Stereoselective Synthesis of a Synthon for the Natural Electron Transfer Inhibitors Myxalamide D and Piericidin A

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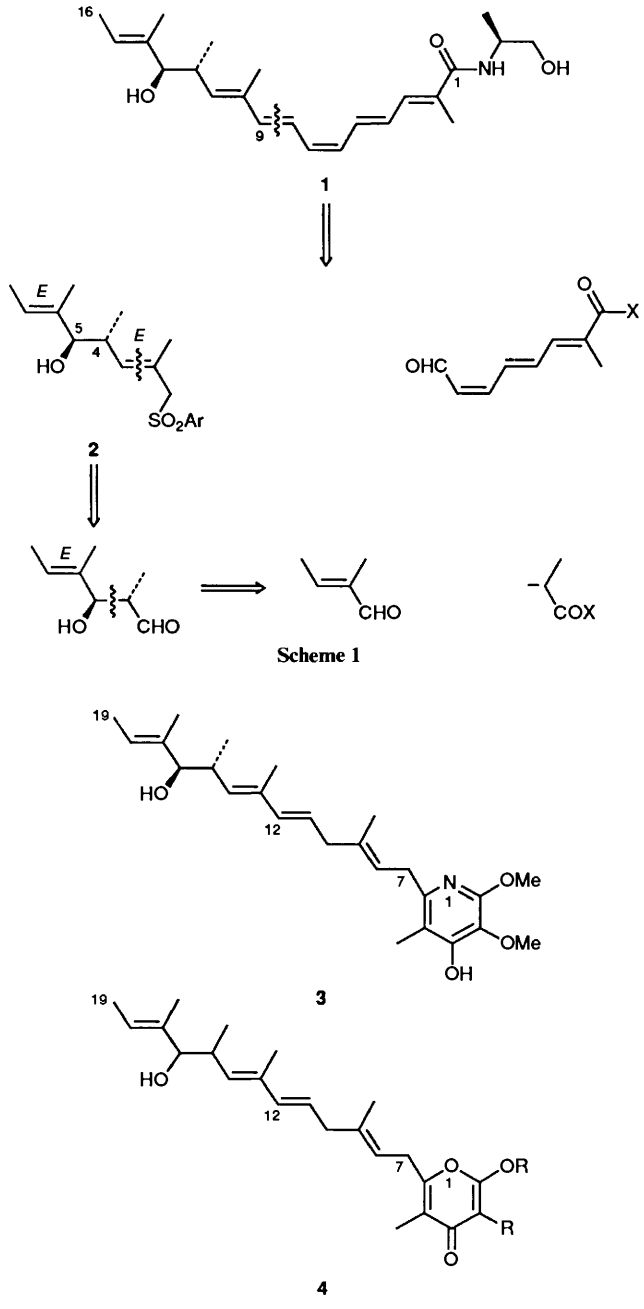
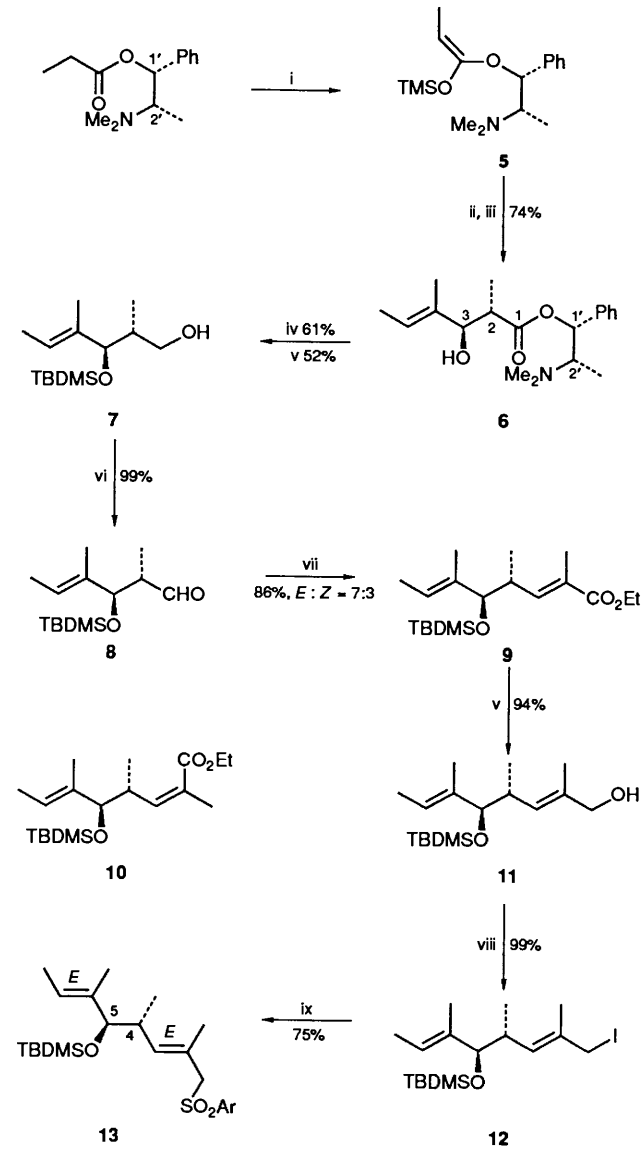
The trimethylsilyl enolate **5** of (1'*R*,2'*S*)-*N*-methylephedrine propionate was condensed with tiglic aldehyde to afford the (1'*R*,2'*S*,2*S*,3*R*)-ester **6** with high stereoselectivity; conversion into the aldehyde **8** was effected without epimerisation, and the sequence **8** ⟶ **9** ⟶ **11** ⟶ **12** ⟶ **13** afforded in 84% e.e. the (+)-(4*R*,5*R*,2*E*,6*E*)-sulphone **13**, a synthon for the electron-transport inhibitors myxalamide D **1** and piericidin A **3**, as well as the actinopyrones **4**.

The section of the respiratory chain which is responsible for the oxidation of NADH to NAD^+, using ubiquinone as hydrogen acceptor, is referred to as Complex I. This complex is sensitive to inhibition by a number of natural compounds, some of which are then potent natural insecticides, *e.g.* rotenone,[1] and piericidin A.[2] Because of this biological activity linked to a well defined site of action, this group of compounds has attracted considerable study. The myxalamides A–D are a new homologous group of antibiotics, found in the gliding bacterium *Myxococcus xanthus* Mx X12,[3] and in *Stigmatella aurantica* Sg a15;[4] the major compound myxalamide B has been shown to be a very effective electron-transfer inhibitor in mitochondria.



Scheme 1



Scheme 2 *Results and conditions:* i, LDA, THF, −73 °C; TMSCl; ii, $TiCl_4$; iii, tiglic aldehyde; iv, TBDMSCl; v, DIBAL; vi, DMSO, $(COCl)_2$, Et_3N; vii, $(EtO)_2P(O)CH^-$, $MeCO_2Et$, room temp., 18 h; viii, Ph_3P, I_2, imidazole; ix, *p*-tolyl SO_2Na.

As part of a general synthetic programme in the area of electron-transport inhibitors, we focussed in myxalamide D **1**, the lowest homologue of the group. In planning a synthesis (Scheme 1) we recognised that the C(9)–C(16) fragment **2** was also a synthon for the C(12)–C(19) unit of piericidin A **3** and the actinopyrones **4**.[5] Thus, stereospecific synthesis of the target sulphone **2** would open the way to three sets of natural products: we report here a route to the (+)-(4*R*,5*R*,2*E*,6*E*)-sulphone, in 84% enantiomeric excess. The essential strategy, Scheme 1, revolves around a chiral aldol condensation between tiglic aldehyde and a suitable propionate, with *anti*-diastereoselectivity. Among the possible literature approaches, that of Gennari and co-workers[6] appeared most suitable. In this method chirality is predictably induced by control from an *N*-methylephedrine ester, with high preference for one of the *anti*-diastereoisomers. Thus we prepared (1′*R*,2′*S*)-*N*-methylephedrine *O*-propionate which was converted into its trimethylsilyl enolate **5** (Scheme 2); the latter was treated sequentially *in situ* with titanium tetrachloride and tiglic aldehyde, to yield the desired hydroxy ester (74% overall)*. Careful NMR examination revealed that one major diastereoisomer **6** was present, with 1′*R*,2′*S*,2*S*,3*R* stereochemistry inferred from the close parallel with Gennari's system. A minor

* In a typical preparation, butyllithium (1.5 mol dm^{-3} in hexane 7.5 cm^3) was added dropwise to a stirred solution of diisopropylamine (1.45 cm^3, 10.2 mmol) in dry THF (20 cm^3) at 0 °C under nitrogen. After 20 min, the solution was cooled to −73 °C, and (1*R*,2*S*)-(2-dimethylamino-1-phenyl)propyl propanoate in THF (10 cm^3) was added dropwise. After the mixture had been stirred at −73 °C for 1 h, trimethylsilyl chloride was added, and the mixture was maintained at −73 °C for 30 min, before being warmed to room temperature during 1–3 h. Evaporation of the solvent gave the silyl ketene acetal **5**. To a solution of this ketene acetal in dichloromethane (8.5 cm^3) at −73 °C under nitrogen was added titanium tetrachloride in dichloromethane (1 mol dm^{-3}, 8.5 cm^3). The dark solution was stirred for 30 min, when (*E*)-2-methylbut-2-enal (0.78 g, 9.3 mmol) in dichloromethane (28 cm^3) was added dropwise. After being stirred at −73 °C for 2–3 h the mixture was quenched with aq. sodium hydrogen carbonate (5 cm^3), and allowed to warm to room temperature. Sodium hydroxide (1 mol dm^{-3}) was added until the pH of the aqueous phase was greater than 7. The mixture was filtered through Celite and extracted with dichloromethane. Evaporation of the dried extracts gave the hydroxy ester **6** (2 g, *ca.* 74%).

amount of the *syn*-isomer (*anti*:*syn*, 9:1) was also present, and a trace of the alternative (1′*R*,2′*S*,2*R*,3*S*) *anti*-isomer (1′*R*,2′*S*,2*S*,3*R*:1′*R*,2′*S*,2*R*,3*S* = 23:2). Purification could be effected at this stage but was more conveniently delayed until after removal of the chiral auxiliary. Thus, after protection of the hydroxy group with *tert*-butyldimethylsilyl, reduction with DIBAL at 0 °C gave the alcohol **7**. The minor *syn* isomer was readily removed by chromatography at this stage, to yield the desired *anti*-(2*R*,3*R*) alcohol **7**; Swern oxidation then afforded the aldehyde **8** without α-epimerisation. Wadsworth–Emmons olefination proceeded slowly at ambient temperature to yield the 2*E*-ester **9**, together with a minor amount of the 2*Z*-isomer **10**; at lower temperatures more 2*Z*-form was produced. Reduction of the ester function, iodination, and displacement with sodium toluenesulphinate all followed smoothly to give the required (+)-sulphone **13**, m.p. 73–75 °C, $[\alpha]_D$ +39.9° ($CHCl_3$), in 84% e.e. [from the *anti*,*anti*′-ratio of ephedrine ester **6**], ready for incorporation into the target natural products **1**–**3** using Julia olefination processes. A higher enantiomeric excess could be achieved at the expense of yield by further chromatographic separation of the required diastereoisomer of the ester **6**.

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