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A CONVENIENT SYNTHETIC ROUTE TO (+)-FARANAL; THE TRAIL PHEROMONE OF PHARAOH'S ANT

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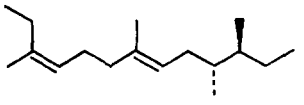
Abstract: (+)-Faranal 1, the trail pheromone of Pharaoh's ant, was synthesized in 10 % overall yield starting from an easily available chiral building block 2 and employing diastereoselective carbon-carbon bond formation.

The trail pheromone of Pharaoh's ant (*Monomorium pharaonis L.*), which is a serious houshold pest all over the world, has been characterised as (3S,4R,6E,10Z)-3,4,7,11-tetramethyl-6,10-tridecadienal 1, named (+)-faranal [1-5].



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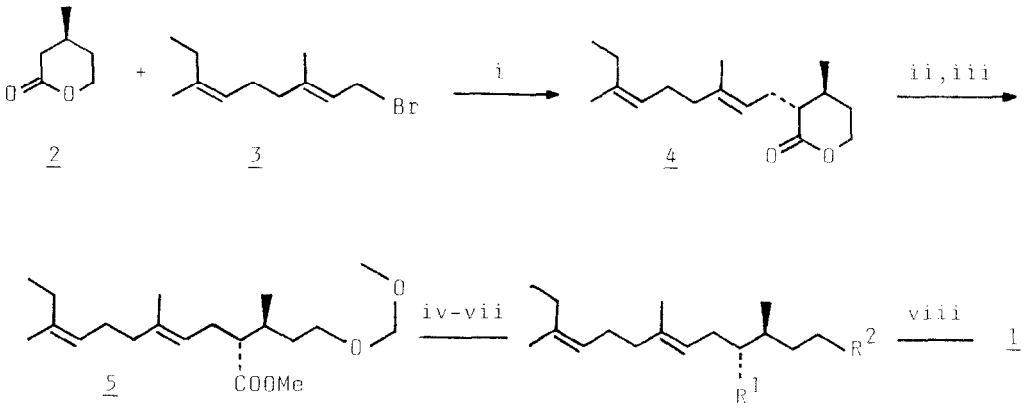
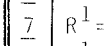
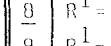
Although four syntheses of (+)-faranal 1 were recorded [2-7], the natural and optically active compound was synthesized only by Kobayashi's group [2,5] and Mori et al. [3,4]. The former procedure gave an approximately 1:1 mixture of diastereomers (3S,4R/3R,4R), while the latter was rather lengthy and required the chemical resolution of an intemediate.

We now report an efficient and stereocontrolled synthesis of (+)-faranal 1, together with a remarkably diastereoselective carbon-carbon bond formation in an electrophilic ester enolate alkylation.



Reagents: i: $LiNEt_2$/THF; ii: Et_3N/MeOH; iii: $ClCH_2OCH_3/Et_3N$, Et_2O; iv: $LiAlH_4$/THF; v: $MsCl/Et_3N$, Et_2O; vi: $LiAlH_4$/THF; vii: MeOH/HCl; viii: PDC/CH_2Cl_2.

6	R^1 = CH_2-OH	R^2 = 
7	R^1 = CH_2-OMs	R^2 = 
8	R^1 = CH_3	R^2 = 
9	R^1 = CH_3	R^2 = OH

Deprotonation of the readily available (S)-(-)-3-methyl-δ-valerolactone 2 [8] (16.7 mmol) with lithium diethylamide (16.7 mmol in THF, -78°C, 1 hr.) generated the corresponding enolate which was reacted with (Z)-6-homogeranyl bromide 3 [9,10] (16.7 mmol, -78°C, 2 hr.). Capillary GC and ^{13}C-NMR analysis of product (63 % isolated yield) showed that the reaction yielded predominantly the desired anti-isomer (2R,3S)-4 [11], together with a small amount of syn-isomer (2S,3S; <6%) [12,13].

The conversion of this lactone 4 into (+)-faranal 1 was accomplished in six steps. Thus, transesterification of 4 with MeOH/Et_3N=2:1 (25°C, 24 hr.) led to a hydroxy ester which was directly converted to protected ester 5 by treatment with chloromethyl methyl ether (3 equiv, 2 equiv of Et_3N, Et_2O, 25°C, 4 hr, 58 % on 4). Reduction of 5 with excess lithium aluminium hydride (2.5 equiv, THF, 30°C, 1 hr, 85 %) gave 6 which was converted to the corresponding mesylate 7 by mesyl chloride in the presence of Et_3N (1.2 equiv, 0 - 20°C, 2 hr, 84 %). The mesylate 7 was reduced by lithium aluminium hydride (4 equiv, THF, reflux, 1 hr, 91 %) and then the protecting group of the resulting ether 8 was removed by acid catalyzed hydrolysis (HCl/MeOH, 25°C, 48 hr, 62 %). Finally, oxidation of the resulting alcohol 9 with pyridinium

dichromate (1.75 mmol, 1.25 equiv, CH_2Cl_2, 25°C, 3 hr, 67%) afforded (+)--faranal 1 in 10 % overall yield (based on 2) and 94 % of isomer purity [14].

In conclusion, our synthetic approach represents a convenient method to prepare large amounts of (+)-faranal 1 in high chemical and stereoisomeric purity.

Acknowledgements: The authors wish to thank to EGIS Pharmaceutical Works for financial support.

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8. Compound 2 was prepared by pig liver esterase (PLE) catalysed enantiotopically-selective hydrolysis of dimethyl 3-methylglutarate followed by ester selective Na - EtOH / NH_3 reduction; see: C. S. CHEN, Y. FUJIMOTO, G. GIRDAUKAS and C. J. SIH: J. Am. Chem. Soc., 104, 7297 (1982); P. MOHR, M. TORI, P. GROSSEN, P. HEROLD and C. TAMM: helv. Chim. Acta, 65, 1412 (1982); P. HEROLD, P. MOHR and C. TAMM: Helv. Chim. Acta, 66, 744 (1983), C. J. FRANCIS and J. B. JONES: J. C. S. Chem. Comm., 579 (1984); reduction: U. JENSEN-KORTE and H. J. SCHAFER: Liebigs Ann. Chem., 1532 (1982).
9. Compound 3 was prepared in 95 % yield from (Z)-6-homogeraniol [10] by treatment with PBr_3 in Et_2O at 0°C under N_2 in darkness.
10. R. M. COATES and M. N. JOHNSON: J. Org. Chem., 45, 2685 (1980).
11. All products showed analytical and spectral (IR, NMR, MS) data consistent with the proposed structures. Some selected characteristics are listed below: 4: IR (film): 1730 (C=O), 1660 (C=C), 1270, 1200, 1140, 1100, 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$,δ): 0.94(t,J=7Hz,3H), 1.09(d,J=6Hz,3H), 1.2 - 1.9(br m,3H), 1.65(br s,6H), 1.9 - 2.8(br m,9H), 4.25(m,2H), 5.09(m,2H); ^{13}C-NMR ($CDCl_3$): 12.81, 16.26, 20.68, 22.85 ($4CH_3$), 24.81, 26.16, 27.79 ($3CH_2$), 29.89 (CH), 30.98, 40.16 ($2CH_2$), 48.32 (CH), 67.48 (OCH_2), 120.69, 123.79, 137.16, 137.72 (4-C=), 173.69 (C=O); (data of the major 3R,4S-isomer);

GC: R_t= 13.84 min, 94 % (3R,4S-isomer); R_t= 13.67 min, 6 % (3S,4S-isomer); 30 m x 0.25 mm SP 2100 glass column, 160 - 260°C, 3°C/min, N_2, FID;

5: IR (film): 173(C=O), 1660(C=C), 1190, 1150, 1105, 1045, 910 cm^{-1}; ^{1}H-NMR (CCl_4,δ): 0.89(d,J=6Hz,3H), 0.95(t,J=6.5Hz,3H), 1.4 - 2.0(br m, 4H), 1.59(s,3H), 1.63(s,3H), 2.0 - 2.4(m,8H), 3.26(s,3H), 3.48(t,J=6.5Hz, 2H), 3.69(s,3H), 4.49(s,2H), 5.03(m,2H).

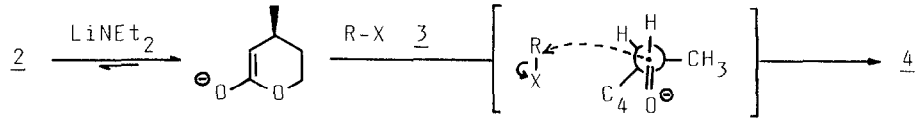
7: IR (film): 1660(C=C), 1360, 1210, 1160, 1100, 1055, 1045, 970, 950 cm^{-1}; ^{1}H-NMR (CCl_4,δ): 0.93 (d and t,6H), 1.5 - 1.9(br m,4H), 1.65 (br s,6H), 2.02(m,8H), 2.88(s,3H), 3.27(s,3H), 3.49(t,J=6Hz,2H), 4.05(d,J=6Hz,2H), 4.49(s,2H), 5.06(m,2H).

9: IR (film): 3350(OH), 1660(C=C), 1450, 1380, 1180, 1110, 1055 cm^{-1}; ^{1}H-NMR (CCl_4,δ): 0.75 - 1.15(d,d,t,9H), 1.4 - 1.9(m,4H), 1.59(s,3H), 1.66(s,3H), 2.0(m,8H), 3.46(s,1H,OH), 3.55(t,J=6Hz,2H), 5.06(m,2H); MS (75 eV): 252(13,M^+), 223(3), 195(12), 179(5), 177(5), 151(7), 137(35), 123(17), 113(13), 109(19), 99(29), 95(49), 83(100), 69(37), 55(79), 41(32).

1: $[\alpha]_D^{23}$= +17.3° (c=2.70, $CHCl_3$); lit [4]: $[\alpha]_D^{23}$= +16.2° (hexane, 90 %ee); IR (film): 2970, 2940, 2880, 2720, 1730, 1665, 1450, 1380, 1120, 1080, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$,δ): 0.84, 0.89, 0.96 (d,d,t,J=6.5,6.5,7Hz,9H), 1.4 - 1.9(br m,4H), 1.59(s,3H), 1.68(s,3H), 2.0(m,8H), 5.10(m,2H), 9.45 (dd,1H); GC: R_t= 21.11 min, 94 % (3S,4R-isomer); 40 m x 0.13 mm OV-1 glass column, 180°C, N_2, FID; MS (75 eV): 250(6,M^+), 232(2), 221(2), 206(2), 203(3), 193(26), 137(21), 123(20), 107(11), 95(18), 83(100), 69(22), 55(78), 43(17), 41(33).

12. The optical purity of the product 1 reflected the enantiomeric purity of lactone 2 (e.e>95 %).

13. This profound anti stereoselection may be rationalized in terms of perpendicular transition states. Here, only one of the possible conformers is stabilized by hyperconjugative interaction.



For recent discussion on stereoselective electrophilic additions to enolates, see: G. J. Mc GARVEY and J. M. WILLIAMS: J. Am. Chem. Soc., 107, 1435 (1985), and references cited therein.

14. GC analysis showed that 1 had 99 % chemical purity and 94 % stereoisomeric purity. R_t(3S,4S-isomer)= 20.87 min (same conditions [11]).

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