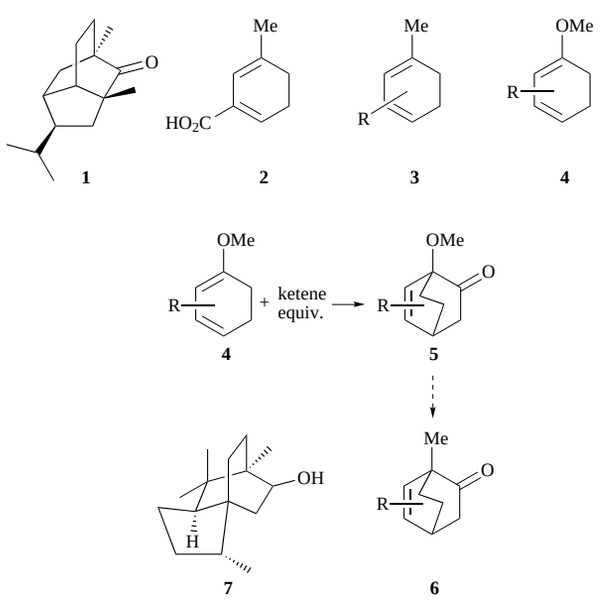
Synthesis based on cyclohexadienes. Part 24.[1] A new total synthesis of pupukean-2-one and a facile entry to copa and ylanga type sesquiterpene skeletons

Krishna Kaliappan and G. S. R. Subba Rao *

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560 012, India

A novel tandem 5-*exo-trig* allyl and 3-*exo-trig* radical cyclisation and rearrangement to copa and ylanga type sesquiterpene skeletons from easily prepared cyclohexadienes is reported. A new total synthesis of pupukean-2-one 8, which belongs to a novel class of sesquiterpenes, involving a 5-*exo-trig* allyl radical cyclisation as the key step is also reported.

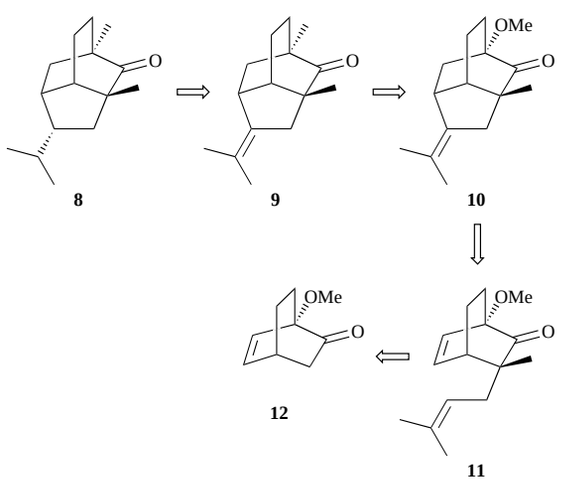
In the total synthesis of 5-*epi*-pupukean-2-one **1** described in the preceding paper,[1] the diene ester **2** was utilised as an equivalent of the substituted 1-methylcyclohexa-1,3-diene **3**. Substituted 1-methoxycyclohexa-1,3-dienes **4**, readily prepared by the metal–ammonia reduction of the corresponding aromatic ethers followed by a base-catalysed conjugation, afford regiospecific adducts of the type **5** upon cycloaddition with a ketene equivalent. If the bicyclic ketone **5** can be transformed into the bicyclic ketone **6**, then the dihydro compound **4** can be used as an equivalent of 1-methylcyclohexa-1,3-diene **3** which essentially involves bridgehead substitution of the methoxy group by a methyl group.



Although this bridgehead substitution methodology has been reported[2,3] earlier, its application to the synthesis of natural products has been dismal. We have investigated[4] this reaction which involved the tricyclic compounds having a bridgehead methoxy group that led to the total synthesis of (±)-*allo*-cedrol (khusiol) **7**. In continuation of our interest in the total synthesis of sesquiterpenes,[5] involving the bridgehead substitution strategy, we describe[6,7] herein a new total synthesis of pupukean-2-one **8** through a 5-*exo-trig* allyl radical cyclisation and a novel tandem 5-*exo-trig* allyl and 3-*exo-trig* radical cyclisation and its rearrangement to copa and ylanga type sesquiterpene skeleton.

Results and discussion

The total synthesis of pupukean-2-one **8** was devised using the bridgehead substitution strategy as depicted in Scheme 1.

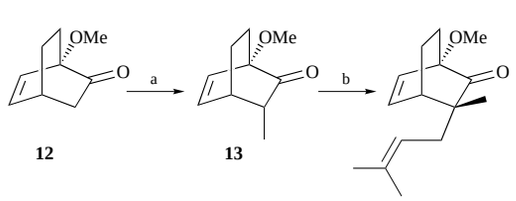


Scheme 1

The retrosynthetic analysis indicated that pupukean-2-one **8** can be obtained from the tricyclic ketone **9** which, in turn, can be prepared from the enone **10** through a bridgehead substitution strategy. The tricyclic ketone **10** can be obtained from the bicyclic ketone **11** having the prenyl group in the *endo* position which, in turn, can be made from the known bicyclic ketone **12**.[8]

Synthesis of the bicyclic ketone 11

Thus, the bicyclic ketone **12** upon alkylation with LDA and MeI afforded the ketone **13** having the methyl group in the *endo* position (Scheme 2), as evidenced by the spectral data. The ^{1}H

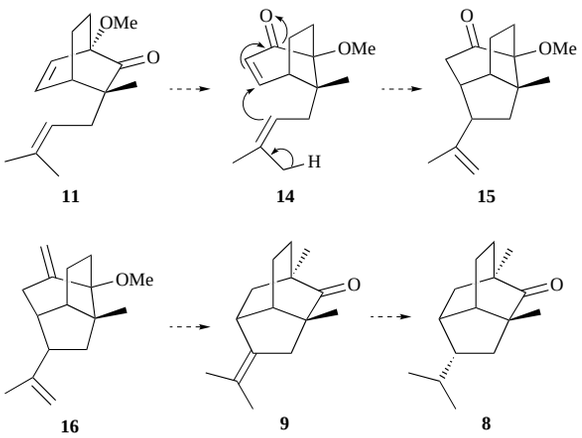


Scheme 2 *Reagents and conditions*: a, LDA, MeI, THF, −78 °C; b, LDA, 3.3-dimethylallyl bromide, THF, HMPA, −78 °C

NMR spectrum of **13** showed a doublet at δ 1.09 for the *endo* methyl group, a multiplet at δ 2.73 for the bridgehead proton

and a singlet at δ 3.52 for the bridgehead methoxy group. The ^{13}C NMR spectrum of **13** showed only 10 lines which supports the stereoselective nature of the alkylation. Further alkylation with prenyl bromide was achieved by treating the ketone **13** with LDA at −78 °C and quenching the resultant enolate with prenyl bromide in HMPA–THF. The ^{1}H NMR spectrum of the resulting ketone **11** showed signals at δ 1.08 (s, Me), 1.59 and 1.73 (both s, allylic Me) and 5.12 (prenyl olefinic H).

The bicyclic ketone **11** having been prepared, the next step was its acid-catalysed rearrangement to generate the tricyclic system. This was achievable through an intramolecular ene cyclisation of the unsaturated ketone **14**, obtained from **11**, to afford the tricyclic enone **15** (Scheme 3). The resulting tricyclic enone **15** was convertible into pupukean-2-one **8**.



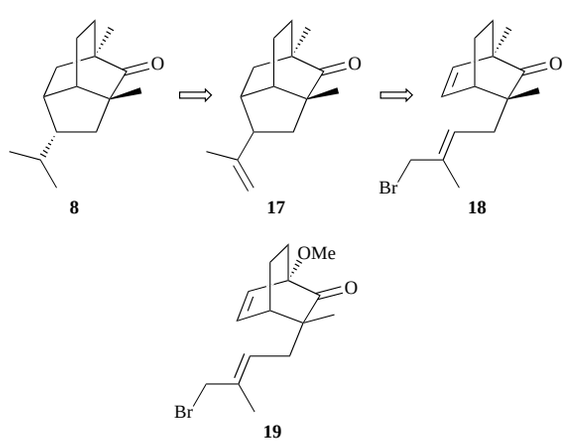
Scheme 3

With this idea, we attempted a novel one-pot tandem acid-catalysed rearrangement and an intramolecular ene cyclisation of the bicyclic ketone **11**: all attempts failed. Thus, treatment of the bicyclic ketone **11** with Lewis acid BF_3·MeOH, at room temperature gave only recovery of starting material, whilst for reactions at higher temperatures, the product decomposed. Treatment of **11** with $SnCl_4$, BF_3·OEt_2 and HCO_2H failed to produce the desired compound as did heating it with PTSA in refluxing benzene.

Stereo- and regio-selective alkylation

Since the acid-catalysed cyclisation of **11** failed to yield the tricyclic skeleton, a radical cyclisation[9] was investigated for the key step to the tricyclic skeleton **15**; this was a new strategy involving a 5-*exo-trig* allyl radical cyclisation.[10]

In this approach, the allyl bromide **18** was considered as the key intermediate (Scheme 4), since it can undergo an intramolecular 5-*exo-trig* allyl radical cyclisation to give the isotwistane **17** which can be elaborated to pupukean-2-one **8**.

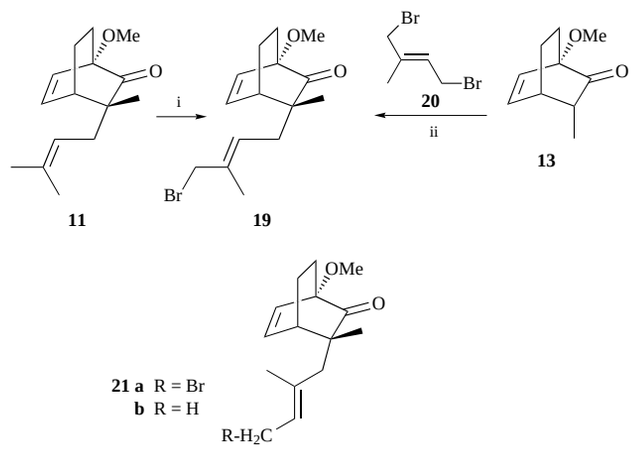


Scheme 4

Although allyl radicals have been known for a decade,[10] their cyclisation has been rarely used synthetically,[11,12] since their greater stability makes them less reactive when compared to their saturated and vinylic counterparts. With this in mind, allyl radical cyclisation of the bromide was investigated as a model system.

Since attempted allylic bromination of the ketone **11** with *N*-bromosuccinimide afforded a complex mixture of products, alkylation of the ketone **13** with the dibromide[13] **20** was investigated.

Alkylation of the lithium enolate of the ketone **13** at −78 °C with 1,4-dibromo-2-methylbut-2-ene[13] **20**, proceeded regio- and stereo-selectively to give, exclusively, the *endo* bromide **19** (Scheme 5), as evidenced from its spectral data. The ^{1}H NMR



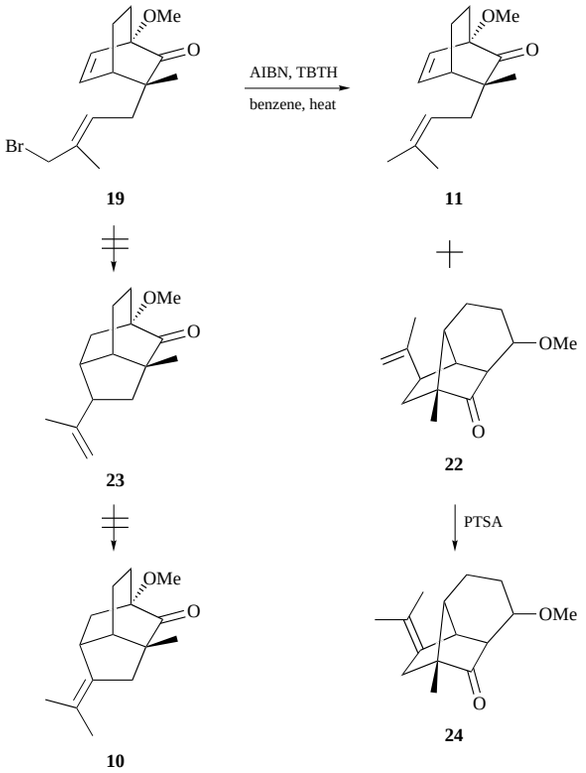
Scheme 5 *Reagents and conditions*: i, NBS/CCl_4; ii, LDA, THF, HMPA, −78 °C

spectrum of **19** showed signals at δ 6.4 (m, olefinic H), 5.73 (t, prenyl olefinic H) and 3.99 (s, CH_2Br); the mass spectrum showed peaks at 313 (M^+) and 315 ($M^+ + 2$) with base peaks at 233 and 110.

The alternative structure **21a** for the product was ruled out on the basis of the NMR data, in particular the coupling of the CH_2Br protons. Further attempted radical cyclisation (see below) of the product gave the ketone **11** as one of the products. If **21a** was formed during the alkylation of **13** with **20**, the reduced product would have structure **21b** whose NMR spectrum would show distinctive signals for the two vinyl methyl groups as a singlet and a doublet. The NMR spectrum of the product was consistent with structure **11** and hence the regioselectivity in the alkylation using the dibromide **20**. The reasons for this regioselectivity is not very clear but appears to be due to the steric hindrance from the methyl group which is being examined now.

A novel radical rearrangement

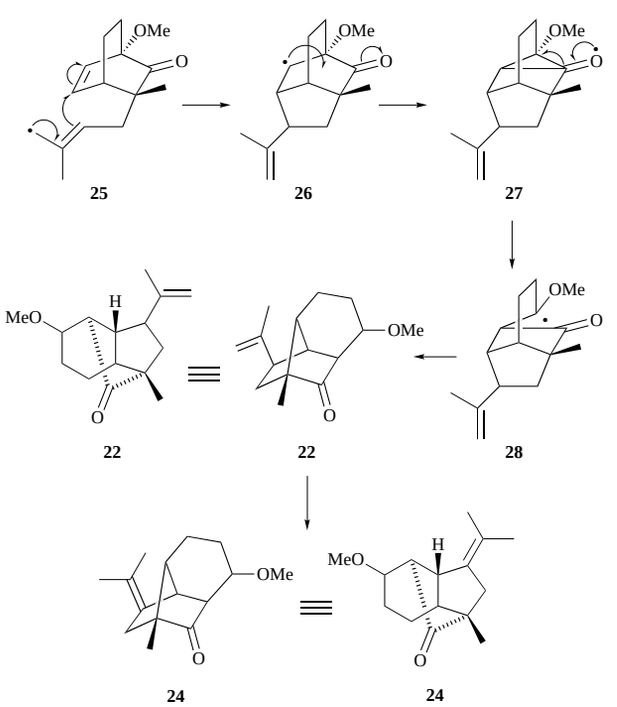
The allyl bromide **19** having been successfully obtained in good yield, its intramolecular allyl radical cyclisation was investigated (Scheme 6). Radical cyclisation under standard conditions[10] (0.005 M benzene solution of **19** with 1.1 equiv. of TBTH and 0.1 equiv. of AIBN, reflux, 1–2 h) afforded a mixture containing the reduced product **11** (5%) and a new compound **22** (60%) whose IR spectrum showed absorption at 1740 cm^{-1}; in its ^{1}H NMR spectrum signals for olefinic protons at δ 6.2, 6.4 and 5.1 were absent, but instead there were signals at δ 4.6 and 4.8 (both d). This clearly suggested that an intramolecular cyclisation has occurred. Since ^{13}C NMR spectrum of **22** showed a methine carbon at δ 78.2 the compound is different from the expected 5-*exo-trig* allyl radical cyclisation product **23**. On treatment with PTSA, compound **22** was quantitatively converted into a new isomer **24**, whose IR spectrum showed carbonyl absorption at 1740 cm^{-1}; moreover, its ^{1}H NMR spectrum showed no signals for olefinic protons, suggest-



Scheme 6

ing that the *exo* olefin is isomerised into a stable tetrasubstituted olefin. The off-resonance ^{13}C NMR spectrum of **24** showed the presence of four singlets, four doublets, three triplets and four quartets, whereas the expected product **10** should have five singlets, two doublets, four triplets and four quartets. Also, a doublet at δ 78.53 clearly showed that OMe is attached to a carbon atom bearing a hydrogen.

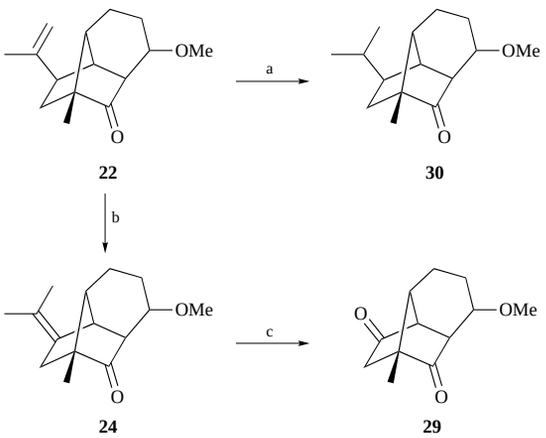
These data clearly established the structure of the cyclised and isomerised products as **22** and **24** respectively (Scheme 6) and that the isopropenyl substituent present in **22** was isomerised to the isopropylidene group under acidic conditions to give **24**. A probable mechanism for the formation of these compounds **22** and **24** is indicated (Scheme 7). As expected, the



Scheme 7

initial 5-*exo-trig* allyl radical cyclisation gave the radical **26** which underwent a 3-*exo-trig* radical cyclisation onto the carbonyl group to give the cyclopropyloxyl radical **27** which further rearranged to **22**. Formation of a stable radical adjacent to the methoxy group appeared to be the driving force for this arrangement.

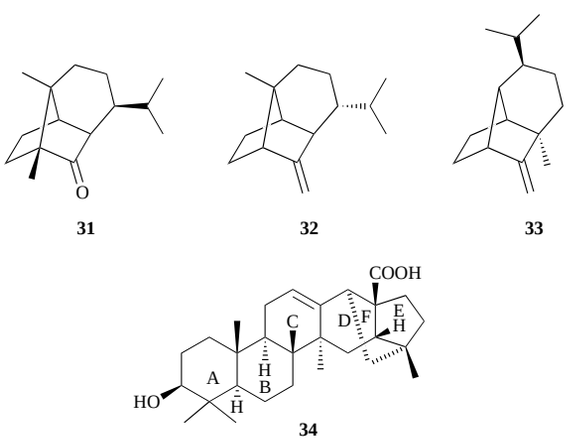
The proposed mechanism was further confirmed by oxidative cleavage of **24** to the diketone **29** (Scheme 8) whose IR spec-



Scheme 8 *Reagents and conditions*: a, H_2/Pd–C, EtOH; b, PTS, benzene, heat; c, $RuCl_3$, $NaIO_4$

trum showed absorption at 1740 cm^{-1} (five-membered ring with a keto group) and in whose ^1H spectrum two allylic methyl groups signals were absent. Hydrogenation of **22** afforded a saturated tricyclic ketone **30** in whose ^1H NMR spectrum olefinic protons signals were absent.

A number of natural products possess this skeleton, *e.g.* copacamphor **31**,[14] sinulurene **32**[15] and sativene **33**[16] (Scheme 9)



Scheme 9

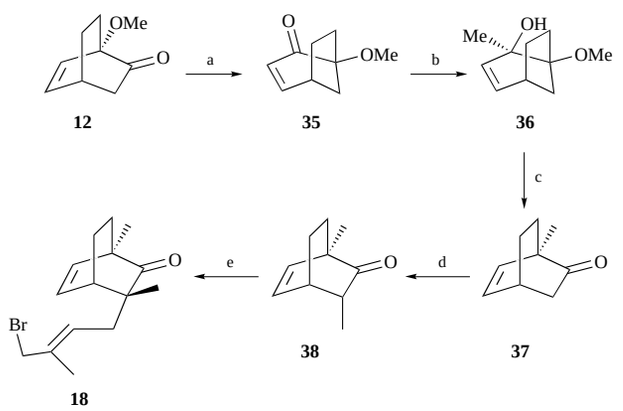
and their total synthesis by the above strategy may be envisaged. Interestingly, pfaffic acid **34**,[17] a nortriterpene with many biologically interesting properties was found to possess this skeleton as part of the DEF ring system.

Total synthesis of pupukean-2-one 8

Since the intramolecular 5-*exo-trig* allyl radical cyclisation of **19** resulted in the tricyclic compound **22**, presumably through the isotwistane intermediate **27**, because of the stabilisation of the radical at the carbon bearing the methoxy group, it was expected that the radical cyclisation of **18** should result in the desired isotwistane moiety **17**.

Thus, the ketone **12** on treatment with PTSA in refluxing benzene, afforded the enone **35**, whose structure was deduced from the spectral data. The enone **35** upon treatment with MeLi

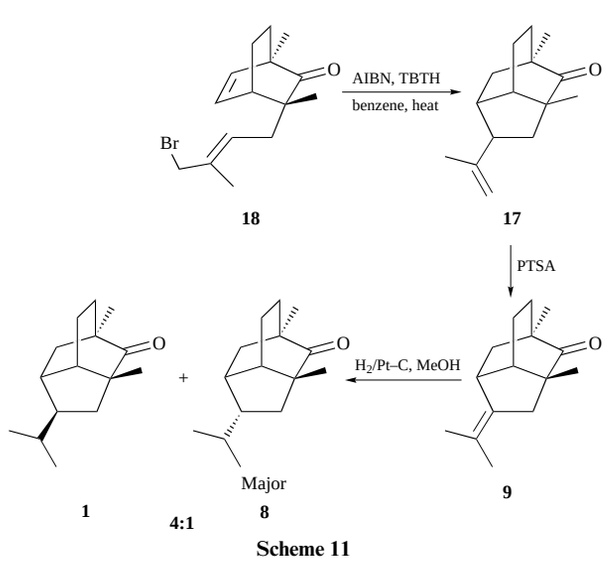
in ether afforded the tertiary alcohol **36**, whose IR spectrum showed the disappearance of carbonyl group absorption and the appearance at 3300 cm^{-1} of hydroxy group absorption. The tertiary alcohol **36** upon treatment with a catalytic amount of perchloric acid afforded the bicyclic ketone **37**, whose structure was deduced from the spectral data and was comparable to that reported.[18] The IR spectrum of **37** showed strong absorption at 1720 cm^{-1} (saturated ketone) whilst its ^1H NMR spectrum showed signals at δ 1.22 (s, bridgehead Me) and 2.94 (bridgehead H) but no methoxy group signal at δ 3.5. The ^{13}C NMR spectrum of **37** showed a quartet, three triplets, three doublets and two singlets confirming the above structure. The mass spectrum showed its base peak at 94 due to the diene formed by the loss of a ketene due to retro Diels–Alder fragmentation. Alkylation of the lithium enolate generated from the bicyclic ketone **37**, with methyl iodide afforded exclusively the ketone **38** having an *endo* methyl group (Scheme 10); its ^1H NMR spectrum



Scheme 10 *Reagents and conditions*: a, PTS, benzene, heat; b, MeLi, Ether, 0 °C; c, $HClO_4$, CH_2Cl_2; d, LDA, MeI, THF, −78 °C; e, LDA, $BrCH_2C(Me)=CHCH_2Br$, THF, HMPA, −78 °C

showed only one doublet at δ 1.02 (*endo*-Me) whilst its mass spectrum showed a base peak at 94 due to the retro Diels–Alder fragment and a molecular ion peak at 150. Further alkylation of the ketone **38** with 1,4-dibromo-2-methylbut-2-ene **21** gave the bicyclic allyl bromide **18** having a five-carbon substituent in the *endo* position; its ^1H NMR spectrum showed signals at δ 5.8 (prenyl olefinic H), 3.98 (s, CH_2Br) and 1.73, 1.21 and 1.05 (all s, Me). The mass spectrum of **18** showed a very weak molecular ion peak at 297 (M^+), a strong peak at 217 (M − Br) and a base peak at 94 for the retro Diels–Alder fragment.

Intramolecular radical cyclisation of **18** under standard conditions afforded the 5-*exo*-*trig* allyl radical cyclised product **17**, as the major product (Scheme 11). The structure of **17** was



Scheme 11

deduced from its spectral data: its ^1H NMR spectrum showed the absence of signals at δ 6.4, 6.3 and 5.8 (olefinic H) whilst those at δ 4.6 and 4.8 (both s, exocyclic olefinic H) confirmed its structure. The mass spectrum of **17** showed its molecular ion peak at 218 as the base peak. The structure of **17** was further confirmed by its isomerisation to the tricyclic ketone **9** with PTSA in refluxing benzene. The ^1H NMR spectrum of **9** showed the absence of the olefinic proton signals which suggested that the double bond had isomerised to a tetrasubstituted situation; there were signals at δ 2.9 (bridgehead H), 1.61 and 1.51 (both s, allylic Me) and 1.14 and 0.89 (bridgehead Me). The mass spectrum of **9** showed its molecular ion peak at 218 which is also the base peak. Hydrogenation of the ketone with Pt–C in MeOH afforded a mixture (4:1) containing pupukean-2-one **8** as the major product whose spectral data are in accordance with that reported.[19]

In conclusion, an efficient method for the construction of the copa and ylanga type sesquiterpene skeleton is reported. This methodology is fairly flexible and can be extended for the total synthesis of pfaffic acid, a highly biologically active nortriterpene. A new total synthesis of pupukean-2-one **8**, which belongs to a novel class of sesquiterpenes, involving a 5-*exo*-*trig*-allyl radical cyclisation as the key step is also reported.

Experimental[20]

1-Methoxy-3-*endo*-methylbicyclo[2.2.2]oct-5-en-2-one 13

A 1 mol dm^{-3} solution of BuLi in hexane (21.7 cm^3, 21.7 mmol) was added to diisopropylamine (2.9 cm^3, 22 mmol) in THF (30 cm^3) at −78 °C under argon. The resultant solution of lithium diisopropylamide was stirred at −78 °C for 1 h after which a solution of the ketone **12** (3 g, 19.7 mmol) in dry THF (40 cm^3) was added dropwise to it. The resultant lithium enolate was stirred at −78 °C for 1 h after which a solution of MeI (2.5 cm^3, 40 mmol) in THF was added at once. After being stirred for 1 h, the reaction mixture was poured onto saturated aqueous NH_4Cl and extracted with ether (3 × 50 cm^3). The combined extracts were washed successively with water, aq. sodium thiosulfate, water and brine, dried (Na_2SO_4) and evaporated. Purification of the residue using column chromatography [ethyl acetate–light petroleum (1:9)] afforded the product **13** as a colourless liquid (2.9 g, 90%); ν_{max}/cm^{-1} 2930, 1715 and 1640; δ_H 1.09 (3H, d, *J* 7.2, CH*Me*), 1.6–2.2 (5H, m), 2.73 (1H, m, bridgehead H), 3.52 (3H, s, OMe) and 6.1–6.5 (2H, m, olefinic H); δ_C 16.75 (q), 24.43 (t), 24.98 (t), 37.56 (d), 43.41 (d), 52.26 (q), 83.6 (s), 129 (d), 134.19 (d) and 210.34 (s); *m*/*z* 166 (M^+, 55%), 138 (100), 122 (100) and 110 (100) (Found: M^+, 166.0986. $C_{10}H_{14}O_2$ requires *M*, 166.0994).

1-Methoxy-3-methyl-3-*endo*-(3-methyl-2-but-2-enyl)bicyclo-[2.2.2]oct-5-en-2-one 11

To a freshly prepared LDA solution [prepared from a 1 M solution of BuLi (8.6 cm^3, 8.6 mmol) and diisopropylamine (1.2 cm^3, 9.4 mmol) in THF (20 cm^3)] at −78 °C under argon, was added dropwise a solution of the ketone **13** (1.3 g, 7.8 mmol) in THF (30 cm^3). The resultant solution was stirred for 1 h at the same temperature after which it was quenched with a solution of prenyl bromide (1.7 cm^3, 15 mmol) in THF and then treated with HMPA (2.8 cm^3, 15 mmol). The reaction mixture was stirred overnight and then poured onto 2 M aq. HCl (100 cm^3). Work-up followed by column chromatography [ethyl acetate–light petroleum (1:9)] afforded compound **11** as a colourless oil (1.35 g, 80%); ν_{max}/cm^{-1} 3020, 2940, 1720 and 1640; δ_H 0.85–2.18 (6H, m), 1.08 (3H, s, Me), 1.59 (3H, s, Me), 1.73 (3H, s, Me), 2.61 (1H, m, bridgehead H), 3.52 (3H, s, OMe), 5.12 (1H, t, *J* 7.1 Hz, olefinic H), 6.17 (1H, dd, *J* 6.7 and 1.7, olefinic H) and 6.45 (1H, dd, *J* 8.2 and 6.7); δ_C 17.6 (q), 21.0 (q), 21.1 (q), 25.7 (t), 26.2 (t), 36.5

(t), 39.5 (d), 47.0 (s), 52.8 (q), 84.2 (s), 118.7 (d), 127.4 (d), 134.6 (s), 136.5 (d) and 213.1 (s); *m/z* 234 (M^+, 90%), 206 (25), 175 (26), 150 (75), 136 (100) and 110 (100) (Found: M^+, 234.1616. $C_{15}H_{22}O_2$ requires *M*, 234.1620).

1,4-Dibromo-2-methylbut-2-ene 20

To a stirred solution of isoprene (6.8 g) in dry chloroform (100 cm^3) under a N_2 atmosphere in the dark, was added Br_2 (16 g) dropwise at room temperature. After being stirred for 12 h, the reaction mixture was evaporated *in vacuo* and the residue was distilled under reduced pressure (bp 60 °C/10 mmHg) to afford the dibromide **20** as a colourless oil (10 g); δ_H 1.85 (3H, s, Me), 3.93 [2H, s, $H_2CC(Me)$=], 3.95 (2H, d, *J* 7.2, H_2CCH=) and 5.92 (1H, t, *J* 8.1, olefinic H).

3-*endo*-4-Bromo-3-methylbut-2-enyl)-1-methoxy-3-methylbicyclo[2.2.2]oct-5-en-2-one 19

To a freshly prepared LDA solution [prepared from 1 mol dm^{-3} solution of BuLi (3.5 cm^3, 3.5 mmol) and diisopropylamine (0.5 cm^3, 3.5 mmol) in THF (10 cm^3)] at −78 °C under argon, was added dropwise a solution of the ketone **13** (1 g, 3.19 mmol) in THF (20 cm^3). The resultant solution was stirred for 1 h at the same temperature and then quenched with a solution of 1,4-dibromo-2-methylbut-2-ene **21** (1.5 g, 15 mmol) in THF and then treated with HMPA (1.2 cm^3, 6.5 mmol). The reaction mixture was stirred overnight and poured onto 2 M aq. HCl (100 cm^3). Work-up followed by column chromatography [ethyl acetate–light petroleum (1:9)] afforded the bromo ketone **19** as a colourless oil (1.3 g, 70%); ν_{max}/cm^{-1} 3010, 2920, 1720 and 1640; δ_H 1.12 (3H, s, Me), 1.2–2.36 (6H, m), 1.76 (3H, s, Me), 2.62 (1H, m, bridgehead H), 3.52 (3H, s, OMe), 3.99 (2H, s, CH_2Br), 5.73 (1H, t, *J* 6.8, olefinic), 6.21 (1H, dd, *J* 6.4 and 1.8, olefinic H) and 6.51 (1H, dd, *J* 8.1 and 6.4, olefinic H); δ_C 14.6, 21.7, 21.8, 26.4, 36.8, 39.9, 40.8, 46.9, 52.7, 84.1, 125.5, 127.6, 134.4, 136.4 and 212.4; *m/z* 315 (M + 2, 5%), 313 (M^+, 5), 233 (30), 205 (70), 137 (100) and 110 (100) [Found: M^+ − Br, 233.1523. $C_{15}H_{21}O_2$(M − Br) requires *M*, 233.1540].

5-Methoxy-8-methyl-10-(prop-2-enyl)tricyclo[4.4.0.0^{2,8}]decan-7-one 22

A solution of TBTH (1.1 cm^3, 3.6 mmol) and AIBN (20 mg) in dry benzene (5 cm^3) was added dropwise to a degassed benzene solution (0.005 mol dm^{-3}) of the bromide **19** (1 g, 3.2 mmol) under a nitrogen atmosphere. After being refluxed for 3 h, the reaction mixture was concentrated *in vacuo* and the residue was taken up in ether and the solution washed with 1% aq. NH_4OH, water and brine, dried (Na_2SO_4) and evaporated. Column chromatography (ethyl acetate–hexane, 1:19) of the residue initially afforded the ketone **11** (38 mg, 5%) and then, with the same eluent, the tricyclic ketone **22** (510 mg, 69%) as a colourless oil; ν_{max}/cm^{-1} 3020, 2920, 1740 and 1620; δ_H 1.0 (3H, s, Me), 1.67 (3H, br, =C–CH_3), 1.1–1.98 (9H, m), 2.4 (1H, m), 3.2 and 3.31 (3H, s, OMe), 3.4 (1H, m, CHOMe), 4.6 and 4.67 (1H, d, *J* 1.1, olefinic), 4.70 and 4.78 (1H, d, *J* 1.1); δ_C(for the major isomer): 9.77, 20.05, 21.26, 24.91, 39.17, 44.15, 46.3, 46.35, 53.6, 54.1, 54.5, 78.2, 107.17, 145.97 and 216.51; *m/z* 234 (20%), 203 (30), 175 (60), 134 (50), 110 (100), 91 (70) and 41 (72) (Found: M^+, 234.1618. $C_{15}H_{22}O_2$ requires *M*, 234.1620).

10-Isopropylidene-5-methoxy-8-methyltricyclo[4.4.0.0^{2,8}]decan-7-one 24

A solution of the ketone **22** (200 mg, 0.8 mmol) and PTSA (catalytic) in dry benzene (10 cm^3) was refluxed for 45 min. The reaction mixture was cooled, washed with saturated aq. $NaHCO_3$ (2 × 5 cm^3) and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on a silica gel column [ethyl acetate–hexane (1:19)] to furnish the tricyclic olefin **24** (95%, 190 mg) which was recrystallised from hexane to give a colourless crystalline solid; mp 98 °C; ν_{max}/cm^{-1} 3040, 2930, 1740 and 1620; δ_H 1.09 (3H, s, Me), 1.5 (3H, s, Me), 1.65 (3H, s, Me), 1.7–2.2 (7H, m), 2.42 (1H, br), 2.68 (1H, d, *J* 1.6), 3.35 (3H, s, OMe) and 3.42 (1H, m, CHOMe); δ_C 10.48 (q), 19.7 (q), 19.72 (q), 20.93 (t), 25.24 (t), 41.28 (t), 48.02 (d), 49.68 (d), 53.21 (d), 54.9 (s), 55.43 (q), 78.53 (d), 121.76 (s), 130.72 (s) and 218.17 (s); *m/z* 234 (M^+, 30%), 159 (50), 134 (80) and 101 (100) (Found: M^+, 234.1624. $C_{15}H_{22}O_2$ requires *M*, 234.1620).

10-Isopropyl-5-methoxy-8-methyltricyclo[4.4.0.0^{2,8}]decan-7-one 30

A suspension of the tricyclic olefin **22** (100 mg, 0.42 mmol) and 10% Pd–C (20 mg) in dry EtOAc (5 cm^3) was magnetically stirred under a H_2 atmosphere (1 atm) for 12 h. The reaction mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure to furnish the ketone **30** as an amorphous viscous liquid (90 mg, 90%); ν_{max}/cm^{-1} 2920 and 1740; δ_H 0.73 (3H, d, *J* 6.4, C*H*Me), 0.85 (3H, d, *J* 6.4, C*H*Me), 0.93 (3H, s, Me), 0.9–1.9 (10H, m), 2.27 (1H, m), 3.26 (3H, s, OMe) and 3.34 (1H, m, CHOMe); δ_C 10.3, 19.6, 19.7, 20.6, 21.1, 25.3, 31.6, 40, 45.9, 46.5, 46.8, 54.9, 55.3, 78.6 and 218.6; *m/z* 236 (15%), 204 (17), 174 (50) and 133 (100) (Found: M^+, 236.1758. $C_{15}H_{24}O_2$ requires *M*, 236.1776).

5-Methoxy-8-methyltricyclo[4.4.0.0.^{2,8}]decane-7,10-dione 29

To a vigorously stirred mixture of the olefin **24** (100 mg, 0.42 mmol), carbon tetrachloride (1 cm^3), acetonitrile (1 cm^3), water (1.5 cm^3) and sodium metaperiodate (375 mg, 1.68 mmol) was added ruthenium trichloride trihydrate (3 mg). After continued stirring for 6 h the mixture was diluted with CH_2Cl_2 (25 cm^3). The organic layer was separated and washed successively with water and brine and then dried (Na_2SO_4) and evaporated. The crude product was chromatographed (ethyl acetate–hexane, 1:9) to afford the diketone **29** as a gummy residue (53 mg, 60%); ν_{max}/cm^{-1} 2920 and 1742; δ_H 1.22 (3H, s, Me), 1.1–2.72 (9H, m), 3.38 (3H, s, OMe) and 3.48 (1H, m, CHOMe); *m/z* 208 (M^+, 28%), 148 (35) and 128 (100) (Found: M^+, 208.1097. $C_{12}H_{16}O_3$ requires *M*, 208.1099).

1-Methoxybicyclo[3.2.1]oct-3-en-2-one 35

A mixture of the ketone **12** (3.5 g, 23 mmol) and PTSA (4 g) in dry benzene was refluxed under a nitrogen atmosphere for 2 h after which it was diluted with benzene and washed with water, saturated aq. sodium hydrogen carbonate and brine and then dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel using ethyl acetate–hexane (1:7) as eluent gave the methoxy enone **35** as a viscous liquid (2.8 g, 60%); ν_{max}/cm^{-1} 3010, 2930, 1670 and 1620; δ_H 1.3–2.3 (6H, m), 3.05 (1H, m, bridgehead H), 3.42 (3H, s, OMe), 5.96 (1H, d, *J* 9.7, olefinic H) and 7.31 (1H, dd, *J* 9.7 and 6.8, olefinic H); δ_C 27.2 (t), 29.4 (t), 37.7 (d), 42.6 (t), 53.2 (q), 89.3 (s), 127.07 (d), 155.9 (d) and 200.5 (s); *m/z* (M^+ 152, 80%), 123 (100) and 81 (50) (Found: M^+, 152.0851. $C_9H_{12}O_2$ requires *M*, 152.0837).

1-Methoxy-2-methylbicyclo[3.2.1]oct-3-en-2-ol 36

To a solution of the enone **35** (2.4 g, 15.7 mmol) in dry ether at 0 °C was added methyllithium (1 mol dm^{-3} solution in ether; 20 cm^3) and the mixture stirred at 0 °C for 2 h. Excess of methyllithium was quenched by addition of saturated aq. ammonium chloride. Work-up afforded the alcohol **36** as a colourless liquid (2.2 g, 83%); ν_{max}/cm^{-1} 3300–2930; δ_H 1.15–2.5 (7H, m), 1.3 (3H, s, Me), 3.35 (3H, s, OMe), 5.29 (1H, d, *J* 9.4, olefinic H), 5.6 (1H, dd, *J* 9.4 and 5.2, olefinic H).

1-Methylbicyclo[2.2.2]oct-5-en-2-one 37

A mixture of the alcohol **36** (12 g, 11.9 mmol), CH_2Cl_2 (50 cm^3) and $HClO_4$ (70% aqueous; 3 drops) was stirred at room tem-

perature for 30 min after which it was diluted with CH_2Cl_2, washed with water, aq. sodium hydrogen carbonate and brine and then dried (Na_2SO_4) and evaporated. Chromatography of the crude product over silica gel [ether–pentane (1:49) as eluent] yielded the ketone **37** as a viscous liquid (1.3 g, 82%); ν_{max}/cm^{-1} 3010, 2925, 1720 and 1630; δ_H 1.22 (3H, s), 1.2–2.22 (4H, m), 2.05 (2H, d, *J*, C*H*$_2$CO), 2.95 (1H, m, bridgehead H), 5.67 (1H, d, *J* 8.2 and 1.6, olefinic H) and 6.47 (1H, dd, *J* 8.2 and 6.6, olefinic H); δ_C 17.3 (q), 25.6 (t), 29.8 (t), 31.8 (d), 40.0 (t), 48.5 (s), 133.3 (d), 136.6 (d) and 212.6 (s); *m*/*z* 136 (M^+, 10%) and 94 (100) (Found: M^+, 136.0890. $C_9H_{12}O$ requires *M*, 136.0888).

1,3-Dimethylbicyclo[2.2.2]oct-5-en-2-one 38

To a freshly prepared LDA solution [prepared from 1 mol dm^{-3} solution of BuLi (7.2 cm^3, 7.2 mmol) and diisopropylamine (1 cm^3, 7.9 mmol) in THF (20 cm^3)] at −78 °C under argon, was added dropwise a solution of the ketone **37** (19, 6.57 mmol) in THF (20 cm^3). After being stirred at −78 °C for 1 h, the reaction mixture was treated with methyl iodide (1 cm^3, 15 mmol) in THF (5 cm^3) and stirring continued for a further 1 h. After this, the reaction mixture was poured onto saturated aq. ammonium chloride and extracted with ether. The extract was washed successively with water, aq. sodium thiosulfate solution, water and brine and then dried (Na_2SO_4) and evaporated. Chromatography of the crude product on silica gel [ether–pentane (1:49)] afforded the ketone **38** (0.9 g, 80%); ν_{max}/cm^{-1} 3005, 2925, 1720 and 1620; δ_H 1.02 (3H, d, *J* 7.4, C*H*CH$_3$), 1.16 (3H, s, me), 1.1–1.9 (5H, m), 2.66 (1H, m, bridgehead H), 5.71 (1H, d, 1/2ABq, *J* 8.2 and 0.8, olefinic) and 6.31 (1H, dd, 1/2Abq, *J* 8.2 and 6.6, olefinic); δ_C 17.2 (2 × q), 26 (t), 29.3 (t); 38.7 (d), 43.9 (s), 48.3 (d), 123.1 (d), 135.4 (d) and 214.4 (s); *m*/*z* 150 (M^+, 8%), 134 (15), 94 (100) and 79 (60) (Found: M^+, 150.1031. $C_{10}H_{14}O$ requires *M*, 150.1045).

3-*endo*-(4-Bromo-3-methylbut-2-enyl)-1,3-dimethylbicyclo-[2.2.2]oct-5-en-2-one 18

To a freshly prepared LDA solution [prepared from 1 mol dm^{-3} solution of BuLi (2.2 cm^3, 2.2 mmol) and diisopropylamine (2.4 cm^3, 2.9 mmol) in THF (10 cm^3)] at −78 °C under argon was added dropwise the ketone **38** (600 mg, 2 mmol). The reaction mixture after being stirred at −78 °C for 1 h, was treated with 1,4-dibromo-2-methylbut-2-ene **21** (1 cm^3) and then immediately with HMPA (1 cm^3). The reaction mixture was stirred overnight and then poured onto 2 M aq. HCl. Work-up followed by chromatography of the crude product over silica gel [ethyl acetate–hexane (1:19)] afforded the bromide **18** as a liquid (820 mg, 70%); ν_{max}/cm^{-1} 3010, 2920 and 1720; δ_H 1.02 (3H, s, Me), 1.17 (3H, s, Me), 1.1–2.2 (9H, m), 2.59 (1H, m, bridgehead H), 3.95 (2H, m, CH_2Br), 5.62 (1H, t, *J* 8.1, olefinic H), 5.78 (1H, dd, *J* 8.4 and 1.2, olefinic H) and 6.46 (1H, dd, *J* 8.4 and 6, olefinic H); δ_C 14.93, 17.74, 18.02, 21.54, 22.22, 26.45, 29.8, 30.09, 37.45, 40.86, 126.88, 131.95, 135.89, 137.82 and 216.66; *m*/*z* 299 ($M^+ + 2$, 2%), 297 (M^+, 1), 217 (90), 121 (60), 94 (100) and 79 (100) (Found: M^+, 297.0839. $C_{15}H_{21}OBr$ requires *M*, 297.0854).

1,3-Dimethyl-5-(prop-2-enyl)tricyclo[4.3.1.0^{3,7}]decan-2-one 17

A solution of TBTH (0.7 cm^3, 2.2 mmol) and AIBN (20 mg) in dry benzene (5 cm^3) was added dropwise to a degassed benzene solution (0.005 mol dm^{-3}) of the bromide **18** (600 mg, 2.0 mmol) under a nitrogen atmosphere. After being refluxed for 3 h, the reaction mixture was concentrated under reduced pressure, and the residue was taken up in ether and the solution washed with 1% aq. NH_4OH, water, brine and then dried (Na_2SO_4) and evaporated. Column chromatography (ethyl acetate–hexane, 1:19) afforded the tricyclic ketone **17** as a colourless oil (240 mg, 60%); ν_{max}/cm^{-1} 3020, 2930 and 1720; δ_H 0.83 and 0.88 (3H, s, Me), 1.11 and 1.16 (3H, s, Me), 0.9–2.3 (14H, m), 4.5 and 4.63 (1H, d, *J* 1.2, olefinic H), 4.69 and 4.73 (1H, d, *J* 1.2, olefinic H); *m*/*z* 218 (M^+, 100%) and 93 (60) (Found: M^+, 218.1675. $C_{15}H_{22}O$ requires *M*, 218.1671).

1,3-Dimethyl-5-isopropylidenetricyclo[4.3.1.0^{3,7}]decan-2-one 9

A solution of the ketone **17** (80 mg, 0.8 mmol) and PTSA (catalytic) in dry benzene (5 cm^3) was refluxed for 45 min after which it was cooled, washed with saturated aq. $NaHCO_3$ (2 × 5 cm^3) and brine and then dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified over a silica gel column [ethyl acetate–hexane (1:19)] to furnish the tricyclic olefin **9** (70 mg, 90%) which was recrystallised from hexane; ν_{max}/cm^{-1} 2920 and 1712; δ_H 0.89 (3H, s, Me), 1.17 (3H, s, Me), 0.9–2.4 (9H, m), 1.52 (3H, s, Me), 1.62 (3H, s, Me) and 2.9 (1H, m, 6-H); *m*/*z* 218 (M^+, 100%), 162 (50) and 134 (80) (Found: M^+, 218.1681. $C_{15}H_{22}O$ requires *M*, 218.1671).

Pupukean-2-one 8

A suspension of the tricyclic olefin **9** (60 mg, 0.3 mmol) and 10% Pt–C (20 mg) in dry MeOH (5 cm^3) was magnetically stirred under a H_2 atmosphere for 12 h after which it was filtered through a Celite pad and once again stirred for 12 h under hydrogen after addition of a further catalytic amount of Pt–C. After this, the reaction mixture was filtered through a pad of Celite and evaporated under reduced pressure to furnish an inseparable mixture of the ketone **8** (50 mg) and the isomeric ketone **43** in the ratio (4:1); ν_{max}/cm^{-1} 1710; δ_H 0.83 and 0.85 (6H, 2d, 2 × CH_3CH), 0.92 (3H, s, Me), 1.13 (3H, s, Me), 1.3–1.8 (11H, m) and 2.32 (1H, m); *m*/*z* 220 (M^+, 30%), 159 (80) and 93 (100) (Found: M^+, 220.1830. Calc. for $C_{15}H_{24}O$: *M*, 220.1828).

Acknowledgements

We thank Professor N. C. Chang of National Sun Yat-Sen University, Kaohsiung, Taiwan, for kindly providing the spectra of **8**. We thank the CSIR, New Delhi, for the award of a fellowship to K. K.

References

1 For part 23 of the series; see, K. Kaliappan and G. S. R. Subba Rao, preceding paper.
2 M. A. Qaseem, N. A. J. Rogers and A. A. Othman, *Tetrahedron*, 1968, **24**, 4535.
3 T. Uyehara, K. Osanai, M. Sugimoto, I. Suzuki and Y. Yamamoto, *J. Am. Chem. Soc.*, 1989, **111**, 7264.
4 P. S. Shanker and G. S. R. Subba Rao, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 621.
5 P. S. Shanker and G. S. R. Subba Rao, *Tetrahedron Lett.*, 1994, 5055.
6 K. Kaliappan and G. S. R. Subba Rao, *J. Chem. Soc.*, *Chem. Commun.*, 1996, 2331.
7 K. Kaliappan and G. S. R. Subba Rao, *Tetrahedron Lett.*, 1997, 2185.
8 D. A. Evans, W. L. Scott and L. K. Truesdale, *Tetrahedron Lett.*, 1972, 121.
9 (*a*) B. Giese, *Radicals in Organic Synthesis*: *Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, 1986; (*b*) A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073; (*c*) B. Giese, *Angew. Chem.*, *Int. Ed. Engl.*, 1983, **22**, 753; (*c*) D. J. Hart, *Science*, 1984, **223**, 883; (*d*) B. Giese, ed., *Selectivity and Synthetic Applications of Radical Reactions*, Tetrahedron Symposia-in-print, *Tetrahedron*, 1985, **41**, 3887; (*e*) B. Giese, *Angew. Chem.*, *Int. Ed. Engl.*, 1985, **24**, 553; (*f*) M. Ramaiah, *Tetrahedron*, 1987, **43**, 3541; (*g*) A. Srikrishna, *Current Science*, 1987, **56**, 392; (*h*) D. P. Curran, *Synthesis*, 1988, 417 and 489; (*i*) G. Pattenden, *Chem. Soc. Rev.*, 1988, **17**, 361; (*j*) C. P. Jasperse, D. P. Curran and T. L. Fevig, *Chem. Rev.*, 1991, **92**, 1237; (*k*) N. A. Porter, B. Giese and D. P. Curran, *Acc. Chem. Res.*, 1991, **24**, 296; (*l*) D. P. Curran, *Synlett*, 1991, 63; (*m*) J. E. Baldwin, *J. Chem. Soc.*, *Chem. Commun.*, 1976, 734.
10 G. Stork and M. E. Reynolds, *J. Am. Chem. Soc.*, 1988, **110**, 6121.
11 N. J. G. Cox and G. Pattenden and S. D. Mills, *Tetrahedron Lett.*, 1989, **30**, 621.
12 S. A. Hitchcok and G. Pattenden, *Tetrahedron Lett.*, 1990, **31**, 3641.

13 H. Staudinger, O. Muntwyler and O. Kupfer, *Helv. Chim. Acta*, 1922, **5**, 756.
14 F. Bohlmann, H. Suding, J. Cuatrecasas, H. Robinson and R. M. King, *Phytochemistry*, 1980, **19**, 2399.
15 C. M. Beecham, C. Djerassi, J. S. Finer and J. Clardy, *Tetrahedron Lett.*, 1977, 2395.
16 P. de Mayo and R. M. Williams, *J. Am. Chem. Soc.*, 1965, **87**, 3275.
17 T. Takemoto, N. Nishimoto, S. Nakai, N. Takagi, S. Hayashi, S. Odashima and Y. Wada, *Tetrahedron Lett.*, 1983, **24**, 1057.
18 (*a*) R. P. Gregson and R. N. Mirrington, *Aust. J. Chem.*, 1976, **29**, 2037; (*b*) A. J. Birch and G. S. R. Subba Rao, *Aust. J. Chem.*, 1970, **23**, 1641.
19 (*a*) G. Frater and J. Wenger, *Helv. Chim. Acta*, 1984, **67**, 1702; (*b*) N. C. Chang and C. K. Chang, *J. Org. Chem.*, 1996, **61**, 4967.
20 For a detailed general note, see ref. 1.

Paper 7/04314G
Received 19*th June* 1997
Accepted 31*st July* 1997