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Syntheses of Differanisole A

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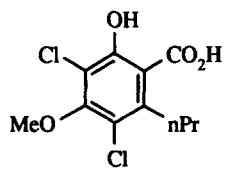
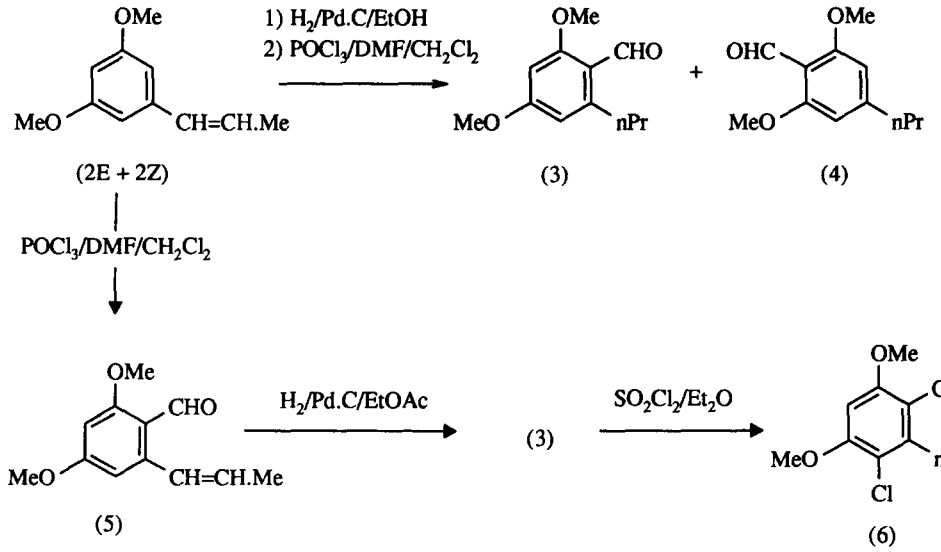
Abstract: Differanisole A has been synthesised by two routes.

In the search for inducers of cell differentiation, Asahi[1] and his co-workers isolated Differanisole A (**1**) from a *Chaetomium* strain which induced the differentiation of several tumour cell lines both *in vitro* and *in vivo*[2]. This represents an interesting synthetic target because of its hexasubstituted aromatic ring. We have undertaken two syntheses of Differanisole A which give multigram quantities in high overall yield and are readily adaptable to the preparation of analogues. The only previous synthesis of this compound[3], although only five steps long, relies upon a notoriously fickle ring-forming reaction and proceeds in an overall yield of around 2.5%

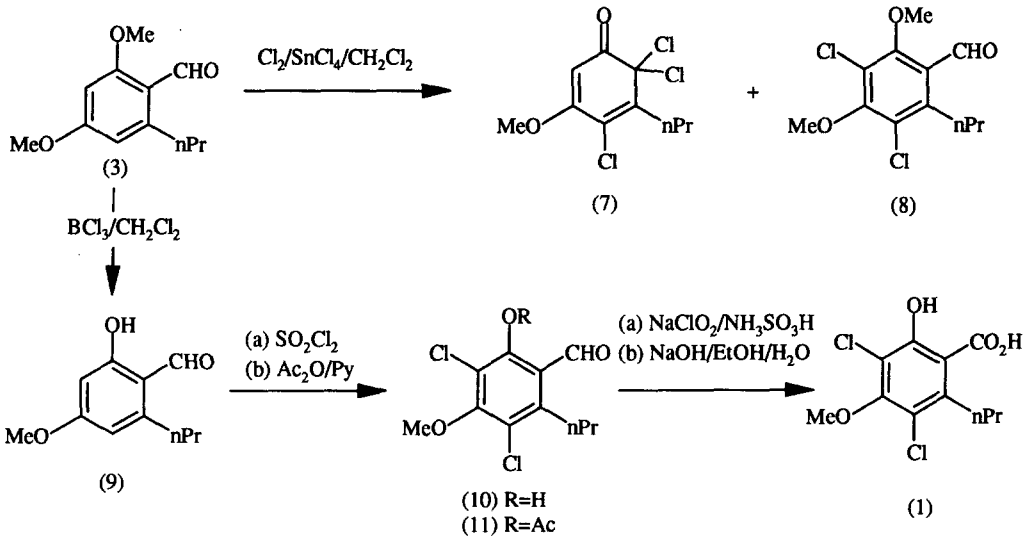


(1)

Reaction of ethyl triphenylphosphorane with 3,5-dimethoxybenzaldehyde gave 1,3-dimethoxy-5-prop-2-enylbenzene (**2**) (Scheme 1) in 91% yield which could be reduced (H_2, Pd/C, EtOH, 90%) and formylated under Vilsmeier conditions ($POCl_3$, DMF, CH_2Cl_2, 24h, RT) to give a readily separable mixture of crystalline aldehydes (**3**) (75%) and (**4**) (21%)[4]. However, the regioselectivity of the Vilsmeier reaction could be improved by formylating the propenylbenzene (**2**) ($POCl_3$, DMF, CH_2Cl_2, 48h, RT); this gave very largely 2,4-dimethoxy-6-propenylbenzaldehyde (**5**) (81%)[5] with only small amounts (5%) of the undesired isomer. Reduction of (**5**) (H_2, Pd/C, EtOAc) gave (**3**) (94%).



Scheme 1

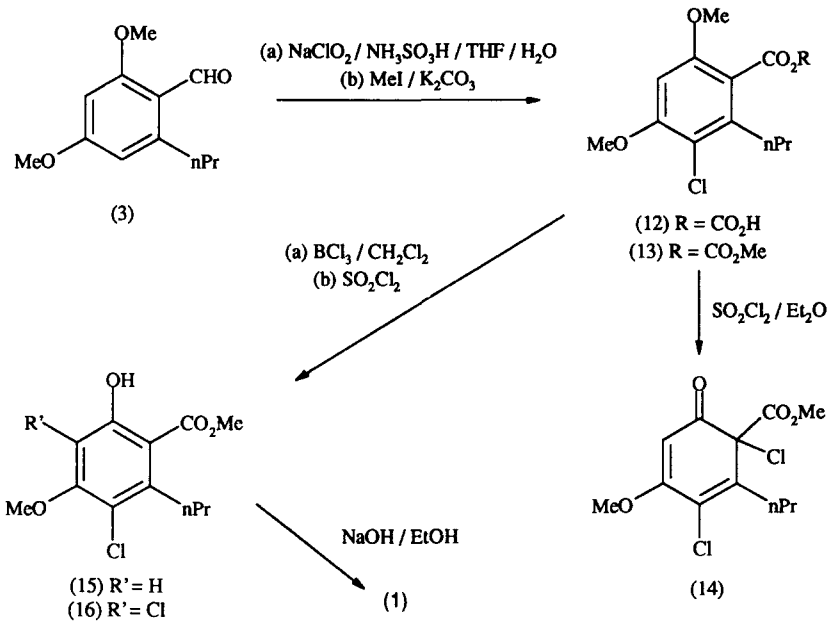


Scheme 2

Chlorination of (**3**) with sulphuryl chloride (SO_2Cl_2,Et_2O, 2h, RT) gave only the deformylated dichloride (**6**)[6], while treatment of (**3**) with chlorine/stannic chloride (Cl_2, $SnCl_4$, CH_2Cl_2, 1h, RT) gave only a 48% yield of the desired dichloride (**8**) along with 14% of the dienone (**7**) (Scheme 2). This was surmounted by chlorinating

the methoxyphenol (**9**) (from treatment of (3) with BCl_3, CH_2Cl_2, 3h, RT, 96%) with neat sulphuryl chloride to give (**10**) as dense yellow crystals in high yield (82%). Direct oxidation of this aldehyde proved to be very difficult with a variety of reagents but the derived acetate (**11**) (Ac_2O, Py, 18h, RT, 91%) oxidised readily with sodium chlorite[7] ($NaClO_2$, NH_3SO_3H, H_2O, THF, 5.5h, RT) to give an unstable acetate which was hydrolysed immediately (NaOH, H_2O, EtOH, 0.75h, RT, 55%) to give (**1**). This material was spectroscopically identical in all respects to Differanisole A isolated by Asahi et al.

Differanisole A could also be prepared from 2,4-dimethoxy-6-propylbenzaldehyde (**3**) by varying the reaction sequence (Scheme 3).



Scheme 3

Oxidation with sodium chlorite ($NaClO_2$, NH_3SO_3H, H_2O, THF, 3h, RT) produced the monochloro-acid (**12**) which could be crystallised directly from the crude reaction product in 71% yield and esterified (MeI, K_2CO_3, Me_2CO, 3h, reflux, 81%) to give (**13**). Treatment of this ester with sulphuryl chloride in ether (SO_2Cl_2, Et_2O, 18h, RT; gave, as the only isolable product, the dienone (**14**, 14%)). The methoxyphenol (**15**) (from (13) by treatment with BCl_3, CH_2Cl_2, 88%) however, upon treatment with sulphuryl chloride (neat SO_2Cl_2, 3h, RT) gave Differanisole A methyl ester (**16**) in high yield (98%). This was hydrolysed to (**1**) under normal conditions (NaOH, H_2O, EtOH, 18h, reflux, 37%).

References and Notes

1. Asahi, K-I.; Oka, H.; Morishima, H.; Sanada, M.; Shiratori, K.; Iimura, Y.; Sanada, M. *J. Antibiotics*, **1985**, 38, 1100; Iimura, Y.; Sakurai, T.; Asahi, K.; Takahashi, N.; Oka, H. *Acta. Crystallogr., sect. C: Cryst. Struct. Commun.*, **1984**, C40 (12), 2058; Takahashi, N.; Asahi, K.; Sakurai, T.; Iimura, Y.; Sanada, M.; Oka, H., Banyu Pharmaceutical Co. Ltd., Japanese Patent 61151149 (**1986**); Kubohara, Y.; Okamoto, K.; Tanaka, Y.; Asahi, K.; Sakurai, A.; Takahashi, N.*FEBS Lett.*, **1993**, 322(1), 73
2. Suzuki, T.; Oka, H.; Okura, A.; Asahi, K.; Takahashi, N.*J. Antibiotics*,**1986**,39,869
3. Mori, K.; Kamada, A; Mori, H. *Liebigs Ann. Chem.*, **1989**, 303
4. These aldehydes were previously reported by Cresp et. al., (Cresp, T.M.; Sargent, M.V.; Elix, J.A.; Murphy, D.P.H. *J. Chem. Soc. (Perkin 1)*, **1973**, 340) but (**3**) was not obtained crystalline.
5. Satisfactory data were obtained for all new compounds. Melting and boiling points were as follows: (**1**) 124-125.5°, (**2**, **E+Z** isomer) 165-170°/0.5mm, (**2**, **E** isomer) 59-62°, (**3**) 36-38°, (**4**) 210-215°/0.5mm, (**5**, E isomer) 54-55°, (**6**) 47.5-48.5°, (**7**) 70-70.5°, (**8**) 103-105.5°, (**9**) 59-60.5°, (**10**) 57.5-58.5°, (**11**) 76.5-78.5°, (**12**) 118-120°, (**13**) 75-76°, (**14**) 90-91°, (**15**) 67-68°.
6. The isomeric identity of this product was evident from the very simple ^{13}C spectrum which indicates symmetry.
7. Lindgren, A.; Nilsson, T. *Acta Chem Scand.*, **1973**, 27, 888: Masschelein, W.J., *Chlorine Dioxide*, (Ed. Rip G. Rice), Ann. Arbor. Science, (Ann Arbor, Mich.), 1979.

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