New Route to (±)-Magydardienediol, a Diterpene Isolated from *Magydaris panacifolia* (Vahl) Lange, *via* a Sequential Intra- and Inter-Molecular Radical C–C Bond-Forming Reaction†

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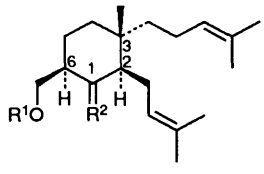
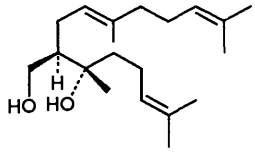
(±)-1-*epi*-Magydardienediol, an intermediate for the synthesis of (±)-magydardienediol and (±)-magydartrienol, diterpenes isolated from *Magydaris panacifolia* (Vahl) Lange, has been synthesized stereoselectively from 3-methylcyclohex-2-enone in 12 steps *via* a sequential intra- and inter-molecular radical C–C bond-forming reaction.

(+)-Magydartrienol, its acetate, and (+)-magydardienediol are diterpenes isolated from *Magydaris panacifolia* (Vahl) Lange (Umbelliferae)[1] and the previously reported structures for these diterpenes have recently been revised to **1**, **2** and **3**, respectively.[2] Structure **3** has also been assigned to bonandiol, which was isolated from *Bonannia graeca* (L.) Halacsy (Umbelliferae), a plant toxic to herbivorous animals.[3] The irregular carbon skeleton of these monocyclic diterpenes may be formed by the head-to-head condensation of two monoterpene units. Peucelinenediol **5**, an acyclic diterpene isolated from *Peucedanum oreoselinum*, also has the irregular carbon skeleton.[4]





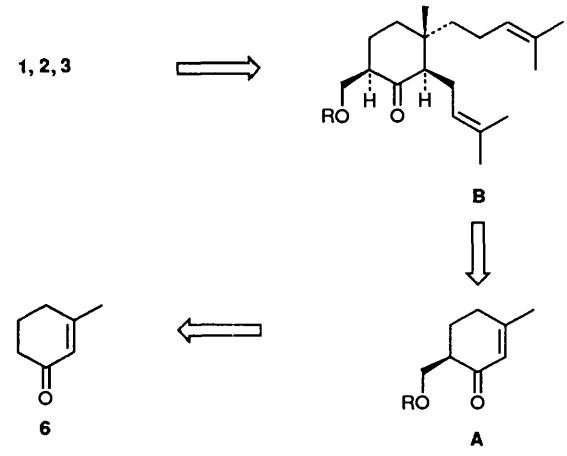
1 R^1 = H, R^2 = CH_2
2 R^1 = Ac, R^2 = CH_2
3 R^1 = H, R^2 = α-OH, β-Me
4 R^1 = H, R^2 = α-Me, β-OH

5

The total synthesis of the diterpenes **1**, **2** and **3** has been reported by de Pascual Teresa *et al.*[5] We now report the first stereocontrolled synthesis of (±)-1-*epi*-magydardienediol **4**, which has already been transformed into (±)-magydardienediol **3** *via* (±)-magydartrienol acetate **2**.[5]

The retrosynthetic pathway for our synthesis is shown in Scheme 1. One-pot introduction of the two side-chains, 4-methylpent-3-enyl and 3-methylbut-2-enyl groups, to the cyclohexenone **A** through conjugate addition of alkylcopper, followed by trapping of the resulting enolate with an alkyl halide, may give a mixture of the cyclohexanone **B** and its diastereoisomers. In our work a sequential intra- and inter-molecular radical C–C bond-forming reaction developed by Stork,[6] an alternative to the above ionic 1,2-addition reaction to the C–C double bond, was applied in order to attain stereoselective introduction of the two side-chains. The synthetic route from 3-methylcyclohex-2-enone **6** to (±)-1-*epi*-magydardienediol **4** is shown in Scheme 2.

Condensation of the kinetic enolate of the enone **6** with a large excess of gaseous formaldehyde at −78 °C gave the β-hydroxy ketone **7** in 65% yield. Protection of the primary hydroxy group of the hydroxy ketone **7** with 2-methoxyethoxymethyl (MEM) chloride gave the MEM ether **8** in 87% yield. Reduction of the enone **8** with lithium aluminium hydride at −78 °C gave an inseparable mixture of the *cis*- and *trans*-allylic alcohols **9** and **10** in the ratio 1:5. The desired *cis*-allylic alcohol

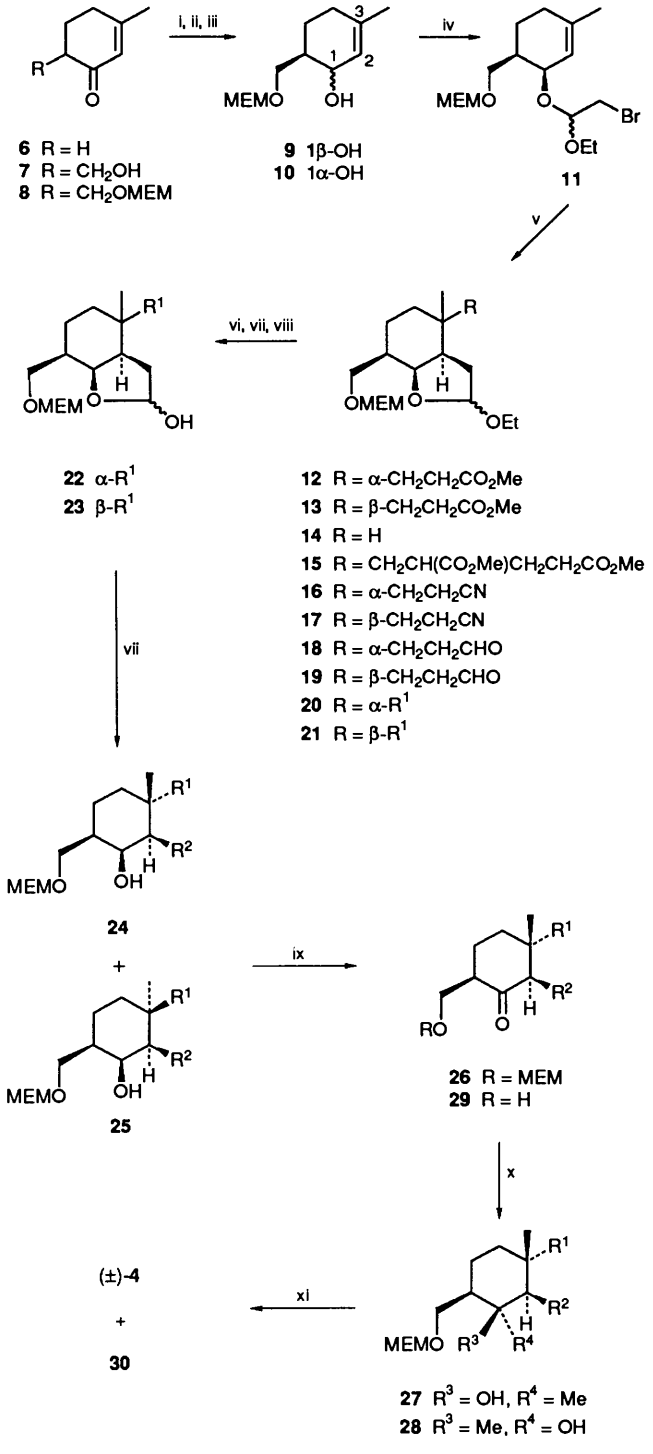


Scheme 1

9 was obtained by reduction of the enone **8** with lithium tri-s-butylborohydride (L-Selectride) at −78 °C in 94% diastereoisomeric excess (de) and 61% yield.[7] The stereochemistry was determined by comparison of the ^{1}H NMR signals of 1-H [**9**: δ 4.20 (m, $w_{\frac{1}{2}}$ *ca.* 10 Hz) and **10**: δ 4.13 (d, *J* 7.7 Hz)] and 2-H [**9**: δ 5.63 (d, *J* 3.6) and **10**: δ 5.36 (br s)] with those of 7-H and 6-H in 7-hydroxycholesterols.[7] The allylic alcohol **9** was then treated with *N*-bromosuccinimide (NBS) in a large excess of ethyl vinyl ether at −20 °C for 3 days to give the bromo acetals **11** as a mixture of diastereoisomers in 56% yield along with the starting material **9** (25% recovery). When the reaction was performed in dichloromethane at −20 °C[6b] the yield of the bromo acetals **11** and the starting material **9** recovery were 47 and 30%, respectively. Treatment of the allylic alcohol **9** with 1,2-dibromoethyl ethyl ether (prepared *in situ* from ethyl vinyl ether and bromine) and triethylamine[8] gave the bromo acetals **11** in 57% yield, but the recovered starting material contained the epimerised *trans*-allylic alcohol **10**.

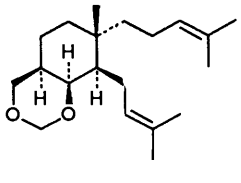
Sequential intra- and inter-molecular radical C–C bond-forming reaction, the key step in this synthesis, was performed by applying the reaction conditions reported by Stork and Sher.[6a,b] A mixture of the bromo acetals **11** in t-butyl alcohol containing methyl acrylate (25 mol equiv.), tributyltin chloride (0.3 mol equiv.), sodium cyanoborohydride (7 mol equiv.) and azoisobutyronitrile (AIBN) (0.5 mol equiv.) was heated at 80 °C under argon to give an inseparable mixture of the bicyclic esters **12** and **13** in the ratio 4:1‡ and 56% yield along with the

† *Preliminary communication:* H. Nagano, Y. Seko and K. Nakai, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2153.
‡ The ratio was determined by integration of the ^{1}H NMR spectrum of the mixture **18** and **19**.



$R^1 = CH_2CH_2CH{=}CMe_2$, $R^2 = CH_2CH{=}CMe_2$

Scheme 2 *Reagents and conditions:* i, $LiNPr^i_2$, $H_2C{=}O$, −78 °C; ii, MEMCl, Pr^i_2EtN; iii, L-Selectride, −78 °C; iv, NBS, $EtOCH{=}CH_2$, −20 °C; v, AIBN, $NaBH_3CN$, Bu_3SnCl, $CH_2{=}CHCO_2Me$, Bu^tOH, 80 °C; vi, DIBAH, toluene, −78 °C; vii, $Ph_3P^+CHMe_2Br^-$, BuLi; viii, aq. AcOH; ix, CrO_3·(pyridine)$_2$; x, MeLi; xi, 1% HCl–acetone, room temp



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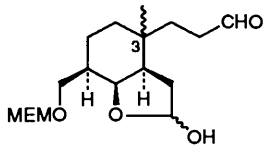
product of reductive debromination, compound **14** (15%), and that of trapping of two molecules of the ester, compound **15** (20%). The *cis*-ring-fused structure, having newly introduced *trans*-substituents at C-2 and C-3, was assigned, by precedent,[6] to the major diastereoisomer **12** and the assignment was confirmed by transformation of the diastereoisomer **12** into the known 1-*epi*-magydardienediol **4** (*vide infra*). When the radical reaction was performed with the more reactive substrate acrylonitrile instead of methyl acrylate[9] the yield of the cyclisation-trapping reaction products (compounds **16** and **17**) increased to 69%, but the ratio decreased to 2:1.



31 3β-Me
32 3α-Me

The diastereoisomeric mixture of compounds **12** and **13** was then transformed as follows. Reduction of the mixture **12** and **13** with diisobutylaluminium hydride (DIBAH) in toluene at −78 °C gave an inseparable mixture of the aldehydes **18** and **19** in 77% yield. Wittig reaction of the aldehydes with isopropylidene(triphenyl)phosphorane gave a mixture of acetals **20** and **21** in 69% yield. Acid-catalysed hydrolysis of the acetals **20** and **21** gave a mixture of hemiacetals **22** and **23** in 86% yield as an inseparable mixture.

Isopropylidene(triphenyl)phosphorane was applied again, in a Wittig reaction of the hemiacetals **22** and **23**, to give the dienes **24** and **25** (72% yield), which were carefully separated by silica gel column chromatography with benzene–ethyl acetate (10:1) as eluent. Acid-catalysed hydrolysis of the acetals **18** and **19**, followed by Wittig reaction, gave the dienes **24** and **25** in poor yield. This may be due to intramolecular aldol condensation of the hemiacetal aldehydes **31** and **32**. The stereochemistry of compound **24** was confirmed on the basis of (i) the pyridine-induced ^1H NMR solvent shift of the 3-methyl signal {δ-([$^2H_5$]pyridine) 1.31 and δ($CDCl_3$) 0.99} due to the hydroxy group and the methyl group being in a 1,3-diaxial relationship,[10] and (ii) the axial methyl singlet at δ 0.71 in the ^1H NMR spectrum of the ketone **26**, which was obtained by oxidation of the alcohol **24**.

Addition of methyllithium to the ketone **26** gave solely the tertiary alcohol **27** in 71% yield, none of the desired alcohol **28** being obtained even in the presence of methylaluminium bis-(2,6-di-t-butyl-4-methylphenoxide).[11] Attempted hydrolysis of the MEM ether **27** with zinc bromide was not successful, although hydrolysis of the MEM ether **26** gave the hydroxy ketone **29**.* Chelation of the tertiary hydroxy group in compound **27** to zinc bromide may prevent the hydrolysis. Finally, compound **27** was hydrolysed with 1% HCl in acetone to give (±)-1-*epi*-magydardienediol **4** (51% yield)* along with the methylene acetal **30** (21% yield), thus completing our formal total synthesis of (±)-magydartrienol **1**, (±)-magydartrienol acetate **2** and (±)-magydardienediol **3**.

Experimental

IR spectra were taken on a JASCO A-3 spectrophotometer for

* Although we were unable to compare directly the spectra of the diol **4** with those of authentic samples, the ^{13}C NMR data were in complete accord with those reported in ref. 5. All the ^1H NMR signals of the hydroxy ketone **29** and the diol **4** were shifted downfield by 0.08 ppm, and the IR absorptions of compound **4** were also slightly shifted from the reported values.

thin-layer films on sodium chloride plates. ^{1}H NMR spectra were recorded on a JEOL GX-270 (270 MHz) spectrometer with $CDCl_3$ as solvent (unless otherwise stated) and $SiMe_4$ as internal standard. *J*-Values are given in Hz. ^{13}C NMR spectra were recorded on the same instrument (67.8 MHz) with $CDCl_3$ as internal standard. Mass spectra were obtained by direct introduction on a JEOL DX-300 mass spectrometer using electron impact (EI) (70 eV) or chemical ionisation (CI) (reagent gas: isobutane) mode. Accurate mass measurements (EI mode) were recorded on the mass spectrometer. Precoated Merck Kieselgel 60 F_{254} was used for general analytical purposes, and silica gel (Wakogel C-300) was used for flash chromatography.

6-Hydroxymethyl-3-methylcyclohex-2-enone **7**.—To a solution of $LiNPr^i_2$, prepared from BuLi (1.2 mol dm^{-3}; 8.25 cm^3) and *N,N*-diisopropylamine (1.4 cm^3) in dry tetrahydrofuran (THF) (50 cm^3) cooled to −78 °C under nitrogen, was added a solution of 3-methylcyclohex-2-enone **6** (874 mg) in dry THF (4 cm^3) and the mixture was stirred at this temperature for 1.5 h. A nitrogen stream containing gaseous formaldehyde, obtained by thermal decomposition of paraformaldehyde (1.0 g; dried over P_2O_5 *in vacuo*) on heating at 150 °C, was introduced through a cold-trap (−50 °C) into the reaction mixture. Saturated aq. ammonium chloride (60 cm^3) was added and the mixture was extracted with diethyl ether several times. The combined extract was dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil, which was then flash chromatographed (eluent: hexane–ethyl acetate 2:1 and then 1:1) to give the hydroxy ketone **7** as a pale yellow oil (602 mg, 54%). An additional crop of compound **7** (126 mg, 11%) was obtained by continuous extraction of the aq. layer with diethyl ether, followed by flash chromatography; ν_{max}/cm^{-1} 3440 and 1660; δ_H 1.98 (3 H, s, 3-Me), 3.18 (1 H, dd, *J* 9.0 and 4.0, OH), 3.74 [2 H, m, C*H*$_2$OH; after addition of D_2O, δ 3.67 (1 H, dd, *J* 11.2 and 4.4) and 3.78 (1 H, dd, *J* 11.2 and 7.6)] and 5.88 (1 H, s, 2-H) (Found: M$^+$, 140.0854. $C_8H_{12}O_2$ requires *M*, 140.0837).

6-{[(2-Methoxyethoxy)methoxy]methyl}-3-methylcyclohex-2-enone **8**.—To a solution of the hydroxy ketone **7** (599 mg) in dry dichloromethane (15 cm^3) were added 2-methoxyethoxymethyl chloride (1.15 cm^3) and *N,N*-diisopropylethylamine (1.45 cm^3) and the mixture was stirred at room temperature for 3 h under nitrogen before being washed successively with water and saturated brine and dried over anhydrous sodium sulphate. After evaporation of the solvent, the oily residue was flash chromatographed (eluent: hexane–ethyl acetate 3:1 and then 3:2) to give compound **8** (849 mg, 87% yield) as an oil; ν_{max}/cm^{-1} 1670; δ_H 1.96 (3 H, s, 3-Me), 3.40 (3 H, s, OMe), 3.57 (2 H, m, CH_2O), 3.69 (2 H, m, CH_2O), 3.76 (1 H, dd, *J* 9.8 and 6.6, C*H*OMEM), 3.86 (1 H, dd, *J* 9.8 and 4.4, C*H*OMEM), 4.72 (2 H, s, OCH_2O) and 5.87 (1 H, s, 2-H); *m/z* 153 (14%, M$^+$ − OCH_2CH_2OMe), 123 (18, M$^+$ − $OCH_2OCH_2CH_2$-OMe) and 110 (100).

cis-*6-{[(2-Methoxyethoxy)methoxy]methyl}-3-methylcyclohex-2-enol* **9**.—To a solution of the enone **8** (214 mg) in dry THF (4 cm^3) cooled to −78 °C was added a solution of L-Selectride (1 mol dm^{-3} 1.0 cm^3) under argon and the mixture was stirred at this temperature for 25 min. Aq. sodium hydroxide (3 mol dm^{-3}; 0.4 cm^3) and 35% hydrogen peroxide (0.4 cm^3) were added. The mixture was stirred at 0 °C for 2.5 h and was then dried over anhydrous sodium sulphate. Flash chromatography of the crude product (eluent: hexane–ethyl acetate 3:1) gave the *cis*-allylic alcohol **9** (132 mg, 61%), containing *ca.* 3% of *trans*-isomer **10**, as an oil; ν_{max}/cm^{-1} 3475; δ_H 1.71 (3 H, s, 3-Me), 2.24 (1 H, d, *J* 5.6, OH), 3.40 (3 H, s, OMe), 3.54 (3 H, m, CH_2O), 3.73 (3 H, m, CH_2O), 4.20 (1 H, m, 1-H), 4.72 (2 H, s, OCH_2O) and 5.63 (1 H, d, *J* 3.6, 2-H); *m/z* 154 (2%, M$^+$ − $HOCH_2$-CH_2OMe), 106 (69), 91 (52), 89 (48) and 59 (100).

^{1}H NMR data of the *trans*-isomer **10**; δ_H 1.70 (3 H, s, 3-Me), 3.40 (3 H, s, OMe), 3.58 (3 H, m, CH_2O), 3.71 (3 H, m, CH_2O), 4.13 (1 H, d, *J* 7.7, 1-H), 4.74 (2 H, s, OCH_2O) and 5.38 (1 H, s, 2-H).

cis-3-[(1ξ)-2-Bromo-1-ethoxyethoxy]-4-{[(2-methoxyethoxy)methoxy]methyl}-1-methylcyclohexene **11**.—To a mixture of the allylic alcohol **9** (43 mg) and ethyl vinyl ether (1 cm^3) cooled to −20 °C was added NBS (46 mg) and the mixture was stirred at this temperature for 3 days under nitrogen. After evaporation, the residue was flash chromatographed (eluent: hexane–ethyl acetate 7:1 and then 2:1) to give the bromo acetal **11** (40 mg, 56%) as an oil, and the starting material (11 mg, 25% recovery).

Spectral data of the bromo acetal **11**: ν_{max}/cm^{-1} 1115, 1045 and 1025; δ_H 1.23 and 1.24 (together 3 H, each t, *J* 7.1, Me), 1.71 (3 H, s, 1-Me), 3.36 (2 H, m, CH_2Br), 3.40 (3 H, s, OMe), 3.49–3.72 (8 H, m, OCH_2), 4.07 and 4.14 (1 H, m, 1-H), 4.73 and 4.75 (2 H, s, OCH_2O), 4.82 (1 H, m, OC*H*OEt) and 5.61 (1 H, m, 2-H); *m/z* (CI mode) 277 (5%, M$^+$ − $OCH_2OCH_2CH_2OMe$), 275 (5, M$^+$ − $OCH_2OCH_2CH_2OMe$), 213 [100, M$^+$ − OCH(OEt)-CH_2Br], 183 (28), 137 (76), 109 (40), 107 (42) and 89 (29) [Found: M$^+$ − $OCH_2OCH_2CH_2OMe$, 275.0693. $C_{12}H_{20}BrO_2$ requires *m/z* (*M* − $OCH_2OCH_2CH_2OMe$) 275.0647].

Methyl (1R*,2R*,5R*,6R*)- *and* (1R*,2S*,5R*,6R*)-*3-[(8ξ)-8-Ethoxy-5-{[(2-methoxyethoxy)methoxy]methyl}-2-methyl-7-oxabicyclo[4.3.0]nonan-2-yl]propionate* **12** *and* **13**.—A mixture of the bromo acetal **11** (455 mg), $NaBH_3CN$ (558 mg), AIBN (104 mg), Bu_3SnCl (0.1 cm^3), and methyl acrylate (2.5 cm^3) in t-butyl alcohol (84 cm^3) was heated at 80 °C for 23 h under argon, and was then washed successively with 3% aq. ammonia (100 cm^3) and saturated brine (2 cm^3). The aq. layers were further washed with dichloromethane three times. The combined organic layers were dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil, which was submitted to flash chromatography (eluent: hexane–ethyl acetate 3:1) to give a mixture of compounds **12**, **13** and **14** along with compound **15** (20%). The fractions containing compounds **12**, **13** and **14** were combined and chromatographed on silica gel (eluent: hexane–ethyl acetate 7:1 and then 4:1) to give compound **14** (15%) and an inseparable mixture of compounds **12** and **13** (56%), ν_{max}/cm^{-1} 1740; δ_H 0.83, 0.91 and 0.95 (together 3 H, s, 2-Me), 1.18 and 1.19 (together 3 H, each t, *J* 7.1, Me), 3.40 (3 H, s, OMe), 3.661 and 3.666 (together 3 H, s, CO_2Me), 3.86 (t, *J ca.* 5) and 4.06 (m) (together 1 H, 6-H), 4.73 (2 H, s, OCH_2O) and 5.03 (1 H, m, 8-H); *m/z* 343 (0.4%, M$^+$ − OEt), 316 [4, M$^+$ − CH(OEt)CH_2], 240 (19, M$^+$ − CO_2Me − $CH_2OCH_2CH_2OMe$), 153 (50), 89 (79) and 59 (100).

Spectral data of compound **14**: $\delta_H(C_6D_6)$ 0.71, 0.81, 0.86 and 1.02 (each d, *J* 6.6, together Me); *m/z* 257 (2%, M$^+$ − OEt), 230 [5, M$^+$ − CH(OEt)CH_2], 213 (4, M$^+$ − CO_2Me − CH_2-OCH_2CH_2OMe) and 59 (100).

Mass spectral data of compound **15**: *m/z* 429 (0.2%, M$^+$ − OEt), 402 [0.7, M$^+$ − CH(OEt)CH_2], 153 (69), 89 (69) and 59 (100).

(1R*,2R*,5R*,6R*)- *and* (1R*,2S*,5R*,6R*)-*3-[(8ξ)-8-Ethoxy-5-{[(2-methoxyethoxy)methoxy]methyl}-2-methyl-7-oxabicyclo[4.4.0]nonan-2-yl]propiononitrile* **16** *and* **17**.—A mixture of the bromo acetal **11** (92 mg), $NaBH_3CN$ (103 mg), AIBN (27 mg), Bu_3SnCl (20 mm^3) and acrylonitrile (0.3 cm^3) in t-butyl alcohol (15 cm^3) was heated at 80 °C overnight. Work-up as described above, followed by flash chromatography (eluent: hexane–ethyl acetate 4:1), gave an inseparable mixture of compounds **16** and **17** (59 mg, 69%) as an oil; ν_{max}/cm^{-1}

2250; δ_H 0.87, 0.91 and 0.99 (together 3 H, s, 2-Me), 1.18 and 1.19 (together 3 H, each t, *J* 7.0, Me), 2.28 (2 H, t, *J* 8.0, CH_2CN), 3.40 (3 H, s, OMe), 3.4–3.75 (8 H, m, CH_2O), 4.07 (1 H, m, 6-H), 4.47 (2 H, s, OCH_2O) and 5.05 (1 H, m, 8-H).

(1R*,2R*,5R*,6R*)- *and* (1R*,2S*,5R*,6R*)-3-[(8ξ)-8-*Ethoxy*-5-{[(2-*methoxyethoxy*)*methoxy*]*methyl*}-2-*methyl*-7-*oxabicyclo*[4.3.0]*nonan*-2-yl]*propanal* **18** *and* **19**.—To a solution of the mixture of esters **12** and **13** (251 mg) in dry toluene (6 cm^3) cooled to −78 °C was added a solution of DIBAH in toluene (1.5 mol dm^{-3}; 0.5 cm^3) and the mixture was stirred at this temperature for 1.1 h. To complete the reaction an additional solution of DIBAH (0.05 cm^3) was added. After addition of few drops of methanol the mixture was diluted with diethyl ether (15 cm^3), warmed to room temperature, washed with aq. ammonium chloride and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oily residue, which was flash chromatographed (eluent: hexane–ethyl acetate 3:1) to give a mixture of the title compounds **18** and **19** (179 mg, 77%) as an oil; ν_{max}/cm^{-1} 1725; δ_H 0.83, 0.84, 0.90 and 0.96 (together 3 H, s, 2-Me), 1.18 and 1.19 (together 3 H, each t, *J* 7.1, Me), 3.40 (3 H, s, OMe), 3.42–3.79 (8 H, m, OCH_2), 3.86 and 4.07 (together 1 H, m, 6-H), 4.733 and 4.737 (together 2 H, s, OCH_2O), 5.02 (1 H, m, 8-H) and 9.78 (1 H, dd, *J* 4 and 2, CHO); *m/z* 313 (0.2%, $M^+ - OEt$), 299 (0.4, $M^+ - CH_2CH_2OMe$), 283 (0.5, $M^+ - OCH_2CH_2OMe$), 269 (0.5, $M^+ - CH_2OCH_2CH_2OMe$), 89 (63, $CH_2OCH_2CH_2OMe$) and 59 (100).

(1R*,2S*,5R*,6R*,8ξ)- *and* (1R*,2R*,5R*,6R*,8ξ)-8-*Ethoxy*-5-{[(2-*methoxyethoxy*)*methoxy*]*methyl*}-2-*methyl*-2-(4-*methylpent*-3-*enyl*)-7-*oxabicyclo*[4.3.0]*nonane* **20** *and* **21**.—To a suspension of isopropyl(triphenyl)phosphonium bromide (444 mg) in dry diethyl ether (5 cm^3) was added a solution of BuLi (1.43 mol dm^{-3}; 0.78 cm^3) under argon and the mixture was stirred for 45 min. A solution of the aldehydes **18** and **19** (135 mg) in diethyl ether (1.5 cm^3) was added and the mixture was stirred for 1 h. After dilution with diethyl ether and filtration, the solution was evaporated to give an oil, which was flash chromatographed. Elution with hexane–ethyl acetate 8:1 gave a mixture of the title compounds **20** and **21** (100 mg, 69%) as an oil; ν_{max}/cm^{-1} 1120, 1100, 1045 and 997; δ_H 0.84, 0.86 and 0.96 (together 3 H, s, 2-Me), 1.18 and 1.20 (together 3 H, each t, *J* 7.1, Me), 1.59 (3 H, s, Me), 1.67 (3 H, s, Me), 3.40 (3 H, s, OMe), 3.39–3.77 (8 H, m, OCH_2), 3.89 (t, *J ca.* 6) and 4.05 (t, *J ca.* 5) (together 1 H, 6-H), 4.73 (2 H, s, OCH_2O) and 5.05 (2 H, m, =CH and 8-H); *m/z* 369 (0.2%, $M^+ - Me$), 339 (0.2, $M^+ - OEt$), 312 [0.7, $M^+ - CH(OEt)CH_2$], 309 (0.6, $M^+ - OCH_2CH_2OMe$), 232 (24), 219 (16), 147 (45), 89 (61), 69 (67, $CH_2CH{=}CMe_2$) and 59 (100, CH_2CH_2OMe) (Found: $M^+ - OEt$, 339.2582. $C_{20}H_{35}O_4$ requires *m/z* 339.2535).

(1R*,2S*,5R*,6R*)- *and* (1R*,2S*,5R*,6R*)-5-{[(2-*Methoxyethoxy*)*methoxy*]*methyl*}-2-*methyl*-2-(4-*methylpent*-3-*enyl*)-7-*oxabicyclo*[4.3.0]*nonan*-8ξ-*ol* **22** *and* **23**.—A solution of the acetals **20** and **21** (98 mg) in 75% acetic acid (4 cm^3) was stirred at room temperature for 9 h. After neutralisation with saturated aq. sodium hydrogen carbonate the mixture was extracted with diethyl ether and the extract was dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil, which was flash chromatographed (eluent: hexane–ethyl acetate 3:1 and then 2:1) to give a mixture of hemiacetals **22** and **23** (78 mg, 86%) as an oil, along with their acetates (6 mg, 6%). Spectral data of the hemiacetals **22** and **23**: ν_{max}/cm^{-1} 3425; δ_H 0.84 and 0.86 (together 3 H, s, 2-Me), 1.59 (3 H, s, Me), 1.67 (3 H, s, Me), 3.41 (3 H, s, OMe), 3.40–3.63 (4 H, m, CH_2O), 3.89 (1 H, t, *J* 8, OCH), 3.93 (1 H, m, OCH), 4.25 (1 H, t, *J* 4, 6-H), 4.71 (2 H, s, OCH_2O), 5.08 (1 H, t, *J* 7.3, =CH) and 5.46 (1 H, t, *J* 4.6, 8-H); *m/z* 318 (0.2%, M^+), 262 (0.3), 109 (38), 89 (47), 81 (23), 67 (26) and 59 (100).

(1R*,2R*,3S*,6R*)- *and* (1R*,2R*,3R*,6R*)-6-{[(2-*Methoxyethoxy*)*methoxy*]*methyl*}-3-*methyl*-2-(3-*methylbut*-2-*enyl*)-3-(4-*methylpent*-3-*enyl*)*cyclohexanol* **24** *and* **25**.—To a suspension of isopropyl(triphenyl)phosphonium bromide (316 mg) in dry diethyl ether (5 cm^3) was added a solution of BuLi (1.43 mol dm^{-3}; 0.55 cm^3) at room temperature under argon. The mixture was stirred for 30 min. A mixture of the hemiacetals **22** and **23** (60 mg) in diethyl ether (1 cm^3) was added and the reaction mixture was stirred at room temperature for 1 h. Work-up as described above gave a crude, oily product, which was flash chromatographed (eluent: benzene–ethyl acetate 10:1) to give the diene **24** (32 mg, 50%) as an oil, and the diene **25** (2.5 mg) as an oil, along with a mixture of dienes **24** and **25** (72% total yield).

Spectral data of the diene **24**: ν_{max}/cm^{-1} 3520; δ_H 0.99 (3 H, s, 3-Me), 1.13 (1 H, dt, *J* 11 and 3, 2-H), 1.59 (3 H, s, Me), 1.65 (3 H, s, Me), 1.68 (3 H, s, Me), 1.69 (3 H, s, Me), 3.39 (3 H, s, OMe), 3.50–3.75 (6 H, m, OCH_2), 3.97 (1 H, br s, 1-H), 4.69 (2 H, s, OCH_2O), 5.09 (1 H, m, =CH) and 5.13 (1 H, m, =CH) [assignment based on a two-dimensional ^1H–^1H correlation (COSY) spectrum]; $\delta_H(C_5D_5N)$ 1.31 (3 H, s, 3-Me), 1.66 (9 H, s, Me), 1.72 (3 H, s, Me), 3.29 (3 H, s, OMe), 3.55 (2 H, m, OCH_2), 3.62 (2 H, m, OCH_2), 3.77 (2 H, m, OCH_2), 3.92 (2 H, m, OCH_2), 4.36 (1 H, m, 1-H), 4.778 (1 H, d, *J* 6.8, OCHO), 4.782 (1 H, d, *J* 6.8, OCHO), 5.25 (1 H, m, =CH) and 5.37 (1 H, m, =CH); δ_C 17.52, 17.77, 19.93, 21.47, 21.85, 23.97, 25.67, 25.87, 35.68, 37.46, 42.84, 43.18, 47.82, 58.96, 66.94, 68.35, 70.78, 71.83, 95.55, 124.04, 125.23, 130.85 and 132.02; *m/z* 382 (0.1%, M^+), 364 (0.1, $M^+ - H_2O$), 223 (44), 110 (23), 95 (22), 89 (37), 81 (21), 69 (100) and 59 (93).

Spectral data of the *diene* **25**: ν_{max}/cm^{-1} 3520; δ_H 0.92 (3 H, s, Me), 1.59 (3 H, s, Me), 1.64 (3 H, s, Me), 1.67 (3 H, s, Me), 1.69 (3 H, s, Me), 3.39 (3 H, s, OMe), 3.53–3.72 (6 H, m, OCH_2), 3.94 (1 H, br s, 1-H), 4.69 (1 H, d, *J* 6.8, OCHO), 4.70 (1 H, d, *J* 6.8, OCHO) and 5.12 (2 H, m, =CH); δ_C 17.55, 17.75, 19.98, 22.72, 24.00, 25.70, 25.82, 27.74, 32.77, 36.08, 36.77, 43.24, 52.85, 59.00, 67.02, 68.30, 70.83, 71.87, 95.66, 124.39, 125.90, 130.48 and 132.08; *m/z* 382 (0.1%, M^+), 364 (0.2, $M^+ - H_2O$), 223 (40), 206 (19), 107 (23), 95 (25), 89 (36), 81 (23), 69 (100) and 59 (82) (Found: M^+, 382.3081. $C_{23}H_{42}O_4$ requires *M*, 382.3083).

(2R*,3S*,6R*)-6-{[(2-*Methoxyethoxy*)*methoxy*]*methyl*}-3-*methyl*-2-(3-*methylbut*-2-*enyl*)-3-(4-*methylpent*-3-*enyl*)*cyclohexanone* **26**.—To a mixture of chromium(VI) oxide (83 mg) and pyridine (0.15 cm^3) in dichloromethane (1 cm^3) was added a solution of the alcohol **24** (33 mg) in dichloromethane (1.5 cm^3) and the mixture was stirred at room temperature for 1 h. The mixture was loaded on a silica gel column and eluted with diethyl ether. Flash chromatography of the crude product (eluent: hexane–ethyl acetate 5:1) gave the *ketone* **26** (32 mg, 96%) as an oil; ν_{max}/cm^{-1} 1708; δ_H 0.71 (3 H, s, Me), 1.58 (3 H, s, Me), 1.62 (3 H, s, Me), 1.63 (3 H, s, Me), 1.69 (3 H, s, Me), 3.40 (3 H, s, OMe), 3.46 (1 H, dd, *J* 10.0 and 6.7, OCH), 3.57 (1 H, m, OCH_2), 3.69 (2 H, m, OCH_2), 3.89 (1 H, dd, *J* 10.0 and 5.6, OCH), 4.71 (1 H, d, *J* 6.7, OCHO), 4.73 (1 H, d, *J* 6.7, OCHO), 5.00 (1 H, m, =CH) and 5.09 (1 H, m, =CH); *m/z* 380 (0.3%, M^+), 365 (0.2, $M^+ - Me$), 123 (21), 109 (49), 95 (32), 89 (26), 81 (28) and 69 (100) (Found: M^+, 380.2873. $C_{23}H_{40}O_4$ requires *M*, 380.2927).

(1R*,2R*,3S*,6R*)-6-{[(2-*Methoxyethoxy*)*methoxy*]*methyl*}-1,3-*dimethyl*-2-(3-*methylbut*-2-*enyl*)-3-(4-*methylpent*-3-*enyl*)*cyclohexanol* **27**.—To a solution of the ketone **26** (7.8 mg) in dry diethyl ether (1 cm^3) cooled to 0 °C was added a solution of MeLi (1 mol dm^{-3}; 0.35 cm^3) in diethyl ether and the mixture was stirred at 0 °C for 2 h. Aq. ammonium chloride was added and the mixture was extracted with diethyl ether. The extract was washed successively with water and aq. sodium hydrogen

carbonate and dried over anhydrous sodium sulphate. The crude, oily product was flash chromatographed (eluent: hexane–ethyl acetate 8:1) to give the tertiary alcohol **27** (5.8 mg, 71%); ν_{max}/cm^{-1} 3540; δ_H 1.02 (3 H, s, 3-Me), 1.17 (3 H, s, 1-Me), 1.58 (3 H, s, Me), 1.64 (3 H, s, Me), 1.67 (6 H, s, Me), 2.76 (1 H, br s, OH), 3.40 (3 H, s, OMe), 3.56 (2 H, m, OCH_2), 3.62 (1 H, dd, *J* 9.8 and 2.4, OCH), 3.70 (2 H, m, OCH_2), 3.99 (1 H, dd, *J* 9.8 and 3.9, OCH), 4.69 (1 H, d, *J* 6.7, OCHO) and 4.71 (1 H, d, *J* 6.7, OCHO); *m/z* 378 (1%, $M^+ - H_2O$), 109 (23), 89 (49), 81 (23) and 69 (100) (Found: $M^+ - H_2O$, 378.3137. $C_{24}H_{42}O_3$ requires *m/z* 378.3134).

(±)-1-epi-*Magydardienediol* **4**.—The alcohol **27** (8.5 mg) was dissolved in 1% hydrochloric acid in acetone (2 cm^3) and the mixture was stirred at room temperature for 24 h. Aq. sodium hydrogen carbonate was added and then the mixture was extracted with diethyl ether. The extract was dried over anhydrous sodium sulphate and the crude product was flash chromatographed (eluent: hexane–ethyl acetate 5:1) to give the methylene acetal **30** (1.5 mg, 21%) and 1-*epi*-magydardienediol **4** (3.4 mg, 51%); ν_{max}/cm^{-1} 3375, 1135, 1105, 1085 and 1045; δ_H 1.01 (3 H, s, 3-Me), 1.28 (3 H, s, 1-Me), 1.59 (3 H, s, Me), 1.64 (3 H, s, Me), 1.67 (6 H, s, Me), 2.62 (1 H, br s, OH), 3.62 (1 H, dd, *J* 2.7 and 11.0, C*H*OH), 4.21 (1 H, dd, *J* 2.9 and 11.0, C*H*OH) and 5.08 (2 H, m, =CH); *m/z* 308 (0.3%, M^+), 290 (5, $M^+ - H_2O$), 275 (0.9, $M^+ - H_2O - Me$), 272 (0.8, $M^+ - 2H_2O$) and 69 (100) (Found: $M^+ - H_2O$, 290.2654. $C_{20}H_{34}O$ requires *m/z* 290.2610).

Spectral data of *compound* **30**: δ_H 1.03 (3 H, s, 3-Me), 1.34 (3 H, s, 1-Me), 1.59 (3 H, s, Me), 1.62 (3 H, s, Me), 1.66 (3 H, d, *J* 1, Me), 1.67 (3 H, d, *J* 1, Me), 3.56 (1 H, d, *J* 11.4, CHO), 4.16 (1 H, dd, *J* 11.4 and 2.7, CHO), 4.83 (1 H, d, *J* 6.5, OCHO), 4.94 (1 H, d, *J* 6.5, OCHO) and 5.10 (2 H, m, =CH); *m/z* 320 (7%, M^+) and 69 (100) (Found: M^+, 320.2684. $C_{21}H_{36}O_2$ requires *M*, 320.2715).

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