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One-pot, three-component, sequential Michael-Michael-ring-closure reactions. Annulation of meta-dicarboxylated aromatic rings. Total synthesis of juncunol

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Abstract. The preparative value of one-pot, multicomponent, sequential Michael-Michael-ring-closure reactions followed by aromatization is illustrated in two ways: (1) by a multi-gram example, and (2) by a total synthesis of juncunol, an unusual vinyldihydrophenanthrene.

Keywords. Sequential Michael-Michael-ring-closure reactions; one-pot reactions; benzannulations; juncunol.

1. Introduction

Recently, there has been considerable interest in preparing regiospecifically polysubstituted aromatic compounds via new cyclization reactions (Bamfield and Gordon 1984; Boger and Mullican 1984; Danheiser and Gee 1984; Dötz 1984; Dieter and Lin 1985). Sometimes such polyfunctionalized aromatics are valuable synthetic intermediates and sometimes they are physiologically active natural products. In 1986, we described a method for annulation of regiospecifically *m*-dicarboxylated aromatic rings onto the $-COCH_2-$ fragment of various ketones via a one-pot, 3-component sequential Michael-Michael-ring-closure (MIMIRC) process followed by a one-pot triple elimination (1) (Posner 1986; Posner *et al* 1986). In this report, we demonstrate the preparative value of this synthetic method by a multi-gram example and by a total synthesis of juncunol (Bhattacharya and Miles 1977; Pelletier *et al* 1978), a member of a biogenetically unusual class of vinylated 9,10-dihydrophenanthrenes isolated from "marsh grass", *Juncus roemarianus*, and closely related structurally to the anti-neoplastic co-metabolite juncusol (Miles *et al* 1977; Bhattacharya 1980) and to some phytoalexins (Fisch *et al* 1973; Juneja *et al* 1987). The structure of juncunol was revised in 1980 (Cossey *et al* 1980); it has been synthesized only once (Cossey *et al* 1980). Other 9,10-dihydrophenanthrenes have been synthesized, including juncusol (McDonald and Martin 1978; Kende and Curran 1979; Schulz and Shen 1981; Carvalho and Sargent 1984).

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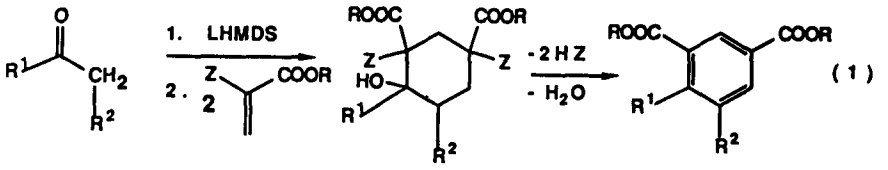
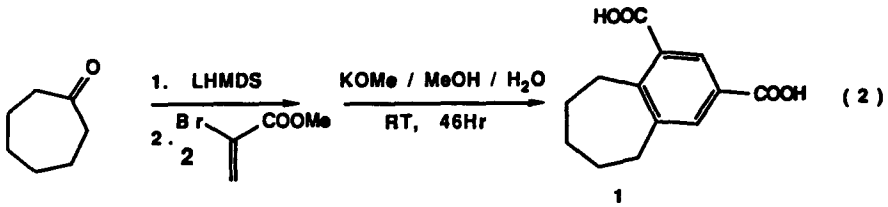


2. Results and discussion

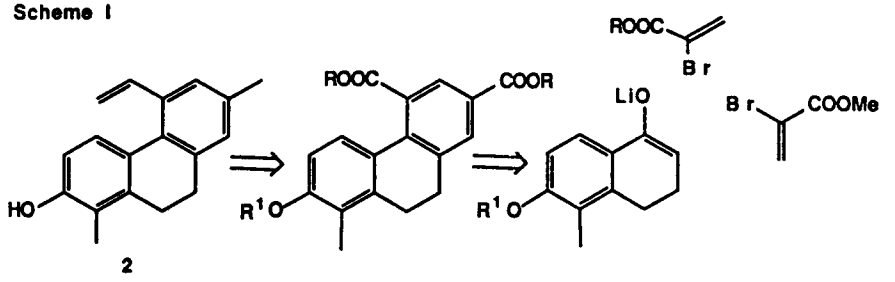
For a new synthetic method to be used often by practising organic chemists, the method should ideally be mild, simple, rapid, and able to produce more than milligram quantities of products. To illustrate mildness, simplicity, rapidity, and multi-gram capabilities, we have converted cycloheptanone into its lithium enolate and have then added two equivalents of methyl α-bromoacrylate. This triply convergent A + B + B annulation (Posner 1986) led to a dibromocyclohexanol which, without purification, was treated with aqueous methanolic potassium hydroxide to effect a triple elimination (–2 HBr, –HOH) forming over 3 grams of pure *m*-dicarboxylated aromatic product **1** in 50% overall yield (2). We see no reason for such one-pot multicomponent annulations not working as well even on a substantially larger scale, if so desired, and therefore industrial applications seem feasible. The triple elimination procedure was explored in depth to determine optimum conditions. Acidic conditions (e.g., methanolic sulphuric acid, trifluoroacetic acid), other basic conditions (e.g., refluxing pyridine, sodium methoxide) and miscellaneous conditions (e.g., pyridinium tosylate, thionyl chloride/pyridine, acetic anhydride/pyridine, DMF/LiCl) did not give better results than those obtained in equation 2 using potassium hydroxide.



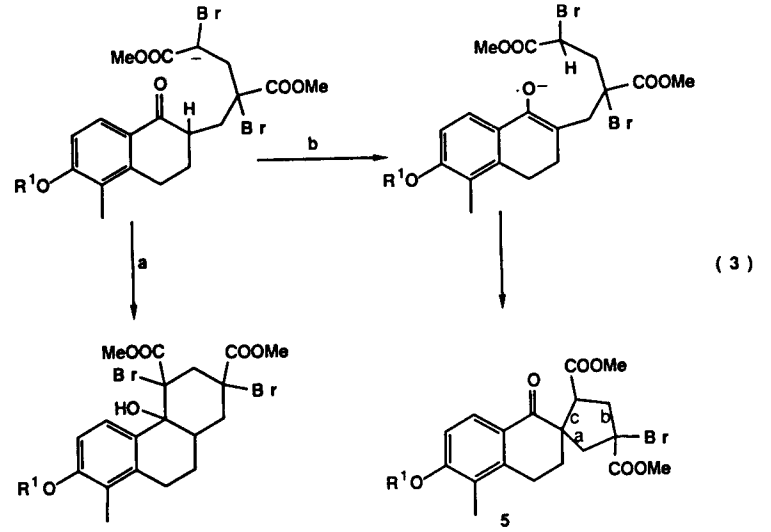
Retrosynthetic analysis of juncunol led us, via a *m*-dicarboxylated 9,10-dihydrophenanthrene intermediate, to the 3-component MIMIRC sequence shown in scheme I. In the synthetic direction, two critical concerns were evident: (1) would the final 1,6-aldol ring closure (path a, equation 3) occur smoothly when the electrophilic carbonyl group is an arylogous ester carbonyl and is flanked by a peri hydrogen atom or would S_Ni ring closure (path b) compete, and (2) would the two carboxylate groups in the intermediate dihydrophenanthrene be susceptible to regioselective manipulation?

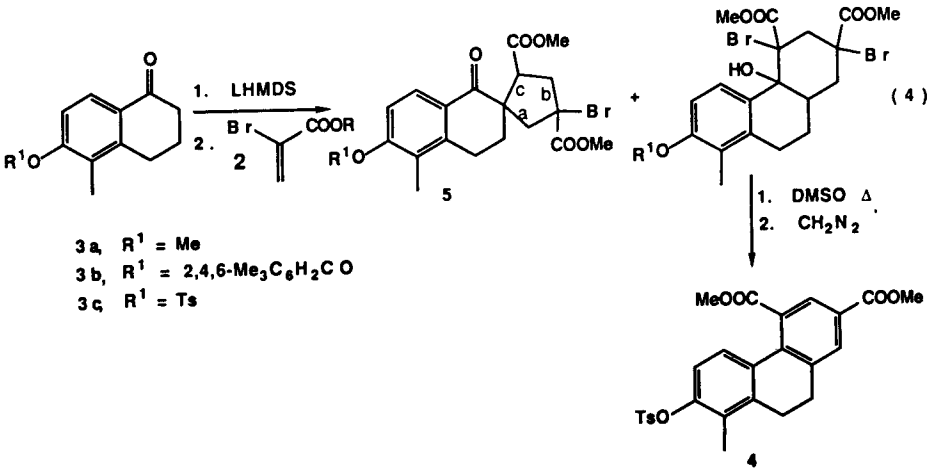
Concerning the first issue, our previous difficulty in effecting a very closely related 1,6-ring closure final step (path a, equation 3) during a one-pot MIMIRC sequence for construction of steroidal estrone (Posner *et al* 1981) was ominous. When the enolate of tetralone **3a** (Martin and Robinson 1943) was prepared and was treated with two equivalents of methyl α-bromoacrylate, the major product was spirocyclopentane **5** (4). NMR spectroscopic evidence convincingly ruled out

Scheme I



formation of a spirocyclopropane. Although annulation product **5** is indeed formed via a MIMIRC sequence (bonds a, b, and c), as precedented in our earlier work on estrone (Posner *et al* 1981), it is obviously not along the desired path to juncunol. As a control, *p*-methoxyacetophenone underwent a successful 2 + 2 + 2 MIMIRC



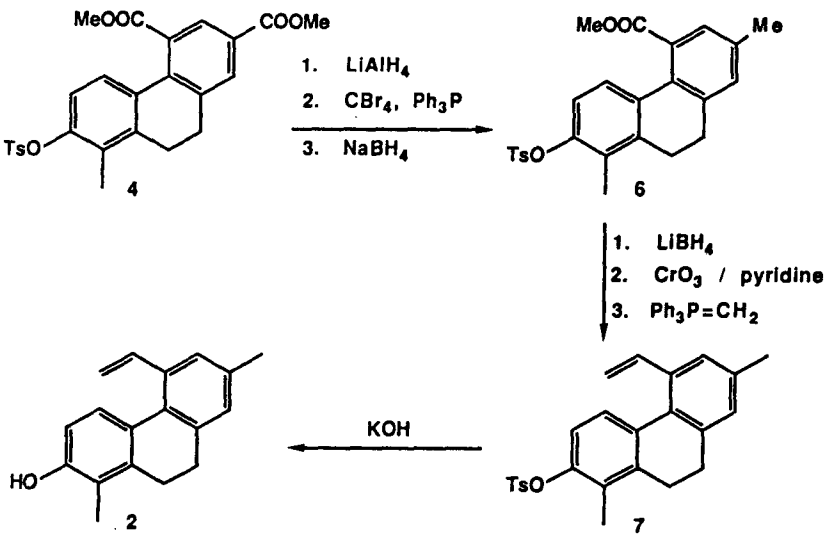


sequence to ultimately form a biphenyl system. Clearly the structural rigidity of the tetralone system in (3) and the difficulty of intramolecular aldol condensation onto the hindered carbonyl in this system cause the reaction pathway b to predominate leading to the undesired spirocycle **5**. To circumvent this difficulty, we sought to make the final 1,6-aldol ring closure easier by diminishing the electronic communication between the phenolic oxygen atom and the tetralone carbonyl group (*i.e.*, making the carbonyl less ester-like and more ketone-like). A second control reaction with the enolate of *un*substituted 1-tetralone and two equivalents of methyl α-bromoacrylate gave a successful 2 + 2 + 2 annulation reaction which was very encouraging. Therefore, the methoxy group of tetralone **3a** (R^1 = Me) was replaced by a 2,4,6-trimethylbenzoyloxy group (**3b**) and separately by a tosylate group (**3c**). The tosylate derivative **3c** was the most successful, producing the desired 2 + 2 + 2 MIMIRC *meta*-dicarboxylated dihydrophenanthrene **4** as the major product in 21–27% overall yield via (4). Of the various triple elimination procedures explored, hot dimethyl sulphoxide was the best in this case.

Concerning the second issue, *i.e.*, differentiation between the two methyl carboxylate groups in diester **4**, the 400 MHz NMR spectrum of this diester was particularly encouraging: one methyl ester singlet appeared at δ 3·93 (characteristic of methyl benzoate) and the other at δ 3·80. In practice, chemical differentiation between the two esters was easy, saponification or reduction occurring almost entirely at the more accessible carboxylate group. Thus the way was clear for highly regiocontrolled functional group manipulation to transform one ester group into the methyl group and the other (more hindered) ester group into the vinyl group characteristic of juncunol.

Controlled reduction of the more exposed ester group using a limited amount of lithium aluminium hydride produced a benzylic alcohol which was brominated and then reduced to form methyl-substituted dihydrophenanthrene **6** in about 50% overall yield from diester **4** (scheme II). Lithium borohydride reduction of

Scheme II



monoester **6** was followed by oxidation to the corresponding aldehyde and vigorous Wittig methylenation to form vinyl-substituted dihydrophenanthrene **7** in about 35–40% overall yield from monoester **6** (scheme II). High-yield basic hydrolysis of the tosylate group gave juncunol (**2**), with spectroscopic and melting point properties identical to those reported in the literature for this compound (Bhattacharyya and Miles 1977; Cossey *et al* 1980). This convergent and flexible synthesis of juncunol involves simple and rapid assembly of the dihydrophenanthrene ring system from readily available acrylates and an easily prepared tosyloxytetralone; the overall sequence compares favourably with Mander's synthesis of juncunol (Cossey *et al* 1980).

3. Experimental

Cycloheptanone (Aldrich Chemical Co.) was distilled at water pump pressure and stored over molecular sieves. Methyl 2-bromo-2-propenoate was prepared by the method of Marvel and Cowan (1939) using triethylamine instead of quinoline; it was distilled (water-pump pressure, b.p. *ca.* 67°C) just prior to use. To prevent polymerization, 0·1 g of 2,6-di-*t*-butyl-4-methylphenol ("BHT") was added to the distilling flask and 0·04 g of BHT was placed in the receiver. Tetrahydrofuran and 1,1,1,3,3,3-hexamethyldisilazane were distilled while *n*-butyllithium in hexane (Aldrich Chemical Co.) was used as received.

Preparation of meta-dicarboxylated aromatic 1: Under anhydrous conditions, 40 ml of tetrahydrofuran and 6·13 ml (0·0290 mol) of 1,1,1,3,3,3-hexamethyldisilazane were introduced into a flask. The mixture was stirred in a dry ice-acetone bath, and 18·13 ml (0·0290 mol) of 1·6 M *n*-butyllithium in hexane were added. After stirring for 1 h, 3·11 ml (0·0263 mol) of cycloheptanone were added, dropwise, over a 10-min period. The resulting solution was stirred for 50 min. Methyl 2-bromo-2-propenoate (5·8 ml, 0·0566 mol) was then added, over a 30-min period, using a syringe pump. The inlet needle was under the surface of the reaction mixture during the addition. Stirring was continued for 2 h, and the reaction was quenched by the addition of 100 ml of saturated ammonium chloride solution. The mixture was allowed to warm to room temperature. It was extracted with three 100 ml portions of ether. The extracts were dried over magnesium sulphate and concentrated *in vacuo* to give 11·1062 g of a slightly cloudy, very pale yellow oil.

Methanol (180 ml) and 360 ml of 22% aqueous potassium hydroxide were added, and the mixture was stirred for 46 h at room temperature. The resulting clear, yellow solution was concentrated *in vacuo* until its volume was reduced by about one-third. Ether (150 ml) was added and 12 M hydrochloric acid was added, dropwise while stirring in an icebath, until the lower layer was at pH 1. The layers were separated and the aqueous layer was extracted with two 150-ml portions of ether. The combined extracts were dried with $MgSO_4$ and concentrated *in vacuo* to give 6·01 g of a light amber crystalline foam. The product was taken up in 450 ml of 7% sodium bicarbonate. The solution was washed with 150 ml of ether and acidified (to pH 1) by dropwise addition of 12 M hydrochloric acid. The resulting mixture of solid and solution was refrigerated overnight. The product was isolated by vacuum filtration. It was washed with 10 ml of ice water and dried *in vacuo*,

giving 3·06 g (49·7%) of an off-white powdery solid, m.p. 275–276°C. NMR ($CDCl_3$): δ 7·887 (*d*, J = 1·8 Hz) and 8·175 (*d*, J = 2·4 Hz). Sublimation gave an analytical sample, m.p. 277–278°C. Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66·66; H, 6·02; Found: C, 66·53; H, 6·17.

5-Methyl-6-tosyloxytetralone (3c): To a 50-ml round-bottomed flask containing a stir bar and 6-methoxy-5-methyltetralone (**3a**, 1·73 g, 9·82 mmol) were added 15 ml of DMSO and sodium cyanide (2·4 g, 49 mmol). The flask was immediately joined to a condenser equipped with a rubber septum and flushed with argon. The apparatus was then lowered into an oil bath equilibrated at 120°C and stirred for 14 h. The reaction mixture was then poured on ice and carefully acidified to pH 1 with concentrated hydrochloric acid. The resulting slurry was then extracted with 3 × 100 ml of ethyl acetate. The combined organic layers were washed with 2 × 50 ml of water, dried with anhydrous magnesium sulphate, and concentrated to a solid. Separation on florisil (methylene chloride) yielded 79% (1·37 g, 7·8 mmol) of the desired phenol, 6-hydroxy-5-methyltetralone, as an off-white powder.

A 100-ml round-bottomed flask containing a stir bar was charged with crude 6-hydroxy-5-methyltetralone (1·37 g, 7·8 mmol), *p*-toluenesulphonyl chloride (2·97 g, 15·6 mmol) and 10 ml of triethylamine. Stirring was commenced and methylene chloride was added until all the materials were dissolved (~50 ml). A few crystals of N,N-dimethylaminopyridine were added, and the flask was flushed with argon, capped, and left to stir for 14 h. The reaction mixture was then concentrated to a solid and dried under high vacuum. Separation on silica gel (12% ethyl acetate, hexanes) gave 81·6% (2·10 g, 6·36 mmol) of the desired 5-methyl-6-tosyloxytetralone (**3c**) as a colourless glass which converted to a white solid on standing for one week. m.p. 104·0–104·5°C. NMR ($CDCl_3$, 80 MHz): δ 2·00–2·35 (2H, *m*), 2·11 (3H, *s*), 2·47 (3H, *s*), 2·60 (2H, *t*, J = 5·6 Hz), 2·82 (2H, *t*, J = 5·6 Hz), 6·9 (1H, *d*, J = 8·6 Hz), 7·34 (2H, *d*, J = 8·1 Hz), 7·77 (2H, *d*, J = 8·4 Hz), 7·85 (1H, *d*, J = 8·2 Hz). IR (CCl_4): 1675, 1600, 1380, 815 cm^{-1}. Anal. Calcd. $C_{18}H_{18}O_4S$: C, 65·44; H, 5·49; S, 9·70; Found: C, 65·34; H, 5·58; S, 9·66.

MIMIRC adduct: To a 25-ml pear-shaped flask containing argon and a stir bar were added hexamethyldisilazane (400 μl, 1·89 mmol) and 800 μl of THF. Stirring was commenced and the flask was cooled to 0°C. Methyllithium (1·09 ml, 1·72 M, 1·87 mmol) was slowly added dropwise via syringe. The ice bath was removed and stirring was continued at ambient temperature for 0·5 h followed by cooling to − 78°C. The 5-methyl-6-tosyloxytetralone (**3c**, 588 mg, 1·78 mmol) dissolved in 3·3 ml of THF was transferred to the lithium hexamethyldisilazide at − 78°C dropwise via cannula. The reaction mixture became amber-coloured and remained homogeneous. After stirring at − 78°C for one hour, methyl α-bromoacrylate (5·0 ml, 0·88 M, 4·4 mmol) in THF was added dropwise via syringe. After stirring at − 78°C for 16 h, the solution appeared greenish and slightly cloudy. A saturated solution (0·5 ml) of ammonium chloride was dripped in slowly (~ 1 drop/3 min) by syringe and stirring was continued for 0·5 h. The reaction mixture was allowed to warm to room temperature and then partitioned between diethyl ether and distilled water. The organic phase was dried with anhydrous magnesium sulphate and concentrated by rotary evaporation to a clear glass which produced 1·22 g of a

white foam when subjected to high vacuum. The major product of this reaction was evidenced by NMR and IR to be the MIMIRC adduct. NMR ($CDCl_3$, 80 MHz): δ2·08 (3H, *s*), 2·18–2·78 (5H), 2·46 (3H, *s*), 2·46 (2H, *t*, *J* = 8 Hz), 3·11 (2H, *s*), 3·59 (3H, *s*), 3·82 (3H, *s*), 6·59 (1H, *d*, *J* = 8·7 Hz), 7·3 (3H, *d*, *J* = 8·3 Hz), 7·74 (1H, *d*, *J* = 8·2 Hz). IR (CCl_4): 3620, 1740, 1600, 1380, 1055 cm^{-1}.

9,10-Dihydrophenanthrene **4**: The crude product was transferred to a 250-ml round-bottomed flask with a stir bar, and was dissolved in 120 ml of DMSO. The flask was connected to a condenser equipped with a rubber septum, flushed with argon, and immersed in a 125°C oil bath for 14 h. The reaction mixture was allowed to cool and the DMSO was removed by vacuum distillation. The crude brown oil which remained was dissolved in 20 ml of diethyl ether and treated with an excess of diazomethane at 0°C. The solution was dried with anhydrous magnesium sulphate and concentrated *in vacuo*. Chromatography on silica gel (benzene) followed by treatment with decolourizing carbon (methylene chloride) gave overall 26·1% (223·3 mg, 0·465 mmol, based on 5-methyl-6-tosyloxytetralone) of the desired dihydrophenanthrene **4** as a glassy solid which could be induced to crystallize slowly from ethyl acetate/hexanes. m.p. 171·2–172·0°C, NMR ($CDCl_3$, 80 MHz): δ 2·17 (3H, *s*), 2·47 (3H, *s*), 2·80 (4H, *s*), 3·75 (3H, *s*), 3·93 (3H, *s*), 6·78 (1H, *d*, *J* = 8·7 Hz), 7·09 (1H, *d*, *J* = 8·7 Hz), 7·33 (2H, *d*, *J* = 8·0 Hz), 7·78 (2H, *d*, *J* = 8·2 Hz), 8·00 (1H, *d*, *J* = 1·8 Hz), 8·16 (1H, *d*, *J* = 1·7 Hz). IR ($CHCl_3$): 1720, 1600, 1370, 1250, 1180, cm^{-1}. Anal. Calcd. for $C_{26}H_{24}O_7S$: C, 64·99; H, 5·03; S, 6·67; Found: C, 65·05; H, 5·04; S, 6·74.

Spirocycle **5**: To a 25-ml pear-shaped flask containing a stir bar was added the solid trimethylsilyl enol ether derivative of 5-methyl-6-methoxytetralone (567 mg, 2·2 mmol). The flask was sealed with a rubber septum and flushed with argon. THF (4 ml) was added by syringe to dissolve the solid while stirring. The reaction vessel was cooled to 0°C before a solution of methyllithium in diethyl ether (1·0 ml, 1·9 M, 1·9 mmol) was slowly dripped in by syringe. After the addition, the cold bath was removed allowing the reaction to stir at ambient temperature for 1 h. The reaction flask was cooled to −78°C and methyl α-bromoacrylate (3·6 ml, 1·1 M, 4·1 mmol) in THF was added dropwise via syringe. The reaction was stirred at −78°C for 20 h. After slow quenching with a saturated solution of ammonium chloride the reaction was allowed to warm to room temperature. The crude product was partitioned with diethyl ether and distilled water. The combined organic layers were dried with anhydrous magnesium sulphate and concentrated. Initial separation on silica gel (16% ethyl acetate, hexanes) yielded 5% of the dihydrophenanthrene (32 mg, 0·09 mmol) and 723 mg of a white foam containing primarily the spirocycle **5** (83%, 1·6 mmol) and a small quantity of MIMIRC product (5%, 0·09 mmol). A portion of this material (132 mg) was further separated on silica gel by preparative TLC (16% ethyl acetate; hexanes; three 2000μ plates). Each plate was developed five times. To facilitate identification of the components, only the middle of each band (visualized by ultraviolet light) was removed for extraction with diethyl ether to obtain:

1. 16·5 mg consisting of the MIMIRC product* and spirocycle **5** in a one-to-one ratio: NMR ($CDCl_3$, 400 MHz) δ: 1·38–3·20 (18H), 2·151 (*s*, 3H), 3·633 (*s*, 3H),

3·670 (*s*, 3H), 3·753 (*s*, 3H), 3·797 (*s*, 3H), 3·835 (*s*, 3H), 3·888 (*s*, 3H), 6·626* (*d*, 1H, J = 8·31 Hz), 6·835 (*d*, 1H, J = 8·54 Hz), 7·381* (*d*, 1H, J = 8·85 Hz), 7·965 (*d*, 1H, J = 8·92 Hz). IR (CCl_4, cm^{-1}): 3500, 1740, 1680.

2. 54·3 mg of spirocycle **5**: NMR ($CDCl_3$, 400 MHz) δ: 1·38–3·14 (9H), 2·136 (*s*, 3H), 3·661 (*s*, 3H), 3·743 (*s*, 3H), 3·878 (*s*, 3H), 6·823 (*d*, 1H, J = 8·48 Hz), 7·950 (*d*, 1H, J = 9·16 Hz). IR (CCl_4, cm^{-1}): 1735, 1680. HRMS, calcd. for $C_{26}H_{24}O_7S$: 438·0677; Found 438·0691.

3. 25·9 mg of spirocycle **5**: NMR ($CDCl_3$, 400 MHz) δ: 1·56–3·04 (9H), 2·147 (*s*, 3H), 3·671 (*s*, 3H), 3·752 (*s*, 3H), 3·886 (*s*, 3H), 6·832 (*d*, 1H, J = 8·85 Hz), 7·94 (*d*, 1H, J = 8·48 Hz). IR (CCl_4, cm^{-1}): 1730, 1675.

By examining the crude NMR spectrum of this reaction, it is obvious that the presence of a large signal for the aromatic hydrogen which is *peri* to the carbonyl (doublets at δ7·9) indicates a large amount of spirocycle. The characteristic aromatic peaks for the desired MIMIRC compound (δ6·6 and 7·4 doublets) are nearly invisible in the crude NMR spectrum.

Conversion of m-dicarboxylated aromatic 4 into methylated aromatic 6. a Reduction: 9,10-Dihydrophenanthrene **4** (82·2 mg, 0·171 mmol) was dissolved in 8 ml of THF in a 25-ml round-bottomed flask under argon at 0°C. A solution of lithium aluminium hydride (1·4 ml, 0·1 M, 0·24 mmol) was dripped in slowly via syringe. The solution on warming to room temperature and stirring for 12 h became slightly greenish in colour. The reaction was quenched by the addition of saturated sodium sulphate solution and the solution diluted with diethyl ether. The aqueous layer was adjusted to pH 7 by addition of a 10% hydrochloric acid solution. The organic layer was extracted, dried with anhydrous magnesium sulphate, and concentrated *in vacuo*. Chromatography on silica gel (25% ethyl acetate, hexanes) gave 67% (51·9 mg, 115 mmol) of the desired ester alcohol as a slow-to-crystallize, glassy solid. m.p.: 151·7–152·7°C. NMR ($CDCl_3$, 80 MHz): δ1·72 (1H, *t*, J = 5·6 –O–H), 2·17 (3H, *s*), 2·46 (3H, *s*), 2·76 (4H, *s*), 3·72 (3H, *s*), 4·72 (2H, *d*, J = 5·8, $-CH_2-OH$), 6·73 (1H, *d*, J = 8·8), 7·03 (1H, *d*, J = 8·7), 7·25–7·47 (4H), 7·78 (2H, *d*, J = 8·4); IR (CCl_4): 3580, 1720, 1600, 1380 cm^{-1}.

b. Bromination: To the diester alcohol (26·4 mg, 58 μmol) stirring in 1 ml of methylene chloride in a 25-ml pear-shaped flask were added carbon tetrabromide (97·0 mg, 292 μmol), followed by triphenylphosphine (76·0 mg, 290 μmol). The reaction flask was flushed with argon and stirred for 14 h, after which the mixture was concentrated by rotary evaporation to a thick oil. Chromatography on silica gel (50% ethyl acetate, hexanes) gave 87% (26 mg, 50 μmole) of the desired benzylic bromide as a white solid. NMR ($CDCl_3$, 80 MHz): δ2·17 (3H, *s*), 2·46 (3H, *s*), 2·76 (4H, *s*), 3·72 (3H, *s*), 4·48 (2H, *s*), 6·73 (1H, *d*, J = 8·8), 7·03 (1H, *d*, J = 8·7), 7·25–7·47 (4H), 7·78 (2H, *d*, J = 8·4).

c. Reduction: The benzylic bromide (9·6 mg, 18·6 μmol) was concentrated into a 1-ml conical reaction vessel, flushed with argon, and dissolved in 10 μl of diglyme. Lithium borohydride (200 μl, 1 M, 200 μmol) in diglyme was added rapidly via syringe. After stirring at ambient temperature for 18 h, the reaction was quenched with saturated ammonium chloride solution, and the mixture partitioned with

diethyl ether. Chromatography on silica gel (25% ethyl acetate, hexanes) gave 51% of the desired alcohol **6** (3·9 mg, 9·5 μmol) as a colourless oil. NMR ($CDCl_3$, 400 MHz): δ1·76 (1H, *t*, *J* = 5 Hz, –OH), 2·17 (3H, *s*), 2·37 (3H, *s*), 2·48 (3H, *s*), 2·58 (4H, *m*), 4·74 (2H, *d*, *J* = 6 Hz, $-CH_2-OH$), 6·83 (1H, *d*, *J* = 12 Hz), 7·07 (1H, *s*), 7·26 (1H, *s*), 7·35 (2H, *d*, *J* = 8 Hz), 7·59 (1H, *d*, *J* = 12 Hz), 7·80 (2H, *d*, *J* = 8·0 Hz). IR (CCl_4): 3600, 1600, 1380, 1049 cm^{-1}.

Preparation of juncunol (2). a. Reduction-oxidation (ester → aldehyde): A 25-ml round-bottomed flask with a stir bar was charged with 2 ml of methylene chloride, 1·5 ml of pyridine and chromium trioxide (200 mg, 2 mmol). The flask was flushed with argon and capped, and the heterogeneous mixture stirred vigorously for 20 min. Some of the resulting slurry was quickly removed with a Pasteur pipette and eight drops of the slurry were rapidly transferred to a stirred solution of the benzyl alcohol (7·9 mg, 19·4 μmol) in 1 ml of methylene chloride under argon. After stirring for 0·5 h, 1 ml of methanol was added and the reaction mixture was concentrated *in vacuo* to a black solid. The solid was dissolved in diethyl ether and washed with distilled water. The organic layer was dried with anhydrous magnesium sulphate and concentrated by rotary evaporation. The resulting residue was dissolved in diethyl ether and passed through a plug of silica gel to give 85% (6·7 mg, 16·6 μmol) of the desired aldehyde as a white solid after evaporation of the diethyl ether. NMR ($CDCl_3$, 80 MHz): δ 2·16 (3H, *s*), 2·36 (3H, *s*), 2·46 (3H, *s*), 2·73 (4H, *s*), 6·71 (1H, *d*, *J* = 8·6 Hz), 7·01 (1H, *d*, *J* = 8·6 Hz), 7·17 (1H, *s*, 7·29–7·37 (3H), 7·77 (2H, *d*, *J* = 8·4 Hz), 10·05 (1H, *s*). IR (CCl_4): 2840, 1680, 1600, 1376 cm^{-1}.

b. Methylenation: To a 50-ml, 3-necked, pear-shaped flask equipped with a cold-finger, stir bar and two rubber septa were added methylenetriphenylphosphonium bromide (375 mg, 1·06 mmol), potassium *t*-butoxide (115 mg, 1·02 mmol) and 2 ml of benzene. The reaction vessel was flushed with argon and immersed in an oil bath heated to 55°C. After 4 h, the above aldehyde (4·0 ml, 9·9 μmol) dissolved in 1 ml of benzene in a 25-ml pear-shaped flask under argon was transferred via cannula to the hot Wittig reagent. The reaction mixture was maintained between 55° and 60°C for 17 h, after which it was cooled, poured into water, and partitioned with diethyl ether. The organic phase was dried with anhydrous sodium sulphate and concentrated to a yellowish solid. NMR ($CDCl_3$, 400 MHz): δ 2·129 (3H, *s*), 2·371 (3H, *s*), 2·470 (3H, *s*), 2·686 (4H, *s*), 5·267 (1H, *d* × *d*, J_{AX} = 10·4 Hz, J_{AB} = 1·56 Hz), 5·702 (1H, *d* × *d*, J_{BX} = 17·6 Hz, J_{AB} = 1·56 Hz), 6·849 (1H, *d*, *J* = 8·98 Hz), 6·906 (1H, *d* × *d*, J_{BX} = 17·4 Hz, J_{AX} = 11 Hz), 7·017 (1H, *s*), 7·241 (1H, *s*), 7·337 (2H, *d*, *J* = 7·86 Hz), 7·405 (1H, *d*, *J* = 8·37 Hz), 7·789 (2H, *d*, *J* = 8·65 Hz).

c. Hydrolysis: To the unpurified tosylate in a 25-ml round-bottomed flask were added 2 ml of methanol, 1 ml of 45% potassium hydroxide solution and 1 ml of distilled water. The reaction vessel was flushed with argon, capped, and stirred for 18 h. Rotary evaporation of the methanol was followed by acidification with concentrated hydrochloric acid to pH 7. The reaction mixture was extracted with diethyl ether; the organic phase was separated and dried with anhydrous sodium sulphate. Concentration *in vacuo* and separation on silica gel (16% ethyl acetate, hexanes) afforded 88·9% (2·2 mg, 8·8 μmol) of the desired juncunol (2) as a white

solid. m.p. 144–145°C ((Cossey *et al* 1980) m.p. 143–144°C); NMR ($CDCl_3$, 400 MHz): δ 2·270 (3H, *s*), 2·367 (3H, *s*), 2·731 (4H, *m*), 4·720 (1H, OH *s*), 5·248 (1H, *d* × *d*, J_{AX} = 11 Hz, J_{AB} = 1·16 Hz), 5·969 (1H, *d* × *d*, J_{BX} = 17·58 J_{BA} = 1·6), 6·688 (1H, *d*, *J* = 8·58), 6·963 (1H, *d* × *d*, J_{BX} = 17·58, J_{AX} = 10·99), 7·015 (1H, *s*), 7·238 (1H, *s*), 7·3855 (1H, *d*, *J* = 8·54). IR ($CHCl_3$, cm^{-1}): 3570, 1610, 1590, 915.

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