Synthetic study of marine lobane diterpenes: efficient synthesis of (+)-fuscol

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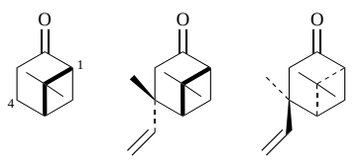
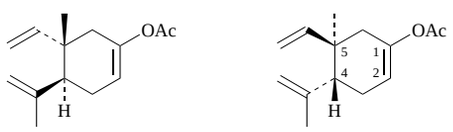
As part of a synthetic study on marine natural products, the enantioselective synthesis of (+)-fuscol 4, a representative lobane diterpene, has been achieved in 10 steps and *ca.* 20% overall yield from (4*R*,5*R*)-1-acetoxy-4-isopropenyl-5-methyl-5-vinylcyclohex-1-ene 3b, which itself has been prepared as a building block directed toward the asymmetric synthesis of natural products, in more than 40% overall yield from (+)-nopinone 1.

Introduction

We have been studying the enantioselective synthesis of natural products from (1*R*,5*S*)-(+)-nopinone **1**, readily obtainable in



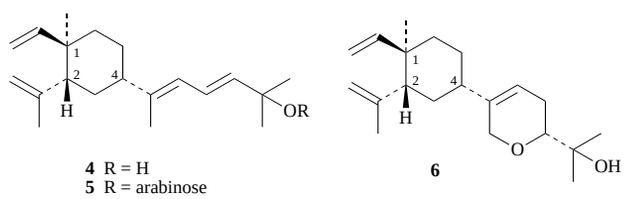
1 **2a** **2b**



3a **3b**

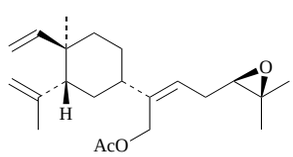
large quantities by ozonolysis of commercially available (−)-β-pinene.[1] In connection with the search for versatile building blocks directed toward natural product synthesis, we have recently reported that, starting with (+)-nopinone **1** as the common starting material, (4*S*,5*S*)-1-acetoxy-4-isopropenyl-5-methyl-5-vinylcyclohex-1-ene **3a** and its enantiomer (4*R*,5*R*)-**3b** were readily prepared in more than 40% overall yields by an efficient chemical transformation to (1*R*,4*S*,5*R*)-4,6,6-trimethyl-4-vinylbicyclo[3.1.1]heptan-2-one **2a** and its enantiomer (1*S*,4*R*,5*S*)-**2b**, followed by $BF_3{\cdot}OEt_2$-promoted cyclobutane opening with little loss of optical purity, respectively.[1c,f,g] Usefulness of the building block **3a** from the viewpoint of natural product synthesis was first demonstrated by the enantioselective synthesis of elemane sesquiterpenoids, (+)-β-elemenone and (+)-eleman-8β,12-olide.[1f] As the next project, we planned chemical transformation of **3** into lobane diterpenes which possess commonly a novel prenylated elemane-carbon skeleton.[2]

Marine lobane diterpenes, for example, fuscol **4**,[3] lobatriene **6**[4] and acetoxylobaoxide **7**,[5] comprise a family of biologically active natural products.[2a] Among these, fuscol **4**, isolated from the gorgonian *Eunicea fusca*,[3a] is representative, and its arabinose glycoside, fuscoside B **5**, is known to be a potent topical antiinflammatory agent and a selective inhibitor of leucotriene synthesis.[3b] Their absolute stereostructures remained unknown. The first elegant asymmetric synthesis of **4** was recently accomplished by Yamada *et al.*,[6] thus indicating the absolute configuration of **4** to be 1*R*,2*R*,4*S*. However, this is a multi-step synthesis and suffers from a poor overall yield. As part of a synthetic study on lobane diterpenoids, we describe



4 R = H
5 R = arabinose

6

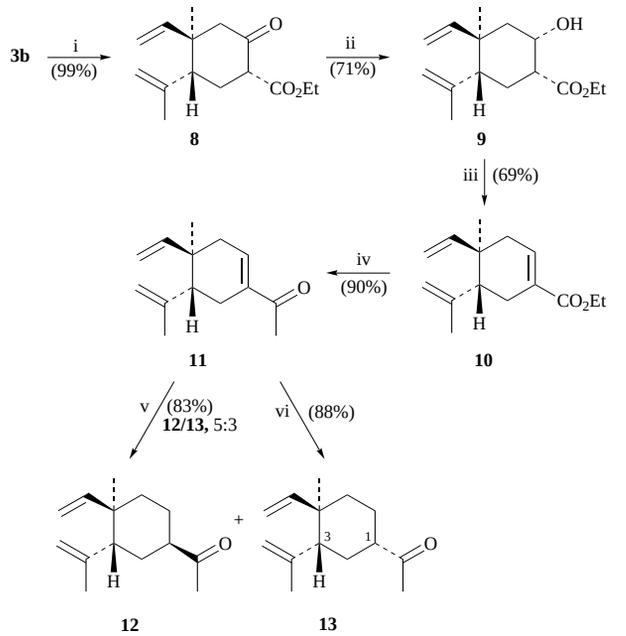


7

here the more ready and efficient synthesis of (+)-fuscol **4** from **3b**, that is, 10 steps and *ca.* 20% overall yield, although the present synthesis contains the same key intermediate that Yamada's synthesis has.

Results and discussion

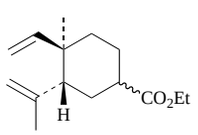
Taking into account the absolute configuration of the target compound **4**, we chose (4*R*,5*R*)-**3b** as the starting material in the present synthesis. Since an enol acetate function is synthetically equivalent to an enolate anion, this function could play an important role in the regioselective introduction of a carbon unit at the C-2 position of **3b**. In fact, ethoxycarbonylation of **3b** on treatment with MeLi (2.0 equiv.) in THF followed by addition of ethyl cyanoformate in the presence of HMPA provided the β-keto ester **8** quantitatively in a regio- and stereo-selective fashion (Scheme 1). Sodium borohydride ($NaBH_4$) reduction of **8** gave a single hydroxy ester **9** by exclusive attack of a hydride from the less hindered β side.[7] This was evidenced by the ^1H NMR analyses; the resonance arising from the proton on the carbon bearing the hydroxy group exhibits a singlet with half band width ($J_{1/2H}$ 8.2 Hz) at δ 4.33, indicating that the configuration of the hydrogen atom is equatorial. In addition, comparison of the chemical shifts of the quaternary methyl group (δ 1.04 for **8** and δ 1.24 for **9**) is indicative of the newly formed hydroxy group being axial; the *cis* relationship between the methyl and hydroxy groups in **9** causes the methyl protons to shift downfield by 0.20 ppm. Dehydration of **9** was carried out by a sequence of conventional reactions: mesylation with methanesulfonyl chloride in the presence of Et_3N followed by treatment of the resulting mesylate with DBU in diethyl ether, gave the α,β-unsaturated ester **10** in 69% overall yield from **9**. Chemical transformation of the ester



Scheme 1 *Reagents and conditions*: i, MeLi (2.1 equiv.), $NCCO_2Et$, THF–HMPA; ii, $NaBH_4$, EtOH; iii, MsCl, Et_3N, then DBU; iv, (1) KOH, EtOH–H_2O, (2) MeLi, Et_2O; v, $LiAlH_4$, CuI, THF; vi, (1) $LiAlH_4$, CuI, THF, (2) K_2CO_3, MeOH

group in **10** into an acetyl group was performed by alkaline hydrolysis of **10**, followed by treatment of the resulting carboxylic acid with MeLi, thus giving the enone **11** in 90% overall yield from **10**.

With both unsaturated carbonyl compounds, **10** and **11**, in hand, conjugate reduction of the α,β-unsaturated carbonyl functions was examined next. The most common method using Li metal in liquid NH_3 was examined for the 1,4-reduction of **10**. However, the reaction provided a mixture of a few products including the desired ester **14** whose yield was very low.



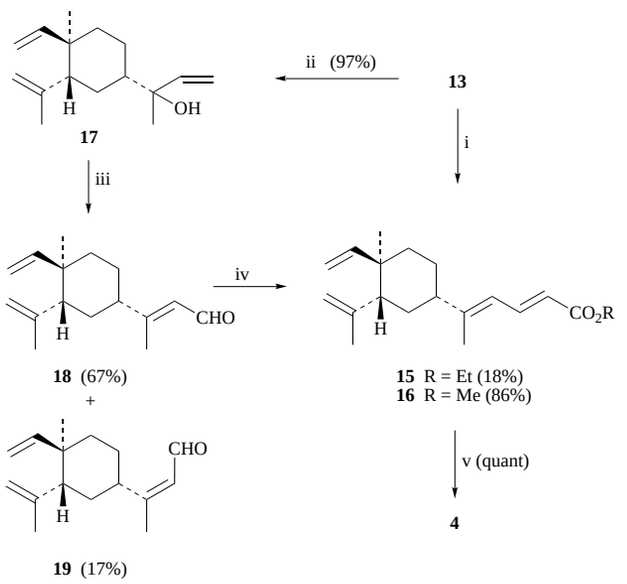
14

Attempted reduction of **10** with $NaBH_4$–$NiCl_2$ in ethanol[8] proved to be fruitless because the resulting mixture was inseparable. Both **10** and **11** resisted palladium-catalyzed conjugate reduction with tributyltin hydride in THF,[9] the starting materials being, for the most part, recovered.

Fortunately, the reagent, $LiAlH_4$–CuI,[10] was found to be an effective reductant for **11**, giving a mixture (a 5:3 ratio) of the methyl ketone **12** and its epimer **13** in 83% combined yield. From the ^1H NMR studies, the stereochemistry of the hydrogen atoms on the carbon flanking the acetyl group in **12** and **13** were established to be equatorial and axial, respectively, on the basis of a singlet (a half band width, 10.8 Hz) at δ 2.65 for the former and a broad singlet (a half band width, 18.9 Hz) at δ 2.42 for the latter, these assignment indicating the stereostructures of **12** and **13** as depicted. The fact that the minor product **13** is a thermodynamically stable compound was evidenced by treatment of the above mixture of **12** and **13** with K_2CO_3 in methanol to give **13** (88%) as a result of facile epimerisation of **12**, along with a very small amount of **12**. Although the compound **13** obtained was the synthetic intermediate in the Yamada's fuscol synthesis,[6] we could prepare this key intermediate in 5 steps and 38% overall yield from **3b**.

It is worth mentioning that the physical data of the methyl ketone **13** agreed with those of a novel metabolite, lobocalone, obtained from the soft coral *Lobophytum caledonense* collected in the South China Sea by Su *et al.*[11] The relative stereostructure of this norsesquiterpene has been established from its spectral data. Agreement between the physical data of the natural and synthetic compounds including the sign of optical rotation indicates that the absolute stereochemistry of lobacalone is 1*S*,3*R*,4*R*.

The remaining task for the synthesis of fuscol **4** was chemical transformation of the acetyl function in **13** into the functionalised eight-carbon side chain, for which two synthetic routes were examined. The methyl ketone **13** was first treated with the lithium salt of 4-(diethylphosphono)crotonate[12] in THF (Scheme 2). Although the only product obtained was the



Scheme 2 *Reagents and conditions*: i, LDA, (*E*)-$(EtO)_2POCH_2$-CH=$CHCO_2Et$, THF; ii, CH_2=CHMgBr, THF; iii, PCC, CH_2Cl_2; iv, NaH, $(Pr^iO)_2POCH_2CO_2Me$, THF; v, MeLi, Et_2O

desired conjugated diene ester **15** in which the geometry of the conjugated diene unit was *E*,*E*, the yield was disappointingly low (18%). This Horner–Wadsworth–Emmons condensation always resulted in more than 60% of unchanged **13**. Attempted condensation using the sodium salt of this reagent (NaH in DME, DMF, or toluene) proved to be fruitless, these reactions giving recovery mostly of unchanged **13**; this is probably because of the readily enolisable character of the methyl ketone function with a base.

As the second variant, we adopted a stepwise introduction of two kinds of the double bonds. Although a 5-step transformation of **13** to the methyl ester **16** by use of Reformatsky condensation with methyl bromoacetate and zinc dust as the key reaction has already been reported by Yamada *et al.*,[6] we designed a 3-step and more efficient construction of the penta-2,4-dienoate function in **13**. Vinylation of **13** with the vinyl Grignard reagent in THF provided in nearly quantitative yield the allylic alcohol **17**, whose oxidative rearrangement with PCC[1c,13] smoothly gave the (*E*)-α,β-unsaturated aldehyde **18** and its (*Z*)-isomer **19** in 67 and 17% yields, respectively, together with a small amount of unchanged **17**. Both aldehydes obtained are unstable, and gradually decomposed when stored at room temperature. Stereochemical assignment of the aldehydes was easily performed by a comparison of their ^1H NMR spectra; the chemical shift of the methyl protons of the butenal function in **18** shows considerable deshielding by the proximate carbonyl group, compared with that of **19** (δ 2.20 in **18** and δ 1.86 in **19**). Construction of the conjugated diene ester unit mentioned above was accomplished by treating the aldehyde **18** with the sodium salt of methyl diisopropylphosphonoacetate to give **16** in a high yield. No geometrical isomer of **16** could be detected in spite of a careful inspection of the reaction mixture.

Finally, treatment of **16** with an excess of MeLi according to a reported procedure[6] led to (+)-fuscol **4**, $[\alpha]_D$ +21.0 ($CHCl_3$), {lit. $[\alpha]_D$ +17.6 ($CHCl_3$),[3b] $[\alpha]_D$ +17.4 ($CHCl_3$)[6]}, quantitatively. The ^1H NMR (400 MHz), IR, and mass spectra of the synthetic **4** were superimposable with those of an authentic sample.[6]

In summary, as part of the enantioselective synthesis of lobane diterpenes from (+)-nopinone **1**, the total synthesis of (+)-fuscol **4** from the enol acetate **3b** was accomplished in 10 steps and *ca*. 20% overall yield in the present study. This overall yield is equivalent to *ca*. 8% on starting from **1**. Since all of the lobane natural products possess commonly a prenylated elemane-carbon skeleton, as seen in the structures, **4**–**7**, and since a set of compounds **3a**,**b** with respect to the absolute configuration of the target natural products are readily available from (+)-nopinone **1**, as aforementioned, it was demonstrated that the compounds **3a**,**b** could serve as the versatile building blocks for the asymmetric synthesis of other lobane diterpenes.

Experimental

Melting points are uncorrected. ^1H NMR spectra were recorded at 400 MHz; *J* values are given in Hz. [*α*] Values are given in units of 10^{-1} deg cm^2 g^{-1}. All reactions were carried out under dry N_2 or Ar atmosphere with use of standard procedures for the exclusion of moisture, except those in aqueous solutions. Dry tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone ketyl. Other organic solvents were purified and dried by using standard procedure. Extracts obtained on aqueous work-up of the reaction mixtures were washed successively with water and brine, and dried over Na_2SO_4, unless otherwise stated. Column and flash column chromatography were performed on 70–230 and 230–400 mesh silica gel (Merck), respectively. Medium-pressure chromatography (MPLC) utilized a 22 diam. 300 mm silica gel (10 μm) column. Solvents for elution are shown in parentheses. Ether refers to diethyl ether.

Ethyl (1*R*,4*R*,5*R*)-5-isopropenyl-4-methyl-2-oxo-4-vinylcyclohexanecarboxylate 8

To a stirred solution of MeLi in ether (1.03 M; 27.8 ml, 28.6 mmol) at −78 °C was added dropwise a solution of **3b**[1c] (97% ee, 2.96 g, 13.4 mmol) in THF (18 ml). Stirring was continued for an additional 1 h, after which the reaction mixture was treated dropwise with HMPA (2.5 ml, 13.7 mmol) followed by ethyl cyanoformate (1.61 ml, 16.3 mmol). The resulting reaction mixture was stirred for an additional 35 min after which it was quenched with aqueous NH_4Cl and extracted with ether. Evaporation of the extract followed by chromatography of the residue on silica gel (hexane–EtOAc, 40 : 1) gave the *title compound* **8** (3.17 g, 99%) as an oil, $[\alpha]_D^{26}$ −21.5 (*c* 0.86 in $CHCl_3$) (Found: C, 71.84; H, 8.64. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%); ν_{max}(neat)/cm^{-1} 3083, 1660, 1621, 1219, 1062, 914, 895 and 827; δ_H($CDCl_3$) 1.04 (3H, s), 1.31 (3H, t, *J* 7.2), 1.75 (3H, s), 2.06 (1H, d, *J* 18.0), 2.16 (1H, dd, *J* 9.2, 6.4), 2.27–2.40 (2H, m), 2.45 (1H, d, *J* 18.0), 4.21 (2H, m), 4.77 and 4.88 (1H, br s each), 4.97 (1H, d, *J* 17.6), 4.99 (1H, d, *J* 10.8), 5.79 (1H, dd, *J* 17.6, 10.8) and 12.19 (1H, s).

Ethyl (1*R*,4*R*,5*R*)-2-hydroxy-5-isopropenyl-4-methyl-4-vinylcyclohexanecarboxylate 9

To a stirred solution of **8** (3.12 g, 12.5 mmol) in ethanol (15 ml) was added dropwise at 0 °C a solution of $NaBH_4$ (473 mg, 12.5 mmol) in ethanol (15 ml). Stirring was continued for an additional 13 h, during which the reaction temperature rose slowly to room temperature. A few drops of aqueous acetic acid followed by water were added to the reaction mixture which was then extracted with $CHCl_3$. Evaporation of the extract followed by purification of the residue with chromatography on silica gel (hexane–EtOAc, 9 : 1) gave the *title compound* **9** (2.24 g, 71%) as crystals, mp 57–59 °C; $[\alpha]_D^{26}$ +59.2 (*c* 0.92 in $CHCl_3$) (Found: C, 70.95; H, 9.40. $C_{15}H_{24}O_3$ requires C, 71.39; H, 8.59%); ν_{max}(KBr)/cm^{-1} 3514, 3078, 1711, 1636, 1203, 1145, 1044 and 904; δ_H($CDCl_3$) 1.24 (3H, s), 1.28 (3H, t, *J* 7.2), 1.52 (1H, d, *J* 15.2), 1.67–1.79 (2H, m), 1.74 (3H, s), 2.02 (1H, dd, *J* 12.9, 2.9), 2.21 (1H, dd, *J* 13.2, 13.2), 2.47 (1H, ddd, *J* 12.9, 3.6, 2.7), 3.15 (1H, dd, *J* 2.0, 2.0), 4.18 (2H, q, *J* 7.2), 4.33 (1H, s, $J_{1/2H}$ 8.2), 4.65 and 4.86 (1H, s each), 4.91 (1H, d, *J* 17.1), 4.92 (1H, d, *J* 11.2) and 5.75 (1H, dd, *J* 17.1, 11.2).

Ethyl (4*R*,5*R*)-5-isopropenyl-4-methyl-4-vinylcyclohex-1-enecarboxylate 10

To a stirred solution of **9** (1.01 g, 4.02 mmol) and Et_3N (1.68 ml, 12.1 mmol) in ether (10 ml) was added dropwise at 0 °C methanesulfonyl chloride (0.6 ml, 7.83 mmol). The reaction mixture was stirred for 3 h after which a solution of DBU (1.12 ml, 7.52 mmol) in ether (5 ml) was added to it. Stirring was continued for an additional 4 h after which the reaction mixture was quenched by the addition of water, and then extracted with ether. The oily residue obtained by evaporation of the extract was chromatographed on silica gel (hexane–EtOAc, 25 : 1) to give the *title compound* **10** (652 mg, 69%) as an oil, $[\alpha]_D^{22}$ −12.8 (*c* 0.84 in $CHCl_3$) (Found: C, 76.80; H, 9.25. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%); ν_{max}(neat)/cm^{-1} 3082, 1713, 1655, 1638, 1247, 1087, 1048, 909 and 894; δ_H($CDCl_3$) 0.99 (3H, s), 1.30 (3H, t, *J* 7.2), 1.74 (3H, s), 2.03 (1H, ddd, *J* 19.3, 4.2, 2.4), 2.19 (1H, dd, *J* 9.0, 2.4), 2.27–2.45 (3H, m), 4.20 (2H, q, *J* 7.2), 4.74 and 4.87 (1H, s each), 4.95 (1H, d, *J* 10.5), 4.97 (1H, d, *J* 17.6), 5.80 (1H, dd, *J* 17.6, 10.5) and 6.95 (1H, br s).

(4*R*,5*R*)-5-Isopropenyl-4-methyl-4-vinylcyclohexen-1-yl methyl ketone 11

To a stirred solution of **10** (2.14 g, 9.15 mmol) in ethanol (30 ml) was added aqueous KOH (3 M, 30 ml). The reaction mixture was gently refluxed for 1 h and then cooled to 0 °C and made slightly acidic by the addition of aqueous HCl (2 M) with stirring; it was then extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated. Filtration of the residue through a short silica gel column (ether) gave (4*R*,5*R*)-5-isopropenyl-4-methyl-4-vinylcyclohex-1-enecarboxylic acid (1.88 g, quant) as crystals, mp 108–109 °C; ν_{max}(KBr)/cm^{-1} 3200–2600, 1685, 1647, 1279, 961 and 914; δ_H($CDCl_3$) 0.98 (3H, s), 1.74 (3H, s), 2.05 (1H, dd, *J* 18.8, 4.4), 2.19 (1H, dd, *J* 8.8, 2.0), 2.30–2.45 (3H, m), 4.74 and 4.87 (1H, s each), 4.95 (1H, d, *J* 17.8), 4.96 (1H, d, *J* 10.4) and 5.79 (1H, dd, *J* 17.8, 10.4).

A stirred solution of the carboxylic acid obtained above in THF (40 ml) was cooled to 0 °C after which a solution of MeLi in ether (1.04 M; 18 ml, 18.72 mmol) was added dropwise to it; stirring was then continued for 40 min. Aqueous NH_4Cl was added to the reaction mixture which was then extracted with ether. Evaporation of the extract followed by purification of the residue with chromatography on silica gel (hexane–ether, 9 : 1) gave the *title compound* **11** (1.69 g, 90%) as an oil, $[\alpha]_D^{23}$ −18.2 (*c* 0.45 in $CHCl_3$) (Found: C, 81.92; H, 9.82. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%); ν_{max}(neat)/cm^{-1} 3082, 1667, 1645, 1244 and 893; δ_H($CDCl_3$) 0.98 (3H, s), 1.74 (3H, s), 2.10 (1H, ddd, *J* 14.1, 4.9, 2.8), 2.16 (1H, dd, *J* 9.6, 5.6), 2.25–2.45 (3H, m), 2.31 (3H, s), 4.72 and 4.86 (1H, s each), 4.97 (1H, dd, *J* 17.8, 0.9), 4.98 (1H, dd, *J* 10.4, 0.9), 5.80 (1H, dd, *J* 17.8, 10.4) and 6.86 (1H, br s).

(1*R*,4*R*,5*R*)-5-Isopropenyl-4-methyl-4-vinylcyclohexan-1-yl methyl ketone 12 and (1*S*,4*R*,5*R*)-5-isopropenyl-4-methyl-4-vinylcyclohexan-1-yl methyl ketone 13

To a stirred mixture of CuI (5.68 g, 29.8 mmol) and THF (60 ml) was added dropwise at 0 °C a solution of $LiAlH_4$ in THF (1.0 M; 7.44 ml, 7.44 mmol). Stirring was continued for 10 min after which the reaction mixture, was treated with a solution of **11** (1.52 g, 7.42 mmol) in THF (15 ml), added dropwise; stirring

was then continued for an additional 1h. After this the reaction mixture was quenched by addition of aqueous NH_4Cl to afford a precipitate, which was filtered off through a pad of Celite 545 with ether. The combined filtrates were washed with brine, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel (hexane–ether, 9:1) gave a mixture of **12** and **13** (1.26 g, 83%) in a 5:3 ratio (from MPLC). The *title compounds* **12** and **13** were obtained in a pure form by purification of a part of the above mixture with MPLC (hexane–EtOAc, 6:1). Compound **12**: an oil, $[\alpha]_D^{22}$ +20.4 (*c* 0.32 in $CHCl_3$) (Found: C, 81.21; H, 10.66. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%); ν_{max}(neat)/cm^{-1} 3082, 1709, 1636, 908 and 892; δ_H($CDCl_3$) 1.00 (3H, s), 1.28 (1H, ddd, *J* 13.4, 4.0, 4.0), 1.53 (1H, ddd, *J* 13.4, 13.4, 4.0), 1.65–1.75 (1H, m), 1.71 (3H, s), 1.82–2.05 (4H, m), 2.16 (3H, s), 2.65 (1H, s, $J_{1/2H}$ 10.8), 4.62 and 4.86 (1H, s each), 4.87 (1H, d with fine splittings, *J* 17.8), 4.88 (1H, d with fine splittings, *J* 10.4) and 5.75 (1H, dd, *J* 17.8, 10.4). Compound **13**: an oil, $[\alpha]_D^{22}$ +31.3 (*c* 0.52 in MeOH) {lit.,[11] $[\alpha]_D^{20}$ +18.5 (*c* 0.13 in MeOH)} (Found: C, 81.13; H, 10.57. $C_{14}H_{22}O$ requires C, 81.40; H, 10.75%); ν_{max}(neat)/cm^{-1} 3082, 1710, 1637, 908 and 898; δ_H($CDCl_3$) 1.00 (3H, s), 1.46–1.62 (3H, m), 1.67–1.82 (3H, m), 1.71 (3H, s), 2.00 (1H, ddd, *J* 15.7, 6.8, 6.8), 2.16 (3H, s), 2.42 (1H, br s, $J_{1/2H}$ 18.9), 4.61 and 4.85 (1H, s each), 4.91 (1H, d with fine splittings, *J* 17.8), 4.92 (1H, d with fine splittings, *J* 10.4) and 5.79 (1H, dd, *J* 17.8, 10.4).

Treatment of the mixture, 12 and 13, with a base

A suspension of a mixture of **12** and **13** (1.08 g, 5.23 mmol), K_2CO_3 (1.45 g, 10.5 mmol) and methanol (15 ml) was stirred for 15 h at room temperature after which most of the solvent was evaporated under reduced pressure. The residue was diluted with water and then extracted with ether. Evaporation of the extract left an oily residue which was purified by MPLC (hexane–EtOAc, 6:1) to give **13** (952 mg, 88%), together with a small amount of **12**.

2-[(1*R*,4*R*,5*R*)-5-Isopropenyl-4-methyl-4-vinylcyclohex-1-yl]but-3-en-2-ol 17

To a stirred solution of **13** (948 mg, 4.60 mmol) in THF (15 ml) was added dropwise at 0 °C a solution of vinylmagnesium bromide in THF (0.97 M; 9.5 ml, 9.2 mmol). Stirring was continued for 1.5 h after which the mixture was treated with aqueous NH_4Cl and extracted with ether. Evaporation of the extract followed by chromatography of the residue on silica gel (hexane–ether, 4:1) gave the *title compound* **17** (1.06 g, 97%) as an oil, $[\alpha]_D^{23}$ +12.0 (*c* 0.22 in $CHCl_3$) (Found: C, 81.81; H, 11.13. $C_{16}H_{26}O$ requires C, 81.99; H, 11.18%); ν_{max}(neat)/cm^{-1} 3082, 1636, 999 and 909; δ_H($CDCl_3$) 0.97 (3H, s), 1.28 (3H, s), 1.23–1.35 (1H, m), 1.37–1.45 (5H, m), 1.58–1.67 (2H, m), 1.70 (3H, s), 1.93 (1H, m), 4.58 and 4.81 (1H, s each), 4.80 (1H, d, *J* 12.0), 4.90 (1H, d, *J* 17.0), 5.08 (1H, dd, *J* 10.7, 1.2), 5.23 (1H, dd, *J* 17.4, 1.2), 5.80 (1H, dd, *J* 17.4, 10.7) and 5.94 (1H, dd, *J* 17.0, 12.0).

(*E*)-3-[(1*R*,4*R*,5*R*)-5-Isopropenyl-4-methyl-4-vinylcyclohex-1-yl]but-2-enal 18 and (*Z*)-3-[(1*R*,4*R*,5*R*)-5-isopropenyl-4-methyl-4-vinylcyclohexan-1-yl]but-2-enal 19

To a stirred mixture of PCC (2.68 g, 12.4 mmol), Celite 545 (*ca.* 1.2 g) and CH_2Cl_2 (25 ml) was added at room temperature a solution of **17** (902 mg, 3.55 mmol) in CH_2Cl_2 (15 ml). Stirring was continued for 17 h after which the reaction mixture was diluted with ether (60 ml) and filtered to remove solids. The combined filtrates were washed successively with aqueous $NaHSO_3$, aqueous $CuSO_4$, water and brine, dried (Na_2SO_4) and evaporated to afford an oily residue. This was purified by MPLC (hexane–ether, 3:1) to give the *title compounds* **18** (594 mg, 67%) and **19** (152 mg, 17%). Compound **18**, an oil, $[\alpha]_D^{22}$ +34.8 (*c* 0.49 in $CHCl_3$) [Found (HRMS,EI): M^+, 232.1834. $C_{16}H_{24}O$ requires *M*, 232.1826]; ν_{max}(neat)/cm^{-1} 3082, 1674, 1634 and 893; δ_H($CDCl_3$) 1.02 (3H, s), 1.47–1.66 (6H, m), 1.72 (3H, s), 2.04 (1H, dd, *J* 11.7, 4.4), 2.07–2.18 (1H, m), 2.20 (3H, s), 4.59 and 4.84 (1H, s each), 4.92 (1H, d, *J* 17.8), 4.92 (1H, d, *J* 10.4), 5.81 (1H, dd, *J* 17.8, 10.4), 5.93 (1H, d, *J* 8.1) and 10.05 (1H, d, *J* 8.1). Compound **19**, an oil, $[\alpha]_D^{24}$ −32.8 (*c* 0.34 in $CHCl_3$) [Found (HRMS,EI): M^+, 232.1826. $C_{16}H_{24}O$ requires *M*, 232.1826]; ν_{max}(neat)/cm^{-1} 3080, 1685, 1631 and 909; δ_H($CDCl_3$) 1.04 (3H, s), 1.35–1.55 (6H, m), 1.66–1.75 (1H, m), 1.72 (3H, s), 1.86 (3H, s), 2.09 (1H, dd, *J* 12.8, 3.2), 4.60 and 4.85 (1H, s each), 4.92 (1H, d, *J* 17.8), 4.93 (1H, d, *J* 10.4), 5.83 (1H, dd, *J* 17.8, 10.4), 5.84 (1H, d, *J* 8.0) and 10.07 (1H, d, *J* 8.0).

Ethyl (2*E*,4*E*)-5-[(1*R*,4*R*,5*R*)-5-isopropenyl-4-methyl-4-vinylcyclohexan-1-yl]hexa-2,4-dienoate 15

To a stirred solution of diisopropylamine (58.6 μl, 0.42 mmol) in THF (0.3 ml) was added dropwise at 0 °C a solution of BuLi in hexane (1.66 M; 0.23 ml, 0.38 mmol). The resulting mixture was stirred for 30 min, and then cooled at −78 °C. After this, a solution of ethyl 4-(diethylphosphono)crotonate[12] (92 mg, 0.34 mmol) in THF (0.7 ml) was added to the mixture which was then stirred at −40 °C for 1 h; it was then treated with a solution of **13** (24 mg, 0.17 mmol) in THF (1 ml). Stirring was continued for an additional 6 h, while the reaction temperature rose slowly to room temperature. The reaction mixture was quenched with water, and extracted with ether. Evaporation of the extract left an oily residue which was purified by MPLC (hexane–EtOAc, 20:1) to give the *title compound* **15** (9 mg, 18%) and recovered **13** (18 mg, 56%). Compound **15**, an oil, $[\alpha]_D^{24}$ +27.7 (*c* 0.51 in $CHCl_3$) (Found: C, 79.29; H, 9.73. $C_{20}H_{30}O_2$ requires C, 79.42; H, 10.00%); ν_{max}(neat)/cm^{-1} 3082, 1715, 1635, 1274, 1128, 1042, 979 and 891; δ_H($CDCl_3$) 1.02 (3H, s), 1.30 (3H, t, *J* 7.2), 1.43–1.66 (6H, m), 1.71 (3H, s), 1.91 (3H, s), 2.02 (1H, dd, *J* 12.5, 3.6), 2.02–2.15 (1H, m), 4.20 (2H, q, *J* 7.2), 4.59 and 4.83 (1H, s each), 4.91 (1H, d, *J* 17.6), 4.91 (1H, d, *J* 10.4), 5.80 (1H, d, *J* 15.1), 5.81 (1H, dd, *J* 17.6, 10.4), 6.04 (1H, d, *J* 11.6) and 7.61 (1H, dd, *J* 15.1, 11.6).

Methyl (2*E*,4*E*)-5-[(1*R*,4*R*,5*R*)-5-isopropenyl-4-methyl-4-vinylcyclohexan-1-yl]hexa-2,4-dienoate 16

To a stirred suspension of NaH (153 mg, 3.83 mmol) in THF (2 ml) was added at 0 °C a solution of methyl (diisopropylphosphono)acetate (1.31 g, 5.48 mmol) in THF (3 ml). Stirring was continued for 30 min after which the reaction mixture was treated with a solution of **18** (443 mg, 1.91 mmol) in THF (5 ml), added dropwise. The resulting mixture was stirred for an additional 40 min after which it was quenched with aqueous NH_4Cl, and extracted with ether. Evaporation of the extract followed by purification of the oily residue with MPLC (hexane–ether, 4:1) gave the *title compound* **16** (474 mg, 86%) as an oil, $[\alpha]_D^{22}$ +29.8 (*c* 0.25 in $CHCl_3$) (Found: C, 78.73; H, 9.76. $C_{19}H_{28}O_2$ requires C, 79.12; H, 9.79%); ν_{max}(neat)/cm^{-1} 3081, 1715, 1634, 1274, 1147, 1013, 979 and 891; δ_H($CDCl_3$) 1.02 (3H, s), 1.45–1.67 (6H, m), 1.71 (3H, s), 1.91 (3H, s), 2.01 (1H, dd, *J* 12.5, 3.6), 2.02–2.15 (1H, m), 3.74 (3H, s), 4.59 and 4.83 (1H, s each), 4.91 (1H, d, *J* 17.6), 4.92 (1H, d, *J* 10.4), 5.80 (1H, d, *J* 15.1), 5.81 (1H, dd, *J* 17.6, 10.4), 6.03 (1H, d, *J* 11.6) and 7.62 (1H, dd, *J* 15.1, 11.6).

(+)-Fuscol 4

Following the procedure described for the synthesis of **4** from **16** by Yamada *et al.*,[6] a solution of **16** (20 mg, 0.068 mmol) in THF (2 ml) was treated at 0 °C with a solution of MeLi in ether (1.04 M; 0.26 ml, 0.27 mmol) to give the title compound **4** (20 mg, quant), $[\alpha]_D^{22}$ +21.0 (*c* 0.31 in $CHCl_3$) {lit., $[\alpha]_D$ +17.6 (*c* 0.9 in $CHCl_3$),[3b] $[\alpha]_D$ +17.4 (*c* 0.16, $CHCl_3$)[6]} whose spectral data (^{1}H NMR, IR and mass) were identical with those of an authentic sample.[6] Similarly, reaction of **15** (5 mg, 0.02 mmol) in THF (1 ml) with a solution of MeLi in ether (1.04 M; 0.05 ml, 0.05 mmol) provided the title compound **4** (4 mg, 90%).

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