Communications to the Editor

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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 44.[1] A NEW GENERAL EFFICIENT SYNTHESIS OF DL-[n]-GINGEROLS AND RELATIVES THROUGH DIRECT C-ACYLATION USING DIETHYL PHOSPHOROCYANIDATE (DEPC)[2]

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DL-[n]-Gingerols (**1**) and their relatives, which have various interesting physiological actions, have been conveniently and efficiently prepared from ferulic acid (**2**) through direct C-acylation using diethyl phosphorocyanidate (DEPC) in the presence of triethylamine.

KEYWORDS —— [n]-gingerol; C-acylation; diethyl phosphorocyanidate; β-ketonitrile; Grignard reaction; β-ketol

[n]-Gingerols (**1**) are known as pungent principles of ginger, in which (*S*)-[6]-gingerol ((*S*)-**1**, n=6) is the major member of the series.[3] Recently, (*S*)-[6]-gingerol and its relatives have been revealed to have various interesting physiological actions such as inhibitory action on prostaglandin biosynthesis,[4] cardiotonic action,[5] and suppressive action on the central nervous system.[6] Reported syntheses[7] of [6]-gingerol and its relatives, except one,[7e] have employed cross aldol condensations as a key step (fission a in **1**), but their efficiency and conveniency are generally moderate.

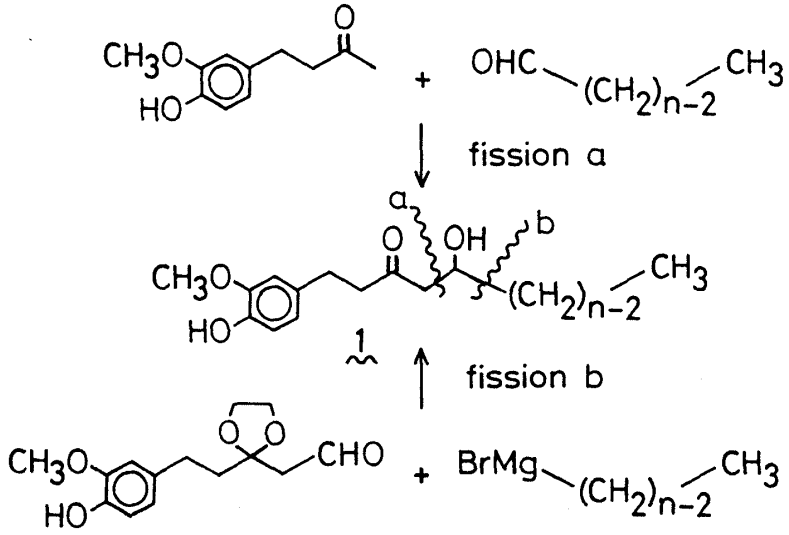

Chart 1

We now report a new general efficient synthesis of DL-[n]-gingerols and their relatives. Salient features of this construction include (1) Grignard reactions with an aldehyde (fission b in **1**), shown in Chart **1**, and (2) direct C-acylation of an active methylene compound with a carboxylic acid using diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) in the presence of triethylamine.[8]

Catalytic hydrogenation of commercially available ferulic acid (**2**) over 5% palladium on carbon in methanol quantitatively afforded 3-(4-hydroxy-3-methoxyphenyl)propionic acid (**3**),[9] mp 90.5-91.5°C. Condensation of tert-butyl cyanoacetate with **3** was conveniently carried out in dimethylformamide by the use of DEPC and triethylamine,[8] giving the C-acylated product **4** in 78% yield as the enolic form: mp 88-89°C; IR (Nujol): 3410 (phenolic OH), 2220 (CN), 1650 (CO_2Bu^t)cm^{-1}; NMR ($CDCl_3$) δ: 1.53 (9H, s, Bu^t), 2.88 (4H, s, CH_2CH_2), 3.85 (3H, s, CH_3O), 5.57 (1H, broad s, phenolic OH, exchangeable with D_2O), 6.43-6.92 (3H, m, aromatic H), 13.93 (1H, broad s, enolic OH, exchangeable with D_2O). Thermal treatment of **4** in dimethylformamide at 145°C for 10 min gave the β-ketonitrile **5** in 97% yield: mp 69.5-71°C; IR (Nujol): 2240 (CN), 1730 (C=O)cm^{-1}. The ketonic function of **5** was protected as the ethylene acetal by treatment with ethylene glycol in refluxing benzene containing p-toluenesulfonic acid using a Dean-Stark water separator, giving the acetal **6**, mp 114-116°C, in 97% yield. Alternatively, direct conversion of **4** to **6** was achieved in 89% yield by similar treatment of **4** with ethylene glycol. Reduction of **6** with diisobutylaluminum hydride in diethyl ether at -20°C for 1 h afforded the aldehyde **7** in 76% yield: mp 80-81°C, IR (KBr): 1720 (C=O)cm^{-1}; NMR ($CDCl_3$) δ: 9.70 (1H, t, J=3Hz, CHO).

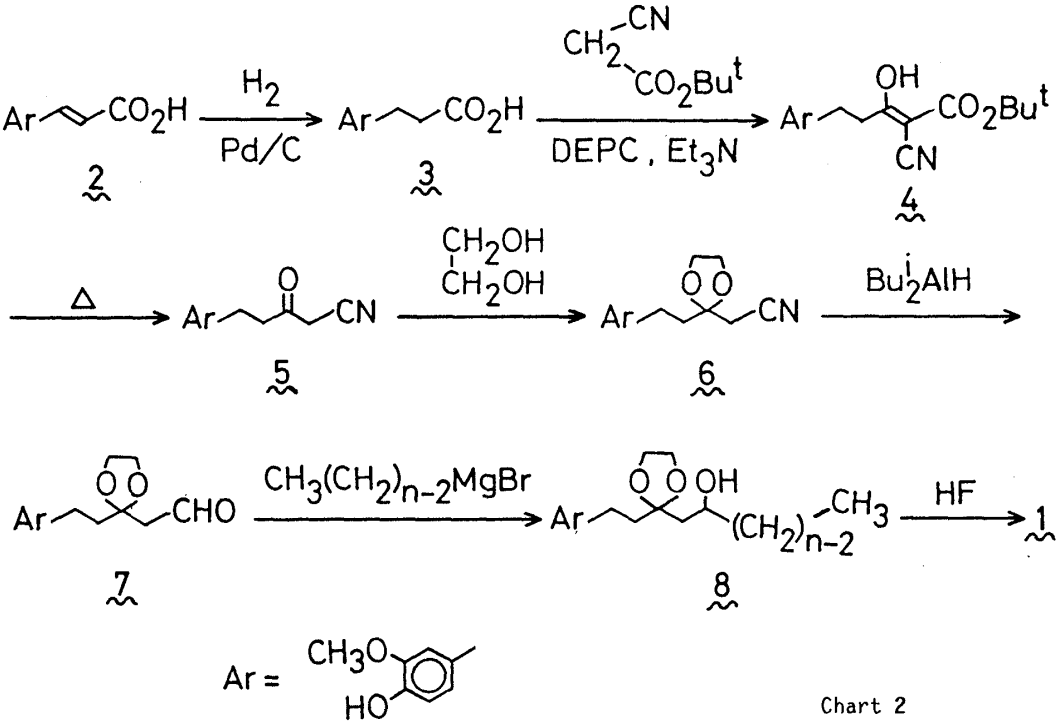

Chart 2

Grignard coupling of the aldehyde **7** with various alkyl magnesium bromides was conducted in tetrahydrofuran at -15°C for 1 h and then at room temperature for 2 h, giving the protected β-ketols **8** in good yields, as summarized in Table I. Treatment of **8** with 46% aqueous hydrogen fluoride in acetonitrile at room temperature for 0.5 h afforded DL-[n]-gingerols (**1**) in excellent yields. The overall yield of DL-[6]-gingerol (**1**, n=6) from readily available ferulic acid (**2**) is 47% which is the highest overall yield ever achieved.[7]

Table I. Preparation of DL-[n]-Gingerols (1)

n	Yield (%) of 8[a)]	Yield (%) of 1	mp (°C) of 1
2	86[b)]	96	67-68.5
4	83	93	72-73
6	89	95	40-41
8	85	94	32-34
10	91	78	44-45
12	73	76	53-54.5
14	85	84	64-65
16	83	96	71-72

a) All of **8** are colorless oils.
b) Methyl magnesium chloride was used.

[1]-Gingerol [5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)pentan-3-one], mp 79.5-81°C, was prepared from the aldehyde **7** by sodium borohydride reduction (84% yield), followed by treatment with hydrogen fluoride (68% yield).

A few derivatives of [6]- and [12]-gingerols were also prepared, shown in Chart **3.** The β-ketonitrile **5** was converted to its O-silylated derivative **9** with N,O-bis(trimethylsilyl)acetamide. Treatment of **9** with tert-butyl magnesium chloride, followed by pentyl magnesium bromide in refluxing benzene for 1 h afforded the enaminoketone **10a,** which was hydrolyzed with 1 N sulfuric

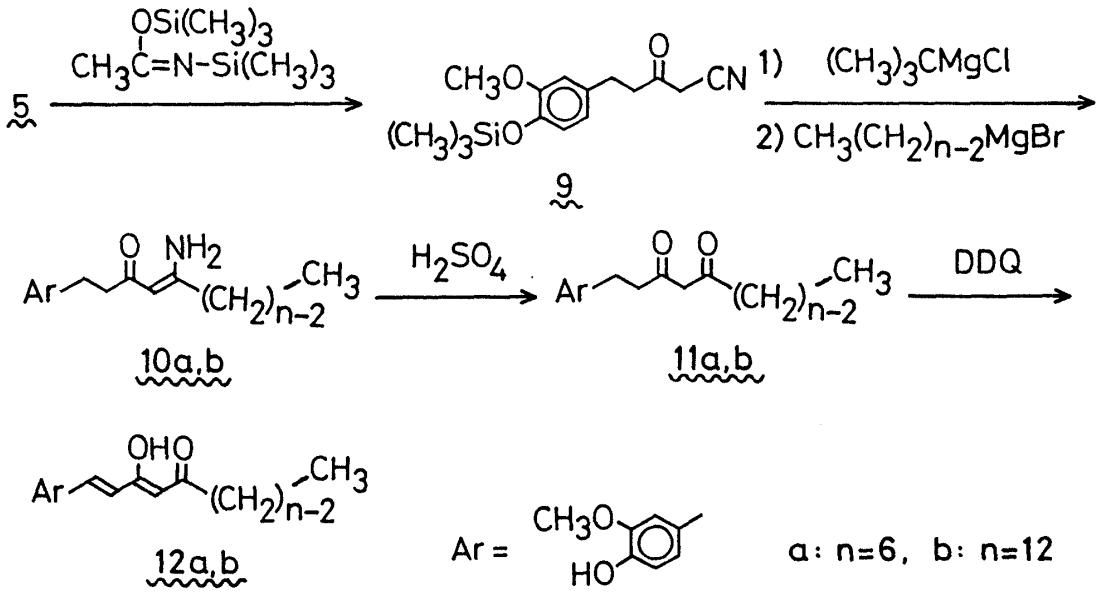

Chart 3

acid in ethanol under reflux for 5 min to give [6]-gingerdione (**11a**), a pale yellow oil,[4] IR (film): 3430, 1700, 1610 cm^{-1}, in 55% overall yield from **5**. [12]-Gingerdione (**11b**), mp 44-45°C, IR (film): 3410, 1700, 1610 cm^{-1}, was also similarly obtained in 53% yield by the use of undecanyl magnesium bromide. Dehydrogenation of **11a** and **11b** with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in dioxane afforded respectively [6]-dehydrogingerdione (**12a**), mp 83.5-84.5°C (lit.[4,7c] 83.5-84.5°C), IR (KBr): 3300, 1625, 1595cm^{-1}, and [12]-dehydrogingerdione (**12b**), mp 70-71°C, IR (KBr): 3410, 1630, 1580cm^{-1}.

The overall process for the preparation of [n]-gingerols and their relatives is simple, convenient, straightforward, economical, and suitable for large scale preparation. Furthermore, the method described here will have a generality as the preparative method for various β-ketols and congeners.

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REFERENCES AND NOTES

1) For Part **43**, see Y. Hamada, A. Mizuno, T. Ohno, and T. Shioiri, Chem. Pharm. Bull., in press.
2) Presented in part at the 10th Symposium on Progress in Organic Reactions and Syntheses, Tokyo, Nov. 1983, Abstracts p. 91.
3) a) D.W. Connell and M.D. Sutherland, Aust. J. Chem., **22**, 1033 (1969); b) T. Murata, M. Shinohara, and M. Miyamoto, Chem. Pharm. Bull., **20**, 2291 (1972); c) Y. Masada, T. Inoue, K. Hashimoto, M. Fujioka, and K. Shiraki, Yakugaku Zasshi, **93**, 318 (1973).
4) F. Kiuchi, M. Shibuya, and U. Sankawa, Chem. Pharm. Bull., **30**, 754 (1982).
5) N. Shoji, A. Iwasa, T. Takemoto, Y. Ishida, and Y. Ohizumi, J. Pharm. Sci., **71**, 1174 (1982).
6) M. Suekawa, A. Ishige, K. Yuasa, K. Sudo, and M. Aburada, J. Pharm. Dyn., to be submitted. We thank Dr. M. Aburada of Tsumura Research Institute for Pharmacology for sending us the manuscript.
7) a) N. Hirao, T. Toyama, A. Takahata, and B. Yasui, Chem. Pharm. Bull., **20**, 2287 (1972); b) K. Banno and T. Mukaiyama, Bull. Chem. Soc. Jpn., **49**, 1453 (1976); c) P. Denniff and D.A. Whiting, Chem. Commun., **1976**, 712; P. Denniff, I. Macleod, and D.A. Whiting, J. Chem. Soc., Perkin Trans. I, **1981**, 82; d) D. Enders, H. Eichenauer, and R. Pieter, Chem. Ber., **112**, 3703 (1979); e) A. Barco, S. Benetti, P.G. Baraldi, M. Guarneri, G.P. Pollini, and D. Simoni, Chem. Commun., **1981**, 599.
8) T. Shioiri and Y. Hamada, J. Org. Chem., **43**, 3631 (1978); Y. Hamada, K. Ando, and T. Shioiri, Chem. Pharm. Bull., **29**, 259 (1981); Y. Hamada, S. Morita, and T. Shioiri, Heterocycles, **17**, 321 (1982).
9) All compounds exhibited satisfactory spectral and physical properties.

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