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# CEMBRANOLIDE TOTAL SYNTHESIS. ANISOMELIC ACID*

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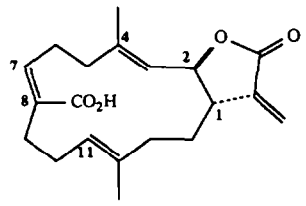
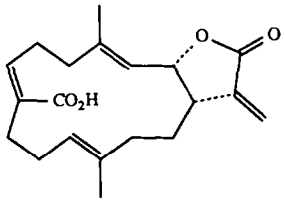
**Abstract.** The stereoselective total synthesis of (±)-anisomelic acid (**34**) has been achieved starting from aldehyde **7**, the ozonolysis product of geranyl acetate. Two key steps ensured the stereoselectivity of the synthesis. The first entailed a highly anti-selective addition of the allyltitanium derived from carbamate **15** to aldehyde **5** affording the enol carbamate allylic alcohol **16**. The second was a highly (*Z*)-selective Horner-Emmons cyclization of the derived phosphono ester aldehyde **25** leading to the conjugated ester **27**. Further conversion led to the crystalline lactone **30** whose structure was confirmed through single crystal X-ray analysis. Equilibration of the conjugated double bond of **30** gave rise to a 1:1 mixture of the (*Z*) and (*E*) isomers. This result was foretold by molecular mechanics calculations.

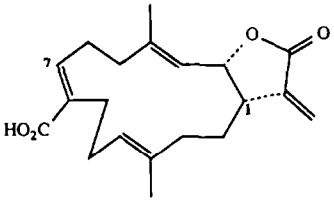
Anisomelic acid (I), lobohedleolide (II) and (7E)-lobohedleolide (III) constitute a close-knit triad of natural cembranolides. Though structurally similar they derive from strikingly different natural sources. Anisomelic acid is found in the South Indian medicinal plant *Anisomeles malabauia* R.Br.[1], whereas the lobohedleolides are constituents of the soft coral *Lobophytum hedleji* Whitelegge, which inhabits a region of Okinawa.[2] Lobohedleolide inhibits growth of Hella cells *in vitro* at 5 μg/mL.[2] No specific biological activity has been reported for the other members of the triad.




anisomelic acid (I)

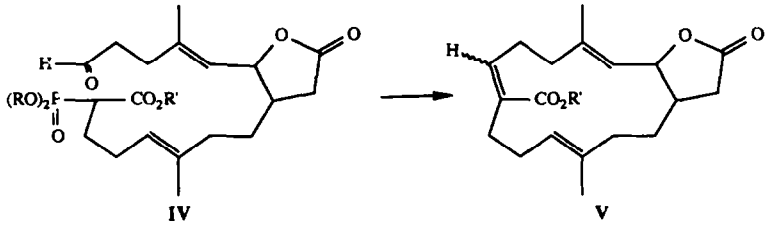



lobohedleolide (II)




(7E)-lobohedleolide (III)

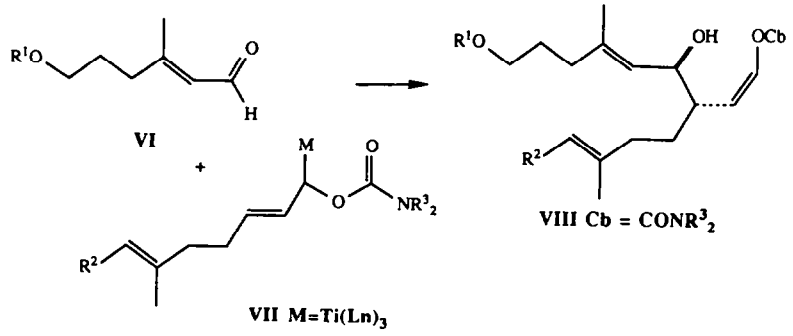
The presence of a conjugated acid moiety at the 7,8-position of the foregoing cembranolides suggested a synthetic strategy involving an intramolecular Horner-Emmons reaction, IV → V, as the key macrocyclization step. At the inception of our work two groups had reported cyclizations of α-phosphono esters leading to conjugated lactones, but no carbocycles had been prepared.[3] Stork's application to macrocyclic lactone synthesis was particularly interesting as it showed that large rings were accessible by the Horner-Emmons methodology.[3b,4]




IV V

*Dedicated to Professor Hans Wynberg on the occasion of his 65th birthday.

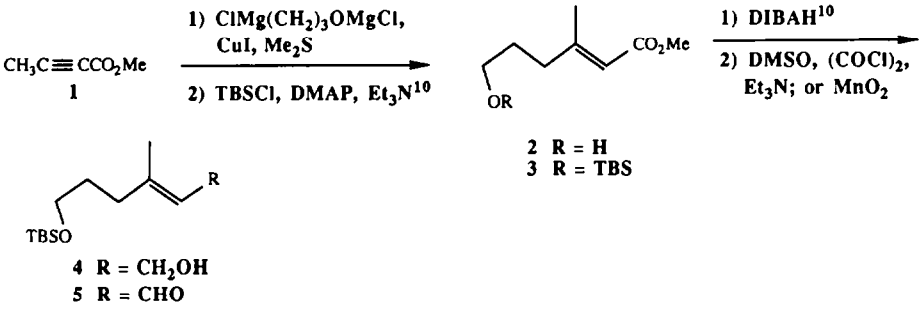
We selected anisomelic acid (I) as the initial test of the foregoing approach. The requisite trans lactone stereochemistry was envisioned as arising from addition of a metallated allyl carbamate, such as VII, to an appropriate conjugated aldehyde VI. Hoppe has shown that such additions proceed with high regio and stereoselectivity.



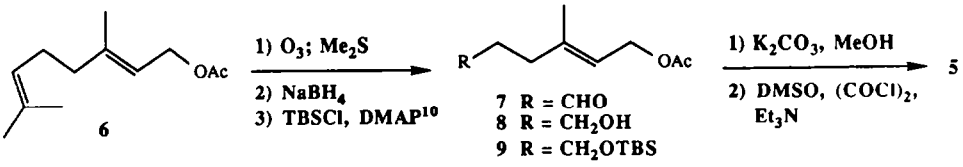

Furthermore, the enol carbamate addition products can be converted to gamma lactols and lactones.[5]

In some preliminary studies on intermolecular Horner-Emmons condensations we found that long chain α-substituents seriously undermine the stereoselectivity of the (*Z*) process.[6] Still's modification employing β,β,β-trifluoroethyl phosphonates (*e.g.* IV, R=$CF_3CH_2$)[7a] gave the highest (*Z*):(*E*) ratios. Accordingly, phosphono ester **24** was targeted as the most promising cyclization precursor.

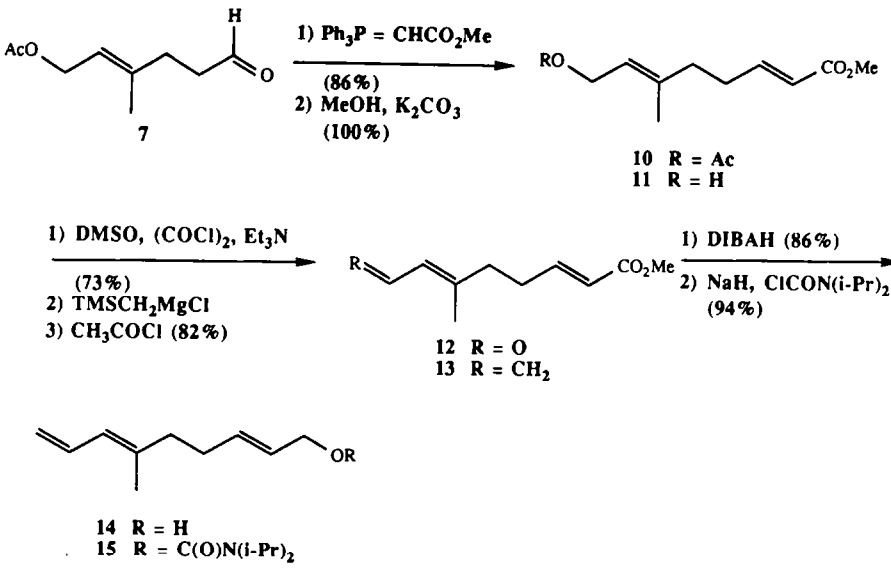
The aldehyde component **5** for our intended assemblage of lactol **24** was prepared from methyl tetrolate (**1**) via CuI promoted 1,4-addition of the Grignard reagent of 3-chloropropanol[8] followed by alcohol protection as the TBS ether.[9,10] Reduction of the ester **3** and Swern[11] or $MnO_2$ oxidation of the derived alcohol **4** gave aldehyde **5**.



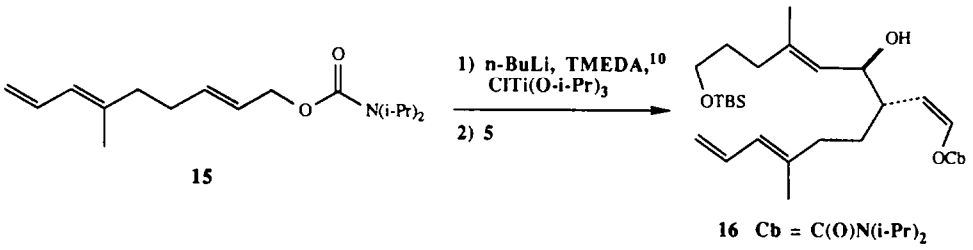

Alternatively, aldehyde **5** was prepared by selective ozonolysis of geranyl acetate (**6**)[12] and reduction of the derived aldehyde **7** followed by alcohol protection, acetate cleavage and Swern oxidation,[11] as before.




The ozonolysis product **7** of geranyl acetate (**6**) also served as a convenient source of the allylic carbamate coupling partner **15**. Addition of methyl α-(triphenylphosphoryliden)acetate and methanolysis of the resulting diester **10** afforded hydroxy ester **11** which was oxidized[11] to the aldehyde **12**. Attempted Wittig methylenation of this aldehyde with methylenetriphenylphosphorane failed. Presumably the strongly basic ylide causes decomposition of the sensitive conjugated ester. The two step Peterson sequence[13] proved satisfactory, however, and trienoate **13** could thus be prepared in 82% yield. Reduction then led to alcohol **14** which readily formed carbamate **15**.

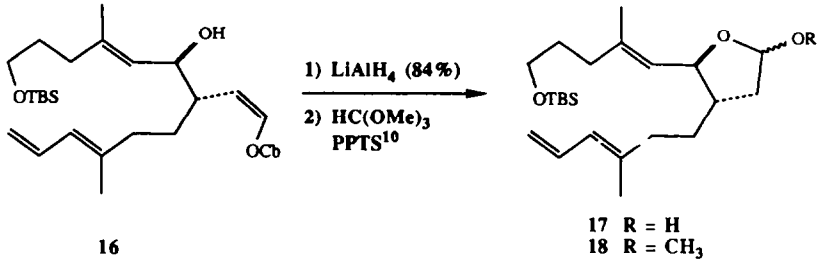



Lithiation of carbamate **15** with *n*-BuLi in ether-TMEDA[10] at -78°C followed by transmetallation with triisopropoxychlorotitanium and subsequent addition of aldehyde **5** gave, after warming to 10°C, the hydroxy enol carbamate **16** in yields ranging from 60-80% with diastereomeric ratios of 90:10 to 95:5.

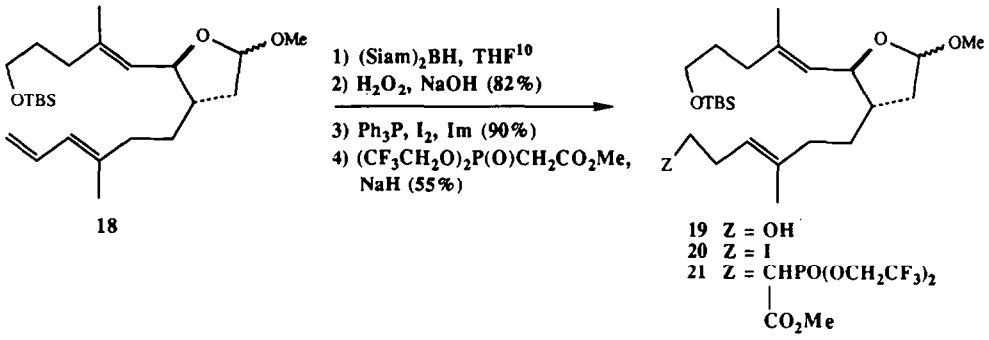



The use of titanium tetraisopropoxide in the transmetallation step resulted in a nearly quantitative yield of addition product but with diminished (80:20) stereoselectivity. Hoppe has observed a similar loss of stereoselectivity with this titanium reagent.[5] The geometry of the enol carbamate was assigned as (*Z*) from the observed 6 Hz coupling of the vinylic protons and by analogy to Hoppe's work. The anti carbinyl diastereoisomer is expected to predominate from mechanistic considerations.[5]

Cleavage of the enol carbamate grouping of **16** proved troublesome. Hoppe has shown that methanolysis of non-allylic γ-hydroxy enol carbamates to lactol methyl ethers is readily effected with methanolic methanesulfonic acid in the presence of Pd(II) chloride or Hg(II) acetate.[14] Attempts to apply this methodology to enol carbamate **16** led to extensive decomposition. No doubt the sensitive allylic alcohol moiety is largely responsible. Although Hoppe found that his enol carbamates were unaffected by lithium aluminum hydride at 65°C, we observed total cleavage of carbamate **16** with one molar equivalent of this reagent in THF at reflux for 1 h. Lactol **17** was thereby obtained in 84% yield along with 10% of the corresponding diol. Lactol **17** yielded the ether **18** as an epimeric mixture upon treatment with trimethyl orthoformate and PPTS.[10]



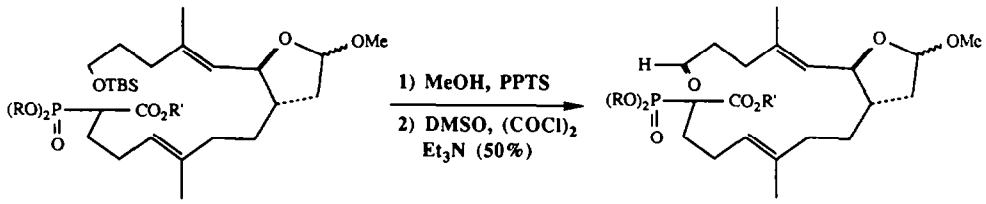
Selective hydroboration of the triene lactol ether **18** afforded alcohol **19** after oxidation. Conversion to the iodide **20**[15] followed by treatment with methyl sodio α-[*bis*-(β,β,β-trifluoroethoxy)phosphinyl]acetate in DMSO[10] gave the desired phosphonate **21** in 55% yield.




**18**

**19** Z = OH
**20** Z = I
**21** Z = $CHPO(OCH_2CF_3)_2$ | $CO_2Me$

Attempted cleavage of the silyl ether **21** with $Bu_4NF$ caused decomposition and led to no useful product. However, acidic cleavage with PPTS[10] in methanol proceeded satisfactorily. The resulting alcohol was directly oxidized to aldehyde **24** in 50% overall yield.



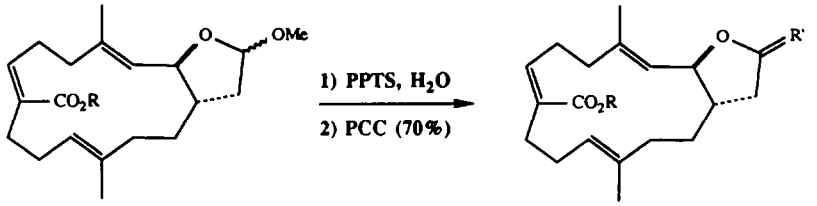

**21** R = $CH_2CF_3$, R' = Me
**22** R = R' = Me
**23** R = i-Pr, R' = Et

**24** R = $CH_2CF_3$, R' = Me
**25** R = R' = Me
**26** R = i-Pr, R' = Et

In our initial effort at macrocyclization we added the phosphono ester aldehyde **24** over 12 h to $K_2CO_3$ in toluene-18-crown-6 at room temperature (Table 1).[7b] The cyclization product **27** was thereby obtained in 30% yield as a single (*Z*) stereoisomer according to $^1H$ NMR analysis. Attempted cyclization at -78°C in THF-18-crown-6 with KHMDS[10] as the base led to recovered starting material whereas KO-*t*-Bu at room temperature in the same solvent caused decomposition of the aldehyde.

We also had occasion to examine the methyl phosphonate aldehyde **25**. This material was prepared analogously to the trifluoroethyl analog, but the $S_N2$ displacement on iodide **20** gave phosphonate **22** in significantly higher yield (85% vs. 55%). A variety of conditions for the cyclization of **25** were employed. These are summarized in Table I. In all cases, the (*Z*) selectivity was higher than 10:1. Interestingly, even the isopropyl phosphonate **26** afforded the (*Z*) cyclization product **28** with greater than 10:1 stereoselectivity. In contrast, the analogous intermolecular Horner-Emmons condensations of isopropyl phosphonates with aldehydes are highly (*E*) selective.[16,6] Thus the double bond stereochemistry in the case at hand is largely a consequence of the macrocyclic environment rather than the phosphonate substituent.

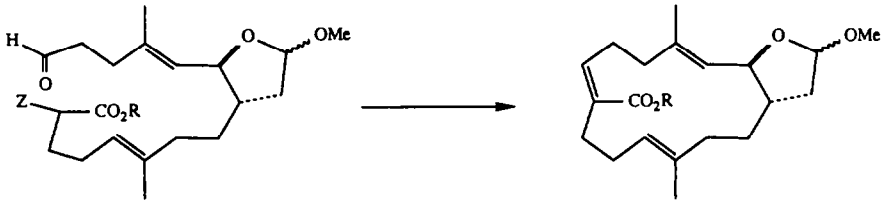
In several of the cyclization trials a more polar product was isolated with spectral properties of a macrocyclic dimer. Although we did not pursue the matter in detail, this by-product was effectively suppressed by longer addition times. The most efficient cyclization (71% yield) of methyl phosphonate **25** was achieved with DBU[10] as the base in acetonitrile-LiCl, conditions devised by Masamune and Roush for intermolecular Horner-Emmons condensations.[17] The derived 95:5 mixture of (*Z*) and (*E*) products was readily separated via flash column chromatography.[18] Hydrolysis of the (*Z*) isomer **27** followed by PCC[10] oxidation[19] of the lactol product **29** yielded the crystalline lactone ester **30** whose structure was confirmed by single crystal X-ray analysis.[20]




27 R = Me
28 R = Et

29 R = Me, R' = H, OH
30 R = Me, R' = O
31 R = Et, R' = O

Table I. Horner-Emmons Macrocyclizations

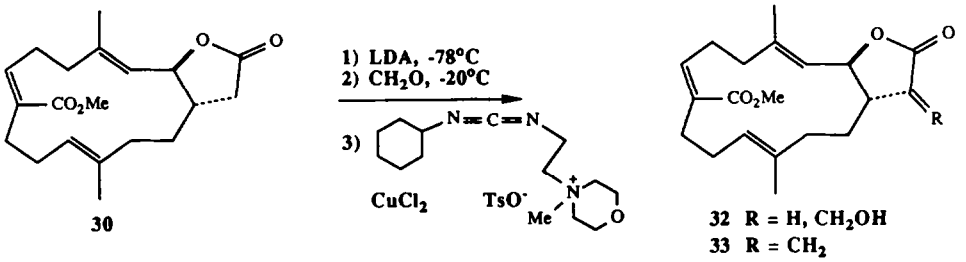



27 R = Me
28 R = Et

| Z | R | base[10] | solvent[10] | additive | temp. | conc. M | yield |
|---|---|---|---|---|---|---|---|
| 24 $(CF_3CH_2O)_2P(O)$ | Me | $K_2CO_3$ | toluene | 18-crown-6 | RT[10] | 0.02 | 30%[a] |
| 24 $(CF_3CH_2O)_2P(O)$ | Me | KHMDS | THF | 18-crown-6 | -78° | 0.01 | S.M. |
| 24 $(CF_3CH_2O)_2P(O)$ | Me | K-OtBu | THF | 18-crown-6 | RT | 0.01 | decomp |
| 25 $(MeO)_2P(O)$ | Me | $K_2CO_3$ | toluene | 18-crown-6 | 80° | 0.01 | 35% (27%)[b] |
| 25 $(MeO)_2P(O)$ | Me | NaH | DME | 18-crown-6 | RT | 0.01 | 53% |
| 25 $(MeO)_2P(O)$ | Me | NaH | DME | none | RT | 0.01 | 52% |
| 25 $(MeO)_2P(O)$ | Me | DBU | $CH_3CN$ | LiCl | RT | 0.003 | 42%[c] (27%)[b] |
| 25 $(MeO)_2P(O)$ | Me | DBU | $CH_3CN$ | LiCl | RT | 0.004 | 71% |
| 26 $(i\text{-PrO})_2P(O)$ | Et | DBU | $CH_3CN$ | LiCl | RT | 0.003 | 20%[d] |
| 26 $(i\text{-PrO})_2P(O)$ | Et | NaH | DME | none | RT | 0.007 | 50% |

a The reaction mixture was not examined for dimeric product.
b Dimeric product.
c The conditions described by Tius in the synthesis of (-)-asperdiol were followed.[24]
d The reaction was extremely slow. After 40 h starting material was present in addition to a by-product of comparable polarity according to TLC analysis.

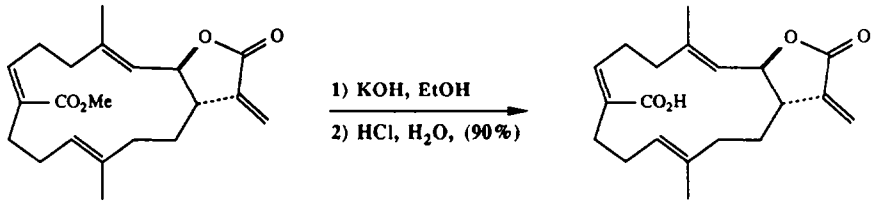
With a view to introducing the α-methylene grouping, we treated lactone **30** with excess LDA[10] at -78°C followed by gaseous formaldehyde at -20°C. The resulting α-hydroxymethylated lactone product was a mixture consisting of (*E*) and (*Z*) conjugated esters, β,γ-unsaturated esters, and *bis*-hydroxymethylated materials. Evidently γ-deprotonation of the conjugated ester had occurred. Therefore the experiment was repeated but with one equivalent of LDA[10] to promote kinetic deprotonation. The crude hydroxymethyl lactone **32** was dehydrated with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[21] in acetonitrile giving the desired α-methylene lactone **33** in 58% yield along with 16% of recovered lactone **30**.[22]




30

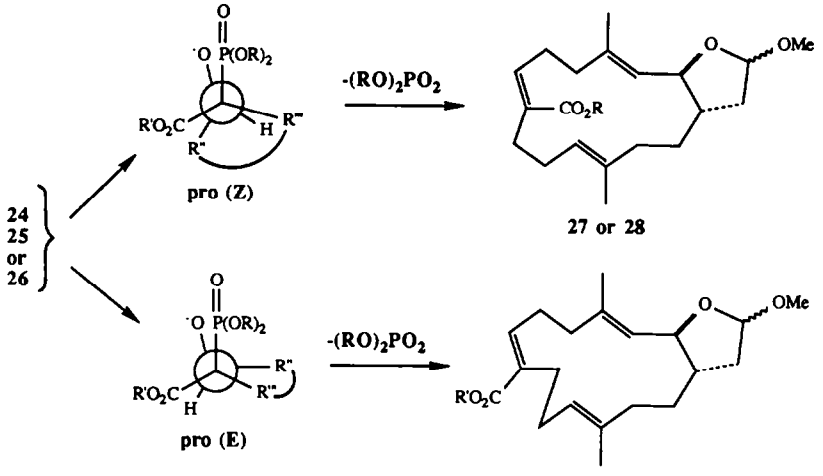
32 R = H, $CH_2OH$
33 R = $CH_2$

Saponification of lactone ester **33** with excess KOH in ethanol followed by acidification of the diacid salt afforded synthetic (±)-anisomelic acid (**34**). This material was identical to an authentic sample according to high field $^1H$ NMR, mass spectral and TLC comparison.



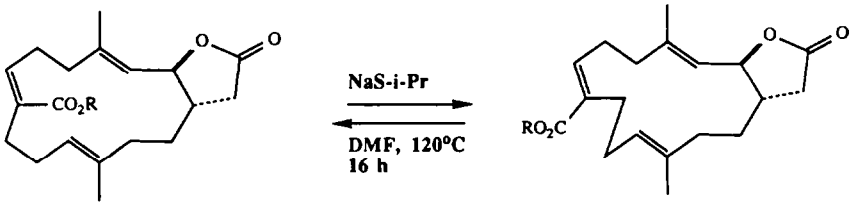

**33** **34**

The contrast in stereoselectivity between the foregoing cyclizations leading to the (*Z*) conjugated esters **27** or **28** and the recent results of others who observed mixtures of (*E*) and (*Z*) or mainly (*E*) products in Horner-Emmons cyclizations leading to 4-carboxy $\Delta^3$-cembranoids is striking.[23,24] Furthermore, the high (*Z*) preference of the diisopropyl phosphonate **26** sharply contrasts with the strong (*E*) direction shown by such phosphonates in intermolecular condensations.[16,6] These differences suggest that conformational preferences of the macrocyclic ring control the formation and possibly influence the elimination of alkoxy phosphonate intermediates in the cyclization reactions.




If the transition state for these eliminations is product-like we might expect the more stable isomer to predominate, provided the addition step is reversible.[25] This situation would be most likely to prevail in the diisopropyl phosphonate case where the steric bulk of the isopropyls slows the rate of elimination.[16,25] Hence it was of interest to determine the relative stabilities of the (*E*) and (*Z*) conjugated esters **36** and **30**. Additionally we felt that isomerization of the (*Z*) conjugated ester might be of value for the production of compounds such as (7*E*)-lobohedleolide (III).[2]

Treatment of the (*Z*) ester lactone **30** with NaS-*i*-Pr in DMF[10] at 120°C for 16 h afforded a 55:45 mixture of (*E*) and (*Z*) isomers **36** and **30** after acidification and esterification with diazomethane to recover material cleaved by the thiolate.[26] The ethyl ester **31** gave identical results except ester cleavage was incomplete. The same (*E*):(*Z*) mixture was obtained when the pure (*E*) isomers **36** or **37** were similarly treated. The predominance of the (*Z*) unsaturated ester **27** in the Horner-Emmons cyclization of **26** thus appears to be determined at the addition stage of the reaction.




**30** R = Me (45%)
**31** R = Et

**36** R = Me (55%)
**37** R = Et

Prior to the above described equilibration experiments we carried out computer assisted molecular modeling of the (*Z*) and (*E*) methyl ester lactones **30** and **36** using the multiconformer submode of Clark Still's Macromodel program.[27] These calculations showed the (*E*) isomer **36** to be 0.5 kcal lower in energy than the (*Z*) isomer **30**, in reasonable agreement with experiment. Computer generated structures are displayed for these lactones in Fig. 1. The remarkably close match between the computer and X-ray structures for the (*Z*) isomer **30** lends confidence to the validity of the computational approach.

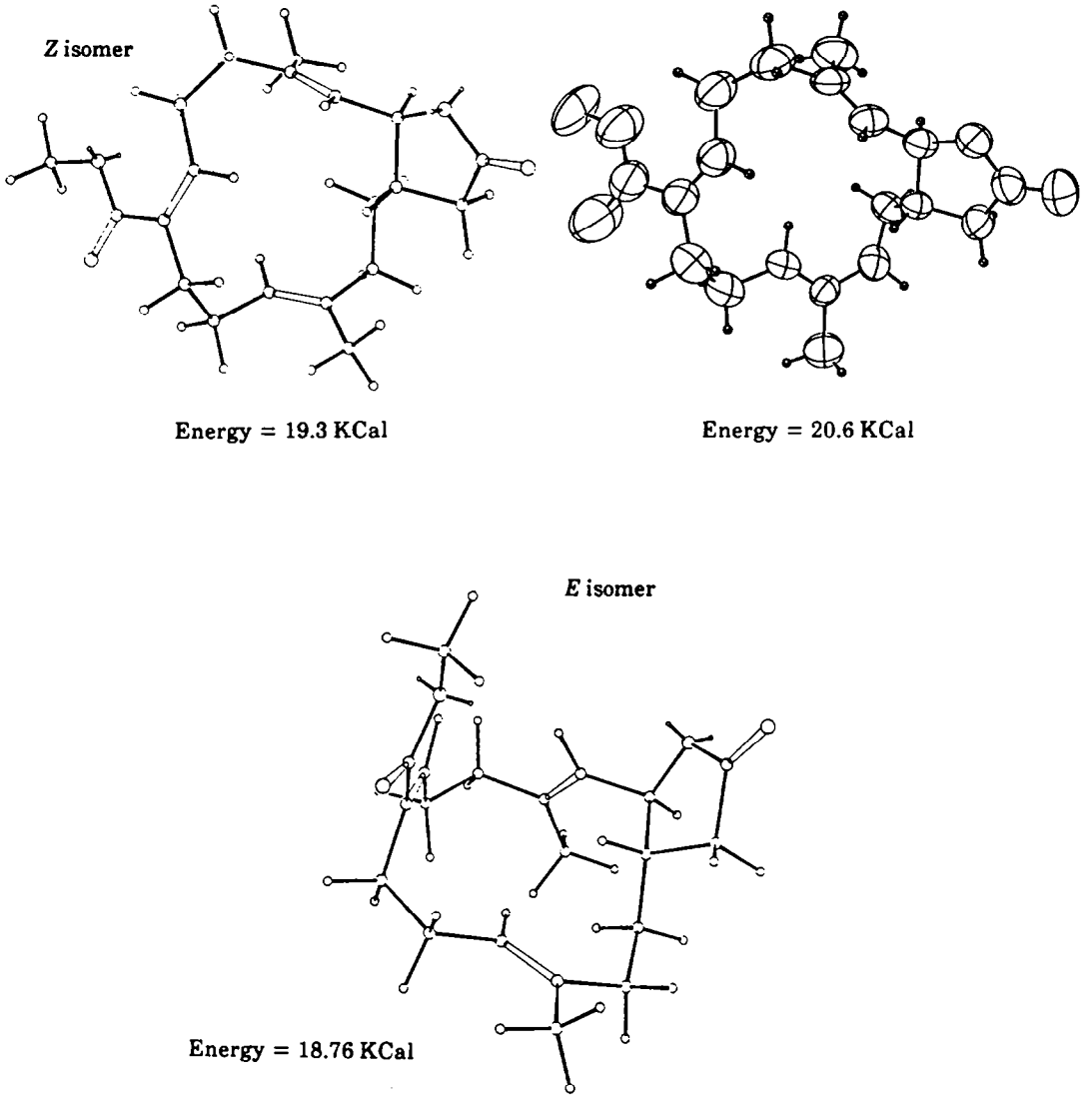



**Figure 1.** X-ray structure for lactone **30** and computer generated structures for lactones **30** and **36**.

**Acknowledgement.** We are indebed to Dr. K. K. Purushothaman, Assistant Director-in-Charge, Captain Srinivasa Murti Drug Research Institute, for an authentic sample of anisomelic acid. Support from the National Institute of General Medical Sciences through research grant 5-RO1 GM29475 is gratefully acknowledged. We thank the NSF for funding of an AM-300 NMR spectrometer through instrument grant CHE-8411172.

## Experimental

The apparatus and methods described by G. W. Kramer, M. M. Midland, and A. B. Levy[28] were used to maintain an argon or nitrogen atmosphere in the reaction flask. Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl (diethyl ether, tetrahydrofuran), calcium hydride (dichloromethane), or sodium (benzene). Infrared absorption maxima are reported in wavenumbers ($cm^{-1}$). Proton magnetic resonance samples were prepared as dilute solutions in deuteriochloroform ($CDCl_3$). Chemical shifts (δ) are reported downfield from tetramethylsilane ($Me_4Si$), in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; pentuplet, p; envelope, e; multiplet, m. Coupling constants (J) are reported in hertz (Hz). Glass capillary gas chromatography was performed on a Superox 4 25M column. Combustion microanalyses were performed by Atlantic Laboratories, Atlanta, GA. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F254 of 0.25 mm thickness, supplied by Brinkmann Instruments, were used. E. Merck silica gel 60 (230-400 ASTM mesh) was employed for column chromatography according to the procedure of Still.[18]

**Methyl (*E,E*)-6-Methyl-8-acetoxy-2,6-octadienoate (10).** A solution of 14.2 g (83.4 mmol) of aldehyde 7[12] in 6 mL of $CH_2Cl_2$ was added dropwise over 1.5 h to a solution of 30.7 g (91.8 mmol) of methyl α-(triphenylphosphoranyliden)acetate in 120 mL of $CH_2Cl_2$ at -20°C. The solution was stirred overnight at -20°C. Removal of solvent left a solid which was triturated twice with hexanes. The solid was removed by filtration and the filtrate was concentrated to an oil. Purification by silica gel chromatography (15% ethyl acetate-hexanes) afforded 16.23 g (86%) of a pale yellow oil: IR (film) ν 2940, 1725, 1660, 1445, 1280, 1240, 1215, 1165, 1035 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.66 (s, vinyl $CH_3$), 2.00 (s, $CH_3CO_2$), 2.11-2.16 (m, allylic $CH_2$), 2.26-2.34 (m, allylic $CH_2$), 3.67 (s, $CO_2Me$), 4.53 (d, J = 7, $CH_2OAc$), 5.31 (t, J = 8, vinyl H), 5.78 (dt, J = 15.7, 1.6, vinyl H), 6.89 (dt, J = 15.7, 6.9, vinyl H). *Anal.* Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.77; H, 8.02.

**Methyl (*E,E*)-6-Methyl-7-formyl-2,6-octadienoate (12).** A slurry of 14.5 g (64.3 mmol) of acetate 10 and a catalytic amount of $K_2CO_3$ in 40 mL of methanol at -20°C was stirred overnight. The mixture was diluted with water and extracted three times with ether. The ether layers were dried over anhydrous $MgSO_4$ and concentrated to 11.8 g (64.3 mmol) of crude product. The product was dissolved in 10 mL of $CH_2Cl_2$ and added to a solution of 6.7 mL (77.2 mmol) of oxalyl chloride and 11.0 mL (154.3 mmol) of DMSO in 150 mL of $CH_2Cl_2$ at -78°C. The resulting slurry was stirred 30 min at -78°C then 44.8 mL (321.5 mmol) of $Et_3N$ was added. The thick mixture was warmed to 0°C and quenched with water. The organic layer was washed twice with water. The combined aqueous layers were extracted with $CH_2Cl_2$ and the organic layers were dried over $MgSO_4$. Removal of solvent left an oil which was purified by silica gel chromatography (20% ethyl acetate-hexanes) affording 8.5 g (73%) of aldehyde 12 as a yellow oil: IR (film) ν 2970, 2940, 2830, 1720, 1665, 1440, 1280, 1200, 1165 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.14 (d, J = 1.3, vinyl $CH_3$), 2.31-2.40 (m, allylic $CH_2$'s), 3.68 (s, $CO_2Me$), 5.79-5.82 (m, vinyl H's), 6.87 (dt, J = 15.7, 6.6, vinyl H), 9.94 (d, J = 7.8, aldehyde H); MS(70eV) $M^+$ 182, M + 1 183, base peak 55; *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.82; H, 7.74.

**Methyl (*E,E*)-6-Methyl-2,6,8-nonatrienoate (13).** To a solution of 8.3 g (45.5 mmol) of aldehyde 12 in 50 mL of THF at -10°C was added 37 mL of 1.3 *M* trimethylsilylmethylmagnesium chloride in THF dropwise over 10 min. The resulting solution was stirred 30 min at -10°C then 3.6 mL (50.0 mmol) of acetyl chloride was added. The solution was stirred 5 min at -10°C then quenched with saturated $NaHCO_3$. The aqueous layer was extracted with ether and the combined organic layers were dried over anhydrous $MgSO_4$. Removal of solvent left an oil which was purified by silica gel chromatography (10% ether-hexanes) yielding 6.97 g (82%) of diene 13 as a pale yellow oil: IR (film) ν 3060, 2940, 1720, 1655, 1440, 1320, 1275, 1210, 1160; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.70 (d, J = 1.6, vinyl $CH_3$), 2.12-2.18, 2.25-2.33 (m, allylic $CH_2$'s), 3.65 (s, $CO_2Me$), 4.93 (d, J = 10.8, vinyl H), 5.05 (d, J = 17, vinyl H), 5.78 (dt, J = 15.6, 1.6, vinyl H), 5.79 (d, J = 10.8, vinyl H), 6.49 (ddd, J = 17, 10.8, 10.8, vinyl H), 6.89 (dt, J = 15.6, 6.7, vinyl H). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.26; H, 8.95.

**(*E,E*)-6-Methyl-2,6,8-nonatrien-1-ol (14).** To a solution of 4.25 g (21.9 mmol) of ester 13 in 25 mL of $CH_2Cl_2$ at -78°C was added 45 mL of 1 *M* DIBAH in hexanes. The resulting solution was stirred 10 min at -78°C then quenched with 50 mL of 10% aqueous NaOH. The mixture was warmed to room temperature and diluted with ether. The organic layer was washed with 10% aqueous NaOH and the combined basic aqueous layers were extracted twice with ether and the ether layers were dried over anhydrous $MgSO_4$. Removal of solvent left an oil. The oil was purified by silica gel chromatography (20% ethyl acetate-hexanes) providing 2.86 g (86%) of volatile alcohol 14: IR (film) ν 3310, 3070, 2905, 2840, 1645, 1600, 1450, 1420, 1110, 990 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.68 (t, J = 5.5, OH), 1.74 (d, J = 1.3, vinyl $CH_3$), 2.08-2.23 (m, allylic $CH_2$'s), 4.06 (m, $CH_2$-OH), 4.98 (dd, J = 10,2, C9 H), 5.09 (dd, J = 16.9,2, terminal vinyl H), 5.63-5.67 (m, vinyl H), 5.84 (d, J = 10.9, vinyl H), 6.55 (dt, J = 16.9, 10, vinyl H). MS (70eV) $M^+$ 152, M-$H_2O$ 134, base peak 81.

**N,N-Diisopropyl (*E,E*)-6-Methyl-2,6,8-nonatrienyl Carbamate (15).** To a slurry of 528 mg (22 mmol) of sodium hydride in 15 mL of DME at room temperature was added 2.86 g (18.8 mmol) of alcohol 14 in 6 mL of DME. The resulting mixture was stirred 10 min then cooled to 0°C and 3.3 g (20.0 mmol) of N,N-diisopropylcarbamoyl chloride was added. The mixture was stirred overnight at room temperature then carefully diluted with water. The solution was extracted three times with ether, dried over anhydrous $MgSO_4$ and concentrated to an oil. The oil was purified by silica gel chromatography (5% ethyl acetate-hexanes) affording 4.94 g (94%) of carbamate 15 as an oil: IR (film) ν 3070, 2960, 2920, 1690, 1445, 1370, 1320, 1290, 1225, 1165, 1140, 1055 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 6.8, $HCMe_2$); 1.74 (d, J = 1, vinyl $CH_3$), 2.12-2.18 (m, allylic $CH_2$'s), 4.50 (d, J = 6, $CH_2OCb$), 4.96 (dd, J = 10,2, C9 H), 5.07 (dd, J = 17,2, C9 H), 5.5-5.76 (m, C2 H, C3 H), 5.84 (d, J = 10.8, C7 H), 6.54 (ddd, J = 17, 10.8, 10.2, C8 H). *Anal.* Calcd for $C_{17}H_{29}O_2$: C, 73.07; H, 10.46. Found: C, 73.15; H, 10.51.

*anti*-(1*Z*,5*E*)-1-(N,N-Diisopropylcarbamoyloxy)-6-methyl-9-*tert*-butyldimethylsilyloxy-3-[(*E*)-3-methyl-3,5-hexadienyl]-1,5-nonadien-4-ol (16). To a solution of 2.56 g (9.2 mmol) of carbamate 15 and 1.7 mL of TMEDA in 30 mL of ether at -78°C was added 4.7 mL of 2.3 *M* n-BuLi in hexanes dropwise over 5 min. The resulting dark solution was stirred 1 h at -78°C during which time the solution became a thick slurry. Addition of 2.6 mL (11.0 mmol) of $ClTi(O\text{-}i\text{-}Pr)_3$ gave a dark solution to which was added 2.3 g (9.5 mmol) of aldehyde 5 in 5 mL of ether. The solution was stirred 2 h at -78°C then allowed to warm to -10°C over ~1-1.5 h. The mixture was poured into ice cold 10% aqueous HCl covered with ether. The aqueous layer was rapidly extracted twice with ether. The ether layers were quickly washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent left an oil which was purified by silica gel chromatography (12% ethyl acetate-hexanes) yielding 2.9 g (61%) of **16** as an oil: IR (film) ν 3450, 2915, 2840, 1690, 1440, 1375, 1305, 1105 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.03 (s, $CH_3Si$); 0.88 (s, *tert*-butyl), 1.23 (br s, $CH(CH_3)_2$), 1.59-1.72 (m, $CH_2$'s), 1.68 (s, vinyl $CH_3$), 1.71 (s, vinyl $CH_3$), 1.89-2.17 (m, allylic $CH_2$'s), 2.58-2.62 (m, allylic CH), 3.59 (t, J = 6.5, $CH_2OTBS$), 4.20 (br t, J = 7, carbinyl H), 4.55 (dd, J = 10.3, $J_{cis}$ = 6, C2 H), 4.95 (d, J = 10, vinyl H), 5.05 (d, J = 16.8, vinyl H), 5.19 (d, J = 9, C5 H), 5.81 (d, J = 10.9, vinyl H), 6.53 (dt, J = 16.8, 10, vinyl H), 7.25 (d, J = 6, C1 H); $^{13}C$ NMR (20 MHz, $CDCl_3$) δ 152.7, 139.6, 139.1, 137.9, 133.3, 125.5, 114.5, 110.8, 70.6, 62.7, 46.1, 42.7, 37.4, 35.9, 31.0, 29.1, 25.9, 20.9, 18.2, 16.9, 16.6, -5.3. *Anal.* Calcd for $C_{30}H_{55}NO_4Si$: C, 69.05; H, 10.62. Found: C, 69.10; H, 10.66.

*rel*-(2*R*,4*S*,5*S*) and *rel*-(2*R*,4*R*,5*R*)-4-[(*E*)-3-Methyl-3,5-hexadienyl]-5-[(*E*)-2-methyl-5-*tert*-butyldimethylsilyloxy-1-pentenyl]-1-oxacyclopentan-2-ol (17). To a slurry of 253 mg (6.6 mmol) of $LiAlH_4$ in 5 mL of THF at 0°C was added 2.9 g (5.55 mmol) of enol carbamate **16** in 4 mL of THF dropwise. The resulting mixture was heated at reflux for 0.5 h and cooled to room temperature. Ethyl acetate (0.5 mL) was added and the mixture was stirred for 0.5 h. The slurry was cooled to -10°C and 260 μL of $H_2O$, 260 μL of 15% aqueous NaOH and 780 μL of $H_2O$ were added sequentially. The reaction mixture was diluted with ether, dried over anhydrous $MgSO_4$ and concentrated to an oil. The oil was purified by silica gel chromatography (20% ethyl acetate-hexanes) providing 1.87 g (85%) of lactol **17** as a clear oil: IR (film) ν 3380, 2925, 2850, 1740, 1450, 1260, 1110 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.02 (s, $CH_3Si$), 0.87 (s, *tert*-butyl), 1.31-1.76 (m, $CH_2$'s), 1.68, 1.71 (br s, vinyl $CH_3$), 1.97-2.15 (m, allylic $CH_2$'s), 3.01, 3.14 (m, OH epimers), 3.57, 3.58 (t, J = 6.5, $CH_2OTBS$), 4.28, 4.48 (t, J = 9, CH-OH epimers), 4.97 (d, J = 10, terminal vinyl), 5.01 (d, J = 18, terminal vinyl), 5.06, 5.23 (d, J = 9, C5 H), 5.41-5.44, 5.50-5.53 (m, carbinyl H), 5.80 (d, J = 11, vinyl H), 6.53 (dt, J = 18, 10, vinyl H). *Anal.* Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73. Found: C, 70.08; H, 10.78.

*rel*-(2*R*,4*S*,5*S*) and *rel*-(2*R*,4*R*,5*R*)-4-[(*E*)-3-Methyl-6-hydroxy-3-hexenyl]-5-[(*E*)-2-methyl-5-*tert*-butyldimethylsilyloxy-1-pentenyl]-2-methoxy-1-oxacyclopentane (19). A solution of 1.24 g (3.14 mmol) of lactol **17**, 1.7 mL of trimethyl orthoformate and a catalytic amount of PPTS[10] in 5 mL of $CH_2Cl_2$ at room temperature was stirred for 5 min then diluted with ether. The mixture was washed twice with 50% saturated sodium chloride solution. The aqueous layers were extracted with ether and the combined ether layers were dried over $MgSO_4$. Removal of solvent left 1.28 g of lactol methyl ether which was unstable to silica gel chromatography and was therefore used crude: IR (film) ν 2920, 2840, 1445, 1255, 1105, 1030, 835 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.03 (s, $CH_3Si$), 0.87 (s, *tert*-butyl), 1.31-1.75 (m, $CH_2$'s), 1.68, 1.71 (br s, vinyl $CH_3$), 3.31, 3.35 (s, epimeric $OCH_3$), 3.58 (t, J = 6.5, $CH_2OTBS$), 4.32 (t, J = 9, C*H*-$OCH_3$), 4.90-5.19 (m, carbinyl H, vinyl H's), 5.80 (d, J = 11, vinyl H), 6.53 (dt, J = 17, 10.5, vinyl H).

To a solution of 6 mL of 1 M $BH_3$·THF at -10°C was added 1.4 mL (13 mmol) of 2-methyl-2-butene. The resulting solution was stirred at -10°C for 2 h then 1.28 g (3.14 mmol) of crude lactol methyl ether in 3 mL of THF was added. The clear solution was stirred 30 min at 0°C then excess disiamylborane was carefully quenched with 5 drops of $H_2O$ followed by 2 mL of 3 M aqueous NaOH and 2 mL of 30% aqueous $H_2O_2$. The solution was warmed to room temperature and stirred for 30 min. The mixture was diluted with $H_2O$ extracted 3 times with ether and the ether extracts were dried over $MgSO_4$. Removal of solvent left an oil. Purification by silica gel chromatography (30% ethyl acetate-hexanes) gave 1.1 g (82%) of alcohol **19** as a clear oil: IR (film) ν 3400, 2925, 2850, 1445, 1390, 1265, 1110 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.02 (s, $CH_3Si$), 0.86 (s, *tert*-butyl), 1.23 (t, J = 7, OH), 1.30-1.71 (m, $CH_2$'s), 1.58 (br s, vinyl $CH_3$), 1.68, 1.71 (d, J = 1.3, vinyl $CH_3$), 1.92-2.13 (m, allylic $CH_2$'s), 2.20-2.42 (m, allylic $CH_2$, methine), 3.30, 3.35 (s, epimeric $OCH_3$), 3.58 (t, J = 6.5, $CH_2OH$, $CH_2OTBS$), 4.30, 4.31 (t, J = 9, epimeric CH), 4.89-4.99 (m, carbinyl H), 5.09-5.16 (m, vinyl CH's). *Anal.* Calcd for $C_{24}H_{46}O_4Si$: C, 67.55; H, 10.87. Found: C, 67.63; H, 10.87.

*rel*-(2*R*,4*S*,5*S*) and *rel*-(2*R*,4*R*,5*R*)-4-[(*E*)-3-Methyl-6-iodo-3-hexenyl]-5-[(*E*)-2-methyl-5-*tert*-butyldimethylsilyloxy-1-pentenyl]-2-methoxy-1-oxacyclopentane (20). To a solution of 1.44 g (3.37 mmol) of alcohol **19**, 1.24 g (4.72 mmol) of triphenylphosphine and 344 mg (5.05 mmol) of imidazole in 6 mL of THF and 2 mL of $CH_3CN$ at -10°C was added 1.37 g (5.39 mmol) of $I_2$. The resulting dark solution was stirred 30 min at -10°C then quenched with saturated aqueous $Na_2S_2O_3$. Ether was added and the organic layer was washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted twice with ether and the combined ether layers were dried over anhydrous $MgSO_4$. Removal of solvent left a white solid. The white solid was dissolved in a minimum amount of $CH_2Cl_2$ and rapidly flashed through a 20-cm plug of silica gel (10% ether-hexanes) which furnished 1.63 g (90%) of iodide **20**: IR (film) ν 2915, 2840, 1440, 1380, 1250, 1100, 1025, 830 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.01, 0.02 (s, $CH_3Si$), 0.86, 0.87 (s, *tert*-butyl), 1.23-1.76 (m, $CH_2$'s), 1.55 (br s, vinyl $CH_3$), 1.67, 1.71 (br s, vinyl $CH_3$), 1.87-2.14 (m, allylic $CH_2$'s), 2.34-2.58 (m, methine, allylic $CH_2$), 3.07, 3.08 (t, J = 7, $CH_2I$), 3.30, 3.34 (s, $OCH_3$), 3.57 (t, J = 6.5, $CH_2OTBS$), 4.31 (t, J = 9, *H*C-$OCH_3$), 4.89-5.18 (m, carbinyl H, vinyl H's).

*rel*-(2*R*,4*S*,5*S*) and *rel*-(2*R*,4*R*,5*R*)-4-[(*E*)-3-methyl-7-(dimethoxyphosphinyl)-7-carbomethoxy-3-octenyl]-5-[(*E*)-2-methyl-5-*tert*-butyldimethylsilyloxy-1-pentenyl]-2-methoxy-1-oxacyclopentane (22). To a slurry of 108 mg (4.5 mmol) of sodium hydride in 5 mL of DMSO[10] at room temperature was added 0.73 mL (4.5 mmol) of methyl α-(dimethoxyphosphinyl)acetate dropwise. The resulting solution was stirred at room temperature for 30 min then 1.32 g (2.46 mmol) of iodide **20** in 2 mL of DMSO was added. The resulting solution was stirred overnight then quenched with water. The mixture was extracted twice with ether and once each with $CH_2Cl_2$ and ethyl acetate. The combined extracts were

dried over anhydrous $MgSO_4$ and concentrated to an oil at reduced pressure. The oil was purifed by silica gel chromatography (80% ethyl acetate-hexanes) yielding 1.25 g (85%) of phosphonate **22**: IR (film) ν 2940, 2915, 2845, 1735, 1450, 1265, 1110, 1035 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ -0.02 ($CH_3Si$), 0.83 (s, *tert*-butyl), 1.20-1.71 (m, $CH_2$'s), 1.47 (s, vinyl $CH_3$), 1.64, 1.68 (s, vinyl $CH_3$), 1.75-2.09 (m, allylic $CH_2$'s), 2.88-2.98 (m, *H*C-$CO_2Me$), 3.26, 3.31 (s, epimeric $OCH_3$), 3.54 (t, J = 6.5, $CH_2OTBS$), 3.70 (s, $CO_2Me$), 3.71 (d, J = 4.5, P(O)OMe), 3.74 (d, J = 4.5, P(O)OMe), 4.27 (t, J = 8.4, epimeric *H*$COCH_3$), 4.86-5.14 (m, carbinyl H, vinyl H's). *Anal.* Calcd for $C_{29}H_{55}O_8PSi$: C, 58.96; H, 9.38. Found: C, 58.82; H, 9.43.

***rel*-(2*R*,4*S*,5*S*) and *rel*-(2*R*,4*R*,5*R*)-4-[(*E*)-3-Methyl-7-(dimethoxyphosphinyl)-7-carbomethoxy-3-octenyl]-5-[(*E*)-4-formyl-2-methyl-1-butenyl]-2-methoxy-1-oxacyclopentane (25).** A solution of 1.24 g (2.09 mmol) of phosphonate **22** and a catalytic amount of PPTS[10] in 6 mL of methanol was heated at reflux for 5 min. The solution was diluted with ether and washed three times with 50% saturated aqueous sodium chloride solution. The aqueous layers were extracted with ether and ethyl acetate and the combined organic layers were dried over anhydrous $MgSO_4$. Removal of solvent left 994 mg of highly polar oil which was used without further purification.

The alcohol (994 mg, 2.09 mmol) in 3 mL of $CH_2Cl_2$ was added to a premixed solution of 260 μl (2.93 mmol) of oxalyl chloride and 420 μl (5.86 mmol) of DMSO in 5 mL of $CH_2Cl_2$ at -78°C. The resulting slurry was stirred 30 min and 1.46 mL (10.45 mmol) of triethylamine was added. The thick white mixture was warmed to 0°C then water was added. The mixture was washed twice with water and the aqueous layers were back extracted with $CH_2Cl_2$. The organic layers were dried over anhydrous $MgSO_4$ and concentrated to an oil. Purification by silica gel chromatography (ethyl acetate) afforded 865 mg (87%) of aldehyde **25**: IR (film) ν 2920, 2840, 1730, 1450, 1270, 1035 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.4-1.75 (m, $CH_2$'s), 1.69, 1.72 (br s, vinyl $CH_3$), 1.76-2.09 (m, allylic $CH_2$'s), 2.28-2.37 (m, $CH_2CHCO_2Me$), 2.50-2.59 (m, $CH_2CHO$), 2.89-3.01 (m, *H*$CCO_2Me$), 3.29, 3.33 (s, epimeric $OCH_3$), 3.72 (s, $CO_2Me$), 3.73, 3.77 (d, J = 4, $(O)P(OCH_3)_2$), 4.28 (t, J = 9, epimeric *H*COMe), 4.88-5.00 (m, carbinyl H, vinyl H), 5.12, 5.17 (br d, J = 8, vinyl H), 10.76 (t, J = 2, CHO).

***rel*-(1*R*,14*R*)-(2*E*,6*Z*,10*E*)-3,11-Dimethyl-7-carbomethyoxy-17-oxa-16-oxobicyclo[12.3.0]hexadeca-2,6,10-triene (30).**

Method A. A solution of 378 mg (0.79 mmol) of phosphonate **25** in 4.5 mL of DME was added dropwise over 2 h to a slurry of 70 mg (2.9 mmol) of sodium hydride and 925 mg (3.5 mmol) of 18-crown-6 in 50 mL of DME at room temperature. The mixture was stirred 0.5 h after the addition was complete. Water was added followed by 10% aqueous HCl. The aqueous layer was extracted three times with ether and the ether layers were dried over anhydrous $MgSO_4$. Removal of solvent left an oil which was dissolved in 4 mL of $CH_2Cl_2$ and treated with 681 mg (3.16 mmol) of PCC buffered with 66 mg (0.8 mmol) of sodium acetate. The mixture was stirred 3 h at room temperature then diluted with ether and filtered through a pad of silica gel covered with Celite. The black residue was thoroughly washed with ether. Removal of solvent left an oil which was purified by column chromatography (18% ethyl acetate-hexanes) providing 105 mg (40% overall for 3 steps) of lactone **30** as a white solid: m.p. 94-96°C; IR ($CHCl_3$) ν 2980, 2920, 2840, 1765, 1710, 1445, 1385, 1195 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.44-1.92 (m, $CH_2$), 1.55, 1.75 (s, vinyl $CH_3$), 2.09-2.31, 2.40-2.50, 2.60-2.82 (m, allylic $CH_2$'s, $CH_2CO$), 3.74 (s, $CO_2Me$), 4.81 (dd, J = 9.3, 7, H1), 4.97 (m, H10), 5.24 (d, J = 9, H2), 5.72 (t, J = 6.3, H6). *Anal.* Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.35; H, 8.53.

Method B. A solution of 378 mg (0.8 mmol) of phosphonate **25** in 4 mL of acetonitrile was added dropwise over 12 h to a slurry of 339 mg (8.0 mmol) of lithium chloride and 600 μl (4.0 mmol) of 1,8-diazobicyclo[5.4.0]undec-7-ene in 80 mL of acetonitrile at room temperature. The solution was filtered through a pad of silica gel with the aid of ether. Removal of solvent left an oil which was purified by chromatography on silica gel affording 198 mg (71%) of lactol methyl ether **27**: IR (film) ν 2975, 2910, 2840, 1715, 1450, 1390, 1210, 1110, 1040, $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.52 (s, vinyl $CH_3$), 1.4-1.7, 1.78-1.9, 2.01-2.2, 2.24-2.7 (m, $CH_2CO$, allylic $CH_2$'s, CH), 3.33, 3.34 (s, epimeric $OCH_3$), 3.72 (s, $CO_2Me$), 4.31-4.41 (m, acetal H), 4.93-5.1 (m, carbinyl and vinyl H), 5.17, 5.22 (d, J = 9, vinyl H), 5.76-5.84 (m, vinyl H).

A solution of 390 mg (1.12 mmol) of lactol **27** and a catalytic amount of PPTS in 5 mL of 1:1 THF-water was heated at reflux for 1.5 h. The mixture was diluted with ether and washed twice with 50% saturated aqueous sodium chloride. The aqueous layers were extracted twice with ether and the ether extracts were dried over anhydrous $MgSO_4$. Removal of solvent left an oil which was dissolved in 3 mL of $CH_2Cl_2$ and exposed to 431 mg (2.0 mmol) of PCC buffered with 41 mg (0.4 mmol) of sodium acetate for 2.5 h. The mixture was subjected to the workup and purification described for method A providing 260 mg (70%) of lactone **30** and 67 mg (17%) of recovered lactol methyl ether **27**.

**(±)-Methyl Anisomelate (33).** To a solution of 183 mg (550 μmol) of lactone-ester **30** in 2 mL of THF at -78°C containing 1,10-phenanthroline as an internal indicator was added 1 M LDA in THF. After a color change was detected (~30 μl), an additional 550 μl of LDA was added. The resulting red solution was stirred at -78°C for 15 min then warmed to -20°C for 5 min and treated with gaseous formaldehyde generated in a stream of argon. The color faded to a pale yellow and the gas flow was halted. The solution was stirred for 5 min at -20°C then quenched with 10% HCl. The mixture was diluted with water and extracted twice with ether and once with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. Removal of solvent left a cloudy, viscous oil. A solution of 199 mg (550 μmol) of the crude hydroxymethyl lactone, 582 mg (1.37 mmol) of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate and a catalytic amount of copper (II) chloride in 3 mL of $CH_3CN$ was heated at 55-58°C for 4 h. The solution was diluted with water and the mixture was extracted three times with ether. The ether layers were dried over anhydrous $MgSO_4$ and the solvent was removed leaving a dark oil. The oil was purified by silica gel chromatography (15% ethyl acetate-hexanes) affording 30 mg (16%) of recovered lactone **30** and 109 mg (58%) of **33** as a yellow oil which eventually solidified, m.p. 65-68°C: IR (film) ν 2900, 2840, 1755, 1705,1660, 1420, 1385, 1275, 1205 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.55, 1.74 (s, vinyl $CH_3$), 1.6-1.8 (m, $CH_2$), 2.0-2.68 (m, allylic $CH_2$'s), 2.75 (sept., J = 6 Hz, allylic CH), 3.71 (s,

$CO_2Me$), 4.84 (dd, J = 9.6, 4.0, carbinyl H), 4.95 (m, vinyl H), 5.13 (d, J = 9.6, vinyl H), 5.55 (d, J = 2, α-$CH_2$), 5.65 (t, J = 6 Hz, vinyl H), 6.20 (d, J = 2, α-$CH_2$). *Anal.* Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.27; H, 8.23.

**(±)-Anisomelic Acid (34).** A solution of 109 mg (316 μmol) of ester **33** and 180 mg of KOH in 3 mL of 1:1 ethanol-water was refluxed for 3 h. The solution was cooled to 0°C, diluted with ether, acidified with 10% HCl and stirred overnight at room temperature. The aqueous layer was extracted twice with $CH_2Cl_2$ and the organic layers were dried over $MgSO_4$. Removal of solvent left a yellow solid which was purified by silica gel chromatography (3% MeOH-$CH_2Cl_2$) providing 94 mg (90%) of a white solid, mp 173-176°C. MS (70 eV) M+ 330, base peak 53. MS (15 eV) M+ 330, M+1 331, base peak 312 (M-$H_2O$). IR ($CHCl_3$) ν 2900, 2840, 1750, 1680, 1440, 1275, 1130 $cm^{-1}$. $^1H$ NMR (300 MHz, $CD_2Cl_2$) δ 1.60, 1.78 (vinyl $CH_3$s), 2.10, 2.25, 2.35, 2.70 (m, allylic $CH_2$s), 2.85 (m, CH), 4.88 (dd, J = 4, 9.7, H2), 5.00 (br, H11), 5.18 (d, J = 9.7, H3), 5.59 (d, J = 2.5, α-$CH_2$), 5.90 (t, J = 6.5, H7), 6.17 (d, J = 2.5, α-$CH_2$). $^{13}C$ NMR ($CDCl_3$) 172.96, 170.39, 146.66, 140.96, 140.57, 132.40, 129.58, 125.20, 124.26, 121.51, 78.99, 42.96, 38.31, 36.03, 34.27, 32.04, 26.01, 24.94, 16.48, 15.67. The spectral properties of this material were identical to those of an authentic sample provided by Dr. K. K. Purushothaman of the Captain Srinivasa Murti Research Institute.

**Equilibration of *rel*-(1*R*, 14*R*)-(2*E*, 6*Z*, 10*E*) and *rel*-(1*R*, 14*R*)-(2*E*, 6*E*, 10*E*)-3,11-Dimethyl-7-carbomethoxy-17-oxa-16-oxobicyclo[12.3.0]hexadecatriene (30 and 36).** A solution of 49.9 mg (150 μmol) of lactone **30** and 405 μL of 0.4 *M* sodium isopropylthiolate in 2 mL of DMF was heated at 100°C for 20 h. The mixture was cooled to room temperature and diluted with ether and water. Acidification with 10% HCl was followed by two extractions with ether. The ether layers were dried over anhydrous $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was dissolved in ether and treated with excess diazomethane (generated from *N*-methylnitrosourea and 40% aqueous KOH). The solvent was removed and the crude product was purified by column chromatography (15% ethyl acetate-hexane) providing 20 mg of lactone **30** and 25 mg of the (*E*) isomer **36**: $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.44, 1.77 (s, vinyl $CH_3$), 1.44-1.57 (m, $CH_2$), 2.01-2.63 (m, allylic $CH_2$'s, $CH_2CO$), 2.81 (m, CH), 3.69 (s, $CO_2Me$), 4.74 (br d, J = 9, vinyl H), 4.86 (dd, J = 3.3, 9.9, carbinyl H), 5.22 (d, J = 9.9, vinyl H), 6.49 (dd, J = 4.6, vinyl H).

A solution of 25 mg (72 μmol) of the (*E*)-unsaturated ester **36** in 1 mL of DMF and 180 μL of 0.4 *M* sodium isopropylthiolate in DMF was heated at 100°C overnight. The products were isolated as described above yielding 26 mg of crude product which was ascertained to be a *ca.* 1:1 mixture of lactones **30** and **36** by 300 MHz $^1H$ NMR analysis.

## References and Notes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10. Abbreviations: DBU = 1,5-diazabicyclo[4.3.0]non-5-ene; DIBAH = diisobutylaluminum hydride; DMAP = 4-(*N*,*N*-dimethylamino)pyridine; DME = 1,2-dimethoxyethane; DMF = *N*,*N*-dimethylformamide; DMSO = dimethyl sulfoxide; Im = imidazole; KHMDS = potassium hexamethyldisilazide = potassium *bis*-(trimethylsilyl)amide; LDA = lithium diisopropylamide; PCC = pyridinium chlorochromate; PPTS = pyridinium *p*-toluenesulfonate; RT = room temperature; Siam = *sec*-isoamyl = $(Me)_2CHCH(Me)$; TBS = *t*-butyldimethylsilyl; THF = tetrahydrofuran; TMEDA = tetramethylethylenediamine.
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20. We are indebted to Dr. Lukasz Lebioda of this department for this analysis.

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