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SYNTHESIS OF ISOPRENOID NATURAL PRODUCTS FROM β-KETO ESTERS

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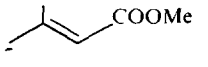
Abstract—The anions of β-keto esters were reacted with diethyl phosphorochloridate to yield the corresponding enol phosphate. These enol phosphates were coupled with lithium dimethylcuprate to give the resulting β-methyl α,β-unsaturated ester stereoselectively and in good yield. When combined with the γ-alkylation of the β-keto ester dianions this overall sequence results in the stereoselective and regioselective incorporation of an isoprene moiety in a synthetic sequence. This transformation has been applied in the synthesis of (*E,E*)-10-hydroxy-3,7-dimethyldeca-2,6-dienoic acid (butterfly compound), *Latia* luciferin, and mokupalide.

General and facile synthetic methods for the stereoselective formation of substituted alkenes play an important role in the arsenal of modern organic chemistry. The wide-spread occurrence of olefinic units in many classes of natural products is a major impetus to the development of these methods. The activity of many physiologically active alkenes is dramatically dependent on the configuration of the olefinic bonds in these substances. Hence, access to stereochemically pure synthetic alkenes is of prime importance for investigations in these areas. In addition, the synthesis of many natural products rely heavily on the chemist's ability to stereoselectively generate olefinic intermediates for subsequent conversion into the target molecules.

Mono- and disubstituted alkenes are relatively easy to prepare, and control over the geometry of the latter does not impose much difficulty. However, the general and stereoselective synthesis of tri- and tetrasubstituted alkenes is challenging and has been the goal of many synthetic endeavours. There are useful solutions to this problem involving additions to acetylenes,[1] cleavage of rings,[2] sigmatropic rearrangements,[3] allylic rearrangements,[4] or additions to carbonyl compounds.[5] While these methods have their own particular synthetic values, they often have certain limitations.

About ten years ago we developed a simple and efficient method to generate the dianion of β-keto esters[6a] and trap the dianion at the γ-carbon with a variety of electrophiles—eqn (1).[6] In the ensuing decade there were many applications of this methodology to the synthesis of natural products.[7] Recently we have developed a new stereoselective method to prepare alkenes from β-keto esters—eqn (2).[8] This method also has its limitations.[8] However in combination with the γ-electrophilic substitution illustrated in eqn (1), it should prove to be very useful in a number of applications. For example, using the sequence of eqns (1) and (2) we are able to stereoselectively introduce the isoprene unit **1** into a synthetic pathway. The utility of this particular



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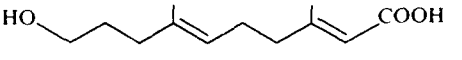
methodology is demonstrated in the three natural products syntheses discussed herein.

A. *Butterfly compound.* (*E,E*)-10-Hydroxy-3,7-dimethyldeca-2,6-dienoic acid (**2**).[9]

The major components in the hairpencil secretion of male danaid butterflies have been isolated and identified as a family of long chain unsaturated acids



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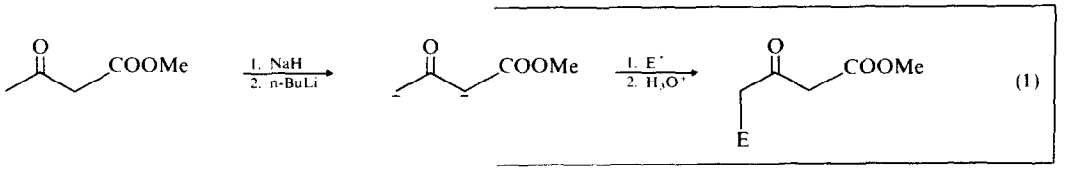

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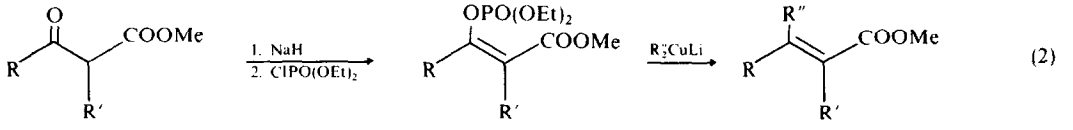
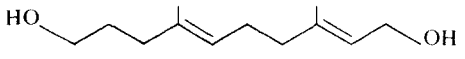


(2)

and alcohols.[10] Among them, the diol **3**[11] from the queen butterfly (*Danaus gilippus*), and the hydroxy acid **2**[12] and diacid **4**[13] from the monarch butterfly (*Danaus plexippus*) represent three closely related compounds whose exact functions still remain unknown. Since it is a formidable task to acquire even minute quantities of these substances from the natural source, further investigations of these compounds calls for their laboratory preparation.



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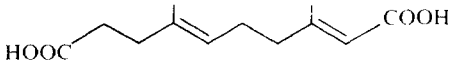

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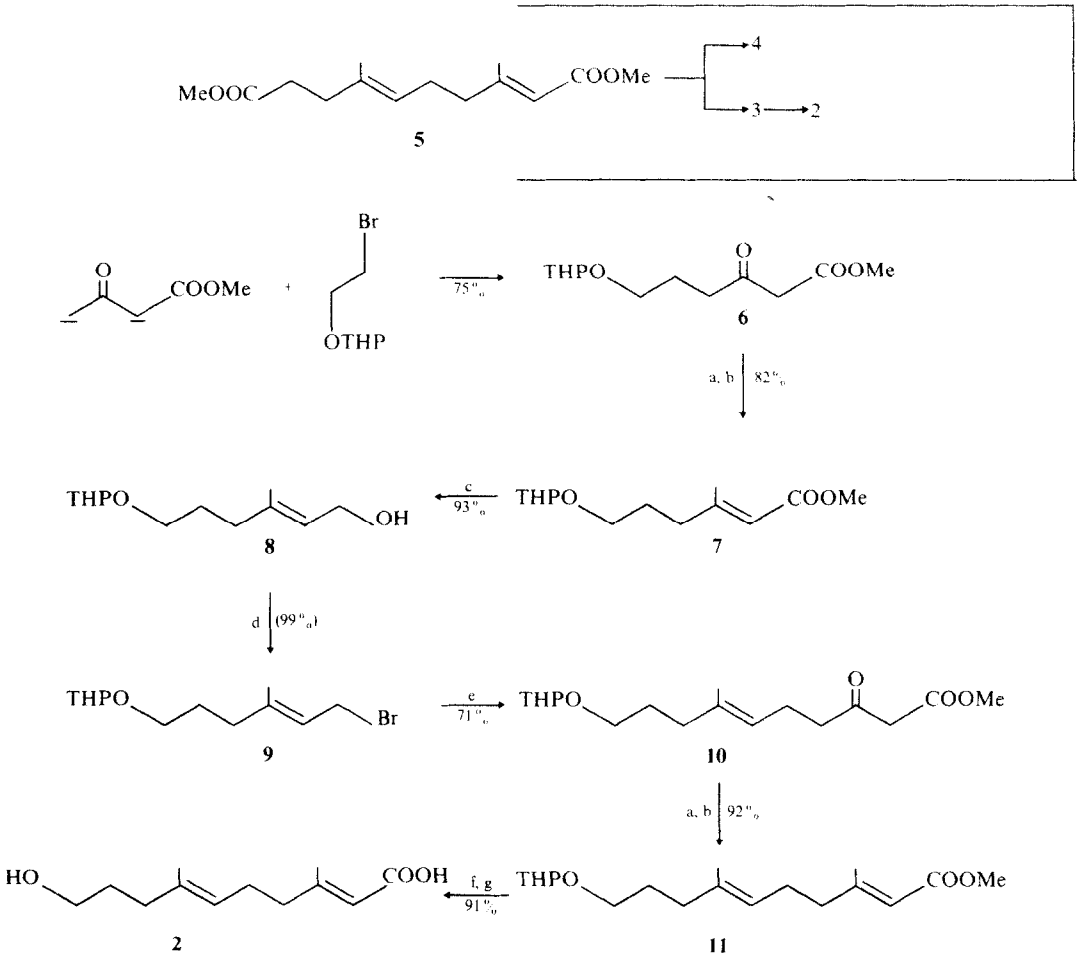
Partial syntheses of diol **3**[11] and diacid **4**[13] from (*E,E*)-farnesol have been reported. In a later publication, Meinwald, Johnson and coworkers[14] jointly reported an improved route to **3** and **4** via the common intermediate, diester **5** prepared by a five-step sequence from acrolein dimethyl acetal. One drawback in the synthesis of **5** was the low stereoselectivity observed in a Wittig-type reaction. Hydroxy acid **2** was also synthesized from **3** by a two-step transformation which involved a selective silver oxide oxidation. Katzenellenbogen and Christy[15] accomplished a stereoselective synthesis of diol **3** from geraniol, using the [3,3]-sigmatropic rearrangement of an allyl siloxyvinyl ether intermediate as the key step.

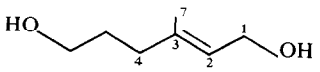
By employing the alkene synthesis developed earlier,[8] we were able to synthesize hydroxy acid **2** as shown in Scheme 1. Hydroxy acid **2** may be regarded as a precursor to both diol **3** and diacid **4**. In fact, Meinwald *et al.* have shown that **2** can be converted into diacid **4**[13] by the Cornforth oxidation and into diol **3**[12] by reduction with LAH.

The tetrahydropyranyl ether of 2-bromoethanol was allowed to react with two equivalents of the dianion of methyl acetoacetate to give **6** in 75% yield. A lower yield (*ca* 50%) of the desired product **6** and a significant amount (*ca* 30%) of recovered alkylating agent were observed when equivalent amounts of the two reactants were used. The β-keto ester **6** was then converted into its enol phosphate and treated with lithium dimethylcurprate at −47° to produce the *E*-α,β-ethylenic ester **7** in 82% yield. Subsequent reduction of the ester with lithium aluminum hydride



Scheme 1. Synthesis of butterfly compound **2**. [a]NaH, $ClPO(OEt)_2$; [b]2eq $LiMe_2Cu$; [c]$LiAlH_4$; [d]LiBr, n-BuLi, $MeSO_2Cl$; [e]$CH_2COCHCOOMe$; [f]OH^-; [g]H_3O^+.

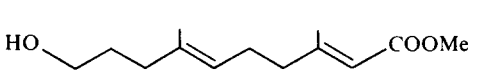
afforded the allylic alcohol **8** in excellent yield. The ^{13}C NMR of diol **12**, derived from cleavage (*p*-toluenesulfonic acid, methanol) of the tetrahydropyranyl ether protecting group in **8**, showed absorptions at δ 16.2 and 35.8 ppm, ascribable to C_7



12

and C_4 respectively. These chemical shifts were consistent with the data reported for such carbons in similar allylic alcohols with the *E* geometry[16] and provided additional evidence for the *E* configuration of the olefinic bond in ester **7**.

Incorporation of the second isoprene moiety was effected by conversion of alcohol **8** into the corresponding bromide **9**, followed by repetition of the foregoing reaction sequence of dianion alkylation, enol phosphate formation and lithium dimethylcuprate coupling. Several bromination methods were found unsatisfactory for the preparation of bromide **9**. However, the difficulty was circumvented by adopting Corey's procedure[17] which involved treating a mixture of alcohol **8** and lithium bromide in ether with n-butyllithium and methanesulfonyl chloride at $-78°$ and allowing the solution to warm to room temperature. The bromide **9**, owing to its unstable nature, was used immediately to alkylate an excess of the dianion of methyl acetoacetate. β-Keto ester **10** was thus obtained in 70% yield overall from alcohol **8**. Transformation of **10** into the dienic ester **11** was accomplished in 92% yield by utilizing the enol phosphate and cuprate coupling sequence. To complete the synthesis, ester **11** was hydrolyzed with aqueous base, and then treated with aqueous acid to give the desired hydroxy acid **2** in 91% yield. The spectral data of **2** were in excellent agreement with those reported for the natural compound.[12] As a final corroboration of the structural assignments, the tetrahydropyranyl ether protecting group in **11** was cleaved (*p*-toluenesulfonic acid, methanol) to give alcohol **13** whose spectroscopic and chromatographic properties were found to be identical with those of an authentic sample.[12]



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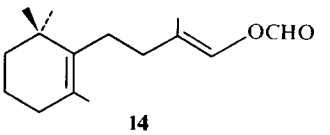
This synthesis of **2** demonstrates the synthetic utility of β-keto esters and their enol phosphates in the stereoselective synthesis of trisubstituted alkenes. Twice in this synthesis the isoprene equivalent **1** was stereoselectively added to an electrophile.

B. *Latia luciferin* **14**.[18]



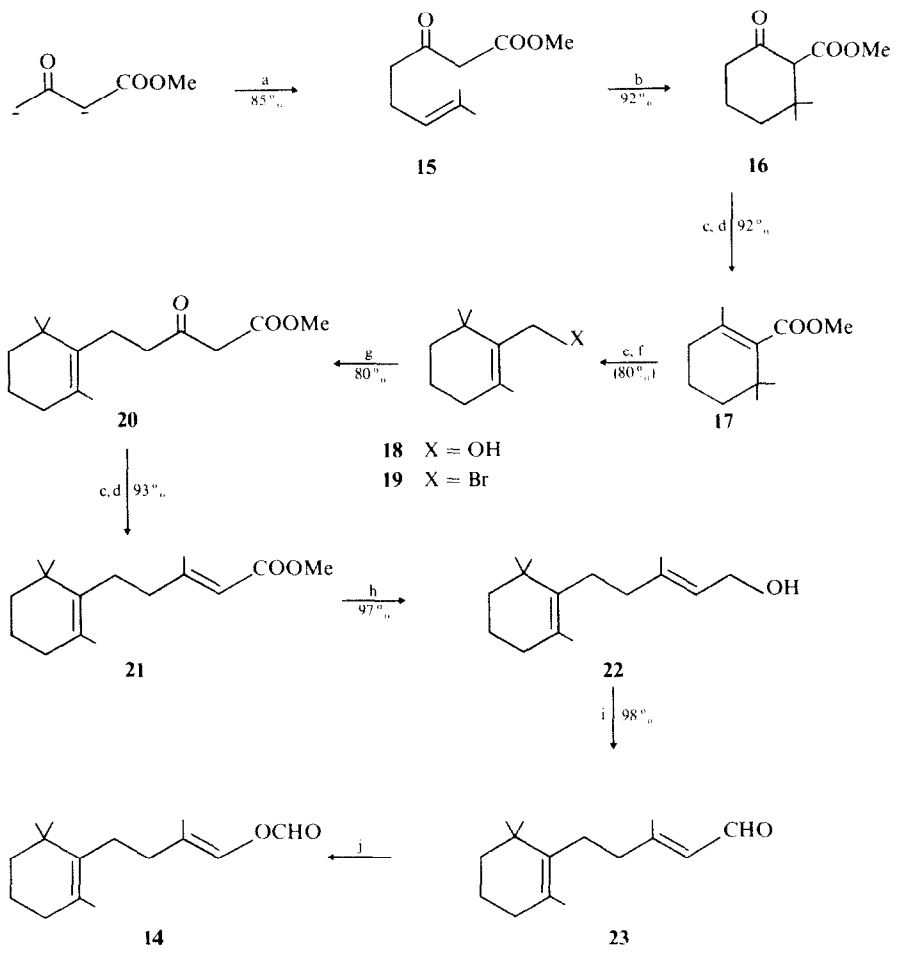
14

Latia luciferin **14** is a specific substrate of the bioluminescence enzyme in the fresh water limpet *Latia neriloides*.[19] The side-chain olefin in natural luciferin has been shown to have the *E* geometry. Nonstereoselective syntheses of *Latia* luciferin, starting from β-ionone, have been reported by two groups.[20] Magnus and Roy accomplished a third synthesis of luciferin via an intermediary α,β-epoxysilane derived from dihydro-β-ionone.[21] The last route was much improved in terms of stereoselectivity over the previous methods—only *ca* 10% of the *Z* isomer was produced.

A stereoselective synthesis of luciferin **14** was achieved, as shown in Scheme 2. Methyl β-cyclogerante (**17**) was prepared as follows. The dianion of methyl acetoacetate was alkylated with dimethylallyl bromide to give **15**[7d] in 85% yield. Exposure of **15** to stannic chloride[7c] produced the cyclic β-keto ester **16** which, upon successive treatment with sodium hydride, diethyl chlorophosphate, and lithium dimethylcuprate afforded **17** in 92% yield.

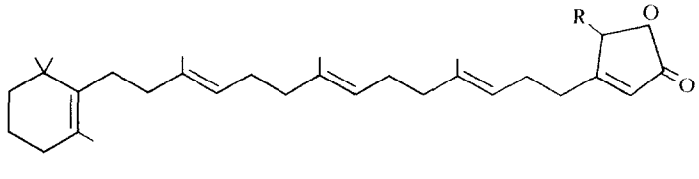
Ester **17** was reduced to alcohol **18**[22] almost quantitatively with lithium aluminum hydride. Several methods were tried to convert the hydroxy group in **18** into a leaving group appropriate for dianion alkylation. While many procedures failed to give satisfactory and reproducible results, it was found that the bromide **19** could be easily prepared, in 80% yield, by treating **18** with concentrated hydrobromic acid and n-pentane in a two-phase system at 0°.[23] The product so obtained was essentially pure according to spectroscopic analysis. Due to its thermal instability, bromide **19** was used immediately after preparation to alkylate the dianion of methyl acetoacetate to give **20**[7c] in *ca* 80% yield. Conversion of **20** into its enol phosphate, followed by reaction with lithium dimethylcuprate at $-78°$ afforded the *E*-α,β-unsaturated ester **21** in 93% yield. No detectable amount of the *Z* isomer was observed by ^1H NMR and tlc analyses.

Diisobutylaluminum hydride reduction of **21** furnished the corresponding alcohol **22** which was then oxidized, with active manganese dioxide[24] in hexane, to the α,β-unsaturated aldehyde **23** in good yield. The spectral data of **23** were identical with those reported[20b] for the *E* isomer of this compound. Since aldehyde **23** has been stereoselectively transformed into the formate **14** using anhydrous hydrogen peroxide and selenium dioxide[20b] this synthesis of **23** completed our approach to *Latia* luciferin **14**.



Scheme 2. Synthesis of *Latia* luciferin **14**. [a]Me_2CCHCH_2Br; [b]$SnCl_4$; [c]NaH, $ClPO(OEt)_2$; [d]$LiMe_2Cu$; [e]$LiAlH_4$; [f]HBr; [g]$CH_2COCHCOOMe$; [h]DIBAL; [i]MnO_2; [j]Reference 20b.

C. *Mokupalide* (**24**).[25]

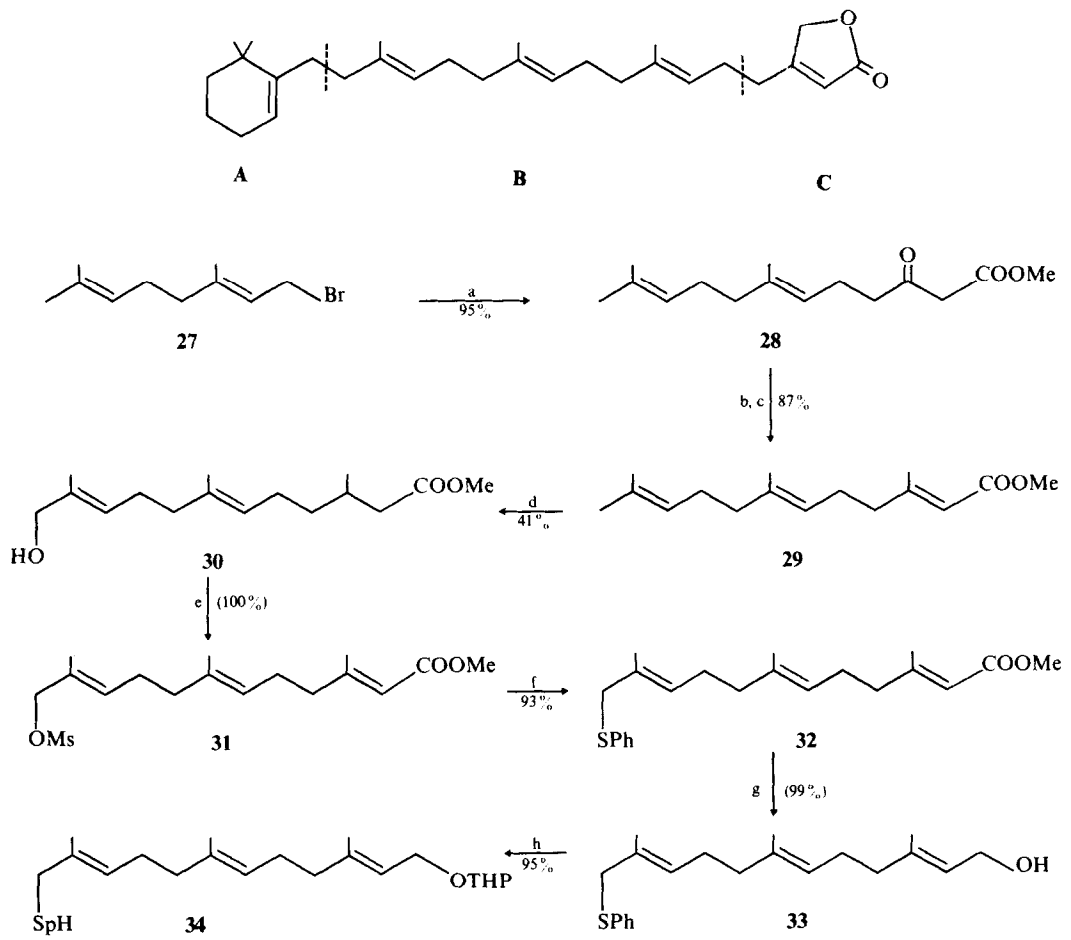


24, R = H
25, R = OH
26, R = OAc

Recently, Scheuer and Yunker isolated three novel hexaprenoids which were named mokupalide, hydroxymokupalide and acetoxymokupalide from a Pacific marine sponge.[26] The mokupalides were shown to have structures **24**–**26** which contain an unusual array of six isoprene units joined together in a head-to-tail fashion. Our interest in exploring the synthetic utility of the newly developed β-keto ester chemistry prompted our effort to prepare mokupalide (**24**).

A brief examination of structure **24** revealed three major synthetic objectives, viz., construction of the cyclohexene moiety, stereoselective synthesis of the three olefinic linkages with *E* geometry, and incorporation of the butenolide end group. Accordingly, the target molecule was envisioned to be composed of three units, A, B and C, as shown below. The design of our synthetic route centred upon the separate syntheses of these individual units which were assembled at appropriate stages then connected in a convergent synthesis.

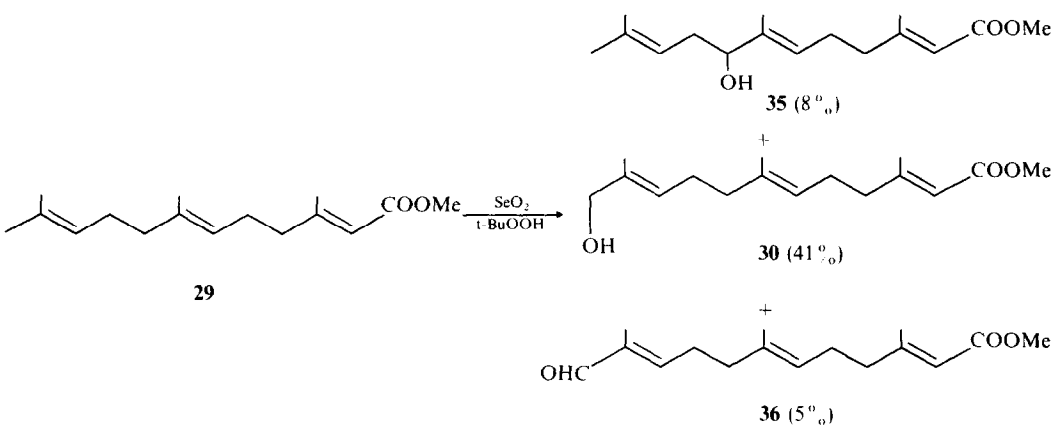
Bromide **19** (Scheme 2) served as the synthetic equivalent of subunit A. The thioether **34** is the functionalized derivative of subunit B which we



Scheme 3. Synthesis of Thioether **34**. [a]$\bar{C}H_2C\bar{O}CHCOOMe$; [b]NaH, $ClPO(OEt)_2$; [c]$LiMe_2Cu$; [d]t-BuOOH, SeO_2; [e]$MeSO_2Cl$, Et_3N; [f]PhSLi; [g]DIBAL; [h]DHP, TsOH.

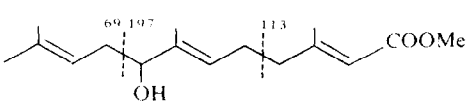
desired and a stereoselective synthesis of **34** is illustrated in Scheme 3. The dianion of methyl acetoacetate was treated with geranyl bromide (**27**) to give the alkylation product **28** in 95% yield. The β-keto ester **28** was stereoselectively converted into the *Z*-enol phosphate which was then coupled with lithium dimethylcuprate to afford (*E,E*)-methyl farnesoate (**29**). The above sequence invariably proceeded in greater than 85% yield and with greater than 98% stereoselectivity.

The oxidation of **29** with selenium dioxide in refluxing ethanol[27] gave unsatisfactory results. A modified procedure, developed by Umbreit and Sharpless[28] involving t-butyl hydroperoxide and a catalytic, or stoichiometric, amount of selenium dioxide was then employed. It was hoped that the mild reaction conditions of this modification might alleviate the complications encountered in using excess selenium dioxide and refluxing ethanol. Indeed, by treating **29** with selenium dioxide (0.5 eq) and 70% *t*-



butyl hydroperoxide **29** (2eq) in dichloromethane (4.5 hr, 10), the allylic alcohol **30** was obtained in 41% yield along with the regioisomer **35** (8%), the aldehyde **36** (5%) and recovered **29** (19%). Careful monitoring of the reaction conditions was crucial for good results, as higher temperatures and prolonged reaction times led to significant formation of the aldehyde product and less efficient conversion into the desired alcohol **30**.

The regiochemistry of the hydroxy group in structures **30** and **35** was established by analysis of their ^{1}H NMR and mass spectral data. The ^{1}H NMR spectrum of **30** (in CCl_4) showed absorptions at δ 1.60 (s, 3 H), 3.83 (s, 2 H) and 5.25 (m, 1 H) which were ascribed to protons at C-13, C-12 and C-10 respectively. Comparison of these data with those reported for the analogous allylic alcohols *E*- and *Z*-**37**[30] (chemical shifts indicated were measured in CCl_4) confirmed the *E* geometry of the C-10 olefinic bond in **30**. Prominent mass fragments at *m/e* 181 and 149 (181−CH_4O) in the mass spectrum of **30** also supported the assigned terminal alcohol structure. Alcohol **35** exhibited a one-proton triplet (J = 7 Hz) at δ 3.93 and a one-proton multiplet at δ 5.3 in its ^{1}H NMR spectrum, which were consistent with absorptions expected for protons at C-8 and C-6 in the suggested structure. The position of the hydroxyl group in **35** was further substantiated by mass spectroscopy which showed major mass peaks at *m/e* 197, 165 (197−CH_4O) and 113, corresponding to the fragmentations illustrated below. The structure of



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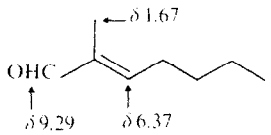
aldehyde **36** was ascertained by comparing its ^{1}H NMR absorptions at δ 1.73 (s, 3 H), 6.37 (m, 1 H) and 9.3 (d, 1 H), attributed to the C-13, C-10 and C-12 protons, with those recorded for structure **38**.[30,31]



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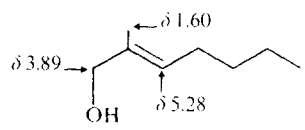
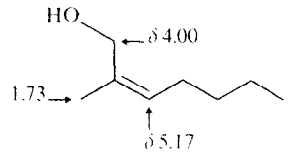
The allylic alcohol **30** was converted[32] into the corresponding mesylate **31**, which was immediately treated with lithium thiophenoxide in tetrahydrofuran to give sulfide **32** in 93% overall yield. The ester function in **32** was reduced with diisobutylaluminum hydride and the resulting alcohol **33** was protected as the tetrahydropyranyl ether furnishing **34** in 95% yield.

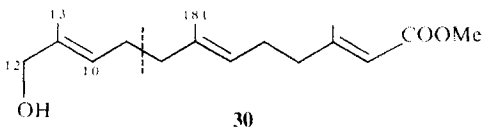
The two compounds **19** and **34**, representing the subunits A and B were assembled as shown in Scheme 4. The anion of **34**, generated by n-butyllithium in the presence of DABCO[33,34] (THF, −23), was alkylated with bromide **19** to produce the α-alkylation product **39** in 75% yield. Biellmann and Ducep have shown that lithium in ethylamine was superior to other methods (Raney nickel, calcium-hexamine, and lithium in ammonia) for the reductive desulfurization of an allylic sulfide in polyene molecules.[34] However, it is quite inconvenient to utilize this method in small scale reactions. A nickel catalyst, prepared from nickel (II) chloride and sodium borohydride, has been developed by Truce and Roberts to desulfurize thioketals.[35] This so-called nickel boride reagent was later applied to reductively cleave benzylthioenol ethers.[36] The facility in the preparation and handling of this reagent stimulated us to test its effectiveness in the desulfurization of the allylic sulfide **39**. Indeed, when **39** was exposed to excess nickel boride in ethanol, the desulfurized compound **40** was obtained



E-**37**



Z-**37**



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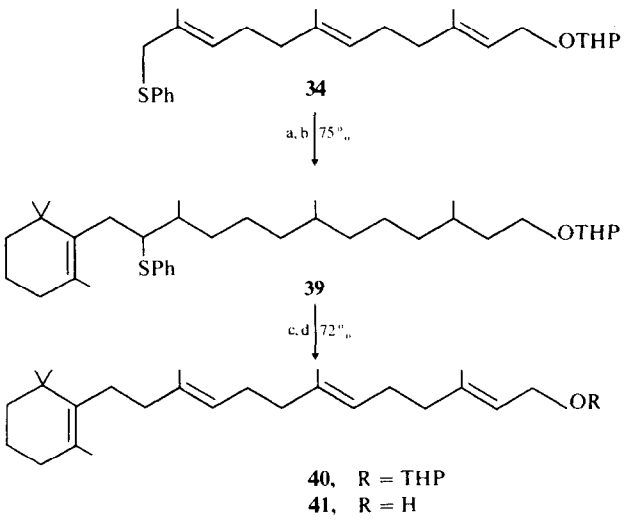
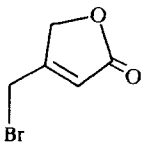


Scheme 4. [a]n-BuLi, DABCO; [b]**19**; [c]$NiCl_2$, $NaBH_4$; [d]TsOH, MeOH.

in *ca* 72% yield. The hydroxy group was subsequently deprotected to give alcohol **41**.

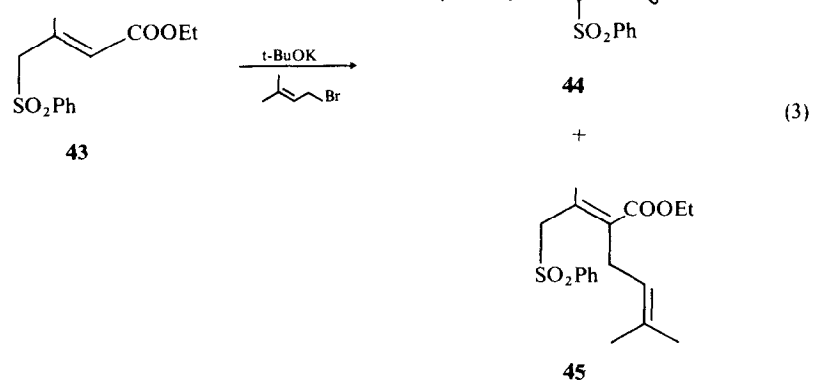
An α′-substituted 3-methyl-2-butenolide is the synthetic equivalent to subunit C. Recently Martin *et al.*[37] have reported a facile synthesis of 3-bromomethyl-2-butenolide (**42**). In a preliminary



42

attempt to assemble the mokupalide skeleton the carbanion of the phenylthioether derived from **41** (–OH → SPh) was treated with the bromo butenolide **42**. Only starting materials were recovered from this reaction. Presumably, proton exchange between the butenolide and the thioether carbanion occurred faster than the desired alkylation. On the basis of this result, it appeared more feasible to use the butenolide as the nucleophile and a derivative of **41** as the alkylating agent in the assembling process.

Julia and Arnould achieved the γ-alkylation of the α,β-unsaturated ester **43** with 1-bromo-3-methyl-2-butene, in tetrahydrofuran, using potassium t-butoxide as base (eqn 3).[38] The γ- and α-alkylation products, **44** (a mixture of *E* and *Z* isomers) and **45**, were obtained in a ratio of 89:11. More recently, the anions of γ-phenylsulfonyl-α,β-unsaturated ketones were reported to undergo selective γ-alkylations with alkyl halides in polar solvent systems.[39] The sulfonyl butenolide **46** was therefore chosen to introduce the butenolide end group C in the final coupling step. Treatment of bromide **42** with sodium benzenesulfinate in dimethylformamide (DMF) at ambient temperature afforded the sulfone **46** in 85% yield. Alkylation of the anion derived from **46** and sodium hydride[39a] (or potassium t-butoxide[39b]) in DMF (or t-butyl alcohol) invariably gave significant quantities of the dialkylated product **48** (eqn 4). This complication

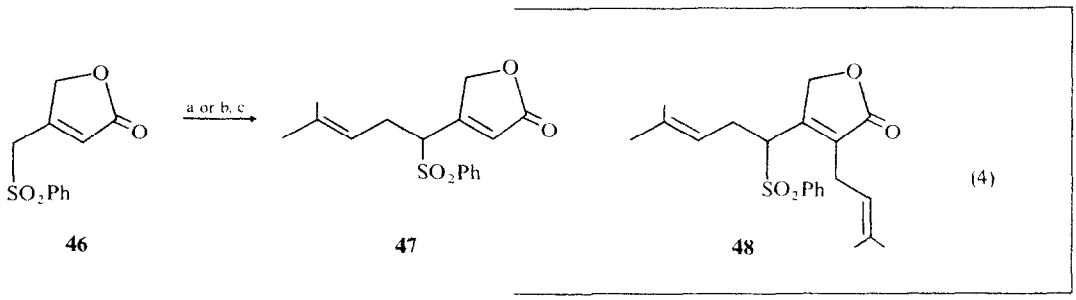


(3)

was alleviated by employing an excess of the sulfonyl anion in the alkylation. With such modification, a markedly improved yield of the desired product **47** was attained. This use of excess **46** is not detrimental when the alkylating agent is the more hard won reagent (as in the application below).

80% yield of mokupalide (**24**). The IR, ^{1}H NMR and mass spectral data of this synthetic product were identical with those of the natural compound.[26]

The above synthesis represents the first synthesis of mokupalide **24** and provides a route which possibly can lead to hydroxymokupalide **25**, and hence

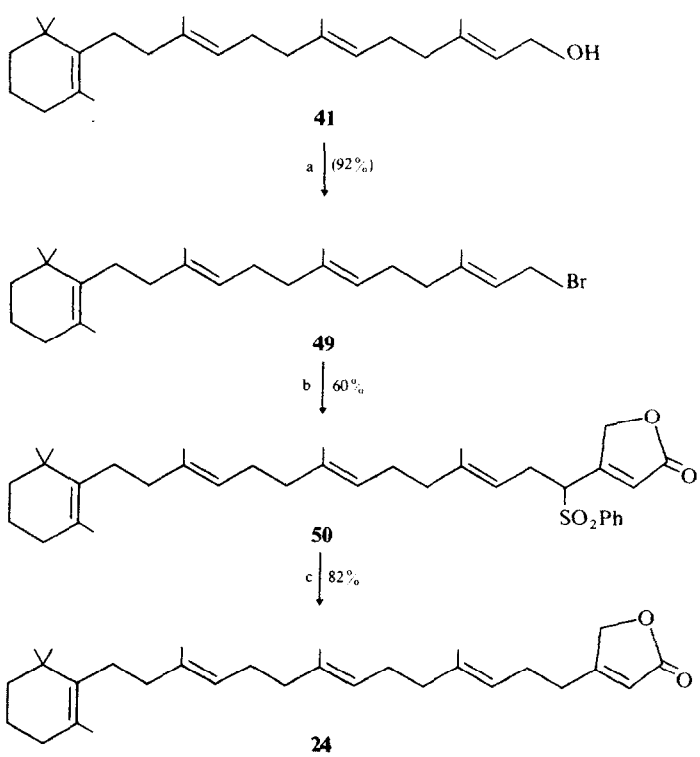


46 **47** **48** (4)

[a]t-BuOK, t-BuOH; [b]NaH, DMF (or THF-HMIA); [c]Me_2CCHCH_2Br

Scheme 5 illustrates the final steps in the synthesis of mokupalide (**24**). Alcohol **41** was converted into the bromide **49** by successive treatment with lithium bromide, n-butyllithium and methanesulfonyl chloride.[17] This unstable bromide was immediately alkylated with an excess of the anion of sulfone **46** in DMF at room temperature to produce the coupled compound **50** in 60% yield from alcohol **41**. The sulfonyl group in **50** was removed reductively with 6% sodium amalgam in methanol[40] to give a greater than acetoxymokupalide **26**, via functionalization of the butenolide moiety.[41]

In summary the enol phosphate–dimethylcuprate alkene synthesis is shown to be applicable to the synthesis of acyclic and cyclic alkenes which may be tri- or tetrasubstituted. The method is stereoselective (we have subsequently found that the method can be stereospecific[42]) and when combined with the alkylation of β-keto ester dianions[6] provides a useful route to isoprenoid compounds.



Scheme 5. Final stages of the synthesis of mokupalide (**24**). [a]LiBr, n-BuLi, MsCl; [b]anion of **46**; [c]Na-Hg, MeOH

EXPERIMENTAL

All temps are stated in degree centigrade. Kugelrohr distillations were performed by means of a Büchi Kugelrohr thermostat. Infrared spectra were recorded in $CHCl_3$ soln (unless otherwise noted), on Perkin–Elmer Model 700 or 710B spectrophotometers, and were calibrated with the 1601 cm^{-1} band of polystyrene. PMR spectra were recorded on Varian Model T-60, HA-100 or XL-100 spectrometers, in $CDCl_3$ soln unless otherwise specified. Chemical shifts are reported in the δ scale using TMS as an internal standard. The multiplicity, coupling constants (if observable) and integrated peak area are indicated in parenthesis after each signal. Low resolution mass spectra were recorded on an Atlas CH-4B mass spectrometer, and high resolution mass measurements were obtained using an AEI MS-9 or MS-50 mass spectrometer. All instruments were operated at an ionizing potential of 70 eV. All mass measurements are reported in atomic mass units. Elemental microanalyses were performed by Mr. Peter Borda, University of British Columbia. The silica gel used was supplied by E. Merck. Silica Gel PF-254 was used for both analytical and preparative tlc, whilst the grade 100–200 mesh ASTM was used for column chromatography. All solvent systems are expressed in ratios by volume (v/v). Vapor phase chromatographic (vpc) analyses were conducted on a Hewlett-Packard Model 5830-A chromatograph using 6 ft. × 1/8 in. columns of 3% OV-17 or 3% OV-101.

The petroleum ether used has the boiling range 30–60°. Dry ethyl ether and THF were obtained by distillation from LAH. CH_2Cl_2 and methanesulfonyl chloride were dried by distilling from P_2O_5. Dry DMF and hexamethyl phosphoramide (HMPA) were obtained by refluxing over calcium hydride, followed by distillation under reduced pressure. Triethylamine was purified and dried by distilling from barium oxide. The anhyd stannic chloride used was reagent grade material purchased from Fisher Scientific Company Ltd. Diethyl chlorophosphate supplied by Aldrich Chemical Company, Inc. was used directly without purification and was handled under dry N_2 at all times. MeLi (in ether), n-BuLi (in hexane) and sec-BuLi (in cyclohexane) were obtained from Aldrich Chemical Company, Inc., while EtLi (in benzene) and t-BuLi (in pentane) were supplied by Alfa Division, Ventron Corporation. The alkyllithium solns were standardized by titration against a 1.0 M soln of t-BuOH in benzene, using 1,10-phenanthroline as indicator. Sodium hydride (from Alfa Division, Ventron Corporation) was weighed as a 50% dispersion in mineral oil and was washed with dry ether to remove the oil prior to use.

General procedure for the preparation of the Z-enol phosphate of β-keto esters

To a stirred suspension of NaH (1.1 eq) in dry ethyl ether, kept under a dry N_2 and cooled in an ice-bath, was added a soln of the β-keto ester (1.0 eq) in ethyl ether. After 15–20 min at 0° (or 10 min at room temp), 1.1 eq of diethyl chlorophosphate was introduced and stirring was continued for 1–2 hr at 0° (or room temp). Progress of the reaction could be easily monitored by tlc. Although the β-keto ester enolate was usually found to react within 30 min at 0°, the reaction was allowed to proceed for a longer period of time to ensure completeness of the transformation. The enol phosphate was isolated from the mixture by either of the following work-up procedures:

(a) For less than 5 mmol scale preparations, the reaction mixture was stirred with excess solid ammonium chloride for 20 min, filtered through celite, and the filtrate was concentrated in vacuo.

(b) For larger than 5 mmol scale preparations, the mixture was quenched with aqueous ammonium chloride and diluted with ethyl ether. The ether soln was then washed with sat $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated under reduced pressure.

The crude enol phosphate so obtained was essentially pure by spectroscopic and chromatographic analyses, and was used directly in reactions with lithium dialkylcuprates.

General procedures for the generation and work-up of lithium dimethylcuprate reactions.

Two equivs of MeLi (in ethyl ether) was added dropwise to a stirred suspension of 1 eq of cuprous iodide (purified according to Kauffman's procedure[43]) in dry ethyl ether at 0° and under a dry N_2. The resulting light tan soln was used for coupling reaction at the appropriate temp.

The mixture was worked up by pouring it into an ice-cold mixture of 50% aqueous ammonium chloride and concd ammonium hydroxide (*ca* 5:1), and the aqueous phase was extracted with ethyl ether. The combined ether extracts were washed with brine, dried over $MgSO_4$ and then concentrated under reduced pressure.

A. *Butterfly compound* (**2**)

Methyl 3-*oxo*-6-(2-*tetrahydropyranyloxy*)*hexanoate* (**6**). A soln of the dianion of methyl acetoacetate was generated[6b] from 6.96 g (60 mmol) of methyl acetoacetate, 3.02 g (63 mmol) NaH (50%) and 37.5 mL (60 mmol) n-BuLi (1.6 M) in 130 mL dry THF. To this soln, cooled in an ice-bath, was added 6.27 g (30 mmol) 2-bromoethanol tetrahydropyranyl ether (prepared from 2-bromoethanol[44]). The resulting yellow suspension was stirred for 2 hr at 0° and then poured into 200 mL ice-cold satd NH_4Cl aq. The aqueous phase was extracted with 2 × 200 mL ethyl ether and the combined organic soln was washed with brine and dried over Na_2SO_4. The crude product obtained after removal of solvents was Kugelrohr distilled to yield 5.46 g (75%) of **6** as a colorless oil: b.p. 116–118°/0.1 Torr; IR 1745, 1715, 1655, 1630, 1440 and 1030 cm^{-1}; ^1H NMR δ 1.2–2.2 (m, 8 H), 2.63 (t, J = 7 Hz, 2 H), 3.45 (s, 2 H), 3.2–4.1 (m, 4 H), 3.71 (s, 3 H), and 4.5 (m, 1 H); mass spectrum *m/e* (rel intensity) 244 (2), 190 (4), 159 (8), 143 (65), 142 (65), 111 (89), 101 (38), 85 (99), 84 (67), 83 (32), 69 (100), 55 (71) and 41 (40). (Found: C, 58.80; H, 8.27. Calc. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.)

Methyl Z-3-(diethylphosphoryloxy)-6-(2-tetrahydropyranyloxy)hex-2-enoate. The enol phosphate was prepared from 12.96 g (53.0 mmol) of **6**, 2.80 g (58.3 mmol) NaH, and 8.43 mL (58.3 mmol) diethyl chlorophosphate in ether at 0° as outlined above. The yield of crude product, suitable for the coupling step, was quantitative and this product had the following spectral data. IR 1725, 1670, 1280 and 1030 cm^{-1}; ^1H NMR δ 1.36 (t, J = 7 Hz, 6 H), 1.2–2.2 (m, 8 H), 2.53 (br t, J = 7 Hz, 2 H), 3.2–4.0 (m, 4 H), 3.65 (s, 3 H), 4.22 (qn, J = 7 Hz, 4 H), 4.50 (m, 1 H) and 5.33 (s, 1 H); mass spectrum *m/e* (rel intensity) 380 (0.1), 349 (2), 296 (5), 279 (6), 251 (8), 219 (10), 155 (100), 142 (42), 127 (18), 111 (25), 99 (20) and 85 (17).

High Resolution Mass Measurement Calc. for $C_{15}H_{26}O_7P$ (P^+–OCH_3): 349.1416. Found: 349.1443.

Methyl E-3-methyl-6-(2-tetrahydropyranyloxy)-hex-2-enoate (**7**). To a soln of lithim dimethylcuprate (8.4 mmol) in ethyl ether, cooled to −47°, was added 1.6 g (4.2 mmol) of the above enol phosphate (dissolved in 2 mL ether). The resulting reddish purple mixture was stirred at −47° for 2 hr and then worked up according to the above general procedure. The crude product (1.02 g, *ca* 100% yield) obtained was 97% pure **7** by vpc analysis (3% OV-17 column, 150°). Preparative tlc (silica gel, 8:1 CCl_4-ethyl ether) of 90 mg of the crude product yielded 74 mg (82%) of 7 (pure by vpc) as a colorless liquid; bp (Kugelrohr distillation) 110–112°/0.1 Torr; IR 1715, 1650, 1155 and 1030 cm^{-1}; ^1H NMR δ 1.2–2.4 (m, 10 H), 2.13 (br s, 3 H), 3.0–4.0 (m, 4 H), 3.63 (s, 3 H), 4.50 (m, 1 H) and 5.63 (m, 1 H); mass spectrum *m/e* (rel intensity) 242 (0.1), 158 (20), 141 (8), 127 (9), 112 (6), 109 (8), 85 (100), 81 (10) and 41 (10). (Found: C, 64.23; H, 9.24. Calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.12%.)

E-3-Methyl-6-(2-tetrahydropyranyloxy)hex-2-en-1-ol (**8**). A soln of 3.63 g (15 mmol) of 7 in dry ethyl ether (10 mL) was added dropwise to a suspension of 374 mg (9.4 mmol) LAH in

60 mL of anhyd ethyl ether at room temp with constant stirring. The mixture, kept under N_2, was heated under reflux for 1 hr. About 4 mL of 5% NaOH aq was then introduced and stirring was continued for 45 min. The resulting suspension was filtered through anhyd Na_2SO_4 and the residue was eluted with more ethyl ether. The combined filtrate was concentrated under reduced pressure to give 3.16 g (98%) of crude **8** which was very pure by tlc (silica gel, 1:1 CCl_4–ethyl ether) and spectroscopic analyses. Purification of the crude product by Kugelrohr distillation furnished 2.98 g (93%) of **8**: colorless oil; b.p. 98–100°/0.05 Torr; IR 3670, 3500 and 1670 cm^{-1}; ^1H NMR δ 1.2–2.3 (m, 11 H), 1.67 (s, 3 H), 3.1–3.9 (m, 4 H), 4.09 (d, J = 7 Hz, 2 H), 4.50 (m, 1 H) and 5.38 (br t, J = 7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 214 (0.5), 196 (1), 130 (5), 112 (6), 101 (10), 97 (11), 85 (100), 84 (20), 69 (10), 67 (14), 57 (15), 55 (15), 43 (14) and 41 (25).

High resolution mass measurement Calc. for $C_{12}H_{22}O_3$: 214.1569. Found: 214.1579.

E-1-Bromo-3-methyl-6-(2-tetrahydropyranyloxy)-2-hexene (**9**). A mixture of **8** (1.50 g, 7.0 mmol) and anhyd LiBr (1.97 g, 23 mmol) in dry ethyl ether (70 mL) was cooled to −78° and kept under N_2. To this stirred mixture was added 4.4 mL (7.0 mmol) n-BuLi (1.6 M in hexene), followed (after 20 min) by 0.57 mL (7.4 mmol) methanesulfonyl chloride. The resulting mixture was warmed to −10° over 1 hr, maintained at −10° for 0.5 hr and then stirred for 6 hr without the cooling bath. The final suspension was poured into 30 mL ice-cold 5% $NaHCO_3$ aq and the aqueous phase was separated and extracted with 30 mL ethyl ether. The combined ether soln was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude **9** (1.91 g, 99%), obtained as a slightly tan oil, showed satisfactory spectral data: IR 1660, 1120, and 1030 cm^{-1}; ^1H NMR δ 1.1–2.4 (m, 10 H), 1.72 (s, 3 H), 3.1–3.9 (m, 4 H), 3.95 (d, J = 8 Hz, 2 H), 4.52 (m, 1 H), and 5.5 (br t, J = 8 Hz, 1 H); mass spectrum *m/e* (rel intensity) 122 (P−C_5H_9O−Br, 11), 98 (13), 97 (100), 85 (33), 84 (77), 83 (38), 71 (12), 69 (13), 67 (16), 56 (24), 55 (93), 54 (21), 43 (45) and 41 (34). Since **9** was sensitive to distillation and chromatographic purification conditions (the crude material decomposed quite rapidly on standing at room temp) no satisfactory analytical data could be obtained.

Methyl E-7-*methyl*-3-*oxo*-10-(2-*tetrahydropyranyloxy*)*dec*-6-*enoate* (**10**). A soln of the dianion of methyl acetoacetate (2.44 g, 21 mmol) in dry THF (50 mL) was prepared[6b] and to this was added 1.91 g (6.9 mmol) of crude **9** at 0°. The resulting yellow suspension was stirred for 2 hr at 0° and then worked up in the same way as for **6**. Kugelrohr distillation of the crude product obtained gave 1.53 g (71%) of the alkylation product **10**: b.p. 120–122°/0.04 Torr; IR 1745 and 1715 cm^{-1}; ^1H NMR δ 1.2–2.7 (m, 14 H), 1.63 (s, 3 H), 3.1–3.9 (m, 4 H), 3.4 (s, 2 H), 3.71 (s, 3 H), 4.52 (m, 1 H), and 5.05 (m, 1 H); mass spectrum *m/e* (rel intensity) 312 (0.8), 248 (10), 228 (7), 220 (5), 210 (4), 206 (4), 192 (7), 170 (5), 164 (5), 155 (14), 152 (5), 149 (5), 143 (15), 130 (6), 127 (7), 101 (9), 95 (11), 94 (15), 85 (83), 84 (83), 83 (40), 69 (20), 67 (14), 56 (35), 55 (100), 54 (32), 43 (35), and 41 (35). (Found: C, 65.38; H, 9.20. Calc. for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03%.)

Methyl (E,E)-3,7-*dimethyl*-10-(2-*tetrahydropyranyloxy*)-*deca*-2,6-*dienoate* (**11**). The enol phosphate of **10** (230 mg, 0.74 mmol) was prepared as above in 5 mL dry ethyl ether and added through a two-way needle into an ether soln of lithium dimethylcuprate (1.5 mmol), cooled to −78°. The resulting orange-yellow suspension was stirred for 0.5 hr at −78° and then for 2 hr at −47° (mixture turned purple after 20 min at −47°). The mixture was worked up in the above manner to give 260 mg crude product, which upon preparative tlc (silica gel, 4:1 CCl_4-ethyl ether) afforded 210 mg (92%) of **11** as a colorless liquid: bp (Kugelrohr distillation) 108–110°/0.04 Torr; IR 1710 and 1650 cm^{-1}; ^1H NMR δ 1.1–2.5 (m, 14 H), 1.61 (s, 3 H), 2.14 (d, J = 1.4 Hz, 3 H), 3.1–4.0 (m, 4 H), 3.64 (s, 3 H), 4.52 (m, 1 H), 5.05 (m, 1 H) and 5.61 (m, 1 H); mass spectrum *m/e* (rel intensity) 310 (0.6), 279 (0.7), 278 (0.7), 227 (4), 226 (11), 196 (5), 195 (6), 194 (4), 149 (5), 121 (4), 114 (18), 95 (43), 85 (100), 84 (12), 83 (14), 67 (12), 55 (16), 43 (11) and 41 (14). (Found: C, 69.80; H, 9.92. Calc. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74%.)

(E,E)-10-*Hydroxy*-3,7-*dimethyldeca*-2,6-*dienoic acid* (**2**). To a soln of 42 mg (0.14 mmol) of **11** in MeOH (2 mL) was added 1 mL 5% NaOH aq. After stirring for 3 hr at 60°, the MeOH was evaporated under reduced pressure and the aqueous soln was acidified with 5% HCl. Dioxane was introduced (*ca* 2 mL) until a homogeneous soln was formed, which was stirred for 1 hr at room temp. The resulting mixture was saturated with NaCl and extracted with ethyl ether. The ether soln was dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was partitioned between 10% $NaHCO_3$ aq and $CHCl_3$. Acidification of the bicarbonate phase with conc HCl, followed by extraction with ethyl ether, and drying ($NaSO_4$) and evaporation of the ether extracts furnished 26 mg (91%) of **2**. The spectra data of this synthetic material were in excellent agreement with those reported previously for the natural compound[12]: IR 3600, 3400–2600 (broad), 1690 and 1640 cm^{-1}; ^1H NMR δ 1.2–2.4 (m, 8 H), 1.6 (s, 3 H), 2.15 (s, 3 H), 3.58 (t, J = 6 Hz, 2 H), 5.05 (m, 1 H), 5.62 (m, 1 H) and 6.73 (br s, 2 H, exchangeable with D_2O); mass spectrum *m/e* (rel intensity) 212 (2), 195 (10), 194 (13), 166 (11), 135 (10), 125 (12), 113 (14), 111 (15), 100 (18), 97 (17), 96 (16), 95 (94), 85 (100), 69 (16), 67 (24), 55 (26), 43 (52) and 41 (27).

High resolution mass measurement Calc. for $C_{12}H_{20}O_3$: 212.1412. Found: 212.1429.

E-3-*Methyl*-1,6-*hex*-2-*enediol* (**12**). A soln of 0.200 g (0.9 mmol) of **8** and 0.010 g *p*-toluenesulfonic acid is 10 mL dry MeOH were stirred at room temp for 3 hr under N_2. The MeOH was evaporated and the residue was dissolved in ethyl ether. The etheral soln was washed with 10% $NaHCO_3$ aq and dried over $MgSO_4$. Evaporation of the organic solvent gave 0.105 g of product which was essentially pure by tlc: ^{13}CNMR δ 16.20, 30.58, 35.80, 59.24, 62.38, 123.91 and 139.01.

Methyl (E,E)-10-*hydroxy*-3,7-*dimethyldeca*-2,6-*dienoate* (**13**). The x-ester **11** (200 mg, 0.64 mmol) and 10 mg *p*-toluenesulfonic acid were dissolved in 10 mL dry MeOH and stirred for 2 hr at room temp. The soln was then concentrated under reduced pressure and the residue was diluted with ethyl ether, washed with sat $NaHCO_3$ aq and dried over $MgSO_4$. Evaporation *in vacuo* yielded 143 mg (99%) of **13** which was identical with an authentic sample[12] by vpc (3% OV-17 column, 150°) as well as tlc (silica gel, 1:1 CCl_4-ethyl ether) analyses. The spectral properties of **13** were in excellent agreement with those of the authentic material: IR (CH_2Cl_2) 3670, 1715, 1650, 1220 and 1150 cm^{-1}; ^1H NMR δ 1.2–2.4 (m, 9 H), 1.61 (s, 3 H), 2.14 (d, J = 1.4 Hz, 3 H), 3.56 (t, J = 6 Hz, 2 H), 3.64 (s, 3 H), 5.06 (m, 1 H) and 5.60 (br s, 1 H); mass spectrum *m/e* (rel intensity) 226 (6), 208 (3), 196 (10), 195 (10), 194 (8), 167 (11), 166 (10), 114 (50), 95 (100), 85 (29), 83 (22), 82 (18), 69 (24), 67 (30), 55 (29), 43 (16) and 41 (28).

B. *Latia luciferin* **14**

Methyl 7-*methyl*-3-*oxooct*-6-*enoate* (**15**). A soln of the dianion of methyl acetoacetate in dry THF (200 mL), prepared[6b] from 11.6 g (0.10 mol) methyl acetoacetate, 5.28 g (0.11 mol) NaH (50% oil) and 65.6 mL (0.105 mol) n-BuLi (1.6 M), was treated with 11.6 mL (0.10 mol) 1-bromo-3-methyl-2-butene at 0°. The mixture was stirred for 1 hr 45 min at 0° and then worked up as described in the preparation of **6** to give 18.6 g crude product. Distillation through a Vigreux column afforded 15.7 g (85%) of **15**: b.p. 67–68°/0.1 Torr; IR 1745, 1718 and 1640 cm^{-1}; ^1H NMR δ 1.6 (s, 3 H), 1.65 (s, 3 H), 1.95–2.73 (m, 4 H), 3.40 (s, 2 H), 3.70 (s, 3 H) and 5.0 (m, 1 H); mass spectrum *m/e* (rel intensity) 184 (13), 169 (10), 166 (15), 153 (10), 149 (24), 129 (19), 116 (27), 111 (38), 110 (35), 109 (20), 101 (42), 95 (48), 83 (36), 82 (75), 74 (100), 69 (98), 67 (64), 59 (35), 55 (45), 43 (48) and 41 (99). (Found: C, 65.35; H, 8.96. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.)

Methyl 2,2-*dimethyl*-6-*oxocyclohexanecarboxylate* (**16**). To a soln of 9.0 mL (77 mmol) anhyd stannic chloride in dry CH_2Cl_2 (200 mL), kept under dry N_2 and cooled in an ice-bath, was added 12.9 g (70 mmol) of **15** dissolved in 15 mL dry

CH_2Cl_2. The resulting soln was stirred at room temp for 18 hr and then poured into 100 mL ice-cold water. The aqueous phase was extracted with 3 × 150 mL ethyl ether, and the combined extracts were washed with 50% brine until neutral and dried over $MgSO_4$. Removal of solvents under reduced pressure gave rise to 12.9 g crude product which contained essentially pure **16** according to its spectral and chromatographic data. Distillation of the crude material afforded 11.9 g (92%) of **16**: b.p. 64–66°/0.1 Torr; IR 1750 (shoulder), 1730 and 1710 cm^{-1}; ^1H NMR δ 1.02 (s, 3 H), 1.08 (s, 3 H), 1.2–2.1 (m, 4 H), 2.1–2.7 (m, 2 H), 3.13 (s, 1 H) and 3.65 (s, 3 H); mass spectrum *m/e* (rel intensity) 184 (26), 169 (20), 153 (38), 141 (19), 137 (53), 111 (58), 100 (68), 83 (85), 74 (74), 69 (79), 55 (100), 43 (96) and 41 (87). (Found: C, 65.00; H, 8.55. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.)

Methyl 2-(diethylphosphoryloxy)-6,6-dimethylcyclohexenecarboxylate. This enol phosphate was prepared according to the above procedure in quantitative yield from 5.52 g (30 mmol) of **16**, 1.58 g (33 mmol) NaH, and 4.8 mL (33 mmol) diethyl chlorophosphate in ether at 0°. The crude product was suitable for the coupling step and it had the following spectral data: IR 1725, 1680, 1280 and 1030 cm^{-1}; ^1H NMR δ 1.15 (s, 6 H), 1.2–1.9 (m, 4 H), 1.32 (t, J = 7 Hz, 6 H), 2.4 (m, 2 H), 3.70 (s, 3 H) and 4.10 (qn, J = 7 Hz, 4 H); mass spectrum *m/e* (rel. intensity) 320 (7), 288 (100), 273 (28), 260 (25), 245 (17), 232 (24), 217 (28), 137 (10), 128 (8) and 99 (10).

High resolution mass measurement Calc. for $C_{14}H_{25}O_6P$: 320.1389. Found: 320.1403.

Methyl 2,6,6-trimethylcyclohexenecarboxylate (**17**). A soln of 9.3 g (30 mmol) of the above enol phosphate in dry ethyl ether (5 mL) was added to a stirred soln of lithium dimethylcuprate (60 mmol) in ethyl ether (150 mL) at 0°. The resulting dark purple mixture was maintained at 0° for 5 hr and then worked up according to the above procedure. The crude product (5.95 g) was distilled (Kugelrohr) to give 5.03 g (92%) of **17** as a colorless liquid: b.p. 81–83°/3.5 Torr; IR 1710, 1660 (weak) and 1070 cm^{-1}; ^1H NMR δ 1.08 (s, 6 H), 1.2–2.1 (m, 6 H), 1.64 (s, 3 H) and 3.69 (s, 3 H); mass spectrum *m/e* (rel intensity) 182 (36), 167 (80), 151 (25), 135 (100), 123 (67), 107 (48), 81 (9), 79 (10) and 77 (8). (Found: C, 72.20; H, 9.87. Calc. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%.)

β-Cyclogeraniol (**18**). To a stirred suspension of LAH (95%; 44 mg, 1.1 mol) in anhyd ethyl ether (4 mL) was added dropwise an ether soln of **17** (182 mg, 1.0 mmol) at room temp. The resulting mixture was brought to reflux under dry N_2 for 2 hr and then cooled in an ice-bath, followed by quenching with 0.4 mL of 5% NaOH aq. Stirring was continued for 30 min at room temp and the resulting suspension was filtered through anhyd $MgSO_4$. The residue was washed several times with ethyl ether and the combined filtrate was evaporated under reduced pressure to give 151 mg (98%) of **18** which was homogeneous on tlc (silica gel, 5:1 CCl_4–ethyl ether) and was 99% pure by vpc (3% OV-101 column) analysis. An analytical sample of **18** was obtained by Kugelrohr distillation of the crude material: b.p. 55–57°/0.2 Torr; m.p. 41°; IR 3670, 3500 and 1650 (weak) cm^{-1}; ^1H NMR δ 1.05 (s, 6 H), 1.3–1.7 (m, 4 H), 1.73 (s, 3 H), 1.8–2.1 (m, 2 H) and 4.10 (s, 2 H); mass spectrum *m/e* (rel intensity) 154 (28), 139 (21), 136 (32), 123 (43), 121 (100), 105 (13), 93 (30), 79 (22) and 41 (16). (Found: C, 77.72; H, 11.91. Calc. for $C_{10}H_{18}O$: C, 77.87; H, 11.76%.)

1-Bromomethyl-2,6,6-trimethyl-1-cyclohexene (**19**). A prechilled soln of 48% HBr (50 mL) was added to 1.22 g (7.0 mmol) of **18** with cooling in an ice-bath'. The mixture, kept under N_2, was stirred for 10 min then 30 mL n-pentane was introduced. Stirring was continued for 3 hr at 0°. The two-phase mixture was then poured into ice-cold water, and the aqueous layer was extracted with n-pentane. The combined extracts were washed with sat $NaHCO_3$ aq and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **19** (1.40 g, 82%) so obtained was homogeneous by tlc analysis (silica gel, 6:1 CCl_4–ethyl ether) and had satisfactory spectral data: pale yellow oil; IR 1645 cm^{-1}; ^1H NMR δ 1.1 (s, 6 H), 1.3–1.7 (m, 4 H), 1.72 (s, 3 H), 2.0 (m, 2 H) and 4.02 (s, 2 H); mass spectrum *m/e* (rel intensity) 137 (P^+–Br, 18), 136 (P^+–HBr, 49), 121 (100), 107 (21), 93 (30) and 79 (17).

Methyl 3-oxo-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-pentanoate (**20**). The dianion of methyl acetoacetate (102 mg, 0.88 mmole) was generated in THF.[6b] To this dianion soln, cooled in an ice-bath, was added 174 mg (0.80 mmol) of the crude bromide **19**. The resulting yellow suspension was stirred for 1 hr 45 min at 0° and then worked up in the usual manner (see **6**). The crude product (181 mg) was chromatographed on silica gel with 5:1 petroleum ether–ethyl ether to afford 160 mg (80%) of **20** as a colorless liquid: IR 1745, 1715, 1655 and 1635 cm^{-1}; ^1H NMR δ 0.97 (s, 6 H), 1.3–1.7 (m, 4 H), 1.55 (s, 3 H), 1.7–2.8 (m, 6 H), 3.40 (s, 2 H) and 3.68 (s, 3 H); mass spectrum *m/e* (rel intensity) 252 (33), 234 (47), 221 (33), 220 (94), 163 (51), 159 (82), 145 (94), 137 (6), 136 (93), 129 (53), 123 (90), 121 (100), 119 (50), 107 (82), 105 (75), 95 (91), 93 (94), 91 (77), 81 (90), 79 (86), 69 (58), 67 (61), 59 (50), 55 (90), 43 (72) and 41 (98).

High resolution mass measurement Calc. for $C_{15}H_{24}O_3$: 252.1726. Found: 252.1726.

Methyl E-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)pent-2-enoate (**21**). The *Z*-enol phosphate of **20** (72 mg, 0.28 mmol) in ethyl ether was prepared in the same manner as described above. This enol phosphate soln was syringed into a soln of lithium dimethylcuprate (0.56 mmol) in dry ethyl ether (3 mL), cooled at −78°. The resulting purple mixture was stirred at −78° for 2 hr and then warmed to −47° over 2 hr. The mixture was worked up according to the above procedure to give 110 mg of crude product which, after preparative tlc (silica gel, 20:1 CCl_4–ethyl ether) purification, furnished 65 mg (93%) of **21**: colorless liquid; b.p. (Kugelrohr distillation) 86–88°/0.02 Torr; IR 1715 and 1650 cm^{-1}; ^1H NMR δ 1.0 (s, 6 H), 1.2–1.7 (m, 4 H), 1.57 (s, 3 H), 1.7–2.1 (m, 2 H), 2.13 (d, J = 1.5 Hz, 3 H), 2.17 (br s, 4 H), 3.63 (s, 3 H) and 5.61 (br s, 1 H); mass spectrum *m/e* (rel intensity) 250 (10), 219 (4), 176 (5), 138 (13), 137 (100), 121 (9), 114 (40), 95 (30), 81 (15) and 41 (10). (Found: C, 76.80; H, 10.40. Calc. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%.)

E-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)pent-2-en-1-ol (**22**). To a soln of 43 mg (0.17 mmol) of **21** in dry hexane (2 mL) was added 0.36 mL (0.36 mmol) diisobutylaluminum hydride (1 M in hexane) at −78°. The mixture was stirred under N_2 for 2 hr at the same temp, followed by quenching with satd NH_4Cl aq. After warming up to room temp, the resulting cloudy suspension was acidified with 10% HCl until the aqueous layer turned clear. The aqueous phase was extracted with ethyl ether and the ether soln was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product (38 mg, 100%) obtained was homogeneous by tlc (silica gel, 5:1 petroleum ether–ethyl ether) analysis and showed essentially pure **22** in the ^1H NMR spectrum. Preparative tlc of the crude product gave an analytical sample of **22** (36.5 mg, 97%): colorless oil; b.p. (Kugelrohr distillation) 93–95°/0.05 Torr; IR 3650, 3500 and 1670 cm^{-1}; ^1H NMR δ 1.0 (s, 6 H), 1.2–2.2 (m, 6 H), 1.6 (s, 3 H), 1.7 (s, 3 H), 2.06 (br s, 4 H), 4.1 (br d, J = 7 Hz, 2 H) and 5.37 (br t, J = 7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 222 (6), 204 (14), 191 (11), 189 (12), 149 (25), 138 (27), 137 (96), 136 (72), 123 (40), 121 (66), 119 (42), 109 (48), 107 (56), 105 (53), 95 (100), 93 (79), 91 (73), 81 (98), 79 (79), 77 (65), 69 (78), 67 (84), 65 (40), 57 (74), 55 (86), 53 (51), 44 (93), 43 (77) and 41 (98). (Found: C, 81.00; H, 11.72. Calc. for $C_{15}H_{26}O$: C, 81.02; H, 11.79%.)

E-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-pentenal (**23**). To a stirred suspension of 340 mg active MnO_2[24a] in dry hexane was added 32 mg (0.14 mmol) of alcohol **22** at 0°. Stirring was continued for 1.5 hr at 0° and 0.5 hr at room temp. The mixture was then filtered through celite and the residue was eluted with n-pentane. The combined filtrate was evaporated under reduced pressure to give 31 mg (98%) crude **23** which was homogeneous by tlc analysis (silica gel, 10:1 petroleum ether–ethyl ether) and

showed the following spectral data:[20] IR 1670 and 1635 cm^{-1}; ^1H NMR δ 1.02 (s, 6 H), 1.2–1.7 (m, 4 H), 1.6 (s, 3 H), 1.7–2.1 (m, 2 H), 2.2 (br s, 7 H), 5.83 (br d, J = 7 Hz, 1 H) and 9.13 (d, J = 7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 220 (1), 219 (2), 191 (5), 177 (10), 153 (17), 139 (16), 137 (56), 135 (34), 125 (22), 123 (45), 121 (39), 119 (23), 111 (42), 109 (63), 107 (50), 95 (73), 93 (55), 91 (46), 81 (64), 79 (50), 77 (39), 71 (51), 69 (71), 67 (66), 55 (74), 43 (100) and 41 (75).

C. *Mokupalide* (**24**)

Methyl (6E)-7,11-*dimethyl*-3-*oxododeca*-6,10-*dienoate* (**28**). The dianion of methyl acetoacetate (6.96 g, 60 mmol) in THF (100 mL) was prepared[6b] and treated with **27** (10.85 g, 50 mmol) at 0° and the yellow suspension formed was stirred for 1 hr at the same temp. Work-up of the reaction mixture by the above procedure led to 12.8 g of crude product, which was purified by Kugelrohr distillation to give 11.97 g (95%, based on geranyl bromide used) of **28** as a colorless liquid: b.p. 90–92°/0.02 Torr; IR 1745, 1715, 1650 and 1630 cm^{-1}; ^1H NMR δ 1.62 (s, 6 H), 1.67 (s, 3 H), 1.97 (br s, 4 H), 2.0–2.7 (m, 4 H), 3.38 (s, 2 H), 3.70 (s, 3 H) and 5.02 (m, 2 H); mass spectrum *m/e* (rel intensity) 252 (25), 234 (18), 209 (13), 191 (16), 151 (17), 137 (16), 136 (53), 129 (29), 123 (27), 121 (28), 116 (24), 110 (17), 109 (100), 107 (18), 105 (26), 101 (36), 95 (28), 93 (25), 81 (47), 69 (86), 55 (22) and 41 (53).

High resolution mass measurement Calc. for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1740.

Methyl (2*Z*,6*E*)-3-(*Diethylphosphoryloxy*)-7,11-*dimethyldodeca*-2,6-10-*trienoate*. The enol phosphate of **28** was prepared from 7.56 g (30 mmol) of **28** in quantitative yield. The crude product had the following spectral data: IR 1725, 1670, 1280 and 1030 cm^{-1}; ^1H NMR δ 1.35 (t, J = 7 Hz, 6 H), 1.60 (s, 6 H), 1.67 (s, 3 H), 1.7–2.3 (m, 6 H), 2.4 (m, 2 H), 3.65 (s, 3 H), 4.23 (qn, J = 7 Hz, 4 H), 5.0 (m, 2 H) and 5.30 (s, 1 H); mass spectrum *m/e* (rel intensity) 388 (12), 357 (5), 343 (3), 319 (4), 287 (18), 252 (25), 234 (20), 220 (28), 202 (13), 192 (14), 155 (100), 127 (50) and 99 (63).

High resolution mass measurement Calc. for $C_{19}H_{33}O_6P$: 388.2015. Found: 388.2024.

Methyl (2E,6E)-3,7,11-*trimethyldodeca*-2,6,10-*trienoate* (**29**). To an ether (30 mL) soln of lithium dimethylcuprate (10 mmol), cooled at −78°, was added 1.94 g (5.0 mmol) of the above enol phosphate in 2 mL ethyl ether. The resulting orange-yellow suspension was stirred at −78° for 2 hr (mixture turned reddish brown at this stage) and then at −47° for 1 hr (mixture turned dark purple). The mixture was worked up as above to give 1.23 g of crude product. Vpc analysis (3% OV-17 column, 160°) indicated a 93% purity of the desired (*E,E*)-isomer. Preparative tlc (silica gel, 50:3 CCl_4-ethyl ether) of 108 mg crude material afforded 96 mg (87%) of **29**: b.p. (Kugelrohr distillation) 96–98°/0.02 Torr; IR 1715, 1650 and 1155 cm^{-1}; ^1H NMR δ 1.60 (s, 6 H), 1.67 (s, 3 H), 1.8–2.3 (m, 8 H), 2.15 (d, J = 1.5 Hz, 3 H), 3.65 (s, 3 H), 5.0 (m, 2 H), and 5.62 (br s, 1 H); mass spectrum *m/e* (rel intensity) 250 (35), 219 (17), 207 (20), 137 (30), 136 (32), 114 (54), 81 (43), 69 (100) and 41 (53).

High resolution mass measurement Calc. for $C_{16}H_{26}O_2$: 250.1933. Found: 250.1929.

Methyl (E,E,E)-12-*hydroxy*-3,7,11-*trimethyldodeca*-2,6,10-*trienoate* (**30**). A suspension of 5.58 g (50 mmol) selenium dioxide (99.4%) in CH_2Cl_2 (250 mL) was stirred with 28.7 mL (200 mmol) of 70% t-butylhydroperoxide for 30 min at room temp in the dark. The resulting soln was cooled to 10°, followed by the addition of 25.0 g (100 mmol) of **29**. The mixture was stirred for 4.5 hr at 10° and then diluted with 150 mL CH_2Cl_2. The organic soln was washed with 10% $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated under reduced pressure. The crude material obtained was chromatographed on silica gel (100–200 mesh) with 3:1 petroleum ether–ethyl ether to give the following components, in order of elution: (a) starting material **29** (4.75 g, 19%);

(b) Compound **36** (1.33 g, 5%): colorless oil: IR 1690 and 1650 cm^{-1}; ^1H NMR δ 1.62 (s, 3 H), 1.73 (s, 3 H), 2.15 (s, 3 H), 2.0–2.4 (m, 8 H), 3.64 (s, 3 H), 5.07 (m, 1 H), 5.60 (m, 1 H), 6.37 (m, 1 H) and 9.30 (d, J = 1 Hz, 1 H); mass spectrum *m/e* (rel intensity) 264 (4), 233 (6), 232 (6), 181 (18), 165 (19), 157 (28), 155 (28), 151 (27), 141 (32), 127 (53), 125 (62), 121 (51), 114 (100), 113 (31), 97 (65), 95 (99), 83 (44), 69 (32) and 55 (54). High resolution mass measurement Calc. for $C_{16}H_{24}O_3$: 264.1726. Found: 264.1728.

(c) Compound **35** (2.13 g, 8%): colorless oil: IR 3600, 1710 and 1650 cm^{-1}; ^1H NMR δ 1.63 (s, 6 H), 1.70 (s, 3 H), 2.17 (s, 3 H), 1.9–2.6 (m, 7 H), 3.63 (s, 3 H), 3.93 (t, J = 7 Hz, 1 H), 5.03 (m, 1 H), 5.3 (m, 1 H) and 5.60 (m, 1 H); mass spectrum *m/e* (rel intensity) 266 (1), 248 (2), 235 (2), 197 (24), 166 (14), 165 (100), 147 (7), 138 (5) metastable peak = $(165)^2/197$, 137 (11), 135 (9), 118 (14), 113 (10), 108 (21), 106 (17), 94 (12), 92 (17), 90 (9), 83 (16), 70 (29), 69 (18), 55 (23), 43 (16) and 41 (30). High resolution mass measurement Calc. for $C_{16}H_{26}O_3$: 266.1882. Found: 266.1870.

(d) **30** (10.91 g, 41%): colorless oil: IR 3550, 1715 and 1650 cm^{-1}; ^1H NMR δ 1.60 (s, 3 H), 1.63 (s, 3 H), 1.8–2.3 (m, 9 H), 2.13 (d, J = 1.2 Hz, 3 H), 3.63 (s, 3 H), 3.94 (s, 2 H), 5.05 (m, 1 H), 5.30 (m, 1 H) and 5.60 (m, 1 H); ^1H NMR (in CCl_4) δ 1.60 (s, 6 H), 1.18–2.3 (m, 8 H), 2.09 (d, J = 1.2 Hz, 3 H), 3.15 (br s, 1 H, exchangeable with D_2O), 3.58 (s, 3 H), 3.83 (s, 2 H), 4.95 (m, 1 H), 5.25 (m, 1 H) and 5.51 (m, 1 H); mass spectrum *m/e* (rel intensity) 266 (4), 248 (7), 234 (12), 181 (31), 164 (30), 149 (38), 135 (50), 125 (40), 123 (28), 121 (100), 114 (87), 109 (43), 107 (66), 105 (36), 97 (31), 95 (68), 93 (90), 81 (63), 69 (50), 67 (50), 55 (68), 43 (62) and 41 (60). High resolution mass measurement Calc. for $C_{16}H_{26}O_3$: 266.1882. Found: 266.1861.

Methyl (E,E,E)-12-*methanesulfonyloxy*-3-7,11-*trimethyldodeca*-2,6-10-*trienoate* (**31**). To a soln of 1.09 g (4.1 mmol) of **30** in dry CH_2Cl_2 (35 mL), cooled at −10° and kept under N_2, was added successively 0.86 mL (6.2 mmol) of anhyd Et_3N and 0.35 mL (4.5 mmol) methanesulfonyl chloride.[32] The resulting suspension was stirred for 2.5 hr at −10°, and then poured into 15 mL ice-cold water. The organic layer was separated, washed with ice-cold 5% HCl aq, sat $NaHCO_3$ aq and brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure yielded 1.41 g (100%) of crude **31** as a pale yellow oil which was homogeneous by tlc analysis (silica gel, 5:1 CCl_4-ethyl ether), and showed satisfactory spectral data: IR 1710, 1650, 1360, 1170 and 1150 cm^{-1}; ^1H NMR δ 1.59 (s, 3 H), 1.70 (s, 3 H), 2.13 (d, J = 1.2 Hz, 3 H), 1.9–2.3 (m, 8 H), 2.95 (s, 3 H), 3.65 (s, 3 H), 4.54 (s, 2 H), 5.03 (m, 1 H), 5.2–5.7 (m, 2 H); mass spectrum *m/e* (rel intensity) 344 (2), 248 (34), 217 (10), 189 (12), 136 (19), 135 (100), 134 (35), 133 (22), 121 (36), 119 (38), 114 (51), 109 (24), 107 (83), 105 (35), 96 (33), 93 (76), 91 (31), 81 (32), 79 (47), 67 (25), 55 (44), 43 (26) and 41 (34).

High resolution mass measurement Calc. for $C_{17}H_{28}O_5S$: 344.1658. Found: 344.1669.

Methyl (E,E,E)-3,7,11-*trimethyl*-12-*phenylthiododeca*-2,6,10-*trienoate* (**32**). A soln of benzenethiol (0.46 mL, 4.5 mmol) in dry THF (15 mL) was allowed to react with 2.58 mL (4.5 mmol) MeLi (1.75 M in ether) for 20 min at 0°, under dry N_2. To the resultant lithium thiophenoxide soln was added 1.35 g (3.9 mmol) of **31** and the mixture was stirred for 4 hr at 0°. The mixture was then diluted with ethyl ether and water. The organic soln was separated, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The ^1H NMR spectrum of the crude product so obtained (1.44 g) showed essentially pure **32**. Preparative tlc (silica gel, 6:1 CCl_4-ethyl ether) purification of 62 mg of the crude material gave 56 mg (93%) of **32** as a colorless liquid: IR 1710, 1650, 1585, 1440 and 1150 cm^{-1}; ^1H NMR δ 1.56 (s, 3 H), 1.72 (s, 3 H), 1.8–2.3 (m, 8 H), 2.14 (d, J = 1.6 Hz, 3 H), 3.45 (s, 2 H), 3.63 (s, 3 H), 5.07 (m, 2 H), 5.60 (m, 1 H) and 6.9–7.4 (m, 5 H); mass spectrum *m/e* (rel intensity) 359 (25), 358 (100), 249 (10), 218 (17), 217 (14), 189 (25), 177 (46), 176 (57), 149 (16), 135 (66), 121 (43), 109 (40), 107 (33), 95 (18), 93 (24), 81 (25), 79 (16), 69 (18), 67 (22), 55 (26), 43 (20) and 41 (29).

High resolution mass measurement Calc. for $C_{22}H_{30}O_2S$: 358.1966. Found: 358.1956.

(E,E,E)-3,7,11-*Trimethyl*-12-*phenylthiododeca*-2,6,10-*trien*-1-*ol* (**33**). To a soln of 1.18 g (3.3 mmol) of **32** in dry ethyl ether (45 mL), cooled at −23° and kept under N_2, was added 9.9 mL (9.9 mmol) diisobutylaluminum hydride (1 M in hexane). The resulting mixture was stirred for 1 hr 50 min at −23° and then quenched with 2 mL MeOH. The cooling bath was removed, and after 20 min, the mixture was treated with 10% HCl aq until the aqueous layer turned clear. The ether soln was separated, washed with brine, and dried over $MgSO_4$. Evaporation of solvents under reduced pressure afforded 1.08 g (99%) crude **33**. Satisfactory elemental microanalysis was obtained on a tlc purified (silica gel, 4:1 CCl_4–ethyl ether) sample: colorless oil; b.p. (Kugelrohr distillation) 145–147°/0.1 Torr; IR 3650, 3500, 1665, 1585 and 1440 cm^{-1}; ^1H NMR δ 1.55 (s, 3 H), 1.66 (s, 3 H), 1.71 (s, 3 H), 1.8–2.3 (m, 9 H), 3.45 (s, 2 H), 4.09 (d, J = 7 Hz, 2 H), 4.8–5.5 (m, 3 H) and 6.9–7.4 (m, 5 H); mass spectrum *m/e* (rel intensity) 330 (29), 312 (10), 221 (32), 220 (19), 203 (46), 177 (100), 176 (28), 163 (30), 147 (30), 135 (88), 134 (63), 121 (54), 110 (67), 109 (89), 107 (78), 95 (42), 93 (72), 81 (73), 69 (55), 68 (45), 67 (70), 55 (60), 43 (45) and 41 (75). (Found: C, 76.64; H, 9.21. Calc. for $C_{21}H_{30}OS$: C, 76.31; H, 9.15%.)

(E, E, E)-1-(2-*Tetrahydropyranyloxy*)-3,7,11-*trimethyl*-12-*phenylthio*-2,6,10-*dodecatriene* (**34**). A mixture of 1.03 g (3.1 mmol) crude **33**, 391 mg (4.65 mmol) dihydropyran and a catalytic amount (10 mg) of *p*-toluenesulfonic acid in dry CH_2Cl_2 (45 mL) was stirred for 2 hr at room temp. The resulting soln was diluted with ethyl ether, washed with 10% $NaHCO_3$ aq, and dried over Na_2SO_4. Removal of solvents under reduced pressure gave 1.29 g of crude material, which after column chromatography (silica gel 100–200 mesh, 6:1 petroleum ether–ethyl ether) furnished 1.23 g (95% yield from **32**) of **34**: colorless liquid; IR 1670, 1585, and 1440 cm^{-1}; ^1H NMR δ 1.56 (s, 3 H), 1.67 (s, 3 H), 1.72 (s, 3 H), 1.3–1.8 (m, 6 H), 1.8–2.2 (m, 8 H), 3.44 (s, 2 H), 3.5–4.2 (m, 4 H), 4.56 (m, 1 H), 5.1 (m, 3 H) and 6.97–7.33 (m, 5 H); mass spectrum *m/e* (rel intensity) 414 (10), 329 (10), 202 (20), 176 (23), 134 (28), 123 (15), 121 (15), 110 (21), 109 (25), 107 (22), 93 (16), 86 (21), 85 (100), 81 (23), 69 (18), 67 (37), 57 (36), 55 (32), 43 (40) and 41 (42).

High resolution mass measurement Calc. for $C_{26}H_{38}O_2S$: 414.2593. Found: 414.2582.

(E,E,E)-13-(2-*Tetrahydropranyloxy*)-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-2-*phenylthio*-3,7,11-*tridecatriene* (**39**). A soln of 1.66 g (4.0 mmol) of **34** and 448 mg (4.0 mmol) diazabicyclo[2.2.2]octane in dry THF (25 mL) was kept under N_2 and cooled to −23°. To this was added 3.75 mL (6.0 mmol) n-BuLi (1.6 M in hexane) and the resulting orange soln was stirred for 3 hr at −23°. A soln of **19** (1.30 g, 60 mmol) in dry THF (2 mL) was then introduced. The light yellow suspension formed was stirred at −23° for 3 hr and warmed to 0° over 50 min. The reaction was worked up by quenching with 20 ml water and extracting the aqueous phase with 2 × 25 mL ethyl ether. The ether extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give 2.78 g crude material, which showed one major spot (besides a fast moving component) on tlc. Purification of 100 mg of the crude product by preparative tlc (silica gel, 10:1 petroleum ether–ethyl ether) afforded 59 mg (75%) of **39** as a colorless oil: IR 1670, 1585 and 1440 cm^{-1}; ^1H NMR δ 0.98 (s, 3 H), 1.05 (s, 3 H), 1.51 (s, 3 H), 1.66 (br s, 9 H), 1.2–2.4 (m, 22 H), 3.4–4.2 (m, 5 H), 4.57 (m, 1 H), 4.75–5.47 (m, 3 H) and 6.93–7.33 (m, 5 H); mass spectrum *m/e* (rel intensity) 550 (0.5), 449 (2), 440 (3), 413 (5), 355 (11), 338 (14), 329 (16), 311 (46), 270 (15), 255 (15), 243 (26), 219 (32), 203 (75), 202 (72), 189 (61), 187 (60), 177 (69), 175 (64), 173 (59), 163 (71), 161 (74), 159 (70), 149 (73), 147 (79), 145 (74), 135 (87), 123 (84), 119 (81), 110 (93), 109 (96), 107 (80), 105 (80), 95 (84), 93 (81), 91 (79), 85 (96), 84 (94), 69 (88), 67 (85), 57 (89), 55 (96), 43 (100) and 41 (88).

High resolution mass measurement Calc. for $C_{36}H_{54}O_2S$: 550.3844. Found: 550.3839.

(E,E,E)-13-(2-*Tetrahydropyranyloxy*)-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-3,7,11-*tridecatriene* (**40**). To a soln of nickel (II) chloride hexahydrate (29.13 g, 122 mmol) in 400 mL abs EtOH, cooled in an ice-bath, was added simultaneously a soln of **39** (1.76 g, 3.2 mmol) in EtOH (40 mL) and a soln of $NaBH_4$ (3.95 g, 100 mmol) in water with vigorous stirring.[35,36] The addition was completed over 20 min, and the resulting black suspension was removed from the cooling bath and stirred for 26 hr at room temp. The mixture was then filtered through celite and the ppt was washed with EtOH. The combined filtrate was evaporated under reduced pressure and the residue was dissolved in ethyl ether. The ether soln was washed with brine and dried over $MgSO_4$. The crude product obtained after removal of solvents was chromatographed on a silica gel (100–200 mesh) column with 20:1 petroleum ether–ethyl ether to give 1.02 g (72%) of **40** as a colorless oil: IR 1670 and 1450 cm^{-1}; ^1H NMR δ 1.0 (s, 6 H), 1.2–2.3 (m, 36 H), 3.4–4.2 (m, 4 H), 4.57 (m, 1 H) and 4.8–5.5 (m, 3 H); mass spectrum *m/e* (rel intensity) 442 (4), 358 (5), 357 (4), 340 (15), 203 (10), 189 (8), 177 (7), 161 (6), 147 (8), 137 (73), 135 (12), 123 (14), 121 (18), 119 (11), 109 (14), 107 (15), 95 (36), 93 (18), 85 (100), 81 (35), 69 (13), 67 (15), 57 (17), 55 (16) and 41 (17).

High resolution mass measurement Calc. for $C_{30}H_{50}O_2$: 442.3811. Found: 442.3796.

(E, E, E)-13-*Hydroxy*-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-3,7,11-*tridecatriene* (**41**). A soln of **40** (486 mg, 1.1 mmol) and *p*-toluenesulfonic acid (20 mg) in 60 mL MeOH-THF (5:1) was stirred for 24 hr at room temp. The soln was then concentrated under reduced pressure to *ca* 1 mL, diluted with ethyl ether, and washed with sat $NaHCO_3$ aq. After drying over $MgSO_4$ and removal of solvents, the residue was evaporated *in vacuo* to afford 395 mg (quantitative yield) of **41**, which was homogeneous by tlc (silica gel) analysis: colorless liquid; IR 3650, 3500, 1670 and 1450 cm^{-1}; ^1H NMR δ 0.98 (s, 6 H), 1.2–2.3 (m, 30 H), 4.1 (d, J = 7 Hz, 2 H) and 4.8–5.5 (m, 3 H); mass spectrum *m/e* (rel intensity) 358 (12), 340 (10), 204 (13), 203 (9), 189 (9), 177 (12), 161 (8), 147 (11), 138 (15), 137 (100), 136 (15), 135 (16), 133 (16), 123 (20), 121 (24), 119 (14), 109 (16), 107 (16), 95 (23), 81 (25), 69 (14), 55 (16) and 41 (15).

High resolution mass measurement Calc. for $C_{25}H_{42}O$: 358.3235. Found: 358.3220.

3-*Phenylsulfonylmethyl*-2-*butenolide* (**46**). Anhyd sodium benzenesulfinate (1.15 g, 7.0 mmol) and 1.03 g (5.8 mmol) 3-bromomethyl-2-butenolide[37] were dissolved in 10 mL dry DMF. The orange-brown soln formed was stirred for 2 hr at room temp under dry N_2. The mixture was worked up by adding 20 mL water and extracting the soln with 4 × 30 mL of $CHCl_3$-n-pentane (1:1). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Removal of residual DMF *in vacuo* gave 1.35 g crude **46** (solid) which was essentially pure by tlc (silica gel) and ^1H NMR analyses. Recrystallization from CH_2Cl_2–ethyl ether–n-pentane yielded 1.18 g (85%) of **46** as colorless flakes: m.p. 125°; IR 1795, 1760, 1650, 1335, 1175 and 1160 cm^{-1}; ^1H NMR δ 4.17 (s, 2 H), 4.87 (br s, 2 H), 5.83 (br s, 1 H) and 7.4–7.9 (m, 5 H); mass spectrum *m/e* (rel intensity) 238 (54), 141 (100), 126 (15), 125 (28), 97 (29), 77 (99), 68 (16), 67 (16) and 51 (27). (Found: C, 55.31; H, 4.14; S, 13.22. Calc. for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46%.)

(E,E,E)-13-*Bromo*-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclo-hexen*-1-*yl*)-3,7,11-*tridecatriene* (**49**). To a mixture of **41** (425 mg, 1.2 mmol) and anhyd LiBr (413 mg, 4.76 mmol) in 25 mL dry ethyl ether, cooled at −78° and kept under N_2, was added 0.86 mL (1.3 mmol) n-BuLi (1.52 M in hexane) with stirring. After 30 min at the same temp, 0.10 mL (1.3 mmol) methanesulfonyl chloride was introduced.[17] The mixture was warmed to −10° over 1 hr, maintained at −10° for 30 min and then at room temp for 6 hr. The resulting suspension was poured into ice-cold water and the aqueous phase was extracted with 2 × 50 mL ethyl ether-n-pentane (1:1). The combined organic soln was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude **49** (463 mg, 92%) obtained was used directly in the next alkylation step without any purification. Satisfactory

spectral data were observed for this crude material (a slightly tan oil): IR 1665, 1455, 1380 and 1180 cm^{-1}; ^1H NMR δ 0.98 (s, 6 H), 1.2–2.3 (m, 30 H), 3.95 (d, J = 8 Hz, 2 H) and 4.7–5.57 (m, 3 H); mass spectrum *m/e* (rel intensity) 422 (7), 420 (7), 341 (6), 340 (8), 204 (15), 203 (9), 189 (10), 177 (12), 149 (10), 147 (10), 138 (15), 137 (100), 136 (15), 135 (13), 123 (18), 121 (21), 119 (13), 109 (16), 107 (18), 105 (12), 95 (36), 81 (24), 69 (13), 67 (13), 55 (15) and 41 (13).

High resolution mass measurement Calc. for $C_{25}H_{41}{}^{81}Br$ and $C_{25}H_{41}{}^{79}Br$: 422.2371 and 420.2391. Found: 422.2399 and 420.2391.

3-(E,E,E)-4,8,12-*Trimethyl*-14-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-1-*phenylsulfonyl*-3,7,11-*tetradecatrien*-1-*yl*]-2-*butenolide* (**50**). To a stirred suspension of 144 mg (3.0 mmol) NaH (50%) in dry DMF (20 mL) was added 714 mg (3.0 mmol) of **46** (dissolved in 1 mL of DMF) at 0°, under N_2. The cooling bath was removed, and an orange-yellow soln was formed after 30 min. To this soln was introduced 460 mg (*ca* 1.2 mmol) crude **49** and the resulting mixture was stirred for 4 hr at room temp. The reaction was quenched with 40 mL ice-cold 5% HCl and the mixture was extracted with 3 × 60 mL ethyl ether-petroleum ether (1:1). The combined extracts were washed with 2 × 40 mL 50% brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 572 mg crude product. Purification of 100 mg crude material by preparative tlc (silica gel, 2:3 petroleum ether–ethyl ether) afforded 72 mg (60% yield from alcohol **41**) of **50** as a thick, colorless oil: IR 1792, 1760, 1640, 1330 and 1150 cm^{-1}; ^1H NMR δ 1.0 (s, 6 H), 1.1–2.2 (m, 30 H), 2.7 (m, 2 H), 4.0 (m, 1 H), 4.8 (d, J = 1.5 Hz, 2 H), 4.6–5.2 (m, 3 H), 5.8 (m, 1 H) and 7.3–7.9 (m, 5 H); mass spectrum *m/e* (rel intensity) 578 (15), 441 (3), 435 (2), 300 (10), 244 (18), 237 (47), 188 (19), 176 (21), 164 (19), 163 (19), 148 (18), 146 (20), 136 (100), 135 (38), 134 (33), 132 (24), 122 (34), 120 (45), 118 (36), 108 (37), 106 (40), 104 (30), 94 (60), 81 (95), 69 (97), 57 (40), 55 (51) and 41 (89).

High resolution mass measurement Calc. for $C_{36}H_{50}O_4S$: 578.3430. Found: 578.3435.

Mokupalide (**24**). A mixture of **50** (29 mg, 0.050 mmol) and disodium hydrogen phosphate (28 mg, 0.20 mmol) was dissolved in 5 mL dry MeOH. To this soln, cooled at −10° and kept under N_2, was added 75 mg (0.20 mmol) of 6% $NaHg^{45}$ in one portion. The resulting mixture was stirred for 20 min at −10°, followed by quenching with satd NH_4Cl aq and extraction with ethyl ether. The combined extracts were washed with satd $NaHCO_3$ aq, dried over $MgSO_4$ and then concentrated under reduced pressure. The crude residue obtained was chromatographed on silica gel with 1:1 petroleum ether–ethyl ether to furnish 18 mg (82%) of **24**[26]: IR 1790, 1755, 1645 and 1450 cm^{-1}; ^1H NMR δ 0.99 (s, 6 H), 1.1–2.2 (m, 32 H), 2.4 (m, 2 H), 4.65 (d, J = 1.5 Hz, 2 H), 5.05 (m, 3 H) and 5.78 (m, 1 H); mass spectrum *m/e* (rel intensity) 438 (23), 423 (5), 395 (3), 296 (5), 278 (4), 245 (5), 217 (5), 204 (12), 189 (11), 177 (24), 161 (13), 149 (28), 137 (100), 136 (36), 135 (36), 133 (28), 123 (32), 121 (52), 119 (27), 110 (29), 108 (37), 98 (46), 95 (65), 93 (41), 91 (25), 81 (83), 79 (31), 69 (65), 67 (32), 57 (40), 55 (54), 43 (28) and 41 (52).

High resolution mass measurement Calc. for $C_{30}H_{46}O_2$: 438.3497. Found: 438.3519.

3-(4-*Methyl*-1-*phenylsulfonyl*-3-*penten*-1-*yl*)-2-*butenolide* (**47**). Compound **46** (48 mg, 0.20 mmol) was alkylated with 1-bromo-3-methyl-2-butene (15 mg, 0.10 mmol) in the manner described in the preparation of **50**. Preparative tlc (silica gel, 5:1 ethyl ether-petroleum ether) of the crude product (27 mg) gave 22 mg (72% yield based on the bromide used) of **47** as colorless flakes (crystallized from petroleum ether–ethyl ether): m.p. 96°; IR 1792, 1760, 1640, 1595, 1455, 1330 and 1150 cm^{-1}; ^1H NMR δ 1.57 (s, 3 H), 1.63 (s, 3 H), 2.7 (m, 2 H), 4.0 (m, 1 H), 4.80 (br s, 2 H), 4.6–5.0 (m, 1 H), 5.8 (m, 1 H) and 7.3–7.9 (m, 5 H); mass spectrum *m/e* (rel intensity) 306 (8), 238 (15), 181 (8), 165 (100), 164 (100), 137 (12), 136 (13), 121 (33), 120 (24), 119 (27), 109 (17), 107 (23), 105 (44), 93 (28), 91 (30), 77 (36), 69 (29) and 41 (38). (Found: C, 62.65; H, 5.97; S, 10.38. Calc. for $C_{16}H_{18}O_4S$: C, 62.73; H, 5.92; S, 10.46%.)

When approximately 1:1 ratios of **46** and 1-bromo-3-methyl-2-butene were used in the alkylation under various conditions (t-BuOK, t-BuOH; NaH, THF-HMPA; or NaH, DMF), the monoalkylation product **47** was obtained in 40–50% yields, along with dialkylation product **48**.

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