Stereocontrol in organic synthesis using silicon-containing compounds. A synthesis of (±)-dihydronepetalactone using the S_E2' reaction of an allylsilane

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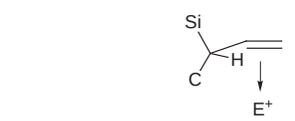
A propargylic alcohol 24 with the propynyl group *exo* on the norbornene framework was used in a stereospecific synthesis of the mixture of allylsilanes 27 and 28. The stereospecific reaction of this mixture with peracid gave, with a high level of stereocontrol, the norbornenol 25 having the alkenyl group *endo* on the norbornene framework. This substrate underwent an oxyanion accelerated Cope rearrangement setting up all four stereocentres in a synthesis of (±)-dihydronepetalactone 6.

Introduction to the series

We established in a series of papers between 1983 and 1992 that the stereochemistry of electrophilic attack on a double bond adjacent to a silicon-bearing stereogenic centre was usually well controlled in the sense **1**.[1] Reactions of this type included the



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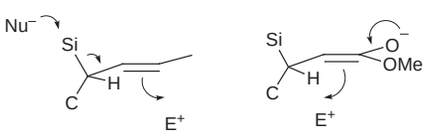

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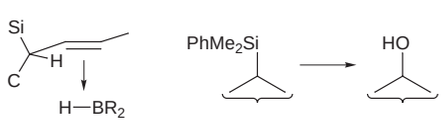
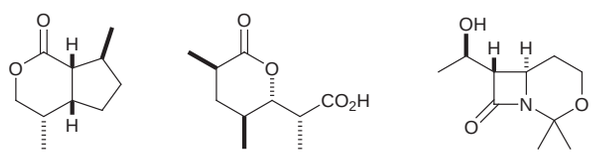


4 **5**

S_E2' reaction of allylsilanes **2**,[2,3] also studied by the Kumada group and others,[4] the alkylation, protonation and aldol reactions of enolates carrying a β-silyl group **3**,[5] and the hydroboration of allylsilanes **4**.[6] For the latter pair of reactions to be useful, we also developed a method for converting the phenyldimethylsilyl group into a hydroxy **5** with retention of configuration,[7] a reaction of great synthetic power.[8] We also developed versatile methods for the stereoselective synthesis of the allylsilanes[2,9] and β-silyl carbonyl compounds[10] used in that work and elsewhere.

Concurrently, to illustrate our methods in a more vivid way, and to test their generality with specific challenges, we carried out a number of syntheses of natural products, or natural product-like molecules, using one or more of these four types of reaction to control the stereochemistry. We now report, successively, and in approximately chronological order, the experimental details of our syntheses of: (i) (±)-dihydronepetalactone **6**, which used the stereospecifically *anti* nature of the S_E2' reaction; (ii) the (±)-Prelog–Djerassi lactone **7**, which used enolate protonation, enolate alkylation, the *anti* S_E2' reaction and silyl-to-hydroxy conversion; (iii) the (±)-thienamycin precursor **8**, which used an aldol reaction of a β-silyl enolate and silyl-to-hydroxy conversion; (iv) the (±)-carbacyclin analogue **9**, which used the protodesilylation of an allylsilane to set up the stereochemistry of an exocyclic double bond; (v) (−)-tetrahydrolipstatin **10**, which used enolate alkylation, the hydroboration of an allylsilane and silyl-to-hydroxy conversion; (vi) the (−)-prostaglandin precursor **11**, which used one of our stereo-



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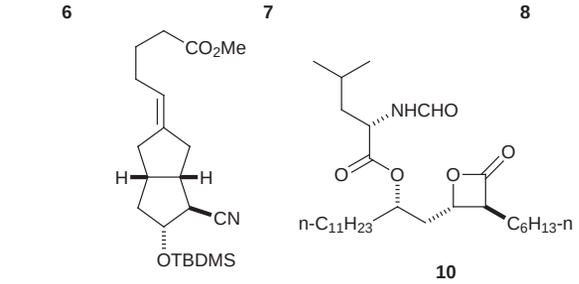

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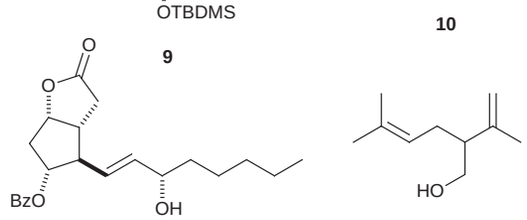

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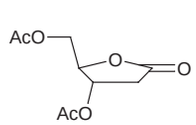

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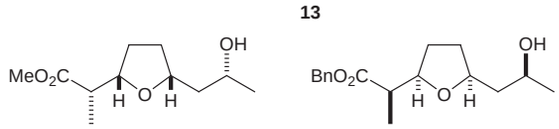

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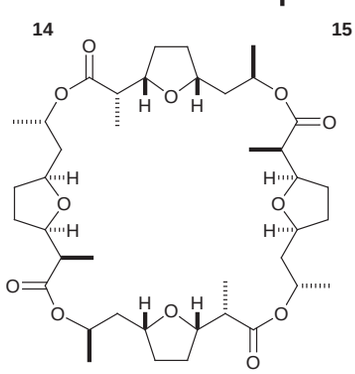

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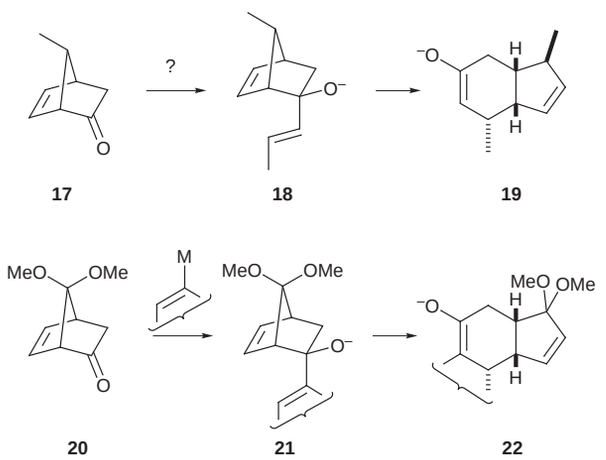
specific allylsilane syntheses and silyl-to-hydroxy conversion; (vii) (±)-lavandulol **12**, which only used silyl-to-hydroxy conversion without stereochemical implications, but in a testing case; (viii) (±)-2-deoxyribonolactone acetate **13** and other sugar lactones, which used enolate hydroxylation and the silyl-to-hydroxy conversion; (ix) methyl (+)-nonactate **14**, which used both of our methods for introducing a silyl group with absolute stereocontrol, enolate alkylation, the hydroboration of an allylsilane and silyl-to-hydroxy conversion; and finally (x) nonactin itself **16**, with the components methyl (+)-nonactate **14** and benzyl (−)-nonactate **15** prepared by a different route, and using the S_E2' reaction, enolate methylation and silyl-to-hydroxy conversion. In almost every case, our methods are adaptable to achieving the opposite stereochemical outcome—we could almost always as easily have prepared any of the diastereoisomers of the compounds in question, as in a sense we did, by preparing both enantiomers of nonactate from a common precursor. We begin in this paper with the synthesis of dihydronepetalactone **6**, already reported in a preliminary communication.[11] The several syntheses of this iridoid lactone, and the many syntheses of other iridoid lactones, have been reviewed.[12]

Results and discussion

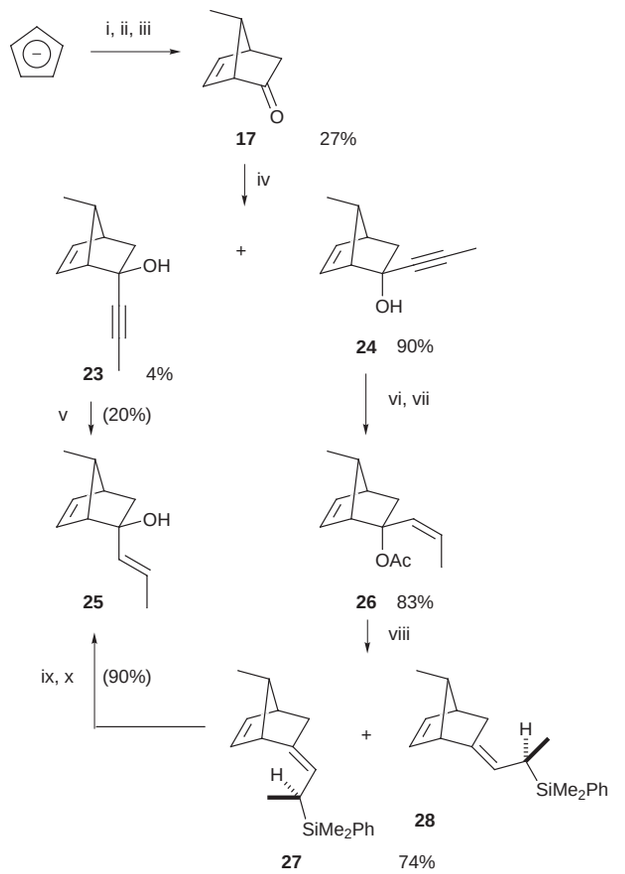
The key step of our synthesis is the oxyanion-assisted Cope rearrangement[13,14] of a norbornene **18** ⟶ **19** (Scheme 1).



Scheme 1

This reaction was known for 7,7-disubstituted norbornenes **21** ⟶ **22**, where it had been easy to introduce the vinyl group on the *endo* surface using a Grignard or organolithium reagent and the ketone **20**.[15] The major problem with this design for general use is to arrange for the alkene substituent to be on the *endo* face, when there is no 7-substituent hindering attack on the *exo* face of a ketone like the norbornenone **17**. We saw that the stereospecific synthesis of allylsilanes that we had already developed,[2] coupled with the introduction of the *exo* hydroxy group as an electrophile by epoxidation-opening of the allylsilane, would solve this problem. We can expect this reaction to be stereochemically well controlled, because the epoxidation will be *exo* to the norbornene ring system, as well as *anti* to the silyl group, provided that we set up the allylsilane stereochemistry in the right sense. This is easy to arrange simply by using an allylic alcohol with the appropriate double bond geometry.

The homochiral ketone **17** was known from Grieco's work,[16] but we chose to make the racemic compound by a shorter route from sodium cyclopentadienide (Scheme 2), following Corey's lead,[17] using the labile 5-methylcyclopentadiene,[18] but without isolating intermediates. The overall yield was unimpressive, but the route was short, and the major byproduct, the 1-methyl



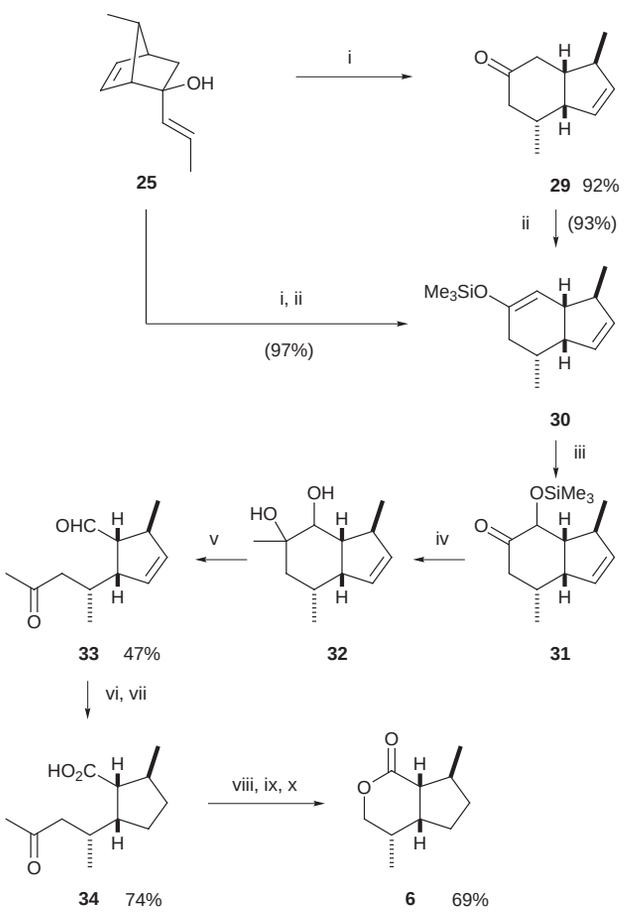
Scheme 2 *Reagents:* i, MeI, THF; ii, $Cl(CN)C{=}CH_2$, $Cu(BF_4)_2$; iii, KOH, DMSO; iv, MeC≡CMgBr, THF; v, $LiAlH_4$, THF; vi, H_2, Pd/$CaCO_3$, $Pb(OAc)_2$, quinoline, THF; vii, Ac_2O, DMAP, Et_3N, CH_2Cl_2; viii, $(PhMe_2Si)_2CuCN\ Li_2$, THF; ix, MCPBA, CH_2Cl_2, Na_2HPO_4; x, TBAF, THF

isomer, was separated easily enough by column chromatography. We did not appear to suffer from cycloaddition taking place *syn* to the methyl group.[19]

The ketone **17** reacted with the propynyl Grignard reagent to give largely the product **24** of *exo* attack, but with some 4% of *endo* attack giving the alcohol **23**, from which we could make directly the alcohol **25** that we actually wanted. The trick, therefore, was to convert the propargylic (prop-2-ynyl) alcohol **24** into the allylic alcohol **25**. To get the stereochemistry right, we converted the triple bond into a *cis* double bond, made the acetate **26** of the allylic alcohol, and treated the acetate with our silylcuprate reagent to give the mixture of allylsilanes **27** and **28**. We already knew that this reaction took place stereospecifically *anti*,[2] and with allylic shift. The only complication is that there are two allylsilanes **27** and **28** fulfilling this criterion. This is of no consequence here, because a stereospecifically *anti* S_E2' reaction on either of these allylsilanes will give the same product, provided that we can rely upon the double bond of the product being *trans* from both of them. This is indeed what happened: epoxidation of the mixture of allylsilanes and treatment of the mixture of epoxides with tetrabutylammonium fluoride gave only the *trans* allylic alcohol **25** with an *exo* hydroxy group. Because we had set it up to do so, the stereospecificity of the epoxidation of the allylsilane in the sense **1** combined with the usual preference for attack on the *exo* face of the norbornene system to make this stereochemically an exceptionally clean reaction. Nor was there any sign of epoxidation at the other double bond, perhaps because it is somewhat protected by the 7-methyl group. The overall yield from ketone **17** to the alcohol **25** was 51%, and we confirmed our expectation that the methyl group was *anti* to the alcohol function by an NOE-difference spectrum, which showed enhancement in the signals from the

olefinic protons in the norbornene ring when the sample was irradiated at the frequency of the methyl signal. The sequence is formally convergent, since we could make the alcohol **25** from both propargylic alcohols **23** and **24**, but the capacity for convergence hardly made any difference to the overall yield in this case, in contrast to our Prelog–Djerassi lactone work,[20] where it was crucial.

We now had the substrate for the oxy-Cope rearrangement **18** ⟶ **19**. It proceeded uneventfully in refluxing ether in 30 min when we used the potassium salt generated from the alcohol **25**. The stereochemistry at the methyl-bearing centre was assigned from our having a *trans* double bond in the substrate **25** by analogy with one of Jung's reactions **21** ⟶ **22**, and also followed from the most plausible looking transition structure. We wanted to trap the first-formed enolate **19**, for a synthesis of iridomyrmecin, but we were unable to do so, no doubt a penalty of our having used the potassium salt. Whether we trapped the enolate with trimethylsilyl chloride directly in the reaction mixture, or after isolating the ketone **29** and regenerating an enolate, we obtained only the silyl enol ether **30**, in excellent yield by either route (Scheme 3). The remaining steps were



Scheme 3 *Reagents:* i, KH, 18-crown-6, Et_2O; ii, Me_3SiCl, Et_3N; iii, MCPBA, light petroleum; iv, MeLi, Et_2O; v, HIO_4, EtOH; vi, PDC, DMF; vii, H_2, PtO_2, THF; viii, CF_3CO_3H, CH_2Cl_2; ix, NaOH, H_2O; x, HCl, H_2O

conventional manipulations: Rubottom epoxidation gave the α-silyloxy ketone **31**, methyllithium reaction gave the diol **32**, and oxidative cleavage of the mixture of stereoisomeric diols gave the aldehydo ketone **33**, all carried out without purification of the intermediates in an overall yield of 47%. Oxidation of the aldehyde, followed by hydrogenation of the double bond in the cyclopentene ring gave the acid **34**. Finally, Baeyer–Villiger reaction on the ketone group, alkaline hydrolysis of the acetate produced, and acidification gave (±)-dihydronepetalactone **6**. Our product had spectroscopic properties (IR, ^{1}H NMR) identical with authentic spectra kindly supplied by Professor J. Wolinsky, who had first isolated dihydronepetalactone[21] and synthesised it earlier.[22] Our synthesis takes fourteen steps and the overall yield was 12% based on the ketone **17**, which may be compared with other syntheses of this and other iridoid lactones reviewed recently.[12]

Experimental

Light petroleum refers to the fraction bp 30–40 °C. Ether refers to diethyl ether.

7-Methylbicyclo[2.2.1]hept-5-en-2-one 17

Freshly distilled cyclopentadiene (10.5 cm^3) was added dropwise to sodium sand (3.2 g) in dry THF (30 cm^3) and the resulting colourless solution was cooled to −40 °C, and added dropwise to methyl iodide (6 cm^3) at −40 °C. The temperature was increased to −10 °C, and the 5-methylcyclopentadiene was distilled directly into a flask containing 2-chloroacrylonitrile (18 cm^3) and copper(II) tetrafluoroborate (15.5 g) in THF (4 cm^3) at 0 °C. After 24 h the mixture was poured into saturated brine, and the products were extracted into ether. The ether was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was kept in DMSO (100 cm^3) and water (20 cm^3) with potassium hydroxide (10 g) for 5 h at 40 °C. The mixture was poured into water and extracted with ether. The ether was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure, and the residue chromatographed (SiO_2, EtOAc–hexane, 1:9) to give the *ketone* (2.64 g, 27%); R_f (EtOAc–hexane, 15:85) 0.55; ν_{max}(film)/cm^{-1} 1742 (C=O); δ_H($CDCl_3$) 6.28 (1 H, dd, *J* 3 and 6, C*H*=CH), 5.78 (1 H, dd, *J* 4 and 6, CH=C*H*), 2.80 (2 H, m, 2 bridgehead Hs), 2.52 (1 H, m, MeC*H*), 1.93 (2 H, m, CH_2) and 1.03 (3 H, d, *J* 6, Me); *m*/*z* 122 (13%, M^+), 96 (22, M − C_2H_2), 95 (17, M − C_2H_3), 80 (100, C_6H_7) and 79 (77, C_6H_6) (Found: M^+, 122.0739. $C_8H_{10}O$ requires M, 122.073l).

(1*RS*,2*RS*,4*SR*,7*RS*)- and (1*RS*,2*SR*,4*SR*,7*RS*)-7-Methyl-2-(prop-1-ynyl)bicyclo[2.2.1]hept-5-en-2-ol 23 and 24

The ketone **17** (1.71 g) was added dropwise in THF (10 cm^3) to propynylmagnesium bromide (18.0 mmol) in THF (40 cm^3) at 0 °C. After 18 h at 20 °C, the mixture was poured into hydrochloric acid (1 mol dm^{-3}), and the aqueous solution extracted with ether. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 1:9), to give the *alcohol* **24** (2.03 g, 90%) as needles, mp 43–45 °C (from hexane); R_f (EtOAc–hexane, 20:80) 0.10; ν_{max}($CHCl_3$/cm^{-1}) 3600 sharp (OH), 3450 br (OH) and 2240 (C≡C); δ_H($CDCl_3$) 6.07 (1 H, dd, *J* 3 and 6, C*H*=CH), 5.76 (1 H, dd, *J* 3 and 6, CH=C*H*), 2.7–2.5 (2 H, m, 2 bridgehead Hs), 2.4–2.1 (2 H, m, MeC*H* and OH), 1.82 (3 H, s, MeC≡C), 1.5–1.0 (2 H, m, CH_2) and 0.82 (3 H, d, *J* 6, *Me*CH); *m*/*z* 162 (4%, M^+), 147 (6, M − Me), 96 (12, C_6H_8O), 95 (17, C_6H_7O) and 80 (100, C_6H_7) (Found: C, 81.4; H, 8.70; M^+, 162.1045. $C_{11}H_{14}O$ requires C, 81.4; H, 8.70%; M, 162.1045), and the *alcohol* **23** (100 mg, 4%); R_f (EtOAc–hexane 20:80) 0.30; ν_{max}(film)/cm^{-1} 3380 br (OH) and 2230 (C≡C); δ_H($CDCl_3$) 6.2–5.7 (2 H, m, CH + CH), 2.8–2.4 (2 H, m, bridgehead Hs), 1.80 (3 H, s, MeC≡C), 0.95 (3 H, d, *J* 6, *Me*CH) and 2.4–1.2 (4 H, m, remainder); *m*/*z* 162 (2%, M^+), 147 (5, M − Me) and 80 (100, C_6H_7) (Found: M^+, 162.1042. $C_{11}H_{14}O$ requires M, 162.1045).

(1*RS*,2*RS*,4*SR*,7*RS*)-(*Z*)-7-Methyl-2-(prop-1-enyl)bicyclo-[2.2.1]hept-5-en-2-ol

The propynyl alcohol (8.8 g) and quinoline (0.5 g) in THF (150 cm^3) were stirred with Lindlar's catalyst (5.2 g) under hydrogen at room temperature and atmospheric pressure for 3 h. The mixture was filtered and the solvent removed under reduced

pressure. The residue was chromatographed (SiO_2, EtOAc–hexane 1:9) to give the *alcohol*; R_f (EtOAc–hexane 10:90) 0.10; ν_{max}(film)/cm^{-1} 3500br (OH) and 1640 (C=C); δ_H($CDCl_3$) 6.15 (1 H, m, endocyclic C*H*=CH), 5.85 (1 H, m, endocyclic CH=C*H*), 5.8–5.1 (2 H, m, C*H*=C*H*Me), 2.55 (2 H, m, bridgehead Hs), 2.4–1.9 (2 H, m, MeC*H* and OH), 1.82 (3 H, d, *J* 6, CH=CH*Me*), 1.8–1.2 (2 H, m, CH_2) and 0.85 (3 H, d, *J* 6, *Me*CH); *m*/*z* 164 (1%, M^+), 149 (8, M − Me), 91 (27, C_7H_7) and 80 (100, C_6H_7) (Found: M^+, 164.1209. $C_{11}H_{16}O$ requires M, 164.1201).

(1*RS*,2*RS*,4*SR*,7*RS*)-(*Z*)-7-Methyl-2-(prop-1-enyl)bicyclo-[2.2.1]hept-5-en-2-yl acetate 26

The alcohol, 4-dimethylaminopyridine (1.2 g), triethylamine (5.5. g) and acetic anhydride (5.5 g) were kept in dichloromethane (100 cm^3) overnight. The solvent was evaporated under reduced pressure, the residue dissolved in ether and washed with hydrochloric acid, aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated to give the *acetate* (83%); R_f (EtOAc–hexane, 10:90) 0.30; ν_{max}(film)/cm^{-1} 1738 cm^{-1} (C=O); δ_H($CDCl_3$) 5.8 (1 H, d, *J* 3 and 5, endocyclic C*H*=CH), 5.5 (1 H, dd, *J* 3 and 5, endocyclic CH=C*H*), 5.6–4.9 (2 H, m, C*H*=C*H*Me), 3.1 (1 H, m, bridgehead H), 2.4 (1 H, m, bridgehead H), 1.80 (3 H, s, MeCO), 1.60 (3 H, d, *J* 6, CH=CH*Me*), 0.81 (3 H, d, *J* 6, *Me*CH) and 2.2–0.9 (3 H, m, remainder); *m*/*z* 164 (14%, M − CH_2CO), 146 (4, M − AcOH), 84 (37, C_5H_8O) and 80 (100, C_6H_8) (Found: *m*/*z*, 164.1204. $C_{11}H_{16}O$ requires M − CH_2CO, 164.1201).

(1*RS*,4*SR*,7*RS*,2′*RS*)-(*E*)- and (1*RS*,4*SR*,7*RS*,2′*SR*)-(*Z*)-1-Methyl-2-(7-methylbicyclo[2.2.1]oct-5-en-2-ylidene)ethyl-dimethylphenylsilane 28 and 27

Phenyldimethylsilyllithium[23] (28 mmol) in THF (65 cm^3) was added to a suspension of dry copper(I) cyanide (1.23 g) in dry THF (45 cm^3) under argon at 0 °C. After 30 min, the temperature was reduced to −50 °C and the allylic acetate (2.70 g) in dry THF (60 cm^3) was added dropwise. After 12 h the mixture was poured into aqueous ammonium chloride and extracted with hexane. The hexane was washed several times with aqueous ammonium chloride, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane) to give a mixture of the *allylsilanes* (2.72 g, 74%); R_f (hexane) 0.50; ν_{max}(film)/cm^{-1} 1422 (Si–Ph), 1242 (Si–Me) and 1108 (Si–Ph); δ_H($CDCl_3$) 7.3 (5 H, m, Ph), 5.7 (2 H, m, CH=CH), 5.2–4.5 (1 H, m, C=CH), 3.0–2.3 (2 H, m, bridgehead Hs), 0.95 (3 H, d, *J* 7, SiCH*Me*), 0.80 (3 H, d, *J* 6 *Me*CH), 0.22 (6 H, s, $SiMe_2$) and 2.2–0.8 (4 H, m, remainder); *m*/*z* 282 (4%, M^+), 146 (8, $C_{11}H_{14}$) and 135 (100, $PhMe_2Si$) (Found: M^+, 282.1814. $C_{19}H_{26}Si$ requires M, 282.1804).

(1*RS*,2*SR*,4*SR*,7*RS*)-(*E*)-7-Methyl-2-(prop-1-enyl)bicyclo-[2.2.1]hept-5-en-2-ol 25

The allylsilanes (2.70 g) and *m*-chloroperoxybenzoic acid (1.65 g) were stirred in dichloromethane (20 cm^3) with disodium hydrogen phosphate (13.6 g) at 0 °C for 1 h. The mixture was filtered, the solvent evaporated and the residue dissolved in ether and washed with 5% aqueous sodium hydrogen carbonate. Evaporation of the ether gave the epoxysilanes, which were kept with tetrabutylammonium fluoride in THF at 20 °C for 15 min. The THF was removed under reduced pressure, the resulting oil dissolved in ether and washed with water. The ether was dried ($MgSO_4$) and evaporated under reduced pressure and the residue chromatographed (SiO_2, Et_2O–light petroleum) to give the alcohol (1.41 g, 90%); R_f (EtOAc–hexane, 20:80) 0.48; ν_{max}(film)/cm^{-1} 3360 broad (OH), 1660 (C=C) and 982 (CH=CH); δ_H(250 MHz; $CDCl_3$) 6.01 (1 H, dd, *J* 3.0 and 5.6, *endocyclic* C*H*=CH), 5.84 (1 H, dd, *J* 3.0 and 5.4, *endocyclic* CH=C*H*), 5.60 (1 H, dq, *J* 15.5 and 6.0, CH=C*H*Me), 5.46 (1 H, dq, *J* 15.5 and 1.0, C*H*=CHMe), 2.67 (1 H, br q, *J* 6.4, MeC*H*), 2.56 (1 H, m, bridgehead H), 2.32 (1 H, m, bridgehead H), 1.90 (1 H, s, OH), 1.73 (1 H, dd, *J* 3.7 and 12.1, *exo* CH), 1.65 (3 H, dd, *J* 6.0 and 10.0, CH=CH*Me*), 1.44 (1 H, d, *J* 12.1, *endo* CH) and 0.88 (3 H, d, *J* 6.4, MeCH); *m*/*z* 146 (29%, M − H_2O), 131 (47, M − H_2O − Me), 117 (100, M − C_2H_7O) and 91 (48, C_7H_7) (Found: *m*/*z*, 146.1090. $C_{11}H_{16}O$ requires M − H_2O, 146.1095).

Reduction of the minor propargyl alcohol

The minor propargyl alcohol **23** (68 mg) was refluxed in THF (5 cm^3) with lithium aluminium hydride (90 mg) for 24 h. The mixture was poured into water and the products extracted into ether. The ether was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 1:9) to give the alcohol **25** (14 mg, 20%), identical to the earlier sample.

(3$_\beta$,3a$_\beta$,7α,7a$_\beta$)-3,3a,4,6,7,7a-Hexahydro-3,7-dimethyl-5*H*-inden-5-one 29

The allylic alcohol (338 mg) and 18-crown-6 (1 mg) were added to a suspension of potassium hydride (35% dispersion in oil, 500 mg) in ether (10 cm^3). The mixture was refluxed for 30 min and then cautiously added to aqueous ammonium chloride. The ether was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 1:3) to give the *ketone* (312 mg, 92%); R_f (EtOAc–hexane, 10:90) 0.25; ν_{max}(film)/cm^{-1} 1704 (C=O); δ_H ($CDCl_3$) 5.8–5.4 (2 H, m, CH=CH), 2.00 (3 H, d, *J* 6.5, Me), 1.96 (3 H, d, *J* 6.5, Me) and 3.3–1.8 (8 H, m, remainder); *m*/*z* 164 (3%, M^+), 149 (10 H, M − Me), 135 (11, M − C_2H_5), 57 (87, C_4H_9) and 55 (100, C_4H_7) (Found: M^+, 164.1201. $C_{11}H_{16}O$ requires M, 164.1201).

(3β,3aβ,7α,7aβ)-3a,6,7,7a-Tetrahydro-3,7-dimethyl-5-(trimethylsilyloxy)-3*H*-indene 30

Method A. The ketone **29** (66 mg) was added to a suspension of potassium hydride (35% dispersion in oil, 150 mg) in ether (10 cm^3). The mixture was refluxed for 30 min and then allowed to cool. Triethylamine (0.3 cm^3) and trimethylsilyl chloride (0.2 cm^3) were added and the mixture was poured into aqueous ammonium chloride. The ether layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the *silyl enol ether* (88 mg, 93%) as a pale yellow oil; R_f (hexane) 0.15; ν_{max}(film)/cm^{-1} 1667 (C=C) and 1257 (Si–Me); δ_H($CDCl_3$) 5.73 (1 H, m, HC-1), 5.56 (1 H, br d, *J* 5.8, HC-2), 4.65 (1 H, d, *J* 3.1, HC-4), 2.86 (1 H, m, HC-3a), 2.47–2.34 (2 H, m, HC-3 and HC-7a), 1.93 (1 H, m, HC-7), 1.81 (2 H, m, H_2C-6), 1.04 (3 H, d, *J* 6.7, Me), 0.99 (3 H, d, *J* 7.0, Me) and 0.14 (9 H, s, $SiMe_3$); *m*/*z* 236 (35%, M^+), 181 (31, M − C_4H_6) and 73 (100, Me_3Si) (Found: M^+, 236.1613. $C_{14}H_{24}OSi$ requires M, 236.1596).

Method B. The alcohol **25** was treated with potassium hydride under the above conditions to form the potassium enolate, and then treated with triethylamine and trimethylsilyl chloride as above to give the silyl enol ether (97%).

(1*RS*,2*SR*,5*RS*,1′*RS*)-2-Methyl-5-(1-methyl-3-oxobutyl)cyclopent-3-ene-1-carbaldehyde 33

The silyl enol ether (390 mg) was dissolved in light petroleum (35 cm^3) and treated with *m*-chloroperoxybenzoic acid (335 mg) at 20 °C for 30 min. The solution was then washed with aqueous sodium bisulfite (5%), followed by aqueous sodium hydrogen carbonate (5%), dried ($MgSO_4$), and evaporated under reduced pressure. The residue in ether (30 cm^3) was treated with methyllithium (1 mol dm^{-3}, 7.5 cm^3). After 15 min the solution was washed with aqueous ammonium chloride, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in ethanol (15 cm^3) and periodic acid dihydrate (250 mg) in water (4 cm^3) was added. After 30 min at 20 °C, the solution was poured into water and extracted with ether. The ether

was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 1:3) to give the *aldehyde* (150 mg, 47%); R_f (EtOAc–hexane, 25:75) 0.80; ν_{max}(film)/cm^{-1} 1718 (C=O); δ_H($CDCl_3$) 9.60 (1 H, d, *J* 2.5, CHO), 5.7–5.3 (2 H, m, CH=CH), 2.2 (2 H, m, CH_2), 2.05 (3 H, s, COMe), 1.00 (3 H, d, *J* 8, CH*Me*), 0.88 (3 H, d, *J* 7, CH*Me*) and 3.3–2.4 (4 H, m, remainder); *m*/*z* 164 (3%, M − CH_2O), 148 (7, M − C_2H_6O), 136 (34, M − C_3H_6O), 121 (38, M − C_4H_9O), 108 (84, C_8H_{12}) and 81 (100, C_6H_9) (Found: *m*/*z*, 164.1196. $C_{11}H_{16}O$ requires M − CH_2O, 164.1201).

(1*RS*,2*SR*,5*RS*,1′*RS*)-2-Methyl-5-(1-methyl-3-oxobutyl)cyclopent-3-ene-1-carboxylic acid

The aldehyde (150 mg) and pyridinium dichromate (1.45 g) were stirred in dry DMF (10 cm^3) at 20 °C under argon for 22 h and then poured into water and extracted with ether. The ether was washed with water and extracted with aqueous sodium carbonate (2 mol dm^{-3}). The aqueous solution was acidified and extracted with ether. The ether was dried ($MgSO_4$) and evaporated under reduced pressure to give the *carboxylic acid* (128 mg, 79%); R_f (EtOAc–hexane, 25:75) 0.30; ν_{max}(film)/cm^{-1} 3650–2400 (OH) and 1700 (C=O); δ_H($CDCl_3$) 8.4 (1 H, s, OH), 5.5 (2 H, m, CH=CH), 2.10 (2 H, m, CH_2), 1.98 (3 H, s, COMe), 1.02 (3 H, d, *J* 6, *Me*CHCH=CH), 0.88 (3 H, d, *J* 6.5, *Me*CH-CH_2CO) and 3.3–1.9 (4 H, m, remainder); *m*/*z* 192 (0.4%, M − H_2O), 164 (7, M − HCO_2H), 152 (24, M − C_3H_6O), 121 (29, C_9H_{13}) and 107 (100, C_8H_{11}) (Found: *m*/*z*, 192.1151. $C_{12}H_{18}O_3$ requires M − H_2O, 192.1151).

(1*RS*,2*SR*,5*RS*,1′*RS*)-2-Methyl-5-(1-methyl-3-oxobutyl)cyclopentane-1-carboxylic acid 34

The carboxylic acid (120 mg) in THF (8 cm^3) was stirred with platinum oxide (20 mg) under hydrogen at room temperature and atmospheric pressure for 15 min. The catalyst was removed by filtration and the solvent removed under reduced pressure to give the *carboxylic acid* (114 mg, 94%) as prisms, mp 77–79 °C (from hexane); R_f (EtOAc–hexane, 25:75) 0.15; ν_{max}(Nujol)/cm^{-1} 3400–2400 (OH), 1708 (C=O) and 1690 (COOH); δ_H($CDCl_3$) 11.2 (1 H, br s, OH), 2.55 (1 H, m, C*H*COOH), 2.11 (3 H, s, MeCO), 1.04 (3 H, d, *J* 6.9, MeC-2), 0.95 (3 H, d, *J* 5.9, *Me*CHC-5) and 2.5–1.2 (9 H, m, remainder); *m*/*z* 194 (8%, M − H_2O), 154 (10, M − C_3H_6O), 137 (14, M − $C_3H_7O_2$), 109 (72, C_8H_{13}) and 85 (100, C_5H_9O) (Found: C, 68.0; H, 9.25; *m*/*z*, 194.1303. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.50%; M − H_2O, 194.1306).

(±)-Dihydronepetalactone 6

The carboxylic acid (59 mg) was dissolved in dichloromethane (2 cm^3), and a solution of peroxytrifluoroacetic acid in dichloromethane (1.3 mol dm^{-3}, 0.7 cm^3) was added at 0 °C. After 30 min the solvent was removed under reduced pressure, and the residue was dissolved in aqueous sodium hydroxide (1 mol dm^{-3}, 8 cm^3) and refluxed for 10 min. The aqueous solution was acidified and extracted with ether. The ether was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 1:1) to give (±)-dihydronepetalactone (32 mg, 69%); R_f (Et_2O–light petroleum, 1:1) 0.30; ν_{max}(CCl_4)/cm^{-1} 1735 (C=O); δ_H($CDCl_3$) 4.07 (1 H, dd, *J* 10.5 and 10.5, H C-3), 4.00 (1 H, ddd, *J* 10.5, 4.2 and 1.2, H C-3), 2.50 (1 H, m, HC-4a), 2.40 (1 H, dd, *J* 10.4 and 9.0, HC-7a), 2.21 (1 H, m, HC-4), 2.02 (1 H, m, HC-7), 1.99–1.08 (4 H, m, H_2C-5-H_2C-6), 1.18 (3 H, d, *J* 6.2, MeC-7) and 0.87 (3 H, d, *J* 7.0, MeC-4); *m*/*z* 168 (11%, M$^+$), 153 (24, M − Me), 128 (23, M − C_3H_4), 126 (21, M − C_3H_6), 113 (37, M − C_4H_7), 95 (28, M − $C_3H_5O_2$) and 81 (100, C_6H_7) (Found: M$^+$, 168.1151. $C_{10}H_{16}O_2$ requires M, 168.1150). The ^{1}H NMR spectrum was identical with that of an authentic sample. Many of the diastereoisomers of this molecule are known and they have distinctively different spectra.[21,22]

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References

1 Summarised in I. Fleming, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3363.
2 I. Fleming and N. K. Terrett, *J. Organomet. Chem.*, 1984, **264**, 99.
3 I. Fleming, P. E. J. Sanderson and N. K. Terrett, *Synthesis*, 1992, 69; M. J. C. Buckle, I. Fleming and S. Gil, *Tetrahedron Lett.*, 1992, **33**, 4479; I. Fleming, N. J. Lawrence, A. K. Sarkar and A. P. Thomas, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3303; I. Fleming, N. J. Lawrence, A. K. Sarkar and A. P. Thomas, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3303.
4 T. Hayashi, M. Konishi, H. Ito and M. Kumada, *J. Am. Chem. Soc.*, 1982, **104**, 4962; T. Hayashi, M. Konishi and M. Kumada, *J. Am. Chem. Soc.*, 1982, **104**, 4963; T. Hayashi, H. Ito and M. Kumada, *Tetrahedron Lett.*, 1982, **23**, 4605; T. Hayashi, M. Konishi and M. Kumada, *J. Chem. Soc.*, *Chem. Commun.*, 1983, 736; T. Hayashi, K. Kabeta, T. Yamamoto, K. Tamao and M. Kumada, *Tetrahedron Lett.*, 1983, **24**, 5661; T. Hayashi, Y. Okamoto, K. Kabeta, T. Hagihara and M. Kumada, *J. Org. Chem.*, 1984, **49**, 4224; T. Hayashi, M. Konishi, Y. Okamoto, K. Kabeta and M. Kumada, *J. Org. Chem.*, 1986, **51**, 3772; T. Hayashi, Y. Matsumoto and Y. Ito, *Organometallics*, 1987, **6**, 884; H. Wetter and P. Scherer, *Helv. Chim. Acta*, 1983, **66**, 118; V. G. Matassa, P. R. Jenkins, A. Kümin, L. Damm, J. Schreiber, D. Felix, E. Zass and A. Eschenmoser, *Isr. J. Chem.*, 1989, **29**, 321; G. Wickham and W. Kitching, *Organometallics*, 1983, **2**, 541; G. Wickham, D. Young and W. Kitching, *Organometallics*, 1988, **7**, 1187; W. Kitching, K. G. Penman, B. Laycock and I. Maynard, *Tetrahedron*, 1988, **44**, 3819; E. Vedejs and C. K. McClure, *J. Am. Chem. Soc.*, 1986, **108**, 1094.
5 R. A. N. C. Crump, I. Fleming, J. H. M. Hill, D. Parker, N. L. Reddy and D. Waterson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3277; I. Fleming and J. D. Kilburn, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3295.
6 I. Fleming and N. J. Lawrence, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3309.
7 I. Fleming, R. Henning, D. C. Parker, H. E. Plaut and P. E. J. Sanderson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 317.
8 I. Fleming, *Chemtracts: Org. Chem.*, 1996, **9**, 1. G. R. Jones and Y. Landais, *Tetrahedron*, 1996, **37**, 7599; K. Tamao, *Adv. Silicon Chem.*, JAI Press, Greenwich, CT, 1996, **3**, 1.
9 I. Fleming, D. Higgins, N. J. Lawrence and A. P. Thomas, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3331. I. Fleming, S. Gil, A. K. Sarkar and T. Schmidlin, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 3351.
10 I. Fleming and N. D. Kindon, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 303.
11 I. Fleming and N. K. Terrett, *Tetrahedron Lett.*, 1984, **25**, 5103.
12 A. Nangia, G. Prasuna and P. B. Rao, *Tetrahedron*, 1997, **53**, 14 507.
13 D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 1975, **97**, 4765.
14 L. A. Paquette, *Tetrahedron*, 1997, **53**, 13 971.
15 M. E. Jung and J. P. Hudspeth, *J. Am. Chem. Soc.*, 1978, **100**, 4309 and 1980, **102**, 2463. See also, N.-C. Chang, H.-M. Day and W.-F. Lu, *J. Org. Chem.*, 1989, **54**, 4083.
16 P. A. Grieco, Y. Ohfune, Y. Yokoyama and W. Owens, *J. Am. Chem. Soc.*, 1979, **101**, 4749. See also, C. W. Gillies, M. Marino and P. A. Timpano, *J. Mol. Spectroscopy*, 1979, **78**, 185.
17 E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, *J. Am. Chem. Soc.*, 1969, **91**, 5675.
18 S. McLean and P. Haynes, *Tetrahedron*, 1965, **21**, 2313.
19 J. E. Letourneau, M. A. Wellman and D. J. Burnell, *J. Org. Chem.*, 1997, **62**, 7272.
20 I. Fleming and H.-F. Chow, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2651.
21 T. Sakan, S. Isoe, S. B. Hyeon, R. Katsumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh and D. Nelson, *Tetrahedron Lett.*, 1965, 4097.
22 J. Wolinsky and E. J. Eustace, *J. Org. Chem.*, 1972, **37**, 3376. See also, E. Lee and C. H. Yoon, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 479.
23 D. Wittenberg and H. Gilman, *Quart. Rev.*, 1959, **13**, 116. M. V. George, D. J. Peterson and H. Gilman, *J. Am. Chem. Soc.*, 1960, **82**, 403; H. Gilman, R. A. Klein and H. J. S. Winkler, *J. Org. Chem.*, 1961, **26**, 2474.

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