Synthesis of Spiroacetals using Organoselenium-mediated Cyclisation Reactions. *X*-Ray Molecular Structure of (2*S*,8*R*)-8-Methyl-2-phenyl-1,7-dioxaspiro-[5.5]undecan-4(*R*)-ol

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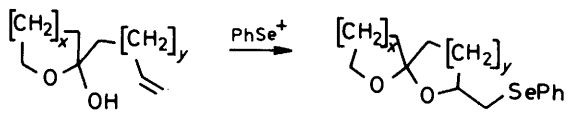
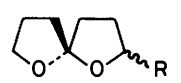
Alkenyl hydroxyketones undergo cyclisation *via* their hemiacetal form, in the presence of *N*-phenylselenophthalimide (NPSP) and a Lewis acid, to give the corresponding phenylseleno-substituted spiroacetals. Using this methodology the synthesis of *trans*- and *cis*-2-methyl-1,6-dioxaspiro-[4.4]nonane (**1**), *trans*- and *cis*-2-ethyl-1,6-dioxaspiro[4.4]nonane (chalcogran) (**2**), *trans*- and *cis*-2-methyl-1,6-dioxaspiro[4.5]decane (**3**), *trans*-7-methyl-1,6-dioxaspiro[4.5]decane (**4**), *trans*-2-methyl-1,7-dioxaspiro[5.5]undecane (**5**), and (2*S*,8*R*)-8-methyl-2-phenyl-1,7-dioxaspiro[5.5]undecane-4-one (**6**) has been achieved, after reductive removal of selenium using Raney-nickel in diethyl ether. Compound (**2**) is the principal aggregation pheromone from *Pityogenes chalcographus* (L), whilst compounds (**3**) and (**4**) constitute the pheromone components of the common wasp, *Paravespula vulgaris*. The structure of the spiroacetal (**6**) was determined as a result of *X*-ray crystallography of a later derivative, obtained by sodium borohydride reduction of (**6**).

The spiroacetal functional group is common to a wide range of natural products, notably insect pheromones,[1] oxygenated terpenoids,[2] polyether antibiotics,[3] the cytovaricins,[4] and the recently isolated potent antiparasitic agents, the milbemycins and avermectins.[5] We report here a new spiroacetal-forming reaction[6] which could prove useful in the preparation of such molecules and their structural analogues.

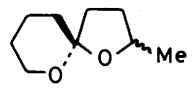


Scheme 1.

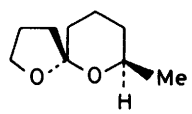
Conceptually the reaction involves the organoselenium-mediated intramolecular trapping of a hemiacetal by a suitably disposed carbon–carbon double bond[7] (Scheme 1). The use of organoselenium-mediated cyclisation reactions in the preparation of oxygen-containing heterocyclic compounds is a rapidly developing and important synthetic strategy;[8] however, application to natural product synthesis has so far been limited.[9] In this work the synthesis of the spiroacetals (**1**)—(**6**) is described. Compound (**2**) is the principal aggregation pheromone from *Pityogenes chalcographus* (L),[10] compounds (**3**) and (**4**) are pheromone components of the common wasp *Paravespula vulgaris*,[11] and compound (**6**) is a useful precursor for avermectin/milbemycin analogues. For the preparation of the spiroacetal (**1**), but-3-enylmagnesium bromide was treated, at 0 °C in diethyl ether, with the known tetrahydropyranyl-protected aldehyde (**7**)[12] to give an adduct, which was oxidised with Collins' reagent to provide the enone (**8**) in 75% yield. Deprotection of (**8**) with camphorsulphonic acid in methanol gave a mixture of the hydroxyketone (**9**) and the hemiacetal (**10**) in 94% combined yield. Treatment of this mixture with one equivalent of *N*-phenylselenophthalimide (NPSP),[13] and a trace of zinc(II) bromide (0.1 equiv.), in dichloromethane at room temperature gave a 1:1 *cis*:*trans* mixture of the spiroacetals (**11**) in 52% yield. The reaction was conveniently followed by t.l.c. and/or by ^{1}H n.m.r. spectroscopy. Reductive removal of the phenylseleno substituent was achieved by treatment with Raney-nickel in diethyl ether, at room temperature under hydrogen, to give an excellent yield of compound (**1**) as a 1:1 mixture of *cis*:*trans* isomers. No attempt



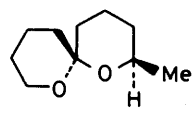
(**1**) R = Me *cis* and *trans*
(**2**) R = Et *cis* and *trans*



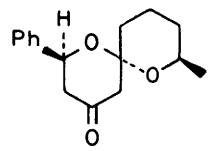
(**3**) *cis* and *trans*



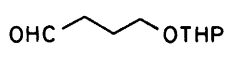
(**4**) *trans*



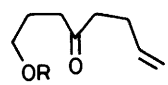
(**5**) *trans*



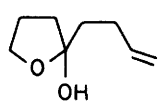
(**6**)



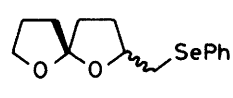
(**7**)



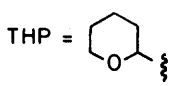
(**8**) R = THP
(**9**) R = H



(**10**)



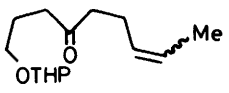
(**11**)



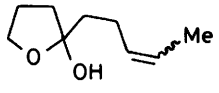
was made to separate these isomers as similar systems are known to undergo equilibration at 5 °C over a period of a few days.[11]

Synthesis of the natural product (**2**) was achieved in a similar fashion, namely reaction of pent-3-enylmagnesium bromide with (7) which gave enone (**12**) after Collins' oxidation. This, upon hydrolysis to (**13**) and selenium-mediated cyclisation, gave the spiroacetals (**14**). Reduction with Raney-nickel afforded compound (**2**) in 34% overall yield.

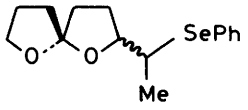
Preparation of the spiroacetals (**3**) was accomplished by a slightly different strategy, in that starting materials were prepared by an alternative route. Accordingly, but-3-enylmagnesium bromide was treated with δ-valerolactone at −78 °C, to give the enone (**15**) in low yield after separation from the other product, that of diaddition of the Grignard reagent to the lactone. Cyclisation of (**15**) with NPSP gave a 1:2 mixture of *cis*:*trans* isomers of compound (**16**) in 78% yield, which after Raney-nickel reduction gave (**3**), again as a 1:2 mixture of *cis*:*trans* isomers in 90% yield. This equilibration ratio was identical with that observed for the natural material.[14]



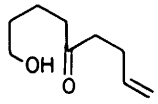
(**12**)



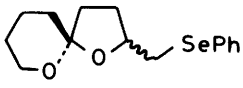
(**13**)



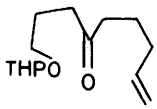
(**14**)



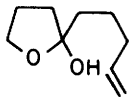
(**15**)



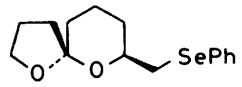
(**16**)



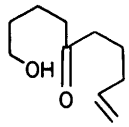
(**17**)



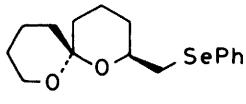
(**18**)



(**19**)



(**20**)

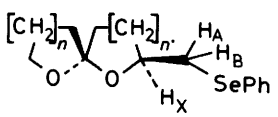


(**21**)

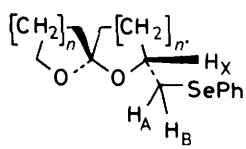
However, during the synthesis of the spiroacetals (**4**) and (**5**) only single *trans* isomers were obtained. Reaction of pent-4-enylmagnesium bromide with the protected aldehyde (7) gave the enone (**17**), after Collins' oxidation, in 96% overall yield. Hydrolysis afforded compound (**18**), which upon subsequent selenium-mediated cyclisation gave the *trans*-phenylselenospiroacetal (**19**) in 73% yield. Finally, Raney-nickel reduction afforded the natural spiroacetal (**4**).

For the synthesis of (**5**), pent-4-enylmagnesium bromide was treated with δ-valerolactone at −78 °C to provide the hydroxyketone (**20**) in poor (22%) yield, after separation by silica gel chromatography from the diaddition product. Compound (**20**) was cyclised with NPSP in the normal way to provide the *trans*-spiroacetal (**21**) (77%) which was reduced to compound (**5**) using Raney-nickel (88%).

Table 1. 250 MHz ^{1}H n.m.r. spectra of the phenylseleno-spiroacetals



trans



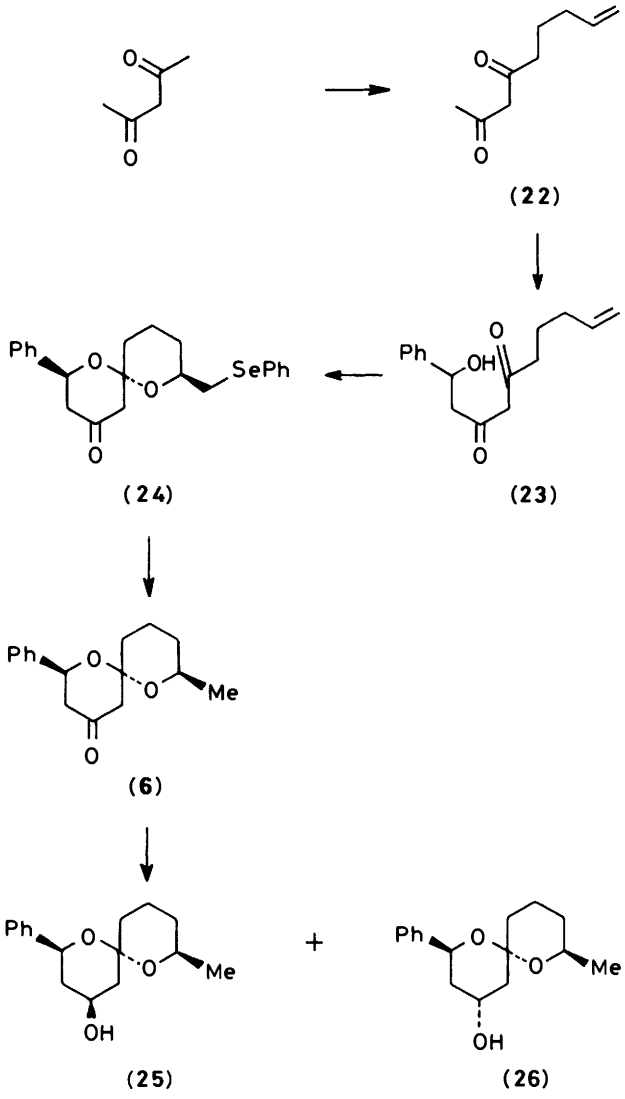
cis

Compound	δ H_A	δ H_B	J_{AX}(Hz)	J_{BX}(Hz)	J_{AB}(Hz)
(**11**) *trans* $n = n' = 1$	3.00	2.96	2.6	3.7	12.5
cis	3.26	3.11	5.9	4.7	12.5
(**16**) *trans* $n = 2, n' = 1$	3.08	2.96	5.8	7.8	11.7
cis	3.29	3.13	5.8	5.0	11.7
(**19**) *trans* $n = 1, n' = 2$	3.04	2.90	6.9	4.7	12.0
(**21**) *trans* $n = n' = 2$	3.12	2.95	8.6	5.1	12.2

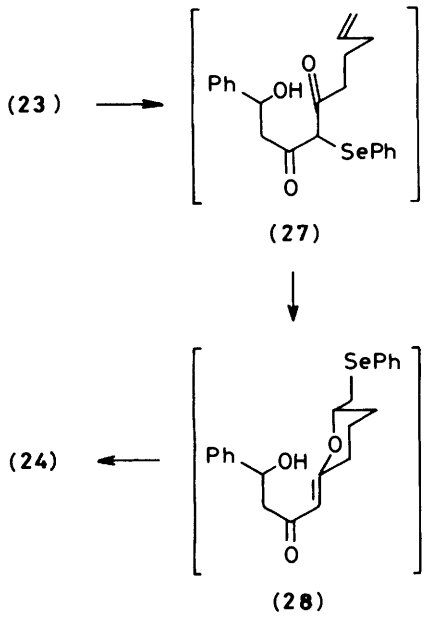
The structural proof of the initially formed phenylseleno-spiroacetals follows from their spectral data, especially their high-field ^{1}H n.m.r. parameters, some key features of which are noted in Table 1.

The last spiroacetal to be studied, (**6**), was designed as a suitable model compound for avermectins/milbemycins. The dianion from pentane-2,4-dione was formed by sequential treatment with sodium hydride in tetrahydrofuran (THF) at 0 °C, followed by n-butyl-lithium at −20 °C. This dianion was treated with 4-bromobut-1-ene to give the kinetically quenched adduct (**22**). Re-formation of the dianion using 2 equivalents of lithium di-isopropylamide followed by reaction with benzaldehyde at −78 °C gave the necessary starting material (**23**) for cyclisation studies. Treatment of (**23**) with NPSP (1.1 equiv.) and $SnCl_4$ (0.1 equiv.) in dichloromethane afforded the spiroacetal (**24**) as the major product (50%) after 96 h at room temperature. The high-field 250 MHz ^{1}H n.m.r. spectrum of (**24**) is entirely in accord with the proposed structure, which was confirmed by *X*-ray crystallographic determination of a later derivative. The phenylseleno group in compound (**24**) was removed by Raney-nickel to give compound (**6**) as a colourless oil in 94% yield. Finally reduction of the carbonyl group in (**6**) was achieved using $NaBH_4$ in dimethoxyethane at 0 °C, to give a separable mixture of the alcohols (**25**) and (**26**) in 61 and 32% yield respectively (Scheme 2). Use of other reducing systems gave a less favourable ratio of the desired isomer (**25**). During the organoselenium-mediated cyclisation of (**23**) to the spiroacetal (**24**), organoselenium-containing intermediates were noticed by means of t.l.c. and ^{1}H n.m.r. spectroscopy, but were not isolated. We propose that the first formed intermediate was that of seleniation on the central carbon of the dicarbonyl system, *i.e.* (**27**), and this then undergoes Lewis acid-catalysed rearrangement, with migration of the phenylseleno group, to form the monocyclic intermediate (**28**). This intermediate subsequently cyclises with anomeric control[15] to give the final product (**24**) (Scheme 3). Evidence for the phenylseleno group migration and the proposed intermediates is based upon our earlier studies on related systems.[16] While the spectroscopic data for the two alcohols (**25**) and (**26**) agree with their structure assignment, unambiguous proof was derived from *X*-ray crystallographic analysis of the minor isomer (**26**) (Figure).

From the above studies, the new selenium-based methodology



Scheme 2.



Scheme 3.

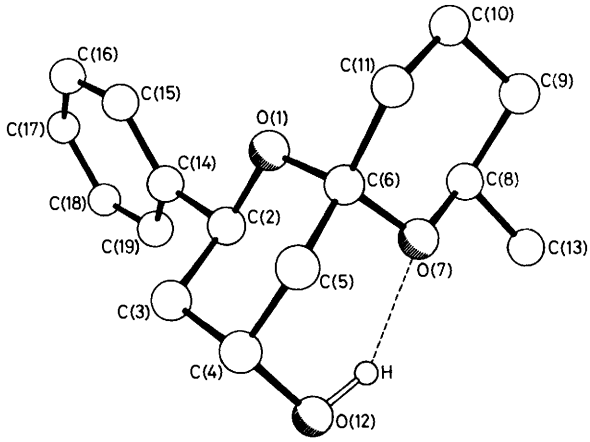


Figure. The molecular structure of (26)

can be used effectively to afford methyl- [4.4]-, [4.5]-, and [5.5]-dioxaspiro systems and compares favourably with current methods of spiroacetal formation.[17]

Experimental

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 298 spectrophotometer and ^{1}H n.m.r. spectra with a Varian EM 360A, or Brucker WH250 spectrometer, for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were obtained using a V.G. Micromass 7070 spectrometer. Light petroleum refers to the fraction boiling in the range 40—60 °C. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods. Chromatography was performed on MN-Silica gel 60, 230—400 mesh, under pressure.

General Procedure for the Reaction of Grignard Reagents with 4-(Tetrahydropyran-2-yloxy)butanal (7) *and Subsequent Oxidation.*—To a solution of compound (7) (2 mmol) in diethyl ether (7 ml) at 0 °C under argon was added a solution of the Grignard reagent (1—2 equiv.) in diethyl ether (5 ml). After the addition, the mixture was stirred for 30 min at room temperature. Saturated aqueous ammonium chloride (7 ml) was added and the organic phase was separated and dried. The solvent was removed under reduced pressure to give the crude product, which was added directly to a solution of Collins' reagent (6—10 equiv.) in dichloromethane (7 ml). The reaction mixture was stirred at room temperature for 2 h, diluted with diethyl ether (60 ml), and filtered through a pad of Celite. The solvent was removed under reduced pressure and the crude product subjected to chromatography (50% diethyl ether–light petroleum) to provide the pure compounds.

Reaction with but-3-enylmagnesium bromide. Reaction of compound (7) with but-3-enylmagnesium bromide [from but-3-enyl bromide (0.41 g, 3.0 mmol) and magnesium (0.08 g)] followed by oxidation and chromatography gave 1-(*tetrahydropyran-2-yloxy*)*oct-7-en-4-one* (**8**) (0.47 g, 75%), δ (250 MHz) 5.80 (1 H, m), 5.00 (2 H, m), 4.53 (1 H, t, *J* 3.0 Hz), 3.83—3.40 (4 H, m), 2.50 (4 H, m), and 2.10—1.10 (10 H, m); $\nu_{max.}$(film) 1 710, 1 630, and 1 120 cm^{-1}; *m/z* 226, 208, 141, and 85 (Found: C, 69.0; H, 10.05. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%).

Reaction with pent-3-enylmagnesium bromide. Reaction of compound (7) with pent-3-enylmagnesium bromide [from pent-3-enyl bromide (0.45 g, 3.0 mmol) and magnesium (0.08 g)] followed by oxidation and chromatography gave 1-(*tetrahy-*

dropyran-2-yloxy)non-7-en-4-one (**12**) (0.50 g, 74%) as an oil, δ (250 MHz) 5.42 (2 H, m), 4.55 (1 H, t, *J* 3.1 Hz), 3.83—3.40 (4 H, m), 2.48 (4 H, m), and 2.30—1.45 (13 H, m); $\nu_{max.}$(CHCl$_3$) 1 717, 1 630, and 1 120 cm^{-1}; *m/z* 240, 155, 139, and 85 (Found: C, 69.85; H, 10.25. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.06%).

Reaction with pent-4-enylmagnesium bromide. Reaction of compound (**7**) with pent-4-enylmagnesium bromide [from pent-4-enyl bromide (0.33 g, 2.2 mmol) and magnesium (0.06 g)] followed by oxidation and chromatography gave 1-*(tetrahydropyran-2-yloxy)non-8-en-4-one* (**17**) (0.48 g, 97%), δ (60 MHz) 6.17—4.70 (3 H, m), 4.54—4.36 (1 H, m), 4.02—3.12 (4 H, m), and 2.63—1.13 (16 H, m); $\nu_{max.}$(film) 2 933, 1 710, 1 635, 1 112, and 1 028 cm^{-1}; *m/z* no M^+ peak, 155, 139, 97, 85, 84, and 41 (Found: C, 69.75; H, 10.2%).

General Procedure for the Removal of the Tetrahydropyran-2-yl Protecting Group.—The tetrahydropyranyl derivative (1.5 mmol) was added dropwise to a stirred solution of camphorsulphonic acid (CSA) (2 mg) in methanol (3 ml). After 30 min at 50 °C the mixture was cooled and filtered through a pad of Celite. Removal of the solvent under reduced pressure gave the crude product which contained the alkenyl-substituted hemiacetal as the major product, together with a small amount of the corresponding open-form hydroxyketone. This mixture, however, could be used directly in the next reaction.

Deprotection of compound (**8**). By the above general method, compound (**8**) (0.24 g, 1.1 mmol) gave the crude hemiacetal (**10**) (0.15 g, 95%), δ (250 MHz) 5.83 (1 H, m), 5.09—4.92 (2 H, m), 3.87 (1 H, m), 3.39 (1 H, m), 2.50 (2 H, m), and 2.35—1.61 (7 H, m).

Deprotection of compound (**12**). By the above general method compound (**12**) (0.34 g, 1.5 mmol) gave the crude hemiacetal (**13**) (0.19 g, 81%).

Deprotection of compound (**17**). By the above general method, compound (**17**) (0.34 g, 1.5 mmol) gave the crude hemiacetal (**18**) (0.21 g, 90%), δ (60 MHz) 6.00—4.69 (3 H, m), 3.98—3.61 (2 H, t), and 2.53—1.28 (11 H, m); $\nu_{max.}$ (film) 3 410, 2 950, 2 389, 1 635, and 913 cm^{-1}; *m/z* 156, 71, 51, and 41.

General Procedure for the Addition of Grignard Reagents to δ-Valerolactone.—A solution of the appropriate Grignard reagent (2.0 mmol) in diethyl ether (2 ml) was added dropwise to a suspension of δ-valerolactone (2.0 mmol) in dry THF (6 ml) under argon at −78 °C during 3 h, *via* a motorised syringe. The mixture was stirred for a further 1 h, after which time saturated aqueous ammonium chloride (2 ml) was added and the mixture was allowed to warm to room temperature. The organic phase was separated, dried, and the solvent was removed under reduced pressure. The residue was subjected to rapid chromatography (30% diethyl ether–light petroleum) to give the product, the hydroxyketo alkene.

Reaction of δ-valerolactone with but-3-enylmagnesium bromide. Using the above procedure, but-3-enylmagnesium bromide [from but-3-enyl bromide (0.27 g, 2.0 mmol) and magnesium (0.06 g)] was treated with δ-valerolactone (2.0 mmol) to give 9-hydroxynon-1-en-5-one (**15**) (38 mg, 12%), δ (60 MHz) 6.09—4.73 (3 H, m), 3.56 (2 H, t), and 2.62—1.43 (11 H, m); $\nu_{max.}$(CHCl$_3$) 3 476, 2 927, 2 872, 1 708, and 1 634 cm^{-1}; *m/z* 156, 87, 69, 58, 55, and 41; and the product of diaddition, 5-but-3-enylnon-8-ene-1,5-diol (34 mg, 8%), δ (60 MHz) 6.16—4.67 (6 H, m), 3.57 (2 H, t), and 2.17—1.31 (16 H, m); $\nu_{max.}$(film) 3 370, 2 923, 2 859, and 1 637 cm^{-1}; *m/z* no M^+ peak, 195, 157, 139, 83, 51, and 41.

Reaction of δ-valerolactone with pent-4-enylmagnesium bromide. Using the above procedure, pent-4-enylmagnesium bromide [from pent-4-enyl bromide (0.3 g, 2.0 mmol) and magnesium (0.06 g)] was treated with δ-valerolactone (2.0 mmol) to give 1-hydroxydec-9-en-5-one (**20**) (77 mg, 23%), δ (60 MHz) 6.03—4.67 (3 H, m), 3.53 (2 H, t), and 2.53—1.27 (13 H, m); $\nu_{max.}$(film) 3 398, 2 930, 1 705, and 1 639 cm^{-1}; *m/z* 170, 116, 101, and 98 (Found: M^+, 170.1312. $C_{10}H_{18}O_2$ requires *M*, 170.1307); and the product of diaddition, 5-pent-4-enyldec-9-ene-1,5-diol (29 mg, 6%), δ (60 MHz) 6.15—4.74 (6 H, m), 3.59 (2 H, br t), 2.70 (2 H, br, exch. D_2O), and 2.20—1.20 (18 H, m); $\nu_{max.}$(film) 3 360, 2 929, 2 858, and 1 638 cm^{-1}; *m/z* no M^+ peak, 222, 171, 84, and 69.

General Procedure for the Selenium-mediated Cyclisation.—To a solution of the appropriate hydroxyalkene (1 mmol) and NPSP (0.33 g, 1.1 mmol) in dry dichloromethane (3 ml) under argon at room temperature was added dry zinc(II) bromide (16 mg, 0.1 equiv.).

The mixture was stirred for 1—2 h, diluted with light petroleum (4 ml), filtered (to remove precipitated phthalimide), washed with saturated aqueous sodium hydrogen carbonate (1 ml), and dried. The solvent was removed under reduced pressure and the residue subjected to chromatography to afford the product.

Cyclisation of compound (**10**). Treatment of compound (**10**) (0.14 g, 0.98 mmol) with NPSP and zinc(II) bromide gave 2-phenylselenomethyl-1,6-dioxaspiro[4.4]nonane (**11**) (0.17 g, 58%) as a 1:1 mixture of diastereoisomers, δ (250 MHz) 7.52 (2 H, m), 7.24 (3 H, m), 4.34 (0.5 H, m, *cis* isomer), 4.22 (0.5 H, m, *trans* isomer), 3.88 (2 H, m), 3.26 (0.5 H, dd, J_{AB} 12.5, J_{AX} 5.9 Hz), 3.11 (0.5 H, dd, J_{AB} 12.5, J_{BX} 4.7 Hz), 3.00 (0.5 H, dd, $J_{A'B'}$ 12.5, $J_{A'X'}$ 2.6 Hz), 2.96 (0.5 H, dd, $J_{A'B'}$ 12.5, $J_{B'X'}$ 3.7 Hz), and 2.31—1.67 (8 H, m); $\nu_{max.}$(CHCl$_3$) 2 940, 1 580, and 1 440 cm^{-1}; *m/z* 298, 141, and 127 (Found: M^+, 298.0466. $C_{14}H_{18}O_2Se$ requires *M*, 298, 0471).

Cyclisation of compound (**13**). Treatment of compound (**13**) (0.16 g, 1 mmol) with NPSP and zinc(II) bromide gave 2-(1-*phenylselenoethyl*)-1,6-*dioxaspiro*[4.4]*nonane* (**14**) (0.14 g, 45%) as a mixture of diastereoisomers, δ (250 MHz) 7.58 (2 H, m), 7.26 (3 H, m), 4.25—3.20 (4 H, m), and 2.20—1.35 (11 H, m, including Me doublets at 1.47 and 1.39); $\nu_{max.}$(film) 2 920, 2 875, and 1 580 cm^{-1}; *m/z* 312, 155, and 127 (Found: C, 57.65; H, 6.4. $C_{15}H_{20}O_2Se$ requires C, 57.88; H, 6.48%).

Cyclisation of compound (**15**). Treatment of compound (**15**) (0.16 g, 1 mmol) with NPSP and zinc(II) bromide gave 2-*phenylselenomethyl*-1,6-*dioxaspiro*[4.5]*decane* (**16**) (0.24 g, 78%) as a 2:1 mixture of *E*:*Z* isomers, δ (250 MHz) 7.54 (2 H, m), 7.24 (3 H, m), 4.40—3.52 (3 H, m), 3.29 (0.3 H, dd, J_{AX} 5.8, J_{AB} 11.7 Hz, H_A *cis* isomer), 3.13 (0.3 H, dd, J_{BX} 5.0, J_{AB} 11.7 Hz, H_B *cis* isomer), 3.08 (0.7 H, dd, J_{AX} 5.8, J_{AB} 11.7 Hz, H_A *trans* isomer), 2.96 (0.7 H, dd, J_{BX} 7.8, J_{AB} 11.7 Hz, H_B *trans* isomer), and 2.24—1.48 (10 H, m); $\nu_{max.}$(CHCl$_3$) 2 920, 2 875, and 984 cm^{-1}; *m/z* 312, 141, and 85 (Found: C, 58.05; H, 6.6. $C_{18}H_{20}O_2Se$ requires C, 57.88; H, 6.48%).

Cyclisation of compound (**18**). Treatment of compound (**18**) (0.16 g, 1 mmol) with NPSP and zinc(II) bromide gave trans-7-*phenylselenomethyl*-1,6-*dioxaspiro*[4.5]*decane* (**19**) (0.25 g, 81%) as an oil, δ (250 MHz) 7.50 (2 H, m), 7.22 (3 H, m), 4.07—3.93 (1 H, m, H_X), 3.92—3.34 (2 H, m), 3.04 (1 H, dd, J_{AB} 12, J_{AX} 6.9 Hz, H_A), 2.90 (1 H, dd, J_{AB} 12, J_{BX} 4.7 Hz, H_B) and 2.09—1.59 (10 H, m); $\nu_{max.}$(CHCl$_3$) 2 936, 1 574, and 1 431 cm^{-1}; *m/z* 312, 241, and 97 (Found: C, 57.95; H, 6.55. $C_{15}H_{20}O_2Se$ requires C, 57.88; H, 6.48%).

Cyclisation of compound (**20**). Treatment of compound (**20**) (0.17 g, 1 mmol) with NPSP and zinc(II) bromide gave trans-2-*phenylselenomethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**21**) (0.25 g, 77%) as an oil, δ (250 MHz) 7.52 (2 H, m), 7.23 (3 H, m), 3.94—3.50 (3 H, m), 3.12 (1 H, dd, J_{AX} 8.6, J_{AB} 12.2 Hz, H_A), 2.95 (1 H, dd, J_{BX} 5.1, J_{AB} 12.2 Hz, H_B), and 1.89—1.21 (12 H, m); $\nu_{max.}$(CHCl$_3$) 2 930 and 978 cm^{-1}; *m/z* 326, 155, and 111 (Found: C, 58.8; H, 6.8. $C_{16}H_{22}O_2Se$ requires C, 59.07; H, 6.82%).

General Procedure for Deselenation using Raney-nickel.—The phenylseleno spiroacetal (1 mmol) were added to a stirred mixture of W-Raney-nickel (5 mass equiv.) in diethyl ether (2 ml) under hydrogen (maintained by a hydrogen-filled balloon) at room temperature. After reduction was complete (3—5 h), the mixture was filtered through a pad of silica gel and the solvent was removed under reduced pressure to give the deselenated product. In most cases no further purification was necessary.

Reduction of compound (**11**). By the above method compound (**11**) (0.145 g, 0.5 mmol) after reduction afforded 2-methyl-1,6-dioxaspiro[4.4]nonane (**1**) (50 mg, 72%) as a 1:1 *cis*:*trans* mixture of isomers, δ (250 MHz) 4.30—3.80 (3 H, m), 2.21—1.40 (8 H, m), 1.34 (1.5 H, d, *cis* isomer CH_3), and 1.25 (1.5 H, d, *trans*-isomer CH_3); $\nu_{max.}$(film) 1 450, 1 380, and 1 180 cm^{-1}; *m/z* 142, 141, and 127, which was identical with the previously reported compound.

Reduction of compound (**14**). By the above general method compound (**14**) (0.25 g, 0.8 mmol) after reduction afforded 2-ethyl-1,6-dioxaspiro[4.4]nonane (chalcogran) (**2**) (0.11 g, 90%) as a 1:1 *cis*:*trans* mixture of isomers, δ (250 MHz) 4.10—3.30 (3 H, m), 2.15—1.70 (10 H, m), and 0.90 (3 H, m); $\nu_{max.}$(film) 2 926, 2 870, and 1 440 cm^{-1}; *m/z* 156, 155, and 127, which was identical with the natural product.

Reduction of compound (**16**). By the above general method compound (**16**) (0.31 g, 1 mmol) after reduction afforded 2-methyl-1,6-dioxaspiro[4.5]decane (**3**) (0.14 g, 90%) as a 1:2 *cis*:*trans* mixture, δ (250 MHz) 4.28—3.25 (3 H, m), 2.20—1.40 (10 H, m), 1.31 (1 H, d, *J* 5.4 Hz, *cis* isomer), and 2.24 (2 H, d, *J* 5.8 Hz, *trans* isomer); $\nu_{max.}$(film) 2 929, 1 435, and 1 367 cm^{-1}; *m/z* 156, 85, 67, 65, and 53.

Reduction of compound (**19**). By the above general method compound (**19**) (0.31 g, 1 mmol) after reduction afforded *trans*-7-methyl-1,6-dioxaspiro[4.5]decane (**4**) (0.14 g, 92%), δ (250 MHz) 3.92—3.60 (3 H, m), 2.07—1.21 (10 H, m), and 1.11 (3 H, d, *J* 6.3 Hz); $\nu_{max.}$($CHCl_3$) 2 940 and 1 050 cm^{-1}; *m/z* 156, 141, and 97.

Reduction of compound (**21**). By the above general method compound (**21**) (0.33 g, 1 mmol) after reduction afforded *trans*-2-methyl-1,7-dioxaspiro[5.5]undecane (**5**) (0.15 g, 88%) as a single isomer, δ (250 MHz) 3.79—3.50 (3 H, m), 1.93—1.33 (12 H, m), and 1.15 (3 H, d, *J* 6.3 Hz); $\nu_{max.}$(film) 2 932 and 1 058 cm^{-1}; *m/z* 170, 155, and 101 (Found: M^+, 170.1303. $C_{10}H_{18}O_2$ requires *M*, 170.1307).

Preparation of Compound (**22**).—Pentane-2,4-dione (5.13 ml, 50 mmol) was added dropwise to a stirred solution of sodium hydride (2.4 g of a 50% dispersion in oil, washed twice with light petroleum and once with THF) in THF (100 ml) at 0 °C under argon. The resulting mixture was stirred for 10 min at 0 °C, cooled to −20 °C, and n-butyl-lithium (34.3 ml of a 1.46M solution in hexane) was added dropwise to form a pale yellow solution. After 30 min at −20 °C the mixture was treated with 4-bromobut-1-ene (6.75 g, 50 mmol) and the mixture was stirred at 0 °C for 3 h, then at room temperature for 2 h. The mixture was poured into a mixture of saturated aqueous ammonium chloride (50 ml) and diethyl ether (50 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (2 × 20 ml). The combined organic layers were dried, concentrated under reduced pressure, and the residue was distilled to give non-8-ene-2,4-dione (**22**) (4.2 g, 55%), b.p. 67—68 °C at 0.9 mmHg; δ (60 MHz) 6.04—4.71 (3.7 H, m including δ 5.38 s, enolic C–H), 3.48 (0.6 H, s, $OCCH_2CO$), and 2.48—1.48 (9.7 H, m, including δ 2.01 s); $\nu_{max.}$(film) 3 420, 2 941, 1 710, 1 607, and 1 421 cm^{-1}; *m/z* 154, 100, and 85.

Preparation of Compound (**23**).—The dione (**22**) (0.2 g, 1.3 mmol) was added dropwise to a stirred solution of lithium di-isopropylamide [from di-isopropylamine (0.382 ml, 2.1 equiv.) and n-BuLi (1.7 ml of a 1.61M solution in hexane, 2.1 equiv.)] at 0 °C) in THF (5 ml) at −78 °C, under argon. The resulting solution was stirred at −78 °C for 3 h, benzaldehyde (0.132 ml, 1.3 mmol) was added, and the mixture was allowed to warm to 0 °C over 3 h and was then poured into saturated aqueous ammonium chloride (5 ml) and the layers were separated. After extraction of the aqueous layer with diethyl ether (3 × 2 ml), the organic layers were combined, dried, and after concentration under reduced pressure gave a residue which was subjected to chromatography to give 1-hydroxy-1-phenyldec-9-ene-3,5-dione (**23**) (0.22 g, 65%), δ (60 MHz) 7.29 (5 H, s), 6.09—4.72 (4.7 H, m including δ 5.4, s, enolic C–H), 3.47 (0.6 H, s, $COCH_2CO$), and 2.88—1.45 (9.7 H, m); $\nu_{max.}$(film) 3 402, 2 917, 1 709, and 1 603 cm^{-1}; *m/z* 260, 113, 107, and 85 (Found: M^+, 260.1404. $C_{16}H_{20}O_3$ requires *M*, 260.1412).

Selenium-mediated Cyclisation of Compound (**23**).—To a solution of compound (**23**) (56.5 mg, 0.22 mmol) in dry dichloromethane (2 ml) containing NPSP (72.2 mg, 1.1 equiv.) at room temperature, under argon, was added tin tetrachloride (22 μl of a 1M solution in dichloromethane, 0.1 equiv.).

The resulting mixture was stirred at room temperature for 96 h, diluted with light petroleum (2 ml), and filtered to remove phthalimide. The solution was washed with saturated aqueous sodium hydrogencarbonate (2 ml) and dried. The solvent was removed under reduced pressure to leave a residue which was subjected to chromatography (10% diethyl ether–light petroleum) to give (2S,8S)-2-*phenyl*-8-*phenylselenomethyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*one* (**24**) (46 mg, 50%) as a low melting solid, δ (250 MHz) 7.50—7.17 (10 H, m), 5.09 (1 H, dd, *J* 4.8, 15.6 Hz), 4.83 (1 H, m, H_X), 3.02 (1 H, dd, J_{AX} 7.6, J_{AB} 12.9 Hz, H_A), 2.89 (1 H, dd, J_{BX} 4.5, J_{AB} 12.9 Hz, H_B), 2.58 (4 H, m), and 1.99—1.47 (6 H, m); $\nu_{max.}$($CHCl_3$) 2 932, 1 716, and 1 190 cm^{-1}; *m/z* 416, 155, and 111 (Found: C, 63.55; H, 5.8. $C_{22}H_{24}O_3Se$ requires C, 63.61; H, 5.82%).

Deselenation of Compound (**24**).—Deselenation of compound (**24**) (0.46 g, 1.1 mmol) with Raney-nickel as in the general procedure (above) gave (2*S*,8*R*)-8-methyl-2-phenyl-1,7-dioxaspiro[5.5]undecan-4-one (**6**) (0.27 g, 94%) as an oil, δ (60 MHz) 7.32 (5 H, m), 4.84 (1 H, dd, *J* 5.0, 9.6 Hz), 3.64 (1 H, m), 2.55 (4 H, m), 2.29—1.23 (6 H, m) and 1.12 (3 H, d, *J* 6.0 Hz); $\nu_{max.}$(film) 2 928 and 1 720 cm^{-1}; *m/z* 266, 154, and 112 (Found: M^+, 260.1417. $C_{16}H_{20}O_3$ requires *M*, 260.1412).

Reduction of Compound (**26**) *with Sodium Borohydride.*—To a solution of compound (**26**) (0.19 g, 0.73 mmol) in dry dimethoxyethane (20 ml) at 0 °C under argon was added sodium borohydride (30.5 mg, 4.4 equiv.). The mixture was stirred at 0 °C for 1 h, then poured into a mixture of saturated aqueous sodium chloride (20 ml) and diethyl ether (50 ml). The layers were separated and the organic layer was washed with saturated aqueous sodium chloride, dried, and evaporated to leave an oil. This oil was subjected to chromatography (20% diethyl ether–light petroleum ⟶ 40% diethyl ether–light petroleum) to give (2S,8R)-8-*methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4(S)-*ol* (**25**) (0.117 g, 61%) as an oil, δ (250 MHz) 7.33 (5 H, m), 4.63 (1 H, dd, *J* 2.2, 11.8 Hz), 4.32 (1 H, m), 3.74 (1 H, m), 2.30—1.12 (11 H, m), and 1.13 (3 H, d, *J* 6.3 Hz); $\nu_{max.}$ (film) 3 335, 2.924, and 984 cm^{-1}; *m/z* 262, 244, and 156 (Found: C, 73.1; H, 8.7. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%) and (2S,8R)-8-*methyl*-2-*phenyl*-1,7-*dioxaspiro*[5.5]*undecan*-4(R)-*ol* (**26**) (61.4 mg, 32%), δ (250 MHz) 7.35 (5 H, m), 4.98 (1 H, dd, *J* 2.5, 12.0 Hz), 4.43 (1 H, br d, exch. D_2O), 4.15 (1 H, m), 3.84 (1 H, m), 2.26—1.24 (10 H, m), and 1.18 (3 H, d, *J* 7.0 Hz); $\nu_{max.}$(film) 3 500, 2 930, and 1 039 cm^{-1}; *m/z* 262, 244, and 112 (Found: C, 73.25; H, 8.4%).

Table 2. Atomic co-ordinates ($\times 10^4$) and temperature factors ($Å^2 \times 10^3$)

Atom	*x*	*y*	*z*	*U*
O(1)	−2 107(2)	4 131(1)	1 722(1)	51(1)*
C(2)	−3 359(3)	4 270(1)	1 935(1)	49(1)*
C(3)	−4 828(4)	4 418(2)	1 751(1)	65(1)*
C(4)	−5 160(4)	3 685(2)	1 530(1)	67(1)*
C(5)	−3 783(4)	3 509(2)	1 329(1)	64(1)*
C(6)	−2 313(4)	3 422(1)	1 520(1)	52(1)*
O(7)	−2 515(2)	2 681(1)	1 705(1)	51(1)*
C(8)	−1 234(3)	2 469(2)	1 906(1)	67(1)*
C(9)	181(4)	2 352(2)	1 702(1)	88(1)*
C(10)	501(4)	3 117(2)	1 506(1)	87(1)*
C(11)	−905(4)	3 357(2)	1 317(1)	71(1)*
O(12)	−5 638(3)	2 956(1)	1 703(1)	77(1)*
C(13)	−1 719(5)	1 699(2)	2 089(1)	98(1)*
C(14)	−2 986(3)	4 991(1)	2 149(1)	49(1)*
C(15)	−2 025(4)	5 637(1)	2 062(1)	60(1)*
C(16)	−1 796(4)	6 313(2)	2 266(1)	73(1)*
C(17)	−2 503(4)	6 334(2)	2 555(1)	77(1)*
C(18)	−3 452(5)	5 694(2)	2 642(1)	80(1)*
C(19)	−3 674(4)	5 026(2)	2 442(1)	69(1)*

* Equivalent isotropic *U* defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table 3. Bond lengths (Å)

O(1)–C(2)	1.436(3)	O(1)–C(6)	1.426(2)
C(2)–C(3)	1.521(4)	C(2)–C(14)	1.499(3)
C(3)–C(4)	1.521(4)	C(4)–C(5)	1.501(4)
C(4)–O(12)	1.434(3)	C(5)–C(6)	1.524(4)
C(6)–O(7)	1.428(2)	C(6)–C(11)	1.506(4)
O(7)–C(8)	1.445(3)	C(8)–C(9)	1.519(5)
C(8)–C(13)	1.510(4)	C(9)–C(10)	1.501(5)
C(10)–C(11)	1.517(5)	C(14)–C(15)	1.378(3)
C(14)–C(19)	1.381(3)	C(15)–C(16)	1.392(3)
C(16)–C(17)	1.372(4)	C(17)–C(18)	1.364(5)
C(18)–C(19)	1.372(4)		

Table 4. Bond angles (°)

C(2)–O(1)–C(6)	113.7(2)	O(1)–C(2)–C(3)	110.3(2)
O(1)–C(2)–C(14)	109.4(2)	C(3)–C(2)–C(14)	112.0(2)
C(2)–C(3)–C(4)	110.9(2)	C(3)–C(4)–C(5)	109.7(2)
C(3)–C(4)–O(12)	111.3(2)	C(5)–C(4)–O(12)	111.8(2)
C(4)–C(5)–C(6)	113.2(2)	O(1)–C(6)–C(5)	110.6(2)
O(1)–C(6)–O(7)	109.8(1)	C(5)–C(6)–O(7)	105.2(2)
O(1)–C(6)–C(11)	107.0(2)	C(5)–C(6)–C(11)	113.2(2)
O(7)–C(6)–C(11)	111.0(2)	C(6)–O(7)–C(8)	114.8(2)
O(7)–C(8)–C(9)	109.1(2)	O(7)–C(8)–C(13)	105.7(3)
C(9)–C(8)–C(13)	114.8(3)	C(8)–C(9)–C(10)	111.5(3)
C(9)–C(10)–C(11)	110.2(3)	C(6)–C(11)–C(10)	112.3(2)
C(2)–C(14)–C(15)	122.9(2)	C(2)–C(14)–C(19)	118.6(2)
C(15)–C(14)–C(19)	118.4(2)	C(14)–C(15)–C(16)	120.0(2)
C(15)–C(16)–C(17)	120.4(3)	C(16)–C(17)–C(18)	119.8(2)
C(17)–C(18)–C(19)	119.9(3)	C(14)–C(19)–C(18)	121.5(3)

Crystal Data.—(**26**) $C_{16}H_{22}O_3$, orthorhombic, $a = 8.749(2)$, $b = 15.916(4)$, $c = 42.316(11)$ Å, $U = 5\,892$ Å^3, space group *F2dd*, $Z = 16$, $M = 262.3$, $D_c = 1.19$ g cm^{-3}. Refined unit-cell parameters were obtained by centering 18 reflections on a Nicolet R3m diffractometer. 1 071 Independent reflections were measured ($\sigma \leqslant 58°$) with Cu-K_α radiation (graphite monochromator) using the omega-scan measuring routine. Of these, 1 045 had $|F|_o > 3\sigma(|F|_o)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors. No absorption correction was applied.

Initial attempts at fully automatic solution of the structure by direct methods were unsuccessful. This was surprising as the structure contains only 19 non-hydrogen atoms. Increasing the size of the starting set did not improve the figures of merit. Incorporation into the starting set of the 4 principal contributers to the list of negative quartets also resulted in very poor figures of merit. However, 3 cycles of automatic ΔE-map recycling for the best solution from this phase expansion (N_{quest}[18] −0.11, R_{alpha}[19] 0.25) gave the positions of all the non-hydrogen atoms.

The non-hydrogen atoms were refined anisotropically. The hydroxy hydrogen atom was clearly located in a ΔF-map and refined isotropically. The positions of the other hydrogen atoms were idealised (C–H 0.96 Å), assigned isotropic thermal parameters, $U(H) = 1.2\ U_{eq}(C)$, and allowed to ride on their parent carbon atoms. Refinement was by block-cascade least-squares to R 0.030, R_w 0.035, $[w^{-1} = \sigma^2(F) + 0.000\,27F^2]$. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[20]

Table 2 lists the fractional atomic co-ordinates. Tables 3 and 4 give the bond lengths and valence angles, respectively. The anisotropic thermal parameters, the structure factors, and the hydrogen co-ordinates and temperature factors have been treated as a Supplementary Publication [SUP No. 23898 (11 pp.)]*.

The structure (Figure) shows the molecule (**26**) to have the spiro configuration with the C(2) Ph and C(8) Me equatorial and the C(4) OH axial. There is an intramolecular hydrogen bond (2.77 Å, O–H···O angle 139°) between O(12) and O(7). The structures is loosely packed with only 1 intermolecular contract of less than 3.4 Å.

* For details of the Supplementary publications scheme, see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1.

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References

1 *E.g.* K. Mori, 'Synthetic Chemistry of Insect Phermones and Juvenile Hormones,' in 'Recent Developments in the Chemistry of Natural Carbon Compounds,' eds. R. Bongar, V. Bruckner, and Cs. Szantay, Heyden, Philadelphia, 1979, vol. 9.

2 (*a*) C. W. Shoppe, 'Chemistry of the Steroids,' Butterworth, London, 1964, p. 398; (*b*) 'Natural Products Chemistry,' ed. K. Nakanishi, Academic Press, New York, 1974, vol. 1, p. 476.

3 (*a*) W. Wierenga, 'Total Synthesis of Ionophores,' in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, 1981, vol. 4, p. 263; (*b*) 'Polyether Antibiotics,' ed. J. W. Westley, Decker, New York, 1983, vol. 2.

4 T. Kihara, H. Kusakabe, G. Nakamura, T. Sakurai, and K. Isono, *J. Antibiot.*, 1981, **34**, 1073.

5 Y. Takiguchi, H. Mishima, M. Okuda, M. Terao, A. Aoki, and R. J. Fukuda, *J. Antibiot.*, 1980, **33**, 1120; G. Albers-Schonberg, B. H. Arison, J. C. Chabala, A. W. Douglas, P. Eskola, M. H. Fisher, A. Lusi, H. Mrozik, J. L. Smith, and R. L. Tolman, *J. Am. Chem. Soc.*, 1981, **103**, 4216.

6 Preliminary communication, S. V. Ley and B. Lygo, *Tetrahedron Lett.*, 1982, **23**, 4625.

7 For a related intermolecular reaction, see S. Current and K. B. Sharpless, *Tetrahedron Lett.*, 1978, 5075.

8 See, for example (with references therein), (*a*) D. L. J. Clive, C. G. Russell, G. Chittattu, and A. Singh, *Tetrahedron*, 1980, **36**, 1399; (*b*) K. C. Nicolaou, *Tetrahedron*, 1981, **37**, 4097; (*c*) A. Toshimitsu, T. Aoai, S. Uemura, and M. Okano, *J. Org. Chem.*, 1981, **46**, 3021; (*d*) Z. Lysenko, F. Ricciardi, J. E. Semple, P. C. Wang, and M. M. Joullie, *Tetrahedron Lett.*, 1978, 2679; (*f*) P. L. Beaulieu, V. M. Morisset, and D. G. Garrett, *ibid.*, 1980, **21**, 129; (*g*) F. Rouessac and H. Zamarlik, *ibid.*, 1981, **22**, 2643; (*h*) G. Jaurand, J. M. Beau, and P. Sinay, *J. Chem. Soc., Chem. Commun.*, 1982, 701.

9 (*a*) M. Petrzilka, *Helv. Chim. Acta*, 1978, **61**, 3075; (*b*) T. R. Hoye and A. J. Caruso, *J. Org. Chem.*, 1981, **46**, 1198; (*c*) D. L. J. Clive, G. Chittattu, N. J. Curtis, W. A. Kiel, and C. K. Wong, *J. Chem. Soc., Chem. Commun.*, 1977, 725; (*d*) S. V. Ley, B. Lygo, H. Molines, and J. A. Morton, *ibid.*, 1982, 1251; (*e*) S. Wells-Rollinson, R. A. Amos, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, 1981, **103**, 4114; P. D. Kane and J. Mann, *J. Chem. Soc., Chem. Commun.*, 1983, 224.

10 W. Franke, V. Heeman, B. Gerken, J. A. A. Renwick, and J. P. Vite, *Naturwissenschaften*, 1977, **64**, 590.

11 W. Franke, G. Hindorf, and W. Reith, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 862.

12 O. P. Vig, R. C. Aggarwal, S. S. Bari, and S. D. Sharma, *Indian J. Chem., Sect. B*, 1979, **18**, 33; H. J. Bestmann, K. H. Koschafzky, W. S. J. Schaetzke, and O. Vostrowsky, *Liebigs Ann. Chem.*, 1981, 1705; M. Kato, M. Kageyama, R. Tanaka, K. Kamahara, and A. Yoshikoshi, *J. Org. Chem.*, 1975, **40**, 1932.

13 K. C. Nicolaou, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.*, 1979, **101**, 3704.

14 K. Hintzer, R. Weber, and V. Schurig, *Tetrahedron Lett.*, 1981, **22**, 55.

15 P. Deslongchamps 'Stereoelectronic Effects in Organic Chemistry', Pergamon Press, Oxford, 1983.

16 W. P. Jackson, S. V. Ley, and J. A. Morton, *Tetrahedron Lett.*, 1981, **22**, 2601.

17 M. T. Crimmins and D. M. Bankaitis, *Tetrahedron Lett.*, 1983, **24**, 4451; P. Kocienski and C. Yeates, *ibid.*, p. 3905; R. Baker, R. H. O. Boyes, D. M. P. Broom, J. A. Devlin, and C. J. Swain, *J. Chem. Soc., Chem. Commun.*, 1983, 829; R. E. Ireland and J. P. Daub, *J. Org. Chem.*, 1983, **48**, 1303; R. E. Ireland, J. P. Daub, G. S. Mandel, and N. S. Mandel, *ibid.*, p. 1312; D. R. Williams and B. A. Barner, *Tetrahedron Lett.*, 1983, **24**, 427; D. R. Williams, B. A. Barner, K. Nishitani, and J. G. Phillips, *J. Am. Chem. Soc.*, 1982, **104**, 4708; A. B. Smith III, S. R. Schow, J. D. Bloom, A. S. Thompson, and K. N. Winzenberg, *ibid.*, p. 4015; S. V. Attwood, A. G. M. Barrett, and J. C. Florent, *J. Chem. Soc., Chem. Commun.*, 1981, 556; E. Hungerbuhler, R. Naef, D. Wasmuth, D. Seebach, H. R. Loosli, and A. Wehrli, *Helv. Chem. Acta*, 1980, **63**, 1960.

18 G. T. Detitta, J. W. Edmonds, D. A. Langs, and H. Hamptman, *Acta Crystallogr.*, 1975, **A31**, 472.

19 P. J. Roberts, R. C. Petterson, G. M. Sheldrick, N. W. Isaacs, and O. Kennard, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1978.

20 G. M. Sheldrick, SHELXTL, 'An Integrated System for Solving, Refining, and Displaying Crystal Structures from Diffraction Data,' University of Göttingen, Federal Republic of Germany, Revised Version 1983.

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