Sulphone-based Elimination Reactions in Synthesis. Part 2. Diumycinol

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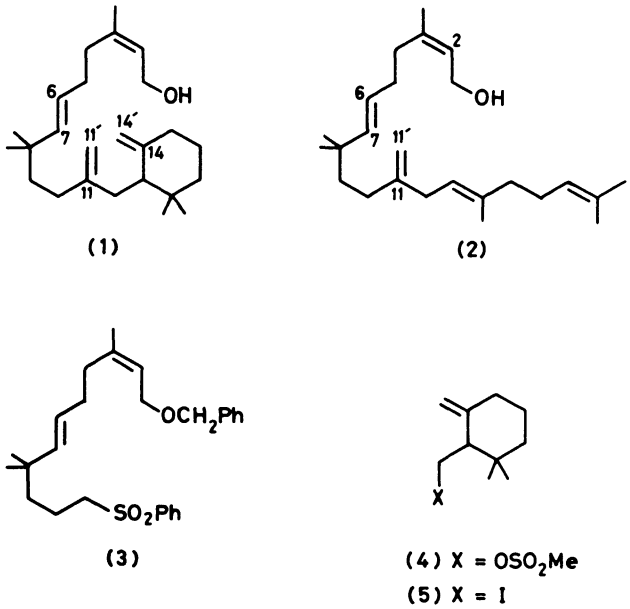
Diumycinol [2(*Z*), 6(*E*)-12-(2-methylene-6,6-dimethyl-1-cyclohexyl)-11-methylene-3,8,8-trimethyldodeca-2,6-dien-1-ol], a hydrolytic product of the antibiotic diumycin, was assembled from three fragments: 1-(2-phenylsulphonylethyl)-2-methylene-6,6-dimethylcyclohexane (28), 3-(2-iodoethyl)-3-methyloxetane (39), and (*Z*)-1-benzyloxy-6-phenylsulphonyl-3-methylhex-2-ene (3). An efficient synthesis of 2-methylene-6,6-dimethylcyclohexylmethanol (15) (γ-cyclogeraniol) was accomplished by a [2,3]sigmatropic rearrangement of 3,3-dimethylcyclohex-1-enylmethoxymethyl-lithium (17).

Diumycinol (1) is obtained on hydrolysis of the antibiotic diumycin. Its structure was deduced from spectral and degradative studies [1] and has been corroborated by synthesis.[2] In the synthesis of the closely related moenocinol (2), the key steps involved the use of a reductive elimination of a β-methanesulphonyloxy sulphone (the Julia reaction [3]) to generate the C(6)–C(7)-*trans* double bond and a fluoride-induced elimination of a β-phenylsulphonylsilane to generate the C(11) methylene.[4] Since diumycinol and moenocinol share an identical skeleton from C(1) to C(11), it was expected that the same strategy could be adapted with only minor modifications to the synthesis of diumycinol. Insurmountable difficulties—largely steric in origin—thwarted this plan and herein we describe some of the detours which were required before a successful synthesis of diumycinol was achieved.[5]

For the synthesis of moenocinol, the fragment (3) incorporating C(1) to C(11) and the double bonds at C(2) and C(6) had been prepared. This same fragment (3) was also intended to form the C(11)–C(12) bond of diumycinol by a nucleophilic displacement reaction involving the lithium derivative of (3) and the γ-cyclogeranyl fragment (4) or (5). Our initial approach to the γ-cyclogeranyl skeleton (Scheme 2) was based on some related work of Hunt and Lythgoe.[6] Starting with the allylic alcohol (6) (prepared in 5 steps from 2-methylcyclohexanone in 36% overall yield [7]), γ-cyclogeraniol (15) was prepared in 20% overall yield by a sequence which includes two noteworthy silicon-mediated steps. In the first of these the trimethylsilylmethylsulphonium salt (9) was selectively deprotonated with Bu^{n}Li at the carbon bearing silicon to give the ylide (10) which underwent rapid [2,3] sigmatropic rearrangement under the reaction conditions.[8] The resultant α-trimethylsilyl sulphide (11) was used in the second key step, a Sila-Pummerer rearrangement [9] of the sulphoxide (12) derived from low temperature oxidation of (11). The rearrangement of (12) to the *O*-trimethylsilyl hemithioacetal (13) was fast even below room temperature and contrasts with similar rearrangement of α-trimethylsilyl phenyl sulphoxides which occur slowly at room temperature.[8–10] Unfortunately the enhanced rate of the rearrangement conferred by methyl substitution on the sulphoxide (12) was accompanied by a substantially depressed rate of hydrolysis of (13) to γ-cyclocitral. Whereas *O*-trimethylsilyl hemiphenylthioacetals hydrolyse rapidly in water,[9] especially in the presence of heavy metal catalysts, the corresponding methylthioacetals hydrolysed more slowly (18 h) and required oxalic acid as a catalyst. For larger scale work, the conversion of (13) into (14) was achieved by allowing a solution of (13) to stand in a 1 : 2 mixture of MeI and propylene oxide. Methylation of the sulphur atom of (13) was presumably followed by a collapse of the sulphonium salt to (14), Me_2S, and Me_3SiI. The propylene oxide was used to trap the Me_3SiI before it could do any mischief to (14). The



(1) (2) (3) (4) X = OSO_2Me (5) X = I

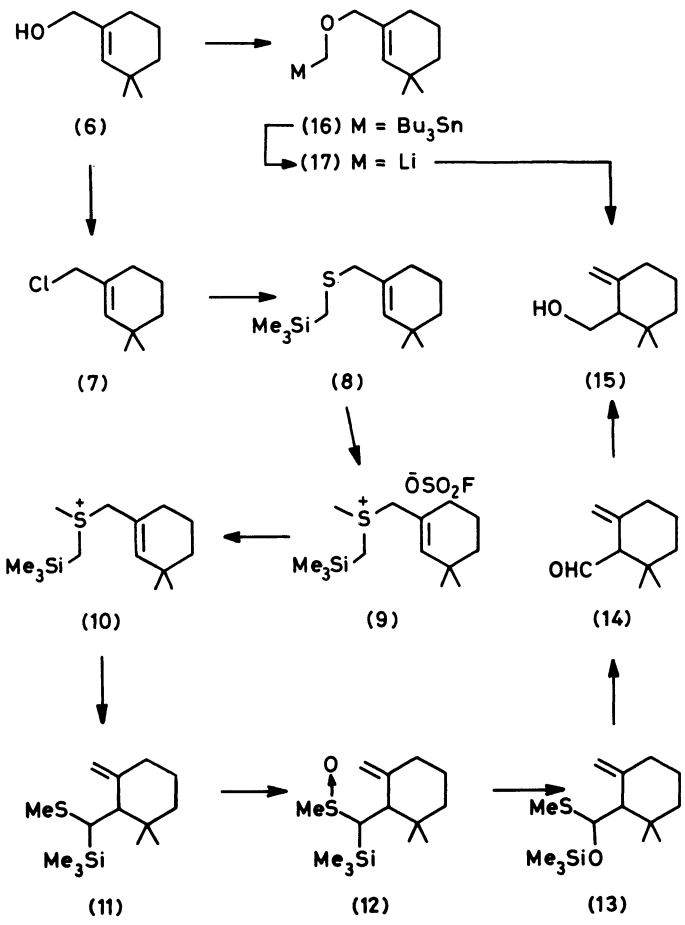
Scheme 1.

aldehyde (14) was not isolated but reduced immediately to the alcohol (15).

Because of its excessive length, the Sila-Pummerer approach to (15) was abandoned in favour of a short and efficient route based on the work of Still.[11] Alkylation of (6) with Bu_3Sn-CH_2I gave the ether (16). A transmetallation occurred on treatment of (16) with Bu^{n}Li to give (17) which underwent [2,3] sigmatropic rearrangement at low temperature affording the desired alcohol (15) in 90% yield.

With adequate supplies of the alcohol (15) in hand, the remainder of the synthesis should have paralleled the moenocinol route. Unfortunately, neither the iodide (5) nor the methanesulphonate (4) from which it was derived would alkylate the lithium anion of the sulphone (3) under a variety of conditions. Elevated temperatures and dipolar aprotic additives were to no avail. This failure was attributed to severe steric factors which were already presaged in the slow rate of displacement of the methanesulphonate group in (4) by iodide ion to give (5).

Rather than pursue further attempts to form the C(11)–C(12) bond by displacement reactions in a sterically crowded environment, we next tried to form the C(10)–C(11) bond by a nucleophilic displacement on the iodide (22) in which the reactive centres were further removed from the bulk of the



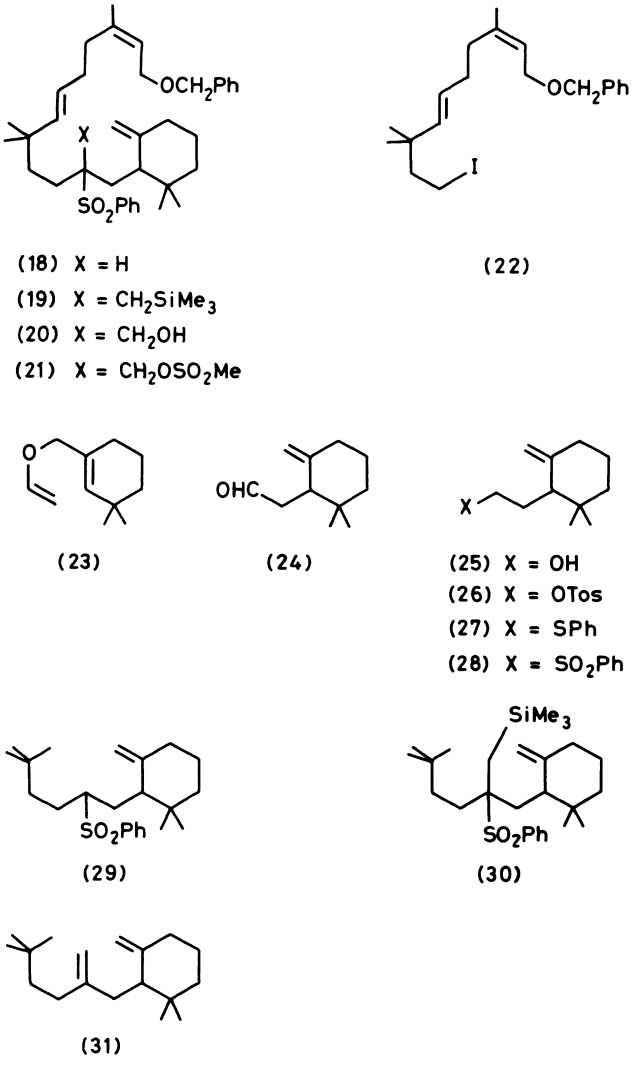
Scheme 2.

cyclohexane ring. However, in order to implement the modified strategy, a synthesis of the sulphone (28) was required.

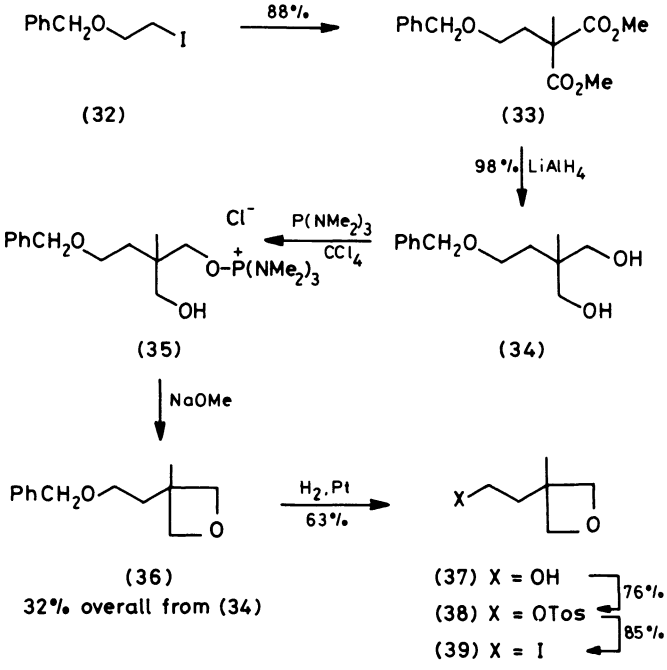
A mercury(II)-catalysed transvinylation reaction was used to convert the alcohol (15) into the vinyl ether (23) (Scheme 3). By heating (23) neat in a base-washed flask at 180 °C for 80 min an optimum yield [12] of the aldehyde (24) was obtained [72% overall from (15)]. Reduction of (24) gave the known [13] alcohol (25) which was converted *via* the toluene-*p*-sulphonate (26) to the sulphide (27). Oxidation of (27) to the sulphone (28) was achieved by two methods. First, *m*-chloroperbenzoic acid was used at low temperature to give (28) in 65% yield. In order to improve the chemoselectivity of the oxidation, the sulphide was oxidised by bis(trimethylsilyl)peroxide [14] in refluxing benzene to give (28) in 83% yield. The oxidation of sulphides to sulphones by bis(trimethylsilyl)peroxide was known [15] but the potential for using this reagent for the chemoselective oxidation of sulphides in the presence of double bonds has not been reported. This procedure complements other methods which have recently been described.[16]

The lithium derivative of (28) reacted smoothly with iodide (22) [4] to give (18) in 70% yield. With the bulk of the diumycinol skeleton now assembled, it merely remained to introduce the C(11) methylene to complete the synthesis. For the moenocinol synthesis the same goal was achieved by a two step sequence [17] involving alkylation of the sulphone anion with Me_3SiCH_2I to give a β-phenylsulphonylsilane which then underwent fluoride-induced elimination to give an olefin, benzenesulphinate anion, and fluorotrimethylsilane. However, neither the lithium nor the potassium derivative of (18) would react with Me_3SiCH_2I or $Me_3SiCH_2OSO_2CF_3$ under a variety of conditions—a failure which may again be attributed to steric factors. This result was especially disappointing since we had anticipated the problem and had shown that the sulphone (29) could be alkylated (albeit slowly) with Me_3SiCH_2I and the resultant β-phenylsulphonylsilane (30) underwent fluoride-induced elimination to give the diene (31) in 37% yield.

Having been twice foiled in attempts to form C–C bonds by displacement reactions in a crowded environment, we decided to abandon any strategies which required intermediates (3) or (22) and focused instead on a new strategy in which the C(11) methylene and the C(10–C(11) bonds were formed in the early stages of the synthesis when steric obstruction could be minimised. Encouraged by the successful conversion of (29) into (31), we attempted an analogous sequence of reactions on the oxetane (40) (Scheme 5) which was prepared in 78% yield by alkylation of sulphone (28) with the iodide (39) prepared as shown in Scheme 4. However, once again the alkylation of the lithium derivative of (40) with Me_3SiCH_2I failed to give the desired β-phenylsulphonylsilane (42) and all efforts to force the reaction by raising the temperature or adding HMPA only resulted in an intramolecular displacement reaction by the sulphone anion on the oxetane to give the cyclopentane derivative (41). Since the oxetane (40) should have offered less steric hindrance than the t-butyl analogue (29), some additional factor such as intramolecular co-ordination of the lithium atom by the oxetane oxygen must have been responsible for the inertness of (40) towards alkylation. Nonetheless, the lithium derivative of (40) did not react rapidly at −20 °C with formaldehyde to give the β-hydroxymethyl sulphone (43) which was



Scheme 3.



Scheme 4.

converted into the methanesulphonate (44). Reductive elimination of (44) using Na(Hg) under the usual conditions [18] then gave the desired diene (45) in 50% yield overall from (40).

To complete the synthesis, the oxetane ring in (45) was cleaved with an excess of Li in ethylenediamine at 15 °C.[19] The temperature in this reaction was critical: at 0—5 °C the reaction was very slow but at ⩾20 °C competing reduction of the exocyclic methylene group occurred. At 15 °C however, the unwanted side reaction was negligible and the desired alcohol (46) was formed in 95% yield. Swern oxidation [20] then gave the aldehyde (47) which reacted with the lithium anion of sulphone (3) to give, after benzoylation, the β-benzoyloxy sulphone (48) as a mixture of diastereoisomers. Reductive elimination then gave diumycinol benzyl ether (49) from which diumycinol was obtained on reductive cleavage of the benzyl group with Na/NH_3. The product was homogeneous by t.l.c. and the 400 MHz ^1H n.m.r. showed a well-defined olefinic region which clearly showed 6(*E*) stereochemistry [21] at the newly formed double bond. The ^1H n.m.r. spectrum was identical with that published by Grieco.[2]

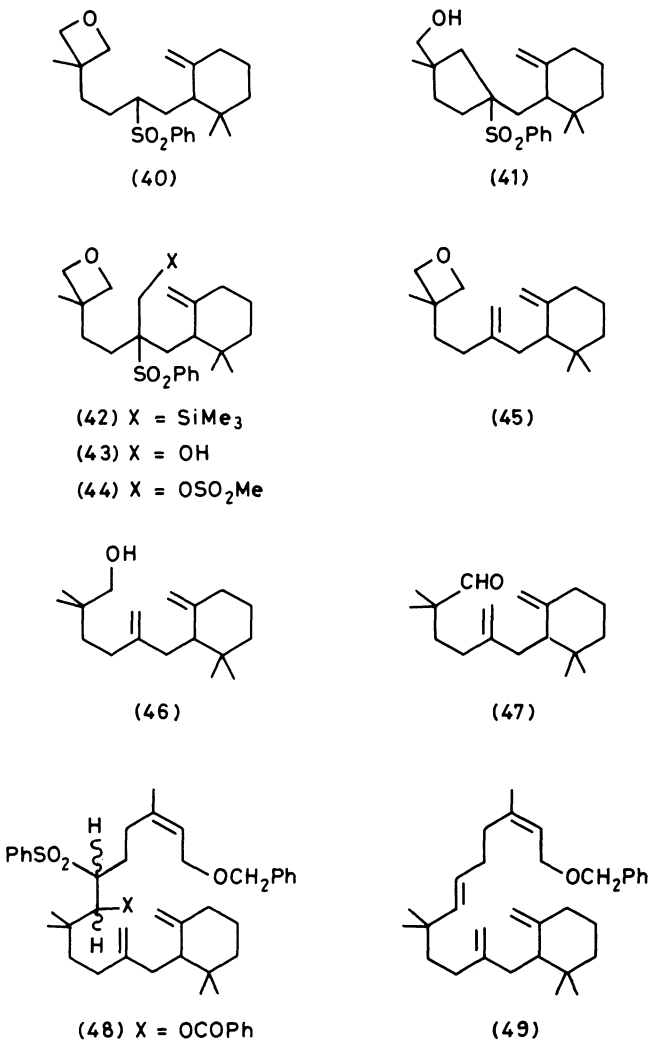
Once the *idée fixe* of using the β-phenylsulphonylsilane elimination for the introduction of the C(11) methylene was abandoned in favour of the Julia reaction,[3] a highly stereoselective and convergent synthesis of diumycinol was achieved. Ironically, the several detours described above were unnecessary; the lithium anion of (18) reacted with formaldehyde to give the β-hydroxymethyl sulphone (20) the methanesulphonate (21) of which underwent clean reductive elimination using Na(Hg) to give (49) in 30% overall yield from (18). Once again the virtue of the Julia olefination in introducing double bonds in sterically crowded environments has been demonstrated as have some of the constraints attending the use of the β-phenylsulphonylsilane elimination. Furthermore, a potentially useful chemoselective oxidation of a sulphide to a sulphone in the presence of an olefinic bond was exemplified as was the use of an oxetane ring as a latent neopentyl alcohol moiety.

Experimental

For general details see previous paper.

1-*Chloromethyl*-3,3-*dimethylcyclohexene* (7).—To a rapidly stirred solution of dimethylformamide (1.095 g, 15 mmol) in benzene (15 cm^3) was added dropwise with ice-bath cooling oxalyl chloride (2.54, 20 mmol). After 15 min at 0 °C the solvent was removed under reduced pressure. The resultant chlorodimethylformiminium chloride (moisture sensitive) was suspended in dimethylformamide (7 cm^3) and cooled to 0 °C. 1-Hydroxymethyl-3,3-dimethylcyclohexene (6) [7] (1.40 g, 10.0 mmol) was added and the mixture stirred at 0 °C for 30 min whereupon it was poured into water (100 cm^3) and the product extracted into light petroleum (b.p. 30—40 °C) (40 cm^3). The organic layer was washed with water, dried, and evaporated to give the chloride as a colourless oil (1.45 g, 92%), b.p. 80 °C (bath)/20 mmHg; δ 5.35br (1 H, s, =CH−), 3.95 (2 H, s, CH_2Cl), and 0.95 (6 H, s) (Found: C, 68.0; H, 9.6; Cl, 22.1. $C_9H_{15}Cl$ requires C, 68.1; H, 9.5; Cl, 22.35%).

1-*Trimethylsilylmethylthiomethyl*-3,3-*dimethylcyclohexene* (8).—To a stirred solution of trimethylsilylmethanethiol (1.26 g, 10.5 mmol) [22] in 1.2M-NaOEt/EtOH (10 cm^3) was added in one portion the chloride (7) (1.45 g, 9.2 mmol). After being



Scheme 5.

stirred at room temperature for 2 h, the mixture was poured into water (100 cm^3) and the product extracted into light petroleum (b.p. 30—40 °C). The organic layer was washed with water, dried, and evaporated to give (8) as a colourless oil (1.97 g, 85%) after short-path distillation, b.p. 120 °C (bath)/1 mmHg; $\nu_{max.}$ (neat) 1 250, 860, and 840 cm^{-1} (all s); δ 5.25br (1 H, s, =CH–), 3.02 (2 H, s, =C–CH_2S), 2.02 (2 H, distorted t, CH_2CH_2C=), 1.60 (2 H, s, CH_2Si), 1.00 (6 H, s), and 0.10 (9 H, s) (Found: C, 64.5; H, 10.8; S, 13.0. $C_{13}H_{26}SSi$ requires C, 64.4; H, 10.8; S, 13.2%).

1-*Methylthiotrimethylsilylmethyl*-2-*methylene*-6,6-*dimethylcyclohexane* (11).—To a stirred solution of the sulphide (8) (1.21 g, 5.0 mmol) in CH_2Cl_2 (5 cm_3) was added dropwise at 0 °C freshly distilled methyl fluorosulphonate (0.57 g, 5.0 mmol). After 5 min, the CH_2Cl_2 was removed under reduced pressure at 0 °C and the crystalline residue suspended in Et_2O and filtered. The resultant white solid discoloured with time and did not give a satisfactory m.p. or combustion analysis; δ 5.82br (1 H, s, =CH), 4.00 and 3.87 (1 H each, d, *J* 12 Hz, =C–CH_2–S), 2.86 (3 H, s, CH_3S), 2.78 and 2.55 (1 H, each, d, *J* 15 Hz, SCH_2Si), 2.03 (2 H, distorted t, CH_2CH_2C=), 1.3—1.85 (4 H, m), 1.00 (6 H, s), and 0.28 (9 H, s). The crude product (9) (1.485 g, 84%) was used directly in the next step.

The crude sulphonium salt (9) (1.454 g, 4.00 mmol) in THF (6.5 cm^3) was cooled to −60 °C and 1.5M-n-BuLi (3.0 cm^3) added dropwise. The mixture was allowed to warm slowly over 1 h to −10 °C whereupon saturated aqueous NH_4Cl was added followed by Et_2O. The organic layer was dried, evaporated, and the residue chromatographed on Kieselgel (1 × 3 cm) with light petroleum as eluant. The product (11) (0.674 g, 66%) was obtained as a colourless oil after short-path distillation: b.p. 110 °C (bath)/0.6 mmHg; $\nu_{max.}$ (film) 1 640w, 1 245s, 895m, 870s, 855s, and 835s cm^{-1}; δ 4.85 and 4.70 (1 H, each, narrow m, =CH_2), 2.17 (3 H, s, SMe), 1.05 and 0.95 (3 H each, s), and 0.10 (9 H, s) (Found: C, 65.45; H, 10.7; S, 12.1. $C_{14}H_{28}SSi$ requires C, 65.55; H, 11.0; S, 12.5%).

2-*Methylene*-6,6-*dimethylcyclohexanecarbaldehyde* (γ-*Cyclocitral* (14).—To a stirred solution of (11) (0.276 g, 1.08 mmol) in CH_2Cl_2 (5 cm^3) at −40 °C was added MCPBA (0.216 g, 1.08 mmol). After 30 min at −40 °C the mixture was diluted with Et_2O, washed with $NaHCO_3$, and evaporated. The residue was dissolved in THF (3.0 cm^3) and $(COOH)_2 \cdot 2H_2O$ (0.115 g) added. Water was added to the cloud point and the mixture set aside at room temperature for 24 h. The mixture was diluted with $NaHCO_3$ and the product extracted into Et_2O. After drying and evaporation, the residue was filtered through a plug of Kieselgel (20% Et_2O in light petroleum) to give of γ-cyclocitral (14) (0.076 g, 46%) after short-path distillation: b.p. 80 °C (bath)/18 mmHg; $\nu_{max.}$ (film) 2 820w, 2 720w, 1 720w, 1 645m, and 895 m cm^{-1}; δ 9.8 (1 H, d, *J* 4 Hz, CHO), 4.93 and 4.79 (1 H each, singlets with fine splitting, =CH_2), 2.78 (1 H, d, *J* 4 Hz, C*H*CHO), 2.1—2.3 (2 H, m, CH_2C=C), 1.3—1.8 (4 H, m), 1.07 and 0.94 (3 H each, s); 2,4-dinitrophenylhydrazone, m.p. 133—135 °C (lit.,[23] m.p. 134—135 °C.

2-*Methylene*-6,6-*dimethylcyclohexylmethanol* (γ-*Cyclogeraniol*) (15).—To a stirred mixture of the alcohol (2.00 g) (6) and NaH (0.75 g; 50% dispersion in oil) in THF (10 cm^3) and DMF (2 cm^3) was added $Bu^n_3SnCH_2I$ (6.47 g) [24] dropwise at 20 °C. After 24 h, the mixture was poured into water and the product extracted into light petroleum (2 × 50 cm^3). The combined organic layers were washed with water, dried, and evaporated. The residue was chromatographed on a 6 × 10 cm column of Kieselgel packed in light petroleum. Elution with light petroleum gave unchanged $Bu^n_3SnCH_2I$ and mineral oil. Further elution with 2% EtOAc in light petroleum gave the desired ether (16) (3.65 g, 58%). Elution with 30% EtOAc in light petroleum gave the unchanged alcohol (6) (0.60 g); therefore the yield of (16) was 89% based on easily recovered starting alcohol.

The ether (16) (3.65 g, 8.25 mmol) in THF (20 cm^3) was cooled to −78 °C and 1.5M-Bu^nLi (6.0 cm^3, 9.00 mmol) added dropwise. After 1 h at −78 °C the mixture was allowed to warm to −20 °C during 1 h. Saturated aqueous NH_4Cl was added and the organic layer separated. The aqueous layer was washed with Et_2O and the combined organic layers dried and evaporated. The residue was chromatographed on a 3.5 × 5.0 cm column of Kieselgel. Elution with 2% EtOAc in light petroleum removed Bu^n_4Sn. Further elution with 30% EtOAc in light petroleum gave the alcohol (15) as a colourless oil (1.143 g, 90%) after short-path distillation: b.p. 100 °C (bath)/20 mmHg (lit.,[23] b.p. 92—98 °C/12 mmHg); $\nu_{max.}$ (film) 3 400s, 1 645m, and 890s cm^{-1}; δ 5.0 and 4.8 (1 H, each s with fine splitting, =CH_2), 3.7 (2 H, m, CH_2O), 0.97 and 0.87 (3 H each, s, Me_2C). The alcohol (15) was also prepared in 79% yield from (14) on a mmol scale by reduction with $NaBH_4$ in the usual way.

(6,6-*Dimethylcyclohex*-1-*enylmethoxy*)*ethene* (23).—The Hg^{II}-catalysed transvinylation was performed according to the procedure of Dauben and Dietsche [12] except the crude

vinyl ether was purified by distillation rather than chromatography on Florisil which results in a 20% lower yield. The vinyl ether (23) (4.81 g, 81%) prepared from the alcohol (6) (5.00 g), was obtained as a colourless oil after short-path distillation: b.p. 100 °C (bath)/20 mmHg; $\nu_{max.}$ (film) 1 610, 1 195, and 810 cm^{-1} (all s); δ 6.33, 4.09, and 3.85 (1 H, each dd each, ABX pattern, J_{AX} 15, J_{BX} 7.5, and J_{AB} 2 Hz), 5.53 (1 H, br s), 3.94 (2 H, s, CH_2O), and 0.87 (6 H, s). The vinyl ether (23) was not stable and was used directly in the next step.

2-*Methylene*-6,6-*dimethylcyclohexylethanal* (24).—The freshly distilled vinyl ether (23) (4.81 g) was placed in a 25 cm^3 round-bottom flask which had been filled with 4M-KOH for 1 h and then washed with distilled water and acetone. The flask was flushed with nitrogen and placed in a Kugelrohr oven pre-heated to 180 °C. After 80 min at 180—185 °C, the pyrolysate was cooled and then distilled at 120 °C (bath)/20 mmHg to give the aldehyde (24) [13] as a colourless oil (3.08 g, 92%): $\nu_{max.}$ (film) 2 710m, 2 810sh, 1 725s, 1 645m, and 895s cm^{-1}; δ 9.65 (1 H, m, CHO), 4.82 and 4.55 (1 H each, s with fine splitting, $=CH_2$), and 1.00 and 0.81 (3 H each, s, Me_2C).

1-(2-*Phenylthioethyl*)-2-*methylene*-6,6-*dimethylcyclohexane* (27).—The known alcohol (25) [13] (3.825 g, 22.8 mmol), prepared in 92% yield by reduction of the aldehyde (24) with $LiAlH_4$, reacted with toluene-*p*-sulphonyl chloride (4.76 g, 25 mmol) in pyridine (20 cm^3) at 0 °C for 5 h to give the toluene-*p*-sulphonate (26) which was added directly to a solution of PhSH (2.75 g, 25 mmol) in 1.1M-NaOEt–EtOH (25 cm^3). After being refluxed for 1 h the mixture was poured into 2M-NaOH and the product extracted into light petroleum. The organic layer was washed with brine, dried, and evaporated. Coloured impurities were removed by passing the crude oil through a plug of Kieselgel in light petroleum. The sulphide (27) (5.805 g, 95%) was obtained as a colourless oil after short-path distillation: b.p. 160 °C (bath)/0.15 mmHg; $\nu_{max.}$ (film) 1 642m, 1 585m, 1 470s, 740s, and 690s cm^{-1}; δ 7.1—7.4 (5 H, m), 4.75 and 4.55 (1 H each, s with fine splitting), and 0.8 and 0.9 (3 H each, s) (Found: C, 78.6; H, 9.35; S, 12.7. $C_{17}H_{24}S$ requires C, 87.4; H, 9.3; S, 12.3%).

1-(2-*Phenylsulphonylethyl*)-2-*methylene*-6,6-*dimethylcyclohexane* (28).—A mixture of the sulphide (27) (0.520 g, 2.00 mmol) and bis(trimethylsilyl) peroxide (0.890 g, 5.00 mmol) [14] in benzene (5 cm^3) was refluxed for 24 h. The solvent and excess peroxide were removed under reduced pressure and the residue chromatographed on Kieselgel (2.5 × 6 cm). Elution with 20% EtOAc in light petroleum followed by crystallisation from cold 10% EtOAc in light petroleum gave the sulphone as white plates (0.57 g, 83%), m.p. 61—65 °C; $\nu_{max.}$ (neat) 1 640m, 1 315s, 1 305s, 1 145s, and 890m cm^{-1}; δ 7.8—7.6 and 7.2—7.5 (2 H and 3 H, m), 4.7 and 4.42 (1 H each, s with fine splitting, $=CH_2$), 2.6—3.0 (2 H, m, CH_2SO_2), and 0.9 and 0.82 (3 H each, s) (Found: C, 69.6; H, 8.0; S, 11.1. $C_{17}H_{24}O_2S$ requires C, 69.8; H, 8.3; S, 11.0%).

Ethyl 4-*Benzyloxy*-2-*methoxycarbonyl*-2-*methylbutanoate* (33).—The solid remaining after washing (12.4 g, 0.26 mmol) of a 50% NaH dispersion with light petroleum was suspended in DMF (150 cm^3) and THF (100 cm^3). With rapid mechanical stirring dimethyl methylmalonate (34.3 g, 0.235 mol) was added dropwise. The mixture was then refluxed for 30 min whereupon 2-benzyloxychloroethane [25] (44 g, 0.29 mol) was added dropwise followed by NaI (1 g). The mixture was refluxed for 24 h and then poured into ice–water (1 l). The organic layer was separated and the aqueous layer extracted with Et_2O (2 × 150 cm^3). The combined organic layers were washed with water, dried, and evaporated. The residue was distilled to give (33) as a colourless oil (47.6 g, 72%), b.p. 120—125 °C/0.01 mmHg; δ 7.40 (5 H, s), 4.47 (2 H, s, $PhCH_2$), 3.62 (6 H, s, OMe), 3.55 (2 H, t, *J* 7 Hz, OCH_2CH_2), 2.22 (2 H, t, *J* 7 Hz, OCH_2CH_2), and 1.44 (3 H, s) (Found: C, 64.35; H, 7.0. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%).

4-*Benzyloxy*-2-*methyl*-2-*hydroxymethylbutan*-1-*ol* (34).—The diester (33) (82 g, 0.292 mol) was added dropwise to a mechanically stirred suspension of $LiAlH_4$ (16.7 g, 0.438 mol) in Et_2O (800 cm^3) with ice-bath cooling. The mixture was refluxed for 4 h and 2M-HCl (500 cm^3) was added with cooling. The organic layer was washed with $NaHCO_3$, dried, and evaporated. The residual oil was distilled to give the diol (34) (60.0 g, 92%), b.p. 115—120 °C/0.01 mmHg; $\nu_{max.}$ (film) 3 100—2 970s cm^{-1}; δ 7.55 (5 H, s), 4.65 (2 H, s, $PhCH_2$), 3.45—3.90 (6 H, m), 3.05—3.45br (2 H, D_2O exchange, OH), 1.76 (2 H, t, *J* 6 Hz, OCH_2CH_2), and 0.80 (3 H, s) (Found: C, 69.9; H, 9.4. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%).

3-(2-*Benzyloxyethyl*)-3-*methyloxetane* (36).—To a stirred solution of the diol (34) (81.1 g, 0.362 mol) in THF (1 l) and CCl_4 (167 g, 1.09 mol) was added dropwise at −40 °C freshly distilled $P(NMe_2)_3$ (65 g, 0.4 mol).[26] The mixture was allowed to warm to 20 °C and the solvent evaporated to give the crude salt (35). This was added dropwise as a solution in MeOH (200 cm^3) to NaOMe–MeOH prepared from Na (36.2 g) and MeOH (800 cm^3). After 16 h at 20 °C, the mixture was refluxed for 4 h and then poured into water (3 l). The product was extracted into Et_2O (3 × 300 cm^3). The combined organic layers were washed thoroughly with water, dried, and evaporated to give a yellow oil (62.9 g) which was chromatographed on Kieselgel (8 × 15 cm) in 3 batches. Elution with 10% ethyl acetate in light petroleum gave the desired oxetane (36). Elution with ethyl acetate gave recovered diol (34). The appropriate fractions were combined to give the oxetane (36) as a colourless oil (8.84 g, 12%), b.p. 95—100 °C (bath)/0.005 mmHg; $\nu_{max.}$ (film) 980 cm^{-1}; δ 7.35 (5 H, s), 4.08 (2 H, s, $PhCH_2$), 3.92 and 4.15 (2 H, each, d, *J* 6 Hz, CH_2OCH_2), 3.2 (2 H, t, OCH_2CH_2), 1.55 (2 H, t, OCH_2CH_2), and 0.9 (3 H, s) (Found: C, 75.75; H, 8.5. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%). A total of 40 g of diol (34) was recovered.

3-(2-*Hydroxyethyl*)-3-*methyloxetane* (37).— A stirred mixture of PtO_2 (100 mg), the benzyl ether (36) (8.8 g), and EtOH (35 cm^3) was hydrogenated at atmospheric pressure in the usual way until 1 equivalent of hydrogen was consumed. The 3-component residue (t.l.c. on Kieselgel with EtOAc as eluant) obtained after filtration and solvent evaporation was chromatographed on an 8 × 10 cm column of Kieselgel. The main component eluted with Et_2O–light petroleum (1 : 1), gave the alcohol (37) as a colourless oil (3.11 g, 63%) after short-path distillation: b.p. 80 °C (bath)/18 mmHg; $\nu_{max.}$ (film) 3 650—3 100br and 970m cm^{-1}; δ 4.45 and 4.22 (2 H each, d, *J* 5.5 Hz), 3.65 (2 H, t, *J* 6 Hz, $HOCH_2$), (t, 2 H, *J* 6 Hz, OCH_2CH_2), 1.52br (1 H, s, D_2O exchange), and 1.32 (3 H, s) (Found: M^+, 116.083 87. Calc. for $C_6H_{12}O_2$: *M*, 116.083 724). The mass spectrum showed a weak molecular ion at *m*/*z* 116; other peaks were found at *m*/*z* 86 (38), 68 (100), 56 (93), and 41 (65%).

3-(2-*Iodoethyl*)-3-*methyloxetane* (39).—The alcohol (37) was converted in the usual way into the iodide (39) by reaction of the toluene-*p*-sulphonate (38) with NaI in refluxing acetone in an overall yield of 65%. The iodide (39) had b.p. 42 °C (bath)/0.1 mmHg; $\nu_{max.}$ (film) 980 cm^{-1}; δ 4.36 and 4.16 (2 H each, d, *J* 6 Hz, CH_2OCH_2), 3.09 (2 H, distorted t, *J* 8 Hz, CH_2CH_2I), 2.22 (2 H, t, *J* 8 Hz, CH_2CH_2I), and 1.27 (3 H, s) (Found: M^+, 225.985 94. Calc. for $C_6H_{11}IO$: *M*, 225.285 645).

3-[4-(2-*Methylene*-6,6-*dimethylcyclohexyl*)-3-*phenylsulphonylbutyl*]-3-*methyloxetane* (40).—To a solution of the sulphone (28) (1.635 g, 5.6 mmol) in THF (5 cm^3) was added dropwise at −78 °C 1.3M-Bu^{n}Li–hexane (5.4 cm^3, 7.0 mmol). After 15 min at −78 °C the iodide (39) (1.90 g, 8.4 mmol) in THF (2 cm^3) was added and the mixture allowed to gradually warm to 20 °C whereat the temperature was maintained for 2 h. Water (75 cm^3) and Et_2O (100 cm^3) was added. The organic layer was washed with aqueous $Na_2S_2O_3$ and water, dried, and evaporated. The residual oil (2.59 g) was chromatographed on Kieselgel with Et_2O–toluene (1 : 1) as eluant to give (40) as a viscous oil (1.715 g, 78%): $\nu_{max.}$ (film) 1 645m, 1 300s, 1 245s, and 980m cm^{-1}; ^1H n.m.r. showed a mixture of two diastereoisomers in the ratio 6 : 4; δ_{major} 4.8 and 4.55 (1 H each, narrow m, $=CH_2$), 4.2—4.35 (4 H, m, CH_2OCH_2), 2.8—3.2br (1 H, $CHSO_2$), 1.22 (3 H, s, OCH_2–C*Me*), and 0.8 and 1.2 (3 H each, s); δ_{minor} 4.75 and 4.60 (1 H each, narrow m, $=CH_2$), 4.2—4.35 (4 H, m, CH_2OCH_2), 2.8—3.2br (1 H, $CHSO_2$), 1.25 (3 H, s, OCH_2CMe), and 0.76 and 0.83 (3 H each, s). A satisfactory combustion analysis was not obtained for this compound and a molecular ion was not observed in the mass spectrum.

3-[4-(2-*Methylene*-6,6-*dimethylcyclohexyl*)-3-*methylenebutyl*]-3-*methyloxetane* (45).—To a stirred solution of Pr$^i_2$NH (0.48 g, 4.7 mmol) in THF (2 cm^3) was added dropwise at −78 °C Bu^{n}Li–hexane (3.4 ml, 4.4 mmol) followed, after 15 min, by a solution of the sulphone (40) (1.315 g, 3.4 mmol) in THF (5 cm^3). After 20 min at −78 °C, the mixture was allowed to warm to −10 °C whereupon gaseous formaldehyde (0.505 g, 16.8 mmol) in a stream of dry N_2 was introduced into the rapidly stirred solution of the sulphone anion. The deep red of the sulphone anion was discharged as reaction occurred to give a pale yellow solution. The mixture was diluted with ether and washed with M-HCl and saturated $NaHCO_3$. After drying and evaporation the residue was chromatographed on Kieselgel with 25% EtOAc in light petroleum as eluant to give the β-hydroxy sulphone (43) (0.925 g, 65%) as a mixture of diastereoisomers. These were treated with methanesulphonyl chloride and Et_3N in CH_2Cl_2 in the usual way to give the methanesulphonates (44) (1.11 g) which, without further purification, were dissolved in THF (8 cm^3) and MeOH (2 cm^3). The mixture was cooled to −10 °C and 5.65% Na(Hg) (10 g) was added. After being stirred for 4 h at −10 °C, the mixture was decanted from the amalgam into Et_2O and washed with water, dried, and evaporated. The crude product was chromatographed on Kieselgel packed in 5% EtOAc in light petroleum. The oxetane (45) (0.43 g) was obtained as a colourless oil after short-path distillation: b.p. 100 °C/0.1 mmHg; $\nu_{max.}$ (film) 1 640, 1 385, 1 360, 980, and 885 cm^{-1} (all s); δ 4.65—4.80 (3 H, m), 4.50 (1 H, narrow m), 4.42 and 4.32 (2 H, each d, *J* 3.5 Hz, CH_2OCH_2), 1.30 (3 H, s), and 0.87 and 0.96 (3 H each, s, Me_2C) (Found: M^+, 262.229 71. $C_{18}H_{30}O$ requires: *M*, 262.229 654).

6-(2-*Methylene*-6,6-*dimethylcyclohexyl*)-5-*methylene*-2,2-*dimethylhexan*-1-*ol* (46).—To a stirred solution of 0.215 g of the oxetane (45) (0.215 g) in Et_2O (5 cm^3) and ethylenediamine (1 cm^3) was added at 0 °C a 30% Li dispersion (75 mg). The mixture was allowed to warm to 15 °C and when the blue-green colour was discharged further Li dispersion (50 mg) was added. After 30 min, the mixture was cooled to 0 °C and excess of Li destroyed with Pr^{i}OH. The mixture was diluted with Et_2O and washed thoroughly with M-HCl and $NaHCO_3$. The organic layer was dried and evaporated and the residue chromatographed on Kieselgel (2 × 4 cm). Elution with 8% EtOAc in light petroleum gave the alcohol (46) (200 mg, 95%) as a colourless oil after short-path distillation: b.p. 110 °C/0.01 mmHg; $\nu_{max.}$ (film) 3 600—3 100br, 1 645s, 1 385m, 1 365m, 1 120s, 1 060s, and 880s cm^{-1}; δ 4.45—4.78 (4, m, 2 × CH_2), 3.26 (2 H, s, CH_2O), 1.09—2.30 (13 H, m), 0.87 (9 H, s, 3 × Me), 0.96 (3 H, s) (Found: M^+, 264.2465. Calc. for $C_{18}H_{32}O$: 264.245 303).

6-(2-*Methylene*-6,6-*dimethylcyclohexyl*)-5-*methylene*-2,2-*dimethylhexan*-1-*ol* (47).—Oxidation of the alcohol (46) (190 mg) by the procedure of Swern [20] gave the aldehyde (47) (175 93%) as a colourless oil, b.p. 100 °C/0.01 mmHg; $\nu_{max.}$ (film) 1 730s, 1 645m, 1 470s, 1 385s, 1 365s, and 885s cm^{-1}; δ 9.36 (1 H, s), 4.40—4.80 (4 H, m, 2 × $=CH_2$), 1.04 (6 H, s, Me_2-CCHO), and 0.86 and 0.95 (3 H each, s) (Found: M^+, 262.229 17. Calc. for $C_{18}H_{30}O$: *M*, 262.229 654).

2(Z),6(E)-12-(2-*Methylene*-6,6-*dimethylcyclohexyl*)-11-*methylene*-3,8,8-*trimethyl*-1-*benzyloxydodeca*-2,6-*diene* (49) (*Diumycinol Benzyl Ether*).—The fragments (3) (290 mg) and (47) (200 mg) were linked *via* the Julia reaction as described in the previous paper [4] for moenocinol benzyl ether to give (49) (75 mg, 33% overall) as a colourless oil: $\nu_{max.}$ (film) 1 645m, 1 385s, 1 365s, 1 070s, 970s, and 885s cm^{-1}; δ (400 MHz) 7.34 (5 H, m), 5.42 (1 H, bt with further splitting, *J* 7 Hz), 5.34 (1 H, d with further splitting, *J* 16 Hz), 5.245 (1 H, m), 4.725, 4.69, 4.615 and 4.495 (1 H, each, narrow m), 4.50 (2 H, s), 4.10 (2 H, dq, *J* 7 and *J'* 1 Hz), 1.75 (3 H, q, *J* 1 Hz), 0.96 (6 H, s), and 0.95 and 0.85 (3 H each, s) (Found: M^+, 448.371 22. Calc. for $C_{32}H_{48}O$: *M*, 448.370 497).

2(Z),6(E)-12-(2-*Methylene*-6,6-*dimethylcyclohexyl*)-11-*methylene*-3,8,8-*trimethyldodeca*-2,6-*dien*-1-*ol* (*Diumycinol*) (1).—Diumycinol benzyl ether (49) (80 mg) was reduced to diumycinol (1) (93%) with Na/NH_3 (1) as described for moenocinol.[4] Diumycinol was obtained as a colourless oil: $\nu_{max.}$ (film) 3 600—3 100br, 1 645m, 1 460s, 1 450s, 1 385s, 1 365s, 1 000s, 975s, and 885s cm^{-1}; δ (400 MHz) 5.44 (1 H, t with further splitting, *J* 7.5 Hz, 2-H), 5.375 (1 H, d with further splitting, *J* 16 Hz, 7-H), 5.26 (1 H, dt, *J* 16 and *J'* 6.5 Hz, 6-H), 4.725 and 4.69 (1 H each, m, $W_{\frac{1}{2}}$ 7.5 Hz, 14'-H_2), 4.615 and 4.49 (1 H, each, m, $W_{\frac{1}{2}}$ 7.5 and 5 Hz respectively, 11'-H_2), 4.11 (2 H, d with fine splitting, *J* 7 Hz, 1-H_2), 2.21—2.27 (1 H, m), 2.07—2.18 (6 H, m), 1.94—2.02 (2 H, m), 1.78—1.94 (2 H, m), 1.75 (3 H, q, *J* 1 Hz, 3-Me), 1.93—1.57 (3 H, m), 1.21—1.44 (5 H, m), 0.96 (6 H, s), and 0.95 and 0.85 (3 H each, s) (Found: M^+, 358.323 64. $C_{25}H_{42}O$ requires *M*, 358.323 549).

Conversion of (18) *into* (49).—To a solution of di-isopropylamine (47 mg, 0.47 mmol) in THF (0.5 cm^3) was added 1.3M-Bu^{n}Li (0.34 cm^3) at 0 °C. After 10 min, the sulphone (18) (180 mg, 0.313 mmol) in THF (2 cm^3) was added dropwise. After a further 20 min at 0 °C, gaseous formaldehyde [from paraformaldehyde (1 g)] was introduced in a stream of dry nitrogen into the rapidly stirred mixture. The orange colour of the sulphone anion was rapidly discharged to leave a pale yellow solution to which was added saturated aqueous NH_4Cl. The products were extracted into Et_2O. The extract was washed with dilute HCl and $NaHCO_3$, dried, and evaporated. The residue was chromatographed on a 3 × 5 cm column of Kieselgel. Elution with 8% EtOAc in light petroleum gave recovered (18) (52 mg, 29%) and (20) (91 mg, 48%) as a viscous oil which was used directly in the next step.

To a stirred solution of (20) (91 mg) in CH_2Cl_2 (2 cm^3) was added at −10 °C Et_3N (61 mg) and methanesulphonyl chloride (51 mg). After 2.5 h at −10 °C, the mixture was diluted with Et_2O (20 cm^3) and washed with aqueous $NaHCO_3$. The crude product obtained on evaporation of solvent (108 mg) was dissolved in THF–MeOH (3 : 1; 5 cm^3) and cooled to 0 °C. Na(Hg) (1 g) was added and the mixture stirred at 0 °C

for 3 h; it was then decanted from unchanged amalgam and evaporated. The residue was partitioned between Et_2O and water, dried, and evaporated to leave a viscous oil from which (49) [42 mg, 63% from (20)] was obtained after elution from a 2 × 4 cm column of Kieselgel with 2% EtOAc in light petroleum. The chromatographically purified product was identical by ^1H n.m.r. spectroscopy with the sample prepared previously (*vide supra*).

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