Syntheses of the (±)-[*n*]-Gingerols (Pungent Principles of Ginger) and Related Compounds through Regioselective Aldol Condensations: Relative Pungency Assays

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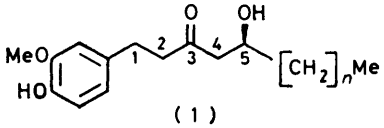
The deprotonation of trimethylsilylzingerone (13) by lithium di-isopropylamide at −78 °C has been found to be regioselective (92 : 8 in favour of less-substituted enolate): the anion was condensed with alkanals and acyl imidazoles to give convenient syntheses of the (±)-[2]—[10]- and -[12]-gingerols (1) and [4]-, [6]-, and [8]-gingerdiones (9). Similarly, 3-methoxy-4-trimethylsilyloxybenzylideneacetone (17) gave the (±)-[2]—[10]-dehydrogingerols (8) and [4]-, [6]-, and [8]-dehydrogingerdiones (10).

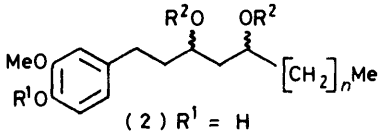
The aldol reaction to [6]-gingerol and methyl [6]-gingerol was also conducted through a vinyloxyborane or through the enol silyl ether ($TiCl_4$ catalysis). Results of organoleptic assays on these compounds are discussed, and the relation between pungency in the gingerols and in capsaicin is commented on. The aldol method was also used to synthesise the natural β-ketols(±)-daphneolone (25) and (±)-hexahydrocurcumin (4).

THE rhizome of ginger (*Zingiber officinale* Roscoe) has long been valued for its flavour and pungency, and its use in food and in medicine is recorded in ancient Sanskrit, Hebrew, and Chinese literature, *e.g.* in the analects of Confucius, *ca.* 500 B.C. Ginger appears to have been introduced into Europe during the ninth century A.D. and was included in the Anglo-Saxon 'Leech books'. Various virtues have been ascribed to the spice; *e.g.* Henry VIII recommended it as a prophylactic against the plague, thus popularising gingerbread men.†

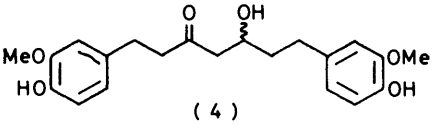
The first modern chemical investigations of the pungent constituents of ginger rhizome were made by Thresh[1] (1879) and the structure (1; $n = 4$, without stereochemistry) for the major phenol was demonstrated by Nomura[2] in 1928. However, the nature of the



(1)

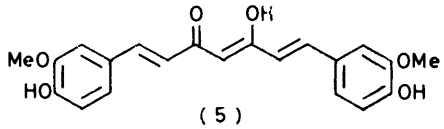


(2) R^1 = H
(3) R^1 = Me



(4)

complex mixture of relatively unstable phenolic substances did not become clear until the work of Connell and Sutherland[3] (1969) demonstrated the presence of an homologous series of phenolic ketones (1). The name [*m*]-gingerol for these compounds was then proposed, where m = chain length of the aldehyde formed in retro-aldo cleavage; thus (1; $n = 4$) is [6]-gingerol, the major member of the series. This nomenclature is used



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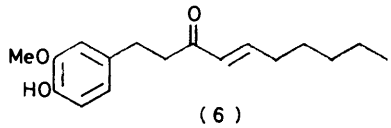

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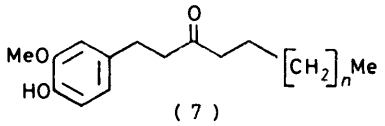

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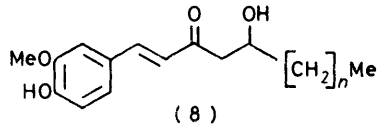

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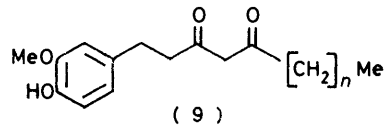
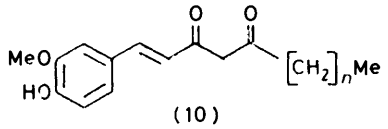


(9)

in this paper, in spite of its drawbacks, to avoid further confusion. The existence of [3]-, [4]-, [5]-, [6]-, [8]-, [10]-, and [12]-gingerols has been demonstrated[3-5]; ginger oleoresin also contains[4] the [6]-, [8]-, and [10]-gingerdiols (2; $n = 4$, 6, 8; R^2 = H), the diacetate (2; $n = 4$; R^2 = Ac), methyl [6]-gingerdiol (3; $n = 4$, R^2 = H) and its diacetate (3; $n = 4$, R^2 = Ac). Hexahydrocurcumin (4) is also present, forming an interesting biogenetic connection between ginger and turmeric

† In 'Love's Labour's Lost,' Costard tells Moth 'An' I had but one penny in the world, thou shouldst have it to buy gingerbread.'

(rhizome of *Curcuma longa*) whose major pigment is curcumin (5). The enone (6), shogaol, is found in ginger oleoresin but not, to our knowledge, in fresh rhizome. Shogaol is usually described as an artefact of extraction: it is, however, an attractive hypothetical intermediate between [6]-gingerol and [6]-paradol (7; $n = 4$) in the biosynthesis of the latter phenol. The paradols [6] (7) are the pungent principles of the seeds of *Ammomum melegueta* (Grains of Paradise). The absolute stereochemistry of (±)-[6]-gingerol has been determined [3] as *S*, as shown. A convenient synthesis for the gingerols,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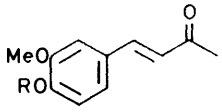
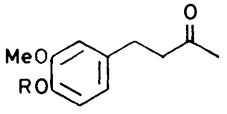
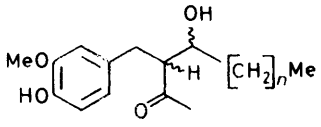

(11) R = H
(17) R = Me_3Si


(12) R = H
(13) R = Me_3Si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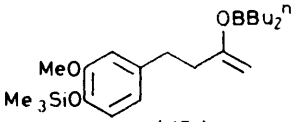
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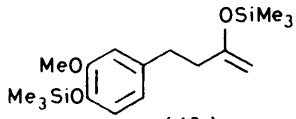
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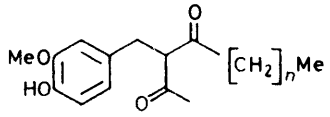
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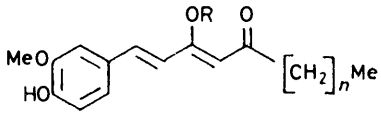

(19) R = H
(20) R = Ac

and related compounds, was desired to provide samples for organoleptic assay, and to prepare labelled compounds for biosynthetic work. In this paper we report two related routes to (±)-[6]-gingerol, based on regioselective aldol reactions. One method was used to prepare the series (±)-[2]—[10]- and [12]-gingerols (1; n = 2—10, 12), the (±)-*E*-[2]—[10]-dehydrogingerols (8; n = 2—10), and certain related β-ketols. The [4]-, [6]-, and [8]-gingerdiones (9; $n = 4$, 6, 8) and the corresponding *E*-dehydrogingerdiones (10; $n = 4$, 6, 8) were also prepared, through regioselective Claisen condensations. Pungency thresholds have been evaluated for each series.

Condensation of vanillin with an excess of acetone was catalysed by aqueous hydroxide to give 4-hydroxy-3-methoxybenzylideneacetone (11) (82%). Hydrogenation of the enone (11) to zingerone (12) over palladium was complicated by rapid further reduction of (12) to the alcohol, zingerol. However specific C–C reduction proceeded smoothly to (12), (96%), over Raney nickel. Zingerone was then converted into its *O*-trimethylsilyl ether (13). Regioselective deprotonation of this ketone was effected at −78 °C using lithium di-isopropylamide (LDA) in tetrahydrofuran, and the resulting anion was treated with hexanal at −78 °C for 1 h. The protecting group was removed during product isolation, by a brief acid wash, and (±)-[6]-gingerol (57%) was then obtained by p.l.c. A pure sample of natural *S*-(+)-[6]-gingerol was not available for comparison, but all spectroscopic data from the synthetic phenol including ^{13}C n.m.r. (see Experimental section) were in accord with its proposed identity, and with available data on the natural compound.[3] One previous method, returning a very low yield, has been described.[7]

Careful examination of the synthetic gingerol before final p.l.c. purification suggested the presence of traces of a second compound. This was isolated through subdivision of the major p.l.c. band, and proved to be a diastereoisomeric mixture of the ketol (14; $n = 4$) (*ca.* 4%), isomeric with [6]-gingerol. The aldol reaction with LDA is thus not entirely regiospecific, although highly selective (92 : 8) towards deprotonation at the terminal methyl. Similar selectivity has been demonstrated, in the course of this work, in related methyl ketone condensations.[8] The product ratio appeared insensitive to variations in the reaction temperature in the range 0 to −78 °C, but the condensation was less regioselective with the weaker base lithium bis(trimethylsilyl)amide. Even at −78 °C, preference for methyl rather than methylene deprotonation was only *ca.* 3 : 1. In a preliminary report,[9] we commented on our inability to detect the minor ketol (14; $n = 4$); our oversight can now be attributed to an incorrect n.m.r. interpretation. The only other products observed in these aldol reactions were unchanged zingerone, and the corresponding alcohol zingerol (*ca.* 10%), presumably arising from crossed Cannizarro reactions with the aldehyde.

Using this method we then prepared the series (±)-[2]—[10]- and -[12]-gingerol; of these, the [7]- and [9]-members are not known in nature. Organoleptic assay is discussed below.

During the course of this work, the possibility of inducing a degree of optical activity into the ketol products was briefly investigated. A modest degree of asymmetric induction in the addition of organometallic species to carbonyl compounds in the presence of chiral ligands has been noted.[10] However, neither the addition of (−)-sparteine,[10a] nor 1,2:5,6-di-*O*-isopropylidene-α-

D-glucofuranose,[10b] nor the use of a chiral base, lithium *N*-trimethylsilyl-1-phenylethylamide [prepared from (−)-1-phenylethylamine] was effective in this respect. Very recently [11] chiral *R*- and *S*-gingerols have been prepared, with optical yields 33—39%, by an aldol procedure using a chiral hydrazone derivative of zingerone.

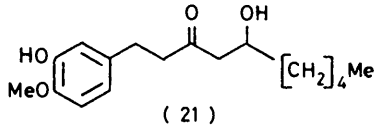
Two other methods of conducting an aldol condensation to [6]-gingerol have been examined. In the first, trimethylsilylzingerone was converted into the vinyloxyborane (15) by treatment with di-n-butylboryl triflate; [12] condensation of (15) with hexanal at −78 °C gave (±)-[6]-gingerol (53%), uncontaminated by methylene aldol products. Efforts to prepare analogous but chiral dialkylboryl triflates, starting from α- or β-pinene, were unavailing. Secondly, the enol silyl ether (16) was condensed with hexanal in the presence of titanium tetrachloride.[13] (±)-*O*-Methyl-[6]-gingerol, spectroscopically identical with the natural methyl ether, was obtained in poor yield (20% isolated, 25% based on recovered starting material). Since this work, conditions have been reported [13c] for the synthesis of [6]-gingerol (92%) from trimethylsilylzingerone, by this method.

In a similar fashion the *E*-(±)-[*n*]-dehydrogingerols (8) with $n = 2$—10, were prepared from *E*-trimethylsilylzingerone and the appropriate aldehyde, using lithium bis(trimethylsilyl)amide as base. There are no problems of regiocontrol in this case, and no products arising from Michael addition of base to starting or final enones were observed. The (±)-dehydrogingerols were all readily crystallised.

[6]-Gingerdione (19; $n = 6$) was obtained by a Claisen-type condensation using the anion generated from (13) and hexanoylimidazole; 2 mol equiv. of lithium bis(trimethylsilyl)amide were employed. The isomeric diketone (18) was not observed, in agreement with previous observations: [14] the equilibrium, in this thermodynamically-controlled process, is in favour of product only in presence of excess of base, and the preferred enolate is that unsubstituted at the inter-carbonyl position (steric inhibition of resonance). Both keto- and enol forms of (9) were present in the liquid state and in chloroform solution; ^{1}H n.m.r. spectroscopy indicates that the enol form predominates (*ca.* 80%) in dilute chloroform solution. Both [4]- and [8]-gingerdiones (9, $n = 4, 8$) were prepared in a similar way. The *E*-dehydrogingerdiones (19; $n = 4, 6, 8$) were also obtained, from (17) and the alkanoyl imidazole; the through-conjugated enolate (19) is the major form both in the solid state and in solution. [6]-Dehydrogingerdione gave the corresponding enol acetate (20; $n = 4$).

To complete a set of compounds for pungency evaluation [6]-shogaol (6) was isolated from commercial ginger oleoresin, and two other β-ketols were prepared, (±)-[6]-isogingerol (21), and (±)-Δ^8-[8]-gingerol (22). Similar methods to those described above were used, but for (21), 3-hydroxy-4-methoxybenzaldehyde was the starting-point for the preparation of 3-hydroxy-4-methoxybenzylideneacetone, isozingerone (23), *etc.*, while for (22) the required oct-4-en-1-al was obtained from the known oct-4-en-1-ol.

Organoleptic Evaluations.—A full discussion of the subject of pungency is inappropriate here, but a review [15] is available. The lowest dilution at which the pungency



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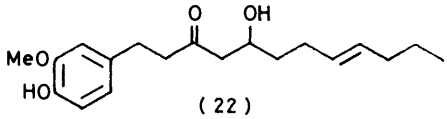

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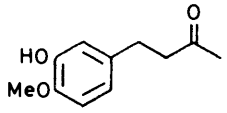

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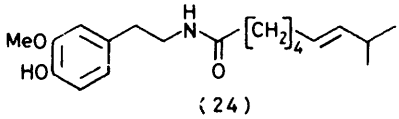

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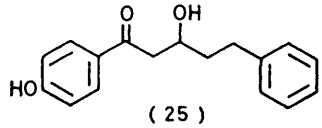


(25)

of a given sample can be detected is described as the 'pungency threshold' and may be expressed as 1 : *n*, where *n* = volume of solution (cm^3) containing 1 g sample.[16] The procedure used was based on that developed for capsaicin,[16b] and employed 1% ethanol solutions of the test substance diluted appropriately with 5% aqueous sucrose. The evaluations reported here were conducted by one of us (I. M.) under the valuable guidance of Mr. P. Werry (Bush Boake Allen). Each sample was tested blind, by several different persons,*

Pungency threshold dilutions

Shogaol (6)	1 : 130 000
Isogingerol (21)	1 : 35 000
Δ^8-[6]-Gingerol (22)	1 : 100 000

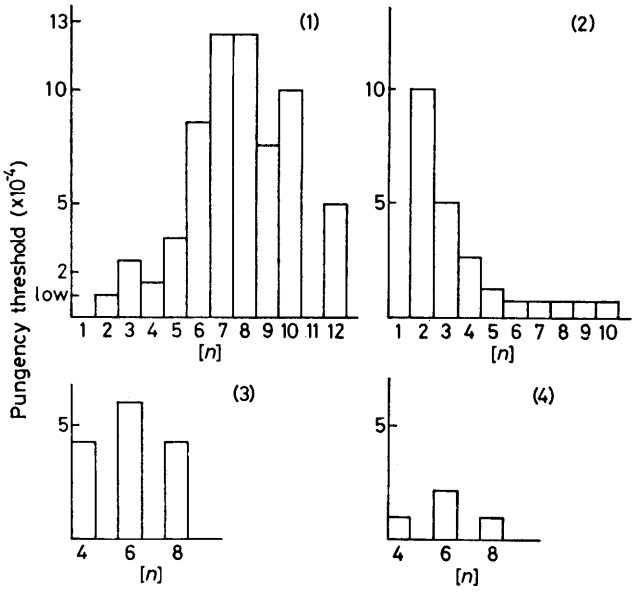
along with randomly distributed blanks. The results are shown in the four histograms, Figures 1—4, and in the Table. It can be seen (Figure 1) that for the (±)-gingerols maximum pungency is reached for the [7]- and [8]-members, and [10]-gingerol is hotter than [6].

Assuming that the same trends are followed in the natural optically active series,† it can be inferred that

* We thank the many participants in these tests, both from Nottingham University and Bush Boake Allen (Flavour Section).

† A threshold dilution of 75 000 has been reported [17] for sample of natural (−)-gingerol (mostly [6]-), *i.e.* a similar magnitude to that of (±)-[6]-gingerol in this study.

although [6]-gingerol is the major component of natural gingerols, the minor components [8]- and [10]-gingerol also make a substantial contribution to the pungency of natural ginger. The [7]-homologue is not known in nature. The threshold dilution for [6]-shogaol, the only



FIGURES 1—4 Pungency thresholds for (1) the [*n*]-gingerols, (2) the [*n*]-dehydrogingerols, (3) the [*n*]-gingerdiones, and (4) the [*n*]-dehydrogingerdiones

member of this series available, was similar to that reported in the literature, and is as great as that of [8]-gingerol. The data reported for the [*n*]-paradols [18] show that [6]-paradol is both the major constituent and the most pungent of the natural compounds, although the unnatural [5] and [7] members have similar thresholds.

An entirely different picture (Figure 2) was obtained for the [*n*]-dehydrogingerols; (±)-[2]-dehydrogingerol had substantial pungency, of similar order to (±)-[10]-gingerol or [6]-paradol, but increasing chain length rapidly decreases the threshold dilution. Of the three gingerdiones, the [6]-homologue is the hottest, while all the dehydrogingerdiones tested had low threshold dilutions. The branched ketols (14; $n = 6$, 10) had negligible pungency and in addition an ' off ' and even bitter flavour. Both [6]-dehydrogingerdione and [6]-dehydrogingerol have been shown to be intermediates in the biosynthesis of [6]-gingerol.[19]

Substantial work has been carried out on the pungency of capsaicin (24) and related compounds, using a ' relative pain-producing potency ' test (a rat eye test) as the biological assay method.[20] On the basis of this work a model for the capsaicin receptor site, in afferent nerve receptor cells, was proposed. Figure 5 shows the similarities between capsaicin and [7]-gingerol; these suggest that the same, or a very similar, receptor is involved (although capsaicin is much more pungent than any member of the gingerol series). It is worth noting that [7]- or [8]-gingerols are closer to capsaicin than the [6]-homologue, and are indeed more pungent. The acylamide linkage of capsaicin has been shown not to be essential to its biological activity, nor is the presence of the acyl olefinic linkage of great importance; however the 4-hydroxy-3-methoxy-substitution pattern is required for maximum heat, and isomers, *e.g.* 3-hydroxy-4-methoxy, are much less pungent. Similar trends were observed in the gingerol series. Thus (±)-[6]-isogingerol (Table) has a much lower threshold dilution than (±)-[6]-gingerol, but (±)-Δ^8-[8]-gingerol is of the same level of heat as (±)-[8]-gingerol. These observations serve to support the view that structure/pungency correlations are similar in the gingerol/capsaicin series. Finally we note in this paper that two other β-ketols of interest can be prepared (see Experimental section) by the aldol

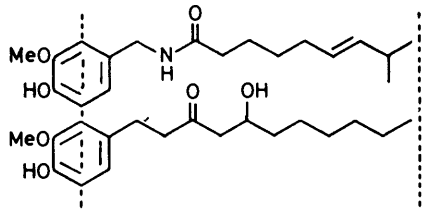


FIGURE 5 Structural comparison of [7]-gingerol with capsaicin

method, (±)-daphneolone (25) and (±)-di-*O*-methylhexahydrocurcumin, *cf.* (4), see above. Daphneolone, isolated from *Daphne odora* [21] has biogenetic interest as the first compound with a C_6–C_5–C_6 skeleton to be found in higher plants. Its biosynthesis may parallel that of [6]-gingerol.

EXPERIMENTAL [4]

Spectroscopic data are separately listed in Supplementary Publication No. SUP. 22898 (7 pp.).* Melting points were recorded on a Kofler hot-stage apparatus· Thin layer (t.l.c.) and preparative layer chromatography (p.l.c.) employed silica HF_{254} (Merck). Solvent system 1 was diethyl ether–light petroleum (b.p. 40—60 °C) (49 : 1). Thin-layer plates were (4 : 1); solvent system 2 was chloroform–ethyl acetate visualised by spraying with conc. sulphuric acid, and baking at 110 °C for 5 min. Yields are quoted for purified products, and were not optimised in any case.

Trimethylsilylzingerone.—Vanillin (16 mmol) in acetone (100 cm³) with 10% aqueous sodium hydroxide (70 cm³) was set aside for 4 days. After acidification, 4-hydroxy-3-methoxybenzylideneacetone was collected, m.p. 128—129 °C from aqueous methanol (lit.,[22] m.p. 128—129 °C) (82%) (Found: C, 68.55; H, 5.85. Calc. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.3%). 4-Hydroxy-3-methoxybenzylideneacetone was hydrogenated in acetone solution at atmospheric pressure and temperature over neutral Raney nickel (10% w/w). Removal of solvent and catalyst gave zingerone (86%), m.p. 40—41 °C from hexane–benzene (lit.[23] m.p. 41—42 °C) (Found: C, 68.3; H, 7.45. Calc. for $C_{11}H_{14}O_3$: C 68.05; H, 7.3%). The phenol (2 g), hexamethyldisilazane (1.8 g) and trimethylchlorosilane (1 cm³) were refluxed together in

* For details of the Supplementary publications scheme, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1979, Index issue.

benzene (25 cm³) until sublimation of ammonium chloride ceased. Evaporation of the solvent and distillation gave the *title compound* (2.3 g, 84%), b.p. 126 °C/2 mmHg (Found: C, 62.75; H, 8.3%; M^+ 266.132. $C_{14}H_{22}O_3Si$ requires C, 63.15; H, 8.25%; *M* 266.134).

(±)-[6]-*Gingerol* [*5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one*].—Trimethylsilylzingerone (220 mg, 0.8 mmol) in dry tetrahydrofuran (2 cm³) was added dropwise, over 30 min, to lithium di-isopropylamide [from di-isopropylamine (81 mg, 0.8 mmol) and n-butyl-lithium (0.8 mmol)] in tetrahydrofuran (5 cm³) at −78 °C, under a nitrogen atmosphere. After a further 30 min hexanal (160 mg, 1.6 mmol) in tetrahydrofuran (2 cm³) was added dropwise, and the mixture stirred at −78 °C for 1 h. Ether (15 cm³) was then added, and the mixture washed with 2M-hydrochloric acid (2 × 5 cm³), aqueous sodium hydrogen carbonate (5 cm³), and water. After evaporation the residue was purified by p.l.c. using solvent 1, and repurified using solvent 2 (multiple elution), to yield (±)-[6]-*gingerol* as an oil (53%) (Found: C, 69.7; H, 9.1%; M^+ 294.184. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.8%; *M*, 294.183). The tail of the major p.l.c. band was separated to yield the (±)-diastereoisomers of *4-hydroxy-3-(4-hydroxy-3-methoxybenzyl)nonan-2-one* (4%) (Found: M^+, 294.187. $C_{17}H_{26}O_4$ requires 294.183). Zingerone (15%) and zingerol (10%) were also isolated from the p.l.c., and identified by comparison with authentic specimens. In a similar experiment, but using lithium bis(trimethylsilyl)amide (0.8 mmol) as base a mixture (66%) of (±)-[6]-gingerol and the isomeric ketol (14; $n = 4$) (*ca.* 3 : 1, by n.m.r.) was obtained.

(±)-[n]-*Gingerols*. The procedure for [6]-gingerol was employed to make (±)-[2]-*gingerol* (49%) (Found: M^+, 238.123. $C_{13}H_{18}O_4$ requires *M*, 238.121); (±)-[3]-gingerol (45%) (Found: M^+, 252.139. $C_{14}H_{20}O_4$ requires *M*, 252.136); (±)-[4]-gingerol (28%) (Found: M^+, 266.151. $C_{15}H_{22}O_4$ requires *M*, 266.152); (±)-[5]-gingerol (29%) (Found: M^+, 280.167. $C_{16}H_{24}O_4$ requires *M*, 280.167); (±)-[7]-gingerol (22%) (Found: M^+, 308.200. $C_{18}H_{28}O_4$ requires *M*, 308.198); (±)-[8]-gingerol (27%) (Found: M^+, 322.213. $C_{19}H_{30}O_4$ requires *M*, 322.214; (±)-[9]-gingerol (25%) (Found: M^+, 336.229. $C_{20}H_{32}O_4$ requires *M*, 336.230; (±)-[10]-gingerol (22%) (Found: M^+, 350.246. $C_{21}H_{34}O_4$ requires *M*, 350.246); (±)-[12]-gingerol (Found: M^+, 378.278. $C_{22}H_{38}O_4$ requires *M*, 378.277). In this last reaction the isomeric ketol (14; $n = 12$), (±)-*4-hydroxy-3-(4-hydroxy-3-methoxybenzyl)pentadecan-2-one* (Found: M^+, 378.274), was also purified.

3-Methoxy-4-trimethylsilyloxybenzylideneacetone.—4-Hydroxy-3-methoxybenzylideneacetone (3.88 g), hexamethyldisilazane (3.6 g), and trimethylchlorosilane (2 cm³) were refluxed in dry benzene (50 cm³) until sublimation of ammonium chloride ceased. Evaporation and distillation gave the *title compound* (4.2 g, 80%), b.p. 194 °C/8 mmHg, m.p. 45 °C (Found: C, 63.5; H, 7.3%; M^+, 264.117. $C_{14}H_{20}O_3Si$ requires C, 63.65; H, 7.55%; *M*, 264.118).

(±)-[6]-*Dehydrogingerol* [*5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dec-1-en-3-one*].—3-Methoxy-4-trimethylsilyloxybenzylideneacetone (219.8 mg, 0.8 mmol) in dry tetrahydrofuran (2 cm³) was added dropwise during 10 min to lithium bistrimethylsilylamide (140 mg, 0.8 mmol) in tetrahydrofuran (5 cm³) maintained at −78° C, under nitrogen. After 30 min hexanol (160 mg, 1.6 mmol) in tetrahydrofuran (2 cm³) was added dropwise. After 1 h at −78 °C, ether (15 cm³) was added, and the mixture washed with dilute hydrochloric acid and water. The dried organic solution was evaporated and the residue purified by p.l.c. (solvent 1). The major band was isolated and crystallised from ethyl acetate–light petroleum to yield the *title compound* (40 mg, 40%, after recrystallisation), m.p. 134—137 °C (Found: M^+, 292.170. $C_{17}H_{24}O_4$ requires *M*, 292.167).

(±)-[n]-*Dehydrogingerols*.—The procedure used for [6]-dehydrogingerol was used to make (±)-[2]-dehydrogingerol, m.p. 150—153 °C (Found: C, 66.05; H, 7.1%; M^+, 236.105. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%; *M*, 236.105); (±)-[3]-dehydrogingerol, m.p. 113.135 °C (Found: C, 67.55; H, 7.5%; M^+, 250.121. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.65%; *M*, 250.121); (±)-[4]-dehydrogingerol, m.p. 155—158 (Found: M^+, 264.133. $C_{15}H_{20}O_4$ requires *M*, 264.136); (±)-[5]-dehydrogingerol, m.p. 144—146 °C (Found: C, 68.55; H, 8.45%; M^+, 278.149. $C_{16}H_{22}O_4$ requires C, 69.05; H, 7.9%; *M*, 278.152); (±)-[7]-dehydrogingerol, m.p. 110—112 °C (Found: C, 70.5; H, 8.1%; M^+, 306.184. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.7%; *M*, 306.183); (±)-[8]-dehydrogingerol, m.p. 88—90 °C (Found: C, 71.45; H, 8.95%; M^+, 320.197. $C_{19}H_{28}O_4$ requires C, 71.25; H, 8.75; *M*, 320.199); (±)-[9]-dehydrogingerol, m.p. 93—94 °C (Found: C, 71.7; H, 9.5%; M^+, 334.219. $C_{20}H_{30}O_4$ requires, C, 71.85; H, 9.0%; *M*, 334.214); (±)-[10]-dehydrogingerol, m.p. 76—77.5 °C (Found: M^+, 348.234. $C_{21}H_{34}O_4$ requires *M*, 348.230). Yields *ca.* 50% before crystallisation were obtained.

[n]-*Gingerdiones and* [n]-*Dehydrogingerdiones*.—The method used for the dehydrogingerols was employed, but using the appropriate alkanoylimidazole (1 mol equiv.) and 2 mol equiv. base. In this way were prepared the following: [4]-gingerdione (Found: M^+, 264.136. $C_{15}H_{20}O_4$ requires *M*, 264.136); [6]-gingerdione (30%) (Found: M^+, 292.169. $C_{17}H_{24}O_4$ requires *M*, 292.167); [8]-gingerdione (Found: M^+, 320.199. $C_{19}H_{28}O_4$ requires *M*, 320.199); [4]-dehydrogingerdione, m.p. 109—110 °C (Found: M^+, 262.121. $C_{15}H_{18}O_4$ requires *M*, 262.121); [6]-dehydrogingerdione (43%), m.p. 83.5—84.5 °C (Found: M^+, 290.151. $C_{17}H_{22}O_4$ requires *M*, 290.152); [8]-dehydrogingerdione, m.p. 48—49 °C (Found: M^+, 318.185. $C_{19}H_{26}O_4$ requires *M*, 318.183).

5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodec-8-en-3-one.—Oct-4-en-1-ol was prepared from 2,3-dichlorotetrahydropyran in three steps, by the literature procedure,[24] and oxidised to the corresponding aldehyde with pyridinium chlorochromate. The method for [6]-gingerol was then followed, using oct-4-enal, to yield the *title compound* (33%) (Found: M^+, 320.200. $C_{19}H_{28}O_4$ requires *M*, 320.199).

[6]-*Isogingerol* [*5-Hydroxy-1-(3-hydroxy-4-methoxyphenyl)-decan-3-one*].—3-Hydroxy-4-methoxybenzylideneacetone, m.p. 89—91 °C (lit.,[25] m.p. 92—93 °C), prepared from isovanillin and acetone with aqueous sodium hydroxide, was hydrogenated (Raney nickel) to give isozingerone, m.p. 28—29 °C (lit.,[25] m.p. 37—38 °C). Condensation of trimethylsilylisozingerone with hexanal, using the methods described above, gave the *title compound* (38%) (Found: M^+, 294.185. $C_{17}H_{26}O_4$ requires *M*, 294.183).

(±)-*Daphneolone*.—*p*-Hydroxyacetophenone was converted in the standard manner into the corresponding *O-trimethylsilyl ether*, b.p. 91—93 °C/7 mmHg (M^+, 208). A sample (600 mg, 2.88 mmol) of the ether in dry tetrahydrofuran was added dropwise to the lithium di-isopropylamide (308 mg, 2.88 mmol) in tetrahydrofuran (10 cm³) at −78 °C. After 40 min 3-phenylpropanal (400 mg, 2.94 mmol) in tetrahydrofuran was added during 15 min, and the mixture stirred at −78 °C for 60 min. Product isolation as above gave a crude product, which crystallised from

ethyl acetate–light petroleum to yield (±)-*daphneolone* (397 mg, 51%), m.p. 93—94 °C (Found: C, 75.25; H, 7.0%; M^+, 270.127. $C_{17}H_{18}O_3$ requires C, 75.55; H, 6.7%; *M*, 270.126).

(±)-*Di*-O-*Methyl Hexahydrocurcumin* [*5-Hydroxy-1,7-bis(3,4-dimethoxyphenyl)heptan-3-one*.—The procedure for [6]-gingerol was used, with *O*-methylzingerone (375 mg), lithium bis(trimethylsilyl)amide, and 3-(3,4-dimethoxyphenyl)propanal. The product was purified by p.l.c. (chloroform–ether, 1 : 1), and crystallised from ether–light petroleum to yield the *title compound* (110 mg, 15%), m.p. 96—98 °C (Found: C, 68.42; H, 7.15. $C_{23}H_{30}O_6$ requires C, 68.65; H, 7.46%).

Vinyloxyborane Route to [6]-*Gingerol*.—Trifluoromethanesulphonic acid (1.0 g, 6.6 mmol) was added dropwise, to a stirred sample of tri-n-butylborane (3.63 g, 19.94 mmol) at 0 °C, under nitrogen. n-Butane was evolved. More acid (1.99 g, 13.27 mmol) was added, dropwise, during 15 min. After 30 min at 0 °C, the mixture was rapidly distilled under reduced pressure, to yield di-n-butylboryl trifluoromethanesulphonate (3.28 g, 70%), b.p. 37 °C/0.12 mmHg. To a stirred solution of the boryl triflate (252 mg, 0.92 mmol) and di-isopropylethylamine (119 mg, 0.9 mmol) in dry ether (5 cm³), under nitrogen at −78 °C, was added trimethylsilylzingerone (222 mg, 0.8 mmol) in ether (2 cm³). After stirring the mixture for 30 min hexanal (84 mg, 0.84 mmol) in dry ether (2 cm³) was added dropwise and the mixture kept at −78 °C for 1 h. The product was diluted with phosphate buffer (pH 7) (25 cm³) and the mixture extracted with ether (3 × 10 cm³). The extracts were evaporated, and the residue, in methanol (3 cm³), was treated with 30% hydrogen peroxide (1 cm³). After 2 h, water (20 cm³) was added to the mixture, and the product isolated in the usual way; [6]-gingerol (105 mg, 53%) was obtained after p.l.c., characterised by ^{1}H.m.r. spectra.

O-*Methyl* [6]-*gingerol* via *Acid-catalysed Aldol Condensation*.—Lithium di-isopropylamide was generated from di-isopropylamine (505 mg, 5 mmol) and n-butyl-lithium (5 mmol) in hexane containing triphenylmethane, at −78 °C. To this was added methylzingerone (1.04 g) in tetrahydrofuran (5 cm³), when the red colour was just discharged. After 30 min at −78 °C, a solution of chlorotrimethylsilane (1 cm³, 7 mmol) in tetrahydrofuran (3 cm³), centrifuged after treatment with triethylamine (0.25 cm³, 2 mmol), was added. After 15 min at −78 °C, the mixture was warmed to room temperature and evaporated to yield methylzingerone trimethylsilyl ether, used without further purification. The enol ether (285 mg, 1 mmol) in dichloromethane (5 cm³) was added to titanium tetrachloride (1.1 mmol) and hexanal (1 mmol) in dichloromethane (5 cm³) and the mixture stirred for 2.5 h. After dilution with water (5 cm³) the mixture was extracted with ether (2 × 5 cm³). The extracts were washed, dried, and evaporated. The residue, after p.l.c., yielded (±)-*O*-methylgingerol (64 mg, 20%) (identified by spectroscopic comparison with an authentic specimen of the methyl ether of natural [6]-gingerol) and methylzingerone (51 mg, 25%).

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