Synthesis of (±)-[6]-Gingerol (Pungent Principle of Ginger) and Relatives *via* Directed Aldol Reactions

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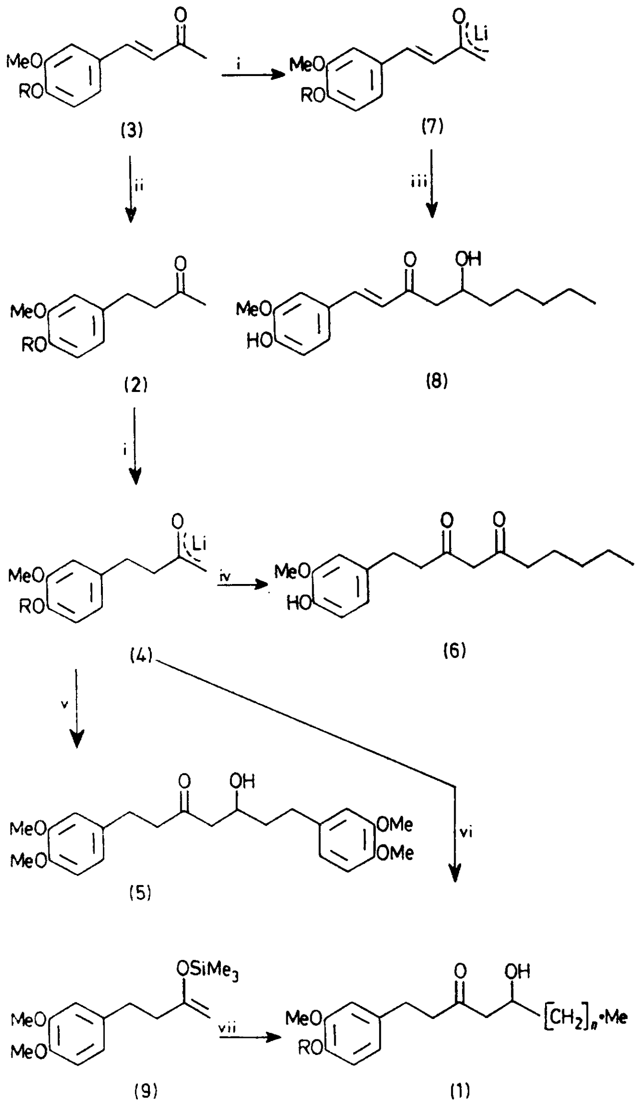
Summary Selective deprotonation of trimethylsilyl zingerone (**2**; R = Me_3Si) and trimethylsilylvanillylacetone (**7**; R = Me_3Si) can be effected; the resulting anions condense readily with aldehydes and acylimidazoles to provide short syntheses of the ginger root constituents (±)-[4]-, (±)-[6]-(an organoleptic principle), (±)-[10]-gingerol, and *di-O*-methylhexahydrocurcumin, and the related dehydro-[6]-gingerol and [6]-gingerdione.



SCHEME

Reagents: i, $(Me_3Si)_2NLi$, tetrahydrofuran, −78 °C; ii, H_2, Raney Ni; iii, a, $Me[CH_2]_4CHO$, −78 °C, b, H_3O^+; iv, a, *N*-n-hexanoylimidazole, b, H_3O^+; v, a, 3,4-$(MeO)_2C_6H_3CH_2CH_2CHO$, −78 °C, b, H_3O^+; vi, a, $Me[CH_2]n$CHO, −78 °C, b, H_3O^+; vii, $Me[CH_2]_4$-CHO, $TiCl_4$, 25 °C.

THE rhizome of ginger (*Zingiber officinale* Roscoe) has long been valued for its flavouring qualities. The pungency has been ascribed to phenolic constituents, particularly the (*S*)-gingerols[1,2] (**1**), of which (+)-[6]-gingerol (**1**; R = H, *n* = 4) is the most abundant, and the only member to have been adequately purified from natural sources. Synthesis of such compounds and various relatives is desirable to provide both pure samples for organoleptic assay and labelled specimens for testing schemes of biosynthesis.[3] We now report a short, and reasonably efficient, synthesis,† as shown in the Scheme.

Zingerone (**2**; R = H), a degradation product of gingerols, was readily prepared by hydrogenation of vanillylacetone (**3**; R = H), and converted into its *O*-trimethylsilyl ether (**2**; R = Me_3Si) with hexamethyldisilazane. Regioselective deprotonation of this ether, under kinetic control, was effected at −78 °C using bistrimethylsilyl lithamide, and the anion (**4**; R = Me_3Si) allowed to react with hexanal. Neutralisation and chromatographic purification gave (±)-[6]-gingerol (**1**; R = H, *n* = 4), 57% isolated (68% based on used zingerone). The base used in this reaction is insufficiently nucleophilic to cleave the silyl ether protecting group, at low temperatures, and the mild isolation methods leave intact the sensitive β-ketol function; we could not detect, either in this reaction or in model condensations, any isomeric β-ketol products arising from deprotonation of (**2**; R = Me_3Si) at the α-methylene group.‡ A little zingerol, the alcohol corresponding to (**2**; R = H) was isolated, presumably arising from crossed Cannizarro reactions with the aldehyde.

By this method we also prepared (±)-[4]-gingerol (**1**; R = H, *n* = 2), m.p. 74—75 °C, and (±)-[10]-gingerol (**1**; R = H, *n* = 8). Using (**4**; R = Me) in condensation with 3-(3,4-dimethoxyphenyl)propanal, the di-*O*-methylether of hexahydrocurcumin (**5**) was obtained; this ketol has recently been identified[4] as a component of ginger oleoresin. The anion (**4**; R = Me_3Si) also reacted smoothly with hexanoylimidazole, in a directed Claisen reaction, to afford [6]-gingerdione (**6**), a likely precursor[3] *in vivo* to [6]-gingerol. Another possible biosynthetic intermediate, dehydro-[6]-gingerol (**8**), m.p. 119—121 °C, was formed on condensation of the anion (**7**; R = Me_3Si) derived from the α-unsaturated ketone (**3**).

Finally, an acid-catalysed condensation for [6]-gingerol was explored. Reaction of hexanal with the enolsilyl ether (**9**) using titanium tetrachloride[5] catalyst gave *O*-methyl-[6]-gingerol (**1**; R = Me, *n* = 4), but in poor yield (20% isolated, 25% based on recovered starting material).

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† One previous method, returning a very low yield, has been described [N. Hirao, T. Toyama, A. Takahata, and B. Yasui, *Chem. Pharm. Bull.* (*Japan*), 1972, **20**, 2287].

‡ Similar selectivity has been demonstrated, in the course of this work, in related methyl ketone condensations [G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, 1974, **39**, 3459; M. Gandemar, *Compt. rend.* (*C*), 1974, **279**, 961].

[1] D. W. Connell and M. D. Sutherland, *Austral. J. Chem.*, 1969, **22**, 1033.
[2] U. Masada, T. Inoue, K. Hashimoto, M. Fujioka, and K. Shiraki, *J. Pharm. Soc. Japan*, 1973, **93**, 318; Y. Masada, T. Inoue, K. Hashimoto, M. Fujioka, and C. Uchino, *ibid.*, 1974, **94**, 735.
[3] P. Denniff and D. A. Whiting, preceding communication.
[4] M. Miyamoto, M. Shinohara, and T. Murata, 88th Annual Meeting Pharm. Soc. Japan, 1968, Abstracts, p. 231; *Chem. Pharm. Bull.* (*Japan*), 1972, **20**, 2291.
[5] T. Mukaiyama and K. Saigo, *Chem. Letters*, 1973, **479**; T. Mukaiyama, K. Banno, and K. Narasaka, *ibid.*, 1011.