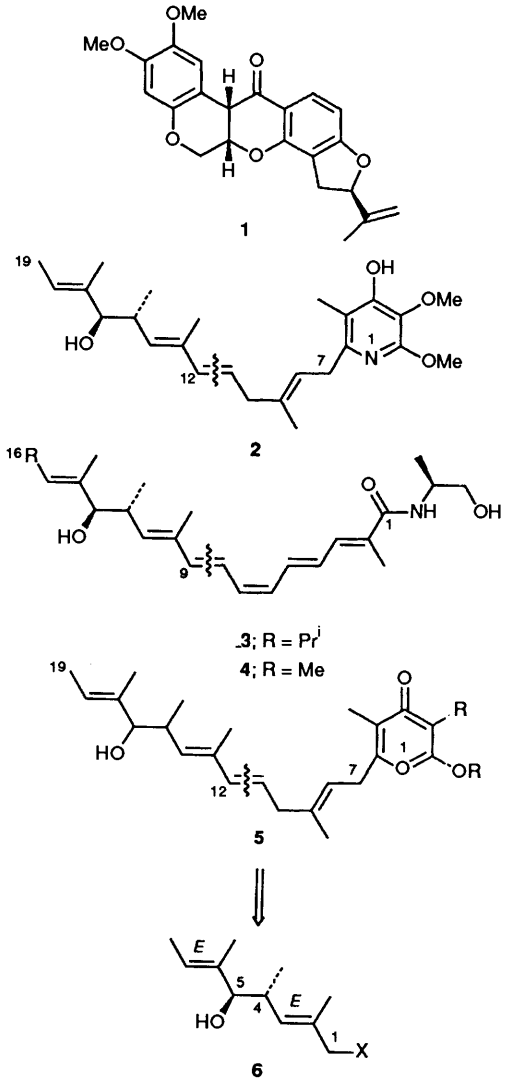
Synthetic Studies on Electron Transport Inhibitors. Part 1. Chiral Synthesis of a Synthon for Myxalamide D, Piericidin A, and the Actinopyrones

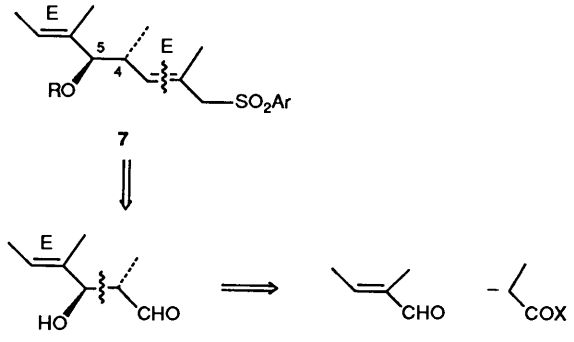
Catherine M. Cox and Donald A. Whiting *
Department of Chemistry, The University, Nottingham, NG7 2RD, UK

The trimethylsilyl enolate **9** 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 **10** with high stereoselectivity; conversion into the aldehyde **12** was effected without epimerisation, and the sequence **12**→**13**→**15**→**19**→**20** afforded in 84% e.e. the (+)-(4*R*,5*R*,2*E*,6*E*)-sulphone **20**, a synthon for the electron transport inhibitors piericidin A **2** and myxalamide D **4**, as well as the actinopyrones **5**.

A central role in cellular bioenergetics is played by the mitochrondrion, which links the energy from oxidation of organic compounds to ATP regeneration. A sequence of redox reactions connects dehydrogenation of substrates to reduction of molecular oxygen. Various elements of this respiration chain have been characterised, and Complex I is that section responsible for the oxidation of NADH to NAD^+ using ubiquinone as hydrogen acceptor.

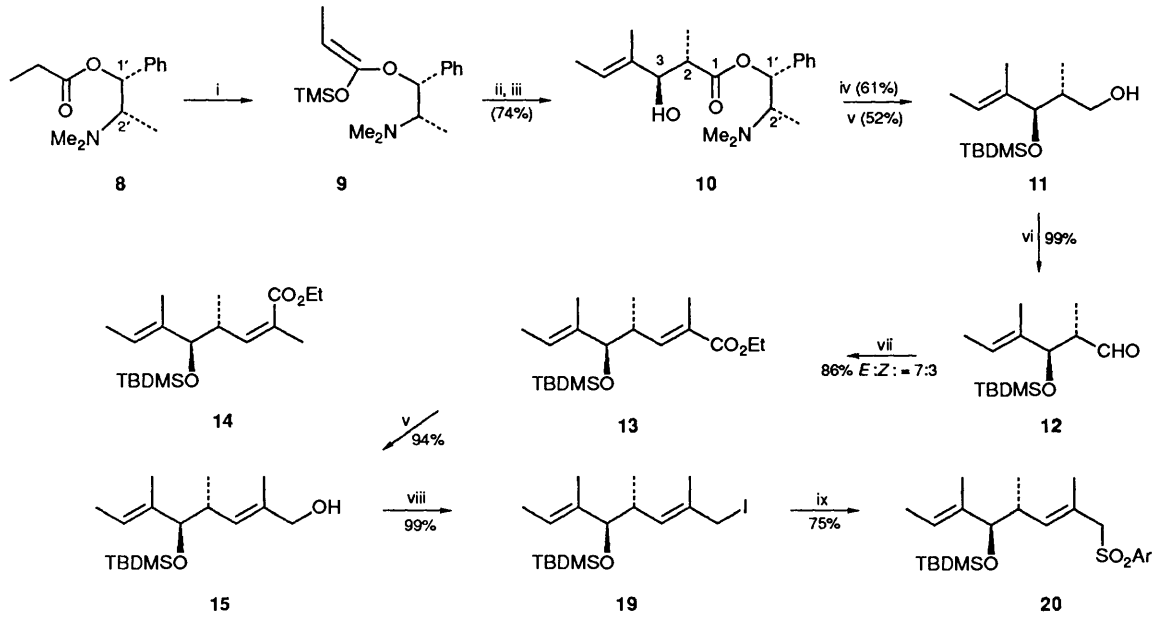
Substances which inhibit Complex I are valuable biochemical tools and are also of potential interest as, for example, insecticides. For these reasons they have been widely studied,[1] and most attention has been paid to inhibitors that act on the ubiquinone side of the electron transfer process, *e.g.* amytal[2] and rotenone **1**.[3–5] Piericidin A **2**[6,7] is one of a group of substituted pyridines isolated from *Streptomyces mobaraensis*. It displays powerful insecticidal properties *via* inhibition of mitochrondial electron transport,[8] binding at the same site as rotenone[9] but more tightly and specifically.[10] The myxalamides[11] are a relatively new group of antibiotics isolated from the gliding bacterium *Myxococcus xanthus* Mx X12 and also identified in *Stigmatella aurantica* Sg a15.[12] Myxalamide B(3), the best studied member of the group, inhibits NADH oxidation at Complex I in beef heart submitochrondrial particles, with 50% inhibition at 170 pm mg^{-1} protein,[11] nearly as effective as piericidin A.





Scheme 1

As part of a general programme on the synthesis and design of electron transport inhibitors we recognised that the C(9)–C(16) substructure of myxalamide D **4** also occurred in piericidin A as C(12)–C(19), and yet again as C(12)–C(19) of the actinopyrone group. The actinopyrones **5** are new physiologically active substances isolated from *Streptomyces pactum*;[13] although the stereochemistry of this group is undefined, it is likely to be parallel to that of the piericidins. Thus, a convergent synthetic route to these natural products was indicated, focussed on the common fragment **6**. As a specific target, the sulphone **7** was selected, with a protected hydroxy group, and with C-1 functionalised to form an *E*-double bond in coupling by the Julia method. In this paper we outline a practical and enantioselective route to this target. The sulphone **7** contains two *E*-olefinic linkages and two chiral centres; we chose to establish these by methods suggested by the disconnections shown in Scheme 1. The essential strategy revolves around a chiral aldol condensation[14,15] between tiglic aldehyde and a suitable propionate. *anti*-Diastereoselectivity was necessary, and it was desirable to be able to direct the synthesis towards

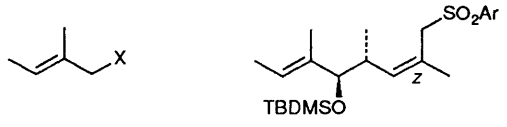


Scheme 2 *Reagents and conditions:* i, LDA, THF, −73 °C, TMSCl; ii, $TiCl_4$; ii, (*E*)-2-methylbut-2-enal; iv, TBDMSCl; v, DIBAL, 0 °C; vi, DMSO-$(COCl)_2$, Et_3N; vii, $(EtO)_2POCH(Me)CO_2Et$, room temp., 18 h; viii, Ph_3P, I_2, imidazole; ix, *p*-tolyl-SO_2Na

either enantiomer (for biological purposes). A number of enantio- and anti-selective aldol strategies have been adumbrated.[16–24] Of these, the approach of Gennari and co-workers[22–24] appeared to be convenient and to offer good selectivity. Chiral control is effected through readily prepared *N*-methylephedrine *O*-ester enolates. Both enantiomers of the control element are available and product chirality is predictably induced. This method was employed by Danishefsky in the synthesis of a zincophorin fragment.[25]

We thus prepared (1′*R*,2′*S*)-*N*-methylephedrine *O*-propionate **8** and formed the corresponding trimethylsilylenolate **9** from the lithium enolate generated at −73 °C. Reaction of the silylketene acetal **9** with titanium tetrachloride and then with (*E*)-2-methylbut-2-enal gave the desired hydroxy ester in 74% overall yield. Careful NMR examination revealed that one major diastereoisomer **10** was present, with 1′*R*,2′*S*,2*S*,3*R* stereochemistry inferred from the close parallel with Gennari's system. A minor 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 removal of the chiral auxiliary. Thus, after protection of the hydroxy group with a *tert*-butyldimethylsilyl group, reduction with diisobutylaluminium hydride (DIBAL) at 0 °C gave the alcohol **11**. The minor *syn* isomer was readily removed by chromatography at this stage, yielding the desired *anti*-(2*R*,3*R*) alcohol **11**; Swern oxidation then afforded the aldehyde **12** without α-epimerisation. Wadsworth–Emmons olefination proceeded slowly at ambient temperature to yield the (2*E*)-ester **13**, together with a minor amount of the (2*Z*)-isomer **14**; at lower temperatures more (2*Z*)-form was produced. The (2*E*)- and (2*Z*)-forms were readily distinguished by NMR, with δ (3-H) 6.62 (13) and 5.77 (14).

Reduction of the ester function with diisobutylaluminium hydride afforded the alcohol **15** in good yield. Before proceeding to formation of the corresponding sulphone we tested two likely protocols using tiglic alcohol as a model. Preparation of the bromide **16** using *N*-bromosuccinimide–dimethyl sulphide at 0 °C, followed by reaction of crude **16** with sodium *t*-toluene-*p*-sulphinate gave sulphone **18** in only 25% yield. However formation of the iodide **17** with triphenylphosphine–iodine–imidazole and immediate conversion into the sulphone **18**



16 X = Br
17 X = I
18 X = SO_2Ar

21

proceeded in 57% yield. This method was then applied to the alcohol **15** to give the required (+)-sulphone **20**, m.p. 73–75 °C, $[\alpha]_D$ = +39.9 ($CHCl_3$), in 84% e.e. (from the *anti,anti′*-ratio of ephedrine ester **10**), ready for incorporation into the target natural products **2**, **4** and **5** 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 **10**.

Carrying through a similar sequence with a mixture of the esters **13** and **14** gave the (2*E*)-sulphone **20** and the (2*Z*)-sulphone **21**, which could be separated chromatographically. Isomers **20** and **21** were distinguished by NMR. Irradiation at 3-H in **20** gave rise to an nOe (3.7%) with 1-H_2; similar irradiation in **21** induced an nOe (5.3%) at the 2-Me. In the ^{13}C NMR spectra of the sulphone **20**, C-1 and 2-Me resonated at δ 60.2 and 24.1 respectively, while the corresponding signals for sulphone **21** appeared at δ 66.7 and 17.1. Work is in progress on utilisation of the sulphone **20** in the synthesis of myxalamide D and other natural and unnatural electron transport inhibitors.

Experimental

M.p.s were determined using a Kofler hot stage and are uncorrected. Kugelrohr distillations were carried out on a Buchi GKR-50 rotating bulb apparatus. Optical rotations were measured on an AA-10/AA-100 digital polarimeter (Optical Activity Ltd.) and $[\alpha]$ values are quoted in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on either an AEI MS 902 or a VG 7070E instrument using EI or CI as appropriate. U.v. spectra were collected with a Phillips PV 8720 spectrometer; log ε follows λ_{max} in parentheses. IR spectra were recorded on a Pye-Unicam SP3-100 instrument as liquid films. ^1H and ^{13}C NMR

spectra were measured on various CW and PFT spectrometers using solutions in deuteriochloroform. Observed splittings (*J*) are given in Hz. In the ^{13}C spectra, CH_3, CH_2, CH and C signals were distinguished by DEPT pulse sequences. Organic solutions were dried with magnesium sulphate; 'evaporation' implies the use of reduced pressure. Thin layer chromatography used Merck Kieselgel 60 F254 or aluminium oxide 60 F254 plates visualised under UV light or by spraying with potassium permanganate, 2,4-dinitrophenylhydrazine, or 10% sulphuric acid as appropriate. 'Ether' means diethyl ether. Temperatures are in °C.

(1R,2S)-2-*Diethylamino*-1-*phenylpropyl Propionate* **8**.—Propionyl chloride (9.5 ml, 0.11 mol) in dry dichloromethane was added dropwise over 20 min to a stirred solution of (1*R*,2*S*)-*N*-methylephedrine (10.69 g, 59.6 mmol) in dichloromethane under nitrogen at 0 °C. The mixture was stirred at room temperature for 4 h and then was treated with saturated aqueous sodium hydrogen carbonate (5 ml). The organic phase was washed with 1 mol dm^3 sodium hydroxide, dried and evaporated to yield the title ester **8** (13.95 g, 99%), sufficiently pure for preparative use. Further purification could be achieved by chromatography on neutral alumina using ether–hexane (1:9); $[\alpha]^{25}$ −46.5 ($CHCl_3$, *c* 1.10) (lit.,[22] $[\alpha]^{23}$ −46.3, $CHCl_3$, *c* 1.19) (Found: *m/z* 235.158. Calc. for $C_{14}H_{21}NO_2$, *M*, 235.157).

(1′R,2′S)-(2′-*Dimethylamino*-1′-*phenylpropyl*) (2S,3R,4E)-3-*Hydroxy*-2,4-*dimethylhex*-4-*enoate* **10**.—Butyllithium (1.5 mol dm^3 in hexane; 7.5 ml) was added dropwise to a stirred solution of diisopropylamine (1.45 ml, 10.2 mmol) in dry THF (20 ml) at 0 °C under nitrogen. After 20 min the solution was cooled to −73 °C, and the ester **8** (2.00 g, 8.5 mmol) in THF (10 ml) was added dropwise. The mixture was stirred at −73 °C for 1 h after which trimethylsilyl chloride (1.3 ml, 10.2 mmol) was added, and the mixture was maintained at −73 °C for 30 min, before being warmed to room temperature over 1–3 h. Evaporation of the solvent gave the silyl ketene acetate **9**. To a solution of this ketene acetal in dichloromethane (8.5 ml) at −73 °C under nitrogen was added titanium tetrachloride in dichloromethane (1 mol dm^{-3}; 8.5 ml). The dark solution was stirred for 30 min, after which tiglic aldehyde (0.78 g, 9.3 mmol) in dichloromethane (28 ml) was added dropwise. After being stirred at −73 °C for 2–3 h the mixture was quenched with aqueous sodium hydrogen carbonate (5 ml), and allowed to warm to room temperature. Sodium hydroxide (1 mol dm^3) was added until the pH of the aqueous phase was >7. The mixture was then filtered through Celite and extracted with dichloromethane. Evaporation of the dried extracts gave the crude aldol product (2 g, *ca.* 74%), which was used in subsequent work without further purification. A sample was purified by chromatography on neutral alumina using ether–hexane (1:5, 1:1, 2:1) to give the title *hydroxy ester* **10** as a pale yellow oil [Found: *m/z* (CI) 320.223; C, 71.15; H, 9.6; N. 4.1. $C_{19}H_{29}NO_3$ requires *M* + H 320.223; C, 71.44; H, 9.15; N, 4.38]; ν_{max}(film)/cm^{-1} 3300br, 1735, 1605, 1585 and 830; δ_H 7.39–7.18 (5 H, m, ArH), 6.34 (1 H, d, *J* 2.8, ArC*H*), 5.75–5.39 (1 H, m, =C*H*), 4.16 (1 H, d, *J* 9.6,C*H*OH), 3.01–2.37 (2 H, m, 2 × C*H*Me), 2.37 (6 H, s, NMe_2), 1.66 (3 H, s, =CRMe), 1.64 (3 H, d, *J* 4, =CH*Me*), 1.14 (3 H, d, *J* 7.0, Me) and 1.00 (3 H, d, *J* 6.8, Me); δ_C 173.9 (s), 139.0 (s), 134.7 (s), 128.1 (2 × d), 127.2 (d), 125.5 (2 × d), 123.2 (d), 79.9 (d), 73.2 (d), 65.4 (d), 45.5 (d), 42.8 (d), 14.1 (q), 12.9 (q), 11.1 (q) and 10.4 (q).

(1′R,2′S)-(2′-*Dimethylamino*-1′-*phenylpropyl*) (2S,3R,4E)-3-(tert-*Butyldimethylsilyloxy*)-2,4-*dimethylhex*-4-*enoate*.—Imidazole (1.55 g, 22.8 mmol) and *tert*-butyldimethylsilyl chloride (2.01 g, 13.3 mmol) were added to a stirred solution of the hydroxy ester **10** (2.17 g, 5.9 mmol) in dry DMF (7 ml) at room temperature under nitrogen. After being stirred at room temperature for 63 h the reaction mixture was quenched by addition of aqueous sodium hydrogen carbonate (25 ml), and the product was extracted into ether. The dried ether extracts were evaporated to leave a brown oil, which was chromatographed in neutral alumina using ether–hexane (1:30, 1:15) to yield the title *silyl ether* (1.57 g, 61%) as an oil [Found: *m/z*(CI) 434.307. $C_{25}H_{43}NO_3Si$ requires *M* + H, 434.309].

(2R,3R,4E)-3-(tert-*Butyldimethylsiloxy*)-2,4-*dimethylhex*-4-*en*-1-*ol* **11**.—Diisobutylaluminium hydride in hexane (1 mol dm^3; 5.1 ml) was added dropwise over 10 min to a stirred solution of the above silyl ester (0.58 g, 1.34 mmol) in dry dichloromethane (30 ml) under nitrogen at 0 °C. After 4 h at 0 °C methanol (10 ml) was added and the mixture was diluted with water (pH 5). The resulting gel was filtered and the aqueous phase was extracted with dichloromethane. Evaporation of the dried organic phases gave an oil which was chromatographed on silica 60 using ether–hexane (1:6, 1:4). The first eluted and major product was the anti-*alcohol* **11** (0.18 g, 52%); $[\alpha]^{25}$ +17.83 ($CHCl_3$, *c* 0.69) (Found: *m/z* 201.133; C, 65.4; H, 12.15%. $C_{14}H_{30}O_2Si$ requires *M* − C_4H_9 201.131; C, 65.06; H, 11.7%); ν_{max}(film)/cm^{-1} 3400br, 1670 and 840; δ_H 5.60–5.22 (1 H, m, =CH), 3.83 (1 H, d, *J* 8.3, CHOSi), 3.74–3.50 (2 H, m, CH_2OH), 2.94 (1 H, t, *J* 5.3, OH), 2.1–1.15 (1 H, m, C*H*CH_2OH), 1.60 (3 H, d, *J* 7.3, =CH*Me*), 1.57 (3 H, s, =CRMe), 0.89 (9 H, s, Bu^t), 0.75 (3 H, d, *J* 7.0, *Me*CH), 0.08 and −0.01 (each 3 H, SiMe); δ_C 136.7 (s), 122.1 (d), 84.8 (d), 67.1 (t), 38.7 (d), 26.0 (3 × q), 18.2 (s), 14.2 (q), 12.9 (q), 11.1 (q), −4.4 (q) and −5.1 (q). A fraction of mixed alcohols (40 mg) was then eluted, followed by the syn-*alcohol* (13 mg, 4%) (Found: *m/z* 201.133); δ_H 5.63–5.24 (1 H, m, =CH), 3.92 (1 H, d, *J* 6.4, CHOSi), 3.6–3.4 (2 H, m, CH_2OH), 2.2–1.6 (1 H, m, C*H*CH_2OH), 1.62 (3 H, d, *J* 5, =CH*Me*), 1.59 (3 H, s, =CRMe), 0.90 (9 H, s, Bu^t), 0.89 (3 H, d, *J* 6.8, *Me*CH) and 0.05 and 0.02 (each 3 H, s, SiMe).

(2S,3R,4E)-3-(tert-*Butyldimethylsiloxy*)-2,4-*dimethylhex*-4-*enal* **12**.—Dry DMSO (0.94 g, 12.1 mmol) was added dropwise to a solution of freshly distilled oxalyl chloride (0.76 g, 6.02 mmol) in dry dichloromethane (20 ml) at −60 °C under nitrogen. The mixture was stirred for 7 min before a solution of the alcohol **11** (0.82 g, 3.17 mmol) in dry dichloromethane (5 ml) was added dropwise. The mixture was stirred at −60 °C for 20 min when triethylamine (2.41 g, 23.8 mmol) was added dropwise. After being stirred at −60 °C for 5 min the mixture was allowed to warm to room temperature over 20 min and then diluted with water. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with brine, dried and evaporated. The residue was taken up in pentane and filtered free of solid ammonium salt. Evaporation afforded the title *aldehyde* **12** (0.81 g, 99%) (Found: *m/z* 199.119. $C_{14}H_{28}O_2Si$ requires *M* − C_4H_9 199.115); ν_{max}(film)/cm^{-1} 2710, 1730 and 840; δ_H 9.75 (1 H, d, *J* 2.9, CHO), 5.7–5.2 (1 H, m, =CH), 4.08 (1 H, d, *J* 8.5, CHOSi), 2.7–2.2 (1 H, m, CHCO), 1.61 (3 H, d, *J* 6.2, =CH*Me*), 1.58 (3 H, s, =CRMe), 0.85 (9 H, s, Bu^t), 0.85 (3 H, d, *J* 6.9, MeC•CO) and 0.02 and −0.03 (each 3 H, s, SiMe).

Ethyl (4R,5R,2E,6E)-5-(tert-*Butyldimethylsilyloxy*)-2,4,6-*trimethylocta*-2,6-*dienoate* **13**.—Triethyl 2-phosphonopropanoate (220 mg, 0.92 mmol) was added dropwise to a stirred suspension of sodium hydride (26 mg, 1.08 mmol) in dry THF (7 ml) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 5 min and at room temperature for 10 min. The aldehyde **12** (229 mg, 0.89 mmol) in THF (4 ml) was then added over 5 min to the mixture, at 0 °C. The reaction mixture was allowed to warm to room temperature after which it was stirred for 18 h; it was then diluted with water and extracted with ether. Work-up gave a

yellow oil which was chromatographed on a short silica column using ether–hexane (1:10) to afford the desired ester (261 mg, 86%) as a 7:3 mixture of 2*E*- and 2*Z*-isomers {GLC 160 °C, 5% Carbowax 20M, R_t 5.0 min (2*Z*) and 7.8 min (2*E*)}. Further chromatography on silica gel 60 with ether–hexane (1:20, 1:15) provided the title (2E)-*ester* **13**, $[\alpha]^{23}$ +13.1 ($CHCl_3$, *c* 1.13) (Found: *m/z* 325.220 and 283.173. $C_{19}H_{35}O_3Si$ requires *M* $-CH_3$ 3.25.220 and *M* $-C_4H_9$ 283.173); λ_{max}(EtOH)/nm 221 (4.072); ν_{max}(film)/cm^{-1} 1710, 1650 and 840; δ_H 6.62 (1 H, d, *J* 10.1, =CHCCO$_2$Et), 5.36 (1 H, q, *J* 7, =CHMe), 4.22 (1 H, dq, *J* 11 and 7.1, OCH*H*Me), 4.41 (1 H, dq, *J* 11 and 7.1, OC*H*HMe), 3.72 (1 H, d, *J* 8.3, CHOSi), 2.64 (1 H, ddq, *J* 10.1, 8.3 and 7, CHMe), 1.85 (3 H, d, *J* 1.3, MeCCO$_2$Et), 1.60 (3 H, d, *J* 7, =CH*Me*), 1.56 (3 H, s, *Me*C=CHMe), 1.28 (3 H, t, *J* 7.1, OCH$_2$*Me*), 0.81 (9 H, s, Bu^t), 0.79 (3 H, d, *J* 7, MeCH), −0.03 and −0.07 (each 3 H, s, SiMe); δ_C 168.5 (s), 146.3 (d), 136.8 (s), 127.5 (s), 122.1 (d), 83.4 (d), 60.2 (t), 38.2 (d), 25.8 (3 × q), 18.2 (s), 16.5 (q), 14.4 (q), 13.0 (q), 12.7 (q), 10.8 (q), −4.7 (q) and −5.0 (q).

(2E)-2-*Methyl*-1-p-*Tolylsulphonylbut*-2-*ene* **18**.—(*a*) Dimethyl sulphide (5.1 g, 82 mmol) was added over 5 min to *N*-bromosuccinimide (12.5 g, 70 mmol) in dichloromethane (200 ml) at 0 °C under nitrogen; the resulting solution was cooled to −23 °C and treated with (*E*)-2-methylbut-2-enol (4.0 g, 46.5 mmol, prepared from tiglic acid). The mixture was stirred in the dark for 1 h and then allowed to warm to 0 °C; after 2.5 h at 0 °C the mixture was diluted with hexane and washed with brine. The aqueous phase was extracted with ether and the combined organic phases were dried and evaporated to yield the crude allylic bromide **16** (10.2 g). This was dissolved in DMF (100 ml) and treated with sodium toluene-*p*-sulphinate hydrate (10 g, 47 mmol). The solution was stirred at room temperature for 15 h, diluted with water and extracted with ether. The washed, dried extracts were evaporated to leave an oil which was chromatographed on silica gel 60 with ether–hexane (1:8, 1:4) to give the *p*-tolyl sulphone **18** (2.36 g, 23% from the alcohol) as white prisms from ether–hexane, m.p. 68–69.5 °C (lit.,[26] m.p. 68.5–69.5 °C) (Found: *m/z* 224.090; C, 64.3; H, 7.4. Calc. for $C_{12}H_{16}O_2S$: *M*, 224.087; C, 64.25; H, 7.19%).

(*b*) Triphenylphosphine (2.98 g, 11.4 mmol) and imidazole (0.87 g, 12.8 mmol) were added to a solution of (*E*)-2-methylbut-2-enol (0.5 g, 5.8 mmol) in dry acetonitrile (10 ml) and ether (15 ml) at 0 °C. Iodine (3.49 g, 13.8 mmol) was added to the mixture over 5 min, and the slurry was stirred in the dark at 0 °C under nitrogen for 30 min. It was then diluted with pentane and washed in turn with saturated aqueous sodium thiosulphate, aqueous cupric sulphate and water. Evaporation of the organic phase gave the allylic iodide **17** (0.9 g, 79%) as a yellow oil. Part (0.78 g) of this sample was dissolved in DMF (10 ml) and treated with sodium toluene-*p*-sulphinate hydrate (1.24 g, 5.8 mmol). The mixture was stirred in the dark under nitrogen for 21 h and then diluted with water and brine. Evaporation of the organic phase afforded the tolyl sulphone **18** (0.65 g, 73%), indistinguishable from the above sample.

(4R,5R,2E,6E)-5-(tert-*Butyldimethylsilyloxy*)-2,4,6-*trimethyl*-*octa*-2,6-*dienol* **15**.—Diisobutylaluminium hydride in hexane (1 mol dm^3; 1.25 ml) was added dropwise to a solution of the ester **13** (99 mg, 0.29 mmol) in dichloromethane (7 ml) at −5 °C under nitrogen. The solution was stirred at −5/0 °C for 5 h, when the product was isolated as in the preparation of compound **11** to yield the *alcohol* **15** (92.2 mg, 94%) as an oil [Found: *m/z*(CI) 281. $C_{17}H_{34}O_2Si$ requires *M* − OH 281]; ν_{max}(film)/cm^{-1} 3315, 1670 and 840; δ_H 5.49–5.12 (2 H, m, 2 × =CH), 4.01 (2 H, m, CH_2OH), 3.66 (1 H, d, *J* 9, CHOSi), 2.8–2.3 (1 H, m, C*H*Me), 1.68 (3 H, d, *J* 1.3, *Me*CCOH), 1.60 (3 H, d, *J* 6, =CH*Me*), 1.56 (3 H, s, *Me*C=CMe), 0.84 (9 H, s, Bu^t), 0.76 (3 H, d, *J* 6.8, CH*Me*), −0.02 and −0.06 (each 3 H, s, SiMe); δ_C 137.3 (s), 134.3 (s), 130.7 (d), 121.3 (d), 83.5 (d), 69.2 (t), 37.0 (d), 25.9 (3 × q), 18.2 (s), 17.5 (q), 14.0 (q), 12.9 (q), 11.0 (q), −4.6 (q) and −5.0 (q).

(4R,5R,2E,6E)-5-(tert-*Butyldimethylsilyloxy*)-2,4,6-*trimethyl*-p-*tolylsulphonylocta*-2,6-*diene* **20**.—Triphenylphosphine (224 mg, 0.85 mmol) and imidazole (74.8 mg, 1.1 mmol) were added in one portion to a stirred solution of the allylic alcohol **15** (126 mg, 0.422 mmol) in dry acetonitrile (0.8 ml) and ether (1.2 ml) at 0 °C. Iodine (280 mg, 1.1 mmol) was added to the mixture over 5 min and the slurry was stirred in the dark at 0 °C under nitrogen for 30 min. The product was isolated as in preparation (*b*) of compound **18** to yield the title iodide **19** (170 mg, 99%) as a pale yellow oil (Found: *m/z* 351.066. $C_{17}H_{33}IOSi$ requires *M* − Bu, 351.064); δ_H 5.51 (1 H, d, *J* 10, HC=CCI), 5.33 (1 H, q, *J* 6, =C*H*Me), 3.94 (2 H, s, CH_2I), 3.67 (1 H, d, *J* 7.4, CHOSi), 2.68–2.17 (1 H, m, C*H*Me), 1.77 (3 H, d, *J* 1.3, MeCCI), 1.58 (3 H, d, *J* 6, =CH*Me*), 1.55 (3 H, s, *Me*C=CHMe), 0.84 (9 H, s, Bu^t), 0.75 (3 H, d, *J* 7, CH*Me*), −0.01 and −0.06 (each 3 H, s, SiMe). The product contained a trace of triphenylphosphine oxide and was used without further purification. Sodium-toluene-*p*-sulphinate hydrate (107 mg, 0.50 mmol) was added to a solution of the iodine **19** (170 mg, 0.42 mmol) in dry DMF (1 ml). The mixture was stirred in the dark at room temperature for 21 h and then diluted with water (1 ml). The product was isolated as in preparation (*b*) of compound **18** to yield a solid product which was purified by flash chromatography on silica gel 60 using ether–hexane (1:22) to give the p-*tolylsulphone* **20** (136 mg, 75%) as needles from ether–hexane, m.p. 73–75 °C; $[\alpha]^{21}$ +39.9 ($CHCl_3$, *c* 1.5) (Found: *m/z* 379.174 C, 66.05; H, 9.25. $C_{24}H_{40}O_3SSi$ requires *M* − Bu, 379.176; C, 66.05;, H, 9.15%); λ_{max}(EtOH)/nm 225 (4.179); ν_{max}/cm^{-1} 1595., 1320, 1305, 1295, 1150, 865 and 840; δ_H 7.71 (2 H, d, *J* 8, ArH), 7.31 (2 H, d, *J* 8, ArH), 5.24 (1 H, q, *J* 6.7, =C*H*Me), 4.85 (1 H, d, *J* 9.7, HC=CS), 3.69 (2 H, s, CH_2S), 3.51 (1 H, d, *J* 7.5, CHOSi), 2.43 (3 H, s, ArMe), 2.55–2.35 (1 H, m, C*H*Me), 1.74 (3 H, d, *J* 1.3, CH_3CCS), 1.55 (3 H, br d, *J* 6.7, =CH*Me*), 1.47 (3 H, s, *Me*C=CHMe), 0.78 (9 H, s, Bu^t), 0.52 (3 H, d, *J* 6.8, CH*Me*), −0.11 and −0.13 (each 3 H, s, MeSi); irradiation at δ 4.85 induced an NOE (3.7%) at δ 3.69; δ_C 144.4 (s), 140.4 (d), 136.8 (s), 135.7 (s), 129.5 (2 × d), 128.7 (2 × d), 122.8 (s), 121.4 (d), 82.8 (d), 66.7 (t), 37.7 (d), 25.8 (3 × q), 21.6 (q), 18.1 (s), 17.1 (q), 16.8 (q), 13.0 (q), 11.0 (q), −4.7 (q) and −5.1.

(4R,5R,2Z,6E)-5-(tert-*Butyldimethylsilyloxy*)-2,4,6-*trimethyl*-1-p-*tolylsulphonylocta*-2,6-*diene* **21**.—In a preparation parallel to the preceding one but using a mixture of 2*E*- and 2*Z*-iodides (150 mg) (from the corresponding 2*E*- and 2*Z*- esters) an oil was isolated which on chromatography on silica gel 60 with ether–hexane (1:20) gave (first eluted) the (2Z)-*sulphone* **21** (36 mg, 22%) as a pale yellow oil (Found: *m/z* 379.179); λ_{max}(EtOH)/nm 225 (4.130); ν_{max}($CHCl_3$)/cm^{-1} 1595, 1315, 1305, 1295, 1145, 865 and 840; δ_H 7.77 (2 H, d, *J* 8, ArH), 7.33 (2 H, d, *J* 8, ArH), 5.23 (1 H, q, *J* 6.7, =C*H*Me), 5.15 (1 H, d, *J* 10, HC–CCS), 4.34 (1 H, d, *J* 14.1, C*H*HS), 3.47 (1 H, d, *J* 14.1, CH*H*S), 3.39 (1 H, d, *J* 8.9, CHOSi), 2.43 (3 H, s, ArMe), 2.11 (1 H, ddq, *J* 10.0, 8.9, 6.6, CHMe), 1.81 (3 H, d, *J* 1.3, MeCCS), 1.55 (3 H, br d, *J* 6.7, =CHMe), 1.44 (3 H, s, *Me*C=CHMe), 0.77 (9 H, s, Bu^t), 0.28 (3 H, d, *J* 6.6, =CH*Me*), −0.12 and −0.13 (each 3 H, s, SiMe); irradiation at δ 5.15 induced NOEs at δ 3.39 (5.7%) and at δ 1.81 (5.3%); δ_C 144.5 (s), 139.0 (d), 136.5 (s), 136.4 (d), 129.7 (2 × d), 128.6 (2 × d), 123.1 (s), 122.1 (d), 83.4 (d), 60.2 (t), 37.4 (d), 25.7 (3 × q), 24.1 (q), 21.6 (q), 18.0 (s), 16.4 (q), 13.0 (q), 10.4 (q), −4.8 (q) and −5.0 (q). The (2*E*)-sulphone (49 mg, 30%), identical to the above sample, was eluted in later fractions.

Acknowledgements

We thank Wellcome Environmental Health for support.

References

1 B. T. Storey, 'Inhibitors of Energy-Coupling Site 1 of the Mitochrondrial Respiratory Chain,' in *Inhibitors of Mitochondrial Functions, International Encyclopedia of Pharmacology and Therapeutics*,' Section 107, ed. M. Erecinska and D. F. Wilson, Pergamon Press, Oxford, 1981.
2 L. Ernster, O. Jalling, H. Low and O. Lindberg, *Exptl. Cell Res. Suppl.*, 1955, **3**, 124.
3 P. E. Lindahl and K. E. Oberg, *Exptl. Cell Res.*, 1961, **23**, 228.
4 L. Ernster, G. Dallner and G. F. Azzone, *J. Biol. Chem.*, 1963, **238**, 1124.
5 T. P. Singer and M. Gutman, *Adv. Enzymol.*, 1971, **34**, 79.
6 (*a*) S. Yoshida, S. Shiraishi, K. Fujita and N. Takahashi, *Tetrahedron Lett.*, 1975, 1863; (*b*) S. Yoshida, S. Shiraishi and N. Takahashi, *Agr. Biol. Chem.*, 1977, **41**, 587.
7 R. Jansen and G. Hofle, *Tetrahedron Lett.*, 1983, **24**, 5485.
8 M. Jeng, C. Hall, F. L. Crane, N. Takahashi, S. Tamura and K. Folkers, *Biochemistry*, 1968, **7**, 1311.
9 D. J. Horgan, T. P. Singer and J. E. Casida, *J. Biol. Chem.*, 1968, **243**, 834.
10 D. J. Horgan, H. Ohno, T. P. Singer and J. E. Casida, *J. Biol. Chem.*, 1968, **243**, 5967.
11 (*a*) K. Gerth, R. Jansen, G. Reifenstahl, G. Hofle, H. Irschik, B. Kunze, H. Reichenbach and G. Thierbach, *J. Antibiotics*, 1983, **36**, 1150; (*b*) R. Jansen, G. Reifenstahl, K. Gerth, H. Reichenbach and G. Hofle, *Liebigs Ann. Chem.*, 1983, 1081.
12 G. Hofle, B. Kunze, C. Zorzin and H. Reichenbach, *Liebigs Ann. Chem.*, 1984, 1883.
13 K. Yano, K. Yokoi, J. Sato, J. Oono, T. Kouda, Y. Ogawa and T. Nakashima, *J. Antibiotics*, 1986, **39**, 32, 38.
14 T. Mukaiyama, *Org. Reactions*, 1982, **28**, 203.
15 D. A. Evans, J. V. Nelson and T. R. Taber, *Topics in Stereochemistry*, 1982, **13**, 1.
16 A. I. Meyers and Y. Yamamoto, *Tetrahedron*, 1984, **40**, 2309.
17 S. Masumune, T. Sato, B. M. Kim and T. A. Wollman, *J. Am. Chem. Soc.*, 1986, **108**, 8279.
18 S. Masumune, T. Kaiho and D. S. Garvey, *J. Am. Chem. Soc.*, 1982, **104**, 5521.
19 K. Narasaka and T. Miwa, *Chem. Lett.*, 1985, 1217.
20 G. Helmchen, U. Leikauf and I. Taufer-Knopfel, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 874.
21 W. Oppolzer and J. Macro-Contelles, *Helv. Chim. Acta*, 1986, **69**, 1699.
22 C. Gennari, A. Bernardi, L. Colombo and S. Scolastico, *J. Am. Chem. Soc.*, 1985, **107**, 5812.
23 C. Palazzi, L. Colombo and C. Gennari, *Tetrahedron Lett.*, 1986, **27**, 1735.
24 C. Gennari, L. Colombo, G. Bertolini and G. Schimperna, *J. Org. Chem.*, 1987, **52**, 2754.
25 R. E. Zelle, M. P. DeNinno, H. G. Selnick and S. J. Danishefsky, *J. Org. Chem.*, 1986, **51**, 5032.
26 P. J. Kocienski, B. Lythgoe and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1045.

Paper 1/00955I
Received 28*th February* 1991
Accepted 16*th April* 1991