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Synthesis of a caryophyllene isoprenologue, a potential diterpene natural product

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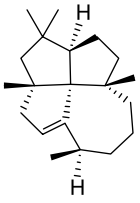
Abstract—(−)-β-Caryophyllene has been converted into three stereoisomers of a new bicyclic compound that is structurally related to the known macrocyclic diterpene, flexibilene, in the same way β-caryophyllene is related to humulene. Key steps are selective cleavage of caryophyllene, addition of a five carbon component by a Wittig reaction and McMurry cyclization.

1. Introduction

During our studies of the tetracyclic diterpene, laurenene (**1**)[1,2] we have been drawn to the similarity of its peripheral methylation pattern with that of the monocyclic diterpene, flexibilene (**2**).[3] We have also noted structural similarities to the triquinane sesquiterpenes, and have entertained the idea that the biosynthesis of laurenene might involve a pathway analogous to that proposed for the biosynthesis of silphenene (**3**) which proceeds through an intermediate with a caryophyllene framework.[4] For this reason we became interested in compound **4** which bears the same relationship to flexibilene (**2**) as caryophyllene (**5**) does to humulene (**6**). Although **4** has not been encountered as a natural product, this relationship to flexibilene renders it a worthwhile synthetic target and the putative connection to laurenene adds further impetus to its synthesis. Here we describe our synthesis of **4** and two of its geometric isomers **7** and **8**.



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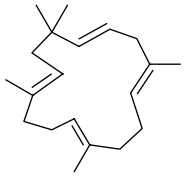
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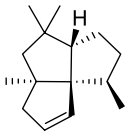

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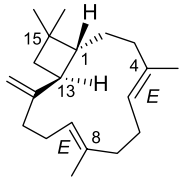

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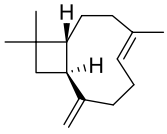

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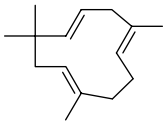
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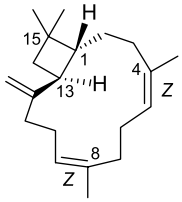

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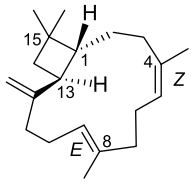

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2. Results and discussion

The readily available (−)-β-caryophyllene (**5**) presented itself as an ideal starting point for our synthesis. The

Keywords: Bicyclic diterpene; Flexibilene; Wittig reaction; Warren modification; McMurry cyclization.
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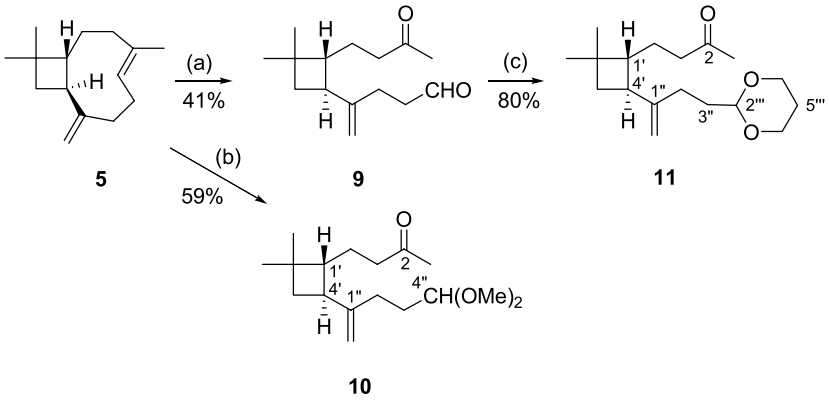
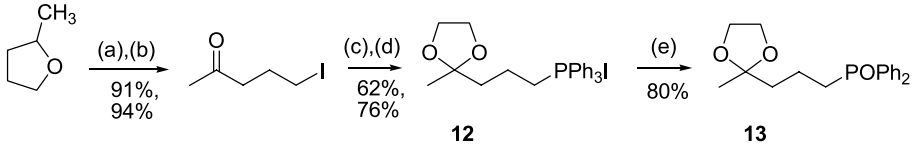


Scheme 1. Selective cleavage of (−)-β-caryophyllene **5**. (a) O_3/MeOH then $(CH_3)_2S$; (b) O_3/MeOH then $(CH_3)_2S$/K-10 clay/MeOH; (c) $HO(CH_2)_3OH/H^+$.



Scheme 2. Synthesis of five carbon subunits **12** and **13**. (a) $AlCl_3$/NaI; (b) $COCl_2$/DMSO; (c) Ph_3P; (d) $(CH_2OH)_2$/PTSA; (e) NaOH.

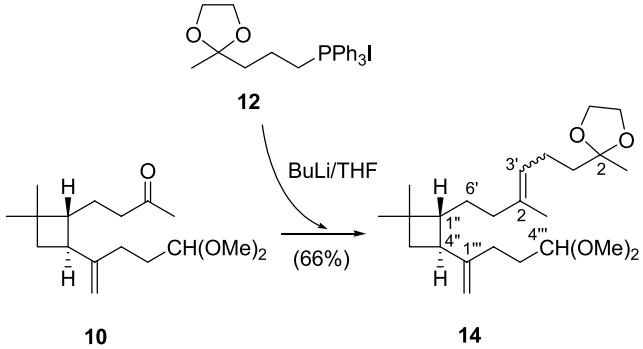
gem-dimethyl substituted cyclobutane, with a *trans* fused ring junction and the exocyclic double bond are already in place. Transformation of diene **5** into triene **4** requires enlargement of the nine-membered ring by insertion of an appropriately functionalized five-carbon unit, to produce the desired 13-membered ring.

Odinokov et al. have reported the selective ozonolysis of β-caryophyllene (**5**) at the endocyclic double bond.[5] This gave ketoaldehyde **9** which was converted into its dimethyl acetal **10**. We found it most convenient to form **10** directly by carrying out the ozonolysis in methanol and treating the resulting solution with both dimethyl sulfide and K-10 clay (Scheme 1). Alternative protection for the aldehyde function was obtained by treatment of **9** with 1,3-propanediol and *p*-toluenesulfonic acid in boiling benzene under Dean–Stark conditions to give acetal **11**.

Conversion of **9** or an equivalent into **4** required the addition of a 1,4-difunctionalised pentane unit with the attachment of the 1-position to the ketone function of **9** and the 4-position to the aldehyde. We chose to commence with functionalization of the ketone. Literature methods, involving ring opening of 2-methyltetrahydrofuran with aluminium trichloride/sodium iodide,[6] Swern oxidation[7,8] to 5-iodo-2-pentanone[9] and reaction with triphenylphosphine and acetal-protection, yielded the desired phosphonium salt **12**.[10,11] Treatment of **12** with boiling aqueous sodium hydroxide solution gave an alternative five-carbon source, the diphenylphosphinoyl derivative **13**[12] (Scheme 2).

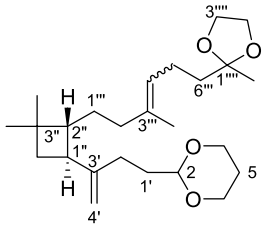
Wittig reaction of phosphonium salt **12** with ketoacetal **10** using *n*-butyl lithium as base in THF gave a 69% yield of an (*E*)/(*Z*) mixture of alkenes **14** (1:2.4 by GC) (Scheme 3). Although the MS of the product, which was isolated in 65% yield, showed no parent ion for $C_{24}H_{42}O_2$, peaks for ions corresponding to loss of CH_3, CH_3OH, and CH_3CH_2OH were noted. ^1H and ^{13}C NMR signals associated with the *gem*-dimethylcyclobutane system, the exocyclic methylene and the methoxy groups were well resolved, and relatively unchanged in chemical shift compared with those of the starting material. Peaks consistent with the dioxolane-protected methyl ketone system [δ_H 1.32 (s), 3.93 (m, $W_{h/2}=7$ Hz); δ_C 23.5 (q), 109.9 (s), 110.0 (s)] indicated that the five-carbon unit had been incorporated as desired. Furthermore, trisubstituted double bond formation was evidenced by olefinic methine [δ_H 5.03–5.15 (m); δ_C 123.8 (d), 124.1 (d)] and methyl peaks [δ_H 1.67 (d, $J=$ 1 Hz), 1.59 (s); δ_C 23.9 (q), 15.9 (q)]. The number of signals observed in these spectra confirmed the formation of both the (*E*)- and the (*Z*)-forms of alkene **14**. Comparison with literature data[13,14] indicated that the (*Z*)-form [δ_H 1.67 (d, $J=1$ Hz), δ_C 23.9 (q)] was dominant and GC indicated a ratio of 5:11. Other Wittig modifications gave lower yields.

Attempts to separate the isomers of **14** were only partially successful. Silica gel radial chromatography provided an enrichment of the major isomer by repeated elution, but neither silver nitrate impregnated plates nor reverse phase C_{18} column chromatography proved effective. An attempt to improve the (*E*)/(*Z*) ratio of the geometric isomers of **14** by



Scheme 3. Wittig reaction of keto acetal **10**.

irradiation in the presence of diphenyldisulphide[15,16] gave very little change in the isomer distribution. In similar fashion, Wittig reaction of ketone **11** gave the previously unreported **15** as an (*E*)/(*Z*) mixture (40%).



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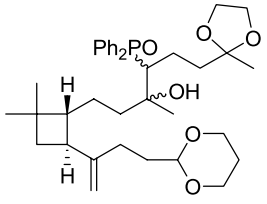
In an attempt to avoid isomeric mixtures, the Warren modification of the Wittig reaction[12,17,18] was attempted. Here the diastereoisomeric mixtures of phosphinoyl alcohols that are generated are frequently separable and able to be transformed stereospecifically into either the (*E*)- or (*Z*)-alkene. Reaction of diphenylphosphinoyl derivative **13** with ketone **10** gave a solid. The IR spectrum of the mixture indicated that an alcohol (ν_{max} 3350 cm^{-1}) was present, and a distinctive band at 1460 cm^{-1} was consistent with the diphenylphosphinoyl group. NMR spectra were complicated, but various resonances supported the expected gross structure **16**. Signals for the geminal methyl groups (δ_H 0.84, 0.88), the exocyclic C=CH_2 unit (δ_H 4.52–5.00, 2H, m; δ_C 106.5, 106.6, 106.7, 106.8, 151.8 and 152.0), the dioxolane grouping (δ_H 3.59–4.28, 4H, m; δ_C 64.2, 64.4 and 67.7), the methoxy groups (δ_H 3.31, 6H, s; δ_C 52.6) and the phenyl groups (δ_H 7.48, 6H, m and 7.79, 4H) were noted. Comparison with reported ^{1}H NMR data[12] enabled the assignment of a two proton multiplet at 2.32 ppm to both the phosphorus-bearing methine and one of the ring-junction methine groups. A group of singlets at δ 0.96, 0.98 and 1.04 was assigned to the CH_3–COH system and a pair of peaks at 1.24 and 1.27 ppm was assigned to the methyl group attached to the dioxolane ring (Scheme 4).

Although the anticipated phosphinoyl alcohols **16** should exist in four diastereoisomeric forms we did not separate these. Reaction of the mixed isomers of **16** in dimethyl formamide with sodium hydride generated the desired alkenes **14**, but only in 30% yield based on transformed starting material. A promising aspect of this reaction was that more of the (*E*)-isomer was formed with a 1:1 ratio of isomers. This was useful in later studies of the McMurry cyclisation (vide infra). However, a considerable amount of keto acetal **10** (35% based on transformed starting material) was also formed. It was noted that a bright red colour was formed upon addition of sodium hydride to the diphenylphosphinoyl alcohol. This suggested that fragmentation may be occurring.

The same sequence was repeated with the alternative substrate **11**. A low yield (15%) of phosphinoyl alcohol diastereoisomers **17** was again obtained, but these were separable by centrifugal chromatography into two fractions of different R_f on silica. By analogy with Warren's findings on similar systems[17] it was anticipated that the two isolated components would correspond to the *erythro* and *threo* forms about the newly created bond. However, when either of these fractions was treated with sodium hydride in dimethyl formamide, a 6:5 mixture of alkene **15** (*E*) and (*Z*)-geometric isomers was obtained. Again, a bright red colour was generated. Lawrence[19] has noted that such loss of stereoselectivity may occur if the alkene is sterically compressed (tri- or tetra-substituted).



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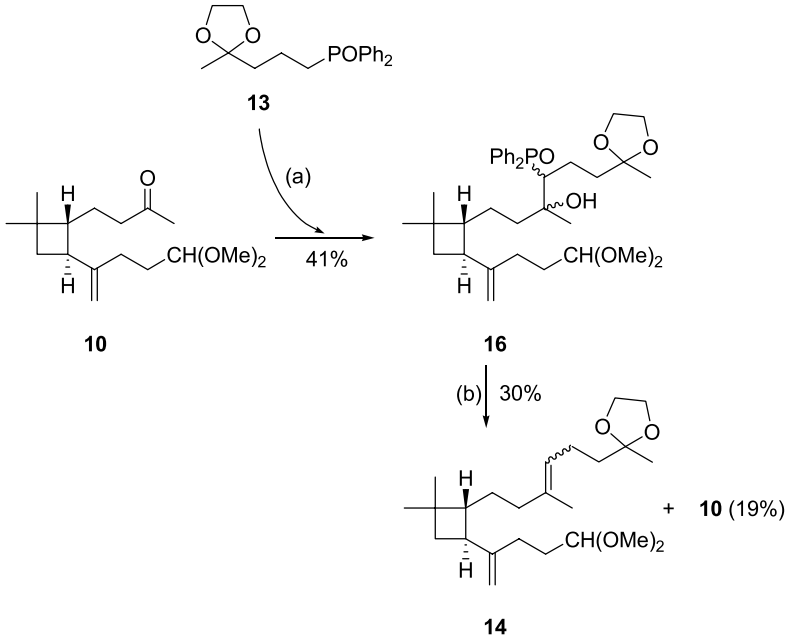
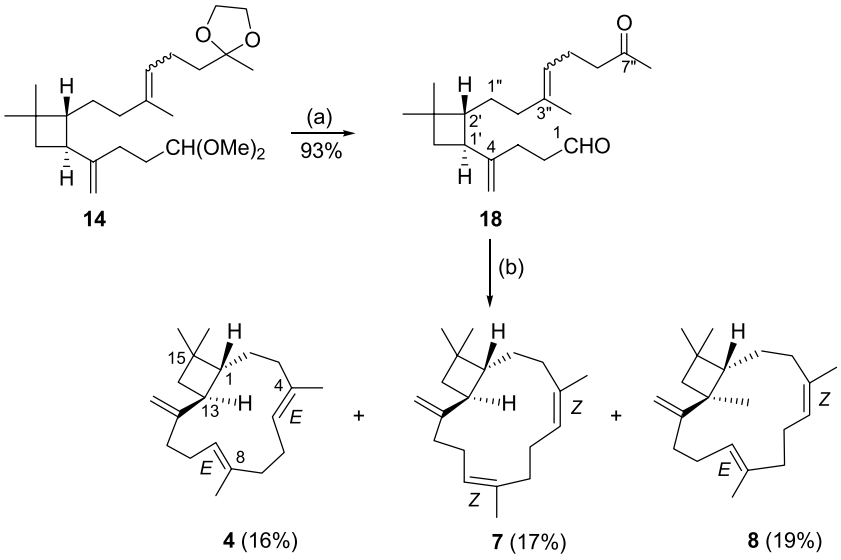


Scheme 4. Warren modification of the Wittig reaction of **10**. (a) BuLi/THF; (b) NaH/DMF.



Scheme 5. Synthesis of trienes **4**, **7** and **8**. (a) $HCl_{(aq)}$/THF; (b) Ti(0)/DME.

Removal of the acetal functions of **14** by acid hydrolysis proceeded efficiently, yielding inseparable (*E*) and (*Z*) isomers of product **18** (Scheme 5). Regeneration of the carbonyl groups was shown by the IR (ν_{max} 2725 (HC═O), 1714 (C═O) cm^{-1}) and NMR spectra (δ_H 2.13, 3H, s and 9.77, 1H, t, $J=2$ Hz; δ_C 202.3, 208.8). The olefinic methyl groups of the two isomers gave rise to ^1H NMR signals at δ_H 1.59 and 1.66 for the (*E*) and (*Z*) alkenes respectively. Isomeric ratios of isomers determined by integration of these signals concurred with those determined by gas chromatography, and (*E*)/(*Z*) mixtures of both 1:1 (from **14** formed by Warren reaction of **10** and **13**) and 5:11 (from Wittig reaction of **10** and **12**) were prepared.

McMurry coupling (Scheme 5) was initially achieved by using a modification of the procedures reported for the synthesis of humulene[20] and cyclotridecene,[21] and employed 8 equivalents of titanium trichloride with a 3.1:1 ratio of Zn/Cu couple to titanium trichloride. Keto aldehyde **18** with an (*E*)/(*Z*) ratio of 1:2.4 was added via syringe pump. GC of the product revealed approximately equal amounts of three components of similar retention index. GC/MS showed similar mass spectra for each peak, with the highest ion recorded at 257 Da, corresponding to a loss of CH_3 (β-caryophyllene (**5**) exhibits similar facile loss of CH_3). The ^1H NMR spectrum, though complicated by peak overlap, suggested that cyclization had taken place as desired. Although no starting material or pinacol species were detected, the isolated yield of trienes was only 20%.

The synthesis of casbene[22] appeared to offer a good analogy for the cyclization of **18**. This synthesis involved the coupling of a methyl ketone with an aldehyde, a 14-membered ring fused to a small ring with a *gem*-dimethyl unit was formed, and apart from the two reacting carbonyls, only alkene functional groups were present. Cyclization of **18** was achieved in a 30% yield by the use of 40 equivalents of titanium trichloride. This was increased to 52% by increasing the reagent preparation time and by adding the substrate more slowly.

With the notable exception of the keto-ester cyclization that enabled formation of the cyclononene ring in an attempted synthesis of β-caryophyllene,[23] the McMurry reaction conditions have not been reported to induce geometric isomerization of existing double bonds. No geometrical or positional isomerization has been observed during the intramolecular coupling reactions of keto-aldehyde reactants.[24] Thus the three products of the McMurry coupling of **18** were expected to retain the (*E*)/(*Z*) ratio of the substrate in the pre-existing double bond. Given the dominance of the (*Z*) isomer in the substrate and the approximate 1:1:1 ratio of triene products, it seemed likely that the (*Z*)-form of **18** had reacted to yield the (4*Z*,8*Z*)-triene **7** and the (4*Z*,8*E*)-triene **8**, while the (*E*)-isomer of **18** had reacted with a high degree of stereoselectivity to yield either the desired (4*E*,8*E*)-triene **4** or its (4*E*,8*Z*)-isomer. This hypothesis was consistent with the results of a dicarbonyl coupling reaction completed with a 1:1 mixture of the isomers of **18**. Here, GC revealed a ca. 1:1:2 ratio of the same triene products.

Although reverse phase chromatography has been applied successfully to the separation of the geometric isomers of casbene,[22] no such separation of **4**, **7** and **8** was attained. However, the three isomers were separated by centrifugal chromatography on silver nitrate impregnated silica. Two components eluted with 3:97 ethyl acetate/hexanes, and the third with 3:17 ethyl acetate/hexanes. This latter component, the (4*Z*,8*E*)-triene **8**, had the greatest signal dispersion in the ^1H NMR spectrum and proved to be the most amenable to full structural characterization.

HRMS data for triene **8** were consistent with the expected molecular formula, $C_{20}H_{32}$. The solution IR spectrum was compatible with an unsaturated hydrocarbon and ^1H and ^{13}C NMR spectroscopy (Table 1) revealed the presence of 1,1-disubstituted and trisubstituted (×2) double bonds in accord with a bicyclic structure.

Long range correlations from the proton resonances at δ_H 1.04, 1.02 to a quaternary carbon signal at δ_C 33.3 were

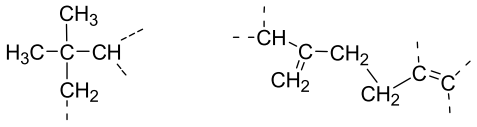
Table 1. NMR data for isomeric trienes **4**, **7** and **8**[a]

Position	δ_C			δ_H[b] [LRHETCOR[c]]
	4 (4*E*,8*E*)	**7** (4*Z*,8*Z*)	**8** (4*Z*,8*E*)	
1	45.3	50.7	47.1	1.92, ddd, 9.5, 10, 10 [n.o.]
2	27.3	28.0	25.1	2.12 [n.o.]; 2.29 [C-3]
3	35.4	28.8	29.1	1.73 [n.o.]; 2.27 [C-4, 4-Me]
4	133.5	137.9†	136.2	—
5	124.2	124.5‡	125.3	5.12, br dd, 7,7 [n.o.]
6	24.5*	30.9	29.6	1.73 [n.o.]
7	39.1	31.5	38.3	1.82 [n.o.]; 2.12 [n.o.]
8	133.7	136.9†	136.9	—
9	125.6	124.0‡	124.6	5.05, br dd, 6.5, 11 [n.o.]
10	25.0*	33.2	30.5	2.10 [n.o.]
11	31.4	37.3	34.4	2.17 [C-10, C-12, 12-=CH_2]
12	149.7	153.7	152.4	—
13	43.5	41.2	41.2	2.34 [C-2]
14	36.3	39.4	41.0	1.35, dd, 9.5, 10 [C-12, 15β-Me]; 1.85, dd, 10, 10 [n.o.]
15	33.7	33.3	33.3	—
15β-Me	31.4	30.8	30.6	1.04, s [C-1, C-15, 15α-Me]
15α-Me	23.3	23.0	22.6	1.02, s [C-14, C-15, 15β-Me]
12-=CH_2	108.6	108.4	108.7	4.78, s [C-13]; 4.87, d, 1.5 [C-11]
4-Me	15.1	23.8*	22.6	1.64, s [C-3, C-4, C-5]
8-Me	16.9	23.6*	19.1	1.61, s [C-7, C-8, C-9]

*,†,‡Values marked with the same symbol within a column may be interchanged.
[a] Recorded in $CDCl_3$ at 75 MHz (^{13}C) or 300 MHz (^1H), referenced to TMS.
[b] Chemical shift in ppm, multiplicity, coupling constants in Hz.
[c] Correlations from proton to signal to designated carbon signal, n.o.—none observed.

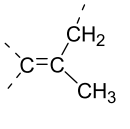
consistent with a *gem* dimethyl unit. Generation of substructure **8a** was enabled by LRHETCOR correlations from the methyl proton signal at δ 1.02 to a methylene carbon signal at δ_C 41.0, and from that at δ 1.04 to a methine carbon signal at δ_C 47.1.

A further substructure **8b** was generated based on chemical shift data, and LRHETCOR correlations. A correlation from one of the olefinic methylene proton signals (δ_H 4.78) to a methine carbon signal at δ_C 41.2 and one from the allylic methylene proton signal at δ_H 2.17 to the olefinic carbon resonances at δ_C 108.7 (t) and 152.4 (s) established the nature of the carbons adjacent to the 1,1-disubstituted double bond. The proton signal at δ_H 2.17 also correlated to a further methylene carbon (δ_C 30.5) associated with an allylic proton signal (δ_H 2.10).



8a

8b



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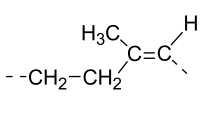
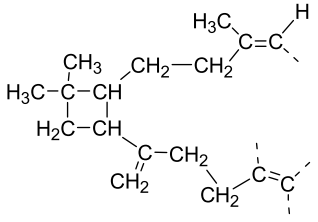


8d



8e

The ^1H NMR spectrum displayed two allylic methyl signals at δ_H 1.61 and 1.64. Each showed LRHETCOR correlation to a methylene carbon signal (δ_C 38.3 and 29.1 respectively). A proton signal associated with the latter of these (δ_H 2.27) correlated to the carbon signal of a further methylene group (δ_C 25.1). This gave rise to two further subunits **8c** and **8d**. The carbon chemical shifts of the two allylic methyl groups were consistent with an (*E*) geometry for the double bond of **8c** and a (*Z*) geometry for that of **8d**.[14] These four substructures **8a–d** encompassed 19 of the 20 carbons.

NMR shift data for the carbons of subunit **8a** indicated that it was, as expected, part of a four-membered ring. The structure of the starting material implied the union of fragments **8a** and **8b** to form a cyclobutane ring. The coupling pattern observed for the ring methylene proton signals (δ_H 1.35, dd, J=9.5, 10 Hz; 1.85, dd, J=10, 10 Hz) concurred with this proposal. LRHETCOR correlation between the proton signal of the methine group of **8b** (δ_H 2.34) and the carbon signal of the terminal methylene unit of **8d** (δ_C 25.1) added further weight to this assertion and

allowed the addition of subunit **8d** as in substructure **8e**. The methylene group in substructure **8c** is not part of substructure **8e** and this, together with only unplaced methylene group (δ_H 1.73, δ_C 29.6), was required to complete the ring as in structure **8**.

The first isomer to elute from the silver nitrate plate, had very similar HRMS and IR spectra to those of **8**. The most significant difference between the ^{13}C NMR spectra of the two isomers was the chemical shift of the peaks assigned to the methyl groups of the trisubstituted double bonds (δ_C 15.1 and 16.9 compared to δ_C 19.1 and 22.6 for **8**). Thus, both double bonds have the (*E*) geometry as in the desired structure **4**.[14] Observed LRHETCOR correlations were consistent with this structure.

The remaining isomer was assigned the (4*Z*,8*Z*) stereochemistry **7** on the basis of the chemical shifts of the two olefinic methyl carbon signals (δ_C 23.6, 23.8). Resonances (Table 1) were assigned with the aid of LRHETCOR correlations and by comparison of chemical shifts with those of **4** and **8**.

3. Conclusions

The synthesis of the caryophyllene isoprenologue **4** with the (4*E*,8*E*) geometry has now been completed. This has also yielded the (4*Z*,8*Z*) and (4*Z*,8*E*) isomers **7** and **8**. Overall, (−)-β-caryophyllene (**5**) has been converted into a 1:1:1 mixture of **4**, **7** and **8** in a 25% yield. Compound **4** is a potential natural product, structurally related to the marine metabolite, flexibilene **2**[3] as humulene **6** is to caryophyllene **5**. The GC retention, MS and NMR data presented here will allow rapid identification of **4**, or isomers **7** and **8**, from natural sources. However, any intention to explore possible connections between **4** and laurenene **1**, must await a synthesis that is more amenable to scale-up.

NMR spectra of the bicycle [11.2.0] compounds **4**, **7** and **8** showed no significant line broadening in contrast to the bicyclic [7.2.0] compound, caryophyllene (**5**)[25,26] where the smaller ring resulted in slowly exchanging rotational isomers.

4. Experimental

4.1. General methods

4.1.1. Chromatography. TLC was performed on silica gel 60 F_{254} 0.2 mm coated aluminium foil. Centrifugal chromatography was performed on a Harrison Research 7942T Chromatotron with plates coated with 1, 2 or 4 mm layers of silica gel 60 PF_{254} with $CaSO_4 \cdot ½H_2O$ applied as a slurry and dried. 4 mm Silver (I) impregnated plates were made by including $AgNO_3$ (5 g) into the slurry. Column chromatography used silica gel 60. GC was performed using a Hewlett–Packard HP 6890 series capillary gas chromatograph fitted with a programmable temperature injector (250 °C) and a flame ionisation detector (260 °C). A 30 m × 0.32 mm HP-1 column (0.25 μm film thickness) was used with helium as carrier gas at 8 PSI with a flow rate of 30 mL min^{-1}. Sample size was 0.1 μL and a sample split ratio of ~20:1 was used. Kovats retention indices[27] were determined from isothermal runs at 170 and 190 °C.

4.1.2. Instrumentation. NMR spectra were recorded on a Varian VXR-300 spectrometer operating at 300 MHz for ^1H and 50 MHz for ^{13}C. Spectra were obtained at 25 °C on ca. 0.075 M $CDCl_3$ solutions and were referenced to the $CHCl_3$ peak (δ 7.26) for ^1H, or to the centre line of the $CDCl_3$ signal (δ 77.08) for ^{13}C. LRHETCOR spectra were optimised for long range coupling of 6–10 Hz. IR spectra were recorded on a Perkin–Elmer 1600 series FT IR instrument. Optical rotations were measured as $CHCl_3$ solutions using a Jasco DIP-370 digital polarimeter.

4.1.3. Inert gas purification. Dry, oxygen free argon (1 to 10 ppm O_2) was prepared by passing argon (NZIG gas code 130) through a column (45 × 500 mm) packed with BASF R 3-11 catalyst. The catalyst was reduced prior to use by slowly passing a stream of H_2 through the pellets and increasing the temperature to 140 °C over 4 h, then maintaining this temperature for 12 h. The catalyst was then dried (200 °C/0.2 mm Hg, 12 h) and the column was connected to the two stage argon cylinder valve. H_2O was removed by a second column (35 × 240 mm) packed with Drierite indicator and powdered P_2O_5. All solvent transfers requiring dry conditions were done using Schlenck apparatus under dry argon and using standard vacuum line techniques. Glassware was flame dried three times. For the McMurry reaction, glassware was also heated overnight at 120 °C and ground glass joints were immediately fitted with a Teflon® sleeve and connected to vacuum prior to flame drying. Molecular sieves (new and recycled) were dried (180 °C, 0.2 mm Hg) for 10 h prior to use.

4.1.4. Solvent purification. For the Wittig reactions, THF was refluxed for 2 h and freshly distilled from Na/K amalgam under an argon atmosphere. DMSO was distilled under reduced pressure, shaken overnight with 4 Å molecular sieves then redistilled on to fresh molecular sieve and stored under dry argon. For the McMurry reactions, potassium was cut under hexane and transferred quickly to a distillation apparatus that had been heated overnight in an oven (120 °C) and then purged with dry argon. DME was then refluxed for 10 h over potassium under dry argon and then distilled onto fresh potassium. The DME was then refluxed over potassium under dry argon for a further 4 h before use in subsequent reactions. Acetone was distilled from 4 Å molecular sieves onto fresh sieve and stored under dry argon for 1 week prior to use. Et_2O was freshly distilled from $LiAlH_4$ under dry argon.

4.1.5. Zn/Cu couple. Zinc dust (489 g) was stirred with aqueous HCl solution (2%, 1500 mL) for 5 min then washed with aqueous HCl solution (2%, 1000 mL), H_2O (3 × 500 mL), EtOH (2 × 750 mL) then Et_2O (2 × 500 mL). The solvents were decanted from the dust in each case. The resultant light grey powder was dried (100 °C/12 mm Hg) for 3 h. A portion was weighed into a conical flask (127.08 g, 2 mol), and a glass filter tube with sinter (grade 4) was fitted. The vessel was evacuated for 1 h and then an argon atmosphere introduced and the equipment evacuated and flushed with argon three times. H_2O (500 mL) was

introduced and the slurry purged with argon for 10 min. $CuSO_4 \cdot 5H_2O$ (11.2 g, 63 mmol) was added and the reaction mixture shaken. After 5 min the solids were collected by filtration and washed with acetone (200 mL), then Et_2O (200 mL), and the dark grey material was dried (100 °C/0.2 mm Hg, 5 h) before being stored under dry argon.

4.1.6. (−)-β-Caryophyllene (5). Commercial β-caryophyllene (*ex* BDH) was purified by silica column chromatography, eluting with hexanes, to remove humulene and oxidised material.

4.2. Synthetic methods

4.2.1. (1′*S*,2′*R*)-3,3-Dimethyl-4-methylene-2-(3-oxobutyl)cyclobutanebutanal (9).[5] {CN 101979-01-5} A solution of (−)-β-caryophyllene (**5**) (5.0 g, 24.3 mmol) in EtOAc (50 mL) was dissolved in MeOH (500 mL) containing hexadecane (0.1 g) and treated with dry, ozonised oxygen at −78 °C. The reaction was monitored by GC. After 35 min there was no diene present with respect to the internal standard (hexadecane). After excess ozone had been removed by purging with nitrogen, Me_2S (5 mL) was added, and the reaction mixture was stirred for 12 h. Evaporation followed by column chromatography, eluting with Et_2O, gave **9** (2.4 g, 41%) as a clear oil; IR as in Ref. 5; ^{1}H NMR δ 1.05 (s, 2×3′-Me), 1.41 (dd, J=7, 8 Hz, H-4′), 1.63 (m, $W_{h/2}$=13 Hz, 2×H-4″), 1.80 (H-4′), 1.86 (m, H-2′), 2.12 (s, 3×H-1″), 2.31 (m, 2×H-2, 2×H-3 and H-1′), 2.57 (m, $W_{h/2}$=7 Hz, 2×H-3″), 4.69 (s, 4-=CH_2), 4.78 (s, 4-=CH_2), 9.75 (s, H-1); ^{13}C NMR δ 22.0 (3′-Me), 24.2 (C-4″), 26.2 (C-3), 29.5 (C-1″), 30.7 (3′-Me), 33.3 (C-3′), 39.3 (C-4′), 41.2 (C-1′), 41.5 (C-3″), 41.5 (C-2), 47.4 (C-2′), 107.2 (4-=CH_2), 150.3 (C-4), 201.7 (C-1), 208.3 (C-2″).

4.2.2. (1′*R*,4′*S*)-4-[4-(4, 4-Dimethoxy-1-methylenebutyl)-2, 2-dimethylcyclobutyl]-butan-2-one (10).[5] {CN 101927-11-1} MeOH (170 mL) was added to a solution of commercial (−)-β-caryophyllene **5** (3.0 g, 70% **5** by GC, 10.2 mmol) in EtOAc (10 mL) and the mixture was treated with dry, ozonised oxygen at −78 °C for 10 min. After excess ozone had been removed by purging with nitrogen and the solution had warmed to room temperature, Me_2S (5 mL) and Montmorillonite K-10 clay (3 g) were added, and the reaction mixture was stirred for 48 h. Filtration, evaporation, followed by column chromatography on silica, eluting with Et_2O/hexanes, 1:1, gave **10** (1.6 g, 59%) as a clear oil, distilled 85 °C/0.02 mm Hg; $[\alpha]_D^{24}$ 51.2° ($CHCl_3$, *c* 1.0); IR as in Ref. 5; ^{1}H NMR δ 1.04 (s, 2′-Me), 1.05 (s, 2′-Me), 1.43 (dd, J=10.5, 10.5 Hz, H-3′), 1.65 (m, 2×H-4), 1.72 (m, 2×H-2″), 1.80 (m, H-3′), 1.88 (m, H-1′), 2.01 (m, $W_{h/2}$=19 Hz, 2×H-3″), 2.11 (s, 3×H-1), 2.35 (m, 2×H-3), 2.38 (m, H-4′), 3.32 (s, 2×OMe), 4.36 (t, J=6 Hz, H-4″), 4.72 (s, 1″-=CH_2), 4.75 (s, 1″-=CH_2); ^{13}C NMR δ 22.4 (2′-Me), 24.7 (C-4), 29.4 (C-3″), 30.0 (C-1), 30.8 (2′-Me), 31.1 (C-2″), 33.6 (C-2′), 39.9 (C-3′), 41.6 (C-4′), 42.1 (C-3), 47.9 (C-1′), 52.7 (2×OMe), 104.2 (C-4″), 107.0 (1″-=CH_2), 151.9 (C-1″), 209.0 (C-2). Anal. Calcd for $C_{17}H_{30}O_2$: C, 72.3; H, 10.7. Found C, 72.5; H, 10.4.

4.2.3. (1′*R*,4′*S*)-4-[4-(3-[1, 3]Dioxan-2-yl-1-methylenepropyl)-2,2-dimethylcyclobutyl]-butan-2-one (11). To a mixture of benzene (30 mL), *p*-toluenesulfonic acid (32 mg, 0.017 mmol) and 1,3 propanediol (0.647 g, 8.5 mmol) was added keto-aldehyde **9** (2.0 g, 8.5 mmol). The reaction was fitted with a Dean–Stark trap and heated under reflux for 2 h. The reaction mixture was cooled, washed with satd aqueous $NaHCO_3$ solution (35 mL), the aqueous layer extracted with ether (2×10 mL) and the combined organic portions dried. Evaporation gave an oil (2.40 g) which, on centrifugal chromatography (Et_2O/hexanes; 1:1) gave **11** (1.9 g, 80%) as a clear liquid; ^{1}H NMR δ 0.99 (s, 2′-Me), 1.00 (s, 2′-Me), 1.30 (m, $W_{h/2}$=2 Hz, H-5‴), 1.39 (t, J=10 Hz, H-3′), 1.54 (dt, J=8, 8 Hz, 2×H-4), 1.64 (m, 2×H-3″), 1.75 (m, H-3′), 1.82 (m, H-1′), 2.00 (m, 2×H-2″), 2.05 (m, H-5‴), 2.07 (s, 3×H-1), 2.29 (m, 2×H-3), 2.32 (m, H-4′), 3.70 (ddd, J=3, 12, 12 Hz, H-4‴, 6‴), 4.05 (dd, J=5, 12 Hz, H-4‴, 6‴), 4.47 (t, J=5.5 Hz, H-2‴), 4.65 (brs, 1″-=CH_2), 4.69 (brs, 1″-=CH_2); ^{13}C NMR δ 22.4 (q, 2′-Me), 24.7 (t, C-4), 25.8 (t, C-5‴), 28.7 (t, C-2″), 29.8 (q, C-1), 31.0 (q, 2′-Me), 33.5 (s, C-2′), 33.5 (t, C-3″), 39.9 (t, C-3′), 41.6 (d, C-4′), 42.0 (t, C-3), 47.8 (d, C-1′), 66.9 (t, C-3‴, 6‴), 101.9 (d, C-2‴), 106.9 (t, 1″-=CH_2), 151.9 (s, C-1″), 208.8 (s, C-2). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.4; H, 10.3. Found C, 73.1; H, 10.2.

4.2.4. (3′*E*,1″*R*,4″*S*)- and (3′*Z*,1″*R*,4″*S*)-2-{6-[4-(4,4-Dimethoxy)-1-methylenebutyl)-2, 2-dimethylcyclobutyl]-4-methyl-3-hexenyl}-2-methyl-1,3-dioxolane (14). (a) *n*-BuLi (871 μL, 1.4 M, 1.22 mmol) was added dropwise over 5 min to a stirred suspension of phosphonium salt **12**[10,11] {CN 21955-58-8} (0.580 mg, 1.11 mmol) in THF (20 mL) at −85 °C. After stirring for 5 min the solution was warmed to room temperature. After stirring for 10 min the bright orange/red solution was cooled to −85 °C and keto acetal **10** (0.300 g, 1.12 mmol) in THF (3 mL) was added dropwise over 5 min. The mixture was warmed to room temperature and stirred for 3 h before being diluted with H_2O (35 mL) and extracted with Et_2O (3×10 mL). Drying over anhyd. $MgSO_4$ and evaporation gave a yellow oil (0.350 g). Centrifugal SiO_2 chromatography (hexanes to Et_2O/hexanes; 1:1) gave a mixture of the (*E*) and (*Z*) isomers of **14** (5:11 by GC) (0.292 g, 66%). Further centrifugal chromatography on a sub-sample (×2, hexanes to Et_2O/hexanes; 3:1) yielded an enriched fraction of **14** with a 1:6 (*E*)/(*Z*) ratio by GC; IR (neat) ν_{max} 1039 (C–O), 924 (CH=C), 875 (CH_2=C) cm^{-1}; MS (EI) *m*/*z* (%) 379 ($M^+ - CH_3$, 5%), 362 ($M^+ -$MeOH, 5%), 347 ($M^+ - C_2H_7O$, 5%), 330 ($M^+ -$2MeOH, 5%). NMR spectra of mixtures of various compositions allowed assignment of most of the resonances for the two isomers. The (*Z*)-isomer had: ^{1}H NMR δ 1.06 (s, 2″-Me), 1.07 (s, 2″-Me), 1.32 (s, 2-Me), 1.67 (d, J=1 Hz, 4′-Me), 2.36 (ddd, J=9.5, 9.5, 9.5 Hz, H-4″), 3.32 (s, 2×OMe), 3.93 (m, $W_{h/2}$=7 Hz, 2×H-4 and 2×H-5), 4.37 (t, J=8 Hz, H-4‴), 4.71 (dd, J=1, 1 Hz, 1‴-=CH_2), 4.76 (s, 1‴-=CH_2), 5.08 (ddd, J=1, 8, 8 Hz, H-3′); ^{13}C NMR δ 22.4 (2″-Me), 22.7 (C-6′), 23.5 (2-Me), 23.9 (4′-Me), 29.5, 29.7, 30.6, 30.9 (C-1′, C-2′, C-2‴ and C-3‴), 31.4 (2″-Me), 33.8 (C-2″), 39.5, 39.6 (C-5′ and C-3″), 41.6 (C-4″), 49.3 (C-1″), 52.8 (2×OMe), 64.7 (C-4 and C-5), 104.3 (C-4‴), 106.9 (1‴-=CH_2), 110.0 (C-2), 124.1 (C-3′), 136.0 (C-4′), 152.2 (C-1‴). The (*E*)-isomer had: ^{1}H NMR δ 1.04 (s, 2″-Me), 1.05 (s, 2″-Me), 1.32 (s, 2-Me), 1.59 (s, 4′-Me), 2.35 (m, H-4″), 3.32 (s, 2×OMe), 3.93 (m, 2×H-4 and

2×H-5), 4.37 (m, H-4‴), 4.70–4.78 (m, 1‴-=CH_2), 5.06 (m, H-3′); ^{13}C NMR δ 15.9 (4′-Me), 33.7 (C-2″), 41.6 (C-4″), 48.5 (C-1″), 52.8 (2×OMe), 64.7 (C-4 and C-5), 104.3 (C-4‴), 106.8 (1‴-=CH_2), 109.9 (C-2), 123.7 (C-3′), 135.5 (C-4′), 152.2 (C-1‴) (other peaks obscured by overlaps with signals of the (*Z*)-isomer). A microanalytical sample was prepared by prep. TLC ($CHCl_3$) followed by microdistillation at 90 °C/4×10^{-4} mm Hg). Anal. Calcd for $C_{24}H_{42}O_4$: C, 73.1; H, 10.7. Found C, 73.1; H, 11.0.

(b) *n*-BuLi in hexanes (1.0 mL, 1.54 M, 1.52 mmol) was added dropwise over 5 min to a stirred solution of phosphine oxide **13**[12] {CN 87109-17-9} (0.456 g, 1.38 mmol) in THF (20 mL) at −78 °C. After stirring for 2 min the solution was warmed to 0 °C. After stirring for 15 min the deep red solution was cooled to −78 °C and a solution of keto acetal **10** (0.390 g, 1.38 mmol) in THF (7 mL) was added dropwise over 2 min. The solution decolourised, was warmed to room temperature, stirred for 5 min then quenched with saturated NH_4Cl (20 mL) and extracted with Et_2O (3×15 mL). Drying of the combined organic phases over anhyd. $MgSO_4$ and evaporation gave a pale yellow solid (0.964 g). Centrifugal chromatography (EtOAc to EtOH/EtOAc; 1:9) gave: (i) a mixture of diastereoisomers of the diphenylphosphinoyl alcohols **16** (0.350 g, 41%); IR (nujol) ν_{max} 3350 (OH), 1549, 1481, 1460, 1261, 1170, 750 cm^{-1}; ^{1}H NMR† δ 0.84, 0.88 (both s, 2″-Me), 0.96, 0.98, 1.04 (all s, 4′-Me), 1.24, 1.27 (both s, 2-Me), 1.25–2.25 (m, unassigned), 2.32 (m, $W_{h/2}$=9 Hz, H-3′ and H-4″), 3.31 (s, 2×OMe), 3.59–4.28 (m, H-4 and H-5), 4.34 (m, $W_{h/2}$=15, H-4‴), 4.52–5.00 (m, 1‴-CH_2), 7.48 (m, $W_{h/2}$=14 Hz, Ph, 6H), 7.79 (m, $W_{h/2}$=36 Hz, Ph, 4H); ^{13}C NMR† δ 20.3–49.2 (multiple peaks, unassigned), 52.6 (OMe), 64.2, 64.4, 67.7 (C-4 and C-5), 75.8, 75.9 (C-4′), 104.06, 104.11 (C-4‴), 106.5, 106.6, 106.7, 106.8 (C-1‴), 109.0 (C-2), 128.3–131.5 (several peaks, Ph), 151.8, 152.0 (C-1‴); (ii) starting material **10** (0.200 g, 55%). The reaction was repeated on scales up to 1.0 g of **10**.

To a stirred solution of the phosphinoyl alcohol mixture **16** (0.525 g, 0.858 mmol) in DMF (5 mL) was added NaH (0.041 g, 60% in oil, 1.7 mmol) and the mixture was stirred at 50 °C. After 1 h, TLC indicated that the starting material had not been fully converted and additional NaH (0.040 g, 1.7 mmol) was added. After a further 1.5 h the mixture was cooled, diluted with Et_2O (10 mL), quenched with saturated NaCl (50 mL) and extracted with Et_2O (3×10 mL). Drying over anhyd. $MgSO_4$ and evaporation gave a brown oil (0.569 mg) that on centrifugal chromatography (hexanes to EtOH/EtOAc; 1:9) gave; (i) a mixture of the (*E*) and (*Z*) isomers of **14** (1:1 by GC) (0.050 g, 16%); (ii) keto acetal **10** (0.045 g, 19%); (iii) unchanged **16** (0.240 g, 46%).

4.2.5. (3‴*E*,1″*S*,2*R*″)- and (3‴*Z*,1″*S*,2*R*″)-2-(3-{3, 3-Dimethyl-2-[3-methyl-6-(2-methyl-[1, 3]dioxolan-2-yl)-hex-3-enyl]-cyclobutyl}-but-3-enyl)-[1,3]dioxane (15). (a) Keto acetal **11** (0.100 g, 0.25 mmol) in THF (1 mL) was reacted with phosphonium salt **12**[10,11] as for the reaction of **10**. The ylide was prepared from *n*-BuLi (177 μL, 1.55 M, 0.27 mmol), **12** (0.130 mg, 0.25 mmol) in THF (4 mL). A yellow oil (0.200 g) was separated by centrifugal SiO_2 chromatography (Et_2O/hexanes; 1:9 to 1:1) to give a mixture of the (*E*) and (*Z*) isomers of **15** (1:2.3 by GC) (0.0.041 g, 40%); IR (neat) ν_{max} 1042 (C–O), 922 (CH=C), 875 (CH_2=C) cm^{-1}; ^{1}H NMR δ 1.03, 1.04, 1.06, 1.07 (each s, 3″-Me), 1.33 (s, 2‴′-Me), 1.58 (brs, 3‴-Me (*E*)-isomer), 1.66 (brs, 3‴-Me (*Z*)-isomer), 2.36 (brddd, *J*=9.5, 9.5, 9.5 Hz, H-1″), 3.72 (ddd, *J*=3, 12, 12 Hz, H-4, 6), 3.93 (m, $W_{h/2}$=6 Hz, 2×H-4⁗, 2×5⁗), 4.10 (dd, *J*=5, 12 Hz, H-4, 6), 4.50 (t, *J*=8 Hz, H-2), 4.70 (m, $W_{h/2}$=13 Hz, 2×H-4′), 5.05–5.15 (m, H-4‴); ^{13}C NMR δ 15.9 (3‴-Me (*E*)-isomer), 48.5, 49.3 (C-2″), 64.7 (C-4⁗, 5⁗), 66.9 (C-4, 6), 102.1 (C-2), 106.9 (C-2⁗), 109.9, 110.0 (C-4′), 123.7, 124.1 (C-4‴), 135.6, 136.1 (C-3‴), 152.2, 152.3 (C-3′). Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.9; H, 10.4. Found C, 73.6; H, 10.7.

(b) Keto acetal **11** (0.100 g, 0.25 mmol) in THF (1 mL) was reacted with the phosphine oxide **13** as for the reaction of **10**. The anion was prepared from *n*-BuLi in hexanes (177 μL, 1.55 M, 0.27 mmol), **13**[12] (0.082 g, 0.25 mmol) in THF (4 mL). A semi-solid (0.188 g) was separated by centrifugal chromatography (EtOAc to EtOH/EtOAc; 1:9) to give: (i) phosphinoyl alcohol **17** isomer fraction 1 (0.028 g, 15%); ^{1}H NMR† δ 1.00, 0.96 (each 3H, s, 3″-Me), 1.02 (3H, s, 3‴-Me), 1.17 (3H, s, 2⁗-Me), 1.25–2.45 (m), 3.10–3.35 (6H, m, H-4, 6, 4⁗, 5⁗), 4.10 (2H, dd, *J*=5, 12 Hz, H-4, 6), 4.50 (1H, t, *J*=6.5 Hz, H-2), 4.69 (2H, brs, H-4′), 7.48 (6H, m, $W_{h/2}$=18 Hz, Ph), 7.82 (4H, m, $W_{h/2}$=32 Hz, Ph); ^{13}C NMR δ 20.5–46.5 (multiple peaks), 48.9 (C-2″), 64.4 (C-4⁗, 5⁗), 66.9 (C-4, 6), 76.1, 76.2 (C-3‴), 102.1 (C-2), 106.6 (C-4′), 109.2 (C-2⁗), 134.0–128.5 (multiple peaks, Ph), 152.2 (C-3′); (ii) phosphinoyl alcohol **17** isomer fraction 2 (0.028 g, 15%); ^{1}H NMR† δ 0.98, 0.95 (each 3H, s, 3″-Me), 1.01 (3H, s, 3‴-Me), 1.19 (3H, s, 2⁗-Me), 1.20–2.45 (m), 3.70 (6H, m, $W_{h/2}$=41 Hz, H-4, 6, 4⁗, 5⁗), 4.09 (2H, $W_{h/2}$=26 Hz, H-4, 6), 4.50 (1H, t, *J*=7 Hz, H-2), 4.69 (2H, $W_{h/2}$=8 Hz, H-4′), 7.50 (6H, m, $W_{h/2}$=18 Hz, Ph), 7.81 (4H, m, $W_{h/2}$=28 Hz, Ph); ^{13}C NMR δ 20.5–46.5 (multiple peaks), 48.9 (C-2″), 64.4 (C-4⁗, 5⁗), 66.9 (C-4, 6), 76.5, 76.5 (C-3‴), 102.0 (C-2), 106.9 (C-4′), 109.1 (C-2⁗), 134–128.5 (multiple peaks, Ph), 152.1 (C-3′); (iii) unchanged keto acetal **10b** (0.075 g, 72%).

The less polar phosphinoyl alcohol **17** fraction (0.028 g, 0.039 mmol) in DMF (0.5 mL) was treated with NaH (1.6 mg, 60% in oil, 0.039 mmol) as for the reaction of **16**. GC of the crude product revealed a 5:6 ratio of the (*Z*) to (*E*) isomers of **15**. The same ratio was obtained from the more polar **17** fraction.

4.2.6. (1′*S*,2′*R*,3″*E*)- and (1′*S*,2′*R*,3″*Z*)-3,3-Dimethyl-4-methylene-2-(3-methyl-7-oxoocta-3-enyl)cyclobutane-butanal (18). A solution of the (*E*) and (*Z*) isomers of **14** (0.649 g, 1.65 mmol, ratio 1:1) in THF (30 mL) containing aqueous HCl (2 M, 3 mL) was heated under reflux for 10 min. The mixture was cooled, quenched with saturated Na_2CO_3 (30 mL), and extracted with Et_2O (3×15 mL). Drying and evaporation gave the (*E*) and (*Z*) isomers of **18** (1:1 ratio by GC) as a clear oil (0.467 g, 93%); IR (neat) ν_{max} 2725 (HC=O), 1714 (C=O), 1634 (C=C) cm^{-1}; ^{1}H NMR δ 1.05, 1.07 (both s, 3′-Me), 1.59 (brs, 3″-Me, (*E*)-isomer), 1.66 (brd, *J*=1 Hz, 3″-Me, (*Z*)-isomer), 2.13 (s,

† Numbering as for **14**.

3×H-8″), 4.67, 4.78, 4.80 (all brs, γ-=CH_2), 5.00–5.09 (m, H-4″), 9.77 (t, J=2 Hz, H-1); ^{13}C NMR low-field signals at δ 107.4, 107.5 (γ-=CH_2), 122.4, 122.8 (C-4″), 136.6, 137.0 (C-3″), 150.8 (C-4), 202.3 (C-7″), 208.8 (C-1). A microanalytical sample was prepared by prep. TLC (CH_2Cl_2) followed by microdistillation at 90 °C/1×10^{-3} mm). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found C, 78.6; H, 10.7. A 5:11 mixture of the (*E*) and (*Z*) isomers of **16** was formed similarly.

4.2.7. (1*R*,4*E*,8*E*,13*S*)-, (1*R*,4*Z*,8*Z*,13*S*)- and (1*R*,4*Z*,8*E*,13*S*)-4,8,15,15-Tetramethyl-12-methylenebicyclo-[11.2.0]pentadeca-4, 8-dienes (4), (7) and (8). To a stirred mixture of $TiCl_3$ (8.14 g, 52.8 mmol) and Zn/Cu couple (11 g, M_r=65.5, 169 mmol) was added dry dimethoxyethane (120 mL). The mixture was gently simmered with vigorous stirring for 17 h. At first a blue-green colour was visible, but after ~5 h a black suspension predominated. A 5:11 mixture of (*E*) and (*Z*) isomers of keto aldehyde **18** (0.408 g, 1.32 mmol) was first dried for 4 h under vacuum at ambient temperature then dissolved in dry dimethoxyethane (49 mL) and added to the reaction via syringe pump at a rate of 0.54 mL h^{-1}. After 4 days, the addition was complete. The mixture was heated for a further 4 h, cooled, filtered through a pad of Florisil® and evaporated to give a yellow oil (0.482 g) containing three major components (1:1:1 ratio) by GC. Centrifugal chromatography on $AgNO_3$ impregnated silica (×2, hexane to EtOAc/hexane; 7:13) gave the following trienes listed in order of elution: (i) with EtOAc/hexanes; 3:97, (4*E*,8*E*)-diene **4** (0.056 g, 16%); $[\alpha]^{24}$ +42° (589 nm); +44° (577 nm); +50° (546 nm); +83° (435 nm); +93° (405 nm); +61° (365 nm) ($CHCl_3$, *c* 1.33); GC RI 1886 (170 °C), 1908 (190 °C); IR (CCl_4) ν_{max} 2928, 2860, 1461, 1381 (C–H), 1635, 921, 902 (C=C) cm^{-1}; ^{1}H NMR [LRHETCOR] δ 1.02 (s, 15α-Me) [15β-Me], 1.05 (s, 15β-Me) [15α-Me], 1.40 (m, $W_{1/2}$=19 Hz, H-2), 1.54 (s, 4-Me) [C-4, C-5], 1.55 (m, H-2), 1.58 (s, 8-Me) [C-8, C-9], 1.63 (m, 2×H-14) [15α-Me, C-12], 1.74 (m, H-3) [C-2, C-5], 1.87 (ddd, J=5.5, 9.5, 9.5 Hz, H-1), 2.01 (m, H-11), 2.04 (m, H-3), 2.08 (m, 2×H-7), 2.13 (m, 2×H-6), 2.21 (m, H-11), 2.28 (m, 2×H-10), 2.50 (ddd, J=9.5, 9.5, 9.5 Hz, H-13) [C-2], 4.74 (s, 12-=CH_2), 4.83 (s, 12-=CH_2) [15β-Me], 4.89 (dd, J=6.5, 6.5 Hz, H-5), 5.21 (dd, J=6.5, 6.5 Hz, H-9); ^{13}C NMR see Table 1; MS (EI) *m/z* [%] 272 [11], 257 [17], 216 [15], 201 [10], 161 [19], 147 [19], 137 [10], 135 [20], 133 [29]; HRMS [M^+] calcd for $C_{20}H_{32}$ 272.2504, found 272.2507; (ii) with EtOAc/hexanes; 3:97, (4*Z*,8*Z*)-diene **7** (0.063 g, 17%); $[\alpha]^{24}$ −23° (589 nm); −25° (577 nm); −29° (546 nm); −61° (435 nm); −78° (405 nm); −31° (365 nm) ($CHCl_3$, *c* 1.06); GC RI 1879 (170 °C), 1901 (190 °C); IR (CCl_4) ν_{max} 2958, 2861, 1461, 1379 (C–H), 1636, 900 (C=C) cm^{-1}; ^{1}H NMR [LRHETCOR] δ 1.03 (s, 15β-Me), 1.04 (15α-Me), 1.27 (m, $W_{1/2}$=23 Hz, H-6), 1.56 (dd, J=12, 12 Hz, H-14) [C-12, 15α-Me, 15β-Me], 1.62 (m, H-7), 1.70 (s, 4-Me and 8-Me), 1.72 (m, H-1), 1.81 (m, H-6), 1.83 (dd, J=12, 12 Hz, H-14) [15α-Me], 1.84 (m, H-10), 1.85 (m, H-2), 1.90 (ddd, J=3, 10, 10 Hz, H-3), 2.09 (m, 2×H-11) [C-12], 2.10 (m, H-10), 2.11 (m, H-3) [C-2], 2.36 (dd, J=15, 15 Hz, H-7) [C-4], 2.37 (m, H-2) [15α-Me], 2.52 (ddd, J=9, 9.5, 9.5 Hz, H-13) [C-12, 15β-Me], 4.71 (dd, J=2, 2 Hz, 12-=CH_2) [C-11], 4.75 (d, J=1 Hz, 12-=CH_2) [C-13], 5.21 (dd, J=8, 8 Hz, H-9), 5.23 (dd, J=8, 8 Hz, H-5); COSY correlations observed between δ 1.27 (H-6) and both δ 1.62 and 2.36 (H-7); ^{13}C NMR see Table 1; MS (EI) *m/z* [%] 272 [9], 257 [8], 216 [10], 201 [6], 161 [12], 147 [10], 137 [5], 135 [12], 133 [22]; HRMS [M^+] calcd for $C_{20}H_{32}$ 272.2504, found 272.2506; (iii) with EtOAc/hexanes; 3:17, (4*Z*,8*E*)-diene **8** (0.069 g, 19%); $[\delta]^{24}$ −84° (589 nm); −88° (577 nm); −103° (546 nm); −194° (435 nm); −245° (405 nm); −175° (365 nm) ($CHCl_3$, *c* 0.99); GC RI 1839 (170 °C), 1860 (190 °C); IR (CCl_4) ν_{max} 2955, 2923, 2859, 1453, 1381 (C–H), 1640, 912 (C=C) cm^{-1}; ^{1}H NMR see Table 1; ^{13}C NMR see Table 1; MS (EI) *m/z* [%] 272 [14], 257 [10], 216 [18], 201 [8], 161 [15], 147 [18], 137 [5], 135 [16], 133 [26]; HRMS [M^+] calcd for $C_{20}H_{32}$ 272.2504, found 272.2505.

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