# Asymmetric Synthesis of a β-Ketol Moiety *via* 3,5-Disubstituted Isoxazoles: Application to (+)-(*S*)-[6]-Gingerol

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A new synthesis of (±)-[6]-gingerol (13), (+)-(*S*)-[6]-gingerol, and (+)-methyl-[6]-gingerol (12c) using 3,5-disubstituted isoxazoles as masked β-ketols, is described. Reductive fission of the labile N–O bond of the isoxazoles (8a) and (8b) gave the enamino-ketones (9a) and (9b) which were converted into the vinylogous imides (10c) and (10b) using *N*-tosyl-L-prolyl chloride. Reduction of (10c) and (10b) gave diastereoisomeric mixtures of the alcohols (11c) and (11b), which on controlled hydrolysis in aqueous acetic acid gave β-ketols. Optical yields of 30—40% were obtained.

Heterocyclic compounds embodying latent functionalities constitute a powerful tool to synthetic chemists.[1] Among them, 3,5-disubstituted isoxazoles play an important role, either as effective means of carbon-carbon bond formation (being derivable through cycloaddition of two separate units, a nitrile oxide and a terminal alkyne) or in masked form where release occurs by suitable reductive opening of the labile N–O bond[2] (Scheme 1).

A recent paper[3] from these laboratories dealing with prostaglandin synthesis illustrated that regiospecific cycloaddition of nitrile oxides to terminal alkynes to give 3,5-disubstituted isoxazoles, in conjunction with a specific reduction-elimination sequence, allows them to be considered as αβ-enone equivalents; more recently we disclosed their novel transformation into β-hydroxy-ketones. We have also described in preliminary form[4] the synthesis of (±)-[6]-gingerol (13), a member of a naturally occurring family of compounds which contain the rather sensitive β-hydroxy-ketone group. Here we detail our previous work and report further findings in this area.

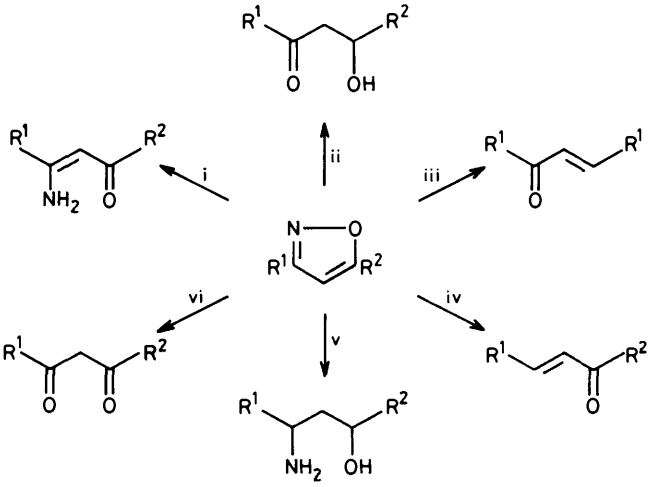
Retrosynthetic analysis suggested that a substituted isoxazole intermediate incorporating the complete carbon atom framework of the target compound (+)-(13) could be constructed *via* a reaction between a suitable isoxazole Wittig reagent and benzyloxyvanillin (Scheme 2).

Thus the required Wittig reagents (6a) and (6b) were prepared in 54 and 50% overall yield respectively starting from methyl pentyl ketone (1) (see Scheme 3).

In addition we were able to improve markedly the yield (90%) of the known isoxazole[5] (3) by modification of the original procedure. The conversion of the isoxazole (3) into the phosphonium salt (6a) and diethyl phosphonate (6b) was carried out by standard methods and illustrates some of the reactions which can be performed while the β-ketol moiety is masked as an isoxazole. Coupling of (6a) with commercially available benzyloxyvanillin (7a) gives rise to a good yield of the styrylisoxazole (8a), which contains the complete carbon atom framework of the title compound.

Platinum-promoted hydrogenolytic fission of the N–O linkage and concomitant saturation of the double bond produces a nearly quantitative yield of the enamino-ketone (9a), without affecting the benzyloxy-protective group.

Treatment of (9a) with benzoyl chloride–pyridine affords the vinylogous imide (10a) which was smoothly reduced by action of methanolic $NaBH_4$ to the alcohol (11a). The latter, without further purification, was dissolved in AcOH–$H_2O$ (9 : 1) and the hydrolytic cleavage of the enamido-function was completed in 2 h at 0 °C to produce the benzyl-gingerol (12a) in 56% yield (Scheme 4).

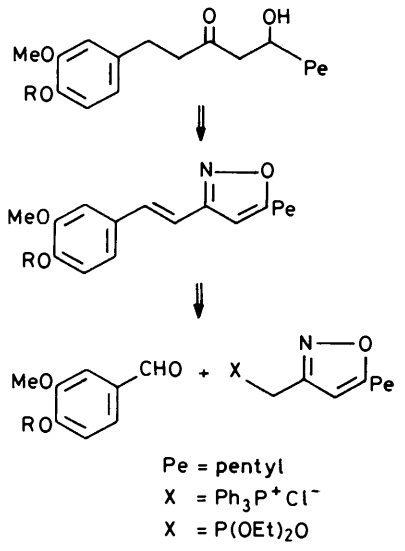



**Scheme 1.** *Reagents*: i, $H_2$, $PtO_2$; ii, $H_2$, $PtO_2$; PhCOCl, Py; $NaBH_4$; 90% AcOH; iii, $H_2$, $PtO_2$; PhCOCl, Py; $NaBH_4$; $H^+$; iv, Na, $NH_{3(l)}$; $SiO_2$; v, Na, n-$C_5H_{11}OH$; vi, $H_2$, $PtO_2$, $H^+$

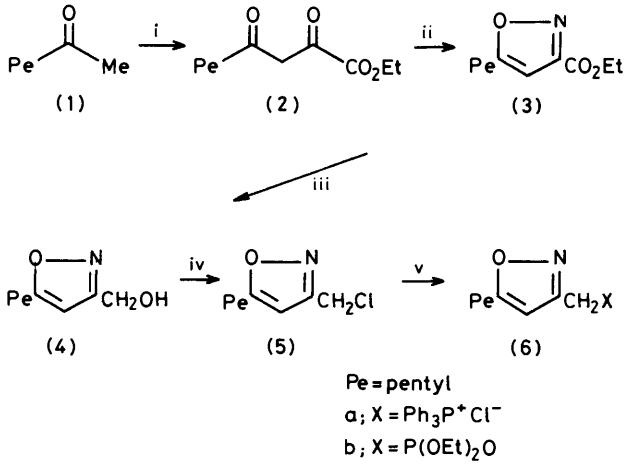
Debenzylation of compound (12a) was accomplished following Ender's method[6] to give the (±)-[6]-gingerol (13) in 80% yield. Having established the feasibility of the route, we investigated the possibility of inducing a degree of optical activity into the β-ketol moiety, the utility of 3,5-disubstituted isoxazoles thereby, as a latent aldol moiety, being greatly enhanced. In seeking a way to induce asymmetry, we planned to repeat the previous sequence using *N*-tosyl-L-prolyl chloride[7] instead of benzoyl chloride,[7] the former compound being available from (*S*)-proline, by a well established procedure.[8]

Thus treatment of compound (9a) with the chiral reagent produced the vinylogous imide (10c) which showed optical activity and was reduced either with sodium borohydride or K-Selectride, to give a mixture of diastereoisomeric alcohols (11c). Removal of the chiral reagent was achieved by hydrolysis with aqueous 90% acetic acid to give the optically active β-ketol (+)-(12a). Finally, the target compound (+)-(13) was obtained by hydrogenolytic debenzylation with C–Pd 10% according to Enders *et al.*[6] The optical yields varied but were in the range of 30—40%, as determined by comparison with the optical rotation of natural [6]-gingerol.

These results parallel well those obtained by Enders[6] on the same compound starting from chiral hydrazone derivatives. Moreover, although the optical purity is not high, the outcome is acceptable when compared with the discouraging




**Scheme 2.**




**Scheme 3.** *Reagents*: i, NaOEt, $(CO_2Et)_2$; ii, $NH_2OH{\cdot}HCl$; iii, $NaBH_4$, MeOH; iv, $SOCl_2$; v, $Ph_3P$, $C_6H_6$ or Na, $HPO(OEt)_2$

experience of Whiting[9] or trying to induce optical activity into the ketol moiety of the same family.

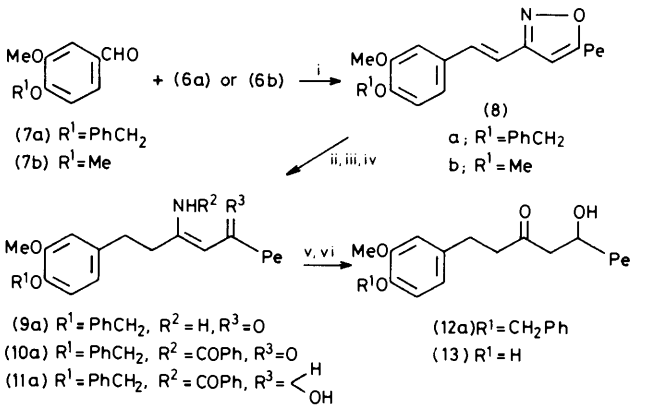
The same sequence was then extended to the synthesis of (+)-(*S*)-methyl-[6]-gingerol (+)-(12c), a compound isolated by Whiting *et al.*[10] after methylation of the crude extract of ginger rhizomes and utilized during their biosynthetic studies.

The enamino-ketone (9b) derived by reductive ring-opening of the styrylisoxazole (8b), in turn obtained by a Wittig reaction of (6a) or (6b) on 3,4-dimethoxybenzaldehyde (7b) (Scheme 5), underwent acylation by treatment with *N*-tosyl-L-prolyl chloride in the presence of pyridine to afford (10b) in good yield. Reductive treatment of the latter as described for (8a) gave (+)-(12c) in 30—40% optical yield (see Scheme 5).

Our results further emphasize the synthetic utility of 3,5-disubstituted isoxazoles as a latent ketol moiety.

## Experimental

M.p.s and b.p.s are uncorrected. The course of reactions and product mixtures were routinely monitored by t.l.c. on silica gel pre-coated 60 $F_{254}$ Merck plates. I.r. spectra were measured



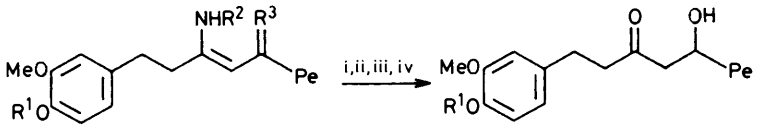

**Scheme 4.** *Reagents*: i, $KOBu^t$, $Me_2SO$; ii, $H_2$, $PtO_2$; iii, PhCOCl, Py; iv, $NaBH_4$, MeOH; v, AcOH 90%; vi, $H_2$, C/Pd 10%

on a Perkin-Elmer 297 spectrometer. $^1H$ N.m.r. spectra were obtained with a Perkin-Elmer R32 spectrometer, and peak positions are given in p.p.m. downfield from tetramethylsilane as an internal standard. All drying operations were performed over anhydrous magnesium sulphate.

*Ethyl 5-Pentylisoxazole-3-carboxylate* (3).—To a solution of ethyl 2,3-dioxo-octanoate[5] (34 g, 159 mmol) in ethanol (250 ml), hydroxylamine hydrochloride (34 g, 490 mmol) was added and the resulting mixture was refluxed for 4 h. The solution was then cooled and concentrated under reduced pressure to leave an oil which was poured into water (300 ml) and extracted with diethyl ether (3 × 100 ml). The combined organic layers were washed with brine (2 × 100 ml), aqueous sodium hydrogen carbonate (100 ml), and brine (100 ml), and then dried and concentrated under reduced pressure. The pale yellow oil was distilled to give a colourless oil (30 g, 90%), b.p. 90—91 °C (0.1 Torr); $\nu_{max.}$ (film) 1 740 and 1 600 $cm^{-1}$; $\delta(CDCl_3)$ 0.9 (3 H, t, *J* 7 Hz, Me), 1.2—1.8 (9 H, m, $CH_2$, $OCH_2Me$), 2.8 (2 H, t, *J* 6 Hz, 5-$CH_2$), 4.4 (2 H, q, *J* 7 Hz, $OCH_2Me_3$), and 6.4 (1 H, s, 4-H) (Found: C, 62.3; H, 8.2; N, 6.5. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11; N, 6.63%).

*5-Pentylisoxazol-3-ylmethanol* (4).—To a stirred and ice-cooled solution of compound (3) (13.4 g, 63.5 mmol) in absolute ethanol (200 ml), sodium borohydride (4.0 g, 131 mmol) was added portionwise. The solution was stirred at room temperature for 5 h, after which the excess of reducing agent was destroyed by careful addition of 5% hydrochloric acid (100 ml). The solution was then concentrated under reduced pressure to eliminate most of ethanol and extracted with diethyl ether (3 × 100 ml). The combined organic layers were washed with brine (2 × 100 ml), dried, and evaporated to dryness. The residue was distilled to afford compound (4) (10.2 g, 94.5%) as a colourless oil, b.p. 98—100 °C (0.1 Torr) $\nu_{max.}$ (film) 3 380 and 1 600 $cm^{-1}$; $\delta(CDCl_3)$ 0.9 (3 H, t, *J* 7 Hz, Me) 4.5 (2 H, s, 3-$CH_2$), 4.9 (1 H, sb, OH), and 6.1 (1 H, s, 4-H) (Found: C, 63.7; H, 8.8; N, 8.2. $C_9H_{15}NO_2$ requires C, 63.88; H, 8.94; N, 8.28%).

*3-Chloromethyl-5-pentylisoxazole* (5).—To a solution of the alcohol (4) (10 g, 59 mmol) in dry diethyl ether, thionyl chloride (15 g, 126 mmol) was added dropwise. The solution was refluxed for 2 h and then concentrated to dryness under reduced pressure. The residual oil was distilled to give compound (5) as a colourless oil (9.1 g, 82.2%), b.p. 130—132 °C (18 Torr), $\nu_{max.}$ (film) 1 600 $cm^{-1}$; $\delta(CDCl_3)$ 0.9 (3 H, t, *J* 7 Hz, Me),

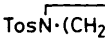


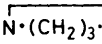

Pe = pentyl

(9b) $R^1$=Me, $R^2$=H, $R^3$=O

(10c) $R^1$=$CH_2Ph$, $R^2$=TosN·$(CH_2)_3$·CH·CO, $R^3$=O

(10b) $R^1$=Me, $R^2$=TosN·$(CH_2)_3$·CH·CO, $R^3$=O

(11c) $R^1$=$CH_2Ph$, $R^2$=TosN·$(CH_2)_3$·CH·CO, $R^3$= 

(11b) $R^1$=Me, $R^2$=TosN·$(CH_2)_3$·CH·CO, $R^3$= 

(+)-(12a; $R^1$=$CH_2Ph$)

(+)-(13 ; $R^1$=H)

(+)-(12c; $R^1$=Me)

**Scheme 5.** *Reagents*: i, TosN·$(CH_2)_3$·CH·COCl/Py; ii, $NaBH_4$, MeOH or K Selectride, THF; iii, AcOH 90%; iv, $H_2$, C-Pd 10%

2.75 (2 H, t, *J* 6 Hz, 5-$CH_2$R), 4.55 (2 H, s, 3-$CH_2$Cl), and 6.10 (1 H, s, 4-H) (Found: C, 57.5; H, 7.6; N, 7.4. $C_9H_{14}ClNO$ requires C, 57.59; H, 7.52; N, 7.46%).

*5-Pentylisoxazol-3-ylmethyl(triphenyl)phosphonium Chloride* (6a).—A mixture of compound (5) (5 g, 27 mmol) and triphenylphosphine (7 g, 27 mmol) in dry benzene was refluxed for 12 h. After the cooled solution had been concentrated under reduced pressure to 50 ml, diethyl ether was added to precipitate (6a) as a white solid; this was filtered off (10.3 g, 86% yield). An analytical sample was purified from a mixture of acetone–diethyl ether (1 : 1) and had m.p. 156—157 °C, δ($CDCl_3$) 0.9 (3 H, t, *J* 7 Hz, $CH_3$), 2.6 (2 H, t, *J* 7 Hz, 5-$CH_2$R), 5.75 (2 H, d, *J* 15 Hz, 3-$CH_2$-P), 6.4 (1 H, s, 4-H), 7.5—8.1 (15 H, m, arom.) (Found: C, 71.9; H, 6.3; N, 3.05. $C_{27}H_{29}ClNOP$ requires C, 72.07; H, 6.50; N, 3.11%).

*Diethyl 5-Pentylisoxazol-3-ylmethylphosphonate* (6b).—To an ice cooled and well stirred suspension of finely pulverized sodium (0.57 g, 25 mg-atom) in dry toluene (20 ml) was added dropwise a solution of diethyl phosphite (3.77 g, 27 mmol) in dry toluene (10 ml), containing a catalytic amount (2—3 drops) of absolute ethanol. During the addition the internal temperature reaction was kept <60 °C. After 1 h, to the resulting yellow solution was added dropwise a solution of the chloromethylisoxazole (5) (4.7 g, 25 mmol) in dry toluene (10 ml) at room temperature. The reaction mixture was heated at 80 °C for 3 h, filtered, and the filtrate washed with water (2 × 10 ml). The organic phase was dried and evaporated under reduced pressure to leave an oily residue which was distilled to give a yellowish oil (5.8 g, 80%), b.p. 128—130 °C/0.05 Torr, $\nu_{max.}$ (film) 1 600, 1 235, and 1 040 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, $CH_3$), 1.3 (6 H, t, *J* 7 Hz, $OCH_2CH_3$), 2.7 (2 H, t, *J* 6.5 Hz, 5-$CH_2$), 3.18 (2 H, d, *J* 20 Hz, 3-$CH_2$), 4.1 (4 H, m, $OCH_2$), and 6.1 (1 H, s, 4-H) (Found: C, 53.65; H, 8.2; N, 4.7. $C_{13}H_{24}NO_4P$ requires C, 53.97; H, 8.36; N, 4.84%).

*General Procedure for the Preparation of Styrylisoxazoles.*—(a) Via *a phosphonium salt*. To a solution of potassium t-butoxide (1.15 g, 10 mmol) in dry dimethyl sulphoxide (10 ml) at room temperature was added the phosphonium salt (6a) (4.6 g, 11 mmol). The mixture was stirred for 10 min until dissolution was complete. The appropriate aldehyde (8.6 mmol) in dimethyl sulphoxide (5 ml) was then added dropwise to the orange-yellow ylide solution. The mixture was stirred for 1 h at 25 °C and then quenched with saturated aqueous sodium chloride (200 ml) and partitioned between diethyl ether and water. The aqueous layer was extracted with additional ether (3 × 50 ml) and the combined ether extracts were washed with saturated aqueous sodium chloride, dried, and evaporated under reduced pressure. The solid residue was chromatographed on silica gel [diethyl ether–light petroleum (1 : 1)] to give a white solid. By this procedure the following compounds were prepared. Compound (7a) from benzylvanillin (3.24 g, 84%), m.p. 80—81 °C (AcOEt–light petroleum, 1 : 1); $\nu_{max.}$ ($CHCl_3$) 1 650, 1 600, and 970 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, *J* 7 Hz, $CH_3$), 2.7 (2 H, t, *J* 7 Hz, 5-$CH_2$R), 3.90 (3 H, s, $OCH_3$), 5.15 (2 H, s, $OCH_2Ph$), 6.15 (1 H, s, 4-H), 6.9—7.2 (5 H, envelope, CH=CH, arom.), and 7.3—7.6 (5 H, m, arom.) (Found: C, 76.15; H, 7.1; N, 3.65. $C_{24}H_{27}NO_3$ requires C, 76.36; H, 7.21; N, 3.71%).

Compound (7b) from methoxyvanillin (1.94 g, 75%), m.p. 56—57 °C (diethyl ether–hexane), $\nu_{max.}$ ($CHCl_3$) 1 650, 1 600, and 960 $cm^{-1}$; δ($CDCl_3$) δ 0.9 (3 H, t, *J* 7 Hz, $CH_3$), 2.75 (2 H, t, *J* 7 Hz, 5-$CH_2$R), 3.87 (3 H, s, $CH_3O$), 3.90 (3 H, s, $CH_3O$), 6.18 (1 H, s, 4-H), and 6.8—7.1 (5 H, m, CH=CH, arom.) (Found: C, 71.7; H, 7.6; N, 4.6. $C_{18}H_{23}NO_3$ requires C, 71.23; H, 7.69; N, 4.65%).

(b) Via *a diethylisoxazolylmethylphosphonate*. A solution of the phosphonate (6b) (4.5 g, 16 mmol) and the aldehyde (benzylvanillin or veratraldehyde, 15 mmol) in dry dimethyl sulphoxide (10 ml) was added dropwise at room temperature to a solution of potassium t-butoxide (1.7 g, 15 mmol) in dry dimethyl sulphoxide (10 ml). After the mixture had been stirred overnight at room temperature, water was added and the aqueous solution extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were washed with saturated aqueous sodium chloride, dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel with diethyl ether–hexane (1 : 1) as eluant. Following this procedure compounds (8a) and (8b) were prepared in 70 and 72% yields respectively; they possessed chemical and spectroscopic properties identical with those reported above.

*General Procedure for the Preparation of Enamino-ketones.*—A solution of styrylisoxazole (10 mmol) in methanol (100 ml) was reduced at atmospheric pressure over a $PtO_2$ catalyst (0.2 g) pre-reduced by adding a small amount of Raney nickel in methanol (20 ml). After the hydrogenation was complete, the mixture was filtered through Celite and concentrated under reduced pressure to give the corresponding enamino-ketone which was used without further purification in the next step. An analytical sample was obtained by chromatography on a silica gel column with diethyl ether as eluant. This procedure

was used in the following cases. Compound (9a), $\nu_{max.}$ ($CHCl_3$) 3 500, 1 620, 1 600, and 1 510 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, *J* 7 Hz, Me), 2.2—2.5 (4 H, m, $PhCH_2CH_2$), 2.8 (2 H, t, *J* 7 Hz, $RCH_2CO$), 3.80 (3 H, s, MeO), 5.0 (1 H, s, =CHCO), 5.05 (2 H, s, $CH_2O$), 6.6—6.9 (3 H, m, arom.), 7.2—7.6 (5 H, m, arom. benzylic), and 9.7 (1 H, sb, NH) (Found: C, 75.4; H, 8.0; N, 3.5. $C_{24}H_{31}NO_3$ requires C, 75.56; H, 8.19; N, 3.67%).

Compound (9b), a gummy oil, $\nu_{max.}$ ($CHCl_3$) 3 500, 1 615, 1 595, and 1 510 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, *J* 7 Hz, Me), 2.15—2.45 (4 H, m, $PhCH_2CH_2$), 2.8 (2 H, t, *J* 7 Hz, $CH_2CO$), 3.8 (3 H, s, $CH_3O$), 3.85 (3 H, s, OMe), 5.0 (1 H, s, CHCO), 6.7—6.9 (3 H, m, arom.), and 9.7 (1 H, sb, NH) (Found: C, 70.7; H, 8.8; N, 4.65. $C_{18}H_{27}NO_3$ requires C, 70.79; H, 8.91; N, 4.59%).

*General Procedure for the Preparation of Vinylogous Imides.*—To an ice-cooled and stirred solution of crude enaminoketone (2.62 mmol) in anhydrous pyridine (6 ml) was added the corresponding acid chloride (8.45 mmol) under nitrogen. After being allowed to stand overnight at room temperature, the mixture was diluted with water (50 ml) and extracted with methylene dichloride (3 × 50 ml). The extracts were washed with saturated aqueous sodium hydrogencarbonate, saturated aqueous sodium chloride, and dried and concentrated under reduced pressure; the residual oil was chromatographed on silica gel. This procedure was used in the following cases. Compound (10a) (eluant: diethyl ether–light petroleum, 7 : 3) (0.95 g, 75%), m.p. 81—82 °C (diethyl ether), $\nu_{max.}$ ($CHCl_3$) 3 500, 1 690, 1 640, and 1 600 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, *J* 6 Hz, Me), 3.9 (3 H, s, MeO), 5.1 (2 H, s, $PhCH_2O$), 5.4 (1 H, s, =CHCO), 6.8—6.95 (3 H, m, arom.), 7.3—8.2 (10H, m, arom. benzoyl), and 12.4 (1 H sb, NH) (Found: C, 76.5; H, 7.05; N, 2.7. $C_{31}H_{35}NO_4$ requires C, 76.67; H, 7.27; N, 2.88%).

Compound (10c) (eluant: diethyl ether–light petroleum, 6 : 4) (1.28 g, 77%), a gummy oil, $\nu_{max.}$ ($CHCl_3$) 3 380, 1 700, 1 650, and 1 600 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, *J* 6 Hz, Me), 2.4 (3 H, s, $MeC_6H_4SO_2$), 3.87 (3 H, s, MeO), 5.1 (2 H, s, $PhCH_2O$), 5.25 (1 H, s, =CHCO), 6.7—6.9 (3 H, m, arom.), 7.3—8.0 (9 H, m, arom.), and 12.8 (1 H, sb, NH), $[\alpha]_D^{24} = -80.58$ (*c* 1, $CHCl_3$) (Found: C, 68.1; H, 6.85; N, 4.4. $C_{36}H_{44}N_2O_6S$ requires C, 68.33; H, 7.01; N, 4.43%).

Compound (10b) (eluant: diethyl ether–light petroleum, 1 : 1) (1 g, 70%) a gummy oil, $\nu_{max.}$ ($CHCl_3$) 3 400, 1 700, 1 650, and 1 600 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, *J* 6 Hz, $Me_3$), 2.45 (3 H, s, $MeC_6H_4SO_2$), 3.85 (3 H, s, OMe), 3.9 (3 H, s, OMe), 5.25 (1 H, s, =CHCO), 6.7—6.9 (3 H, m, arom.), 7.55 (4 H, m, arom.), and 12.9 (1 H, sb, NH); $[\alpha]_D^{24} = -94.5$ (*c* 1, $CHCl_3$) (Found: C, 64.6; H, 7.1; N, 4.95. $C_{30}H_{40}N_2O_6S$ requires C, 64.73; H, 7.24; N, 5.03%).

*General Procedure for the Reduction of Vinylogous Imides.*—(a) Via *sodium borohydride.* To an ice-cooled solution of vinylogous imide (2 mmol) in methanol (30 ml), $NaBH_4$ (10.5 mmol) was added portionwise. The mixture was stirred for 1 h at 0 °C, neutralized with 30% aqueous $NaH_2PO_4$, and extracted with chloroform (3 × 50 ml). The dried extracts were evaporated under reduced pressure to leave the crude alcohol as an oil which was used in the next step without further purification.

By this procedure the following compounds were prepared. Compound (11a) an oil (90%), $\nu_{max.}$ ($CHCl_3$) 3 380, 1 680, and 1 600 $cm^{-1}$; δ($CDCl_3$) 3.85 (3 H, s, OMe) 5.0 [1 H, d, *J* 6 Hz, CH=CH(OH)], and 5.1 (2 H, s, $CH_2Ph$).

Compound (11c) an oil (92%), $\nu_{max.}$ ($CHCl_3$) 3 380, 1 680, and 1 600; δ($CDCl_3$) 2.4 (3 H, s, *p*-Me), 3.85 (3 H, s, OMe), 5.05 [1 H, d, *J* 6 Hz, CH=CH(OH)], 5.1 (2 H, s, $CH_2Ph$).

Compound (11b) an oil (89%), $\nu_{max.}$ ($CHCl_3$) 3 380, 1 680, and 1 600 $cm^{-1}$; δ($CDCl_3$) 2.45 (3 H, s, *p*-Me), 3.85 (3 H, s, OMe), 3.9 (3 H, s, OMe), and 5.05 [1 H, d, *J* 6 Hz, CH=CH-(OH)].

(b) Via *K Selectride.* A 0.5M-solution of K selectride in THF (16 ml, 8 mmol) was added dropwise to a solution of vinylogous imide (3 mmol) in dry THF (20 ml) maintained at —78 °C under nitrogen. After 1 h 30% aqueous $NaH_2PO_4$ (10 ml) was added and the resulting mixture was washed with saturated aqueous sodium chloride. The dried organic phase was evaporated and the crude alcohol used in the next step without further purification. Following this procedure the alcohols (11c) and (11b) possessing the above reported spectral data were obtained in 85 and 88% yield respectively.

(±)-1-(4-*Benzyloxy*-3-*methoxyphenyl*)-5-*hydroxydecan*-3-*one* (12a).—To an ice-cooled and stirred mixture of acetic acid–water (9 : 1; 10 ml) was added the crude alcohol (11a) (1.2 g, 2.3 mmol) in acetic acid (5 ml). The resulting solution was stirred at 0 °C for 2 h, diluted with water (50 ml), and carefully neutralized with solid sodium hydrogencarbonate. The aqueous solution was extracted with diethyl ether (3 × 50 ml) and the combined organic extracts were washed with saturated aqueous sodium chloride, dried, and evaporated under reduced pressure. The residual oil was chromatographed on silica gel with diethyl ether–hexane (6 : 4) as eluant to afford pure compound (12a) (0.53 g, 56%), which solidified with time (m.p. 50—52 °C). An analytical sample was obtained from hexane (m.p. 53—54 °C) or methanol–water (1 : 1) (m.p. 58—59 °C), $\nu_{max.}$ (film) 3 440, 1 710, 1 605, and 1 590 $cm^{-1}$; δ($CDCl_3$) 0.9 (3 H, t, Me), 1.25 (8 H, m, 6-, 7-, 8-, 9-$CH_2$) 2.5 (2 H, m, 4-$CH_2$), 2.8 (4 H, m, 1-, 2-, $CH_2$), 3.87 (3 H, s, OMe), 4.0 [1 H, m, CH(OH)], 6.6—6.9 (3 H, m, $C_6H_3$), 7.3—7.6 (5 H, m, $C_6H_5$); all spectroscopic properties fully agree with the literature values (Found: C, 74.9; H, 8.3. $C_{24}H_{32}O_4$ requires C, 74.97; H, 8.39%).

(+)-1-(4-*Benzyloxy*-3-*methoxyphenyl*)-5-*hydroxydecan*-3-*one* (+)-(12a).—A solution of the crude alcohol (11c) (1.5 g, 2.4 mmol) in acetic acid–water (9 : 1) (10 ml) was stirred for 24 h at room temperature after which the mixture was diluted with water (50 ml) and carefully neutralized with solid sodium hydrogencarbonate. The aqueous solution was extracted with diethyl ether (3 × 50 ml) and the combined organic extracts were dried and evaporated under reduced pressure. The oily residue was chromatographed on silica gel with diethyl ether–hexane (6 : 4) as eluant to afford the pure compound (+)-(12a); this tends to crystallize in a refrigerator (0.59 g, 65%). All spectroscopic properties are identical with those above described for (±)-(12a), $[\alpha]_D^{24} = +7.9$ (*c* 1.1, $CHCl_3$).

(+)-(S)-1-(3,4-*Dimethoxyphenyl*)-5-*hydroxydecan*-3-*one* (+) (12c).—This compound was obtained starting from compound (11b) in a manner essentially identical with that described above for (+)-(12a). After chromatographic purification on silica gel (+)-(12c) was obtained as a colourless oil (60%), which partially solidified in a refrigerator; $[\alpha]_D^{24} = +8.6$ (*c* 1.3, $CHCl_3$). The optical purity, calculated in comparison with the value of the natural compound $[\alpha]_D^{22} = 27.0$ (*c* 1.0, $CHCl_3$)[6], was 32%.

(+)-(S)-1-(4-*Hydroxy*-3-*methoxyphenyl*)-5-*hydroxydecan*-3-*one* (+)-(13), (*S*)-[6]-*Gingerol.*—Following Enders's method (+)-(12a) was debenzylated to give (+)-(*S*)-[6]-gingerol as an oil, $[\alpha]_D^{24} = 9.5°$ (*c* 2.1, $CHCl_3$). The optical purity as calculated by comparison with the value of the natural compound $[\alpha]_D^{24} = 25.1°$ (*c* 1, $CHCl_3$),[6] was 38%.

All the spectroscopic data are identical with those reported.[6]

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