A Convergent Synthesis of Methylenomycin B and Analogues *Via* Selenium Assisted Cyclopenta-annelation [1]

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Reaction of the lithium enolate of 4-chloro-4,5-dimethylhex-5-en-3-one **2** with benzeneselenenyl bromide at −78 °C gives 2,3,5-trimethyl-5-phenylselenocyclopent-2-enone **3**. Treatment of compound **3** with 15% H$_2$O$_2$ in methylene dichloride at 0 °C gave methylenomycin B *via syn* selenoxide elimination. Similarly, the lithium enolate of **7** reacted with benzeneselenenyl bromide to give 2,3-dimethyl-5-phenylselenocyclopent-2-enone **10**. Compound **10** can be converted into compound **3** *via* alkylation of its lithium enolate with methyl iodide. The lithium enolate of compound **2** also reacted with benzenesulphenyl chloride and benzoyl chloride to give 2,3,5-trimethyl-5-phenylthiocyclopent-2-enone **13** and 5-benzoyl-2,3,5-trimethylcyclopent-2-enone **14** respectively. Using this cyclization other methylenomycin B analogues were prepared from readily available starting materials.

The isolation of methylenomycins A and B from a streptomycete strain and the elucidation of their structure in 1974[2] were followed by disclosure of their synthesis by several groups.[3-6] The interest that the methylenomycins have elicited is due to their unusual structure and promising profile of antibiotic and antineoplastic activity. Methylenomycin B for example is active against both gram positive and gram negative bacteria and is cytotoxic *in vitro* in the KB assay.[2,7]
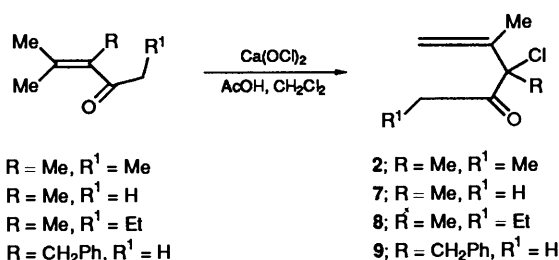
We recently reported novel routes to substituted cyclopent-2-enones by the reaction of ethyl 2,3-dialkyl-2-chlorobut-3-enoates with sulphur[8] and nitrogen[9] stabilized carbanions and by base induced cyclization of several fully substituted α-chloro-β,γ-unsaturated ketones.[10] These cyclizations were proposed to proceed through an intramolecular S$_N$2' type reaction.

Most of the reported synthesis of methylenomycin B proceed through 2,3-dimethylcyclopent-2-enone[11] as the key intermediate for introducing the exocyclic double bond. Although we reported a highly efficient synthesis of this intermediate by base induced cyclization of 3-chloro-3,4-dimethylhex-4-en-2-one,[10] we sought a more direct synthesis of methylenomycin B. Since nitrogen and sulphur stabilized carbanions underwent this novel cyclopenta-annelation with extreme ease, it appeared feasible to extend this reaction to selenium substituted enolates.

Results and Discussion

In the past decade, recognition of the selenoxide *syn* elimination as a powerful olefin forming method has led to the discovery of valuable selenium based reagents and conditions.[12] We now report the facile synthesis of 2,3,5-trialkyl-5-phenylselenocyclopent-2-enones that can undergo *syn*-selenoxide elimination resulting in a highly convergent synthesis of methylenomycin B and its analogues. Thus, the readily available 4,5-dimethylhex-4-en-3-one[13] **1** and enones **4-6**[14] were converted into 4-chloro-4,5-dimethylhex-5-en-3-one **2**[10] and **7-9** respectively using hypochlorous acid[10,15] (Scheme 1).

Addition of these allylic halides to 1 equiv. of LDA (lithium diisopropylamide)-THF (tetrahydrofuran) at −70 °C followed by the rapid addition of benzeneselenenyl bromide[16] in THF gave the methylenomycin B precursors **3**, **10**, **11** and **12** in modest isolated yields. In addition, the lithium enolate of compound **2** reacted with benzenesulphenyl chloride and benzoyl chloride to give cyclopentenones **13** and **14** respectively (Table 1).

1; R = Me, R^1 = Me
4; R = Me, R^1 = H
5; R = Me, R^1 = Et
6; R = CH$_2$Ph, R^1 = H

2; R = Me, R^1 = Me
7; R = Me, R^1 = H
8; R = Me, R^1 = Et
9; R = CH$_2$Ph, R^1 = H

Scheme 1

The reaction most likely proceeds in two steps.* The lithium enolate of compound **2** rapidly reacts with benzeneselenenyl

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* The cyclization of the lithium enolate of intermediate **15** may involve an intramolecular S$_N$2' process wherein selenium plays an important role possibly by forming a selenium ylide. Another plausible mechanism can invoke a Favorski type process where selenium helps stabilize the intermediate Zwitterion, *i.e.*
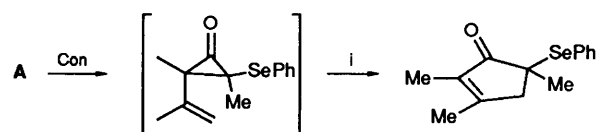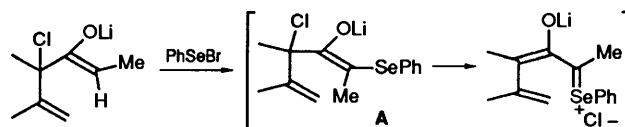
i, Vinyl cyclopropane rearrangement

A mechanism proposed by one of the referees for this paper is noted below and involves the S$_H$2' attack of diisopropyl amine to the enolate of **15** to give **A** which closes in a 5-*exo tet* manner resulting in the product.
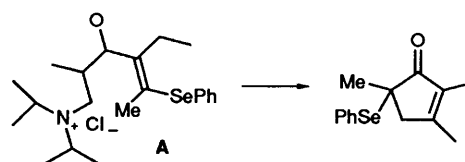
**Table 1** Synthesis of 5-phenylselenocyclopentenones
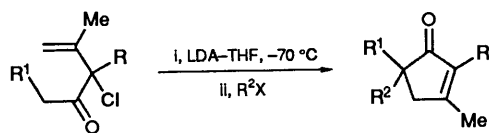
R	R^1	R^2	X	Product	Yield (%)
Me	Me	PhSe	Br	3	48
Me	H	PhSe	Br	10	54
Me	Et	PhSe	Br	11	46
Bz	H	PhSe	Br	12	52
Me	Me	PhS	Cl	13	41
Me	Me	PhCO	Cl	14	36

Table 2 Alkylation of 5-phenylselenocyclopentenones
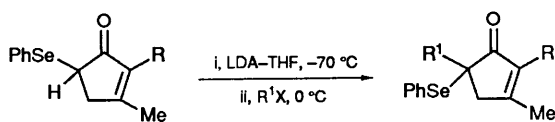
R	R^1	Product	Yield (%)
Me	Me	3	91
CH$_2$Ph	Me	16	89
Me	CH$_2$=CH–CH$_2$	17	90

bromide at $-70\ ^\circ$C to give the α-phenylseleno ketone intermediate 15. Proton transfer [17] from compound 15 to the original enolate gives the α-phenylseleno enolate that undergoes a S$_N$2' cyclization resulting in the formation of compound 3.

The selenium must favourably assist this cyclization because the cyclopentenone can be isolated within a few minutes of mixing the reagents. We have observed that lithium or potassium enolates of 2 which are devoid of sulphur or selenium do not undergo this reaction at low temperature.[10] An intriguing aspect of this cyclization is that a second equivalent of LDA is not required for this process. In fact, addition of a second equivalent of LDA after the addition of benzeneselenyl bromide does not increase the yield. Furthermore, treating ketone 2 with 2 equiv. of LDA followed by addition of
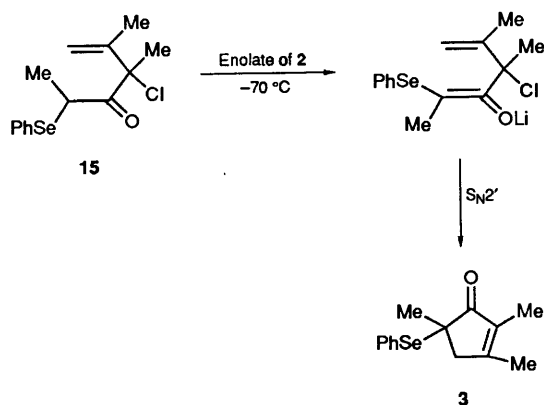
benzeneselenenyl bromide resulted in a very low yield of the cyclopentenone (20%). When the reaction was performed by inverse addition (normally this technique minimises proton transfer between product and original enolate in acylation reactions [18]), i.e. cannulation of a cold ($-70\ ^\circ$C) solution of the

Table 3 Methylenomycins by *syn*-selenoxide elimination
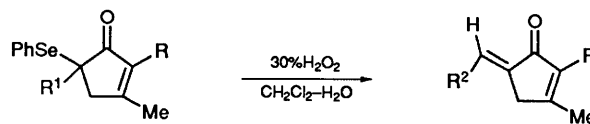
R	R^1	R^2	Product	Yields (%)
Me	Me	H	18	96
Me	Et	Me	19	93
CH$_2$Ph	Me	H	20	91
Me	CH$_2$=CH–CH$_2$	CH=CH$_2$	21	95

lithium enolate of compound 2 in THF to a solution of benzeneselenenyl bromide in THF at $-70\ ^\circ$C, cyclopentenone 3 was isolated in only 14% yield. Taken collectively, all of these observations lend support to the proposed reaction pathway. It is quite possible that due to extended conjugation, the methyl hydrogens on the β carbon of the α,β-enone system in compound 3 are more acidic than the methyl hydrogens of ketone 2 and the use of excess of LDA will deprotonate 3 and therefore will not increase the yield of the cyclization. Although at this time it is not clear why the unchanged ketone 2 is not recovered from the reaction mixture, a plausible explanation may be that it forms a water soluble salt with diisopropylamine and therefore be lost during the conventional work-up.

It must be pointed out that while the enolate of compound 2 reacts with benzeneselenenyl bromide and benzenesulphenyl chloride at low temperature to give cyclopentenones, its reaction with benzoyl chloride gave cyclopentenone only at room temperature. This confirms the role of sulphur and selenium in accelerating the rate of this cyclization.[10]

Furthermore, an alternate approach to methylenomycin B and analogues was also discovered (Table 2). Thus, 5-phenylselenocyclopentenones 10 and 12 were alkylated with LDA–THF–MeI to give the methyleneomycin B precursors 3 and 16 in high yield. The cyclopentenone 10 was also alkylated with allyl bromide to give the 5-allylcyclopentenone 17 in 90% yield.

Reaction of the seleno ketones 3, 11, 16 and 17 with 15% hydrogen peroxide (3 equiv.) in methylene dichloride at 0 $^\circ$C gave, *via syn* selenoxide elimination,[19,20] methylenomycin B 18 and the analogues 19–21 respectively (91–96%) (Table 3).

Despite the modest yield in the crucial cyclization step which gives methyleneomycin B in an overall yield of only 35% from enone 1, gram quantities of this antibiotic can be prepared in a single day. Since enone 1 can be easily prepared in multigram scale from inexpensive starting materials, this route may be comparable to the best known route to methylenomycin B [6] which gives an overall yield of 64%. However, the method uses α-lithio-α-(methoxymethyl)allene.[21] As shown in Table 3, we were able to prepare the methylenomycin B analogue 19 in comparable yield starting from the readily available 5,6-dimethylhept-5-en-4-one 5.[14] This suggests that other alkyl substituted methylenomycins can readily be accessed by this route.

The highly conjugated dienone [22] 21 is surprisingly stable to flash column chromatography and can be stored in the freezer for several months without decomposition (as indicated by ^{1}H NMR spectroscopy). A ^{1}H NMR homonuclear spin decoupling study [23] of this compound indicated that the central carbons of this diene had a *trans* arrangement (*S-transoid*) of the vinyl hydrogens ($J = 12$ Hz) and that the vinyl hydrogen closest to the ring carbonyl oxygen was *cis* to the oxygen as indicated by the proton chemical shift (δ 6.90). Similarly in enone 19, the

relationship between the methyl group on the exocyclic double bond and the carbonyl ring oxygen was *trans(anti)* as evidenced by the downfield proton resonance shift (δ 6.65) of the vinyl proton from TMS (tetramethylsilane) (this being the only isomer produced by the *syn* elimination of the selenoxide **11**).

In conclusion, the present method offers a highly convergent synthesis of the antibiotic methylenomycin B and its analogues. The method is useful because of the simple procedure and ready availability of starting materials.

Experimental

M.p.s were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Elemental analyses were performed by Galbriath Laboratories, Knoxville, Tennessee. The ^{13}C NMR spectra were obtained on JEOL-FX 60 spectrometer operating at 15.04 MHz. ^{1}H NMR spectra were obtained on a Perkin-Elmer R-32 90-MHz spectrometer and Gemini XL-300. The chemical shifts (+) are downfield from tetramethylsilane (TMS) and all NMR data were obtained in CDCl$_3$ solution. *J* Values are given in Hz throughout. IR spectra were obtained on a Beckman AccuLab 8 spectrometer. Mass spectra were obtained on a Dupont instruments DP-1 Mass spectrometer system. Flash column chromatography[24] was performed with silica gel 60(230–440 mesh) purchased from Merck. All commercial chemicals were used as received. THF used was either distilled from LiAlH$_4$ or Gold Label anhydrous THF supplied by Aldrich Chemical company. Reagent Grade CH$_2$Cl$_2$, EtOAc, hexane and ether were used. All reactions were done under nitrogen unless specified. All products obtained were liquids unless specified otherwise. Diisopropyl amine was distilled from calcium hydride prior to use. 30% H$_2$O$_2$ supplied by Mallinckrodt, Inc. were used for oxidations. Anhydrous MgSO$_4$ was used for drying unless specified otherwise.

4,5-Dimethylhex-4-en-3-one[10] **1** and 3,4-dimethylpent-3-en-2-one[10] **4** were prepared by the acylation of 3-methylbut-2-ene with propionyl chloride and acetyl chloride respectively following the literature procedure[13] and purified by flash column chromatography.

2,3-Dimethylhept-2-en-4-one **5**.—This compound was prepared by the acylation of 3-methylbut-2-ene with butyryl chloride following the literature procedure[12] and purified by flash column chromatography. B.p. 90 °C/20 mmHg; δ_H 2.56 (t, *J* 7, 2 H), 1.85 (s, 6 H), 1.73 (s, 3 H), 1.10 (m, 2 H), 0.95 (t, *J* 7, 3 H) and δ_C 212.12, 131.43, 113.24, 38.73, 22.26, 20.74, 18.21, 15.65 and 14.13; ν(neat)/cm^{-1} 1700; (Found: C, 78.5; H, 10.25. Calc. for C$_9$H$_{16}$O: C, 78.26; H, 10.14%).

3-Benzyl-4-methylpent-3-en-2-one **6**.—This compound was prepared by a modification of the literature method.[10] To a stirred solution of potassium hexamethyldisilazide (12 g, 60 mmol) in THF (100 cm^3) was added HMPA (hexamethyl-phosphoramide) (10 cm^3) at room temp. The solution was cooled to −70 °C and then a solution of mesityl oxide (6.0 g, 60 mmol) in THF (20 cm^3) was added dropwise. After 20 min, benzyl chloride (7.7 g, 61 mmol) in ether (4 cm^3) was added. The brown suspension was stirred for 1 h and then allowed to warm to room temp. The resulting cake was stirred with water (25 cm^3) and ether (40 cm^3) and the organic layer separated, washed with 5% HCl (20 cm^3), and processed to give a yellow oil (9 g). This oil was mixed with toluene-*p*-sulphonic acid (200 mg) and heated at 140 °C for 20 min. Flash column chromatography of the cooled reaction mixture (5% EtOAc–hexane) gave the enone **6** (6.2 g, 61%); δ_H 7.20 (m, 5 H), 3.65 (s, 2 H), 2.15 (s, 3 H), 1.90 (s, 3 H) and 1.80 (s, 3 H); δ_C 206.56, 141.50, 131.59, 130.18, 129.68, 127.96, 117.50, 36.85, 31.84, 23.96

and 23.11; ν/cm^{-1} 1695 and 1620 (Found: C, 82.75; H, 8.45. C$_{13}$H$_{16}$O requires C, 82.97; H, 8.51%).

3-Chloro-3,4-dimethylpent-4-en-2-one[10] **7**.—To a stirred ice-cold solution of compound **4**[14] (11.2 g, 100 mmol) in CH$_2$Cl$_2$ (500 cm^3) was added Ca(OCl)$_2$ (10.6 g, 74.6 mmol) and water (50 cm^3). Glacial acetic acid (6.0 g, 100 mmol) was added dropwise at such a rate so that the internal temperature did not exceed 5 °C. After being stirred at this temperature for 20 min the mixture was diluted with water (100 cm^3). The organic layer was separated and washed with NaHCO$_3$ (100 cm^3), water (100 cm^3) and dried (CaCl$_2$ and MgSO$_4$). Evaporation of solvents at 25 °C under reduced pressure gave a crude yellow oil. This was filtered through silica gel (20 g) eluting with hexane. The colourless solution was evaporated to give allylic halide **7** sufficiently pure for further reactions; δ_H 5.30 (s, 1 H), 5.10 (s, 1 H), 2.25 (s, 3 H), 1.85 (s, 3 H) and 1.75 (s, 3 H); δ_C 205.76, 120.05, 115.20, 57.45, 26.17, 24.69 and 19.48.

4-Chloro-4,5-dimethylhex-5-en-3-one **2**. Following the above general procedure, the enone **1**[13] gave crude product **2** as a pale yellow oil. δ_H 5.35 (s, 1 H), 5.15 (s, 1 H), 2.70 (q, *J* 7, 2 H), 1.96 (s, 6 H) and 1.15 (t, *J* 7, 3 H); δ_C 205.67, 120.23, 117.65, 59.76, 28.56, 24.45, 19.76 and 12.32 (Found: C, 59.55; H, 7.85; Cl, 21.8. C$_8$H$_{13}$ClO requires C, 59.81; H, 8.09; Cl, 22.11%).

3-Chloro-2,3-dimethylhept-1-en-4-one **8**. Following the general procedure, the *enone* **5** (3 g) gave compound **8** (2.8 g, 78%) as a colourless oil after flash column chromatography (5% EtOAC–hexane); δ_H 5.35 (s, 1 H), 5.10 (s, 1 H), 2.75 (t, *J* 7, 2 H), 1.85 (s, 6 H), 1.55 (m, 2 H) and 0.95 (t, *J* 7, 3 H); δ_C 205.67, 120.23, 117.65, 59.76, 28.56, 24.45, 19.76, 14.32 and 11.56 (Found: C, 61.6; H, 8.75; Cl, 20.6. C$_9$H$_{15}$OCl requires C, 61.89; H, 8.59; Cl, 20.34%).

3-Benzyl-3-chloro-4-methylpent-4-en-2-one[10] **9**. δ_H 7.25 (m, 5 H), 5.15 (s, 1 H), 5.10 (s, 1 H), 3.35 (s, 2 H), 2.25 (s, 3 H) and 1.80 (s, 3 H); δ_C 203.64, 141.70, 136.14, 131.43, 128.28, 127.36, 117.07, 81.35, 42.84, 25.80 and 20.25; *m/z* 223, 187 and 171.

2,3,5-Trimethyl-5-(phenylseleno)cyclopent-2-enone **3**.—To a stirred solution of diisopropylamine (10.5 g, 100 mmol) in THF (50 cm^3) was added BuLi (2.5 mol dm^{-3}; 42 cm^3, 104 mmol) dropwise at 0 °C. After 20 min, the pale yellow solution was cooled to −78 °C and then a solution of compound **2** (16 g, 100 mmol) in THF (20 cm^3) was added dropwise in 10 min. After 5 min the deep-orange solution was treated rapidly with a solution of benzeneselenenyl bromide (23 g, 98 mmol) in THF (40 cm^3). The pale yellow clear solution was then allowed to slowly warm to 0 °C and then quenched with saturated aqueous NH$_4$Cl (50 cm^3) and ether (100 cm^3). The organic layer was separated, washed with water (2 × 10 cm^3) and dried. Evaporation gave a crude brown oil (28 g). Flash column chromatography (5% EtOAc–hexane) gave cyclopentenone **3** (12.9 g, 48%) as a viscous yellow oil; δ_H 7.20–7.70 (m, 5 H), 2.6–2.8 (m, 2 H), 1.85 (s, 3 H), 1.65 (s, 3 H) and 1.50 (s, 3 H); δ_C 207.32, 164.69, 137.48, 134.02, 128.98, 128.50, 127.25, 48.97, 48.43, 23.04, 16.41 and 8.07 (Found: C, 60.65; H, 5.85. C$_{14}$H$_{16}$OSe requires C, 60.43; H, 5.75%).

2,3-Dimethyl-5-(phenylseleno)cyclopent-2-enone **10**. Following the above general procedure using compound **7** (7 g, 50 mmol), there was obtained after flash column chromatography *cyclopentenone* **10** (7.5 g, 54%) as a yellow viscous oil; δ_H 7.20–7.70 (m, 5 H), 3.85 (d of d, 1 H), 2.70–2.90 (m, 2 H), 1.95 (s, 3 H) and 1.75 (s, 3 H); δ_C 205.74, 167.55, 132.23, 128.98, 127.12, 47.64, 40.24, 17.06 and 8.29 (Found: C, 59.3; H, 5.15. C$_{13}$H$_{14}$OSe requires C, 59.09; H, 5.30%).

5-Ethyl-2,3-dimethyl-5-(phenylseleno)cyclopent-2-enone **11**. δ_H 7.20–7.70 (m, 4 H), 2.65 (m, 2 H), 1.85 (s, 3 H), 1.80 (q, *J* 7, 2 H), 1.65 (s, 3 H) and 0.90 (t, *J* 7, 3 H); δ_C 207.24, 164.76, 137.45, 132.71, 128.90, 127.56, 48.56, 47.65, 23.34, 17.98, 16.48 and 8.89

(Found: C, 61.85; H, 6.35. $C_{15}H_{18}OSe$ requires C, 61.64; H, 6.16%).

2-*Benzyl-3-methyl-5-(phenylseleno)cyclopent-2-enone* **12.** δ_H 7.05–7.75 (m, 10 H), 3.85 (d of d, 1 H), 3.55 (s, 2 H), 2.25–2.80 (m, 2 H) and 1.85 (s, 3 H); δ_C 204.90, 169.46, 138.82, 132.19, 128.82, 128.43, 127.52, 126.09, 47.65, 40.36, 29.08 and 17.40; m/z 341, 231 (Found: C, 66.6; H, 5.15. $C_{19}H_{18}OSe$ requires C, 66.86; H, 5.27%)

2,3,5-*Trimethyl-5-(phenylthio)cyclopent-2-enone* **13.** δ_H 7.20–7.60 (m, 5 H), 2.6–2.8 (m, 2 H), 1.85 (s, 3 H), 1.65 (s, 3 H) and 1.50 (s, 3 H); δ_C 207.32, 165.69, 137.48, 134.02, 128.98, 128.50, 127.25, 48.97, 48.43, 23.04, 16.41 and 8.07 (Found: C, 72.65; H, 6.75; S, 13.85. $C_{14}H_{16}OS$ requires C, 72.41; H, 6.89; S, 13.79%).

5-*Benzoyl-2,3,5-trimethylcyclopent-2-enone* **14.**—To a stirred solution of diisopropylamine (2 g, 20 mmol) in THF (10 cm³) at 0 °C was added dropwise BuLi (2.5 mol dm⁻³; 8 cm³, 20 mmol) via a syringe. After 20 min, the yellow solution was cooled to −78 °C and a solution of compound **2** (3 g, 19 mmol) in THF (20 cm³) was added in the course of 5 min. After a further 5 min, the deep-orange solution was treated rapidly with a solution of benzoyl chloride (2.8 g, 20 mmol) in THF (5 cm³) in 30 s. The yellow solution slowly warmed to room temp. in the course of 1 h and was kept at room temp. for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 cm³) and diluted with ether (40 cm³). The organic layer was separated, washed with water (10 cm³), HCl (1 mol dm⁻³; 20 cm³), water (10 cm³) and saturated aqueous $NaHCO_3$ (20 cm³), and dried. Evaporation gave an orange viscous oil (4.6 g). Flash column chromatography (10% EtOAc–hexane) gave *cyclopentenone* **14** (1.6 g, 36%) as a yellow viscous oil; δ_H 7.30–7.80 (m, 5 H), 3.10 (d of m, 1 H), 2.40 (d of m, 1 H), 2.10 (s, 3 H), 1.85 (s, 3 H) and 1.40 (s, 3 H); δ_C 207.37, 199.03, 167.56, 132.34, 128.55, 128.34, 127.98, 125.52, 59.88, 46.84, 22.86, 17.89 and 8.45; v(neat)/cm⁻¹ 2980, 1709 and 1675; m/z 229, 206, 125, 105 (Found: C, 79.15; H, 7.2. $C_{15}H_{16}O_2$ requires C, 78.94; H, 7.01%).

2-*Benzyl-3,5-dimethyl-5-(phenylseleno)cyclopent-2-enone* **16.**—To a stirred solution of diisopropylamine (2 g, 20 mmol) in THF (10 cm³) at 0 °C was added dropwise BuLi (2.5 mol dm⁻³; 8 cm³, 20 mmol) via a syringe. After 20 min, the yellow solution was cooled to −78 °C and a solution of compound **12** (6.7 g, 19.4 mmol) in THF (20 cm³) was added dropwise via a syringe in the course of 10 min. After 30 min, a solution of MeI (2.9 g, 20 mmol) in THF (2 cm³) was added rapidly. The orange solution was slowly warmed to room temp. in the course of 1 h and kept at room temp. for 1 h. The reaction mixture was then quenched with NH_4Cl (2 mol dm⁻³; 10 cm³) and ether (20 cm³). The organic layer was separated, washed with water (10 cm³), HCl (1 mol dm⁻³; 20 cm³) and $NaHCO_3$ (1 mol dm⁻³; 20 cm³), and dried. Evaporation gave an orange viscous mass (7.5 g). Flash column chromatography gave pure *cyclopentenone* **16** (6.3 g, 89%) eluting in 10% EtOAC–hexane; δ_H 7.05–7.65 (m, 10 H), 3.50 (s, 2 H), 2.80 (br s, 2 H), 1.80 (s, 3 H) and 1.55 (s, 3 H); δ_C 206.45, 165.82, 139.81, 137.54, 136.79, 128.93, 128.44, 128.28, 127.09, 125.98, 48.78, 48.05, 29.14, 23.24 and 16.79; (Found: C, 67.6; H, 5.55. $C_{20}H_{20}OSe$ requires C, 67.79; H, 5.64%).

5-*Allyl-2,3-dimethyl-5-(phenylseleno)cyclopent-2-enone* **17.**—Following the above general procedure using compound **10**, (2.64 g, 10 mmol), and allyl bromide (1.40 g, 11 mmol) there was obtained, after flash column chromatography, the *cyclopentenone* **17** (2.7 g, 90%) as a yellow viscous oil eluting in 10% EtOAc–hexane; δ_H 7.10–7.70 (m, 5 H), 5.40–5.80 (m, 1 H), 4.80–5.20 (m, 2 H), 2.40–2.80 (m, 4 H), 1.80 (s, 3 H) and 1.60 (s, 3 H); δ_C 207.34, 167.56, 137.70, 134.30, 131.40, 128.98, 127.45,

115.18, 47.64, 40.54, 30.87, 17.02 and 8.45 (Found: C, 63.3; H, 6.05. $C_{16}H_{18}OSe$ requires C, 63.15; H, 5.92%).

2,3-*Dimethyl-5-methylenecyclopent-2-enone* (*Methylenomycin B*, **18**).[5]—To a stirred solution of compound **3** (5.6 g, 20 mmol) in methylene dichloride (50 cm³), at 0 °C, was added dropwise 15% hydrogen peroxide (12.5 cm³, 60 mmol). The deep-yellow solution was stirred at ice-bath temperature for 30 min, and then warmed to ambient temperature and quenched with water (10 cm³). The organic layer was separated, washed with water (10 cm³) and 20% aqueous $NaHCO_3$ (20 cm³) and dried. Evaporation gave a colourless viscous oil (2.7 g) which was shown by ¹H NMR spectroscopy to be at least 95% methylenomycin B. Flash column chromatography gave pure methylenomycin B **18** (2.4 g, 96%) eluting in 20% EtOAc–hexane, δ_H 6.05 (s, 1 H), 5.30 (s, 1 H), 3.05 (s, 2 H), 2.05 (s, 3 H) and 1.80 (s, 3 H); δ_H 196.85, 164.20, 141.77, 138.14, 114.84, 36.94, 16.68 and 8.24: m/z 122, 107, 91 and 79; v(neat)/cm⁻¹ 1965, 1655 and 1625 (Found: C, 78.55; H, 8.05. Calc. for $C_8H_{10}O$: C, 78.68; H, 8.19%).

5-*Ethylidene-2,3-dimethylcyclopent-2-enone* **19.** Following the above procedure using compound **11** (5.9 g, 20 mmol) there was obtained compound **19** (2.5 g, 93%) as a pale yellow powder after flash column chromatography. M.p. 42 °C; δ_H 6.65 (q of t, 1 H), 3.00 (s, 2 H), 2.05 (s, 3 H), 1.80 (d, 3 H) and 1.70 (s, 3 H); δ_C 196.11, 162.09, 138.14, 135.86, 127.96, 34.99, 16.57, 14.84 and 8.18; m/z 136, 121 and 93; v(neat)/cm⁻¹ 1690 and 1655 (Found: C, 79.25; H, 8.7. $C_9H_{12}O$ requires C, 79.41; H, 8.82%).

2-*Benzyl-3-methyl-5-methylenecyclopent-2-enone* **20.** Following the general oxidation procedure using compound **16** (3.70 g, 10 mmol), there was obtained after flash column chromatography compound **20** (1.9 g, 91%) as a yellow viscous oil; δ_H 7.20 (s, 5 H), 6.05 (s, 1 H), 5.30 (s, 1 H), 3.65 (s, 2 H), 3.10 (s, 2 H) and 2.15 (s, 3 H); δ_C 195.47, 162.45, 141.50, 141.39, 139.28, 128.39, 126.01, 115.45, 37.16, 29.25 and 16.95; m/z 198, 183, 155, 128 and 91; v(neat)/cm⁻¹ 1691, 1655, 1625, 1601 and 756 (Found: C, 84.7; H, 6.9. $C_{14}H_{14}O$ requires C, 84.84; H, 7.07%).

5-*Allylidene-2,3-dimethylcyclopent-2-enone* **21.** Following the general oxidation procedure using compound **17** (3 g, 10 mmol), there was obtained after flash column chromatography compound **21** (1.40 g, 95%) as a yellow powder; m.p. 34 °C; δ_C 196.81, 162.19, 138.74, 135.00, 132.83, 128.98, 125.30, 35.26, 16.63 and 8.28; δ_H 6.30–7.00 (m, 2 H), 5.40–5.75 (m, 2 H), 3.10 (s, 2 H), 2.05 (s, 3 H) and 1.80 (s, 3 H); m/z 148, 133, 105 and 83; v(neat)/cm⁻¹ 1682, 1622, 1090 and 923 (Found: C, 81.25; H, 8.05. $C_{10}H_{12}O$ requires C, 81.08; H, 8.10%).

3-*Methyl-5-methylene-2-pentylcyclopent-2-enone* **22.** δ_C 195.89, 163.98, 142.74, 141.82, 114.90, 37.06, 31.80, 27.95, 23.34, 22.48, 16.68 and 14.03; δ_H 6.02 (s, 1 H), 5.45 (s, 1 H), 5.45 (s, 1 H), 3.04 (s, 2 H), 2.25 (m, 2 H), 2.10 (s, 3 H), 1.25 (m, 6 H) and 0.85 (t, 3 H); v(neat)/cm⁻¹ 2930, 1695, 1657, 1628 and 935; m/z 178 and 163 (Found: C, 81.05; H, 10.2. $C_{12}H_{18}O$ requires C, 80.89; H, 10.11%).

References
1 Preliminary communication: J. Mathew, *J. Chem. Soc., Chem. Commun.*, 1990, 1264.
2 T. Haneishi, N. Kitahara, Y. Takiguchi, M. Arai and S. Sugawara, *J. Antibiot.*, 1974, **27**, 386.
3 J. Jernow, W. Tautz, P. Rosen and T. H. Williams, *J. Org. Chem.*, 1979, **44**, 4212.
4 A. G. Cameron, A. T. Hewson and M. I. Osammor, *Tetrahedron Lett.*, 1984, 4141.

5 M. A. Tius, D. P. Astrab, A. H. Fauq, J. B. Ousset and S. Trehan, *J. Am. Chem. Soc.*, 1986, **108**, 3438.

6 (a) S. C. Welch, J. N. Assercq, J. P. Loh and S. A. Glase, *J. Org. Chem.*, 1987, **52**, 1440; (b) G. M. Strunz and G. Sankar Lal, *Can. J. Chem.*, 1982, **60**, 2528.

7 M. A. Tius, G. M. Patterson and D. P. Astrab, *J. Antibiot.*, 1985, **38**, 1061.

8 J. Mathew and B. Alink, *J. Chem. Soc., Chem. Commun.*, 1990, 684.

9 J. Mathew, *J. Org. Chem.*, 1990, **55**, 5294.

10 J. Mathew, *J. Org. Chem.*, 1991, **56**, 713.

11 (a) R. F. Newton, D. P. Reynolds and T. Eyre, *Synth. Commun.*, 1981, **11**, 527; (b) M. Mikolajczyk, S. Grzejszczak and P. Kyzwa, *Tetrahedron Lett.*, 1982, **23**, 2237.

12 For a detailed discussion, see D. Liotta and T. G. Back, *Organoselenium Chemistry*, John Wiley & Sons, Inc., NY, 1987; pp. 2–32.

13 D. D. Faulk and A. Fry, *J. Org. Chem.*, 1970, **35**, 364.

14 H. O. House, S. Chu and Y. Omen, *J. Org. Chem.*, 1975, **40**, 1461.

15 S. G. Hegde, D. Beckwith, R. Doti and J. Wolinsky, *J. Org. Chem.*, 1985, **50**, 894.

16 For reactions of ketone enolates with benzene selenenyl bromides, see (a) J. Blumbach, D. A. Hammond and D. A. Whiting, *Tetrahedron Lett.*, 1982, **23**, 3949; (b) M. Nishizawa, P. A. Greico,

S. D. Burke and W. Metz, *J. Chem. Soc., Chem. Commun.*, 1978, 76.

17 H. J. Reich, J. M. Renga and I. L. Reich, *J. Am. Chem. Soc.*, 1975, **97**, 5434.

18 (a) D. A. Evans, M. D Ennis, T. Le and N. Mandel, *J. Am. Chem. Soc.*, 1984, **106**, 1154; (b) D. A. Evans, J. Bartroli and T. Shih *J. Am. Chem. Soc.*, 1981, **103**, 3099.

19 P. A. Grieco and M. Miyashita, *J. Org. Chem.*, 1974, **39**, 120.

20 H. J. Reich and M. J. Kelly, *J. Am. Chem. Soc.*, 1982, **104**, 1119.

21 T. Kawamata, S. Inayama and K. Sata, *Chem. Pharm. Bull.*, 1980, **28**, 277.

22 For the only other reported synthesis of this type of dienone, see: M. Pokinakoir and S. Chancharunee, *Tetrahedron Lett.*, 1984, **25**, 4141.

23 For a detailed study of long range coupling of compound **19** and similar systems using selective decoupling NMR study see: G. Hajdukovic and M. L. Martin, *J. Mol. Struct.*, 1977, **40**, 57.

24 W. C. Still, H. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.