 0.5 h, add (**6**), then −78 to 20 °C; ii, MeOH, HCl, heat or CH_2N_2, Et_2O; iii, Me_2NNH_2, EtOH, AcOH (cat.), heat, 6.5 h; iv, $NaN(SiMe_3)_2$, Et_2O, heat, 2 h; v, MeI (5 equiv.), EtOH, H_2O, heat, 8 h; vi, 2.2 equiv. LDA, THF, −78 °C, 40 min, then $BrCH_2C(O)Et$ (1.2 equiv.) and HMPA (*ca.* 5 equiv.), −78 °C, 1.5 h to 0 °C; vii, $KOBu^t$ (3 equiv.), $THF–Bu^tOH$ (20 : 1), 40 °C, 1.25 h; viii, K_2CO_3, $MeOH–H_2O$ (7.5 : 1), 20 °C, 4 h; ix, KOH, $MeOH–H_2O$, 20 °C, 6 h.

acid (**5**), either from itaconic acid[6] or from 4-phenyloxazole[7] and methyl tetrolate using Diels–Alder chemistry.[7,8] Metallation[5] of furoic acid (**5**) (5—10 g scale) using 2 equiv. of lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C provided the required dianion (**4**) which was condensed[9] with 3-methylglutaric anhydride (**6**), to provide routinely the keto-diester (**7a**) in *ca.* 56% yield,† after esterification and chromatography. Protection of the ketone function as the corresponding dimethylhydrazone (**7b**) (84%) was followed by Dieckmann cyclisation using sodium bis(trimethylsilyl)amide as base. The required keto-easter (**8a**), isolated in 62% yield on a 2—3 g scale, was deprotected using iodomethane in wet ethanol to give the rather sensitive diketo-ester (**8b**) (65%) as a three-component mixture of both possible diastereoisomers together with the corresponding enol tautomer of the β-keto-ester function (ratio *ca.* 1 : 1 : 1). Deprotonation of this material (0.5—1 g) using 2 equiv. of LDA in THF at −78 °C provided a second dianionic species which was alkylated by 1-bromobutan-2-one (1.2 equiv.) in the presence of hexamethylphosphoric triamide (HMPA) (*ca.* 5 equiv.). The desired homologue (**9**) was isolated in 52% yield, after column chromatography, as a single diastereoisomer containing *ca.* 15% of the corresponding keto tautomer. The other diastereoisomer was not detected; we assume that this selectivity arises simply because the incoming electrophile approaches the bis-enolate of diketo-ester (**8b**) *trans* to the substituent methyl group. Treatment of compound (**9**) (0.5 g) with potassium t-butoxide in $THF–Bu^tOH$[10] resulted in a smooth intramolecular aldol condensation leading to cyclopentenone (**10**) (entirely in the keto-form) as a mixture of two diastereoisomers, epimeric about the methoxycarbonyl function. Finally, this mixture was saponified and decarboxylated by treatment with potassium carbonate in wet methanol to give, after chromatography and crystallisation, only gnididione (**1**) in 51% yield from compound (**9**) which showed m.p. 102—103 °C (lit.,[2] m.p. 110—111 °C) and which was identical (^1H and ^{13}C n.m.r.; i.r.; mass) with the natural material. When the final hydrolysis step was carried out using aqueous methanolic potassium hydroxide the product, isolated in lower yield, was a mixture of gnididione (**1**) and isognididione (**2**) in a ratio of *ca.* 1 : 4, from which the latter was isolated by column chromatography. This sample was also identical (^1H n.m.r.; mass) to the naturally derived material (**2**).

We thank Drs. C. D. Buttery and A. G. Cameron for some preliminary work and the S.E.R.C. for financial support.

Received, 24th October 1986; Com. 1523

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† All yields refer to pure isolated products which exhibited satisfactory spectroscopic and analytical data.