ChemPubSoc Europe

DOI: 10.1002/ejoc.201800800

EurJOC European Journal of Organic Chemistry

Full Paper

Natural Product Synthesis

# Synthesis of *trans*-β-Elemene

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**Abstract:** Highly efficient syntheses of the anti-cancer agent *trans*-β-elemene have been achieved by using the readily available (±)-limonene as starting material. The syntheses were achieved in only nine to eleven steps with good overall yields. The key step in these reaction sequences is a stereoselective radical cyclization, induced by titanocene chloride.

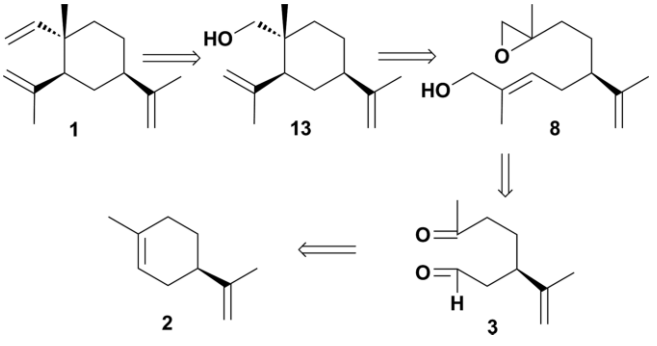
## Introduction

Elemanes are a family of sesquiterpenes and are minor components of the essential oils of numerous plants widely occurring in nature. From a bioactive point of view, (–)-*trans*-β-elemene (**1**; see Scheme 1) is the most important member of the elemane group, owing to its extensive and potent antineoplastic activity against a wide variety of tumours, including brain, breast, liver, lung and prostate as well as other tumours resistant to traditional drugs. This topic has been extensively reviewed by Adio.[1]

Despite the wide range of bioactivity of this sesquiterpene family, there are few references regarding its synthesis, most of which use related naturally occurring compounds as starting materials.[1] In the case of β-elemene (**1**), some studies on its synthesis have been reported,[2] however, most of these refer to a Cope–Claisen rearrangement as the critical step.

In this paper we describe a convenient method for synthesising elemane **1** by using (±)-limonene (**2**) as the starting material. This method can also be extended to the synthesis of other elemanes, by using many available compounds related to limonene as starting materials.

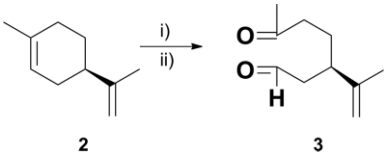
Retrosynthetic analysis, summarized in Scheme 1, suggests a four-step sequence from the target molecule β-elemene (**1**) to limonene (**2**), which is a readily available and affordable starting material. In this approach, radical cyclization, promoted by titanocene chloride, is the key step in the construction of the elemane skeleton. According to the analysis, the draft synthesis would consist of four general stages starting from limonene (**2**). The first stage would involve the selective cleavage of one of the double bonds, followed by an elongation of three carbon atoms and transformation of the functional groups. The third stage, which is decisive for the completion of this project, would consist of a 6-*exo* radical cyclization, followed by elimination of the hydroxy group, promoted by titanocene chloride, to generate cyclohexane and a terminal double bond in the correct position. The last stage involves an elongation of one carbon atom.




Scheme 1. Retrosynthetic analysis of β-elemene (**1**).

## Results and Discussion

The first step was carried out by a selective reaction using ozone at –78 °C in dichloromethane, followed by treatment of the intermediate ozonide with methyl sulfide.[3] The yield of the resulting ketoaldehyde **3** was 80 % (Scheme 2).




Scheme 2. Reagents and conditions: i) $O_3$, –78 °C, $CH_2Cl_2$; ii) $Me_2S$, $CH_2Cl_2$, 80 %.

The second general stage was achieved by using a five-step sequence starting from the ketoaldehyde **3**: a) chemoselective reduction with sodium borohydride, b) methylenation using the Corey–Chaykovsky method, c) oxidation with pyridinium chlorochromate (PCC), d) Horner–Wadsworth–Emmons elongation and e) reduction with $LiAlH_4$. The overall yield for the series of reactions was 50 % (Scheme 3).

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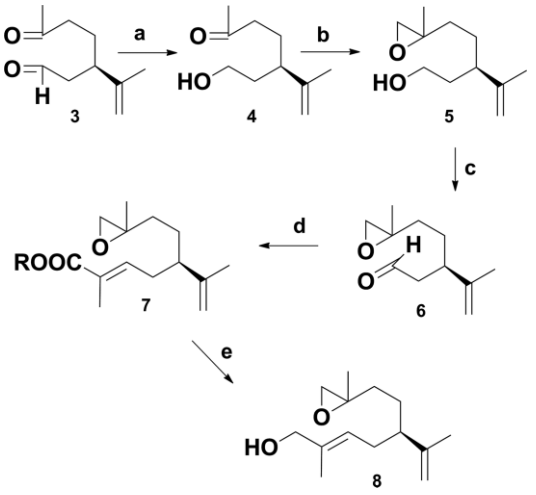
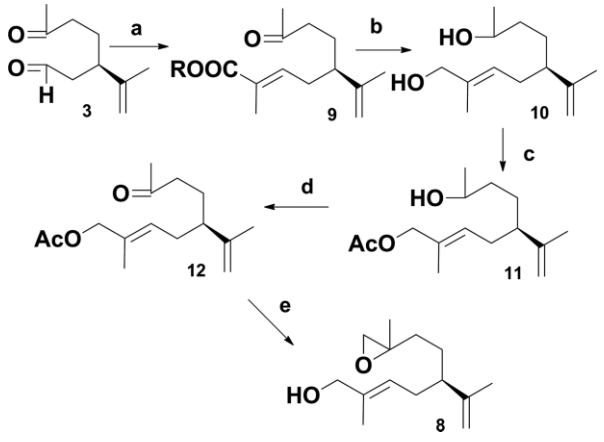



Scheme 3. Reagents and conditions: a) $NaBH_4$, –10 °C, 76 %; b) $Me_2SOCH_2Na$, DMSO, 50 °C, 95 %; c) PCC, $CH_2Cl_2$, 89 %; d) $(EtO)_2POCNa(CH_3)COOEt$, Tol, 0 °C, 63 %; e) $LiAlH_4$, $Et_2O$, 0 °C, 87 %.

The unsaturated epoxy alcohol **8** was also prepared by an alternative route consisting of five steps from the ketoaldehyde **3**: a) Horner–Wadsworth-Emmons chemoselective reaction, b) reduction with lithium aluminium hydride, c) chemoselective acetylation, d) oxidation with pyridinium chlorochromate and e) methylenation. The overall yield of this series of reactions was 66 % (Scheme 4).

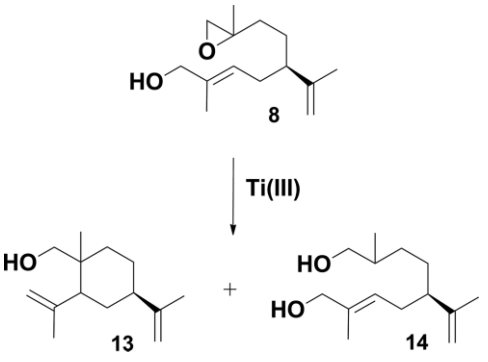



Scheme 4. Reagents and conditions: a) $(EtO)_2POCNa(CH_3)COOEt$, Tol, 0 °C, 92 %; b) $LiAlH_4$, $Et_2O$, 0 °C, 87 %; c) $ClCOCH_3$, DMAP, pyr, 0 °C, 63 %; d) PCC, $CH_2Cl_2$, 98 %; e) i. KOH, MeOH, room temp., ii. $Me_2SOCH_2Na$, DMSO, 90 %.

In both sequences, in all compounds the geometry of the C=C double bond is represented as the *E* isomer. This assignment is based on numerous precedents of Horner–Wadsworth-Emmons reactions with aldehydes as well as on the $^1H$ NMR spectra.[4]

The third stage is key in the synthesis of β-elemene (**1**) by this approach. It was carried out by starting with the unsaturated epoxy alcohol **8** and titanocene chloride as promoter of the cyclization under different reaction conditions. All reactions were carried out in tetrahydrofuran by adding 3.3 equivalents of $Cp_2TiCl$ to 1.0 equivalent of the epoxy alcohol **8**. In all cases the reagent was added dropwise to the substrate over different periods of time and at different temperatures.[5]

In all cases a mixture of cyclized and non-cyclized products was obtained. The structure of the major compound isolated has been identified as the alcohol **13** presented in Scheme 5.




Scheme 5. Reaction of **8** with $Ti^{III}$.

Although the overall yield was similar for all reaction conditions, the shortest experiment gave the best yield of the cyclized product **13** (45 %). The spectroscopic analysis of this product indicated that it is comprised of a mixture of two isomers in a ratio of 5:1.

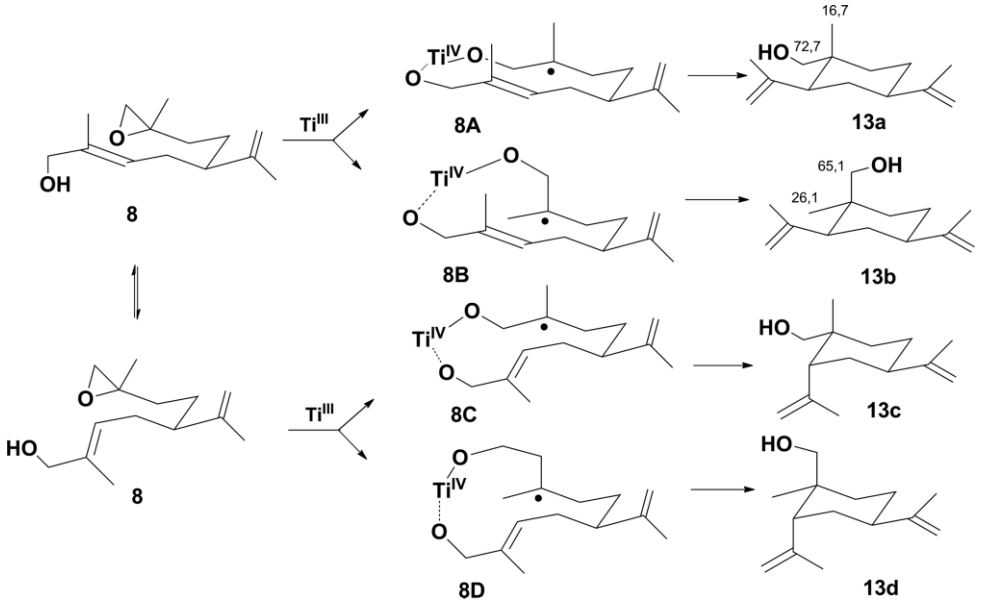
Conformational analysis of the cyclization of epoxy alcohol **8** showed that the most favourable intermediate, according to bibliographic precedents, should be **8A**,[6] which leads to the unsaturated cyclic alcohol **13a** as the major product (Scheme 6). The minor isomer **13b** must be generated from the intermediate **8B**. In both isomers there are three equatorial substituents on the cyclohexane. The relative configuration of the **13a** isomer was confirmed by its conversion into β-elemene.

Although the sequence shown in Scheme 6 provides the cyclic intermediate with the suitable configuration for obtaining β-elemene (**1**), the yield of the titanocene-induced radical cyclization was relatively low, which instigated the search for a more efficient alternative, maintaining the strategy of the proposed synthesis.

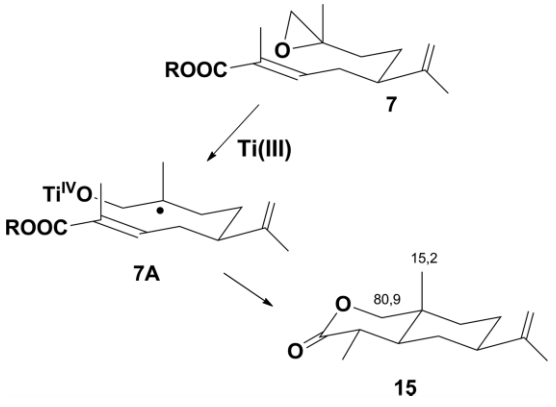
Radicals produced by the opening of epoxides with $Ti^{III}$ are nucleophilic in nature, so double bonds conjugated to an electron-withdrawing group undergo addition more quickly and more efficiently.[7] This induced us to test the unsaturated epoxy ester **7** as a substrate for the cyclization reaction.

Cyclization of the epoxy ester **7** was affected by the addition of 2.2 equivalemts of titanocene chloride to 1 equivalent of substrate for 1 minute at room temperature. The reaction mixture was treated with a saturated $NaH_2PO_4$ aqueous solution to allow for ester hydrolysis and subsequent cyclization to give a lactone mixture with a 96 % yield. The mixture could not be resolved by chromatography. Spectroscopic analysis of the crude product showed it to be comprised of a mixture of diastereoisomers, with lactone **15** representing 75 % of the total product (Scheme 7).

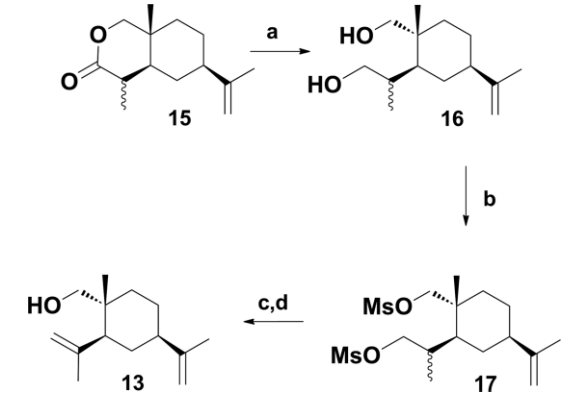
Conformational analysis of the cyclization of epoxy ester **7** showed that the most favourable intermediate, according to




Scheme 6. Cyclization intermediates.




Scheme 7. Reaction of **7** with $Ti^{III}$.




Scheme 8. Reagents and conditions: a) $LiAlH_4$, $Et_2O$, 0 °C, 81 %; b) MsCl, $Et_3N$, $CH_2Cl_2$, 86 %; c) i. *t*BuOK, *t*BuOH, 80 °C%; ii. KOH, MeOH, 81 %.

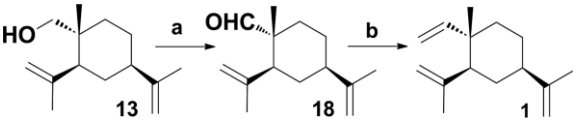
bibliographical precedents,[6] must be **7A**, which leads to unsaturated lactone **15** as the major product.

The relative configuration of the lactone **15** was determined by spectroscopy and its subsequent conversion into β-elemene (**1**).

The transformation of lactone **14** into alcohol **13** was carried out in three stages: reduction, mesylation and elimination, with an overall yield of 43 % (Scheme 8).

To complete the synthesis of β-elemene (**1**) from alcohol **13**, only two reactions were necessary: alcohol oxidation and Wittig condensation. The first reaction was performed with PCC in dichloromethane at room temperature and the second with methylenetriphenylphosphorane in THF. The overall yield of the two reactions was 67 % (Scheme 9).

The spectroscopic properties of the product obtained by this synthetic procedure coincide with those of the β-elemene (**1**) described in the literature.[2c,8]




Scheme 9. Reagents and conditions: a) PCC, $CH_2Cl_2$, 82 %; b) BuLi, $Ph_3PCH_2Br$, –78 °C, 82 %.

## Conclusions

β-Elemene (**1**) has been synthesized from limonene by three reaction sequences of nine, nine and eleven steps with overall yields of 12, 15 and 17 %.

The key step of all the synthetic sequences is a radical cyclization, induced by titanocene chloride. In these cyclization processes two stereocentres are created selectively with yields close to 45 % in the cyclization of epoxy alcohol **8** and 70 % in the cyclization of epoxy ester **7**.

The relative configuration of the major products resulting from these cyclizations promoted by titanocene chloride coincides with that of β-elemene, with one axial and three equatorial substituents on cyclohexane, as demonstrated by NMR spectroscopy.

## Experimental Section

**General Methods:** $^1$H NMR spectra were measured at either 200 or 400 MHz, and $^{13}$C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS ($^1$H) or solvent ($^{13}$C), unless indicated otherwise. IR spectra were recorded of neat samples on NaCl plates, unless otherwise noted. Standard mass spectra were acquired by GC–MS in EI mode with a maximum *m/z* range of 600. When required, all solvents and reagents were purified by standard techniques: THF was purified by distillation from sodium and benzophenone and degassed before use. All reactions were conducted under a positive pressure of argon, using standard benchtop techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel by using flash column chromatography on Merck silica gel 60 (0.040–0.063 mm). The yields reported are for chromatographically pure isolated products unless otherwise mentioned.

**(3*R**)-6-Oxo-3-(prop-1-en-2-yl)heptanal (3):** A solution of limonene (**2**; 5 g, 37.5 mmol) in MeOH (40 mL) was cooled to –78 °C under argon. Then $O_3$ (50 L/h, 90 % conversion) was bubbled through the solution for 150 min. After the reaction was complete, excess ozone was removed by purging with argon (10 min) and dimethyl sulfide (20 mL) was slowly added. Stirring was continued for 1 h at this temperature and for 2 h at room temp. Then a saturated $Na_2CO_3$ solution (50 mL) was added. The organic layer was separated and the aqueous phase was extracted with hexane. The combined organic extracts were washed with brine and then dried ($Na_2SO_4$). Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 7:3) to furnish (3*R**)-6-oxo-3-(prop-1-en-2-yl)heptanal (**3**; 5.04 g, 80 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3080, 2938, 2720, 1721 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.63 (s, 3 H), 1.70 (m, 2 H), 2.09 (s, 3 H), 2.41 (m, 4 H), 2.65 (m, 1 H), 4.74 (s, 1 H), 4.80 (s, 1 H), 9.63 (s, 1 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 18.5 ($CH_3$), 26.6 ($CH_2$), 30.2 ($CH_3$), 40.9 (CH), 41.1 ($CH_2$), 47.6 ($CH_2$), 113.5 ($CH_2$), 145.2 (C), 202.0 (CH), 208.4 (C) ppm. HRMS (ESI): calcd. for $C_{10}H_{16}O_2Na$ 181.1150; found 181.1145.

**(5*R**)-5-(2-Hydroxyethyl)-6-methylhept-6-en-2-one (4):** $NaBH_4$ (284 mg, 7.5 mmol) was added to a solution of **3** (2.5 g, 14.8 mmol) in MeOH (10 mL) at 0 °C under argon. The mixture was stirred for 3 h at this temperature and water (5 mL) was added dropwise. MeOH was evaporated and diethyl ether (20 mL) was added. The organic layer was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine and then dried ($Na_2SO_4$). Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 6:4) to furnish (5*R**)-5-(2-hydroxyethyl)-6-methylhept-6-en-2-one (**4**; 1.88 g, 75 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3321, 3074, 2916, 1720 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.42 (s, 3 H), 1.5–1.8 (m, 4 H), 1.94 (s, 3 H), 2.02 (m, 1 H), 2.19 (t, *J* = *7.5* Hz, 2 H), 3.07 (br. s, 1 H), 3.37 (m, 2 H), 4.54 (s, 1 H), 4.61 (s, 1 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 17.7 ($CH_3$), 26.7 ($CH_2$), 30.1 ($CH_3$), 36.1 ($CH_2$), 41.5 ($CH_2$), 43.3 (CH), 60.7 ($CH_2$), 112.4 ($CH_2$), 146.4 (C), 209.5 (C) ppm. HRMS (ESI): calcd. for $C_{10}H_{18}O_2Na$ 193.1204; found 193.1202.

**(3*R**)-4-Methyl-3-[2-(2-methyloxiran-2-yl)ethyl]pent-4-en-1-ol (5):** $Me_3SOI$ (2.7 g, 12.4 mmol) was added portionwise to a suspension of NaH (449 mg, 11.8 mmol) in DMSO (12 mL). The reaction mixture was stirred under argon for 1 h. Then a solution of **4** (1.00 g, 5.9 mmol) in DMSO (2 mL) was added and the resulting mixture was vigorously stirred under argon for 3 h at 50 °C. A 10 % $NaHCO_3$ aqueous solution (20 mL) was added and the resulting heterogeneous mixture was vigorously stirred for 25 min. The organic layer was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with a 5 % $NaHCO_3$ aqueous solution and brine, and then dried ($Na_2SO_4$). Removal of the solvent furnished (3*R**)-4-methyl-3-[2-(2-methyloxiran-2-yl)ethyl]-pent-4-en-1-ol (**5**; 952 mg, 95 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3072, 2927, 2718 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.25 (s, 3 H), 1.36 (m, 6 H), 1.54 (s, 3 H), 1.55 (m, 1 H), 2.14 (br. s, 1 H), 2.52 (m, 2 H), 3.50 (m, 2 H), 4.67 (s, 1 H), 4.70 (s, 1 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 17.8 ($CH_3$), 21.2 ($CH_3$), 28.7 ($CH_2$), 34.6 ($CH_2$), 36.3 ($CH_2$), 44.2 (CH), 54.1 ($CH_2$), 57.2 (C), 61.2 ($CH_2$), 112.6 ($CH_2$), 146.9 (C) ppm. HRMS (ESI): calcd. for $C_{11}H_{20}O_2Na$ 207.1361; found 207.1360.

**(3*R**)-4-Methyl-3-[2-(2-methyloxiran-2-yl)ethyl]pent-4-enal (6):** A solution of the alcohol **5** (950 mg, 5.16 mmol) in dry $CH_2Cl_2$ (20 mL) was added to a stirred suspension of PCC (1.33 g, 6.2 mmol) in dry $CH_2Cl_2$ (20 mL). The reaction mixture was vigorously stirred at room temp. under argon for 3 h. Then $Et_2O$ (40 mL) was added and the mixture was filtered. Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 1:1) to furnish (3*R**)-4-methyl-3-[2-(2-methyloxiran-2-yl)ethyl]pent-4-enal (**6**; 836 mg, 89 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3074, 2936, 2720, 1726, 1275 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.25 (s, 3 H), 1.3–1.5 (m, 4 H), 1.58 (m, 1 H), 1.58 (s, 3 H), 2.52 (m, 2 H), 2.60 (m, 2 H), 4.70 (s, 1 H), 4.76 (s, 1 H), 9.51 (s, 1 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 18.7 ($CH_3$), 21.2 ($CH_3$), 28.4 ($CH_2$), 34.2 ($CH_2$), 41.5 (CH), 47.6 ($CH_2$), 53.9 ($CH_2$), 58.9 (C), 113.1 ($CH_2$), 145.5 (C), 202.3 (CH) ppm. HRMS (ESI): calcd. for $C_{11}H_{18}O_2Na$ 205.1204; found 205.1207.

**Ethyl (5*R**,*E*)-2,6-Dimethyl-5-[2-(2-methyloxiran-2-yl)ethyl]-hepta-2,6-dienoate (7):** Triethyl 2-phosphonopropionate (1.1 mL, 5.2 mmol) was added to a suspension of NaH (208 mg, 55 % mineral oil, 5.2 mmol) in toluene (4 mL) at 0 °C. After 30 min a solution of **6** (950 mg, 5.2 mmol) in toluene (3 mL) was added dropwise and the reaction mixture was stirred under argon at that temperature for 3 h and then diluted with diethyl ether and a saturated aqueous $NH_4Cl$ solution. The organic layer was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine and then dried ($Na_2SO_4$). Removal of the solvent furnished ethyl (5*R**,E)-2,6-dimethyl-5-[2-(2-methyloxiran-2-yl)ethyl]hepta-2,6-dienoate (**7**; 873 mg, 63 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 2938, 1713, 1275 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.29 (s, 3 H), 1.2–1.6 (m, 7 H), 1.59 (s, 3 H), 1.80 (s, 3 H), 1.85 (m, 1 H), 2.20 (m, 2 H), 2.54 (m, 2 H), 4.15 (m, 2 H), 4.68 (s, 1 H), 4.76 (s, 1 H), 6.68 (t, *J* = *6* Hz, 1 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 12.7 ($CH_3$), 14.5 ($CH_3$), 18.6 ($CH_3$), 21.2 ($CH_3$), 28.3 ($CH_2$), 33.1 ($CH_2$), 34.5 ($CH_2$), 46.8 (CH), 54.0 ($CH_2$), 57.1 (C), 60.6 ($CH_2$), 112.7 ($CH_2$), 128.5 (C), 140.5 (CH), 146.2 (C), 168.3 (C) ppm. HRMS (ESI): calcd. for $C_{16}H_{26}O_3Na$ 289.1779; found 289.1780.

**(5*R**,*E*)-2,6-Dimethyl-5-[2-(2-methyloxiran-2-yl)ethyl]hepta-2,6-dien-1-ol (8):** $LiAlH_4$ (150 mg, 6.0 mmol) was added to a solution of **7** (1.07 g, 4.0 mmol) in diethyl ether (10 mL) at 0 °C. The reaction mixture was vigorously stirred at room temperature under argon for 45 min, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$ (5 g) and stirred for an additional 45 min. The resulting mixture was filtered and then the filtrate was washed with $Et_2O$. Removal of the

solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 9:1) to furnish (5*R**,*E*)-2,6-dimethyl-5-[2-(2-methyloxiran-2-yl)ethyl]hepta-2,6-dien-1-ol (**8**; 682 mg, 87 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3370, 3049, 2929, 2853, 2375 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 1.26 (s, 3 H), 1.3–1.5 (m, 4 H), 1.51 (s, 3 H), 1.61 (s, 3 H), 1.94 (m, 1 H), 2.03 (m, 2 H), 2.54 (m, 2 H), 3.94 (s, 2 H), 4.63 (s, 1 H), 4.71 (s, 1 H), 5.30 (m, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 14.0 ($CH_3$), 18.5 ($CH_3$), 21.3 ($CH_3$), 28.2 ($CH_3$), 31.9 ($CH_2$), 34.7 ($CH_2$), 47.4 (CH), 54.1 ($CH_2$), 57.4 (C), 69.0 ($CH_2$), 112.1 ($CH_2$), 124.5 (CH), 135.6 (C), 147.0 (C) ppm. HRMS (ESI): calcd. for $C_{14}H_{24}O_2Na$ 247.1674; found 247.1671.

**Ethyl (5*R**,*E*)-2-Methyl-8-oxo-5-(prop-1-en-2-yl)non-2-enoate (9):** Triethyl 2-phosphonopropionate (5.5 mL, 26.0 mmol) was added to a suspension of NaH (1.04 g, 55 % mineral oil, 26.0 mmol) in toluene (20 mL) at 0 °C. After 30 min a solution of **3** (4.36 g, 26.0 mmol) in toluene (12 mL) was added dropwise and the reaction mixture was stirred under argon at that temperature for 3 h and then diluted with diethyl ether and a saturated aqueous $NH_4Cl$ solution. The organic layer was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine and then dried ($Na_2SO_4$). Removal of the solvent furnished **9** (6.00 g, 92 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3321, 3074, 2916, 1720, 1713 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 1.19 (m, 3 H), 1.43 (m, 2 H), 1.54 (s, 3 H), 1.75 (s, 3 H), 2.04 (s, 3 H), 1.40–2.20 (m, 5 H), 2.30 (m, 2 H), 4.11 (q, *J* = *8* Hz, 2 H), 4.65 (s, 1 H), 4.75 (s, 1 H), 6.63 (t, *J* = *6* Hz, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 12.6 ($CH_3$), 14.2 ($CH_3$), 18.3 ($CH_3$), 26.5 ($CH_2$), 30.1 ($CH_3$), 33.0 ($CH_2$), 41.4 ($CH_2$), 46.3 (CH), 60.5 ($CH_2$), 113.0 ($CH_2$), 128.5 (C), 140.3 (CH), 145.8 (C), 168.1 (C), 206.6 (C) ppm. HRMS (ESI): calcd. for $C_{15}H_{24}O_3Na$ 275.1623; found 275.1620.

**(5*R**,*E*)-2-Methyl-5-(prop-1-en-2-yl)non-2-ene-1,8-diol (10):** $LiAlH_4$ (945 mg, 33.0 mmol) was added to a solution of **9** (5.67 g, 22.5 mmol) in diethyl ether (50 mL) at 0 °C. The reaction mixture was vigorously stirred at room temp. under argon for 45 min, after which it was quenched with $Na_2SO_4{\cdot}10H_2O$ (15 g) and stirred for a further 45 min. The resulting mixture was filtered and then the filtrate was washed with $Et_2O$. Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 6:4) to furnish **10** (3.80 g, 87 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3402, 3077, 2938 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 1.14 (d, *J* = *8* Hz, 3 H), 1.58 (s, 3 H), 1.63 (s, 3 H), 1.1–2.20 (m, 9 H), 3.70 (m, 1 H), 3.96 (s, 2 H), 4.70 (s, 1 H), 4.75 (s, 1 H), 5.32 (m, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 14.1 ($CH_3$), 18.6 ($CH_3$), 23.7 ($CH_3$), 28.6 ($CH_2$), 32.0 ($CH_2$), 37.0 ($CH_2$), 47.7 (CH), 68.0 (CH), 68.5 ($CH_2$), 111.8 ($CH_2$), 124.7 (CH), 135.5 (C), 147.5 (C) ppm. HRMS (ESI): calcd. for $C_{13}H_{24}O_2Na$ 235.1674; found 235.1673.

**(5*R**,*E*)-8-Hydroxy-2-methyl-5-(prop-1-en-2-yl)non-2-en-1-yl Acetate (11):** $ClCOCH_3$ (10.5 mL, 147.0 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) was added at 0 °C to a solution of **10** (2.88 g, 14.7 mmol) in pyridine (5.8 mL). The reaction mixture was vigorously stirred at this temperature under argon for 72 h, after which it was quenched with iced-water and stirred for a further 1 h. The organic layer was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with 10 % $NH_4Cl$, 10 % $NaHCO_3$ and brine and then dried ($Na_2SO_4$). Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 7:3) to furnish **11** (873 mg, 63 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3395, 3067, 2923, 1732 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 1.20 (s, 3 H), 1.56 (s, 3 H), 1.59 (s, 3 H), 1.1–2.20 (m, 7 H), 2.01 (s, 3 H), 3.67 (m, 1 H), 4.39 (s, 2 H), 4.63 (s, 1 H), 4.71 (s, 1 H), 5.36 (m, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 14.3 ($CH_3$), 18.5 ($CH_3$), 21.5 ($CH_3$), 23.6 ($CH_3$), 28.8 ($CH_2$), 32.0 ($CH_2$), 37.3 ($CH_2$), 47.4 (CH), 68.3 (CH), 70.5 ($CH_2$), 112.0 ($CH_2$), 123.3 (CH), 130.4 (C), 147.1 (C), 171.2 (C) ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_3Na$ 277.1779; found 277.1776.

**(5*R**,*E*)-2-Methyl-8-oxo-5-(prop-1-en-2-yl)non-2-en-1-yl Acetate (12):** A solution of the alcohol **11** (3.90 g, 15.4 mmol) in dry $CH_2Cl_2$ (60 mL) was added to a stirred suspension of PCC (4.01 g, 18.6 mmol) in dry $CH_2Cl_2$ (60 mL). The reaction mixture was vigorously stirred at room temp. under argon for 3 h. Then $Et_2O$ 100 mL was added and the mixture was filtered. Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 7:3) to furnish **12** (3.78 g, 98 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3321, 3074, 2916, 1732, 1713 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 1.56 (s, 3 H), 1.61 (s, 3 H), 1.4–1.8 (m, 5 H), 2.07 (s, 3 H), 2.16 (s, 3 H), 2.38 (t, *J* = *8* Hz, 2 H), 4.40 (s, 2 H), 4.64 (s, 1 H), 4.74 (s, 1 H), 5.36 (m, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 14.3 ($CH_3$), 18.3 ($CH_3$), 21.7 ($CH_3$), 26.4 ($CH_2$), 30.2 ($CH_3$), 32.0 ($CH_2$), 41.7 ($CH_2$), 47.1 (CH), 70.4 ($CH_2$), 112.6 ($CH_2$), 128.6 (CH), 130.9 (C), 146.5 (C), 171.2 (C), 209.2 (C) ppm. HRMS (ESI): calcd. for $C_{15}H_{24}O_3Na$ 275.1623; found 275.1621.

**(5*R**,*E*)-2,6-Dimethyl-5-[2-(2-methyloxiran-2-yl)ethyl]hepta-2,6-dien-1-ol (8):** KOH (3 M) (10 mL, 30 mmol) was added to a solution of **12** (3.78 g, 15 mmol) in MeOH (20 mL) and the mixture was stirred for 1 h at room temp. Then the mixture was diluted with $Et_2O$ and quenched with an aqueous solution of $NH_4Cl$. The organic layer was washed with 10 % $NaHCO_3$ and brine and then dried ($Na_2SO_4$). Removal of the solvent furnished a crude residue, which was used without further purification. $Me_3SOI$ (2.7 g, 12.4 mmol) was added portionwise to a suspension of NaH (2.00 g, 47.0 mmol) in DMSO (12 mL) and the reaction mixture was stirred under argon for 1 h. Then the crude residue previously obtained (15.0 mmol) in DMSO (2 mL) was added and the resulting mixture was vigorously stirred under argon for 13 h at 75 °C. A 10 % $NaHCO_3$ aqueous solution (20 mL) was added and the resulting heterogeneous mixture was vigorously stirred for 25 min. The organic layer was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with 5 % $NaHCO_3$ and brine and then dried ($Na_2SO_4$). Removal of the solvent furnished **8** (3.00 g, 90 %) as a colourless oil.

**(1*R**,2*S**,4*R**)-1-Methyl-2,4-di(prop-1-en-2-yl)cyclohexylmethanol (13):** A mixture of $Cp_2TiCl_2$ (3.30 mmol) and Zn (6.60 equiv.) in rigorously deoxygenated THF (10 mL) was stirred at a determined temperature until the red solution turned green. In a separate flask, the epoxy compound **8** (224 mg, 1 mmol) was dissolved in rigorously deoxygenated THF (10 mL). The green $Ti^{III}$ solution was slowly added through a cannula to the epoxide solution. After 60 min, an excess of saturated $NaH_2PO_4$ was added and the mixture was stirred for 20 min. The mixture was filtered to remove insoluble titanium salts. The product was extracted into diethyl ether and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$) and filtered. After removal of the solvent, the crude product was purified by flash chromatography (hexane/diethyl ether, 8:2) to furnish a diastereomeric mixture of alcohols (94 mg, 0.45 mmol, 45 %) as a colourless oil in which alcohol (1*R**,2*S**,4*R**)-1-methyl-2,4-di(prop-1-en-2-yl)cyclohexylmethanol (**13**) predominates. IR (neat): $\tilde{\nu}$ = 3380, 3074, 2938 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 0.95 (s, 3 H), 1.1–1.8 (m, 6 H), 1.78 (s, 6 H), 1.90 (m, 2 H), 3.35 (m, 2 H), 4.69 (s, 4 H), 4.76 (s, 1 H), 4.83 (s, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 22.8 ($CH_3$), 22.9 ($CH_3$), 26.2 ($CH_3$), 26.7 ($CH_2$), 33.0 ($CH_2$), 36.8 ($CH_2$), 45.7 (CH), 50.1 (CH), 72.3 ($CH_2$), 108.5 ($CH_2$), 113.0 ($CH_2$), 149.1 (C), 150.4 (C) ppm. HRMS (ESI): calcd. for $C_{14}H_{24}ONa$ 231.1724; found 231.1720.

**(4a*S**,6*R**,8a*R**)-4,8a-Dimethyl-6-(prop-1-en-2-yl)hexahydro-1*H*-isochromen-3(4*H*)-one (15):** A mixture of $Cp_2TiCl_2$ (3.97 mmol) and Zn (24.0 mmol) in rigorously deoxygenated THF (18 mL) was stirred at a room temperature until the red solution turned green. In a separate flask, the epoxy compound **7** (480 mg, 1.8 mmol) was dissolved in rigorously deoxygenated THF (18 mL). The green $Ti^{III}$ solution was slowly added through a cannula to the epoxide solution. After 60 min, an excess of saturated $NaH_2PO_4$ was added and the mixture was stirred for 20 min. The mixture was filtered to remove insoluble titanium salts. The product was extracted into diethyl ether and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$) and filtered. After removal of the solvent, the crude product was purified by flash chromatography (hexane/diethyl ether, 8:2) to furnish a diastereomeric mixture of lactones (383 mg, 1.7 mmol, 96 %) in which the lactone (4a*S**,6*R**,8a*R**)-4,8a-dimethyl-6-(prop-1-en-2-yl)hexahydro-1*H*-isochromen-3(4*H*)-one (**15**) predominates (75 %) as a colourless oil. IR (neat): $\tilde{\nu}$ = 2931, 1733 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 1.00 (s, 3 H), 1.09 (s, 3 H), 1.20 (d, $J$ = 6 Hz, 3 H)*, 1.23 (d, $J$ = 6 Hz, 3 H), 1.0–1.6 (m, 14 H), 1.69 (s, 3 H)*, 1.70 (s, 3 H), 1.90 (m, 2 H), 2.17 (m, 2 H), 3.81 (m, 2 H)*, 4.07 (m, 2 H), 4.65 (s, 2 H)*, 4.69 (s, 2 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 14.3 (2 $CH_3$), 15.1 (2 $CH_3$), 21.0 (2 $CH_3$), 25.6 (2 $CH_2$), 30.5 (2 $CH_2$), 32.7 (2 $CH_2$), 34.5 (2 C), 38.5 (2 CH), 45.3 (2 CH), 46.1 (2 CH), 80.8 (2 $CH_2$), 108.6 ($CH_2$)*, 109.3 ($CH_2$), 149.5 (C), 150.5 (C)*, 174.2 (2 C) ppm. HRMS (ESI): calcd. for $C_{14}H_{22}O_2Na$ 245.1517; found 245.1514.

**2-[(1*S**,2*R**,5*R**)-2-(Hydroxymethyl)-2-methyl-5-(prop-1-en-2-yl)cyclohexyl]propan-1-ol (16):** $LiAlH_4$ (38 mg, 1.35 mmol) was added to a solution of **15** (200 mg, 0.9 mmol) in diethyl ether (5 mL) at 0 °C. The reaction mixture was vigorously stirred at room temperature under argon for 45 min, after which it was quenched with $Na_2SO_4{\cdot}10H_2O$ (1.0 g) and stirred for a further 45 min. The resulting mixture was filtered and then the filtrate was washed with $Et_2O$. Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 8:2) to furnish a diastereomeric mixture of diols (141 mg, 0.73 mmol, 81 %) in which diol **15** predominates as a colourless oil. IR (neat): $\tilde{\nu}$ = 3400, 3080, 2936 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 0.8–1.9 (m, 8 H), 0.75 (s, 3 H), 1.01 (d, $J$ = 6 Hz, 3 H), 1.82 (m, 1 H), 1.72 (s, 3 H), 3.38 (m, 2 H), 3.68 (m, 2 H), 4.68 (s, 2 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 13.3 ($CH_3$), 16.4 ($CH_3$), 21.2 ($CH_3$), 27.7 ($CH_2$), 28.5 ($CH_2$), 32.9 (CH), 36.3 ($CH_2$), 37.8 (C), 39.0 (CH), 45.3 (CH), 67.6 ($CH_2$), 69.9 ($CH_2$), 108.3 ($CH_2$), 151.0 (C) ppm. HRMS (ESI): calcd. for $C_{14}H_{26}O_2Na$ 249.1830; found 245.1827.

**2-[(1*S**,2*R**,5*R**)-2-Methyl-2-(methylsulfonyloxymethyl)-5-(prop-1-en-2-yl)cyclohexyl]propyl Methanesulfonate (17):** Methanesulfonyl chloride (0.2 mL, 1.9 mmol) was added to a stirred solution of the alcohol **16** (200 mg, 0.9 mmol) in $CH_2Cl_2$ (1 mL) and $Et_3N$ (0.35 mL) at 0 °C . The reaction mixture was stirred under argon for 12 h and then diluted with diethyl ether and saturated aqueous $Na_2CO_3$. The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with sat. $NaHCO_3$ and brine, dried ($Na_2SO_4$) and filtered. Removal of the solvent afforded a crude residue of **16** (265 mg, 0.76 mmol, 86 %) as a colourless oil. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 0.8–2.2 (m, 8 H), 0.93 (s, 3 H), 1.10 (d, $J$ = *6* Hz, 3 H), 1.71 (s, 3 H), 2.99 (s, 6 H), 3.8–4.4 (m, 4 H), 4.69 (s, 2 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 13.0 ($CH_3$), 16.5 ($CH_3$), 21.2 ($CH_3$), 27.0 ($CH_2$), 27.5 ($CH_2$), 31.8 (CH), 36.6 ($CH_2$), 36.7 (2 $CH_3$), 37.8 (CH), 39.8 (C), 45.1 (CH), 74.0 ($CH_2$), 76.4 ($CH_2$), 108.8 ($CH_2$), 149.9 (C) ppm.

**(1*R**,2*S**,4*R**)-1-Methyl-2,4-di(prop-1-en-2-yl)cyclohexylmethanol (13):** A solution of **17** (292 mg, 0.9 mmol) in *t*BuOH (0.88 mL) was added at room temperature to a solution of 1 M *t*BuOK in *t*BuOH (2.2 mL, 2.2 mmol). The reaction mixture was heated to 80 °C and stirred under argon for 6 h. Then the mixture was cooled to room temperature and quenched with water (40 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with sat. $NaHCO_3$ and brine, dried ($Na_2SO_4$) and filtered. Removal of the solvent afforded a crude residue, which was dissolved in MeOH (1.68 mL). Then 5 M KOH (, 0.3 mL, 1.41 mmol) was added and the mixture was stirred for 1 h under argon. Then the mixture was diluted with diethyl ether and a saturated aqueous $NH_4Cl$ solution. The organic layer was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine and then dried ($Na_2SO_4$). Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 8:2) to furnish a diastereomeric mixture of alcohols (106 mg, 81 %) in which alcohol **13** predominates as a colourless oil.

**(1*R**,2*S**,4*R**)-1-Methyl-2,4-di(prop-1-en-2-yl)cyclohexanecarbaldehyde (18):** A solution of the alcohol **13** (100 mg, 0.5 mmol) in dry $CH_2Cl_2$ (6 mL) was added to a stirred suspension of PCC (1.26 g, 0.6 mmol) in dry $CH_2Cl_2$ (6 mL). The reaction mixture was vigorously stirred at room temperature under argon for 3 h. Then $Et_2O$ 10 mL was added and the mixture was filtered and then immediately purified by flash chromatography (hexane/diethyl ether, 1:1) to furnish a diastereomeric mixture of aldehydes (98 mg, 82 %) as a colourless oil in which aldehyde **18** predominates. IR (neat): $\tilde{\nu}$ = 2916, 2720, 1725 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 0.95 (s, 3 H), 1.1–1.6 (m, 6 H), 1.54 (s, 3 H), 1.65 (s, 3 H), 1.92 (m, 2 H), 4.64 (m, 4 H), 9.38 (s, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 13.2 ($CH_3$), 23.4 ($CH_3$), 25.5 ($CH_3$), 28.5 ($CH_2$), 31.4 ($CH_3$), 31.5 ($CH_3$), 31.5 ($CH_2$), 33.1 ($CH_2$), 45.0 (CH), 47.4 (CH), 50.0 (C), 109.0 ($CH_2$), 113.5 ($CH_2$), 145.9 (C), 206.6 (CH) ppm. HRMS (ESI): calcd. for $C_{14}H_{22}ONa$ 229.1568; found 229.1564.

***trans*-β-Elemene (1):** A three-necked round-bottomed flask was fitted with a reflux condenser, an addition funnel, a mechanical stirrer and a gas inlet tube. A gentle flow of Ar through the apparatus was maintained throughout the reaction. An ethereal solution of *n*-butyllithium (2.4 mmol) and anhydrous THF (5 mL) was added to the flask. The solution was stirred and cooled to –75 °C. Then triphenylmethylphosphonium bromide (3.59 mmol) was added cautiously over 5 min and the solution was stirred for 15 min at room temperature. After cooling the mixture to –75 °C, (1*R**,2*S**,4*R**)-1-methyl-2,4-di(prop-1-en-2-yl)cyclohexanecarbaldehyde (**17**; 100 mg, 0.49 mol) was added dropwise. The solution turned colourless and a white precipitate separated. The mixture was stirred for 30 min, allowed to warm to room temperature and the precipitate removed by suction filtration. The precipitate was washed with diethyl ether (100 mL) and the combined ethereal filtrates were extracted with 100 mL portions of $NH_4Cl$ until neutral and then the combined organic extracts were washed with 10 % $NaHCO_3$ and brine and then dried ($Na_2SO_4$). Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/diethyl ether, 95:5) to furnish a diastereomeric mixture of trienes (81 mg, 82 %) as a colourless oil in which triene **1** predominates. IR (neat): $\tilde{\nu}$ = 3080, 2916, 2820 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 1.4–1.8 (m, 6 H), 1.01 (s, 3 H), 1.70 (s, 3 H), 1.72 (s, 3 H), 1.99 (m, 2 H), 4.6–5.0 (m, 6 H), 5.83 (dd, $J_1$ = *6*, $J_2$ = *12* Hz, 1 H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 16.8 ($CH_3$), 21.2 ($CH_3$), 25.0 ($CH_3$), 27.0 ($CH_2$), 33.1 ($CH_2$), 40.0 (C), 40.1 ($CH_2$), 45.9 (CH), 52.9 (CH), 108.3 ($CH_2$), 110.5 ($CH_2$), 112.2 ($CH_2$), 147.3 (C), 150.5 (CH), 150.6 (C) ppm. HRMS (ESI): calcd. for $C_{15}H_{24}Na$ 227.1878; found 227.1875.

## Acknowledgments

Financial support from the Regional Government of Castile and Leon is gratefully acknowledged. D. B. I. and P. H. T. thank the Regional Government of Castille and Leon and the University of Salamanca for fellowships that have allowed them to carry out this work.

**Keywords:** Terpenoids · Radicals · Natural products · Titanium

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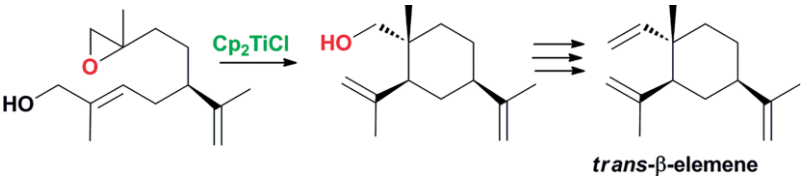
Received: May 24, 2018

**Natural Product Synthesis**






Highly efficient syntheses of the anticancer agent *trans*-β-elemene have been achieved by using the readily available (±)-limonene as starting material. The syntheses were achieved in only nine to eleven steps with good overall yields. The key step in these reaction sequences is a stereoselective radical cyclization, induced by titanocene chloride.

**DOI: 10.1002/ejoc.201800800**