Synthetic Studies towards Δ6-Protoilludene. A Formal Synthesis

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Hansen, T. V., M'dachi, S., Skattebøl, L. and Stenstrøm, Y., 1998. Synthetic Studies towards Δ6-Protoilludene. A Formal Synthesis. – Acta Chem. Scand. 52: 1373–1379. © Acta Chemica Scandinavica 1998.

A synthetic strategy towards Δ6-protoilludene included an intramolecular allene–ene cycloaddition reaction as a key step; however, the thermal reaction furnished a stereoisomeric mixture of 9-methyl-1,4,4,8-tetramethyltricyclo-[6.2.0.0^{2,6}]decane, which has a ring assembly isomeric with that of the target molecule. Another approach to Δ6-protoilludene required cis-4,4-dimethyl-2-isopropenylcyclopentylacetic acid, which was obtained from the mixture of stereoisomers by column chromatographic separation of the corresponding iodolactones. The cis-acid was further converted into cis-ethyl 4-(2-isopropenyl-4,4-dimethylcyclopentyl)-3-methyl-2-butenoate which has previously been transformed by others into Δ6-protoilludene. Hence, our approach constitutes formally a new synthesis of Δ6-protoilludene.
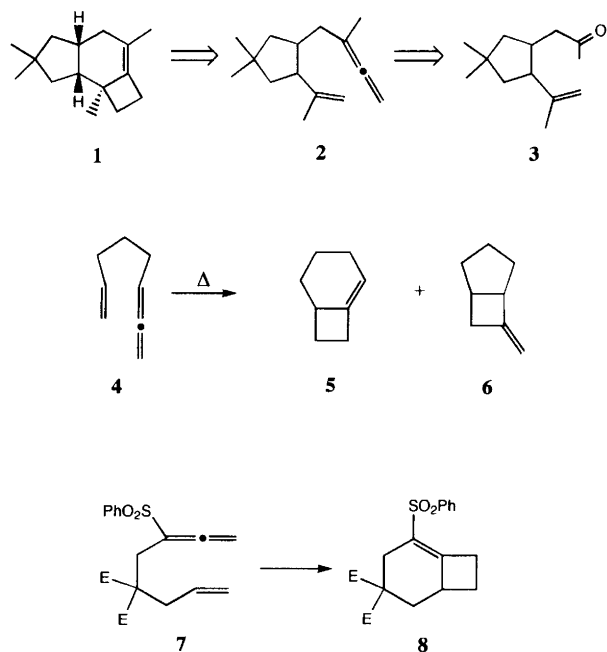
Over the past two decades several sesquiterpenes with the unique 4/6/5 ring system have been isolated from natural sources and characterised.[1] Δ6-Protoilludene (1) is the parent compound of one subclass, the protoilludanes. It has been isolated from the fungi *Fomitopsis insularis, Omphalotus olerius*[2a] and *Ceratocycstis piceae*[1c] and has been found to exhibit interesting antibacterial activity. Equally interesting is its possible role as an intermediate in the biosyntheses of other sesquiterpenes.[1c,2b,c] Finally, the unique skeleton of 1 represents a synthetic challenge, and few syntheses have so far appeared.[3] In the present paper we report on some synthetic work with Δ6-protoilludene as the target; one approach includes an intramolecular allene–ene cyclo-addition as the key step.

The retrosynthetic analysis of 1 may lead to the allene 2 and the ketone 3. We had reason to believe that the allene 2 might undergo a thermally induced intramolecular cycloaddition to give Δ6-protoilludene as one of the products since 1,2,7-octatriene (4) has been converted thermally into a 1:1 mixture of bicyclo[4.2.0]oct-1-ene (5) and the isomer 7-methylenebicyclo[3.2.0]octane (6).[4] Moreover, after the present work was completed Padwa *et al.* showed that the phenylsulfonyl-substituted allene reacted thermally to give the bicyclic compound 8 with the desired endocyclic double bond.[5] The transformation of 3 into the allene 2 was not expected to cause any problems. The acid 9 was readily obtained according to the literature as a 7:3 mixture of *cis* and *trans* isomers,

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respectively,[6] and we have previously shown that this mixture of the acid reacts with methyllithium furnishing the ketone 3 in 88% yield.[7] Attempts to separate by column chromatography the isomers of the ketone 3 as well as those of the acid 9 and its methyl ester were unsuccessful. Before getting further involved in this separation problem we decided to transform the mixture of the ketones 3 into the allene 2 in order to try the thermal reaction, the key step in our strategy towards Δ6-protoilludene.

The reaction of 3 with ethynylmagnesium bromide furnished the acetylenic alcohol 10a in 91% yield. However, we encountered some difficulties in converting the alcohol into the desired allene 2. The reaction with $AlCl_3$–$LiAlH_4$ in THF afforded a mixture of the allene and the allylic alcohol 11. The compounds were easily separated by column chromatography but the yield of isolated allene was only 43%. The formation of 11 should not come as a surprise since reduction of an acetylenic bond under such conditions has been observed previously.[8] Attempts to prepare the allene by first treating the acetylenic alcohol with HCl–$CaCl_2$ and subsequently with $LiAlH_4$ failed at the halogenation step; a mixture of products was formed and according to spectral data it seemed that addition of HCl to the triple bond had also taken place. The use of thionyl chloride was equally unsuccessful in providing the chloride in an acceptable yield. A palladium(II) acetate-catalysed reaction of the formate 10b probably led initially to the allene, that subsequently rearranged under the reaction conditions
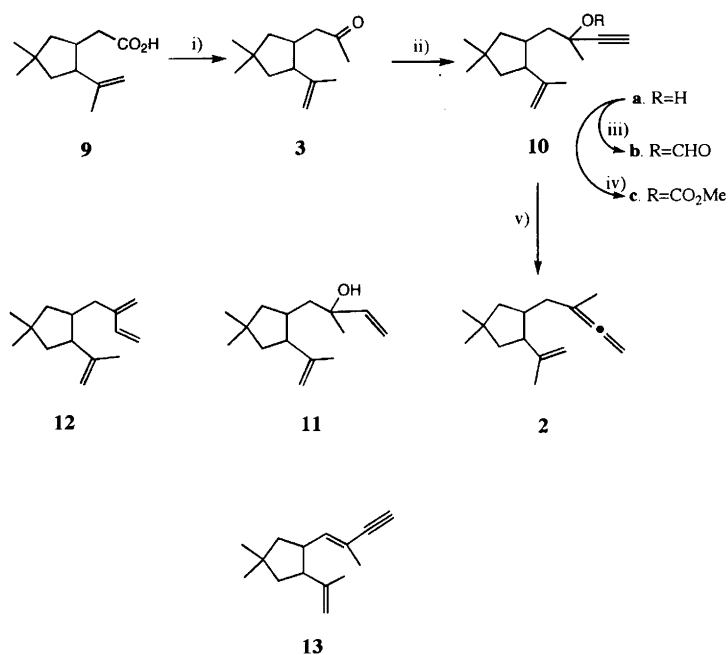
Scheme 1.

to the triene **12**. The latter was formed as a mixture of stereoisomers, which was separated by preparative GLC and characterised spectroscopically. However, this result was encouraging and by applying the palladium(0)-catalysed hydrogenolysis method described by Tsuji and co-workers[9] to the carbonate **10c**, the allene **2** was obtained in 77% yield; the preparation of the carbonate from **10a**, in 78% yield, was accompanied by a small amount (4%) of the vinylacetylene **13** that was easily

separated. Thus, without isolating the acetylenic alcohol the ketone **3** was transformed into the allene as a mixture of stereoisomers in 60% overall yield. The allene exhibited the characteristic strong absorption at 1950 cm^{-1} in the IR spectrum and moreover the NMR spectra were in agreement with the assignment. The results are summarised in Scheme 2.

The thermal reactions of the allene **2** were carried out both in the condensed phase and in the gas phase. Heating of a degassed sample of neat allene at 210 °C resulted in complete conversion into a complex product mixture of which three components with very close GLC retention times constituted 74%. A pure sample of one component (25%) was obtained by preparative GLC. The IR spectrum showed absorptions characteristic of a methylene double bond, and in particular, the C C stretching vibration at 1673 cm^{-1} indicated attachment to a cyclobutane ring. The NMR spectra were conclusive. In the ^{1}H spectrum the methylene double bond protons gave rise to triplets at 4.72 and 4.82 ppm coupled to allylic methylene protons appearing as a triplet at 2.35 ppm; furthermore, signals for a methylene carbon at 104.57 ppm and a quaternary carbon at 160.91 ppm in the ^{13}C spectrum confirmed the presence of this structural entity. The other spectral data were in complete agreement with the tricyclic structure **14**. The two remaining components were separated as a mixture by preparative GLC, and the very similar IR and NMR spectra to those above leave little doubt that they were also stereoisomers of **14**. The spectra of the crude mixture did not indicate that any Δ^6-protoilludene was formed in the reaction. Attempts to promote intramolecular cycloaddition of the allene by Lewis acid catalysts such

Scheme 2. (i) MeLi, 85%; (ii) HC≡CMgBr, 91%; (iii) HCO$_2$H, Ac$_2$O, 70%; (iv) ClCO$_2$Me, 78%; (v) Pd$_2$(dba)·CHCl$_3$, Bu$_3$P, HCO$_2$NH$_4$, 77%.

as $EtAlCl_2$ and $SnCl_4$ at $-78\,°C$ resulted only in complex product mixtures. The gas phase reaction was even less encouraging. Passage of the allene under reduced pressure through a quartz tube kept at $410\,°C$ resulted in a complex product mixture containing the cyclopentene derivative **15** as the major component (39%) and no compound **14** or Δ^6-protoilludene. A pure sample of **15** was collected by preparative GLC and identified spectroscopically. Incomplete conversion of the allene resulted when the tube temperature was lowered to $340\,°C$ yielding a similar complex reaction mixture, including the cyclopentene **15**. The formation of the latter seems to be the preferred reaction in the gas phase and is readily explained as the product of a retro-ene reaction of the allene as depicted in Scheme 3.

Unsatisfied with the above results, we sought alternative strategies towards Δ^6-protoilludene (**1**). The ester *cis*-**16a** was an intermediate in the synthesis of **1** by Oppolzer and Nakao,[3b] and both the ketone *cis*-**3** and the ester **17** seemed convenient precursors. The latter was prepared from the ketone **18**, obtained as the *E*-isomer in 83% yield from a reaction of 3,3,6-trimethyl-5-heptenal[10] with triphenylphosphoranylideneacetone.[11] The reaction of the ketone with the anion of trimethyl phosphonoacetate was quite sluggish; heating the reaction mixture at $70\text{–}80\,°C$ for 12 h afforded the ester **17**, but only 40% yield as a 2:1 mixture of *E/Z* isomers, respectively. The isomers were separated by column chromatography and identified spectroscopically. A degassed sample of **17**, when heated at $210\,°C$, underwent the expected ene reaction furnishing the ester **16a** as a minor product (16%) while the bicyclic ester **19** was the main product (54%). The latter resulted from a Diels–Alder reaction with reversed electron demand, which is apparently favoured over the ene-reaction.

Hence, we addressed the problem of separating *cis*-**9** from the mixture of stereoisomeric acids. If iodolactonization were to take place selectively with the *cis*-stereoisomer of the acid, the subsequent reaction with zinc should recover *cis*-**9** and separation of the isomers would actually have been achieved. The reaction of **9** with iodine under basic conditions afforded the iodolactone **20** albeit as a 7:3 mixture of *cis–trans* isomers, demonstrating complete

lack of selectivity in the lactone formation; however, only two isomers were present in the mixture indicating that the new stereogenic centre is formed stereoselectively. Fortunately, the isomeric lactones were easily separated by flash chromatography. Treatment of either isomer of **20** with zinc furnished the corresponding pure isomer of **9** in 51% overall yield. The major isomer *cis*-**9** was further transformed with methyllithium into the desired ketone *cis*-**3** in 88% yield. We have previously established unequivocally the configuration of this compound as *cis* based on X-ray diffraction studies on a derivative.[7]

Reaction of **3** with trimethyl phosphonoacetate using sodium hydride as base furnished the ester **16a** in 71% yield, but a small amount (3%) of the deconjugated ester **21** was formed as well, probably due to the strongly basic reaction conditions. This was avoided by using the commercially available ylide ethyl (triphenylphosphoranylidene)acetate, which on reaction with *cis*-**3** afforded *cis*-**16b** in 68% yield as the sole isolated product, and we assign tentatively the *E*-configuration to the double bond. With the preparation of the ethyl ester *cis*-**16b** we have actually accomplished a formal synthesis of Δ^6-protoilludene. Oppolzer and Nakao,[3b] prepared the methyl ester *cis*-**16** in eight steps from 2,2-dimethyl-4-pentenal which is not commercially available. Our preparation of the ester compares favourably with that reported particularly with respect to yields and simplicity.

Experimental

General. The NMR spectra were recorded on Varian Gemini 200 and JEOL JNM-GX270 instruments using $CDCl_3$ as the solvent and TMS as an internal standard. ^1H spectra are recorded at 200 and 270 MHz, and ^{13}C spectra were recorded at 50 and 67.5 MHz, respectively. IR spectra were recorded on either a Perkin–Elmer Paragon 500 FT spectrometer or a Magna-IR Spectrometer 550. MS spectra were recorded on GC–MS JEOL DX-303. For analytical GLC a 25 m SP2100 capillary column was used.

4,4-Dimethyl-1-(2-hydroxy-2-methyl-3-butynyl)-2-iso-propenylcyclopentane (**10a**). To a solution of ethynyl-magnesium bromide[12] in THF (71 ml, 0.059 mol), kept at $0\,°C$ under N_2, the ketone 3^7 (5.74 g, 29.5 mmol) in THF (10 ml) was added dropwise. When the reaction was complete (3.5 h), it was quenched with saturated aq. NH_4Cl and extracted with ether. The dried $(MgSO_4)$ extract was evaporated and flash chromatography (silica; pet. ether–EtOAc 95:5) of the residue yielded 5.87 g (91%) of the alcohol **10a**. ^1H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 6 H), 1.10–1.63 (multiplets, 4 H), 1.47 (s, 3 H), 1.70 (s, 3 H), 1.71–2.05 (m, 3 H), 2.20 (m, 2 H), 2.34 (s, 1 H), 4.74 (s, 2 H). IR (film): 3400 (s), 3280 (s), 3045 (w), 2900 (s), 1630 (m), 1440 (s) 1360 (s), 1120 (s), 880 (s) cm^{-1}.

The formate **10b**: formic acid (1.03 g, 22.5 mmol) was

14　　　　　　　　　**15**

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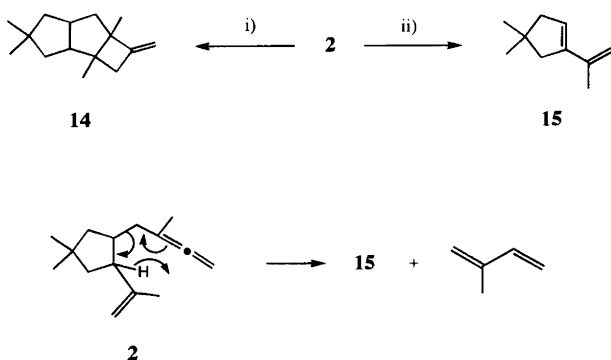
Scheme 3. (i) Δ/condensed phase; (ii) Δ/gas phase/$440\,°C$.
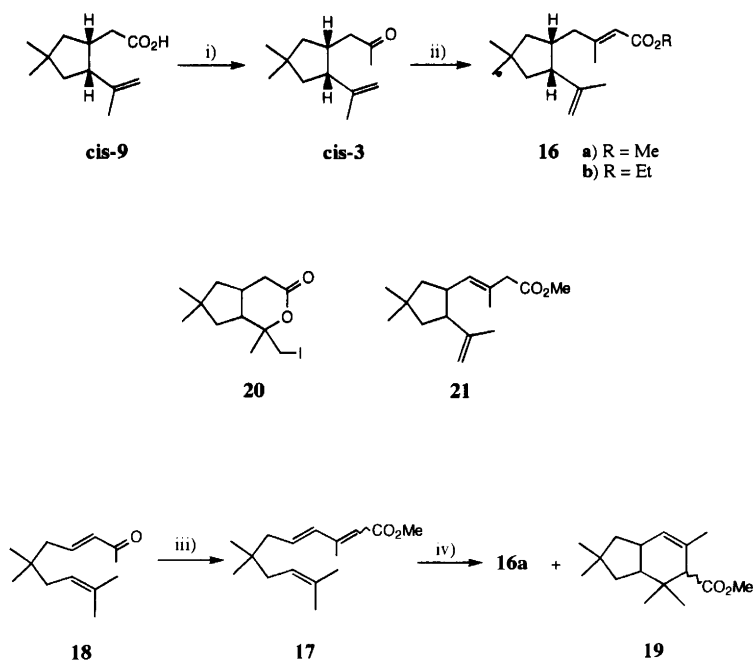
Scheme 4. (i) MeLi, 85%; (ii) Ph₃P CHCO₂Et, 68%; (iii) (MeO)₂P(O)CH₂CO₂Me, NaH, 40%; (iv) Δ condensed phase.

added to acetic anhydride (2.30 g, 22.5 mmol) while maintaining the temperature below 45 °C. The resulting solution was kept at 45 °C for 1 h and then the alcohol **10a** (3.3 g, 15 mmol) was added. The reaction mixture was kept at 50 °C until complete consumption of the alcohol (26 h), poured into saturated aq. Na₂CO₃ (50 ml) and extracted with ether. The dried (MgSO₄) extract was evaporated and purified by flash chromatography (silica; pet. ether–EtOAc 95:5) to yield 2.6 g (70%) of the formate **10b**. ¹H NMR (200 MHz, CDCl₃): δ 1.03 (s, 3 H), 1.12 (s, 3 H), 1.20–1.76 (multiplets, 4 H), 1.69 (s, 3 H), 1.74 (s, 3 H), 1.85–2.50 (multiplets, 4 H), 2.68 (s, 1 H), 4.75 (br s, 2 H), 8.23 (s, 1 H). IR (film): 3245 (s), 3040 (w), 2920 (s), 2840 (s), 2100 (w), 1720 (s), 1630 (m), 1365 (s), 1155 (s), 1070 (s), 880 (s) cm⁻¹.

The carbonate **10c**: before quenching the above Grignard reaction product, from the ketone **3** (3.0 g, 15.4 mmol), methyl chloroformate (3.80 g, 40 mmol) dissolved in THF (5 ml) was added. After being stirred at room temperature for 5 h, the reaction mixture was poured into water and extracted with ether. The extract was washed with brine and dried (MgSO₄). Column chromatography (silica; 95:5 pet. ether–EtOAc) gave 3.34 g (78%) of **10c** and 0.13 g (4%) of 4,4-dimethyl-2-isopropenyl-1-(2-methylbut-1-en-3-ynyl)cyclopentane (**13**).

10c: MS: 278 (*M⁺*, 4), 263 (4), 188 (15), 187 (100), 159 (19), 146 (35), 145 (34), 137 (79), 131 (43), 121 (39), 107 (21), 105 (21), 95 (45), 91 (29), 55 (21), 43 (27), 41 (43), 39 (20). ¹H NMR (200 MHz, CDCl₃): δ 1.02 (s, 6 H), 1.66 (s, 3 H), 1.68 (s, 3 H), 1.10–2.20 (envelope of multiplets, 8 H), 2.57 (s, 1 H), 3.74 (s, 3 H), 4.73 (s, 2 H). IR (film): 3295 (w), 2953 (s), 2864 (m), 1756 (s), 1643 (w), 1441 (m), 1375 (w), 1270 (s) cm⁻¹.

13: MS: 202 (*M⁺*, 4), 187 (73), 173 (24), 159 (45), 145 (86), 131 (100), 121 (53), 119 (35), 105 (57), 95 (67), 91 (64), 81 (42), 77 (42), 69 (39), 55 (43), 41 (81), 29 (17). ¹H NMR (200 MHz, CDCl₃): δ 1.04 (s, 3 H), 1.06 (s, 3 H), 1.69 (s, 3 H), 1.83 (s, 3 H), 1.20–2.40 (envelope of multiplets, 6 H), 2.86 (s, 1 H), 4.74 (s, 2 H), 5.30 (d, *J* 2 Hz, 1 H). IR (film): 3309 (m), 3075 (w), 2952 (s), 2932 (s), 2866 (m), 1643 (w), 1609 (w), 1450 (m), 1365 (m), 1260 (m), 890 (m) cm⁻¹.

4,4-Dimethyl-2-isopropenyl-1-(2-methyl-2,3-butadienyl)-cyclopentane (**2**). *From* **10a**. To a stirred solution of anhydrous AlCl₃ (2.26 g, 17 mmol) in dry THF (50 ml) was added portionwise LiAlH₄ (2.58 g, 68 mmol) at 0 °C. After complete addition of LiAlH₄ the resultant suspension was stirred for 0.5 h, and then the alcohol **10a** (1.25 g, 5.7 mmol) in dry THF (50 ml) was added dropwise at 0 °C. Stirring at this temperature was continued for 15 min, and then the reaction mixture was heated under reflux for 1 h. The usual work-up followed by flash chromatography (silica; pet. ether–EtOAc 95:5) gave 0.50 g (43%) of the allene **2** and 0.39 g (34%) of 4,4-dimethyl-2-isopropenyl-1-(2-hydroxy-2-methyl-3-butenyl)cyclopentane (**11**).

2: MS: 204 (*M⁺*, 6), 189 (76), 175 (23), 161 (34), 147 (33), 133 (45), 123 (55), 121 (100), 119 (53), 107 (59), 105 (54), 95 (44), 93 (61), 91 (48), 81 (58), 79 (44), 77 (33), 69 (38), 67 (37), 55 (33), 41 (94), 39 (33), 29 (18), 27 (19). ¹H NMR (200 MHz, CDCl₃): δ 1.03 (s, 6 H), 1.52–1.83 (multiplets, 6 H), 1.68 (br s, 6 H), 1.90–2.35 (multiplets, 2 H), 4.55 (m, 2 H), 4.73 (s, 2 H). ¹³C NMR (50 MHz, CDCl₃): δ 19.95, 20.32, 32.22 (CH₃), 37.66 (C), 39.66 (CH), 41.85, 47.70, 48.58 (CH₂), 54.74 (CH), 98.51, 110.84 (=CH₂), 119.04, 147.26 (=C), 206.53 (=C=).

IR (film): 3045 (w), 2920 (s), 2840 (s), 1950 (s), 1630 (m), 1435 (s), 1355 (m), 880 (s), 840 (s) cm^{-1}.

11: ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.02 (s, 6 H), 1.10 (m, 1 H), 1.25 (s, 3 H), 1.35 (m, 2 H), 1.53 (m, 2 H), 1.65 (s, 3 H), 1.68–2.00 (m, 3 H), 2.20 (m, 1 H), 4.76 (s, 2 H), 5.03 (m, 1 H), 5.20 (m, 1 H), 5.88 (m, 1 H). ^{13}C (50 MHz, CDCl$_3$): δ 19.90, 20.01, 29.04, 29.80, 32.20, 32.31 (CH$_3$), 38.06, 38.18 (C), 39.16, 39.37 (CH), 46.70, 47.04, 47.40, 48.11, 50.50, 50.79 (CH$_2$), 55.70 (CH), 74.06, 74.47 (C–O), 111.56, 111.63, 111.70, 111.80 (=CH$_2$), 145.68, 146.17 (=CH), 147.04, 147.32 (=C). IR (film): 3420 (s), 3045 (w), 2925 (s), 2845 (s), 1630 (m), 1445 (s), 1355 (s), 990 (m), 915 (s), 880 (s) cm^{-1}.

From the carbonate **10c**: the hydrogenolysis method by Tsuji et al.[13] was adopted. A mixture of Pd$_2$(dibenzylideneacetone)$_3$(CHCl$_3$) (52 mg, 0.10 mmol), prepared according to the literature,[14] Bu$_3$P (100 µl, 0.4 mmol), and ammonium formate (126 mg, 2 mmol) in THF (3 ml) was stirred at 25 °C for 5 min under argon. A solution of the carbonate **10c** (278 mg, 1.0 mmol) in THF (2 ml) was then added and the mixture was stirred at 25 °C under argon. When the reaction was complete (12 h), the mixture was filtered and the filtrate concentrated under vacuum. The residue was purified by column chromatography (silica; 95 : 5 pet. ether–EtOAc) to give 157 mg (77%) of the allene **2**.

4,4-Dimethyl-2-isopropenyl-1-(2-methylene-3-butenyl)-cyclopentane (**12**). To a solution of Pd(OAc)$_2$ (0.23 g, 1.0 mmol) in dry THF (20 ml) was added Bu$_3$P (250 µg, 1.0 mmol), which resulted in the formation of a pale yellow solution.[9] The formate **10b** (2.5 g, 10 mmol) in a small volume of THF was added dropwise. The reaction was kept at 30 °C until complete consumption of the starting material. The mixture was filtered through a short column of Celite, the filtrate was concentrated and the residue purified by flash chromatography (silica; pet. ether–EtOAc 95 : 5) to give 1.01 g (49%) of the title compound as a mixture of stereoisomers. A pure sample of each stereoisomer was obtained by preparative GLC.

trans-**12**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.99 (s, 3 H), 1.01 (s, 3 H), 1.01–1.10 (m, 1 H), 1.40 (dd, J 10.9, 12.7 Hz, 1 H), 1.51–1.66 (m, 2 H), 1.68 (s, 3 H), 1.78 (dd, J 3.3, 3.6 Hz, 1 H), 2.05 (m, 1 H), 2.25 (m, 1 H), 2.51 (m, 1 H), 4.74 (s, 2 H), 4.97 (m, 3 H), 5.13 (d, J 18 Hz, 1 H), 6.32 (dd, J 10.8, 18 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.31, 33.43, 33.56 (CH$_3$), 38.63 (CH$_2$), 38.76 (C), 43.20 (CH), 49.04, 50.08 (CH$_2$), 56.61 (CH), 112.95, 115.31, 118.33 (=CH$_2$), 141.23 (=CH), 148.03, 148.96 (=C). IR (film): 3085 (w), 2954 (s), 2868 (s), 1642 (m), 1595 (s), 1455 (m), 1375 (m), 1366 (s) cm^{-1}.

cis-**12**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.98 (s, 3 H), 1.09 (s, 3 H), 1.33–1.81 (m, 6 H), 1.76 (s, 3 H), 2.17 (dd, J 2.7, 12 Hz, 1 H), 2.37 (m, 1 H), 2.72 (m, 1 H), 4.68 (s, 1 H), 4.82 (m, 1 H), 4.91 (s, 1 H), 5.02 (d, J 12 Hz, 2 H), 5.17 (d, J 18 Hz, 1 H), 6.31 (dd, J 10.8, 18 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.43, 31.17, 31.86 (CH$_3$), 32.22 (CH$_2$), 36.68 (C), 38.52 (CH), 43.24, 45.58

(CH$_2$), 49.20 (CH), 110.40, 113.01, 116.66 (=CH$_2$), 139.24 (=CH), 145.46, 145.93 (=C). IR (film): 3085 (w), 2950 (s), 2864 (s), 1648 (m), 1595 (s), 1465 (m), 1452 (m), 1363 (m), 997 (s), 895 (s) cm^{-1}.

9-Methylene-1,4,4,8-tetramethyltricyclo[6.2.0.0^{2,6}]decane (**14**). The allene **2** (345 mg, 1.69 mmol) was placed in a glass ampoule which was degassed by three freeze–pump–thaw cycles. Argon was introduced and the tube was sealed. The ampoule was heated at 210 °C (bath temperature) for 8 h, after which GLC analysis showed complete conversion of the starting material and the formation of three major components: two comprising 49% with nearly identical retention times on the GLC and one comprising 25% of the product mixture. An analytical sample of the latter was isolated by preparative GLC (10% SP2100) and shown to be **14**. The former two components were inseparable by preparative GLC and were identified from the NMR spectra as a mixture of stereoisomers of **14**. ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.90 (s, 3 H), 0.97–1.09 (m, 2 H), 1.03 (s, 3 H), 1.05 (s, 3 H), 1.10 (s, 3 H), 1.20–1.50 (m, 4 H), 1.80–2.20 (m, 2 H), 2.35 (t, J 2.2 Hz, 2 H), 4.72 (t, J 2.2 Hz, 1 H), 4.82 (t, J 2.2 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 15.82, 21.70, 32.29, 32.34 (CH$_3$), 38.59, 40.46 (CH$_2$), 40.75 (C), 42.66, 43.37 (CH$_2$), 44.24 (C), 50.34 (CH), 62.11 (CH), 63.05 (C), 104.57 (=CH$_2$). 160.91 (=C). IR (film): 3067 (w), 2948 (s), 2864 (s), 1673 (m), 1456 (m), 1442 (w), 1363 (w), 875 (m) cm^{-1}.

4,4-Dimethyl-1-isopropenylcyclopentene (**15**). The allene **2** (330 mg, 1.61 mmol) was distilled at 0.1 mmHg through a quartz tube kept at 440 °C and the reaction mixture collected in a cold trap kept at -78 °C. After one distillation of the allene GLC analysis showed complete conversion of the starting material and the formation of four major components comprising 36%, 27%, 13% and 12% of the mixture. The major component was isolated by preparative GLC (10% SP2100) and identified as the cyclopentene **15**. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.09 (s, 6 H), 1.91 (s, 3 H), 2.25 (br s, 2 H), 2.29 (br s, 2 H), 4.81 (s, 1 H), 4.86 (s, 1 H), 5.62 br s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.47, 30.13 (CH$_3$), 38.26 (C) 47.58, 48.45 (CH$_2$), 111.81 (=CH$_2$), 126.17 (=CH), 140.40, 143.0 (=C). IR (film): 2956 (s), 2921 (s), 1632 (m), 1465 (s), 1368 (s), 1165 (s) cm^{-1}.

(E)-6,6,9-Trimethyl-3,8-decadien-2-one (**18**). To a suspension of triphenylphosphoranylideneacetone[11] (38.2 g, 0.12 mol) in dry benzene (250 ml) under a N$_2$ atmosphere was added 3,3,6-trimethyl-5-heptenal[10] (18.37 g, 0.12 mol) in one portion. The reaction mixture was then heated at reflux until complete consumption of the aldehyde (52 h). Most of the benzene was evaporated off and the semi-solid residue was extracted with pet. ether (40–60 °C). The combined extracts were concentrated to leave a yellow oil which was flash chromatographed (silica; 9 : 1 pet. ether–EtOAc) to give 19.1 g (83%) of **18**.

^{1}H NMR (200 MHz, CDCl$_3$): δ 0.89 (s, 6 H) 1.58 (s, 3 H), 1.72 (s, 3 H), 1.90 (d, *J* 7.8 Hz, 2 H), 2.10 (dd, *J* 1.4, 7.8 Hz, 2 H), 2.29 (s, 3 H), 5.16 (t, *J* 7.8 Hz, 1 H), 6.05 (d, *J* 15.8 Hz, 1 H), 6.85 (m, 1 H). ^{13}C NMR (50 MHz, CDCl$_3$): δ 18.42, 26.55, 27.36, 27.46 (CH$_3$), 35.66 (C), 40.79, 45.24 (CH$_2$), 120.89, 133.68 (=CH), 133.89 (=C), 146.52 (=CH), 198.96 (C=O). IR (film): 2920 (s), 1670 (s), 1620 (s), 1440 (m), 350 (s), 1250 (s), 1175 (m), 880 (s) cm^{-1}.

Methyl 3,7,7,10-tetramethyl-2,4,9-undecatrienoate (**17**). To a suspension of NaH (54 mg, 2.25 mmol) and trimethyl phosphonoacetate (375 mg, 2.06 mmol) in diglyme (5 ml) was added **18** (0.4 g, 2.06 mmol) in diglyme (2 ml). The reaction mixture was then heated at 70–80 °C overnight. Water was added, the product extracted with ether and the extract dried (MgSO$_4$). Evaporation and flash chromatography (silica; pet. ether–EtOAc 95:5) of the residue gave 200 mg (40%) of **17** as a 2:1 *E/Z* mixture. IR (both isomers) (film): 2925 (s), 2700 (w), 1705 (s), 1620 (m), 1595 (s), 1420 (s), 1370, (s), 1345 (s), 1225 (s), 1145 (s), 1030 (m), 960 (m), 960 (m). 860 (m) cm^{-1}.

E-**17**: ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.86 (s, 6 H), 1.58 (s, 3 H), 1.72 (s, 3 H), 1.88 (d, *J* 7.6 Hz, 2 H), 2.04 (d, *J* 6.2 Hz, 2 H), 2.27 (s, 3 H), 3.69 (s, 3 H), 5.17 (t, *J* 7.6 Hz, 1 H), 5.69 (s, 1 H), 6.01–6.25 (m, 1 H), 6.09 (s, 1 H). ^{13}C NMR (50 MHz, CDCl$_3$): δ 18.39, 26.57, 27.43 (CH$_3$), 35.67 (C), 40.70, 45.82 (CH$_2$), 51.39 (C–O), 117.68, 121.31 (=CH), 130.19 (=C), 135.25, 136.14 (=CH), 153.31 (=C), 168.18 (C=O).

Z-**17**: ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.86 (s, 6 H), 1.58 (s, 3 H), 1.72 (s, 3 H), 1.99 (s, 3 H), 2.04 (d, *J* 6.2 Hz, 2 H), 2.10 (d, *J* 7.6 Hz, 2 H), 3.68 (s, 3 H), 5.17 (t, *J* 7.6 Hz, 1 H), 5.60 (s, 1 H), 6.12 (s, 1 H), 6.01–6.25 (m, 1 H). ^{13}C NMR (50 MHz, CDCl$_3$): δ 14.38, 21.65, 27.43 (CH$_3$), 35.67 (C), 40.91, 46.08 (CH$_2$), 51.39 (C–O), 115.70, 121.41 (=CH), 133.52 (=C), 133.57, 136.95 (=CH), 151.92 (=C), 167.20 (C=O).

4-Methoxycarbonyl-3,5,5,8,8-pentamethylbicyclo[4.3.0]-non-2-ene (**19**). A degassed sample of the ester **17** (100 mg, 0.40 mmol) in a glass ampoule was heated at 200–210 °C (bath temperature) for 8 h. GLC analysis showed the formation of two major components comprising 16 and 54% of the mixture in addition to 9% of starting material. They were isolated by preparative GLC and identified as the esters **16a** (16%) and **19** (54%); ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.84 (s, 3 H) 0.86 (s, 3 H), 1.02 (s, 3 H), 1.03, (s, 3 H), 1.15–1.25 (m, 3 H), 1.70–1.90 (m, 3 H), 1.61 (s, 3 H), 2.65 (s, 1 H), 3.68 (s, 3 H), 5.67 (s, 1 H). IR (film): 2959 (s), 2866 (s), 1740 (s), 1438 (w), 1155 (s) cm^{-1}.

cis- and *trans-4,4-Dimethyl-2-isopropenylcyclopentyl-acetic acid* (**9**). A 7:3 mixture of and *cis* and *trans* isomers of **9**,[6] (741 mg, 3.75 mmol) in THF (15 ml) was added at room temperature to a stirred solution of KI

(1.87 g, 11.25 mmol) and NaHCO$_3$ (0.95 g, 11.30 mmol) in water (20 ml) under N$_2$. After 15 min, iodine (2.85 g, 11.25 mmol) was added and the solution was left in the dark with stirring for 5 days. Sodium thiosulfate (2.30 g in 25 ml water) was added and the product extracted with EtOAc. The dried extract (MgSO) was evaporated, affording the iodolactone **20** (940 mg, 77%) as a 7:3 mixture of *cis* and *trans* isomers. The isomers were separated by flash chromatography (silica; 5:95 EtOAc–hexane), yielding pure *cis*-**20** (525 mg) and *trans*-**20** (200 mg). MS: 322 (*M*$^+$, 5), 256 (60), 181 (100), 128 (55), 125 (95). IR (film): 1725 cm^{-1}.

cis-**20**. ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.02 (s, 3 H), 1.06 (s, 3 H), 1.38–1.40 (m, 1 H), 1.42–1.46 (m, 1 H), 1.52–1.54 (m, 1 H), 1.69–1.73 (m, 1 H), 1.98–2.02 (m, 1 H), 2.20 (s, 3 H), 2.26–2.28 (m, 1 H), 2.62–2.68 (m, 1 H), 2.70–2.75 (m, 1 H), 2.94 (s, 2 H). ^{13}C NMR (67.5 MHz, CDCl$_3$): δ 14.84 (CH$_2$), 23.36, 30.65, 31.82 (CH$_3$), 34.30 (C), 35.92, 37.56 (CH$_2$), 43.14 (CH), 46.50 (CH$_2$), 46.95 (CH), 82.66 (C), 172.12 (C=O).

trans-**20**. ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.03 (s, 3 H), 1.05 (s, 3 H), 1.24–1.26 (m, 1 H), 1.54–1.58 (m, 2 H), 1.70–1.72 (m, 1 H), 2.04–2.08 (m, 1 H), 2.18 (s, 3 H), 2.24–2.28 (m, 2 H), 2.44–2.46 (m, 1 H), 2.90 (s, 2 H). ^{13}C NMR (67.5 MHz, CDCl$_3$): δ 13.48 (CH$_2$), 18.77, 29.96, 30.22 (CH$_3$), 34.70 (C), 35.42, 37.96 (CH$_2$), 42.94 (CH), 46.20 (CH$_2$), 46.75 (CH), 82.32 (C), 171.10 (C=O).

A mixture of *cis*-**20** (496 mg, 1.55 mmol) and Zn powder (492 mg, 7.5 mmol) in dry ether (10 ml) was left in the dark overnight. Filtration and evaporation of the solvent yielded *cis*-**9** (257 mg, 84%). In a similar manner (200 mg, 0.5 mmol) was converted into *trans*-**9** (84 mg, 85%).

cis-**9**. ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.01 (s, 3 H), 1.12 (s, 3 H), 1.34 (dd, *J* 4.5 Hz, 13.5 Hz, 1 H), 1.42–1.45 (m, 1 H), 1.48 (dd, *J* 6.0 Hz, 12.5 Hz, 1 H), 1.71 (s, 3 H), 1.82 (dd, *J* 7.0 Hz, 12.5 Hz, 1 H), 2.02 (dd, *J* 10.5 Hz, 14.5 Hz, 1 H), 2.20 (dd, *J* 4.5 Hz, 14.5 Hz, 1 H), 2.62–2.68 (m, 1 H), 2.70–2.75 (m, 1 H), 4.64 (s, 1 H), 4.81 (s, 1 H), 11.74 (br s, 1 H). ^{13}C NMR (67.5 MHz, CDCl$_3$): δ 23.16, 30.88, 31.62 (CH$_3$), 37.70 (C), 43.14 (CH), 46.58, 48.48, 51.30, 53.82 (CH$_2$), 111.84 (=CH$_2$), 145.62 (C), 179.92 (C=O). IR (film): 3310 (br), 2932 (w), 1685 (m) cm^{-1}.

trans-**9**. ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.04 (s, 3 H), 1.05 (s, 3 H), 1.16 (dd, *J* 10 Hz, 12.5 Hz, 1 H), 1.54–1.60 (m, 2 H), 1.68 (s, 3 H), 1.74 (dd, *J* 7.5 Hz, 12.5 Hz, 1 H), 2.07–2.10 (m, 1 H), 2.24–2.28 (m, 2 H), 2.44 (dd, *J* 4.5 Hz, 14.5 Hz, 1 H), 4.72 (s, 2 H), 11.76 (br s, 1 H). ^{13}C NMR (67.5 MHz, CDCl$_3$): δ 18.90, 31.23, 31.35 (CH$_3$), 36.66 (C), 38.72 (CH), 46.50, 47.60 (CH$_2$), 49.82 (CH), 53.94, 112.42 (=CH$_2$), 145.90 (C), 179.68 (C=O).

cis-1-(2-Oxopropyl)-4,4-dimethyl-2-isopropenylcyclo-pentane (*cis*-**3**). A solution of MeLi in ether (1.25 ml of 1.6 M, 2 mmol) was added dropwise to a solution of the *cis*-**9** (197 mg, 1 mmol) in dry ether (15 ml) kept at 0 °C under nitrogen. Stirring at this temperature was con-

tinued for 25 min and then saturated NH_4Cl (15 ml) was added. The aqueous phase was extracted with ether, and the extract was washed with 10% aq. $NaHCO_3$ and brine, and then dried ($MgSO_4$), affording the ketone *cis*-**3** (166 mg, 85%). ^1H NMR (270 MHz, $CDCl_3$): δ 0.98 (s, 3 H), 1.06 (s, 3 H), 1.20–1.23 (m, 2 H), 1.35–1.60 (m, 2 H), 1.67 (s, 3 H), 2.06 (s, 3 H), 2.10–2.38 (m, 2 H), 2.50–2.68 (m, 2 H), 4.64 (s, 1 H), 4.75 (s, 1 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 23.90, 31.12, 31.95, 32.32 (CH_3), 37.02 (C), 37.64 (CH), 44.04, 46.90, 48.38 (CH_2), 49.14 (CH), 111.37 (=CH), 146.27 (C), 209.02 (C=O). IR (film): 1722 (s), 1648 (w), 1365 (m) cm^{-1}.

cis-Ethyl 4-(2-isopropenyl-4,4-dimethylcyclopentyl)-3-methyl-2-butenoate (**16b**). To a suspension of ethyl triphenylphosphinoacetate (296 mg, 0.85 mmol) in dry benzene (5 ml) under N_2 was added the ketone (166 mg, 0.85 mmol) in benzene (2 ml) in one portion. The reaction mixture was refluxed for 48 h, cooled, and most of the benzene was evaporated off. The semi-solid residue was extracted with hexane, and the extract dried ($MgSO_4$), concentrated and chromatographed (silica; 9:1 hexane–EtOAc) to give the ester **16b** (152 mg, 68%). ^1H NMR (270 MHz, $CDCl_3$): δ 1.00 (s, 3 H), 1.04 (s, 3 H), 1.21–1.25 (m, 2 H), 1.28 (t, J 7.5 Hz, 2 H), 1.33–1.63 (m, 2 H), 1.66 (s, 3 H), 2.12 (s, 3 H), 2.14–2.38 (m, 2 H), 2.50–2.68 (m, 2 H), 4.15 (q, J 7.5 Hz, 3 H), 4.64 (s, 1 H), 4.78 (s, 1 H), 5.66 (s, 1 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 14.62, 19.85, 23.80, 31.32, 31.65 (CH_3), 36.92 (C), 37.64 (CH), 42.48, 44.04, 46.80 (CH_2), 49.18 (CH), 65.26 (CH_2), 111.19 (=CH_2), 123.75 (=CH), 146.11, 161.53 (C), 164.37 (C=O). IR (film): 1720 (s), 1645 (m), 1437 (m) cm^{-1}.

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