Synthesis of (3S*,4R*,6E,10Z)-3,4,7,11-tetramethyltrideca-6,10-dienal (faranal) using stereospecific 1,4-cis-hydrogenation of conjugated double bonds

Andrei A. Vasil'ev,[a] Lars Engman[b] and Edward P. Serebryakov *[a]

[a] N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
117913 Moscow, Russia
[b] Institute of Chemistry, Department of Organic Chemistry, Uppsala University,
Box 531, 751 21 Uppsala, Sweden

(±)-Faranal was synthesised by a convergent route involving 1,4-cis-hydrogenation of two properly substituted conjugated diene building blocks to introduce stereospecifically the 6(E) and 10(Z) double bonds of the final target molecule. meso-2,3-Dimethylsuccinic acid was used to prepare a building block for the 'right-hand' part of faranal carrying two vicinal erythro-configured methyl groups.

The tiny Pharaoh's ant, *Monomorium pharaonis* L., can be a vector of salmonellosis or post-operational microbial infections in hospitals. Its trail pheromone, faranal [(3S,4R,6E,10Z)-3,4,7,11-tetramethyltrideca-6,10-dienal] **1**,[1] could be a good tool to control this insect. Faranal contains two trisubstituted double bonds and a chiral vicinal *erythro* dimethyl structural motif. Since the 3R,4S-antipode of natural faranal does not inhibit the biological effect of **1**,[2] both the natural (3S,4R) and the racemic forms of the *erythro*-configured 'right-hand' building block have been used in the syntheses of this semiochemical.
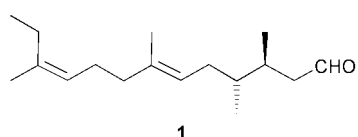
Natural: (+)-(3S,4R)
Synthetic (this work): (±)-(3S*,4R*)

To create the (10Z) double bond, the addition of organo-copper reagents to terminal acetylenes,[3,4] the use of (Z)-1-bromo-3-methylpent-2-ene as a building block[5] and a five-step protocol of geraniol homologation involving stereospecific epoxidation of an intermediate allylic alcohol[6] were explored. For construction of the (6E) double bond the same organo-copper approach[4] and the Horner–Emmons–Wadsworth (HEW) olefination[5] were employed, as well as a protocol using geraniol as a starting material.[6] To provide for the *erythro* arrangement of the two vicinal methyls, the use of suitably functionalised building blocks (all derived from *cis*-1,2,3,6-tetrahydrophthalic anhydride),[3–5,7] substituent-directed *anti*-alkylation of a 3-methylpentan-5-olide carbanion,[6] *erythro* addition of an alkenylmanganese chloride to methyl crotonate,[8] 1,2-*syn*-hydrogenation of a Z-tetrasubstituted olefin,[9] as well as biocatalytic reduction of the corresponding α,β-enal[2] were reported.

In comparison with the efforts spent on creating the right configuration at stereogenic atoms C(3) and C(4),[5–10] little attention had been paid in recent years to rational ways of securing the right configuration of the double bonds of faranal. In earlier syntheses of **1** the E/Z ratio for the Δ[6] bond varied

from 46:54 to 85:15 for Wittig olefination[3,5] to practically 100:0 for using Normant's organocuprate addition to an alkyne[4] or for using geraniol as a starting material.[6] In the latter work the formation of the Z-configured Δ[10] bond of **1** was implemented in five steps to result in a Z:E ratio of 92:8.[6]

Here we report a novel synthesis of racemic (3S*,4R*)-faranal where 1,4-cis-hydrogenation of conjugated dienes over (η[6]-arene)chromium tricarbonyl complexes is used (for a review, see ref. 11) for stereospecific construction of both trisubstituted double bonds in compound **1**. Recent success in stereospecific synthesis of insect pheromones based on this reaction[12,13] prompted us to develop a synthetic protocol for faranal.

Retrosynthetic analysis of faranal (Scheme 1) suggested the conjugated diene **2** as a crucial intermediate. Compound **2**, in turn, could be prepared by olefination of the properly substituted acrolein **3**. For the olefination, we reasoned, organoselenium chemistry[14–16] would be superior to conventional Wittig-type methodology which is often substrate-dependent. The Z-configured double bond in aldehyde **3** could be formed *via* 1,4-cis-hydrogenation of the dienoic ester **4**, which in turn is readily available from tiglic aldehyde **5**.[17] Selenoacetal **6** with an *erythro*-configured CHMe-CHMe fragment, we envisaged, could be prepared from commercially available *meso*-2,3-dimethylsuccinic acid **7** (the corresponding diol **14** was earlier used in the synthesis of lasiol,[18] which contains the same structural motif).
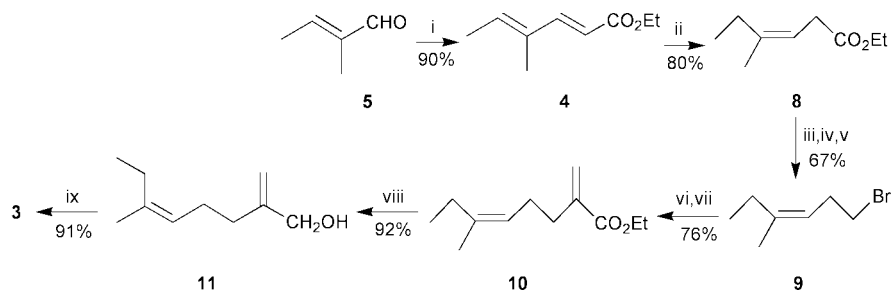
Results and discussion

Tiglic aldehyde **5** proved to be a good starting material for the preparation of the 'left-hand' part of faranal (Scheme 2). Its reaction with triethyl phosphonoacetate (TEPA) promoted by NaH[17a] afforded dienoic ester **4** in 90% yield (the use of aqueous K₂CO₃[19] gave only a 57% yield). 1,4-cis-Hydrogenation of diene **4** was performed at 70–75 °C and 50 atm H₂, employing (η[6]-naphthalene)chromium tricarbonyl as the catalyst. Ethyl (Z)-4-methylhex-3-enoate **8** thus formed (diagnostic 4-Me signal at δ 22.8 in the ¹³C NMR) furnished, upon LiAlH₄ reduction, (Z)-4-methylhex-3-en-1-ol, which was transformed into bromide **9** (67% yield based on ester **8**). Previous stereoselective syntheses of (Z)-4-methylhex-3-en-1-ol were either tedious and difficult to scale up[4,20a–c] or did not proceed cleanly enough for our purposes.[20d–g]

DOI: 10.1039/b002343o

J. Chem. Soc., Perkin Trans. 1, 2000, 2211–2216   **2211**

Scheme 1
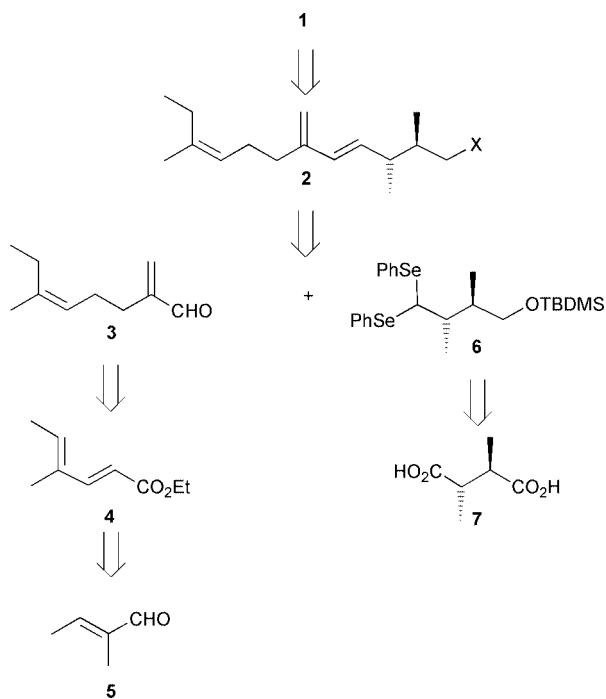
Further transformation of bromide **9** into acrolein **3** *via* acrylate **10** involved C-alkylation with TEPA followed by HEW olefination with formaldehyde. Previous procedures employing K$_2$CO$_3$[21] or EtONa in EtOH[22] proved to be inefficient for the preparation of the alkylated phosphonate **12**. Similarly,
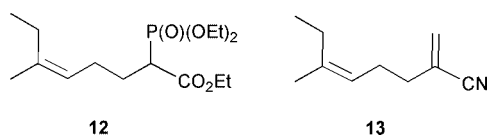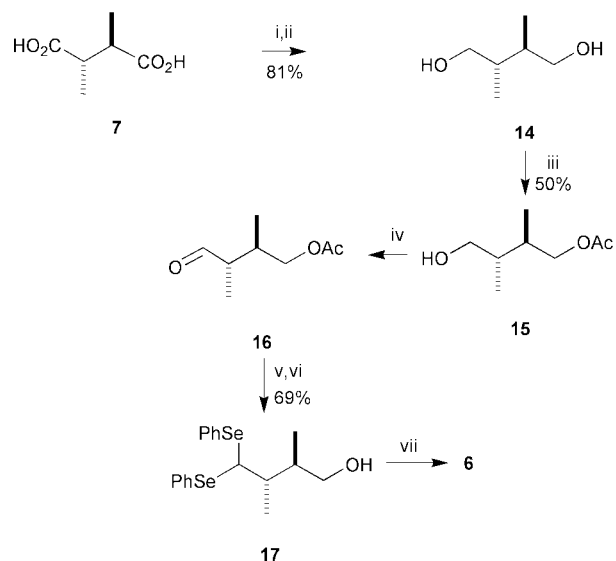

LDA in THF (although causing complete deprotonation of the starting phosphonate), did not lead to alkylation, probably because THF is not the optimal solvent for nucleophilic substitution. By contrast, polar solvents such as DMSO or DMF accelerated the alkylation of TEPA with bromide **9**. In the most convenient procedure, NaH in DMSO was used as a base, and the *in situ*-produced phosphonate **12** was treated with K$_2$CO$_3$ and aq. formaldehyde to afford the acrylate **10** in 76% yield. The most high-yielding transformation of ester **10** into aldehyde **3** involved DIBAL-H reduction (to give alcohol **11**) followed by Swern oxidation (85% yield over two steps). Low-temperature DIBAL-H reduction of ester **10** to aldehyde **3** was unselective. As an alternative, nitrile **13** was prepared in a good yield from bromide **9** analogously to the preparation of ester **10**. However, DIBAL-H reduction of **13** gave aldehyde **3** in only 40% yield. The overall yield of aldehyde **3** from **5** was 30.7%.
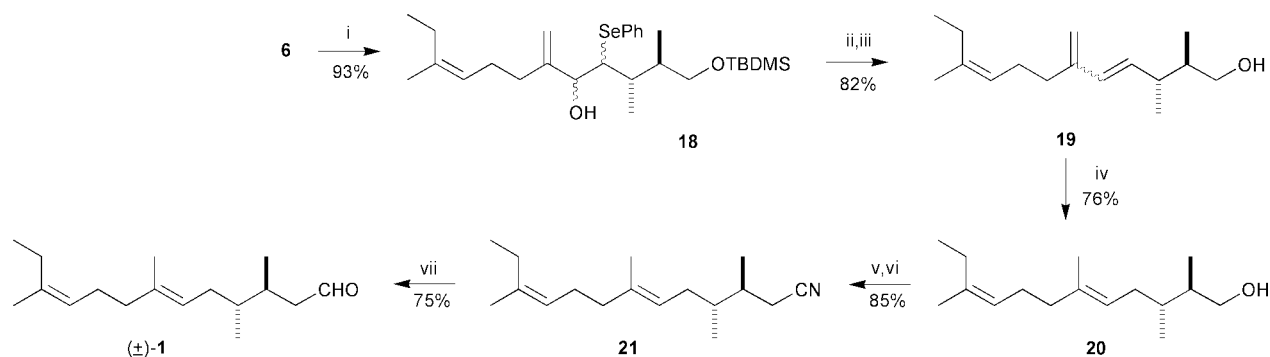
meso-2,3-Dimethylsuccinic acid **7** served as the starting material for the preparation of the 'right-hand' part of faranal (Scheme 3). Esterification of **7** followed by LiAlH$_4$ reduction in

Scheme 3 *Reagents and conditions*: i, EtOH, benzene, TsOH; ii, LiAlH$_4$, THF; iii, Ac$_2$O (1 equiv.), AcOH, 20 °C, 12 h; iv, (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −50 °C; then DIPEA; v, PhSeH, ZnCl$_2$, CCl$_4$, 0–20 °C; vi, MeOH, K$_2$CO$_3$; vii, TBDMSCl, imidazole, DMF.

THF afforded *meso*-2,3-dimethylbutane-1,4-diol **14** in 81% yield (56% in diethyl ether[23]). The diol **14** was treated with Ac$_2$O (1 equiv.) to give monoacetate **15** in 50% yield along with the corresponding diacetate (16%) and recovered diol (26%). Alcohol **15** was subjected to Swern oxidation using diisopropylethylamine (DIPEA) instead of triethylamine to minimise the risk of racemisation of the resulting aldehyde.[24] The crude aldehyde **16** was converted into a selenoacetal using PhSeH in the presence of ZnCl$_2$.[14a] The acyl group was replaced by *tert*-butyldimethylsilyl (TBDMS) *via* transesterification and silylation of alcohol **17**. The total yield of the TBDMS-protected selenoacetal **6** was 27.9% over seven steps (or 45.7% taking the recovery of diol **14** and its diacetate into account).

The coupling of the 'left-hand' and 'right-hand' building blocks of (±)-faranal is shown in Scheme 4. Lithium–selenium exchange in selenoacetal **6** promoted by *n*-BuLi gave a selenium-stabilised carbanion[14b] which on treatment with aldehyde **3** afforded the β-phenylseleno alcohol **18** as a mixture of four diastereomers. Elimination of the vicinal phenylseleno and hydroxy substituents occurred on treatment with methanesulfonyl chloride and triethylamine.[15] After removal of the TBDMS group, the conjugated diene was isolated as a 3:2 mixture of (4*E*)- and (4*Z*)-isomer. 1,4-*cis*-Hydrogenation of conjugated dienes with this substitution pattern has previously[13a,b,25] been shown to cleanly afford *E*-trisubstituted alkenes. In fact, hydrogenation of **19** over (η^6-naphthalene)-chromium tricarbonyl led to the known Mori intermediate

Scheme 2 *Reagents and conditions*: i, NaH, (EtO)$_2$P(O)CH$_2$CO$_2$Et, benzene; ii, H$_2$ (50 atm), (naphthalene)Cr(CO)$_3$, THF, 70 °C, 4 h; iii, LiAlH$_4$; iv, TsCl, Py; v, NaBr, DMF, 50 °C, 4 h; vi, NaH, (EtO)$_2$P(O)CH$_2$CO$_2$Et, DMSO, 50 °C, 6 h; vii, CH$_2$O, K$_2$CO$_3$; viii, DIBAL-H, (2 equiv.), −30 °C; ix, (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −50 °C; then Et$_3$N.

Scheme 4 *Reagents and conditions*: i, BuLi, THF, −78 °C; then **3**; ii, MsCl, Et₃N, CH₂Cl₂, 3 h; iii, Bu₄NF, THF; iv, H₂ (50 atm), (naphthalene)Cr(CO)₃, THF, 50 °C, 3 h; v, TsCl, Py, CH₂Cl₂; vi, NaCN, DMSO, 50 °C, 3 h; vii, DIBAL-H, toluene, −15 °C

20[5] as the sole product. The (9Z)-olefinic bond remained unaffected in this reaction. Conversion of alcohol **20** into homologous nitrile **21** was performed according to the method of Mori and Ueda.[5] Simple DIBAL-H reduction of nitrile **21** in toluene at −78 °C produced (±)-faranal **1** with a better than 94.5% isomeric purity (GLC using a capillary column) in better yield (75%) than the saponification–reduction–PCC oxidation sequence previously used.[5]

In summary, we have demonstrated that 1,4-*cis*-hydrogenation of conjugated dienes over (η⁶-arene)tricarbonylchromium catalysts is an efficient reaction for the stereospecific construction of both the 6*E*- and 10*Z*-trisubstituted double bonds of faranal. The corresponding conjugated diene precursors were readily accessible by the HEW and Krief reactions. Provided the non-racemic *erythro*-building block is used, the scheme developed is applicable to the preparation of optically active faranal. The yield of (±)-faranal **1** from tiglic aldehyde **5** is 14.9% over fifteen steps (or 10.0% from the *meso* acid **7** over fourteen steps, unoptimised).

Experimental

NMR spectra were recorded in CDCl₃ at 399.95 MHz (¹H), 100.57 MHz (¹³C) and 57.21 MHz (⁷⁷Se). Multiplicities of signals in the ¹H NMR spectra are given as observed. ⁷⁷Se Chemical shifts are given in ppm relative to neat Me₂Se. Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany. (η⁶-Naphthalene)tricarbonylchromium[26] and benzeneselenol[27] were prepared according to the literature. Tiglic aldehyde **5** and TEPA (Lancaster) and *meso*-2,3-dimethylsuccinic acid **7** (Aldrich) were used as purchased. Column chromatography was performed using silica gel MATREX LC 60A/35-70 MY 80/25 85040 (GRACE Davison) and mixtures of pentane and ethyl acetate as eluent (both freshly distilled).

Ethyl (E,E)-4-methylhexa-2,4-dienoate 4

This product, bp 110 °C (15 mmHg), was prepared as described.[17a] ¹H NMR data were in a good agreement with the literature;[17b] δ_C 11.7 q, 14.3 q, 14.5 q, 60.1 t, 115.2 d, 133.7 s, 136.2 t, 149.4 t, 167.6 s.

Ethyl (Z)-4-methylhex-3-enoate 8

A solution of diene ester **4** (8.85 g) and (η⁶-naphthalene)chromium tricarbonyl (0.75 g) in absolute THF (35 mL) was placed in a stainless steel autoclave under an atmosphere of argon. The vessel was sealed and filled/evacuated three times with H₂ (at 10 atm) to remove traces of O₂. The hydrogen pressure was adjusted to 50 atm, and hydrogenation was carried out at 70–75 °C for 4 h. After decompression, the autoclave was rinsed with diethyl ether, and the resulting solution concentrated under reduced pressure. After dissolution in pentane, filtration through Celite and concentration under reduced pressure, final distillation *in vacuo* afforded 7.20 g (80%) of the title compound **8** as a colourless liquid, bp 80 °C

(15 mmHg); δ_H 0.97 (t, *J* 7.6 Hz, 3H), 1.25 (t, *J* 7.1 Hz, 3H), 1.72 (q, *J* 1.2 Hz, 3H), 2.03 (q, *J* 7.2 Hz, 2H), 3.02 (d, *J* 7.2 Hz, 2H), 4.12 (q, *J* 7.1 Hz, 2H), 5.27 (br t, *J* 7.2 Hz, 1H); δ_C 12.5 q, 14.2 q, 22.8 q, 25.0 t, 33.4 t, 60.5 t, 115.3 d, 141.0 s, 172.5 s.

(Z)-1-Bromo-4-methylhex-3-ene 9

Ethyl (Z)-4-methylhex-3-enoate **8** (7.20 g, 46.1 mmol) was reduced with LiAlH₄ (1.226 g, 32.3 mmol) in diethyl ether (30 mL). After conventional work-up the crude (Z)-4-methylhex-3-en-1-ol thus obtained was treated with TsCl (9.668 g, 51 mmol) in CH₂Cl₂ (30 mL) in the presence of pyridine (5.46 g, 69.2 mmol) at 0 °C for 15 h. Methanol (2 mL) was added to quench excess of TsCl, the mixture was poured into ice-cold water and extracted with diethyl ether. The combined extracts were consecutively washed with 5% HCl, brine, NaHCO₃ (aq.) and again with brine, dried (MgSO₄), and concentrated *in vacuo*. The crude tosyl ester was vigorously stirred with NaBr (30 g) in DMF (60 mL) at 50 °C for 4 h. The mixture was diluted with water, extracted with pentane, and the combined extracts were washed with brine and dried (CaCl₂). The solvents were distilled off at normal pressure through a 30 cm Vigreux column. Distillation of the residue afforded 5.45 g (67% from compound **8**) of the title bromide **9**, bp 100–103 °C (100 mmHg). ¹H NMR data were in close agreement with the literature;[20b] δ_C 12.8 q, 22.9 q, 24.9 t, 31.4 t, 33.0 t, 120.5 d, 140.7 s.

Ethyl (Z)-6-methyl-2-methyleneoct-5-enoate 10

Sodium hydride (0.480 g of a 60% dispersion in mineral oil, 12 mmol) was washed four times with pentane, and DMSO (15 mL) was added. TEPA (2.69 g, 12 mmol) was then added dropwise under nitrogen with stirring until the evolution of hydrogen ceased. (Z)-1-Bromo-4-methylhex-3-ene **9** (1.779 g, 10 mmol) was added in one portion and the mixture was stirred at 50 °C for 6 h. After cooling of the mixture to r.t., K₂CO₃ (4.14 g, 30 mmol) was added followed by formaldehyde (4 mL; 37% aq.), and the mixture was stirred for 3 h at ambient temperature and then for another 3 h at 60 °C. The mixture was diluted with water (40 mL) and extracted with diethyl ether. The combined extracts were washed with brine, dried (CaCl₂), and concentrated *in vacuo*. Column chromatography (50 mL silica; 1–3% EtOAc in pentane) afforded 1.483 g (76%) of the title ester **10** as a colourless oil, δ_H 0.96 (t, *J* 7.5 Hz, 3H), 1.30 (t, *J* 7.2 Hz, 3H), 1.67 (q, *J* 1.2 Hz, 3H), 2.01 (q, *J* 7.6 Hz, 2H), 2.16 (q, *J* 7.8 Hz, 2H), 2.32 (t, *J* 7.8 Hz, 2H), 4.21 (q, *J* 7.2 Hz, 2H), 5.08 (br t, *J* 7.1 Hz, 1H), 5.51 (br s, 1H), 6.14 (br s, 1H); δ_C 12.8 q, 14.2 q, 22.8 q, 24.7 t, 26.6 t, 32.4 t, 60.5 t, 123.0 d, 124.6 t, 138.0 s, 140.6 s, 167.3 s. (Calc. for C₁₂H₂₀O₂: C, 73.43; H, 10.27. Found: C, 73.26; H, 10.35%).

(Z)-6-Methyl-2-methyleneoct-5-en-1-ol 11

To a stirred solution of ethyl (Z)-6-methyl-2-methyleneoct-5-enoate **10** (1.15 g, 5.86 mmol) in pentane (20 mL) was added a

solution of DIBAL-H in toluene (1.5 M solution; 8.5 mL, 12.75 mmol) at $-30\,^\circ$C and the mixture was kept at this temperature for 3 h. The temperature was then allowed to raise to $0\,^\circ$C and methanol (1 mL) and water (10 mL) were added. Cold 5% HCl was added to dissolve the solid formed. After diethyl ether extractions, washings of the extract with aq. $NaHCO_3$, drying ($MgSO_4$), concentration *in vacuo* and column chromatography (50 mL silica; 5, 10 and 15% EtOAc in pentane), 0.836 g (92%) of the title alcohol **11** was isolated as a colourless oil, δ_H 0.97 (t, J 7.6 Hz, 3H), 1.49 (br s, 1H), 1.68 (q, J 1.3 Hz, 3H), 2.03 (q, J 7.6 Hz, 2H), 2.08–2.15 (several peaks, 4H), 4.08 (s, 2H), 4.98 (s, 1H), 5.03 (s, 1H), 5.09 (br t, J 6.8 Hz, 1H); δ_C 12.8 q, 22.8 q, 24.8 t, 26.0 t, 33.3 t, 66.0 t, 109.3 t, 123.4 d, 137.7 s, 148.9 s. (Calc. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.70; H, 11.69%).

(Z)-6-Methyl-2-methyleneoct-5-enonitrile 13

A mixture of (diethylphosphono)acetonitrile (2.12 g, 12 mmol), bromide **9** (1.779 g, 10 mmol), K_2CO_3 (6.62 g, 48 mmol) and DMSO (15 mL) was stirred at ambient temperature overnight and then treated with formaldehyde (4 mL; 37% aq.). After additional stirring for 1 h, the mixture was diluted with water and extracted with diethyl ether. Drying ($MgSO_4$), concentration *in vacuo* and column chromatography (70 mL silica; 1–5% EtOAc in pentane) afforded 1.081 g (72%) of nitrile **13** as a colourless oil, δ_H 0.97 (t, J 7.5 Hz. 3H), 1.68 (s, 3H), 2.03 (q, J 7.5 Hz, 2H), 2.26 (br s, 4H), 5.01 (br t, J 7.0 Hz, 1H), 5.70 (s, 1H), 5.83 (s, 1H); δ_C 12.8 q, 22.8 q, 24.8 t, 25.7 t, 35.0 t, 118.7 s, 121.1 d, 122.9 s, 130.4 t, 139.4 s. (Calc. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.20; H, 10.23%).

(Z)-6-Methyl-2-methyleneoct-5-enal 3

(**a**) Standard Swern oxidation[28] of alcohol **11**, followed by column chromatography (1–2% EtOAc in pentane), afforded 91% of the title compound **3**.

(**b**) DIBAL-H reduction of nitrile **13** followed by usual work-up and column chromatography afforded 40% of the title compound **3**, δ_H 0.94 (t, J 7.8 Hz, 3H), 1.66 (q, J 1.3 Hz, 3H), 1.99 (q, J 7.8 Hz, 2H), 2.14 (q, J 8.0 Hz, 2H), 2.27 (t, J 7.0 Hz, 2H), 5.04 (br t, J 7.0 Hz, 1H), 5.99 (s, 1H), 6.24 (s, 1H), 9.53 (s, 1H); δ_C 12.8 q, 22.8 q, 24.7 t, 25.8 t, 28.2 t, 122.8 d, 134.2 t, 138.2 s, 149.8 s, 194.7 d.

erythro-4-Acetoxy-2,3-dimethylbutan-1-ol 15

A mixture of *meso*-2,3-dimethylsuccinic acid **7** (3.0 g, 20.5 mmol), ethanol (7 mL), benzene (18 mL) and toluene-*p*-sulfonic acid (0.05 g) was refluxed for 12 h using a Dean–Stark trap. By this time the white solid in the reaction flask had disappeared. The reaction mixture was concentrated *in vacuo*, dissolved in absolute THF (10 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (1.1 g, 28 mmol) in THF (40 mL). When the exothermic reaction was over, the mixture was stirred for an additional 2 h, cooled to $0\,^\circ$C and quenched by a slow addition of a solid mixture of finely powdered $Na_2SO_4 \cdot 10H_2O$ (6 g) and an equal volume of Celite. Water (4 mL) was then added, and after the grey colour of the solid phase had turned white, the reaction mixture was filtered through Celite, and the filter cake was rinsed with diethyl ether. Concentration of the filtrate, followed by pumping (6 h at 1 mmHg), afforded practically pure *meso*-2,3-dimethylbutane-1,4-diol **14** (2.658 g, 81%) as a colourless, viscous syrup [δ_H 0.89 (d, J 7.0 Hz, 6H), 1.81 (m, 2H), 3.50 (dd, J 10.9, 4.1 Hz, 2H), 3.55 (dd, J 10.9, 6.8 Hz, 2H), 3.64 (br s, 2H); δ_C 13.4 q, 38.7 d, 65.4 t].

The diol thus obtained was acetylated with Ac_2O (2.0 g) in AcOH (10 mL) during overnight stirring at r.t. The mixture was concentrated *in vacuo*, neutralised with $NaHCO_3$ (aq., followed by portions of the solid), and extracted with diethyl ether. The extracts were dried ($MgSO_4$) and subjected to column chromatography on 100 mL of silica. Elution with 15% EtOAc in

pentane afforded 0.646 g (16%) of *erythro*-2,3-dimethylbutane-1,4-diyl diacetate.

Continued elution with 30–40% EtOAc in pentane gave 1.642 g (50%) of the title monoacetate **15**, δ_H 0.92 (d, J 6.9 Hz, 3H), 0.96 (d, J 7.0 Hz, 3H), 1.70 (m, 1H), 1.75 (br s, 1H), 1.91 (m, 1H), 2.04 (s, 3H), 3.50 (dd, J 10.8, 6.5 Hz, 1H), 3.62 (dd, J 10.8, 6.2 Hz, 1H), 3.89 (dd, J 10.9, 7.2 Hz, 1H), 4.12 (dd, J 10.9, 5.6 Hz, 1H); δ_C 13.5 q, 14.7 q, 21.0 q, 34.2 d, 38.0 d, 65.8 t, 67.3 t, 171.3 s.

Finally, elution with 80% EtOAc in pentane gave 0.637 g (26%) of recovered diol **14**.

erythro-2,3-Dimethyl-4,4-bis(phenylseleno)butan-1-ol 17

A solution of oxalyl dichloride (1.485 g, 11.8 mmol), CH_2Cl_2 (34 mL) and DMSO (1.7 mL) was stirred at $-50\,^\circ$C for 5 min. To this solution was added acetoxy alcohol **15** (1.642 g, 10.2 mmol). Then, after 15 min, DIPEA (9.0 mL) was added dropwise and the mixture was allowed to warm to r.t. After aqueous work-up and ethereal extraction, the organic phase was washed successively with 5% HCl and brine, dried ($CaCl_2$) and concentrated *in vacuo*. The crude aldehyde **16** thus obtained was mixed under argon with benzeneselenol (3.365 g, 21.4 mmol) and CCl_4 (3 mL), and this solution was added dropwise at $0\,^\circ$C under argon to a vigorously stirred suspension of anhydrous $ZnCl_2$ (0.695 g, 5.1 mmol) in CCl_4 (2 mL). After 2 h of stirring at r.t., the mixture was diluted with diethyl ether (20 mL). The organic phase was washed with HCl (5% aq.) and several times with $NaHCO_3$ (aq.) until the aqueous washings remained clear. The organic phase was dried ($CaCl_2$), and concentrated *in vacuo*. The residue was stirred overnight in methanol (20 mL) in the presence of K_2CO_3 (0.05 g). The solvent was removed *in vacuo* and the residue subjected to column chromatography (100 mL silica; 5–20% gradient EtOAc in pentane) to afford 2.923 g (69%) of seleno alcohol **17** as a colourless, viscous oil, δ_H 0.89 (d, J 6.3 Hz, 3H), 1.22 (d, J 6.3 Hz, 3H), 1.87 (m, 2H), 3.49 (dd, J 10.7, 5.4 Hz, 1H), 3.66 (dd, J 10.7, 3.7 Hz, 1H), 4.73 (d, J 2.7 Hz, 1H), 7.20–7.32 (several peaks, 6H), 7.47 (m, 2H), 7.61 (m, 2H); δ_C 15.0 q, 15.6 q, 39.0 d, 41.3 d, 52.8 d, 65.9 t, 127.8 d, 127.9 d, 129.0 d, 129.1 d, 130.2 s, 131.8 s, 134.2 d, 134.4 d; δ_{Se} 346.5, 410.9 (Calc. for $C_{18}H_{22}OSe_2$: C, 52.44; H, 5.38. Found: C, 52.53; H, 5.32%).

erythro-4-(tert-Butyldimethylsilyloxy)-2,3-dimethyl-1,1-bis-(phenylseleno)butane 6

To a stirred solution of alcohol **17** (2.697 g, 6.55 mmol) and imidazole (0.535 g, 7.86 mmol) in DMF (6 mL) was added *tert*-butyldimethylsilyl chloride (1.085 g, 7.2 mmol) in small portions during 20 min, and the mixture was kept at ambient temperature for an additional 1 h. The mixture was then treated with $NaHCO_3$ (aq.) and extracted with diethyl ether–pentane (1 : 1 v/v). After drying ($MgSO_4$) and concentration *in vacuo*, column chromatography (150 mL silica; 1–2% EtOAc in pentane) afforded 3.366 g (97%) of the required TBDMS derivative **6** as a yellowish viscous oil, δ_H −0.02 (s, 6H), 0.82 (s, 9H), 0.84 (d, J 6.3 Hz, 3H), 1.20 (d, J 6.2 Hz, 3H), 1.85 (m, 2H), 3.53 (dd, J 10.0, 4.7 Hz, 1H), 3.56 (dd, J 10.0, 3.2 Hz, 1H), 4.78 (d, J 2.3 Hz, 1H), 7.20–7.31 (several peaks, 6H), 7.47 (m, 2H), 7.63 (m, 2H); δ_C −5.5 q, 14.9 q, 16.0 q, 18.2 s, 25.8 q, 38.9 d, 40.7 d, 52.9 d, 65.9 t, 127.7 d, 127.8 d, 128.3 d, 128.9 d, 129.0 d, 130.3 s, 131.8 s, 134.1 d, 134.4 d; δ_{Se} 339.2, 406.1 (Calc. for $C_{24}H_{36}OSe_2Si$: C, 54.75; H, 6.89. Found: C, 54.91; H, 7.00%).

(2S*,3R*,9Z)-1-(tert-Butyldimethylsilyloxy)-2,3,10-trimethyl-6-methylene-4-(phenylseleno)dodec-9-en-5-ol 18

To a stirred solution of selenoacetal **6** (1.137 g, 2.16 mmol) in THF (15 mL) at $-78\,^\circ$C was added *n*-BuLi (1.6 M solution in hexane; 1.35 mL, 2.16 mmol). The mixture was stirred for 5 min and treated with a solution of dienal **3** (0.329 g, 2.16

mmol) in THF (1.5 mL). The temperature was raised to 20 °C, and the reaction mixture was quenched with $NaHCO_3$ (aq.) and extracted with diethyl ether. The extracts were dried ($MgSO_4$), concentrated *in vacuo*, and subjected to column chromatography (80 mL silica; 1–2% EtOAc in pentane) to afford 1.059 g (93%) of seleno alcohol **18** as a mixture of four diastereomers, δ_H (characteristic peaks) 0.01 and 0.03 (both s, Σ 6H), 0.86–1.06 (several peaks, 18H), 1.60–2.21 (several peaks, 11H), 2.40, 2.46, 2.68 and 2.99 (all br d, Σ 1H), 3.38–3.68 (several peaks, 3H), 4.18–4.36 (several peaks, 1H), 4.90–5.30 (several peaks, 3H), 7.18–7.30 (several peaks, 3H), 7.42–7.63 (several peaks, 2H); δ_C (characteristic peaks) 56.4 d, 56.9 d, 60.0 d, 61.6 d, 65.4 t, 65.6 t, 65.7 t, 65.8 t, 73.5 d, 75.1 d, 76.1 d, 78.0 d, 110.9 t, 111.0 t, 112.0 t, 113.2 t, 123.3 d, 123.4 d, 123.6 d, 123.7 d, 137.5 s, 137.6 s, 147.4 s, 148.1 s, 149.4 s, 149.9 s; δ_{Se} 238.3, 255.2, 268.7, 321.6.

(4*EZ*,9*Z*)-*erythro*-2,3,10-Trimethyl-6-methylenedodeca-4,9-dien-1-ol 19

To a stirred solution of selenide **18** (0.900 g, 1.72 mmol) and triethylamine (1.2 mL) in CH_2Cl_2 (9 mL) was added methanesulfonyl chloride (0.42 mL) dropwise at r.t. After 3 h the mixture was treated with $NaHCO_3$ (aq.) and extracted with diethyl ether. After drying ($CaCl_2$), and concentration *in vacuo*, the residue was subjected to column chromatography (60 mL silica; 1–1.5% EtOAc in pentane) to afford 0.576 g (93%) of TBDMS-protected title alcohol.

Deprotection was effected by overnight stirring in THF in the presence of tetrabutylammonium fluoride (1.7 mL; 1 M solution in THF). The alcohol **19** thus formed [a 3:2 mixture of (4*E*,9*Z*)- and (4*Z*,9*Z*)-isomer] was difficult to free from some *tert*-butyldimethylsilanol by-product by column chromatography. An analytically pure sample was obtained after acetylation, column chromatography (40 mL silica; 2% EtOAc in pentane), transesterification (MeOH–K_2CO_3, for the procedure see compound **17**) and chromatography (15% EtOAc in pentane). During this operation, two fractions substantially enriched in the (4*Z*)-**19** (eluted first) and (4*E*)-**19** isomers of the title alcohol were obtained. (4*Z*,9*Z*)-Isomer: δ_H 0.89 (d, *J* 7.0 Hz, 3H), 0.96 (t, *J* 7.6 Hz, 3H), 1.02 (d, *J* 6.9 Hz, 3H), 1.43 (br s, 1H), 1.57 (m, 1H), 1.67 (s, 3H), 2.02 (q, *J* 7.7 Hz, 2H), 2.10 (m, 4H), 2.83 (m, 1H), 3.44 (dd, *J* 10.7, 6.2 Hz, 1H), 3.54 (dd, *J* 10.7, 6.1 Hz, 1H), 4.87 (s, 1H), 4.96 (s, 1H), 5.08 (br t, *J* 6.5 Hz, 1H), 5.34 (t, *J* 11.4 Hz, 1H), 5.82 (d, *J* 11.8 Hz, 1H); δ_C 12.8 q, 12.9 q, 19.1 q, 22.9 q, 24.8 t, 26.4 t, 33.2 d, 37.8 t, 41.1 d, 66.6 t, 112.8 t, 123.8 d, 129.8 d, 135.0 d, 137.5 s, 145.7 s. (4*E*,9*Z*)-Isomer: δ_H 0.88 (d, *J* 7.1 Hz, 3H), 0.96 (t, *J* 7.5 Hz, 3H), 1.05 (d, *J* 6.9 Hz, 3H), 1.42 (br s, 1H), 1.65 (m, 1H), 1.68 (s, 3H), 2.02 (q, *J* 7.6 Hz, 2H), 2.12–2.24 (several peaks, 4H), 2.36 (m, 1H), 3.45 (dd, *J* 10.5, 6.3 Hz, 1H), 3.55 (dd, *J* 10.5, 6.2 Hz, 1H), 4.88 (s, 1H), 4.91 (s, 1H), 5.12 (br t, *J* 6.0 Hz, 1H), 5.60 (dd, *J* 15.9, 8.7 Hz, 1H), 6.05 (d, *J* 15.9 Hz, 1H); δ_C 12.9 q (two peaks), 18.4 q, 22.8 q, 24.8 t, 26.6 t, 32.6 t, 38.4 d, 41.0 t, 66.5 t, 113.7 t, 123.7 d, 131.9 d, 132.5 d, 137.4 s, 145.9 s. Total yield: 0.333 g (82% on **18**) (Calc. for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.10; H, 11.83%).

(5*E*,9*Z*)-*erythro*-2,3,6,10-Tetramethyldodeca-5,9-dien-1-ol 20

The hydrogenation of (4*EZ*,9*Z*)-*erythro*-2,3,10-trimethyl-6-methylenedodeca-4,9-dien-1-ol **19** (0.252 g) in THF (10 mL) in the presence of (η^6-naphthalene)tricarbonylchromium (0.3 g) was performed at 50 bar† and 50 °C for 3 h essentially as described for the preparation of compound **8**. Final column chromatography (20 mL silica; 5–30% Et_2O in pentane) afforded 0.192 g (76%) of the title compound **20** as a colourless oil. The NMR ^1H data were in good agreement with the literature;[5] δ_C 12.8 q, 13.8 q, 16.1 q, 17.0 q, 22.9 q, 24.8 t, 26.3 t,

---

† (1 bar = 10^5 Pa).

31.3 t, 35.5 d, 40.2 d, 40.3 t, 66.2 t, 123.6 d, 123.9 d, 135.6 s, 137.1 s.

(6*E*,10*Z*)-*erythro*-3,4,7,11-Tetramethyltrideca-6,10-dienonitrile 21

This was prepared in 85% yield from (5*E*,9*Z*)-*erythro*-2,3,6,10-tetramethyldodeca-5,9-dien-1-ol **20** as described.[5] The NMR ^1H data were in good agreement with the literature;[5] δ_C 12.8 q, 16.2 q, 17.1 q, 21.5 t, 22.9 q, 24.8 t, 26.2 t, 31.5 t, 34.8 d, 37.6 d, 40.1 t, 119.5 s, 122.4 d, 123.8 d, 136.4 s, 137.2 s.

(6*E*,10*Z*)-*erythro*-3,4,7,11-Tetramethyltrideca-6,10-dienal (*rac*-faranal) 1

To a stirred solution of (6*E*,10*Z*)-*erythro*-3,4,7,11-tetramethyltrideca-6,10-dienonitrile **21** (0.100 g, 0.4 mmol) in toluene (2 mL) was added DIBAL-H (1.5 M solution in toluene; 0.29 mL, 0.43 mmol) at −15 °C. Then, during 30 min, the temperature was allowed to reach 20 °C, and the reaction mixture was quenched with NH_4Cl (aq.). The thick solid precipitate was dissolved by adding cold 5% HCl, and the mixture was extracted with diethyl ether. The extract was washed successively with brine and aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (10 mL silica; 1.5% EtOAc in pentane) afforded 0.076 g (75%) of the title compound **1** as a colourless oil. ^1H NMR data were in good agreement with the literature;[4–6] δ_C 12.8 q, 16.0 q, 16.1 q, 17.6 q, 22.9 q, 24.8 t, 26.2 t, 31.9 t, 32.0 d, 38.5 d, 40.1 t, 47.4 t, 123.1 d, 123.9 d, 135.9 s, 137.1 s, 203.3 d.

Acknowledgements

References

1 F. J. Ritter, I. E. M. Brüggemann-Rotgans, P. E. J. Verweil, C. J. Persons and E. Talman, *Tetrahedron Lett.*, 1977, 2617.
2 (*a*) M. Kobayashi, T. Koyama, K. Ogura, S. Seto, F. J. Ritter and I. E. M. Brüggemann-Rotgans, *J. Am. Chem. Soc.*, 1980, **102**, 6602; (*b*) T. Koyama, M. Matsubara and K. Ogura, *Naturwissenschaften*, 1983, **70**, 469.
3 D. W. Knight and B. Ojhara, *J. Chem. Soc., Perkin Trans. 1*, 1983, 955.
4 R. Baker, D. C. Billington and N. Ekanayake, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1387.
5 K. Mori and H. Ueda, *Tetrahedron*, 1982, **38**, 1227.
6 L. Poppe, L. Novak, P. Kolonits, A. Bata and C. Szantay, *Tetrahedron*, 1988, **44**, 1477.
7 K. Mori and N. Murata, *Liebigs Ann.*, 1995, 2087.
8 A. N. Kasatkin, T. Yu. Romanova, I. P. Podlipchuk and G. A. Tolstikov, *Khim. Prir. Soedin.*, 1993, 459. [*Chem. Nat. Comp. (Engl. Transl.)*, 1993, **29**, 397].
9 A. A. Vasil'ev, L. Engman and E. P. Serebryakov, *Mendeleev Commun.*, 2000, 101.
10 M. J. Södergren, S. K. Bertilsson and P. G. Andersson, *J. Am. Chem. Soc.*, 2000, in press.
11 M. Sodeoka and M. Shibasaki, *Synthesis*, 1993, 643.
12 (*a*) A. A. Vasil'ev, A. L. Vlasyuk, G. V. Kryshtal and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 2026 [*Russ. Chem. Bull. (Engl. Transl.)*, 1995, **44**, 1946]; (*b*) A. A. Vasil'ev and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2350 [*Russ. Chem. Bull.*, 1996, **45**, 2232].
13 (*a*) A. A. Vasil'ev, G. V. Kryshtal and E. P. Serebryakov, *Mendeleev Commun.*, 1995, 41; (*b*) A. A. Vasil'ev, A. A. Vlasyuk, G. L. Gamalevich and E. P. Serebryakov, *Bioorg. Med. Chem.*, 1996, **4**, 389; (*c*) A. A. Vasil'ev, L. Engman and E. P. Serebryakov, *Acta Chem. Scand.*, 1999, **53**, 611.
14 (*a*) M. Clarembeau, A. Cravador, W. Dumont, L. Hevesi, A. Krief, J. Lucchetti and D. Van Ende, *Tetrahedron*, 1985, **41**, 4793; (*b*) A. Krief, W. Dumont, M. Clarembeau and E. Badaoui, *Tetrahedron*,

1989, **45**, 2023; (*c*) J. Remion and A. Krief, *Tetrahedron Lett.*, 1976, 3743.

15 H. J. Reich and F. Chow, *J. Chem. Soc.*, *Chem. Commun.*, 1975, 790.

16 Y. Yamamoto, H. Yatagai, Y. Saito and K. Maruyama, *J. Org. Chem.*, 1984, **49**, 1096.

17 (*a*) G. Vidari, S. Ferrino and P. A. Grieco, *J. Am. Chem. Soc.*, 1984, **106**, 3539; (*b*) T. K. M. Shing and Y. Tang, *Tetrahedron*, 1990, **46**, 2187.

18 H. A. Lloyd, T. H. Jones, A. Hefetz and J. Tengö, *Tetrahedron Lett.*, 1990, **31**, 5559.

19 J. Villieras and M. Rambaud, *Synthesis*, 1983, 300.

20 (*a*) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman and B. W. Erickson, *J. Am. Chem. Soc.*, 1968, **90**, 5618; (*b*) K. Mori, M. Ohki, A. Sato and M. Matsui, *Tetrahedron*, 1972, **28**, 3739; (*c*) G. Gil, E. Ferre, M. Barre and J. le Petit, *Tetrahedron Lett.*, 1988, **29**, 3797; (*d*) S. Wadman, R. Whitby, C. Yeates, P. Kocienski and K. Cooper, *J . Chem. Soc.*, *Chem. Commun.*, 1987, 241; (*e*) J. C.

Ewing, G. S. Ferguson, D. W. Moore, F. W. Schultz and D. W. Thompson, *J. Org. Chem.*, 1985, **50**, 2124; (*f*) E. Moret and M. Schlosser, *Tetrahedron Lett.*, 1985, **26**, 4423; (*g*) K. Fujita, E. Moret and M. Schlosser, *Chem. Lett.*, 1982, 1819.

21 B. Kirschleger and R. Queignec, *Synthesis*, 1986, 926.

22 P. Ferraboschi, S. Casati, P. Grisenti and E. Santaniello, *Tetrahedron: Asymmetry*, 1993, **4**, 9.

23 G. E. McCasland and S. Proskow, *J. Am. Chem. Soc.*, 1954, **76**, 3486.

24 G. Guanti, L. Banfi, R. Riva and M. T. Zannetti, *Tetrahedron Lett.*, 1993, **34**, 5483.

25 Y. Naruse, T. Esaki and H. Yamamoto, *Tetrahedron Lett.*, 1988, **29**, 1417.

26 M. Uemura, T. Minami, K. Hirotsu and Y. Hayashi, *J. Org. Chem.*, 1989, **54**, 469.

27 H. J. Reich and M. L. Cohen, *J. Org. Chem.*, 1979, **44**, 3148.

28 A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.