Tetrahedron Letters,Vol.30,No.47,pp 6521-6524,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

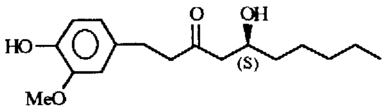
AN ORGANO-IRON MEDIATED CHIRAL SYNTHESIS OF (+)-(S)-[6]-GINGEROL.

Thierry Le Gall, Jean-Paul Lellouche and Jean-Pierre Beaucourt

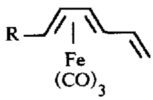
Service des Molécules Marquées, Bt 547, CEN Saclay,
91191 Gif-sur-Yvette Cédex, France.

Summary : A short and efficient synthesis of (+)-(S)-[6]-Gingerol is described. The key step is a highly stereoselective cycloaddition of a nitrile oxide with a chiral iron complexed triene.

The β-hydroxyketone (+)-(S)-[6]-Gingerol 1 is the major pungent principle of *Zingiber officinale* Roscoe. Since its structure has been established (1,2), three enantioselective syntheses of 1 have been reported. Their key steps are an aldol reaction involving the anion of a chiral hydrazone (3), the enantioselective reduction of a chiral vinylogous amide (4) and the separation of diastereomeric chiral 3-sulphinyl methyl-Δ^2-isoxazolines (5).

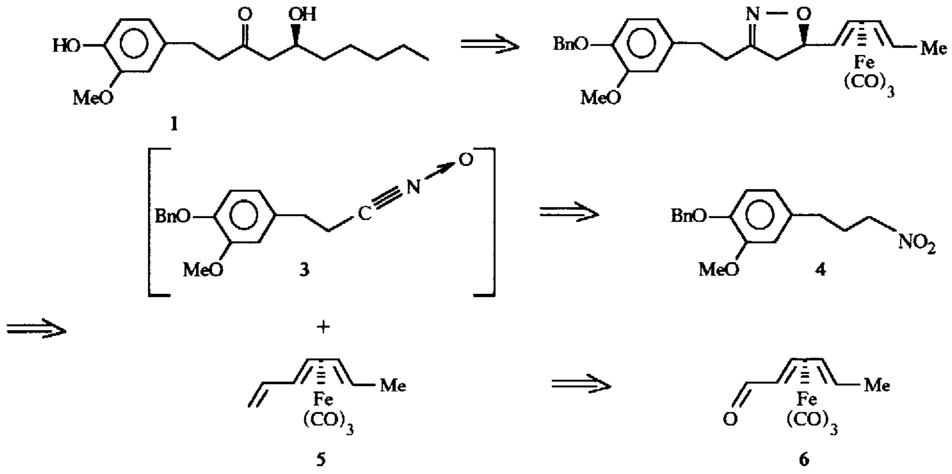


1



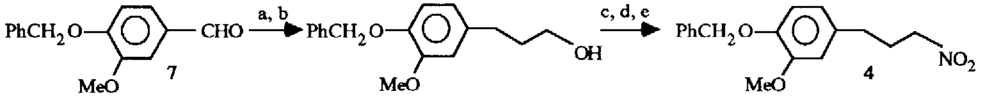
2

The cycloaddition of nitrile oxides with iron complexed trienes of general structure 2 affords the corresponding Δ^2-isoxazolines (6), known as precursors of β-hydroxyketones with good yield and diastereoselectivity. Therefore, using this cycloaddition reaction, we developed a highly enantioselective preparation of 1 according to the retrosynthetic approach shown in scheme 1.



Scheme 1

The nitro compound **4** was prepared in five steps with 33 % overall yield starting from the readily available 4-benzyloxy 3-methoxy benzaldehyde 7 (scheme 2).

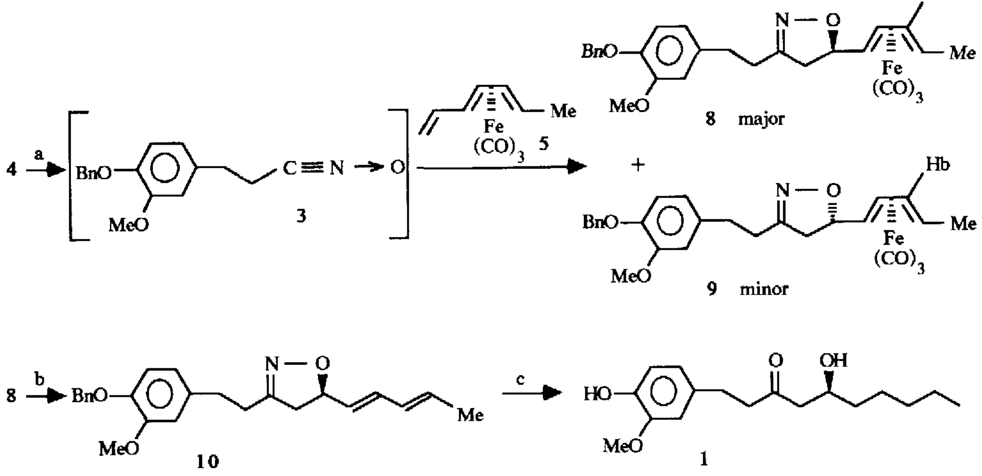


a) $(EtO)_2$ $P(O)CH_2CO_2Et$, NaH, DME, reflux, 24 h (75 %) ; b) $LiAlH_4$, THF-ether : 1-2, room temp., 18 h (86 %) ; c) TsCl, pyridine, + 5°C, 16 h (76 %) ; d) NaI, acetone, room temp., 21 h (86 %) ; e) $AgNO_2$, benzene, room temp., 64 h (78 %).

Scheme 2

Compound 5 was obtained, as previously described for the racemic series (6). The Peterson olefination of the known chiral aldehyde **6** ($[\alpha]^{21}_D$ = - 79°, c = 0.8, MeOH) (7) afforded the iron complexed triene 5 ($[\alpha]^{21}_D$ = + 241°, c = 1.0, MeOH) in 71 % yield. Addition of nitrile oxide 3 generated in situ from **4** (8) to the dipolarophile 5 gave the diastereomeric isoxazolines **8** and **9** (**8**/**9** : 89/11). The **8**/**9** ratio was assayed by integration of the olefinic protons Ha and Hb of the ^{1}H-NMR spectrum of the crude material (C_6D_6, 300 MHz). The major, less polar adduct **8** was recovered in 75 % yield after silica gel chromatography (8:2 hexane/ethyl acetate). The stereochemistry of **8** (9) was based on previous cycloaddition results (6) and on the sign of the optical rotation of the final product 1.

Treatment of **8** with $Ce(NH_4)_2(NO_3)_6$ in methanol at - 20°C afforded the decomplexed isoxazoline **10** (10) in 62 % yield.



a) PhNCO, cat. Et_3N, benzene, room temp., 48 h (yield in **8** : 75 %) ; b) $Ce(NH_4)_2(NO_3)_6$, MeOH, 25 mn, - 20°C (62 %) ; c) 1 atm H_2, Raney Ni, $B(OH)_3$, $MeOH$-H_2O 5-1, room temp., 3.5 h and then 1 atm H_2, 10 % Pd/C, MeOH, room temp., 40 mn (66 %).

Scheme 3

(S)-[6]-Gingerol **1** was obtained from **10** by a two-step hydrogenation process. Cleavage of the isoxazoline ring led to the corresponding β-hydroxyketone (11) (1 atm H_2, Raney Nickel, $B(OH)_3$, $MeOH$-H_2O 5-1, room temperature, 3.5 h). The diene moiety was also partially reduced in this step. The crude mixture was then hydrogenated in presence of 10 % Pd/C (1 atm H_2, MeOH, room temperature, 40 mn), affording compound **1** (12) in 66 % overall yield from **10**.

The optical rotation of **1**, $[\alpha]^{21}_D = + 24°$ (c 1.0, $CHCl_3$), compared to the reported value for optically pure (S)-[6]-Gingerol, $[\alpha]^{24}_D = + 25.1°$ (c 1.0, $CHCl_3$) (2) indicated a 96 % enantiomeric excess.

This paper shows a new application of chiral acyclic iron complexes to the synthesis of optically active compounds. Since it is possible to selectively functionnalize the isoxazoline ring (13), α-substituted as well as unsubstituted chiral β-hydroxyketones may be prepared similarly. Results obtained in the field of eicosanoid chemistry will be reported later.

References and Notes

1 - D.W. Connell, M. D. Sutherland, Aust. J. Chem., 1969, 22, 1033.

2 - T. Murata, M. Shinohara, M. Miyamoto, Chem. Pharm. Bull., 1972, 20, 2291.

3 - D. Enders, H. Eichenauer, R. Pieter, Chem. Ber., 1979, 112, 3703.

4 - P.G. Baraldi, F. Moroder, G.P. Pollini, D. Simoni, A. Barco, S. Benetti, J. Chem. Soc. Perkin Trans. I, 1982, 2983.

5 - M. Cinquini, F. Cozzi, A. Gilardi, J. Chem. Soc., Chem. Comm., 1984, 551.

6 - T. Le Gall, J.P. Lellouche, L. Toupet, J.P. Beaucourt, Tetrahedron Lett., 1989 : see the preceeding paper.

7 - M. Franck-Neumann, D. Martina, M.P. Heitz, Tetrahedron Lett., 1982, 23, 3493.

8 - T. Mukaiyama, T. Hoshino, J. Am. Chem. Soc., 1960, 82, 5339.

9 - **8** (yellow oil) ; IR (film, ν cm^{-1}) : 2940, 2020, 1970, 1610, 1595, 1515, 1455, 1265 ; ^{1}H-NMR (300 MHz, C_6D_6, δ ppm) : 7.36 (d, 2H, J = 7.5 Hz) , 7.20-7.00 (m, 3H), 6.73 (d, 1H, J = 7.9 Hz), 6.63 (s, 1H) , 6.62 (d, 1H, 7.9 Hz), 4.84 (s, 2H), 4.62 (dd, 1H, J = 8.2, 4.9 Hz), 4.27 (dd, 1H, J = 8.8, 4.9 Hz), 4.07 (m, 1H), 3.47 (s, 3H), 2.80-2.60 (m, 2H), 2.55 (dd, 1H, J = 16.8, 10.1), 2.45-2.20 (m, 3H), 0.98 (d, 3H, J = 6.3 Hz), 0.85-0.65 (m, 2H) ; M.S. (EI) : m/z (% intensity) = 461 (2), 433 (6), 342 (6), 177 (16), 91 (100), 56 (34) ; $[\alpha]^{21}_D$ = + 6° (c 1.0, $CHCl_3$).

10 - **10** (white solid, F = 62°C) ; IR (KBr pellet, ν cm^{-1}) : 2870, 1660, 1610, 1590, 1520 ; ^{1}H-NMR (300 MHz, C_6D_6, δ ppm) : 7.36 (d, 2H, J = 7.3 Hz) , 7.20-7.00 (m, 3H), 6.73 (d, 1H, J = 7.6 Hz), 6.65-6.50 (m, 2H), 6.18 (dd, 1H, J = 15.1, 10.4 Hz), 5.95 (dd, 1H, J = 15.7, 9.7 Hz), 5.60-5.40 (m, 2H), 4.85 (s, 2H), 4.75 (m, 1H), 3.47 (s, 3H), 2.71 (t, 2H, J = 7.7 Hz), 2.45-2.25 (m, 3H), 2.13 (dd, 1H, J = 16.8, 8.6 Hz), 1.53 (d, 3H, J = 7.0 Hz) ; M.S. (EI) : m/z (% intensity) = 377 (13 ; M^+), 286 (3), 241 (4), 150 (10), 91 (100), 79 (20), 65 (4) ; $[\alpha]^{21}_D$ = - 112° (c 1.0, $CHCl_3$).

11 - D.P. Curran, J. Am. Chem. Soc., 1983, 105, 5826.

12 - **1** (colorless oil) ; IR (film, ν cm^{-1}) : 3440, 2930, 1705, 1600, 1515, 1465, 1270 ; ^{1}H-NMR (300 MHz, C_6D_6, δ ppm) : 7.0 (d, 1H, J = 8.4 Hz) , 6.53 (d, 1H, J = 8.4 Hz), 6.46 (s, 1H), 5.48 (s, 1H), 3.93 (m, 1H), 3.21 (s, 3H), 2.84 (s, 1H), 2.73 (t, 2H, J = 7.3 Hz), 2.26 (t, 2H, J = 7.3 Hz), 2.10 (dd, 1H, J = 17.1, 8.7 Hz), 1.98 (dd, 1H, J = 17.1, 3.3 Hz), 1.5-1.1 (m, 8H), 0.90 (t, 3H, J = 7.0 Hz) ; M.S. (EI) : m/z (% intensity) = 294 (31 ; M^+), 276 (4), 205 (5), 179 (9), 150 (54), 137 (100) ; $[\alpha]^{21}_D$ = + 24° (c 1.0, $CHCl_3$).

13 - V. Jäger, W. Schwab, Tetrahedron Lett., 1978, 3129.

(Received in France 14 August 1989)