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NEW STRATEGIES FOR THE CONSTRUCTION OF MACROLIDE ANTIBIOTIC SUBUNITS USING ORGANOIRON PRECURSORS†

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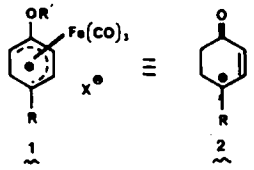
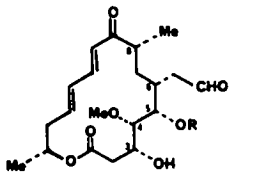
Abstract—Tricarbonyldienyliron complexes **6**, **7** and **17** are used as precursors to a range of dienylacetic acid derivatives which are not readily available from other sources. The phenylselenolactonization of these dienes occurs in a regio- and stereocontrolled manner with conjugate attachment of a PhSe group *anti* to the lactone moiety in the case of cyclohexadiene derivatives. Oxidation of the allylic selenium compounds occurs with concomitant selenoxide (2,3)-sigmatropic rearrangement to give hydroxylactones.

Tricarbonyldienyliron complexes show considerable promise as intermediates for organic synthesis, there being a range of natural product types accessible using the properties of these organometallic reagents. Thus, it is now well-known that alkoxy substituents appropriately placed on the dienyl ligand control the regiochemistry of nucleophile addition, thereby allowing the preparation of a large number of 4,4-disubstituted cyclohexenones.[2] In this respect, complexes such as **1** may be considered as the synthetic equivalent of cyclohexenone γ-cations (**2**).



1 ≡ **2**



3

In addition to its ability to stabilize dienyl cations which lead to interesting and useful regiocontrolled nucleophile addition, the $Fe(CO)_2L$ group [L = CO, PPh_3, $P(OPh)_3$] shows a powerful stereochemical directing effect. This can also be usefully employed for synthetic purposes. For example, we have shown that consecutive *cis* addition of two nucleophiles can be accomplished in both six- and seven-membered ring dienyl complexes, leading to 1,2- and 1,3-stereocontrol,[3] respectively, as summarized in Scheme 1.

Both of the above properties illustrate that fairly complex organic molecules are very easily prepared using dienyliron complexes. In order to illustrate the considerable utility of combining organoiron chemistry with other methods of diene functionalization, we chose to examine the preparation of simple dienylacetic acid derivatives using tricarbonyldienyliron complexes and their cyclofunctionalization using the techniques which are well-established for analogous mono-olefinic carboxylic acids.[4,5] To our knowledge there is only one previously reported example of cyclofunctionalization of acyclic conjugated dienes, in that case phenylselenoetherification.[6] No information concerning the stereochemistry of this reaction is available. Therefore, we considered that studies on the lactonization of conjugated diene acids would form an interesting chemical investigation in itself. As it turns out, the reaction is mechanistically interesting and synthetically useful.

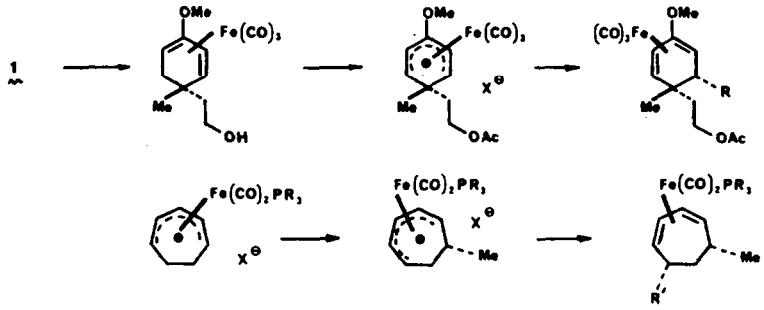
Carbomycin B (**3**) is a 16-membered ring macrolide antibiotic[7] which we considered to be a useful framework for demonstrating applicability of cyclohexadienyliron complexes as precursors for the synthesis of complex molecules. The interesting part of this macrolide is the right-hand half, which contains five asymmetric centres and we anticipated that controlled functionalization of a cyclohexadiene derivative, followed by ring cleavage, would give access to an acyclic fragment with relative stereochemistry corresponding to the contiguous centres C-4, C-5 and C-6. The results of our studies in the elaboration of such subunits, together with related investigations, are disclosed in the present paper.[8]

RESULTS AND DISCUSSION

Cyclohexadiene derivatives

Tricarbonylcyclohexadienyliron tetrafluoroborate (or hexafluorophosphate) (**6**) is the first dienyliron complex to have been prepared[9] and is obtained quantitatively as a stable yellow microcrystalline compound by hydride abstraction from tricarbonylcyclohexadieneiron. The same complex is prepared, more cheaply, by treatment with concentrated sulphuric acid[10] of the mixture of complexes **4** and **5** obtained[11] from the reaction of dihydroanisole with $Fe(CO)_5$. The sulphate derivative so obtained is easily converted to the hexafluorophosphate by treatment of an aqueous solution with NH_4PF_6. This

† Part 34 in the series "Organoiron Complexes in Organic Synthesis". For Part 33 see Pearson *et al.*[1]



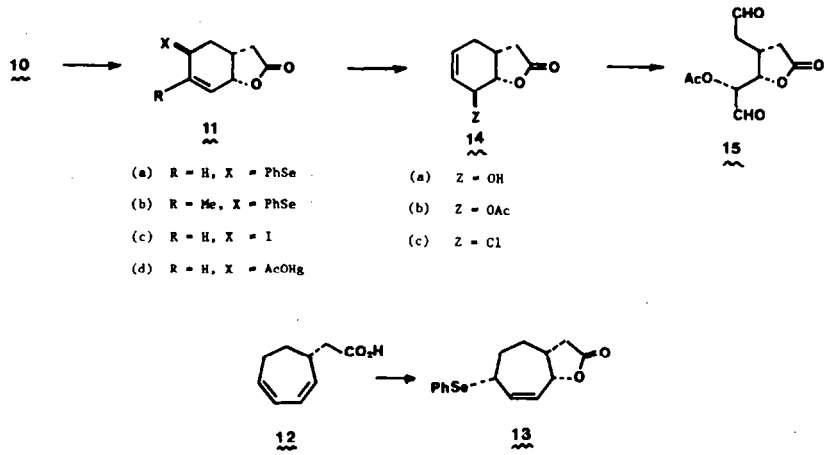
Scheme 1.

technique is, in fact, the only way in which the pure 2-methyl-substituted dienyl complex, **7**, can be prepared,[10] as illustrated in Scheme 2.

Reaction of dienyl complexes **6** or **7** with $NaCH(CO_2Me)_2$ occurs virtually instantaneously in THF at 0° to give, cleanly, the diester derivatives **8a** and **8b** in essentially quantitative yield. These complexes were smoothly demetallated, by a modification of Shvo and Hazum's method,[12] giving the cyclohexadienylmalonic ester derivatives **9a** and **9b** in high yield, which were converted to the monoesters and, thence, to the carboxylic acids **10** by standard procedures. It may be noted that these compounds are very easily prepared by the organoiron method, but are not available using standard organic synthesis techniques, thereby demonstrating the efficacy of the organoiron approach.

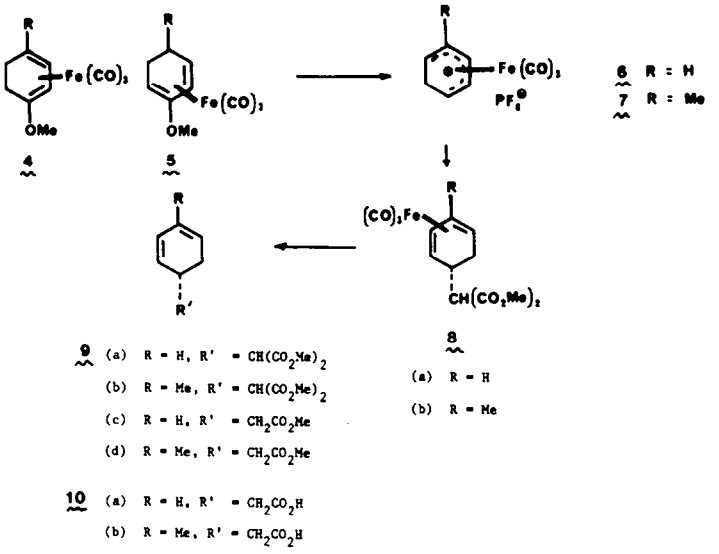
iodine or mercuric acetate gave conjugate lactonization products **11c** and **11d**, respectively, whose stereochemistry was assumed to be the same as for **11a** by comparison of ^{1}H-NMR spectra.

The stereochemistry of these conjugate lactonizations is mechanistically interesting, since it is in stark contrast to the recorded *cis*-1,4-bromination of 1,3-cyclohexadiene.[14] On the other hand, reaction of lithium dimethylcuprate with cyclohexadiene monoepoxide is known to give *trans*-4-methyl-2-cyclohexenol.[15] Thus, the stereochemical course of conjugate lactonization of the cyclohexadiene derivatives is identical to the conjugate epoxide opening. A plausible explanation is that *diaxial* 1,4-addition to the diene and *diaxial* vinylogous epoxide opening, shown in Scheme 3, are the preferred modes of reaction. The



With the required carboxylic acids in hand, we were in a position to study their lactonization reactions. Treatment of either **10a** or **10b** with phenylselenenyl chloride under the usual conditions (PhSeCl, Et_3N, CH_2Cl_2, $-78°$ to 23°) gave crystalline phenylselenolactones **11** in good yield. Despite extensive double resonance experiments we were unable to make unambiguous assignment of the stereochemistry of these compounds using ^{1}H-NMR spectroscopy, although the fact that lactonization occurs exclusively by 1,4-addition to the diene was readily ascertained. In the event, X-ray analysis of lactone **11a** established the stereochemistry shown, with a PhSe group *anti* to the *cis* lactone moiety.[13] Similarly, treatment of **10a** with 1,4-bromination of cyclohexa-1,3-diene is slightly anomalous in this respect, probably because it proceeds via a tight bromonium–bromide ion pair which dictates the *cis* stereochemistry.[14] Interestingly, we have observed[8,16] that conjugate phenylselenolactonization of cycloheptadienylacetic acid (**12**) occurs in a *cis* manner to give **13** and this is again consistent with a diaxial 1,4-addition but, this time, in a seven-membered ring which requires the opposite stereochemical relationship between nucleophile and nucleofuge (shown in Scheme 3).

The stereochemistry of cyclohexadienylacetic acid lactonization turns out to be synthetically useful. Treatment of the selenolactone **11a** with hydrogen

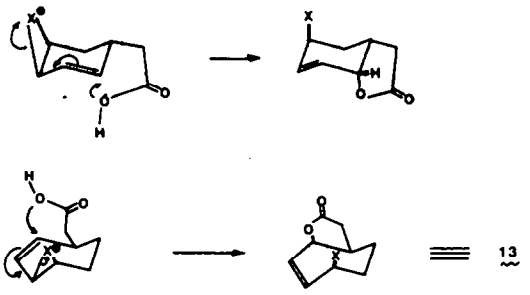


Scheme 2.

peroxide, followed by aqueous work-up, afforded the hydroxylactone **14a** via (2,3)-sigmatropic rearrangement of the allylic selenoxide,[17] which was converted to the acetate **14b**. Ozonolysis of **14b** gave the dialdehyde **15** which has relative stereochemistry corresponding to C-4, C-5 and C-6 of the macrolide antibiotic carbomycin B (**3**). We anticipate that this conjugate selenolactonization–selenoxide rearrangement sequence will be useful for regio- and stereocontrolled functionalization of cyclohexadienes leading to a range of useful synthetic intermediates.

Treatment of the selenolactone **11a** with *N*-chlorosuccinimide[18] also proceeded cleanly to give the chlorolactone **14c**, thereby providing a complementary method for diene functionalization.

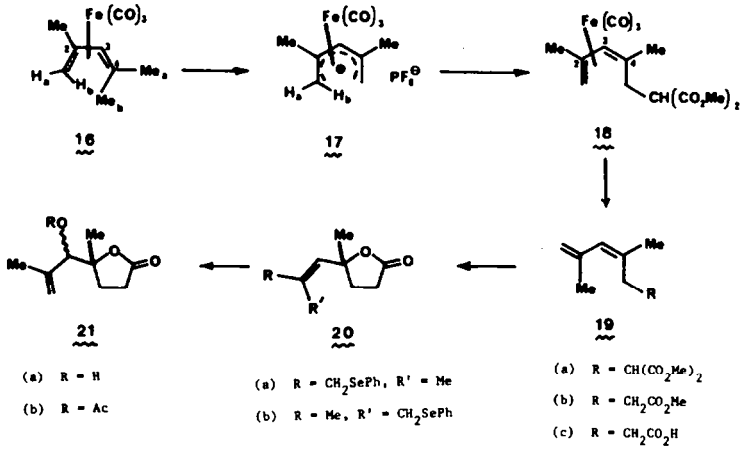
Acyclic dienyl-$Fe(CO)_3$ complexes have previously received attention in terms of their basic chemistry, but no attempts have been made to seek their organic synthesis application. The conjugate selenolactonization discussed above provides an opportunity to specifically functionalize 1,3-dienes which might be readily accessible using acyclic dienyl-$Fe(CO)_3$ complexes and, in order to demonstrate the utility of this approach, we chose the symmetrically dimethylated complex **17**, which was prepared from diene complex **16**, itself readily accessible from commercially available 2,4-dimethyl-1,3-pentadiene. Hydride abstraction from **16** ($Ph_3C^+PF_6^-$) was sluggish, requiring an unusually long reaction time in refluxing CH_2Cl_2 (cf. hydride abstraction from cyclohexadiene-$Fe(CO)_3$ which is complete after 40 min at room temperature[9]), but gave a good yield of **17**. Reaction of **17** with $NaCH(CO_2Me)_2$ occurred cleanly to give the adduct **18** and this was readily decomplexed to give the dienylmalonic ester **19a**. Decarboxylation of **19a** using the Krapcho method,[19] followed by alkaline hydrolysis, gave the carboxylic acid **19c** via monoester **19b** and we were now in a position to examine the phenylselenolactonization of the acyclic system. This proceeded smoothly to afford an approximately 4:1 mixture of double bond isomers **20a** and **20b**. That the major component was the (*E*)-isomer was established by NMR NOE difference spectroscopy:† irradiation at the vinyl proton singlet (δ 5.13) caused pronounced enhancement of the CH_2SePh singlet (δ 3.42) and small enhancement of the angular methyl group singlet (δ 1.36), but no effect on the vinylmethyl group singlet (δ 1.9). Since, in the acyclic system, attack by the selenium electrophile *syn* or *anti* to the carboxylate nucleophile has no influence on the double bond geometry in the final product, we can conclude that cyclofunctionalization occurs on a preferred *transoid* diene conformation, shown in structure **19**. Oxidation of the mixture of selenolactones **20** proceeded with concomitant allylic selenoxide rearrangement to give the alcohol **21a**, homogeneous on TLC. Acetylation of this product gave acetate **21b**, again homogeneous on TLC, but which was shown to be an approximately 3:2 mixture of diastereomers by 200 MHz NMR spectroscopy. Thus, the selenoxide rearrangement in this case



Scheme 3.

† We are grateful to Mr Ian C. Richards, Case Western Reserve University (U.S.A.) and Dr E. Constable, Cambridge University (U.K.) for performing these experiments.

proceeds with a very small degree of stereoselectivity, although the overall transformation of dienylacetic acid to hydroxylactones is a highly regiospecific process.



CONCLUSIONS

From the above experiments, it can be seen that organoiron chemistry provides ready access to dienylacetic acids which would otherwise be obtainable only with considerable difficulty. These molecules provide interesting substrates for conjugate lactonization and, coupled with rearrangement of, e.g. derived allylic selenoxides, lead to potentially useful precursors for the synthesis of complex molecules.

EXPERIMENTAL

IR spectra were recorded with a Perkin–Elmer 1420 instrument and NMR spectra with Varian EM-360 or XL-200 spectrometers. Mass spectra were determined by the Department of Pharmacology, Case Western Reserve University. All solvents used in reactions were freshly distilled under N_2 as follows: THF and C_6H_6 from Na–benzophenone; Et_2O from $LiAlH_4$; CH_2Cl_2 from CaH_2; pyridine from BaO. Compounds which were characterized with IR, NMR and mass spectral data only were ascertained to be ≥95% pure by sharp m.ps, TLC and/or HPLC (Gilson 802 instrument) and 200 MHz NMR spectroscopy.

Preparation of tricarbonyl [2 - 5 - η - (*dimethylcyclohexa* - 2,4 - *dienylmalonate*)]*iron* (**8a**) *and tricarbonyl* [2 - 5 - η - (*dimethyl* - 4 - *methylcyclohexa* - 2,4 - *dienylmalonate*)]*iron* (**8b**). To a stirred suspension of NaH (0.96 g, 20 mmol of 50% dispersion in mineral oil, washed under N_2 with pentane) in THF (90 ml) at 0° was added dropwise a soln of dimethylmalonate (2.64, 20 mmol) in THF (10 ml), to give a suspension of dimethyl sodiomalonate.

Compound **6** (8.0 g, 22 mmol) or **7** (8.32 g, 22 mmol) was added as a solid in one portion, with backflushing of N_2 and stirring was continued until a clear soln was obtained (15 min). The soln was concentrated, poured into Et_2O (250 ml), washed with H_2O (3 × 100 ml), dried ($MgSO_4$) and evaporated to give **8a** (7.0 g, 100%) or **8b** (7.20 g, 99%) which were sufficiently pure for the next step. Analytical samples were obtained by recrystallization from 5% Et_2O in pentane.

Compound **8a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2950, 2050, 1975, 1750 (sh), 1730, 1440, 1350, 1280 (b), 1150, 1000, 900; ^{1}H-NMR ($CDCl_3$): 5.25 (2H, m), 3.69 (3H, s), 3.66 (1H, obscured), 3.64 (3H, s), 2.95 (3H, m), 2.04 (1H, ddd, J = 15.3, 9.8, 3.8 Hz), 1.36 (1H, dt, J = 15.3, 2.6 Hz. (Found: C, 47.8; H, 3.8; $[M]^+$, 350. Calc for $C_{14}H_{14}FeO_7$: C, 48.03; H, 4.03%.)

Compound **8b**: m.p. 74°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 2950, 2860, 2050, 1975, 1750 (sh), 1735, 1510, 1470, 1440, 1370, 1240 (b), 1100, 1050, 900; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.25 (1H, m), 3.70 (6H, s), 3.66 (1H, obscured), 2.95 (3H, m), 2.00 (3H, s), 2.00 (1H, obscured), 1.4 (1H, m).

Preparation of dimethylcyclohexa - 2,4 - *dienylmalonate* (**9a**) *and dimethyl* 4 - *methylcyclohexa* - 2,4 - *dienylmalonate* (**9b**). To a soln of **8a** (3.50 g, 10 mmol) or **8b** (3.64 g, 10 mmol) in *N,N*-dimethyl acetamide (75 ml), anhyd trimethylamine oxide (7.5 g) was added and the mixture was stirred vigorously at room temp for 8 hr. The mixture was poured into sat brine (200 ml), cooled and extracted with Et_2O (3 × 100 ml). The Et_2O soln was washed with H_2O (3 × 100 ml), dried ($MgSO_4$) and evaporated. The residue was flash chromatographed on silica gel (eluated with 25% EtOAc in hexane) to give **9a** (1.9 g, 90%) or **9b** (2.00 g, 90%) as colourless oil.

Compound **9a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 2980, 2960, 2880, 1750, 1730, 1480, 1440, 1330, 1260–1210, 1150, 1030; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.8 (4H, m, vinyl), 3.73 (6H, s, 2 × CO_2Me), 3.5 [1H, d, J = 9 Hz, C<u>H</u>$(CO_2Me)_2$], 3.1 (1H, m), 2.2 (2H, m); MS: *m/z* (%) 210 $[M]^+$ (1.5), 208 $[M-2]^+$ (8.8), 149 $[208-CO_2Me]^+$ (12), 132 (100), 118 (14.6), 100 (50.6). (Found: $[M]^+$ 210.0872; $C_{11}H_{14}O_4$ requires: $[M]^+$ 210.0891.)

Compound **9b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 3000, 2950, 1750, 1735, 1450, 1435, 1260, 1200, 1150, 1020; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.8 (2H, m), 5.4 (1H, m), 3.73 (6H, s, 2 × CO_2Me), 3.55 [1H, d, J = 9 Hz, C<u>H</u>$(CO_2Me)_2$], 3.1 (1H, m), 2.22 (2H, m), 1.9 (3H, bs, <u>Me</u>); MS: *m/z* (%) 224 $[M]^+$ (3), 222 $[M-2]^+$ (19.4), 163 $[222-CO_2Me]^+$ (23.8), 132 (100), 100 (44.8). (Found: $[M]^+$ 224.1057; $C_{12}H_{16}O_4$ requires: $[M]^+$ 224.1049.)

Preparation of methylcyclohexa - 2,4 - *dienylacetate* (**9c**) *and methyl* - 4 - *methyl* - *cyclohexa* - 2,4 - *dienylacetate* (**9d**). NaCN (0.49 g, 10 mmol) was dissolved in wet DMSO (25 ml containing 0.5 ml H_2O) which was previously freed from O_2. A soln of **9a** (1.05 g, 5 mmol, to get **9c**) or **9b** (1.12 g, 5 mmol, to get **9d**) in DMSO (5 ml) was added and the mixture was stirred under Ar at 110° for 24 hr. It was cooled, poured into sat NaCl aq (100 ml) and extracted with Et_2O (3 × 50 ml). The combined Et_2O extracts were washed with H_2O (3 × 100 ml), dried (Na_2SO_4) and evaporated. The monoester so obtained was purified by chromatography using 25% EtOAc in hexane as eluent to give a colourless oil.

Compound **9c** (0.47 g, 62%): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2975, 2930, 2850, 1735, 1600, 1450, 1380, 1340, 1280, 1115; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 5.75 (4H, m, vinyl), 3.74 (3H, s, CO_2Me), 2.6 (1H, m), 2.3 (2H, m), 2.15 (2H, m); MS: *m/z* (%) 152 $[M]^+$ (12), 150 $[M-2]^+$ (100), 91 (30). (Found: $[M]^+$ 152.0818; $C_9H_{12}O_2$ requires: $[M]^+$ 152.0837.)

Compound **9d** (0.54 g, 65%): IR ν_{max} cm^{-1}: 3000, 2980, 2920, 1735, 1600, 1520, 1470, 1440, 1420, 1220, 1050, 1030, 930, 880, 850; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.70 (2H, m, vinyl), 5.35 (1H, m, vinyl), 3.68 (3H, s, CO_2Me), 2.6 (3H, m), 2.3 (2H, m), 1.7 (3H, s, Me); MS: *m/z* (%) 166 $[M]^+$ (25.4), 164 $[M-2]^+$ (38.4),

124 (64.4), 105 (58.5). (Found: $[M]^+$ 166.0977; $C_{10}H_{14}O_2$ requires: $[M]^+$ 166.0994.)

Preparation of cyclohexa-2,4-dienylacetic acid (**10a**) *and 4-methylcyclohexa-2,4-dienylacetic acid* (**10b**). Ester **9c** (1.52 g, 10 mmol) or **9d** (1.66 g, 10 mmol) was dissolved in MeOH (75 ml) and KOH aq (5 g, in 30 ml H_2O) was added. The mixture was stirred under Ar at room temp for 4 hr. The soln was slightly acidified with ice-cold 10% HCl and extracted with Et_2O. The Et_2O soln was washed with H_2O, dried ($MgSO_4$) and evaporated giving the acid as a colourless oil.

Compound **10a** (1.24 g, 90%): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400–3100 (b), 3000, 2900, 2850–2400, 1700, 1400, 1280, 1020, 940; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 9.3 (1H, bs, $CO_2\underline{H}$), 5.72 (4H, m, vinyl), 2.6 (1H, m), 2.32 (2H, m), 2.15 (2H, m); MS: *m/z* (%) 138 $[M]^+$ (26.4), 136 $[M-2]^+$ (35.7), 79 (71.2), 60 (100%). (Found: $[M]^+$ 138.0660; $C_8H_{10}O_2$ requires: $[M]^+$ 138.0681.)

Compound **10b** (1.35 g, 90%): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350–3200 (b), 3000, 2990, 2950, 2870–2420, 1700, 1410, 1260, 1010, 950; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 9.3 (1H, bs, $CO_2\underline{H}$), 5.82 (2H, bs), 5.48 (1H, m), 2.5 (3H, m), 1.9 (2H, m); MS: *m/z* (%) 152 $[M]^+$ (16.7), 150 $[M-2]^+$ (33.2), 105 (100), 93 (78.4), 60 (42.9). (Found: $[M]^+$ 152.0817; $C_9H_{12}O_2$ requires: $[M]^+$ 152.0837.)

Selenolactones **11a** and **11b**. A soln of the acid **10a** (0.138 g, 1 mmol) or **10b** (0.152 g, 1 mmol) in dry CH_2Cl_2 (20 ml) was stirred with Et_3N (0.101 g, 1 mmol) at 30° for 15 min, cooled to −72° and treated slowly with phenylselenenyl chloride (0.211 g, 1.1 mmol). It was allowed to warm to room temp and further stirred for 1 hr. The soln was concentrated and chromatographed using 50% CH_2Cl_2 in hexane as eluent. The selenolactones so obtained (70%) were crystallized from Et_2O as colourless needles.

Compound **11a**: m.p. 80°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2900, 2850, 1770, 1425, 1380, 1330, 1240, 1180, 1155, 1120, 1040, 1010, 970, 910, 890, 845; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.598–7.552 (2H, m, Ph—H), 7.335 (3H, m, Ph—H), 6.335 (1H, dd, $J_{3,4}$ = 9.79, $J_{4,5}$ = 5.42 Hz, H-4), 5.973 (1H, dd, $J_{3,4}$ = 9.79, $J_{3,2}$ = 3.91 Hz, H-3), 4.776 (1H, dd, $J_{2,1}$ = 5.37 and $J_{3,2}$ = 3.91 Hz, H-2), 3.983 (1H, m, H-5), 3.015–2.885 (1H, m, H-1), 2.883 (1H, dd, $J_{7\alpha,\beta}$ = 16.50, $J_{7\beta,1}$ = 8.2 Hz, H-7β), 2.278 (1H, d, $J_{7\alpha,\beta}$ = 16.50 Hz, H-7α), 1.90 (2H, m, H-6). Decoupling experiment: irradiating signal at δ 6.335, collapses H-3 at δ 5.973 to a d, J = 3.91 Hz; irradiating signal at δ 5.973, collapses H-4 at δ 6.335 to a d, J = 5.4 Hz and H-2 at δ 4.776 to a d, J = 5.37 Hz; irradiating signal at δ 4.776, collapses H-3 at δ 5.973 to a d, J = 9.79 Hz; irradiating signal at δ 3.983, collapses H-4 at δ 6.335 to a d, J = 9.79 Hz; irradiating signal at δ 2.99, collapses H-2 at δ 4.776 to a d, J = 3.91 Hz; irradiating signal to δ 2.883, collapses H-7α at δ 2.278 to a s; and irradiating signal at δ 2.278, collapses H-7β at δ 2.883 to a d, J = 8.2 Hz. MS: *m/z* (%) (Cl) 294 $[M+1]^+$ (39), 293 $[M]^+$ (2.1), 157 $[PhSeH]^+$ (63.8), 136 $[M-PhSeH]^+$ (58.2), 91 (100). (Found: $[M]^+$ 293.0414; $C_{14}H_{14}O_2Se$ requires: $[M]^+$ 293.0594.)

Compound **11b**: m.p. 74°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2940, 2840, 1770, 1580, 1470, 1440, 1380, 1330, 1280, 1170, 950, 910; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.599–7.552 (2H, m, Ph—H), 7.345–7.261 (3H, m, Ph—H), 5.76 (1H, d, J = 3.9 Hz, H-3), 4.716 (1H, dd, $J_{2,3}$ = 3.9 Hz, $J_{2,1}$ = 4.17 Hz, H-2), 3.722 (1H, dd, J = 3.69, 2.77 Hz, H-5), 2.940 (1H, m, H-1), 2.836 (1H, dd, $J_{7\alpha,\beta}$ = 16.55 Hz, $J_{7\beta,1}$ = 8.2 Hz, H-7β), 2.244 (1H, d, $J_{7\alpha,\beta}$ = 16.55 Hz, H-7α), 2.024 (3H, s, Me), 1.941 (1H, ddd, J = 2.77, 8.84, 13.45 Hz, H-6β), 1.744 (1H, dd, J = 13.45, 3.69 Hz, H-6α); MS: *m/z* (%) 308 $[M+1]^+$ (13.4), 307 $[M]^+$ (5.5), 157 $[PhSeH]^+$ (29.1), 150 $[M-PhSeH]^+$ (47.6), 105 (100), 91 (36.3). (Found: $[M]^+$ 307.0771; $C_{15}H_{16}O_2Se$ requires: $[M]^+$ 307.0750.)

Preparation of iodolactone **11c**. A soln of **10a** (0.138 g, 1 mmol) in dry acetonitrile (15 ml) was stirred with I_2 (0.28 g) at 0° for 1 hr. The mixture was partitioned between Et_2O and $NaHCO_3$ aq and decolourized by sodium thiosulphate soln. It was washed with brine and dried ($MgSO_4$). Removal of Et_2O followed by preparative TLC afforded the iodolactone as a colourless oil (0.16 g, 60%) which darkened on standing: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2925, 2850, 1775, 1450 (b), 1380, 1340, 1290, 1240, 1180, 1120, 1090, 1010, 970, 900, 850; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 6.30 (1H, dd, J = 9, 5 Hz, H-4), 5.8 (1H, dd, J = 9, 4 Hz, H-3), 4.9 (2H, m, H-2, H-5), 2.8 (1H, m, H-1), 2.5–1.5 (4H, m).

Preparation of mercurilactone **11d**. A soln of mercuric acetate (0.32 g, 1 mmol) in abs MeOH (10 ml) containing BF_3 (0.5 mmol) as catalyst was added to a soln of **10a** (0.138 g, 1 mmol) in MeOH (5 ml). The mixture was stirred for 2 hr at 27°, diluted with H_2O and extracted with Et_2O in the usual way, followed by purification by chromatography. The lactone **11d** was obtained as a colourless oil (0.2 g, 60%); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2920, 2850, 1770, 1720, 1450, 1400, 1330, 1280 (b), 1170, 1090, 1010, 960, 930; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 6.2 (1H, m, vinyl), 5.8 (1H, m, vinyl), 4.8 (1H, m, H-2), 4.2 (1H, m, H-5), 3.4 (3H, s, OCOMe), 2.9 (1H, m), 2.5 (2H, m), 1.8 (2H, m).

Preparation of hydroxylactone **14a**. A soln of **11a** (0.15 g, 0.5 mmol) in THF (20 ml) was cooled to −20°. H_2O_2 (5% v/v, 1 ml) was added and the mixture was stirred for 2 hr. Et_3N (1 ml) was then added and the temp of the stirred mixture was allowed to reach 23°. After 10 min it was extracted with $CHCl_3$, washed with H_2O, dried ($MgSO_4$) and concentrated. The hydroxylactone so obtained was purified by chromatography (0.046 g, 60%); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 3340 (b), 2980, 2960, 2850, 1770, 1570, 1460, 1430, 1410, 1380, 1310, 1260, 1210 (b), 1160, 1050, 1000; ^{1}H-NMR (60 MHz, $CDCl_3$): δ 5.8 (2H, bs, vinyl), 4.6 (1H, t, J = 5 Hz, H-2), 4.25 (1H, m, H-3), 3.2 (2H, m, H-1, H-7), 2.7–2.2 (3H, m, H-7, $C\underline{H}_2$-6).

Preparation of acetoxylactone **14b**. A soln of Ac_2O (0.2 ml) and **14a** (0.05 g) in pyridine (0.5 ml) was set aside at room temp overnight. It was treated with cold H_2O (5 ml), acidified with 10% HCl and extracted with Et_2O. The organic layer was washed with H_2O, $NaHCO_3$ aq and, finally, with H_2O, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography to give the acetate as a colourless oil (0.05 g); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2940, 1770, 1735, 1420, 1360, 1240, 1160, 1140, 1020, 900, 860; ^{1}H-NMR (60 MHz, $CDCl_3$): δ 6.1 (1H, bs, H-4), 5.85 (1H, m, H-5), 5.25 (1H, m, H-3), 4.6 (1H, t, J = 5 Hz, H-2), 3.6 (1H, m, H-1), 2.8 (2H, m), 2.2 (2H, m), 2.05 (3H, s, OCOMe).

Preparation of chlorolactone **14c**. To a stirred soln of **11a** (0.073 g) in CCl_4 (10 ml), *N*-chlorosuccinimide (0.05 g) was added. The mixture was refluxed for 0.5 hr, cooled and filtered. The residue on evaporating the solvent was chromatographed over silica gel. The **14c** was obtained (0.026 g, 60%) as colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2975, 2925, 1770, 1450, 1425, 1380, 1320, 1290, 1020, 985; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.8 (2H, bs, vinyl), 4.6 (1H, m), 4.4 (1H, m), 2.9–1.5 (5H, m); MS: *m/z* (%) 173 $[M]^+$ (18), 171 (30.4), 137 (49.4). (Found: $[M]^+$ 172.5240; $C_8H_9O_2Cl$ requires: $[M]^+$ 172.52317.)

Preparation of dialdehydelactone **6**. O_3 gas was bubbled through a soln of **14b** (0.05 g) in CH_2Cl_2 (10 ml), at −72° for 5 min until the colour became blue. N_2 gas was then passed to expel the excess O_3 whereupon the soln became colourless. Me_2S (0.5 ml) was added and the mixture was set aside at room temp for 2 hr. It was taken-up with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$) and evaporated. The dialdehyde so obtained was purified by chromatography as a colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2940, 2900, 2840, 1750, 1710, 1450, 1420, 1360, 1250, 1180, 1080, 1000; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 9.8 and 9.5 (each 1H, s), 5.2 (1H, m), 4.9 (1H, m), 2.20 (3H, s), 2.1 (3H, m), 1.2 (2H, m).

Tricarbonyl (2,4-*dimethyl*-1,3-*pentadiene*)*iron* (**16**). 2,4-Dimethyl-1,3-pentadiene (20 g) and pentacarbonyliron (50 ml) were added to di-*n*-butylether whilst N_2 gas was bubbled through. The mixture was stirred and boiled under reflux in an N_2 atmosphere for 46 hr, cooled and filtered through Celite (*care*! pyrophoric iron is produced in this reaction). Solvent and excess pentacarbonyliron were removed on a rotary evaporator fitted with a dry ice–Me_2CO trap and the product was purified by chromatography to give **16** as a golden oil (25 g, 51%); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2037, 1970; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 5.15 (1H, s, H-3), 2.18 (3H, s, Me-2), 1.79 (1H, s, H-1a), 1.57 (1H, s, H-1b), 1.565 (3H, s, Me-4a), 1.145 (3H, s, Me-4b), MS: *m/z* (%) 236 (3), 208 (12), 180 (8), 152 (100). (Found: C, 50.7, H, 5.2%; $C_{10}H_{12}FeO_3$ requires: C, 50.9; H, 5.1%.)

Tricarbonyl (2,4 - *dimethylpentadienyl*)*iron hexafluorophosphate* (**17**). The complex **16** (14.0 g) and triphenylmethyl hexafluorophosphate (28.0 g) were boiled under reflux in an N_2 atmosphere in dry CH_2Cl_2 (100 ml) for 18 hr. The cooled mixture was added to stirred Et_2O (1000 ml) containing a little H_2O (2.0 ml). The mixture was filtered, the residue washed thoroughly with Et_2O and dried in air to afford pure **17** (18.0 g, 80%); IR ν_{max}^{MeCN} cm^{-1}: 2115, 2068; ^{1}H-NMR (CD_3CN, 60 MHz): δ 6.75 (1H, s, H-3), 3.48 (2H, d, J = 4 Hz, H-1b, H-5b), 2.30 (6H, s, 2 × Me), 2.27 (2H, d, H-1a, H-5b). (Found: C, 31.8; H, 2.8%; $C_{10}H_{11}FeO_3PF_6$ requires: C, 31.6; H, 2.9%.)

Tricarbonyl[2 - 5 - η - *dimethyl*(2,4 - *dimethylpenta* - 2,4 - *dienyl*)*malonate*]*iron* (**18**). This was prepared in a similar way from **17** as described for **8a**. The crude compound was purified by flash chromatography on silica gel eluting with 25% EtOAc in hexane to yield **18** (90%); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2900, 2050, 1975, 1750, 1730, 1480, 1440, 1380, 1300, 1250, 1160, 1050, 1020, 960; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 4.94 (1H, d, J = 8.5 Hz, vinyl), 3.71 (6H, s, 2 × CO_2Me), 3.544 [1H, t, J = 7.81 Hz, C<u>H</u>($CO_2Me)_2$], 2.648 (2H, d, J = 7.81 Hz, allylic C<u>H</u>$_2$), 2.43 (1H, m, vinyl), 0.896 and 0.863 (each 3H, s, 2 × Me).

Dimethyl(2,4 - *dimethyl* - 2,4 - *pentadienyl*)*malonate* (**19a**). This was prepared from **18** as for **9a** above and purified by column chromatography, using 25% EtOAc in C_6H_6 as eluent (75% yield); IR ν_{max} cm^{-1}: 3030, 1750, 1730, 1520, 1440, 1220, 1050, 930, 900; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.8 (1H, bs, vinyl), 4.8 (2H, m, vinyl), 3.7 [1H, obscured, C<u>H</u>($CO_2Me)_2$], 3.7 (6H, s, 2 × CO_2Me), 2.85 (2H, d, J = 7 Hz, C<u>H</u>$_2$), 1.8 and 1.77 (each 3H, s, Me); MS: *m/z* (%) 226 $[M]^+$ (5), 161 (46.8), 108 (36.6), 95 (100). (Found: $[M]^+$ 226.1220; $C_{12}H_{18}O_4$ requires: $[M]^+$ 226.1205.)

Methyl 4,6 - *dimethyl* - 4,6 - *heptadienoate* (**19b**). This was prepared by the decarbomethoxylation of **19a**, using the procedure described for the preparation of **9c**. The monoester **19b** was purified by flash chromatography using 20% EtOAc in hexane as eluent and was obtained as a colourless oil (60% yield); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 1730, 1470, 1430, 1380, 1250, 1215, 1170, 1100, 860, 700; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.8 (1H, bs, vinyl), 4.8 (2H, m, vinyl), 3.7 (3H, s, CO_2Me), 2.3 (4H, m), 1.8 and 1.75 (each 3H, s, Me); MS: *m/z* (%) 168 $[M]^+$ (5.9), 107 (80.6), 95 (100). (Found: $[M]^+$ 168.1130; $C_{10}H_{16}O_2$ requires: 168.1150.)

4,6 - *Dimethyl* - 4,6 - *heptadienoic acid* (**19c**). This was prepared by the hydrolysis of **19b**, using the procedure described for the preparation of **10a**. The acid was obtained as colourless oil (90%); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2980, 1710, 1650, 1600, 1450, 1380, 1300, 1250, 1215, 920, 870, 780; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 5.8 (1H, bs, vinyl C<u>H</u>), 4.8 (2H, m, vinyl C<u>H</u>$_2$), 2.3 (4H, m), 1.8 and 1.75 (each 3H, s, Me); MS: *m/z* (%) 154 $[M]^+$ (26.5), 139 (28), 107 (69.3), 95 (100). (Found: $[M]^+$ 154.1010; $C_9H_{14}O_2$ requires: $[M]^+$ 154.09938.)

Preparation of selenolactones, **20a** *and* **20b**. A soln of **19c** (0.154 g, 1 mmol) in dry CH_2Cl_2 was treated with Et_3N and phenylselenenyl chloride, using the same procedure as that for **11a**, to afford a mixture of **20a** and **20b** in a 4 : 1 ratio (70% total yield). The structure of each individual isomer was established by an NOE experiment (see Results and Discussion).

Compound **20a**: IR ν_{max} 3000, 2940, 1770, 1585, 1480, 1440, 1420, 1390, 1300, 1270, 1240, 1200, 1180, 1160, 1080; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.593–7.461 (2H, m, Ph—H), 7.295–7.225 (3H, s, Ph—H), 5.131 (1H, s, vinyl), 3.415 (2H, s, CH_2—Se), 2.38 and 1.94 (1H, dd, J = 20.26, 7.55 Hz and 1H, d, J = 20.26 Hz, respectively, C<u>H</u>$_2$CO), 1.899 (3H, s, Me), 1.364 (3H, s, Me), 1.68 and 1.417 (1H, dd, J = 15.68, 7.44 Hz and 1H, d, J = 15.68 Hz, respectively, C<u>H</u>$_2$CH$_2$CO); MS: *m/z* (%) (CI), 310 $[M+1]^+$ (46.6), 309 $[M]^+$ (5), 153 (25.9), 99 (100). (Found: $[M]^+$ 309.0925; $C_{15}H_{18}O_2Se$ requires: $[M]^+$ 309.0907.)

Preparation of hydroxylactone **21a**. Oxidative rearrangement of **20a** was done using the same procedure as was described for **11a** to furnish **21** as a colourless oil (60%); IR ν_{max} 3600, 2980, 1770, 1450, 1380, 1220 (b), 1150, 1070, 1010, 950; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 4.9 (2H, s, vinyl), 4.0 (1H, s, C<u>H</u>OH), 2.2 (2H, m, CH_2CO), 1.75 (3H, s, <u>Me</u>), 1.2 (3H, s, Me), 1.0 (2H, m).

Preparation of acetoxylactone **21b**. A mixture of Ac_2O (0.2 ml) and a soln of **21a** (0.085 g) in pyridine (0.5 ml) was set aside at room temp overnight. It was treated with cold H_2O (5 ml), acidified with 10% HCl and extracted with Et_2O. The organic layer was washed with H_2O, $NaHCO_3$ aq and, finally, with H_2O, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography to give the acetate as a colourless oil (0.08 g); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2920, 1770, 1735, 1500, 1440, 1360, 1250 (s), 1170, 1020, 910; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 5.080 (3H, m, vinyl and C<u>H</u>OAc), 2.568 (3H, m), 2.098 and 2.081 (3H total, 2 × s, 3 : 2 ratio, COMe), 2.09 (1H, m), 1.807 (3H, s, Me), 1.397 (3H, s, Me); $[M]^+$ 212.

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