Total Synthesis of Halicholactone and Neohalicholactone[1]

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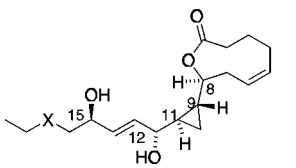
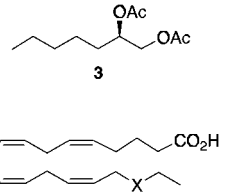
The total synthesis of the marine natural products neohalicholactone (**1**) and halicholactone (**2**), in enantiomerically pure form, are reported. Key steps in the synthesis of each compound include a *cis*-selective Wittig reaction, stereoselective cyclopropanation, nine-membered lactone formation using the Yamaguchi method and late-stage stereoselective Cr(II)/Ni(II) mediated coupling of vinyl iodides **39** and **50** with aldehyde **14**. In the case of the neohalicholactone synthesis the two major components which were coupled in this convergent synthesis were each derived from the enantiomers of commercially available malic acid. The synthesis served to confirm the original assignment of absolute configuration which was made by Yamada and Clardy. We also demonstrated, through the preparation of diastereoisomers, that another reported compound closely related to neohalicholactone is likely to be the C-15 epimer **67**.

Introduction

Examination of the constituents of the marine sponge *Halichondria okadai*, collected off the coast of Japan by the Yamada group, led to the isolation of the fatty acid metabolites neohalicholactone (**1**) and halicholactone (**2**).[2a] The structural elucidation of these metabolites was achieved by evaluation of spectral data, coupled with chemical evidence. The absolute stereochemistry at carbon fifteen of halicholactone (**2**) was shown to be of *R* configuration by chemical degradation of its diacetate. This gave the *R*-diacetate of 1,2-heptanediol (**3**) as one of the fragments, the absolute stereochemistry of which was confirmed by comparison with authentic material. In a more recent publication the relative stereochemistry of **1** was established by an X-ray crystallographic study.[2b] Since it is likely that a similar biosynthetic pathway yields both **1** and **2** then, in combining the aforementioned stereochemical knowledge, it seems reasonable to speculate that the absolute stereochemistry in both molecules should be (8*S*,9*R*,11*R*,12*R*,15*R*) as shown below.



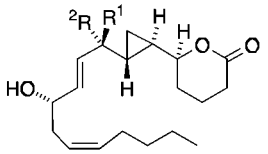
1 Neohalicholactone (X=*cis* CH:CH)
2 Halicholactone (X=CH_2CH_2)



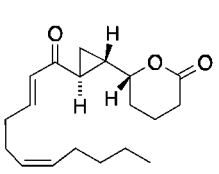
4 X=CH_2CH_2 arachidonic acid
5 X=*cis*-CH:CH eicosapentaenoic acid

Compound **2** has been shown to exhibit inhibitory activity ($IC_{50} = 630\ \mu m$), against 5-lipoxygenase of guinea pig polymorphonuclear leukocytes. These factors, as well as the necessity to unambiguously confirm the absolute stereochemistry of **1** and **2**, encouraged us to undertake an enantioselective total synthesis.

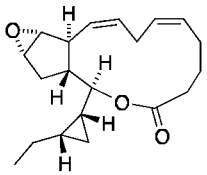
Halicholactone and neohalicholactone are believed to be formed from arachidonic acid (**4**) and eicosapentaenoic acid (**5**), respectively, probably *via* lipoxygenation reactions followed by intramolecular cyclizations. Although the details of the mechanism have not yet been fully determined, the structurally related marine natural products of the constanolactone series **6**, the related lactone **7**, and hydridalactone (**8**) provide some clues. Corey's general hypothesis for marine prostanoid biosynthesis involves an initial (8*R*) lipoxygenase oxidation of arachidonic acid (**4**) followed by formation of an allene



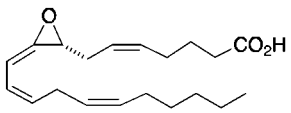
6a (R^1=H, R^2=OH) Constanolactone A
6b (R^1=OH, R^2=H) Constanolactone B



7 (racemic)



8 Hybridalactone



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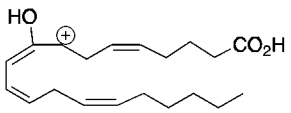

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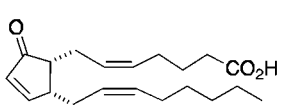

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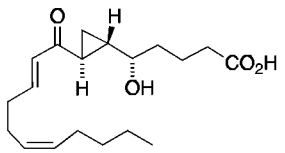

12

oxide **9** and subsequent ring opening to give a cation **10**

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(1) Preliminary communications: (a) Critcher, D. J.; Connolly, S.; Wills, M. *J. Chem. Soc., Chem. Commun.*, **1995**, 139. (b) Critcher, D. J.; Connolly, S.; Wills, M. *Tetrahedron Lett.*, **1995**, *36*, 3763.

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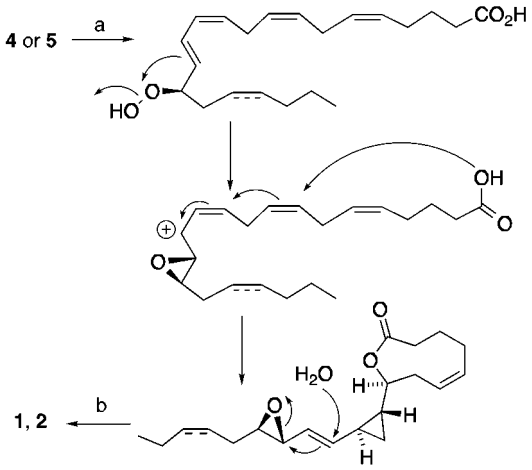
Scheme 1



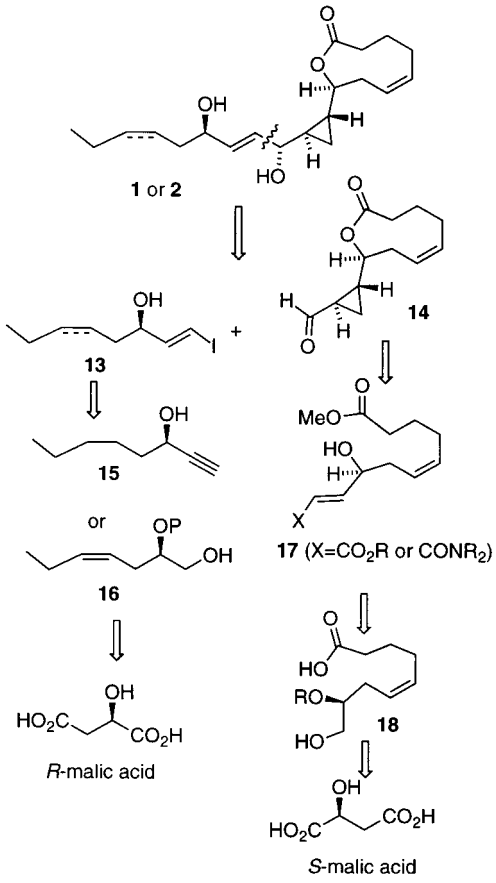
Reagents and conditions: (a) (15R)-lipoxygenase; (b) H_2O.

which cyclizes to give the prostanoid **11**.[3] Incubation of arachidonic acid with an acetone powder from the coral *Plexaura homomalla* gave, as well as the expected **11**, a small amount of an eicosanoid **12** containing a cyclopropane, that was easily cyclized to the lactone **7** to aid characterization.[4]

Recently, Gerwick has isolated a series of constanolactones (**6**), which are closely related to **7**, from the red marine alga *Constantinea simplex* off the Oregon coast.[5a,b] Gerwick also assigned the absolute stereochemistry of these compounds using a degradative method. During the course of our studies, White reported an elegant synthesis of **7** and constanolactones A (**6a**) and B (**6b**) using a route that mimics the proposed biosynthetic pathway and that serves to confirm the indicated absolute stereochemistry of these compounds.[6] While the biosynthesis of constanolactones fits within the extended Corey model, Gerwick has proposed an alternative, but related, route that depends critically on an initial 12-lipoxygenase oxidation to give the 12*S*-epoxide and subsequently the 12-alcohol of the same configuration.[5b] The biosynthesis of hybridalactone (**8**), from the marine alga *Laurencia hybrida*, also depends critically on an initial *S*-selective 12-lipoxygenation reaction, in this case of eicosapentaenoic acid. The absolute stereochemistry and biosynthetic route to this compound was determined by Corey.[7]

In the case of halicholactone and neohalicholactone, therefore, it is likely that a similar pathway is operating to that leading to constanolactones. A 12-lipoxygenation pathway[2a] and a 15-lipoxygenation pathway (Scheme 1)[8] have been proposed, the latter of which was suggested

Scheme 2. Retrosynthetic Analysis of Neohalicholactone and Halicholactone



in a paper by Gerwick during the course of our studies and will be discussed in more detail later.[8] The pathway would, of course, require an initial *R*-selective lipoxygenation process, which would not be in accord with the pathway described above for the related materials, although it would not be without precedent for marine natural products.[9] A total synthesis to confirm the absolute configuration of these molecules was therefore undertaken.

Synthetic Approach

Our retrosynthetic approach is shown in Scheme 2. Disconnection of the C12−C13 bond will give two fragments **13** and **14**. The "left hand" fragment **13** could be made either from (*R*)-(+)-1-octyn-3-ol (**15**) (in the case of halicholactone) or from alcohol **16** (in the case of neohalicholactone) which could be prepared from *R*-malic acid.

The synthesis of cyclopropanes, and in particular, their enantioselective synthesis, has been an area of intensive research in recent years. Disconnection of **14** to the acyclic unsaturated synthons **17** may be appropriate. The transformation of **17** to **14** may be achieved using dimethylsulfoxonium methylide.[10] This method necessitates that **17** has either α,β-unsaturated ester or amide functionality.[11] The presence of α-alkoxy functionality at C(8) would be expected to promote preferential reagent attack to one face of the electron-poor olefin, thus

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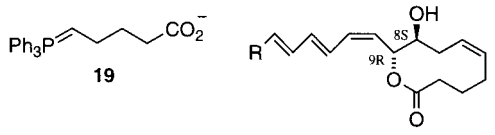
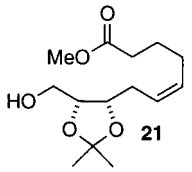
providing all the chemical information required for a diastereoselective reaction. Synthon **17** would be prepared from the precursor **18** that we anticipated would in turn be available from *S*-malic acid.

Results and Discussion

As discussed above, we anticipated that a key intermediate in the synthesis of the right hand fragment of **1** and **2** would be a C_8-protected derivative of methyl (*S*)-8,9-(*Z*)-dihydroxynon-5-enoate (**18**). The synthesis of this portion of a target molecule has been successfully achieved, in numerous cases, *via* Wittig olefination using ylide **19** derived from (4-carboxybutyl)triphenylphosphonium bromide.[12−14]





One example of the use of this strategy may be found in the preparation of (8*S*,9*R*)-neodidemnilactone (**20**).[13] This was efficiently completed by building on the 14*E*,12*E*,10*Z* side chain from the unprotected C_{10} hydroxy group in **21**. The acetonide protecting group was then cleaved, and after basic hydrolysis of the ester group, the resulting (8*S*,9*R*)-dihydroxy acid was preferentially cyclized to the ten-membered lactone product using the method described by Yamaguchi. Significantly, the final cyclization step had a choice of forming the ten-membered lactone product or its nine-membered alternative; the formation of the latter is, however, not mentioned in the publication.

We anticipated that direct lactonization of a C_9-hydroxy protected derivative of (**18**) to a nine-membered lactone would then be followed by a problematical C_9-hydroxy deprotection step. It is reasonable to expect such a compound to be converted to its more stable ten-membered lactone isomer during C_9-hydroxy deprotection *via* a facile translactonization reaction.[14] For this reason we favored a late-stage lactonization strategy. We wished to prepare (3*S*)-3-*O*-(((*p*-methoxyphenyl)methyl)oxy)-γ-butyrolactol (**22**) and condense this lactol with ylide **19**. The synthesis of a derivative of **18** should then be possible in just seven steps.

The antipodal trityl-protected analog of **22** has been reported and has been employed in a Wittig olefination during the synthesis of the $C_{11}-C_{20}$ segment of leukotriene B_4.[15] However, its preparation required nine steps from L-ascorbic acid using the procedure first described by Tanaka.[16] Shorter routes to the precursor (3*R*)-hydroxy-γ-butyrolactone have been published.[17,18] Significantly, it is possible to differentiate the two carboxylic acid groups in malic acid using a combination of borane−dimethyl sulfide complex in the presence of a catalytic amount of sodium borohydride.[18] Subsequent lactonization of the reduction product to (3*S*)-hydroxy-γ-butyrolactone has been accomplished using standard acidic conditions in 90% yield. It was this three-step high-yielding approach that we wished to exploit. Our synthesis of the "right hand" portion is shown in Scheme 3.

(*S*)-Malic acid was dissolved in a 3% anhydrous hydrochloric acid/methanol solution to give dimethyl (*S*)-malate in yields in excess of 80% after distillation.[19] In our hands, the selective reduction of the diester became extremely exothermic upon addition of a catalytic amount of sodium borohydride. We took the precaution of only performing this reaction on a moderate scale (between 5 and 10 g). If the mixture was cooled to 0 °C prior to the addition of $NaBH_4$ and subsequently allowed to warm slowly to room temperature, the reaction was controllable and selective. It should be noted that while we were able to isolate methyl (*S*)-3,4-dihydroxybutanoate in high yield (>90%), methyl (*S*)-2,4-dihydroxybutanoate was also present. Cyclization of methyl (*S*)-3,4-dihydroxybutanoate to the hydroxylactone was achieved using an aqueous 18 N H_2SO_4/THF solution in 75% yield.[20]

We investigated the (*p*-methoxyphenyl)methyl (which will be abbreviated to the more commonly employed PMB, or *p*-methoxybenzyl) protection of 3-hydroxy-γ-butyrolactone using 2,2,2-trichloroacetimidate methodology.[21−23] PMB-2,2,2-trichloroacetimidate is more reactive than its benzyl analogue and extremely sensitive to acids. It is best prepared immediately before use, and the benzylation reaction requires only 0.3 mol % of TfOH; addition of 10 mol % of TfOH causes instant decomposition. The use of 10 mol % of a weak acid, 10-camphorsulfonic acid (CSA), has also been reported as a suitable alternative to 0.3 mol % TfOH.[22] We found that the PMB-protection of 3-hydroxy-γ-butyrolactone furnished **23** in yields in excess of 70% using either 0.3 mol % TfOH or 5 mol % CSA.

The reduction of lactone **23** was achieved using a slight excess of diisobutylaluminum hydride, in toluene, at low temperature (<−20 °C). The target lactol **22** was either isolated in quantitative crude yield or could be chromatographed in which case the isolated yield was slightly lower (but still >80%). However, **22** was usually employed in the next Wittig olefination step without further purification. The Wittig reaction was carried out using a slight modification to the conditions first described by Holmes[14] using *fresh* sodium bis(trimethylsilyl)amide in toluene. Before adding the deep red ylide (cooled to −78 °C) to the lactol at −78 °C, **22** was first deprotonated using 1 equiv of sodium bis(trimethylsilyl)amide. This presumably produces the acyclic aldehyde derivative, which was kept at low temperature (−78 °C) in toluene. Since the anion was quite insoluble in toluene at low

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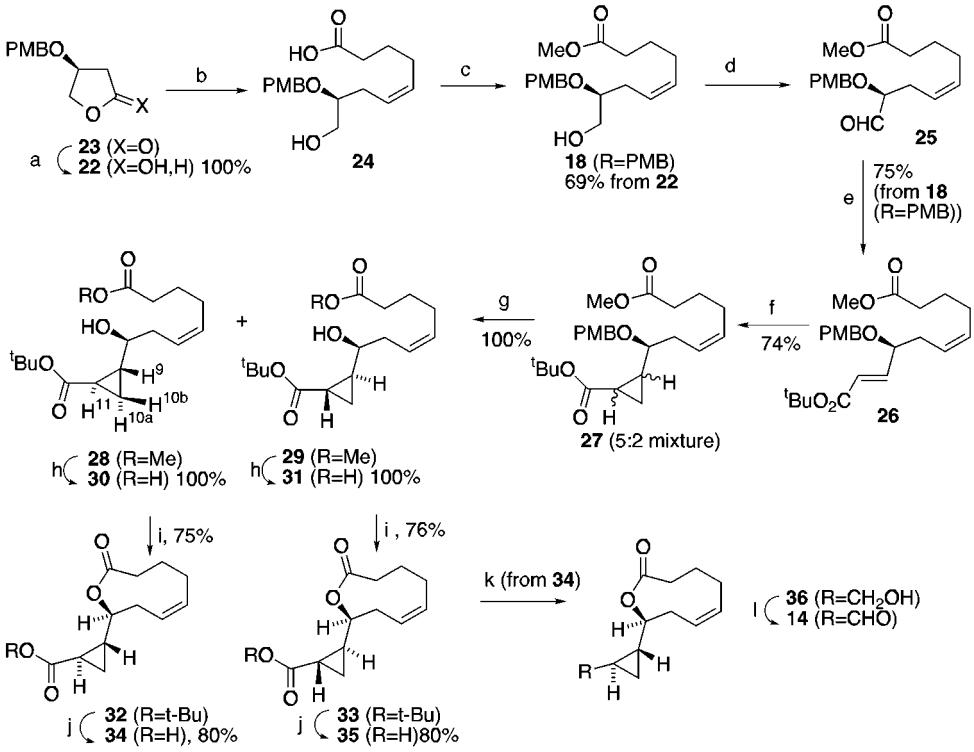
Scheme 3



Reagents and conditions: (a) DIBAL-H, toluene, -20°C; (b) $HO_2C(CH_2)_4PPh_3Br$, NaHMDS; (c) AcCl, MeOH; (d) Swern oxidation; (e) t-$BuO_2CCH_2PO(OEt)_2$, DBU, LiCl; (f) $Me_3S(O)I$, NaH, DMSO; (g) DDQ, CH_2Cl_2:H_2O 18:1; (h) LiOH, THF-MeOH-H_2O, 4:1:1; (i) Yamaguchi lactonisation; (j) TFA, CH_2Cl_2; (k) EtOCOCl, Et_3N, THF, then $NaBH_4$; (l) TPAP, NMO.

temperatures, the volume of toluene was increased relative to that used in the Holmes procedure. The addition of the preformed ylide to the sodium alkoxide of **22** was found to be more satisfactory than the inverse of this addition. We found that **22** was prone to decomposition if sufficiently low temperatures were not maintained. The crude (*Z*)-olefinic carboxylic acid **24** was then converted to its methyl ester **18** (R = PMB) using a HCl/methanol solution at pH 4−5.

Using this approach, methyl (8*S*,5*Z*)-8-*O*-(PMB)-8,9-dihydroxynon-5-enoate (**18** (R = PMB)) was consistently isolated on a gram scale in yields greater than 60% for the three-step transformation from lactone **23**. Swern oxidation[24] gave the corresponding aldehyde **25** which was subsequently condensed with *tert*-butyl diethylphosphonoacetate using conditions described by Masamune and Roush,[25] to furnish (*E*)-γ-alkoxy-α,β-unsaturated-*tert*-butyl ester (**26**) in 75% yield.

Ester **26** was treated with 2 equiv of DMSY (prepared from trimethylsulfoxonium iodide and NaH) in dimethyl sulfoxide, and the solution was heated at 90 °C for 20 h.[26−29] An inseparable 5:2 mixture of two diastereomeric cyclopropanes **27** were isolated in good yield (74%). No products corresponding to addition of DMSY to the exposed methyl ester were observed. We found that more elevated temperatures were required in our reaction than those described by Magnus.[29]

Deprotection of the (*p*-methoxybenzyl)methyl group in **27** using DDQ[30] gave the two (8*S*)-hydroxycyclopropane diastereoisomers **28** and **29** in quantitative yield. Fortunately, these two compounds were separable by chromatography, and the major isomer **28** was isolated in 51% yield for the two-step transformation from *tert*-butyl ester **26**. From the coupling constants of the terminal cyclopropane protons (H_{10a} and H_{10b}) in the ^{1}H-NMR spectrum of the major isomer **28**, it was clear that a *trans*-cyclopropane ring was in place. Excellent agreement with coupling constants of the cyclopropane protons H_{7a} and H_{7b} of *trans*-cyclopropane, and lactone-containing compound **7** were observed.[6a,b]

The cyclopropane protons gave unresolvable splitting patterns in the minor diastereomer **29**. However, subsequent manipulations of **29** gave derivatives whose coupling constants for H_{10a} and H_{10b} were in very good agreement with those described for **28**. An X-ray crystal structure of the derived acid[1a] confirmed the *trans*-substitution pattern and had the correct relative stereochemistry (8*S*,9*R*,11*R*) required to complete the synthesis of the right-hand fragment of neohalicholactone (**1**) and halicholactone (**2**). The most likely explanation for the exclusive formation of the *trans*-isomers **27** is direct kinetic control in the cyclopropanation reaction.[31,32]

Assuming that the addition of DMSY to **26** is irreversible, we offered the following stereochemical arguments. The reaction of γ-alkoxy-α,β-unsaturated esters with a

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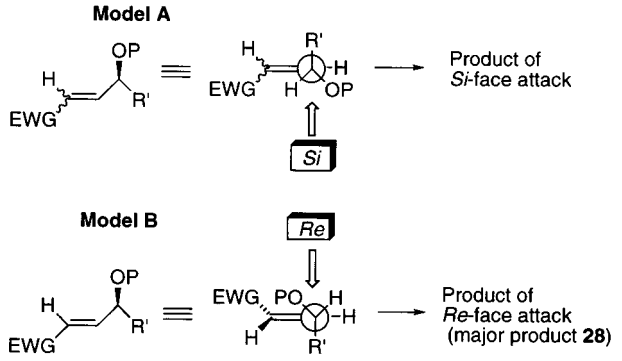

Figure 1.

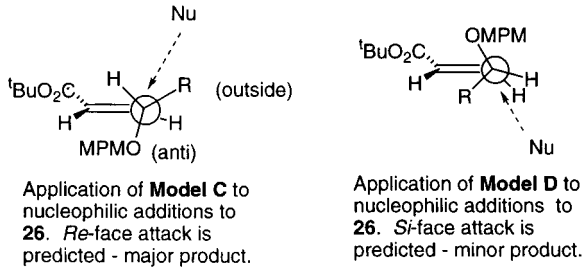

Figure 2.

variety of nucleophiles has been studied.[31,33−35] For either (*E*)- or (*Z*)-γ-alkoxy unsaturated esters, the reactive conformation shown in **model A** (Figure 1) explains the stereochemical outcome of reactions with reagents such as 1-acetoxy-2-((trimethylsilyl)methyl)-2-propene, cyclopentadiene, isopropylidenediphenylsulfurane, and amines. The approach of the reagent takes place from the least hindered side of the starting unsaturated ester adopting the conformation shown in **model A**, whatever the stereochemistry of its C=C bond.[31] In this model, the large alkyl substituent R' is perpendicular to the conjugated double bond, and the hydrogen atom eclipses the conjugated double bond. However, there is also a set of reagents which will react with (*Z*)-γ-alkoxy unsaturated esters to give products whose β-stereochemistry can also be rationalized using **model A**, while the same nucleophiles will give the opposite β-stereochemistry if the (*E*)-double bond isomer is used. The conformation shown in **model B** is thought to result from a favorable interaction between the p-orbitals on the double bond and an unshared pair of electrons of the γ-oxygen. Such an interaction is only active if an (*E*)-double bond is present. Reagents that are consistent with these experimental findings are osmium tetraoxide, organocopper−boron trifluoride complexes, and isopropylidenetriphenyphosphorane. Therefore, the 5:2 mixture of cyclopropane isomers was the result of (8*S*)-(*E*)-γ-alkoxy-α,β-unsaturated-*tert*-butyl ester **26** preferentially reacting *via* the conformation shown in **model B**, since only this model predicts the generation of a 9*R*,11*R* cyclopropane product.

Houk[36] has studied stereoselective additions to double bonds using *ab initio* quantum mechanics to predict transition state structures (see Figure 2). By researching both nucleophilic and electrophilic additions to chiral allylic ethers the following generalizations have been made. For nucleophilic attack on π bonds, an electronegative allylic ether group (A = electron acceptor) would prefer to adopt an *anti* position so that the withdrawal of electrons from the π-system can be maximized. The most electropositive allylic substituent (B = electron donor) prefers the *outside* position in order to minimize the donation of electrons to the already electron rich π-system of the transition state, see **model C**. Frontier molecular orbital theory has been used to understand qualitatively these preferences. When the s^*_{C-A} orbital is aligned *anti* to the forming bond, its overlap with the HOMO of the transition state (which consists of the nucleophile HOMO and the alkene LUMO) is maximized, and the transition state is stabilized. An electropositive group prefers the *outside* position since the interaction of an occupied s_{C-D} orbital with the transition state HOMO is destabilising. **Model C** summarizes this information (Figure 2).

Application of the nucleophile addition **model C** to our DMSY addition to α,β-unsaturated ester **26** predicts the stereochemical preference that we observed experimentally: *re*-face attack. However, in **model C** the large sterically demanding alkyl chain is positioned in the *outside* region where it presents a steric obstacle to the approaching nucleophile. It is possible that this factor accounts for the modest stereoselectivity we observed. The alkyl chain would be less obstructive in the *inside* position. Nucleophilic attack would occur, once again, *anti* to the electron-withdrawing group as shown in **model D**, and *si*-face attack is now predicted.

The cyclization of hydroxy acids to furnish *saturated* nine-membered lactones is known to be problematical. The three standard macrolactonization method, the 2-thiopyridyl ester method of Corey,[37] the utilization of 1-methylchloropyridinium iodide—the method of Mukaiyama,[38] and the formation of a carboxylic 2,4,6-trichlorobenzoic anhydride, as described by Yamaguchi,[39] afford at best nine-membered lactones in 25%, 13% and 18% yields, respectively. However, in 1982, Still reported[40] that the presence of a (*Z*)-olefinic linkage provides "substantial enthalpic, as well as entropic benefit to the desired cyclization". The enthalpic benefit is due to the elimination of important transannular repulsions in the product.

We were able to synthesize the required nine-membered lactones in good yield by employing the lactonization conditions first described by Yamaguchi.[39] Initially, enantiomerically pure hydroxy *trans*-cyclopropane compounds **28** and **29** were smoothly converted to their nine-membered lactones by basic hydrolysis to give intermediate ω-hydroxy acids **30** and **31** that were then lactonized to provide **32** and **33** in 75% and 76% yield, respectively. The only observed side-product was a dimeric species which formed readily if high dilution and slow addition conditions were not employed. However, this unwanted eighteen-membered lactone was usually formed in less

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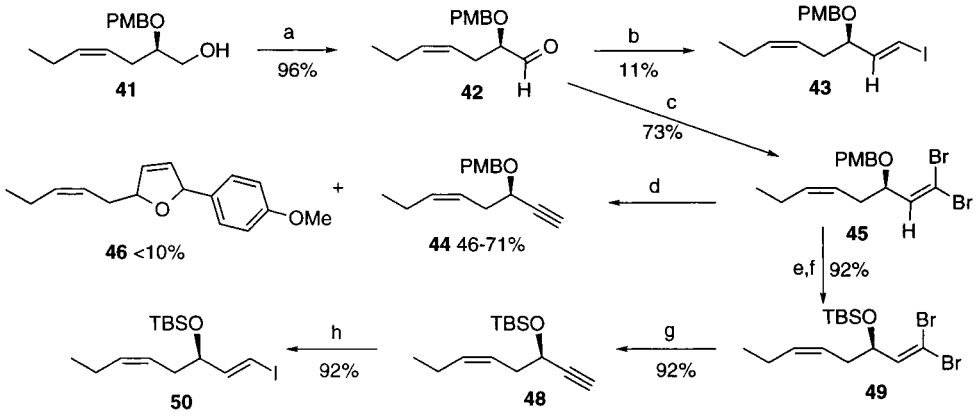
Scheme 4



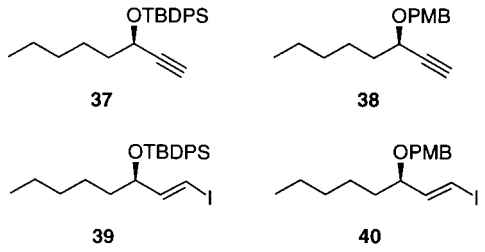
Reagents and conditions: (a) Swern oxidation; (b) 2 eq. CHI_3, 6 eq. $CrCl_3$ THF, rt, 16h; (c) 2eq. CBr_4, 4 eq. PPh_3, 8 eq. Et_3N, CH_2Cl_2, rt then 1.0 eq. crude aldehyde, 0°C, CH_2Cl_2; (d) *n*-BuLi, THF, -78-0°C; (e) 1.1 eq. DDQ, 18:1 CH_2Cl_2:H_2O; (f) 1.2 eq. TBDPSCl, 2.5 eq. imidazole, DMF; (g) 1.5 eq. LDA, THF, -78 to 0°C, 30 min. then 2.2 eq. *n*-BuLi, -78°C, 5 min.; (h) 1.2 eq. Cp_2ZrHCl, 1.2 eq. I_2, THF, rt.

than 5% yield and could be separated from the nine-membered lactones by chromatography, hydrolyzed to the hydroxy acid (using lithium hydroxide) in excellent yield (84%) and relactonized.

Conversion of **32** and **33** to their carboxylic acid derivatives **34** and **35** was achieved using trifluoroacetic acid in dichloromethane. The X-ray structure of **34**[1a] revealed that this isomer contains the correct 8*S*,9*R*,11*R* relative stereochemistry for the completion of the synthesis of both neohalicholactone (**1**) and halicholactone (**2**). It is interesting that **34** adopted a very similar conformation to the corresponding region of neohalicholactone itself.[1a]

With 8*S*,9*R*,11*R*-carboxylic acid **34** in hand, its reduction to an aldehyde involved the initial formation of a carbonic−carboxylic anhydride that was then reduced using sodium borohydride ($NaBH_4$).[41] Carboxylic acid **34** dissolved in tetrahydrofuran was treated with ethyl chloroformate in the presence of triethylamine to yield the corresponding mixed anhydride. The deposited triethylamine hydrochloride was filtered and the purified mixed anhydride reduced with sodium borohydride to afford **36** in 77% yield. Finally **36** was oxidized to aldehyde **14** using TPAP.[42] Therefore, the synthesis of the right hand fragment was completed in 16 steps from (*S*)-malic acid in a satisfactory 7.5% overall yield. Using the reaction sequence described, we were able to prepare several hundreds of milligrams of enantiomerically pure 8*S*,9*R*,11*R*-aldehyde **14**.

We synthesized suitably protected 1-iodo-1-octene-3-ol derivatives **37** and **38** from (*R*)-1-octyn-3-ol (**15**) in two steps. Using the *tert*-butyldiphenylsilyl chloride/imidazole/*N*,*N*-dimethylformamide protocol, **37** was isolated in 89% yield. The (*p*-methoxyphenyl)methyl derivative **38** was also synthesized with using *p*-methoxybenzyl chloride/sodium hydride/catalytic tetra-*n*-butylammonium iodide/DMF in 56% yield. The hydrozirconation−iodination procedure first reported by Schwartz[43] gave (3*R*,1*E*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-iodo-1-octen-3-ol (**39**) and (3*R*,1*E*)-3-(((*p*-methoxyphenyl)methyl)oxy)-1-iodo-1-octen-3-ol (**40**) in 94% and 77% yields, respectively, from **37** and **38**. The hydrozirconation reaction was far more problematical with the PMB-protected substrate **38**. The reaction needed to be performed at low temperature (0 °C) and required 2.2 equiv of bis(cylopentadienyl)zirconium chloride hydride to achieve full conversion.



For the preparation of the corresponding fragment of neohalicholactone (Scheme 4), we found that the best results were obtained when we performed the Wittig reaction of **19** with (*R*)-**22** without the prior formation of the sodium alkoxide. In this case, 2.1 equiv of the ylide were prepared as before, and this, at −78 °C, was added to lactol (*R*)-**22**, also at −78 °C, *via* cannula. The resulting mixture was maintained at low temperature for 5 min, and warmed to 0 °C, followed by stirring at this temperature for 30 min. The reaction was quenched using a saturated aqueous ammonium chloride solution. After chromatography, the desired (*Z*)-olefin **41** was now isolated in 76% yield. The only detected byproduct was the nonpolar trimethylsilyl primary hydroxyl protected derivative of **41**, in 11% yield. The partial trimethylsilyl protection of the desired compound was presumably a result of the protonation of hexamethyldisilazide during workup. As for the "right-hand" fragment, we avoided the use of silyl protecting groups in this transformation due to their known tendancy to migrate to less hindered positions.

The trimethylsilyl protecting group is very labile to hydrolysis,[44] and we were, therefore, able to cleave it in

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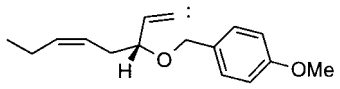
quantitative yield under mildly acidic conditions (dilute hydrochloric acid/tetrahydrofuran solution) which left the *p*-methoxyphenyl)methyl group intact. The total yield for the olefination reaction was at least 87%. The oxidation of the key alcohol **41** to give (2*R*,4*Z*)-2-*O*-(((*p*-methoxyphenyl)methyl)oxy)-4-heptenal (**42**) was achieved quantitatively using the Swern oxidation conditions.[24] Aldehyde **42** could also be isolated in yields in excess of 96% after chromatography. A closely related approach to a homologue of **42** has been reported, the subsequent elaboration of which provided an excellent precedent for our proposed strategy.[45]

With aldehyde **42** in hand, we examined the Takai olefination reaction,[46] in the formation of (3*R*)-(1*E*,5*Z*)-3-O-(((*p*-methoxyphenyl)methyl)oxy)-1-iodo-1,5-octadiene (**42** (R = PMB)) directly in one step. However, the reaction of **42** with 6.0 equiv of chromium chloride and 2.0 equiv of iodoform in tetrahydrofuran for 16 h at room temperature resulted in only a 11% yield of pure, but unstable, *trans*-iodo alkene **43**. White has reported the Takai olefination of both (*Z*)-4-decenal and (2*S*,4*Z*)-2-*O*-((*tert*-butyldiphenylsilyl)oxy)-4-decenal to give the *trans*-iodo alkenes in 95% yield in each case (after just 3 h at 0 °C) and a more modest 54% yield (after 18 h at 0 °C), respectively.[6a,b] Therefore, it appears that oxygen functionality in the substrate severely retards the desired reaction which in our case appeared to permit alternative reaction pathways to become competitive.

We then considered an alternative approach to a suitably protected *trans*-iodo alkene which would involve the intermediacy of alkyne **44**. The synthesis of alkynes directly from aldehydes has been described, where the anion of dimethyl (diazomethyl)phosphonate (Gilbert's reagent) is generated using potassium *tert*-butoxide at low temperature (−78 °C) in tetrahydrofuran.[47,48]

However, we decided to synthesize the desired alkyne **44** *via* a two-step process involving an intermediate dibromide **45**. Using a modification of the Corey−Fuchs procedure[49] (2.0 equiv of carbon tetrabromide, 4.0 equiv of triphenylphosphine, and *8.0 equiv of triethylamine* in dichloromethane at −78 °C), (3*R*,5*Z*)-3-*O*-((*p*-methoxyphenylmethyl)oxy)-1,1-dibromo-1,5-octadiene (**62** was synthesized in good yield (73%).[50−52] The reaction of dibromide **45** with 2 equiv of *n*-butyllithium in tetrahydrofuran at low temperature gave a mixture of compounds from which alkyne **44** was isolated in 71% yield. The major impurity formed in this reaction (10% yield) was assigned as the 2,5-disubstituted 3,4-dihydrofuran derivative **46** based on the ^{1}H-NMR and mass spectral data. Intriguingly, **46** appeared to be diastereomerically pure since we did not observe any doubling of peaks in its ^{1}H-NMR spectrum. There is substantial evidence, that in common with our own experimental finding, to suggest that the mechanism involves initial metal−halogen exchange to give an α-halo-metallic compound. Dibromoalkenes have been reacted with alkyllithiums and then quenched at low temperature to produce mono bromoalkenes.[53] By allowing the α-halo-metallic compound to warm, then α-elimination of lithium bromide takes place and an alkylidene carbene **47** is produced.[54] Such species are known to undergo very rapid 1,2-



47

hydrogen shift to produce alkynes.[55,56a] However, alkylidene carbenes are also known to undergo intramolecular 1,5-insertion[57] as well as intermolecular insertion reactions.[58] It is the former intramolecular process that we believe results in the formation of the 3,4-dihydrofuran derivative **46**. Baird and colleagues have generated alkylidene carbenes from 1,1-dibromo-2-methyl alkenes.[54] Their results clearly provide evidence for the well known 1,2-migration step to give alkynes, as well as the intramolecular insertion of a carbenoid into a C(5)−H bond to yield 3,4-dihydrofuran ring systems.

Conventional PMB deprotection of **44** was smoothly achieved using DDQ,[30] to provide a crude sample of propargylic alcohol intermediate which was then silylated under standard conditions to give the *tert*-butyldiphenylsilyl derivative **48** in high yield (93%).

However, in view of the fact that the 71% yield for the transformation of PMB-protected dibromide **45** was not fully reproducible, we felt that the earlier introduction of the *tert*-butyldiphenylsilyl protecting group (before the alkyne was produced) would improve the overall efficiency of the synthesis of the desired left-hand fragment. Therefore dibromide **45** was now deprotected (DDQ) and then reprotected using *tert*-butyldiphenylsilyl chloride to give **49** in 92% overall yield (Scheme 4).

We now anticipated that the reaction of *tert*-butyldiphenylsilyl-protected dibromide **49** with 2 equiv of *n*-butyllithium would afford the desired alkyne **48** cleanly in high yield. However, **48** was isolated in a modest yield (67%). A substantial amount of nonpolar materials was

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also isolated after chromatography. Therefore, we examined the possibility of affecting a complete change in the mechanism of the dibromide to acetylene transformation. By adding at least 1 equiv of lithium diisopropylamide to the dibromide **49**, literature precedent suggested that the corresponding bromo alkyne should form *via* an *anti*-dehydrobromination reaction.[59] *In situ* metal−halogen exchange using an alkyllithium would then be expected to produce a terminal acetylene.

The addition of 1.5 equiv of lithium diisopropylamide to **49** at −78 °C in tetrahydrofuran followed by 2.2 equiv of *n*-butyllithium (1 equiv of *n*-butyllithium is required to neutralize the proton of diisopropylamine) afforded the desired alkyne **48** in 92% yield.[52]

Alkyne **48** was converted to (3*R*)-(1*E*,5*Z*)-3-*O*-((*tert*-butyldiphenylsilyl)oxy)-1-iodo-1,5-octadiene (**50**) using Schwartz's reagent (Cp_2ZrHCl) in tetrahydrofuran, and the resultant vinyl metal species was then treated with iodine.[43a] After chromatography, **50** was isolated in high yield (92%), but this material was contaminated with <8% of unreacted starting material. *trans*-Iodo alkene **50** was used directly without further purification due to the sensitivity of *iodo* alkenes to sunlight and acids.

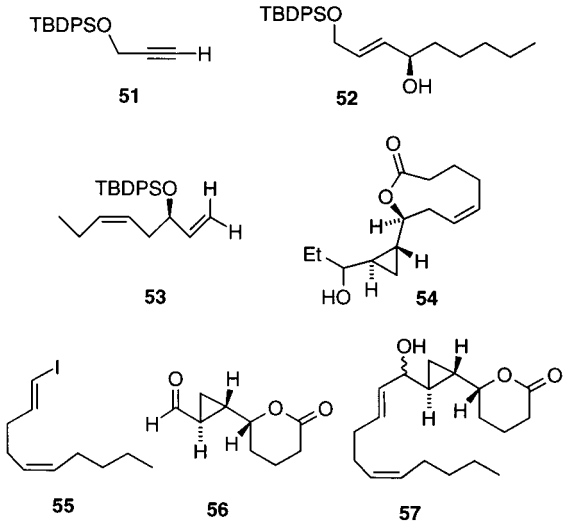
In summary, we were able to prepare *tert*-butyldiphenylsilyl-protected *trans*-iodo alkene **50** in 12 steps (24% yield) starting from (*R*)-malic acid.

The chromium(II) chloride/nickel(II) chloride methodology developed by Kishi[60a] and Takai[60b] has excellent precedent for its efficient application to the coupling reactions of *trans*-iodo alkenes with aldehydes. However, we believed that if high diastereoselectivity was to be observed in the coupling reaction, then the use of asymmetric catalysis would be essential.[61] The presence of the adjacent *trans* 1,2-disubstituted cyclopropane moiety in aldehyde **14** would prevent any inherent control in the coupling reaction, since the bulky lactone-containing substituent would be oriented away from the aldehyde functionality.

Oppolzer has reported that (*S*)-diphenyl(1-methylpyrrolidin-2-yl)methanol ((*S*)-DPMPM) directed the (1-alkenyl)zinc/aldehyde addition with excellent yields and enantiomeric excesses, and we were able to show that we could successfully repeat this work. By closely following the reported reaction conditions, we were able to synthesize the allylic alcohol from the coupling of oct-1-yne and heptaldehyde using 1 mol % of (*S*)-DPMPM in 79% yield.[62] We then introduced oxygen functionality into our model substrate by preparing *tert*-butyldiphenylsilyl-protected propargyl alcohol **51**. Unfortunately, however, we were not unable to isolate any of the desired allylic alcohol. Oxygen functionality in substrates as well as oxygen-containing solvents can interfere with the desired asymmetric alkenyl transfer reaction. Bulky silyl ethers such as *tert*-butyldiphenylsilyl or triisopropylsilyl ethers have been shown to diminish the chelating ability of the oxygen functionality in the presence of certain organometallic reagents.[63]

In 1994, Wipf and Xu reported that allylic alcohols could be prepared via a hydrozirconation reaction of an alkyne followed by transmetalation with dimethyl- or diethylzinc and subsequent addition of the (1-alkenyl-)ethylzinc species to an aldehyde.[62c] They were able to show that a modest enantiomeric excess could be achieved in the coupling of hex-1-yne with benzaldehyde in the presence of 8 mol % of the proline-derived ligand (*S*)-DPMPM. The reaction was tolerant to *tert*-butyldiphenylsilyl ethers and ester functionality. We were pleased to find that application of this methodology, in the absence of directing ligand (*S*)-DPMPM, enabled us to react the oxygen-containing model substrate **51** with hexanal to produce racemic allylic alcohol **52** in 51% yield.

However, the reaction of **48** with **14** afforded none of the desired allylic alcohol product under the reaction conditions used to synthesize **52**. The crude ^{1}H-NMR spectrum indicated that the hydrozirconation reaction had proceeded smoothly since almost all of the alkyne **48** had been consumed, but it had simply been converted to its alkene derivative **53**. It appeared that aldehyde **14** reacted with excess diethylzinc to give the alcohol product **54**.



Organochromium-mediated transformations were now investigated.[60] It has been established that the stereochemistry of a disubstituted *trans*-iodo olefin is retained in the Cr(II)/Ni(II)-coupled product and that dimethyl sulfoxide solvent is critical; a substantial amount of an α,β-unsaturated aldehyde was isolated if DMF or mixtures of DMF and DMSO were used. However it was noted that reactions were generally faster in DMF or DMF/DMSO mixtures whereas the use of DMSO alone resulted in fewer byproducts.

The synthesis of the related natural product **7** was reported in 1993 by White.[6a] One of the key steps in the synthesis is the Takai−Kishi coupling of *trans*-iodo

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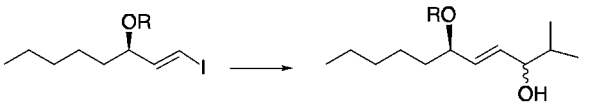
(60) (a) Jin, H.; Uenishi, J.; Christ, W. S.; Kishi, Y. *J. Am. Chem. Soc.*, **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.*, **1986**, *108*, 6048.

(61) (a) Cintas, P. *Synthesis*, **1992**, 248. (b) Hodgson, D. M. *J. Organomet. Chem.*, **1994**, *476*, 1. (c) Kishi, Y. *Pure Appl. Chem.*, **1992**, *64*, 343. During the course of our work Kishi published in detail on his attempts to design an efficient chiral ligand for the Ni(II)/Cr(II) coupling reaction. To date the best ligand is based on a 2,2′-dipyridyl ring system, which has only produced modest levels of diastereoselection in chosen coupling reactions. (d) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.*, **1995**, *60*, 5386.

(62) (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.*, **1991**, *32*, 5777. (b) Oppolzer, W.; Radinov, R. N. *Helv. Chem. Acta*, **1992**, *75*, 170. (c) Wipf, P.; Xu, W. *Tetrahedron Lett.*, **1994**, *35*, 5197. (d) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1257. (e) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.*, **1993**, *115*, 1593. (f) Oppolzer, W.; Radinov, R. N.; Brabander, J. N. *Tetrahedron Lett.*, **1995**, *36*, 2607.

(63) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.*, **1992**, *114*, 1778.

Scheme 5



Reagents and conditions: (a) 1 eq. *i*-PrCHO, (3 eq. **39**/**40**, 6 eq. $CrCl_2$, cat. $NiCl_2$, DMSO, rt.

alkene **55** with aldehyde **56**. A 1:1 mixture of allylic alcohols **57** resulted from the coupling reaction. This result confirmed our suspicions that the *trans* cyclopropane ring prevents any inherent stereocontrol in the coupling reaction.

We therefore expected that any diastereocontrol in the coupling of *trans*-iodo alkenes **39** and **50** with aldehyde **14** would have to come from the enantiomerically pure vinylic anion species. This is obviously disfavored due to the remote location of the chiral centre in the *trans*-iodo olefin. In order to determine to what extent the (3*R*)-ether center of the *trans*-vinylic chromium species could control the addition, we reacted *trans*-iodo alkenes **40** and **39** with a prochiral aldehyde, 2-methylpropanal (Scheme 5). We isolated the (*p*-methoxyphenyl)methyl-protected allylic alcohol **58** as a 1:1 mixture of diastereomers, whereas a 2.1:1 mixture of allylic alcohol diastereomers **59** was isolated in the latter case (major product relative configuration not determined). The differently protected allylic alcohols **58** and **59** were both isolated in quantitative yield following the experimental conditions reported by Kishi.[60a]

We applied this methodology to the synthesis of halicholactone (**2**) (Scheme 6). The reaction of 1.0 equiv of aldehyde **14** with 1.7 equiv of *trans*-iodo alkene **39** in the presence of 3.3 equiv of chromium(II) chloride (containing 0.5 wt % $NiCl_2$) provided the desired allylic alcohol **60** as a 2:1 mixture of diastereomers in good yield (73%). The two diastereomers **60a** (major) and **60b** (minor) were partially separated by repeated chromatography so that the major isomer **60a** was isolated in 44% yield. With **60a** in hand, we attempted the final deprotection step which would give, if this diastereomer possessed the correct relative stereochemistry at C_{12}, enantiomerically pure halicholactone (**2**). This reaction required surprisingly vigorous conditions; the reaction of **60a** with 2.5 equiv of TBAF in THF at reflux for 3 h gave the desilylated product in almost quantitative yield (99%). The 400 MHz ^{1}H-NMR (in C_6D_6) and 125 MHz ^{13}C-NMR (in $CDCl_3$) spectra for this compound exactly matched the data reported for halicholactone (**2**). The optical rotation of our product, $[\alpha]^{18}_D = -91.7$ (*c* 0.29 in chloroform), corresponded well with the literature value, $[\alpha]^{23}_D = -85.4$ (*c* 1.16 in chloroform).

We were able to confirm unequivocally that we had synthesized halicholactone (**2**) and not the C_{12}-epimer by performing the following transformations. The reaction of 1.2 equiv of **39** with 2.13 equiv of *tert*-butyllithium followed by aldehyde **14** provided the coupled product **60** in disappointing yield, 28%, but with improved diastereoselectivity, **60a**:**60b** ratio of 3.2:1. It was likely that the vinyllithium anion was quenched by abstraction of an α-hydrogen from aldehyde **14** at a competitive rate to which it was adding to the aldehyde center. While we were able to separate the diastereomers **60a** and **60b** by flash chromatography, both of these compounds were contaminated by unreacted aldehyde **14**. Therefore, we chose to recombine the two mixtures of compounds and subject the mixture to pyridinium chlorochromate oxidation. In doing so we hoped to be able to recover the pure aldehyde **14**, while the alcohols would be converted to a single compound, enone **61**. In the event, we were able to recover 87% of **14** and isolated enone **61** in 54% yield from the oxidation reaction after chromatography.

The reaction of enone **61** with 3.0 equiv of tetrabutylammonium fluoride in tetrahydrofuran at room temperature gave the desired product **62** in 81% yield after just 1 h. In view of this, the desilylation of **60a** was slow due to a retardation effect caused by the presence of the proximal C_{12} hydroxyl group. We reduced **62** by employing Luche conditions[64] and isolated halicholactone (**2**) and its C_{12} epimer **63** as a 1:1 mixture of diastereomers in a modest 40% yield. The reaction confirmed our suspicions that carbonyl reduction adjacent to the *trans*-cyclopropane ring would not be a diastereoselective process, and this was in keeping with other literature reports on related systems.[65] Importantly, the 400 MHz ^{1}H-NMR spectrum of the 1:1 mixture of diastereomers (**2** and **63**) provided conclusive evidence that the isomerically pure compound we had earlier isolated by direct desilylation of **60a** was halicholactone (**2**). The signals which belonged to **63** in the 400 MHz ^{1}H-NMR of the 1:1 mixture could be determined by subtraction of the signals that we knew belonged to **2**.

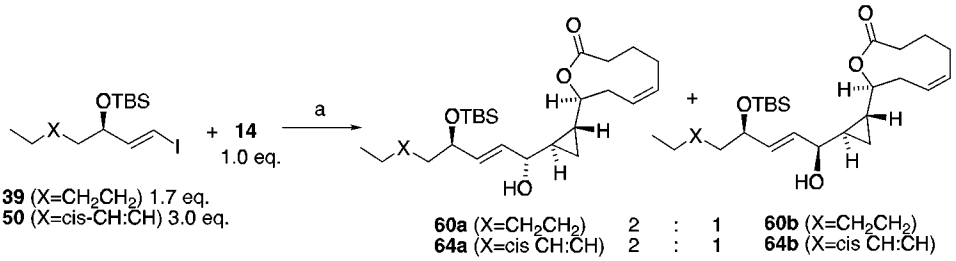
We have therefore completed a convergent 20-step synthesis of halicholactone (**2**) in 3.1% overall yield starting from commercially available materials.

The synthesis of neohalicholactone (**1**) (Scheme 6) now became relatively straightforward since we could draw on the knowledge we had earlier gained in the synthesis of **2**. The coupling of 1 equiv of aldehyde **14** with 2 equiv of *trans*-iodo alkene **50** mediated by 6 equiv of chromium(II) chloride (containing 0.5 wt % $NiCl_2$) gave as before a 2:1 mixture of diastereomers **64a** and **64b** which were isolated in 61% yield. Due to solubility problems, this reaction was carried out in a 1:1 mixture of DMSO and DMF, and the full consumption of aldehyde **14** was observed after just 3 h at room temperature.

A small amount (22 mg) of the 2:1 mixture of diastereomers **64a** and **64b** was desilylated with 3.0 equiv of tetrabutylammonium fluoride in tetrahydrofuran at reflux for 2 h to give a mixture of neohalicholactone **1** and the C_{12}-epimer of neohalicholactone **65** in 90% yield. From the 400 MHz ^{1}H-NMR spectrum (in C_6D_6) of this diastereomeric mixture, it was clear that the major compound, a result of the mildly selective coupling reaction, was most likely to be **1**. The distinguishing features of the ^{1}H-NMR spectrum were the signals that belonged to the C_{10} cyclopropane protons and the C_{12} proton. In the original 500 MHz ^{1}H-NMR data of the authentic sponge-derived **1**, these signals were found at 0.27 (H_{10a}, ddd, $J = 8.5, 5.0, 5.0$), 0.45 (H_{10b}, ddd, $J = 8.5, 5.0, 5.0$), and 3.52 (H_{12}, m), respectively. Our 400 MHz ^{1}H-NMR spectrum clearly showed that it was the major isomer **1** that was in excellent agreement with this published data: 0.31 (H_{10a}, ddd, $J = 8.6, 5.2, 5.2$), 0.51 (H_{10b}, ddd, $J = 8.9, 5.2, 5.2$), and 3.58 (H_{12}, dd, $J = 6.7, 3.4$). The agreement for the minor isomer **65** was less consistent with the published data for neohalicholactone;

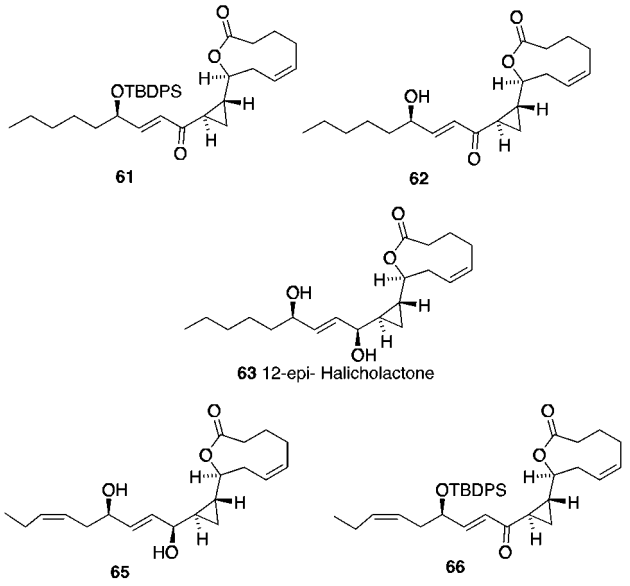
(64) Luche, J.-L. *J. Am. Chem. Soc.*, **1978**, *100*, 2226.
(65) Delanghe, P. H. M.; Lautens, M. *Tetrahedron Lett.*, **1994**, *35*, 9513.

Scheme 6



Reagents and conditions; (a) for **39**; 3.3 eq. $CrCl_2$, cat. $NiCl_2$, DMSO/DMF (1:1), rt; 73%, for **50**; 6.0 eq. $CrCl_2$, cat. $NiCl_2$, DMSO/DMF (1:1), rt; 61%.

0.31 (H_{10a}, m), 0.42 (H_{10b}, ddd, J = 8.6, 4.9, 4.9), and 3.50 (H_{12}, dd, J = 6.7, 3.4). Therefore, we returned to our diastereomeric mixture of **64a** and **64b** and separated them, and the major compound **64a** was desilylated to provide a pure sample of neohalicholactone (**1**) (74%). From our pure sample of **1**, we obtained an identical 500 MHz ^{1}H-NMR (in d_6-benzene) spectrum and 125 MHz ^{13}C-NMR (in $CDCl_3$) spectrum to those generously supplied by Professor K. Yamada for the sponge-derived sample of **1**. The optical rotation we obtained, $[\alpha]^{18}_D = -54.6$ (*c* 0.76 in chloroform), was also in excellent agreement with the literature value, $[\alpha]^{16}_D = -54.2$ (*c* 0.73 in chloroform). Finally, in an attempt to convert the otherwise wasted C_{12}-epimer **64b** into **64a** we performed the following reactions. The minor isomer **64b** (containing a small amount of **64a**) was oxidized to **66** using 5 mol % TPAP/1.5 equiv of NMO conditions in 91% yield. However, the reduction of the carbonyl group in **66** under Luche conditions[68] returned a 3:1 mixture of **64b**:**64a** (58%). The undesired isomer, **64b**, was unfortunately the diastereomer which formed in excess.



Therefore in summary, we have completed the first total synthesis of an enantiomerically pure sample of **1**. The convergent synthesis was achieved in 30 steps and 0.65% overall yield starting from commercially available materials, (*R*)- and (*S*)-malic acid. The total synthesis of **1** and **2** unambiguously confirmed that the relative stereochemistry of both these *Halichondria okadai* metabolites is 8*S*,9*R*,11*R*,12*R*,15*R*, as had been assigned by Yamada and Clardy[2] at the outset of this project.

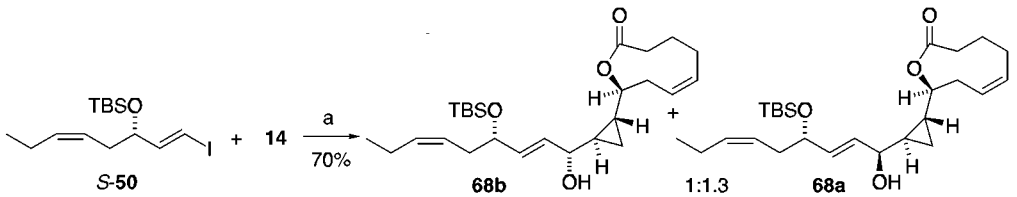
Concomitant with the publication of our results,[1b] White published a total synthesis of constanolactones A and B (**6a** and **6b**).[6b] A key step in this process was the Cr(II)/Ni(II)-mediated reaction of a vinyl iodide bearing a silyloxy group with aldehyde **56**, which gave a selectivity (2:1) in the same relative direction as our result. However, the final seemingly trivial task of removing the silyl protecting group from the addition products could not be achieved. It is interesting to note that this problem was solved by performing the chromium-mediated coupling reaction using the desilylated derivative of the vinyl iodide. The problematical final desilylation step reported by White is in keeping with our own findings.

In 1993, Gerwick and Proteau reported that the brown alga, *Laminaria sinclairii*, produced a variety of interesting oxylipins including several hydroxy-containing compounds including methyl (15*S*)-hydroxy-(5*Z*,8*Z*,11*Z*,13*E*,-17*Z*)-eicosapentaenoate and methyl (15*S*)-hydroxy-(11*Z*,13*E*,17*Z*)-eicosatetraenoate.[66] The isolation of these compounds suggests that *L. sinclairii* possesses an active lipoxygenase with positional specificity for C_{15} in C-20 substrates, and significantly that the C_{15} hydroxy center that is formed is of S stereochemistry. In December 1994, when we were approaching the completion of the synthesis of neohalicholactone (**1**), Gerwick and co-workers reported the isolation of "neohalicholactone" from *L. sinclairii*.[8] From spectroscopic analysis, Gerwick reported that his isolate of "neohalicholactone" was identical in every way, overall structure and relative and absolute stereochemistry, to neohalicholactone (**1**) isolated from the marine sponge *H. okadai*. The maximal difference in the ^{13}C-NMR was 0.1 ppm and in the ^{1}H-NMR it was 0.05 ppm. Further, the optical rotation value they had obtained for *L. sinclairii* derived material was $[\alpha]^{27}_D = -77$ (*c* 0.14 in chloroform). The corresponding value for the *H. okadai* derived material was $[\alpha]^{16}_D = -54.2°$ (*c* 0.73 in chloroform). Therefore, Gerwick and colleagues concluded that since the optical rotation value of the *L. sinclairii* derived material was not substantially different from the original value and of the same sign (negative rotation) that they had isolated an identical sample of neohalicholactone (**1**). Since the absolute stereochemistry of **1** had not been reported at this time (Yamada proved the absolute configuration of **2**), Gerwick's group went on to perform a conclusive degradative study which established the absolute stereochemistry at C_{15} of *L. sinclairii* derived "neohalicholactone".

This result was in keeping with other C_{15} hydroxyl metabolites from the same source. They concluded that

(66) Proteau, P. J.; Gerwick, W. H. *Lipids*, **1993**, *28*, 783.

Scheme 7

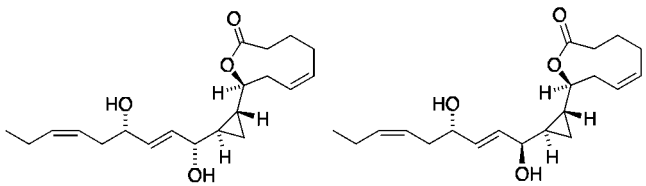


Reagents and conditions (a). 1.0 eq. **14**, 2.0 eq. *S*-**66**, 4.4 eq. $CrCl_2$ (containing 0.5 wt% $NiCl_2$), DMSO, 16 hr, RT, 70% yield, (b) (using a 5:1 mixture of **87a**:**87b**), 2.5 eq. TBAF (1m in THF), THF, reflux, 5 hr.

in both the algae- and sponge-derived neohalicholactone samples, the absolute stereochemistry was in fact (8*R*,9*S*,11*S*,12*S*,15*S*) and therefore opposite to that originally proposed. However, as already described in section 2.3, the (8*S*,9*R*,11*R*,12*R*,15*R*) sample of neohalicholactone (**1**) we had synthesized matched exactly every piece of spectroscopic data published for the original sponge-derived material, including most significantly the sign and magnitude of the optical rotation value.[1] Therefore, a curious disparity existed between our findings and those reported by Gerwick.[8] Since we knew the absolute stereochemistry of our starting materials and the relative configurations in the advanced intermediate **34** (X-ray), we considered the possibility that Gerwick had actually isolated a C_{15} epimer of neohalicholactone which possessed very similar spectroscopic properties to those of *H. okadai* derived neohalicholactone.

It was our belief that the $C_{13}-C_{14}$ *trans* olefin would form a natural break in the stereochemical information of the molecule such that inversion of stereochemistry at C_{15} would not significantly manifest itself in the ^{1}H- or ^{13}C-NMR spectra. Further, Gerwick had obtained his ^{1}H-NMR at 300 MHz and ^{13}C-NMR at 75 MHz, while we, in common with Yamada, performed our corresponding analyses at 500 MHz and 125 MHz, respectively. We believed that if Gerwick had isolated C_{15}-*epi*-neohalicholactone (**67**) then it would only be in the higher field ^{1}H-NMR spectrum that any differences between **67** and **1** would reveal themselves. We prepared a sample of **67** in order to test this. (3*S*)-(1*E*,5*Z*)-3-*O*-((*tert*-butyldiphenylsilyl))oxy)-1-iodo-1,5-octadiene (**50**) was prepared as previously described but starting from (*S*)-malic acid. The coupling of 2.0 equiv of *trans*-iodo alkene (S)-**50** and 1.0 equiv of aldehyde **14** was performed using 4.4 equiv of chromium(II) chloride (containing 0.5 wt % $NiCl_2$) in DMSO at room temperature over 16 h. A 1:1.3 mixture of isomers **68a** and **68b** resulted, and after careful separation of these isomers during five chromatography runs, the minor isomer **68b** was isolated in 24% yield which was unfortunately still contaminated with 17% of **68a**. However, the major isomer **68a** was isolated pure in 30% yield, while a further 16% yield of a 1:1 mixture of **68a**:**68b** was isolated. This implies that the overall yield for the coupling reaction was at least 70% (Scheme 7).

Encouragingly, the ^{1}H-NMR and ^{13}C-NMR of **68b**, the minor isomer of the coupling reaction, were in excellent agreement with those we had previously obtained for **64a** which had then been converted to **1**. The minor isomer would be expected, in this case, to be of *R* configuration at C-12 based on the known directing effect of **50**. Further, the data we obtained from **68a** were quite different from both **64a** and **68b**. Therefore we presumed that **68b** possessed the correct relative stereochemistry for the synthesis of C_{15}-*epi*-neohalicholactone (**67**). Compound **68b** (contaminated with 17% of **68a**) was desilylated using tetrabutylammonium fluoride and **67** (contaminated with 17% of C_{15},C_{12}-*epi*-neohalicholactone (**69**)) was isolated in 84% yield. We obtained 400 MHz and 270 MHz ^{1}H-NMR spectra of this 5:1 mixture of isomers (**67**:**69**), as well as a 67.8 MHz ^{13}C-NMR spectrum. From our proton NMR comparisons with the data Gerwick had compiled from a 300 MHz ^{1}H-NMR spectrum of *L. sinclairii* derived "neohalicholactone", it became apparent that the latter material could indeed be C_{15}-*epi*-neohalicholactone (**67**). Remarkably the ^{1}H-NMR and ^{13}C-NMR spectra of **67** and **1** were indistinguishable at the



quoted field strengths. Also, due to the 17% of **69** (of (8*S*,9*R*,11*R*,12*S*,15*S*) absolute stereochemistry) being present in the ^{1}H-NMR spectra, it was clear that this isomer did not closely match Yamada's and our own data for **1**. In order to obtain an accurate optical rotation value for our sample of **67**, the small amount of **69** contaminant was removed by very careful column chromatography purification. Our purified sample of **67** had an optical rotation value of $-84.9°$ (*c* 0.43 in chloroform). This value was of the same sign and similar magnitude to that reported for *L. sinclairii* derived "neohalicholactone", $-77.0°$ (*c* 0.14 in chloroform).[8] Finally we obtained a 500 MHz ^{1}H-NMR spectrum of **67** in d_6-benzene. Comparison of this spectrum with our 500 MHz spectrum of **1**, and that provided by Yamada for the sponge derived **1**, was quite illuminating. Every signal appeared to be identical in every respect (shape, size, position, and coupling constants) throughout the spectra of **67** and **1** *except* for the signals resulting from the C_{16} protons. The splitting pattern for the C_{16} protons in **67** was significantly more dispersed than that found in **1**.

Therefore, we found that 500 MHz ^{1}H-NMR was able to distinguish between **67** and **1**. However to date only a 300 MHz ^{1}H-NMR of *L. sinclairii* derived "neohalicholactone" exists. A 500 MHz ^{1}H-NMR of this material is subject to it being reisolated from more collections of *L. sinclairii* in the future. Therefore until this final ^{1}H-NMR experiment is performed we are only able to conclude that the *L. sinclairii* derived "neohalicholactone" is *probably* a C_{15}-epimer of the sponge derived material **1** that we originally synthesized. The biosynthetic implications of this conclusion, that two different marine organisms possess lipoxygenases with different enantiospecifities yet identical preferences for enantioselective

formation of the nine-membered lactone, which is presumably also an enzyme-controlled process, must remain the subject of future debate.

Experimental Section

Tetrahydrofuran and ether were freshly distilled from sodium using benzophenone as an indicator. Toluene was freshly distilled from sodium; dichloromethane from phosphorus pentoxide; acetonitrile, dimethyl sulfoxide, and hexane from calcium hydride. All the aforementioned solvents were distilled under an inert atmosphere of either argon or nitrogen. Reagents were either used as received, from commercial sources or purified by recognized methods.[67] Petroleum ether refers to that fraction which boils in the range 60−80 °C, and it was distilled prior to use as was ethyl acetate.

All reactions were carried out in vacuum-flame-dried Schlenk tubes under an argon atmosphere, unless otherwise stated.

Flash chromatography[68] was performed using Matrex normal phase silica, pore size 60 Å. All reactions were monitored by thin layer chromatography using aluminum sheets precoated with 250 nm silica gel and were visualized by UV light and then by potassium permanganate solution, phosphomolybdic acid solution, ninhydrin solution, or anisaldehyde solution.

(3*S*)-3-*O*-(((p-Methoxyphenyl)methyl)oxy)-γ-butyrolactone (23). To (3*S*)-hydroxy-γ-butyrolactone (5.41 g, 53.0 mmol) in dry dichloromethane (120 mL) and cyclohexane (50 mL) at room temperature under a nitrogen atmosphere was added PMB-trichloroacetimidate (13.2 mL, 63.6 mmol). After 5 min a catalytic amount of TfOH (14.0 μL, 0.16 mmol) was injected into the reaction mixture, and within a few minutes trichloroacetamide could be seen precipitating out of solution as the reaction progressed. After 2 h there was still starting material visible by thin layer chromatography, and therefore a further 2.0 mL (9.6 mmol) of (*p*-methoxyphenyl)methyl trichloroacetimidate was required to achieve full consumption of starting material. The reaction was quenched after a total reaction time of 3 h by adding solid $NaHCO_3$ until neutral pH was obtained. The mixture was then diluted with a solution of CH_2Cl_2 (100 mL):cyclohexane (50 mL) followed by suction filtration. The filter cake was washed with a 2:1 mixture of CH_2Cl_2 and cyclohexane (150 mL), and the solvent was removed from the organic washings under reduced pressure. The residue was purified by column chromatography on silica eluting with EtOAc/ hexane (1:2) to afford **23** (8.9 g, 75%) as a colorless oil. R_f 0.5 (2:1, hexane/EtOAc); $[\alpha]^{22}_D$ −18.1 (*c* 0.18, $CHCl_3$); IR (neat) 1780 (s, CO) cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 2.60 (1H, dd, *J* = 2.7, 18.0), 2.68 (1H, dd, *J* = 5.4, 18.0), 3.81 (3H, s), 4.34−4.40 (3H, m), 4.44 (1H, d, J_{AB} = 11.4), 4.48 (1H, d, J_{AB} = 11.4), 6.89 (2H, d, *J* = 8.6), 7.25 (2H, d, *J* = 8.6); ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ 34.9 (t), 55.2 (q), 70.9 (t), 72.5 (t), 73.5 (d), 113.8 (d), 128.7 (s), 129.4 (d), 159.5 (s), 175.4 (s); MS (EI) *m*/*z* 222 (M^+, 15%), 121 (100); HRMS *m*/*z* 222.0903 (calcd for $C_{12}H_{14}O_4$ (M^+) 222.0892). A side product was identified as (2*S*)-2-*O*-(((*p*-methoxyphenyl)methyl)oxy)-γ-butyrolactone; IR (neat) 1780 (s, CO) cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 2.17−2.31 (1H, m), 2.39−2.47 (1H), 3.81 (3H, s), 4.15 (1H, t, *J* = 7.7), 4.20−4.24 (1H, m), 4.36−4.44 (1H, m), 4.67 (1H, d, J_{AB} = 11.4), 4.86 (1H, d, J_{AB} = 11.4), 6.89 (2H, d, *J* = 8.5), 7.31 (2H, d, *J* = 8.5); MS (EI) *m*/*z* 222 (M^+, 5%), 137 (82), 121 (100). An alternative procedure used to obtain **23** was as follows: To (3*S*)-hydroxy-γ-butyrolactone (3.70 g, 36.3 mmol) in dichloromethane (40 mL) under at argon atmosphere at room temperature was added (*p*-methoxyphenyl)methyl trichloroacetimidate (11.3 mL, 54.4 mmol) followed by solid camphorsulfonic acid (422 mg, 1.82 mmol). The reaction was stirred at room temperature for 16 h and then diluted with petroleum ether (100 mL), and the precipitate was removed by filtration. The filtrate was then washed saturated aqueous $NaHCO_3$ (40 mL) and the organic layer dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica, eluting with EtOAc/hexane (1:2). The product **23** (5.87 g, 73%) was isolated as a colorless oil.

(3*S*)-3-*O*-(((*p*-Methoxyphenyl)methyl)oxy)-γ-butyrolactol (22). To lactone **23** (2.00 g, 9.00 mmol) in dry toluene (60 mL) at −20 °C under a nitrogen atmosphere was added DIBAL-H (1.5 M, 6.6 mL, 9.9 mmol) slowly over a 5-min period (making sure that the internal temperature did not rise above −20 °C). After a few minutes the reaction was complete (by TLC analysis) and was quenched with H_2O (6.6 mL), and the solution was then warmed to rt. Solid $NaHCO_3$ and EtOAc (50 mL) were added sequentially, and the mixture was stirred vigorously for approximately 0.5 h. After this time the mixture was suction filtrated, and the filter cake was washed with EtOAc. The organic washings were evaporated under reduced pressure to give the crude lactol **22** (2.02 g, 100%), as a mixture of epimers (3:2) and as a colorless crystalline solid. R_f 0.3 (2:1, hexane/ethyl acetate). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3, H, 7.14. Found: C, 64.1; H, 7.16. IR (Nujol) 3419 (br, OH), 1780 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 1.84−2.20 (2H, m), 2.64 (0.4H, d, *J* = 2.8), 3.68 (0.6H, d, *J* = 11.2) 3.80 (1.2H, s), 3.81 (1.8H, s), 3.80−4.55 (5H, m), 5.42 (0.6H, dd, *J* = 5.0, 11.1), 5.68 (0.4H, dd, *J* = 2.7, 5.2), 6.87−6.90 (2H, m), 7.24−7.27 (2H, m); MS (FAB) *m*/*z* 247 ($[M+Na]^+$, 11%), 224 (M, 8%), 223 ($[M-1]^+$, 8%), 121 (100); HRMS Found: *m*/*z* 224.1046 (calcd for $C_{12}H_{16}O_4$ (M^+), 224.1049).

Methyl (8*S*,5*Z*)-8-*O*-(((*p*-Methoxyphenyl)methyl)oxy)-8,9-dihydroxynon-5-enoate (18 (R = PMB)). To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (**19**) (5.15 g, 11.62 mmol) in dry toluene (50 mL) at room temperature under an argon atmosphere was added sodium bis(trimethylsilyl)amide (20.3 mL, 20.3 mmol, 1.0 M solution in THF) slowly over 5 min at 0 °C. The solution was then stirred at rt for 0.5 h, and a red color developed, at which time the mixture was cooled to −78 °C. Then in a different reaction vessel, to a solution of lactol **22** (2.17 g, 6.89 mmol) in dry toluene (100 mL) at −78 °C under an argon atmosphere was added sodium bis(trimethylsilyl)amide (10.17 mL, 10.17 mmol, a new bottle as a 1.0 M solution in tetrahydrofuran) quite rapidly (*ca* 0.5 min). The solution now containing the sodium alkoxide of **22** was stirred for 15 min at −78 °C. The phosphonium ylide was then transferred *via* cannula into the sodium alkoxide solution of **22** over a 20 min period while both mixtures were kept at −78 °C. After the addition, the resultant red solution was left at −78 °C for 5 min and allowed to warm to 0 °C over 45 min. At this time the solution was a pale yellow color, and TLC analysis indicated that full consumption of starting material had occurred. The reaction mixture was quenched by adding MeOH (20 mL) and 5% HCl (10 mL) at −60 °C. After warming to room temperature, CH_2Cl_2 (150 mL) and more 5% HCl (enough to make the solution pH 2−3) were added, and the two layers were then separated. The aqueous solution was further extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4. After the solvent had been evaporated at reduced pressure, the residue was dissolved in MeOH (20 mL), and a MeOH/AcCl (30 mL: 0.5 mL) mixture was then added until the reaction mixture was at pH 4 and slow conversion to the methyl ester could be monitored by TLC. After 3.5 h the solvent was removed under reduced pressure and the residue purified by column chromatography on silica eluting with EtOAc:petroleum ether (1:1). The product **18** (R = PMB) (2.15g, 69%) was a colorless oil. R_f 0.5 (2:1, hexane/EtOAc). Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.1; H, 8.15%. Found: C, 67.0; H, 8.07. $[\alpha]^{22}_D$ +23.3 (*c* 0.24 in $CHCl_3$); IR (neat) 3440 (br, OH), 1740 (s, CO) cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 1.69 (2H, pentet, *J* = 7.5) 2.05−2.11 (2H, m) 2.29−2.35 (4H, m), 3.48−3.52 (2H, m), 3.60−3.65 (1H, m) 3.66 (3H, s, OCH_3), 3.80 (3H, s), 4.47 (1H, d J_{AB} = 11.2), 4.60 (1H, d, J_{AB} = 11.2), 5.40−5.50 (2H, m), 6.88 (2H, d, *J* = 8.5), 7.27 (2H, d, *J* = 8.5); ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ 24.7 (t), 26.6 (t), 28.7(t), 33.4 (t), 51.5 (q, OCH_3), 55.2 (q, OCH_3), 64.0 (t), 71.2 (t), 79.1 (d), 113.9 (d), 125.7 (d), 130.1 (d), 130.4 (s), 131.1 (d, olefinic *C*H), 159.3 (s), 174.0 (s, C=O); MS (FAB) *m*/*z* 407/409 ($[M+Rb]^+$, 5%), 323 ($[M+H]^+$, 6%), 250 (5), 241 (11), 185 (4), 154 (10), 137 (15), 121 (100), 93 (14).

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Oxidation of 34 (R = PMB) To Give Aldehyde 25. A solution of oxalyl chloride (0.65 mL, 7.45 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C under an argon atmosphere, and a solution of DMSO (1.06 mL, 14.9 mmol) in CH_2Cl_2 (15 mL) was added over a 5-min period *via* a dropping funnel. Stirring was continued at −78 °C for 10 min followed by addition of **18** (R = PMB) (2.0 g, 6.21 mmol) over *ca*. 5 min. The reaction mixture was stirred for 15 min, and triethylamine (4.3 mL, 31.1 mmol) was added with stirring at −78 °C. The cooling bath was then removed, and water (20 mL) was added at room temperature. Stirring was continued for 10 min, and the two layers were then separated. The aqueous phase was extracted with dichloromethane (3 × 30 mL), the organic layers were combined and dried over anhydrous magnesium sulfate, and the solvent was evaporated to give crude aldehyde **25** (1.99 g, quantitative yield) as a pale yellow colored oil which was used directly in the next step.

(*E*)-γ-Alkoxy-α,β-unsaturated *tert*-Butyl Ester (26). To a stirred suspension of LiCl (316 mg, 7.45 mmol) in MeCN (40 mL) at rt under an argon atmosphere was added *tert*-butyl diethylphosphonoacetate (2.33 mL, 9.94 mmol), DBU (0.93 mL, 6.21 mmol), and finally a solution of aldehyde **25** (1.99 g, 6.21 mmol) in dry MeCN (40 mL). The reaction mixture was stirred at rt for 5 h at which time it was quenched by adding H_2O (30 mL). The aqueous layer was then extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$. After the solvent had been evaporated at reduced pressure, the residue was purified by column chromatography on silica eluting with hexane−EtOAc (6:1). Product **26** (1.95g, 75% for the two steps from **18** (R = PMB)) was a colorless oil. R_f 0.6 (5:1, hexane/EtOAc); $[\alpha]^{21}_D$ -35.2 (*c* 0.05 in $CHCl_3$); IR (neat) 1740 (s, CO), 1720 (s, CO) cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 1.50 (9H, s), 1.65 (2H, pentet, *J* = 7.4), 2.01−2.07 (2H, m), 2.28 (2H, t, *J* = 7.5), 2.32−2.41 (2H, m), 3.66 (3H, s), 3.81 (3H, s), 3.92 (1H, q, *J* = 6.5), 4.32 (1H, d, J_{AB} = 11.5), 4.52 (1H, d, J_{AB} = 11.5), 5.40−5.47 (2H, m), 5.92 (1H, d, *J* = 15.7), 6.73 (1H, dd, *J* = 6.6, 15.6), 6.87 (2H, d, *J* = 8.5), 7.25 (2H, d, *J* = 8.5; ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ 24.7 (t), 26.8 (t), 28.1 (q), 32.9 (t), 33.5 (t), 51.5 (q), 55.3 (q), 70.7 (t), 77.6 (d), 80.5 (s), 113.8 (d), 124.1 (d), 125.3 (d), 129.3 (d), 130.2 (s), 131.2 (d), 146.6 (d), 159.2 (s), 165.5 (s), 174.0 (s); MS (FAB) *m*/*z* 505/503 ($[M + Rb]^+$, 5%), 419 ($[M + H]^+$, 2%), 363 (3), 241 (6), 207 (4), 154 (4), 137 (7), 121 (100); HRMS *m*/*z* 419.2423 (calcd for $C_{24}H_{34}O_6$ ($M^+ + 1$) 419.2434).

Cyclopropanation Reaction To Give 27 as a Mixture of *Trans*-Diastereomers. Dimethylsulfoxonium methylide (2.2 equivs generated from trimethylsulfoxonium iodide, 757 mg, 3.44 mmol, and sodium hydride (138 mg, 5.73 mmol, 60% dispersion in mineral oil) in dry DMSO (6 mL) at rt was treated with *tert*-butyl ester **26** (720 mg, 1.72 mmol) in DMSO (6 mL). The mixture was stirred for 0.5 h at rt and then 20 h at 90 °C. The reaction was then quenched at rt by adding saturated aqueous NH_4Cl (10 mL). The product was extracted with EtOAc, the combined organic extracts were dried with anhydrous Na_2SO_4, and the solvent was evaporated at reduced pressure. The crude residue was then purified by column chromatography on silica eluting with EtOAc/hexane (1:6) which gave **27** (550 mg, 74%) as a colorless oil. The product was a 5:2 mixture of inseparable but exclusively *trans*-diastereomers where the major diastereomer contained the desired relative stereochemistry (8*S*,9*R*,11*R*). R_f 0.5 (6:1, hexane/ethyl acetate). Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.4; H, 8.33%. Found: C, 68.9; H, 8.54. Reverse phase HPLC (75% to 95% MeOH/25% to 5% H_2O + 0.1% trifluoroacetic acid) retention time 5.4 min, 95% pure; IR (neat) 1740 (s, CO), 1720 (s, CO) cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) *major isomer*, δ 0.62−1.55 (4H, m), 1.45 (9H, s), 1.69 (2H, pentet, *J* = 7.4), 2.05−2.11 (2H, m), 2.30 (2H, t, *J* = 7.4), 2.35−2.42 (2H, m), 2.91 (1H, q, *J* = 6.5), 3.66 (3H, s), 3.80 (3H, s), 4.45−4.58 (2H, m), 5.40−5.60 (2H, m), 6.86−6.88 (2H, m), 7.23−7.26 (2H, m), *minor isomer* (360 MHz, $CDCl_3$) δ 1.43 (9H, s), 3.00 (1H, q, *J* = 6.5) all other peaks were coincidental with the *major isomer*; ^{13}C-NMR (67.8 MHz, $CDCl_3$) *major isomer* δ 10.8 (t), 20.2 (d), 24.7 (t), 25.4 (d), 26.6 (t), 28.1 (q), 32.8 (t), 33.4 (t), 51.4 (q), 55.2 (q), 70.6 (t), 79.2 (d), 80.1 (s), 113.7 (d), 126.3 (d), 129.0 (d), 130.5 (d), 130.6 (s), 159.1 (s), 172.9 (s), 173.9 (s), *minor isomer* δ 13.1 (t), 18.3 (d), 24.7 (t), 25.1 (d), 26.6 (t), 28.1 (q), 32.7 (t), 33.4 (t), 51.4 (q), 55.2 (q), 70.3 (t), 79.3 (d), 80.1 (s), 113.7 (d), 126.2 (d), 129.0 (d), 130.5 (d), 130.6 (s), 159.1 (s), 172.9 (s), 173.0 (s); MS (FAB) *m*/*z* 433 ($[M + H]^+$, 2%), 377 ($[M - {}^tBu]^+$, 3%), 239 (6), 189 (5), 137 (6), 121 (100), 57 (8).

DDQ Deprotection of 37 and Subsequent Separation of Isomers 28 and 29. To **27** (2.13 g, 4.93 mmol) in a CH_2Cl_2/H_2O mixture (30 mL:1.6 mL) was added solid DDQ (1.23 g, 5.42 mmol) at room temperature. After 1 h the reaction was complete, and the solvent was evaporated. Complete separation of the two hydroxy isomers **28** and **29** required repeated column chromatography eluting with hexane/EtOAc (4:1). The products (combined yield of 1.54 g, 100%) were both oils where the major isomer **28** was isolated pure (1.06 g, 69%). $R_{f_{major}}$ 0.5 (5:1, hexane/ethyl acetate) and $R_{f_{minor}}$ 0.47 (5:1, hexane/EtOAc); *major isomer* **28** $[\alpha]^{21}_D$ −114.1 (*c* 0.7 in $CHCl_3$); IR (neat) 3500, 1740, 1720 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 0.79 (1H, ddd, *J* = 4.3, 6.2, 8.3), 1.08−1.13 (1H, m), 1.43 (9H, s), 1.47−1.57 (2H, m), 1.70 (2H, pentet, *J* = 7.4), 1.86 (1H, bs), 2.10 (2H, q, *J* = 7.2,), 2.30−2.34 (4H, m), 3.14 (1H, q, *J* = 6.6), 3.66 (3H, s), 5.45−5.56 (2H, m); ^{13}C-NMR δ (90.6 MHz, $CDCl_3$) 12.2 (t), 18.9 (d), 24.7 (t), 26.6 (t), 27.6 (d), 28.1 (q), 33.3 (t), 34.9 (t), 51.5 (q), 73.2 (d), 80.3 (s), 125.8 (d), 131.8 (d), 173.0 (s,), 174.1 (s); MS (FAB) *m*/*z* 313 ($[M + H]^+$, 47%), 257 (65), 239 (97), 221 (57), 189 (85), 57 (100); HRMS *m*/*z* 313.2012, (calcd for $C_{17}H_{29}O_5$ $(M + H)^+$ 313.2015). *minor isomer* **29**; $[\alpha]^{21}_D$ +30.4 (*c* 0.09 in $CHCl_3$); ^{1}H-NMR (360 MHz, $CDCl_3$) δ 0.89−0.94 (1H, m), 1.06−1.11 (1H, m), 1.44 (9H, s), 1.48−1.57 (2H, m), 1.70 (2H, pentet, *J* = 7.3), 2.11 (2H, q, *J* = 7.2), 2.31−2.40 (4H, m), 3.28 (1H, m), 3.67 (3H, s), 5.45−5.58 (2H, m); ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ 11.7 (t), 18.9 (d), 24.7 (t), 26.6 (t), 27.0 (d), 28.1 (q), 33.3 (t), 35.2 (t), 51.5 (q), 72.3 (d), 80.3 (s), 125.8 (d), 132.0 (d), 173.0 (s), 174.1 (s); MS (FAB) *m*/*z* 313 ($[M + H]^+$, 44%), 257 (47), 239 (100), 221 (54), 207 (16), 189 (75), 57 (97); HRMS *m*/*z* 313.2009 (calcd for $C_{17}H_{29}O_5$ $(M + H)^+$ 313.2015).

Ester Hydrolysis of 28 to Give a Hydroxy Acid Intermediate (20) Which was Subsequently Lactonized to 32. To (8*S*,9*R*,11*R*)-**28** (250 mg, 0.80 mmol) in a THF/H_2O/MeOH (4 mL:1 mL:1 mL) solution was added solid LiOH (67.0 mg, 1.60 mmol) at rt. After being stirred for 16 h, the mixture was quenched with 5% HCl (2 mL). The aqueous layer was then extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and then the solvent was removed under reduced pressure. The crude oil **30** (0.24 g, 100%) was used directly in the next step; IR (neat) 3500−2800, 1712 cm^{-1}, ^{1}H-NMR (360 MHz, $CDCl_3$) δ 0.80 (1H, ddd, *J* = 4.4, 6.3, 8.3), 1.10−1.15 (1H, m), 1.44 (9H, s), 1.49−1.60 (2H, m), 1.72 (2H, pentet, *J* = 7.3), 2.10−2.17 (2H, m), 2.35−2.43 (4H, m), 3.15 (1H, q, *J* = 6.5), 5.47−5.57 (2H, m), 5.50−6.00 (2H, bs). To a solution of crude 8*S*,9*R*,11*R*-hydroxy acid **30** (650 mg, 2.18 mmol) in THF (6 mL) under an argon atmosphere was added Et_3N (0.49 mL, 3.49 mmol) at rt with stirring for 10 min. Then at rt, 2,4,6-trichlorobenzoyl chloride (0.37 g, 2.40 mmol) was added slowly with stirring for 2 h. After dilution with toluene (60 mL) this solution was added (using a syringe pump) to excess DMAP (4.00 g, 32.7 mmol) in toluene (100 mL) at reflux over 6 h. After the addition had been completed, the reaction mixture was allowed to cool to rt and the solvent was then evaporated. The residue was purified by column chromatography on silica eluting with petroleum ether/EtOAc (10:1 to 5:1). The product **32** (460 mg, 75%) was isolated as a colorless oil. R_f 0.6 (10:1, petroleum ether/ethyl acetate). The only observed side product was the dimeric species (16.6 mg, 2.7%). R_f 0.4 (10:1, petroleum ether/ethyl acetate) . The dimer was formed in much larger quantities if the addition was too rapid or the mixture was too concentrated. (In the event of significant amounts of dimer being formed it was hydrolyzed back to the starting hydroxy acid). Monomer **32**: Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.6; H, 8.57%. Found: C, 68.5; H, 8.75. $[\alpha]^{21}_D$ −81.5 (*c* 0.01, $CHCl_3$); IR (neat) 1740 cm^{-1}; the assignment of all the proton and carbon signals was achieved using phase-sensitive ^{1}H−^{1}H COSY, normal ^{1}H−^{13}C correlation, and long-range ^{1}H−^{13}C correlation; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.80−0.86 (1H, m, cyclopropane C*H*H (10)),

1.13−1.18 (1H, m, cyclopropane CH*H* (10′)), 1.45 (9H, s, ^{t}Bu (14)), 1.60−1.68 (2H, m, 2 × cyclopropane C*H* (9+11)), 1.77 (1H, dddd, J = 6.5, 11.9, 11.9, 11.9, C*H*H (3)), 2.04−2.09 (2H, m, C*H*H and CH*H* (4) and (3′)), 2.13−2.18 (1H, m, -C*H*H- (7)), 2.22−2.26 (1H, m, -C*H*H-(2)), 2.29−2.36 (1H, m, -CH*H*-(2′)), 2.45−2.56 (2H, m, 2 × CH*H* (7′) and (4′)), 4.27 (1H, ddd, J = 1.5, 7.5, 10.9, C*H*OCO), 5.45−5.49 (2H, m, C*H*=C*H*); ^{13}C-NMR (125.8 MHz, $CDCl_3$) 12.5 (t, (10)), 19.6 (d, (9 or 11), 24.6 (d, (9 or 11)), 25.3 (t, (4)), 26.4 (t, (3)), 28.1 (q, (14)), 33.6 (t, (2)), 33.7 (t, (7), 74.6 (d, (8)), 80.5 (s, (13)), 124.4 (d, (6)), 134.9 (d, (5)), 172.7 (s, (12)), 174.0 (s, (1)); MS (GC/EIMS) *m/z* 224 (3), 207 (7), 110 (100), 82 (92), *m/z* (FAB) 281 ([M + H]$^+$, 32%), 225 (100), 207 ([M − ^{t}BuO$^-$]$^+$, 83%), 189 (43); HRMS *m/z* 281.1749 (calcd for $C_{16}H_{25}O_4$ (M + H)$^+$ 281.1753). Dimeric compound: IR (neat) 1723 (C=O) cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.77−0.88 (2H, m, 2 × cyclopropane C*H*), 1.12−1.18 (2H, m), 1.44 (18H, s), 1.55−1.73 (8H, m), 2.05−2.35 (10H, m), 2.50-2.59 (2H, m), 4.45−4.56 (2H, m), 5.30−5.50 (4H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 12.4 (t), 19.6 (d), 24.4 (d), 25.2 (t), 26.3 (t), 28.1 (q), 32.5 (t), 33.5 (t), 74.6 (d), 80.4 (s), 125.6 (d), 131.6 (d), 172.6 (s), 173.1 (s); MS (FAB) *m/z* 583 ([M + Na]$^+$, 16%), 561 ([M + H]$^+$, 11%), 449 (35), 225 (100), 207 (82); HRMS *m/z* 559.3285 (calcd for $C_{32}H_{47}O_8$ (M − 1)$^+$ 559.3271).

Hydrolysis of the Dimeric Compound. To the dimeric compound (56.0 mg, 0.10 mmol) in a 3:1:1 THF (1.0 mL), H_2O (0.3 mL), and MeOH (0.3 mL) mixture was added solid LiOH (17.0 mg, 0.4 mmol) in one portion. The resultant homogeneous solution was stirred at rt for 16 h. The reaction was quenched by adding 2 N HCl until pH 1−2 was obtained. The aqueous phase was extracted with EtOAc. The solvent was then removed from the combined organic extracts under reduced pressure to give the crude hydroxy acid **30** (50.3 mg, 84%).

Acid Hydrolysis of *tert*-Butyl Ester 32. To the lactone **32** (160 mg, 0.57 mmol) in CH_2Cl_2 (6 mL) at rt under an argon atmosphere was added CF_3SO_2H (1.5 mL) dropwise. The reaction was complete after 2 h, and the solvent was then removed under reduced pressure. To ensure all the CF_3SO_2H had been removed, toluene (4 mL) was added to the crude residue, and the solvent was again removed under reduced pressure. This process was then repeated several times to give a crude solid which was then crystallized from CH_2Cl_2 and cyclohexane to give (8*S*,9*R*,11*R*)-**34** (103 mg, 80%) as a colorless crystalline solid. {Some less pure material (22.2 mg, 17%) was also obtained by removal of the solvent under reduced pressure from the mother-liquor}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.14%. Found: C, 64.3; H, 7.44. $[\alpha]^{21}_D$ −238.0 (*c* 0.06, $CHCl_3$); IR (neat) 3300−2400, 1740 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.01 (1H, ddd, J = 4.6, 6.6, 8.1), 1.33 (1H, ddd, J = 4.8, 4.8, 9.0), 1.71−1.79 (3H, m), 2.00−2.10 (2H, m), 2.11−2.21 (1H, m), 2.23−2.37 (2H, m), 2.41−2.60 (2H, m), 4.31 (1H, ddd, J = 1.5, 7.5, 11.0), 5.42−5.55 (2H, m); ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ 13.5 (t), 18.2 (d), 25.3 (t), 26.0 (d), 26.3 (t), 33.4 (t), 33.7 (t), 74.2 (d), 124.1 (d), 135.0 (d), 173.9 (s), 179.4 (s); MS (ESI-LOOP, ammonium acetate) *m/z* 447 ((2M − H])$^+$, 99%), 283 ((M + OAc)$^+$, 100%), 223 ((M − H)$^+$, 59%. An X-ray crystal structure of **34** was obtained which confirmed the absolute stereochemistry. Suitable crystals for X-ray analysis were grown from a solution of hexane/EtOAc (10:1) over a two-week period.[1]

The Following Set of Experimental data was Compiled from the Minor 8*S*,9*S*,11*S* Cyclopropane Diastereomer 29. Yamaguchi Lactonization To Give 33. A similar procedure to that already described in the preparation of **32** was used. A crude sample of 8*S*,9*S*,11*S* hydroxy acid was prepared by basic hydrolysis of **31** (2.0 equiv of LiOH, THF:H_2O:MeOH (4:1:1), room temperature, 16 h, quantitative crude yield). Then to this crude sample of 8*S*,9*S*,11*S* hydroxy acid (461 mg, 1.55 mmol) in THF (10 mL), under an argon atmosphere, were added Et_3N (0.34 mL, 2.48 mmol) and 2,4,6-trichlorobenzoyl chloride (0.27 mL, 1.70 mmol) at rt and the resulting mixture was stirred for 2.5 h. The precipitate was then removed by filtration, and the filtrate was diluted with toluene (50 mL). This dilute solution was added (using a syringe pump) to excess 4-(dimethylamino)pyridine (2.83 g, 23.2 mmol) in toluene (100 mL) at reflux over 3 h. After the addition, the reaction mixture was allowed to cool to rt, and the solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (7:1). The product **33** (329 mg, 76%) was isolated as a colorless crystalline solid. R_f 0.6 (7:1, petroleum ether/ethyl acetate). $[\alpha]^{20}_D$ −2.1 (*c* 1.55, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (1H, ddd, J = 4.3, 6.4, 8.5), 1.12 (1H, ddd, J = 4.6, 4.6, 8.9), 1.45 (9H, s), 1.53 (1H, ddd, J = 4.6, 4.6, 8.5), 1.58−1.65 (1H, m), 1.77 (1H, dddd, J = 6.7, 11.9, 11.9, 11.9), 2.02−2.34 (5H, m), 2.44−2.54 (2H, m), 4.38 (1H, ddd, J = 1.2, 7.3, 10.7), 5.44−5.49 (2H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 12.5 (t), 19.2 (d), 24.4 (d), 25.3 (t), 26.4 (t), 28.1 (q), 33.5 (t), 33.8 (t), 74.1 (d), 80.6 (s), 124.4 (d), 134.8 (d, olefinic *C*H), 173.0 (s), 179.0 (s); MS (FAB) *m/z* 281 ([M + H]$^+$, 33%), 225 (100), 207 (85), 189 (45).

Acidic Hydrolysis of the *tert*-Butyl Ester in 33. To **33** (300 mg, 1.07 mmol) in CH_2Cl_2 (5 mL) at rt under an argon atmosphere was added freshly distilled CF_3SO_2H (1.5 mL) in CH_2Cl_2 (5 mL) dropwise. The reaction was complete after 2 h, and the solvent was then removed under reduced pressure. To ensure all the CF_3SO_2H had been removed, toluene (15 mL) was added to the crude residue, and the solvent was again removed under reduced pressure. This process was then repeated to give a crude residue which was purified by column chromatography on silica eluting with ethyl acetate/petroleum ether (1:1). The product **35** (191 mg, 80%) was isolated as a colorless oil. $[\alpha]^{21}_D$ −17.0 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.14. Found: C, 64.3; H, 7.25. IR (neat) 1736 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.07−1.14 (1H, m), 1.28 (1H, ddd, J = 4.8, 4.8, 8.8), 1.63 (1H, ddd, J = 4.4, 4.4, 8.4), 1.69−1.87 (2H, m), 2.00−2.37 (5H, m) 2.44−2.56 (2H, m), 4.40 (1H, ddd, J = 1.5, 7.3, 11.0), 5.40−5.54 (2H, m) 9.93 (1H, bs); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 13.6 (t), 18.0 (d), 25.2 (t), 25.7 (d), 26.3 (t), 33.6 (t), 33.7 (t), 73.8 (d), 124.1 (d), 134.9 (d), 173.9 (s), 179.6 (s); MS (CI-isobutane) *m/z* 225 ([M + H]$^+$, 15%), 207 ([M − OH]$^+$, 100%), 189 (60), 179 (5), 110 (32).

Selective Reduction of the Carboxylic Acid Functionality in the (8*S*,9*R*,11*R*) Isomer 34 To 8*S*,9*R*,11*R*-carboxylic acid **34** (67.3 mg, 0.30 mmol) in THF (1 mL) under an argon atmosphere at rt was added Et_3N (30.3 mg, 0.3 mmol), and the mixture was stirred for 5 min. After cooling the mixture to −5 °C, EtOCOCl (32.4 mg, 0.3 mmol) in THF (0.5 mL) was added dropwise. Stirring was continued at −5 °C for 0.5 h, and then the precipitated Et_3NHCl was filtered and washed with THF (2 mL). The mixed anhydride was then slowly added to a solution of $NaBH_4$ in H_2O (0.3 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 0.5 h and subsequently at rt until effervescence ceased (*ca*. 0.5 h). Addition of 2 N HCl (1 mL) followed, and the aqueous layer was repeatedly extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica eluting with EtOAc/petroleum ether (1:2). The product **36** (48.5 mg, 77%) was isolated as a colorless oil. R_f 0.4 (2:1, hexane/ethyl acetate); $[\alpha]^{20}_D$ −86.2 (*c* 1.75, $CHCl_3$) IR (neat) 1734 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.55−0.64 (2H, m), 0.94−1.04 (1H, m), 1.14−1.25 (1H, m), 1.75 (1H, bs), 1.70−1.85 (1H, m), 2.03−2.60 (7H, m), 3.45 (1H, dd, J = 7.2, 11.4), 3.52 (1H, dd, J = 6.6, 11.4), 4.19 (1H, ddd, J = 1.5, 8.4, 10.4), 5.41−5.53 (2H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 8.3 (t), 19.8 (d), 20.5 (d), 25.3 (t), 26.5 (t), 33.7 (t), 33.8 (t), 66.0 (t), 76.4 (d), 124.7 (d), 134.6 (d), 174.1 (s); *m/z* (GC/EIMS) 282 ([M − H + TMS]$^+$, 1%), 182 ([M − H_2O]$^+$, 5%), 110 (100), 82 (85), and *m/z* (FAB) 233 ([M + Na]$^+$, 100%), 211 ([M + H]$^+$, 71%), 193 ([M + H − H_2O]$^+$, 85%).

Aldehyde 14. To (8*S*,9*R*,11*R*) alcohol **36** (60.0 mg, 0.29 mmol) in CH_2Cl_2 (3 mL, containing powdered molecular sieves) under an argon atmosphere at rt was added NMO (50.2 mg, 0.43 mmol) followed by TPAP (5.0 mg, 0.014 mmol). The mixture was stirred at rt for 20 min and then filtered directly down a silica column eluting with petroleum ether/EtOAc (2:1). The product **14** (59 mg, quantitative yield) was isolated as a colorless oil. R_f 0.7 (10:3, petroleum ether/ethyl acetate); IR (neat) 1730 (CO + CHO) cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.12 (1H, ddd, J = 4.9, 6.4, 8.4), 1.36−1.43 (1H, m), 1.69−

1.85 (2H, m), 1.98−2.58 (8H, m), 4.35 (1H, ddd, J = 1.7, 7.9, 11.0), 5.41−5.54 (2H, m), 9.24 (1H, d, J = 4.6). Aldehyde **14** was used directly in the next step.

(*R*)-3-*O*-((*tert*-Butyldiphenylsilyl)oxy)-1-octyn-3-ol (37). To (*R*)-(+)-octyn-3-ol (0.58 mL, 3.96 mmol) in DMF (10 mL) under an argon atmosphere at rt was added imidazole (0.67 g, 9.90 mmol). Once the imidazole had dissolved, TBSCl (1.24 mL, 4.75 mmol) was added slowly over a 5 min period. The reaction mixture was then stirred at rt for 3 h and then quenched with ice. The two layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography on silica eluting with EtOAc/petroleum ether (1:10). The product **37** (1.29 g, 89%) was a colorless oil. R_f 0.6 (neat petroleum ether). Anal. Calcd for $C_{24}H_{32}OSi$: C, 79.1; H, 8.80. Found C, 78.9; H, 9.00. $[\alpha]^{20}_D$ +39.2 (*c* 0.66 in $CHCl_3$); IR (neat) 2361 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 6.6), 1.09 (9H, s), 1.17−1.70 (8H, m), 2.31 (1H, d, J = 2.01), 4.32 (1H, dt, J = 2.2, 6.2), 7.35−7.47 (6H, m), 7.68−7.77 (4H, m); MS (FAB) *m*/*z* 365 ($(M + H)^+$, 13%), 319 (15), 308 ($(M + H - {}^tBu)^+$, 85%), 237 (41), 207 (100), 199 (92).

(*R*,*E*)-((*tert*-Butyldiphenylsilyl)oxy)-1-iodo-octen-3-ol (39). To **37** (255 mg, 0.70 mmol) in degassed THF (5 mL) at rt under an argon atmosphere was added bis(cylopentadienyl)zirconium chloride hydride (266 mg, 0.91 mmol) rapidly. Once a homogeneous solution had formed, we analyzed the reaction by TLC which indicated that all the starting material had been consumed. Therefore iodine (212 mg, 0.84 mmol) was added, and the solution was stirred at rt for 30 min. Then an equal volume of saturated aqueous NH_4Cl and Et_2O were added, the two layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed at reduced pressure. The residue was then purified by column chromatography on silica, eluting with neat petroleum ether. The product **39** (322 mg, 94%) was a colorless oil. R_f 0.8 (neat petroleum ether). Anal. Calcd for $C_{24}H_{33}OSiI$: C, 58.5; H, 6.70. Found C, 58.4; H, 6.9. $[\alpha]^{20}_D$ +79.8 (*c* 0.48 in $CHCl_3$); IR (neat) 1607 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 6.6), 1.06 (9H, s), 1.03−1.47 (8H, m), 4.06 (1H, qm, J = 6.6), 5.90 (1H, dd, J = 1.0, 14.5), 6.45 (1H, dd, J = 6.8, 14.5), 7.34−7.46 (6H, m), 7.60−7.67 (4H, m); MS (FAB) *m*/*z* 492 ($[M]^+$, 0.5%), 491 ($(M - H)^+$, 2.5%), 435 (26), 415 (16), 365 ($(M - 1)^+$, 8%), 309 (40), 199 ($(Ph_2SiOH)^+$, 100%).

(3*R*)-3-*O*-((*p*-Methoxyphenyl)methyl)oxy)-1-octyn-3-ol (38). NaH (190 mg, 4.75 mmol, 60% dispersion in mineral oil) was washed twice with petroleum ether in order to remove the mineral oil. The remaining NaH was then dried at reduced pressure prior to the reaction. To the solid NaH was added DMF (8 mL) followed by the slow addition of (*R*)-(+)-1-octyn-3-ol (0.58 mL, 3.96 mmol) at 0 °C under an argon atmosphere. The reaction was left at 0 °C until the effervescence had ceased (*ca*. 30 min), and then tetrabutylammonium iodide (73.0 mg, 0.20 mmol) and 4-methoxybenzyl chloride (0.59 mL, 4.36 mmol, freshly distilled) were added sequentially at rt. The resultant mixture was left at rt for 2 h and then quenched using saturated aqueous NH_4Cl. The aqueous layer was repeatedly extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a crude residue which was purified by column chromatography on silica eluting with petroleum ether/EtOAc (10:1). The product **38** (543 mg, 56%) was obtained as a colorless oil. R_f 0.8 (10:1 petroleum ether/ethyl acetate); $[\alpha]^{18}_D$ +102.4 (*c* 1.27 in $CHCl_3$); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.0), 1.18−1.30 (4H, m), 1.37−1.42 (2H, m), 1.64−1.74 (2H, m), 2.41 (1H, d, J = 2.0), 3.76 (3H, s,), 3.99 (1H, dt, J = 2.0, 6.6), 4.39 (1H, d, J_{AB} = 11.4), 4.69 (1H, d, J_{AB} = 11.4, 6.83 (2H, d, J = 8.8), 7.52 (2H, d, J = 8.8); MS (GC/EI) *m*/*z* 246 ($(M)^+$, 8%), 121 ($(CH_3OC_6H_4CH_2)^+$, 100%).

(*R*,*E*)-(((*p*-Methoxyphenyl)methyl)oxy)-1-iodoocten-3-ol (40). To **38** (161 mg, 0.58 mmol) in THF (5 mL) at 0 °C under an argon atmosphere was added Cp_2ZrHCl (0.24 mg, 0.81 mmol) rapidly. Once a homogeneous solution had formed, iodine (177 mg, 0.70 mmol) was added, and the solution was stirred at rt for 35 min. Then an equal volume of saturated aqueous NH_4Cl and Et_2O were added. The two layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were then washed with aqueous $Na_2S_2O_3$ and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave a residue which was purified by column chromatography on silica eluting with neat petroleum ether. ^{1}H-NMR analysis of the purified material revealed that we had isolated a 1:1 mixture of starting material **38** and product **40**. Therefore this 1:1 mixture of compounds were redissolved in CH_2Cl_2 (4 mL) and treated sequentially with Cp_2ZrHCl (123 mg, 0.42 mmol), with stirring at rt for 45 min, followed by the addition of iodide (107 mg, 0.42 mmol). After 30 min the reaction was worked up as previously described and the product **40** (181 mg, 77%) isolated pure as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.8), 1.21−1.48 (8H, m), 3.70 (1H, q, J = 7.3), 3.80 (3H, s), 4.28 (1H, d, J_{AB} = 11.4), 4.52 (1H, d, JAB = 11.4), 6.26 (1H, d, J = 14.5,), 6.46 (1H, dd, J = 7.7, 14.5), 6.87 (2H, d, J = 8.8, aryl), 7.52 (2H, d, J = 8.8). This compound was used directly after its preparation and was therefore not fully characterized.

(2*R*,4*Z*)-2-*O*-((p-Methoxyphenyl)methyl)-4-heptene-1,2-diol (41). Propyltriphenylphosphonium bromide (2.82 g, 7.32 mmol) in toluene (10 mL) was treated with NaHMDS (7.14 mL, 7.14 mmol, 1 M solution in THF) at 0 °C under an argon atmosphere. After 10 min at 0 °C and then 30 min at rt, the red-orange mixture was cooled to −78 °C, and **22** (800 mg, 3.57 mmol) dissolved in toluene (5 mL) was added slowly *via* cannula. After stirring at −78 °C for 5 min and 0 °C for 30 min the reaction mixture was quenched with saturated aqueous NH_4Cl. The two layers were separated, and the aqueous phase was extracted with EtOAc. The organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography on silica, eluting with EtOAc/petroleum ether (1:4). The desired product **41** (676 mg, 76%) and trimethylsilyl-protected derivative (126 mg, 11%) were both isolated as colorless oils. Data for **41**: R_f 0.5 (4:1, petroleum ether/EtOAc); $[\alpha]^{24}_D$ −23.3 (*c* 0.22, $CHCl_3$); IR (neat) 1612, cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) d 0.96 (3H, t, J = 7.5), 2.02−2.12 (2H, m), 2.20−2.45 (2H, m), 3.49−3.67 (3H, m), 3.80 (3H, s), 4.46 (1H, d, J_{AB} = 11.2), 4.62 (1H, d, J_{AB} =, 11.2), 5.29−5.53 (2H, m), 6.88 (2H, d, J = 8.6), 7.28 (2H, d, J = 8.6); ^{13}C-NMR (67.8 MHz, $CDCl_3$) d 14.1 (q), 20.6 (t), 28.6 (t), 55.3 (q), 64.2 (t), 71.2 (t), 79.3 (d), 113.9 (d), 123.7 (d), 129.4 (d), 130.4 (s), 134.2 (d), 159.3 (s); MS (CI, NH_3) *m*/*z* 268 ($(M + NH_4)^+$, 6%), 138 (22), 121 (100); HRMS: 268.1913 (calcd for $C_{15}H_{26}O_3N$ $(M + NH_4)^+$ 268.1913). Data for silylated derivative: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.11 (9H, s), 0.95 (3H, t, J = 7.5), 2.04 (2H, pentet, J = 7.3), 2.20−2.40 (2H, m), 3.40−3.50 (1H, m), 3.55−3.63 (2H, m), 4.53 (1H, d, J_{AB} = 11.2), 4.58 (1H, d, J_{AB} = 11.2), 5.32−5.52 (2H, m), 6.86 (2H, d, J = 8.8), 7.27 (2H, d, J = 8.8). [Note that by stirring the silylated derivative in a mixture of tetrahydrofuran and dilute mineral acid it could be quantitatively converted to **41**].

(2*R*,4*Z*)-2-*O*-(((*p*-Methoxyphenyl)methyl)oxy)-4-heptenal (42). A solution of oxalyl chloride (62.8 mL, 0.72 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −78 °C under an argon atmosphere, and a solution of DMSO (0.1 mL, 1.44 mmol) in CH_2Cl_2 (2 mL) was added over a 5-min period *via* syringe. Stirring was continued at −78 °C for 10 min followed by addition of **41** (150 mg, 0.60 mmol) in CH_2Cl_2 (2 mL) over *ca*. 10 min. The reaction mixture was stirred for 20 min, and Et_3N (0.42 mL, 3.0 mmol) was added slowly with stirring at −78 °C. The cooling bath was removed, and at rt water (4 mL) was added. Stirring was continued for 5 min, and then the layers were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated to give crude aldehyde **42** (188 mg, greater than quantitative yield) as a pale yellow oil. Crude aldehyde **42** was either used directly or was purified by column chromatography eluting with petroleum ether/ethyl acetate (5:1). Aldehyde **42** (144 mg, 96%) was now isolated as a colorless oil. R_f 0.6 (5:1, petroleum ether/ethyl acetate); IR (neat) 1727 (s), cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.5), 2.00−2.20 (2H,

m), 2.42−2.50 (2H, m), 3.75 (1H, dt, J = 2.2, 6.6), 3.81 (3H, s), 4.53 (1H, d, J_{AB} = 11.5), 4.59 (1H, d, J_{AB} = 11.5), 5.31−5.41 (1H, m), 5.48−5.57 (1H, m), 6.88 (2H, d, J = 8.6), 7.27 (2H, d, J = 8.6), 9.61 (1H, d, J = 2.2). No further data was obtained since the aldehyde appeared to be quite unstable and was therefore used directly in subsequent steps.

(3*R*)-(1*E*,5*Z*)-3-*O*-(((*p*-Methoxyphenyl)methyl)oxy)-1-iodo-1,5-octadiene (43). To a stirred suspension of $CrCl_2$ (357 mg, 2.90 mmol) in THF (4 mL) under an argon atmosphere was added dropwise a solution of pure **42** (120 mg, 0.48 mmol) and CHI_3 in THF (3 mL). The mixture was stirred for 1 h at 0 °C and then left at rt for 16 h. Water (4 mL) was then added followed by EtOAc (10 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography on silica eluting with petroleum ether/EtOAc (2:1). The product **43** (20 mg, 11%) was isolated as a colorless oil. R_f 0.5 (10:1, petroleum ether/EtOAc); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.5), 2.02 (2H, pentet, J = 7.1), 2.23−2.40 (2H, m), 3.73 (1H, q, J = 7.0), 3.80 (3H, s), 4.31 (1H, d, J_{AB} = 11.4), 4.52 (1H, d, J_{AB} = 11.4), 5.35−5.25 (1H, m), 5.52−5.41 (1H, m), 6.29 (1H, d, J = 14.7), 6.48 (1H, dd, J = 7.5, 14.7), 6.88 (2H, d, J = 8.8), 7.24 (2H, d, J = 8.8).

(3*R*,5*Z*)-3-*O*-(((*p*-Methoxyphenyl)methyl)oxy)-1,1-dibromo-1,5-octadiene (45). To a solution of PPh_3 (2.31 g, 8.8 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere at rt was added CBr_4 (1.46 g, 4.4 mmol) followed by Et_3N (2.47 mL, 17.6 mmol). After 15 min at rt a deep burgundy colored solution had developed, and the mixture was cooled to −78 °C. Crude aldehyde **42** (546 mg, 2.20 mmol) dissolved in CH_2Cl_2 (10 mL) was then added slowly *via* cannula. The temperature was allowed to warm to 0 °C slowly over a 2 h period and was then left at rt for 16 h. The burgundy colored solution was poured into 100 mL of stirring petroleum ether, and the precipitated solids were removed by suction filtration. The filtrate was concentrated by evaporation of the solvent, and the residue was purified by column chromatography on silica eluting with petroleum ether/EtOAc (15:1 to 10:1). The product **45** (650 mg, 73% from **41** was isolated as a colorless oil. R_f 0.6 (15:1, petroleum ether/ethyl acetate); $[\alpha]^{22}_D$ +20.8 (*c* 0.98, $CHCl_3$); IR (neat) 1614 cm^{-1}; H-NMR (270 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.5), 2.00−2.10 (2H, m), 2.25−2.45 (2H, m), 3.79 (3H, s), 4.04−4.12 (1H, m), 4.35 (1H, d, J_{AB} = 11.4), 4.53 (1H, d, J_{AB} = 11.4), 5.29−5.55 (2H, m), 6.41 (1H, d, J = 8.6), 6.87 (2H, d, J = 8.6), 7.28 (2H, d, J = 8.6); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.1 (q), 20.7 (t), 32.1 (t), 55.2 (q), 70.6 (t), 78.7 (d), 91.1 (s), 113.7 (d), 122.8 (d), 129.4 (d), 130.1 (s), 134.6 (d), 139.7 (d), 159.2 (s); MS (FAB) *m*/*z* 406 ([M]$^+$, 0.7%), 404 ([M]$^+$, 1.5%), 402 ([M]$^+$, 0.7%), 121 (100); HRMS *m*/*z* 401.9816 (calcd for $C_{16}H_{20}O_2Br_2$ (M^+) 401.9830; also *m*/*z* 400.9750 (calcd for $C_{16}H_{19}O_2Br_2$ $(M-1)^+$) 400.9752).

(3*R*,5*Z*)-3-*O*-(((*p*-Methoxyphenyl)methyl)oxy)-5-octen-1-yne (44) (and Side Product 46). To a solution of dibromide **45** (123 mg, 0.30 mmol) in THF (1 mL) at −78 °C under an argon atmosphere was added *n*-BuLi (0.40 mL, 0.61 mmol, 1.5M in hexanes) dropwise. The reaction was stirred at −78 °C for 30 min and then allowed to warm to 0 °C for 5 min. Then saturated aqueous NH_4Cl (1.5 mL) and EtOAc (3 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (2 × 5 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography on silica eluting with petroleum ether/EtOAc (10:1). The reaction produced several products, and we isolated the desired product **44** (53 mg, 71%) and the side product **46** (7.7 mg, 10%). Data for **44**. R_f 0.6 (10:1, petroleum ether/ethyl acetate); $[\alpha]^{187}_D$ +87.3 (*c* 0.63 in $CHCl_3$); IR (neat) 3292 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.5), 2.06 (2H, pentet, J = 7.5), 2.47 (1H, d, J = 2.0), 2.47−2.53 (2H, m), 3.79 (3H, s), 4.05 (1H, dt, J = 2.0, 6.8), 4.45 (1H, d, J_{AB} = 11.5), 4.53 (1H, d, J_{AB} = 11.5), 5.37−5.58 (2H, m), 6.87 (2H, d, J = 8.6), 7.28 (2H, d, J = 8.6); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.1 (q), 20.7 (t), 33.5 (t), 55.2 (q), 67.9 (d), 70.1 (t), 73.8 (d), 82.7 (s), 113.7 (d), 123.2 (d), 129.6 (d), 129.8 (s), 134.5 (d), 159.2 (s); MS (FAB) *m*/*z* 267 ($(M+Na)^+$, 1.5%), 244 ($(M)^+$, 3%), 243 ($(M)^+$, 4%), 121 (100). HRMS *m*/*z* 243.1387 (calcd for $C_{16}H_{19}O_2$ $(M-H)^+$ 243.1385. Data for 2,5-disubstituted 3,4-dihydrofuran derivative **46**. R_f 0.5 (15:1, petroleum ether/EtOAc); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.5), 2.03 (2H, pentet, J = 7.5), 2.30−2.52 (2H, m), 3.79 (3H, s), 4.81−4.90 (1H, m), 5.35−5.55 (2H, m), 5.69−5.72 (1H, m), 5.83 (1H, ddd, J = 2.2, 2.2, 6.1), 5.93 (1H, ddd, J = 1.3, 2.4, 6.1), 6.86 (2H, d, J = 8.8, 7.24 (2H, d, J = 8.8); MS (EI) *m*/*z* 244 ([M]$^+$, 3%), 175 ([M − C_5H_9]$^+$, 90%), 121 ([$MeOC_6H_4CH_2$]$^+$, 100%).

(3*R*,5*Z*)-3-*O*-((*tert*-Butyldiphenylsilyl)oxy)-1,1-dibromo-1,5-octadiene (49). To a solution of **45** (309 mg, 0.77 mmol) in CH_2Cl_2 (6 mL) and water (0.3 mL) was added DDQ (191 mg, 0.84 mmol) in one portion. The reaction was stirred at rt for 30 min, and then the volume of solvent was reduced by evaporation under reduced pressure. The concentrated mixture was placed directly onto a column containing a plug of silica eluting with petroleum ether/EtOAc (5:1). The desired hydroxyl intermediate (7.65 mmol) was isolated contaminated with 4-methoxybenzaldehyde. The crude hydroxyl intermediate was then reprotected. To the aforementioned material dissolved in DMF (4 mL) was added imidazole (125 mg, 1.84 mmol) followed by TBDMSCl (0.24 mL, 0.92 mmol) at rt under an argon atmosphere. After stirring the mixture at rt for 16 h, water (5 mL) was added. The aqueous phase was extracted with Et_2O, and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed by evaporation under reduced pressure and the residue purified by column chromatography eluting with neat petroleum ether. The product **49** (368 mg, 92%) was isolated as a colorless oil. R_f 0.7 (neat petroleum ether). Anal. Calcd for $C_{24}H_{30}OBr_2Si$: C, 55.2; H, 5.75. Found: C, 55.5; H, 5.86. $[\alpha]^{18}_{365}$ +10.5 (*c* 0.73 in $CHCl_3$) IR (neat) 1620 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.5), 1.06 (9H, s), 1.92 (2H, pentet, J = 7.3), 2.18−2.40 (2H, m), 4.32−4.39 (1H, m), 5.29−5.43 (2H, m), 6.40 (1H, d, J = 8.2), 7.35−7.43 (6H, m), 7.63−7.69 (4H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.1 (q), 19.2 (s), 20.6 (t), 26.9 (q), 34.5 (t), 73.9 (d), 89.0 (s), 122.7 (d), 127.6 (d, aryl), 129.7 (d), 133.5 (s), 133.6 (s), 134.7 (d), 135.9 (d), 141.0 (d); MS (FAB) *m*/*z* 521 ([M − 1]$^+$, 1%), 465 ([M − ^{t}Bu]$^+$, 13%), 359 (10), 239 (16), 199 (73), 135 (100).

(3*R*,5*Z*)-3-*O*-((*tert*-Butyldiphenylsilyl)oxy)-5-octen-1-yne (48). To a solution of dibromide **49** (120 mg, 0.23 mmol) in THF (1 mL) at −78 °C under an argon atmosphere was added LDA (0.35 mmol), prepared by adding *n*-BuLi (0.14 mL, 0.35 mmol, 2.5M solution in hexanes) to diisopropylamine (48 mL, 0.35 mmol) in THF (2 mL) at 0 °C and then warming to rt after 15 min, *via* cannula. The reaction was stirred at −78 °C for 30 min and then allowed to warm to 0 °C for 20 min. After cooling to −78 °C, *n*-BuLi (0.20 mL, 0.51 mmol) was added slowly, and the mixture was allowed to warm to rt. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and EtOAc (5 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with neat petroleum ether. The product **48** (76 mg, 92%) was isolated as a colorless oil. R_f 0.5 (petroleum ether/ethyl acetate); $[\alpha]^{20}_D$ +14.5 (*c* 1.47, $CHCl_3$); IR (neat) 2361, 1651 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.5), 1.09 (9H, s), 1.83−2.00 (2H, m), 2.34 (1H, d, J = 2.0), 2.39−2.43 (2H, m), 4.32 (1H, dt, J = 2.0, 6.4), 5.38−5.50 (2H, m), 7.35−7.44 (6H, m), 7.69−7.78 (4H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.2 (q), 19.3 (s), 20.7 (t), 26.9 (q), 36.2 (t), 63.6 (d), 72.6 (d), 84.8 (s), 123.2 (d), 127.4 (d), 127.6 (d), 129.7 (d), 129.8 (d), 133.4 (s), 133.6 (s), 134.6 (d), 135.9 (d), 136.0 (d); MS (FAB) *m*/*z* 363 ($(M+H)^+$, 9%), 319 (15), 305 ($(M-{}^t\text{Bu})^+$, 34%), 227 (29), 207 (31), 199 (100); HRMS *m*/*z* 363.2155 (calcd for $C_{24}H_{30}OSi$ $(M+H)^+$ 363.2144).

(3*R*)-(1*E*,5*Z*)-3-*O*-((*tert*-Butyldiphenylsilyl)oxy)-1-iodo-1,5-octadiene (50). To **48** (322 mg, 0.89 mmol) in THF (10 mL) at rt under an argon atmosphere was added Cp_2ZrHCl (312 mg, 1.07 mmol) rapidly. Once an homogeneous solution had formed we analyzed the reaction by TLC, and all the starting material (**48**) had been consumed. Therefore iodine

(271 mg, 1.07 mmol) was added, and the solution was stirred at rt for 45 min. Then an equal volume of saturated aqueous NH_4Cl and Et_2O were added. The two layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$ followed by evaporation of the solvent under reduced pressure. The residue was then purified by column chromatography on silica eluting with neat petroleum ether. The product **50** (404 mg, 92%) was a colorless oil which still contained *ca.* 8% starting material **48**. R_f (neat petroleum ether) 0.8; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.5), 1.06 (9H, s), 1.83 (2H, pentet, J = 7.3), 2.10−2.25 (2H, m), 4.06 (1H, q, J = 6.6), 5.16−5.24 (1H, m), 5.31−5.42 (1H, m), 5.97 (1H, dd, J = 1.0, 14.5), 6.48 (1H, dd, J = 6.4, 14.5), 7.34−7.46 (6H, m), 7.61−7.77 (4H, m). No further purification was attempted, and this material was used directly.

Enantioselective Addition of Oct-1-yne to Heptanal Using (*S*)-Diphenyl(1-methylpyrrolidin-2-yl)methanol as Catalyst. To borane dimethyl-sulfide complex (100 mL, 1.00 mmol, 10 M solution) in degassed hexane (1 mL) was added cyclohexene (203 mL, 2.00 mmol) dropwise at 0 °C with stirring at this temperature for 1 h. Then oct-1-yne (147 mL, 1.00 mmol) was added at 0 °C with stirring for 30 min followed by warming to rt for 30 min. At −78 °C Et_2Zn (1.0 mL, 1.00 mmol, 1.0M solution in hexane) was added slowly, followed by (*S*)-DPMPM (2.7 mg, 0.01 mmol), and the solution was warmed to −20 °C for 10 min. Then at −20 °C, heptaldehyde (139 μL, 1.00 mmol) in hexane (4 mL) was added slowly. After 5 min the solution was warmed to 0 °C and left at this temperature for 2 h followed by stirring at rt overnight. Saturated aqueous NH_4Cl (4 mL) and EtOAc (7 mL) were added, and the two layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated at reduced pressure and the residue purified by column chromatography eluting with petroleum ether/EtOAc (5:1). The product allylic alcohol (179 mg, 79%) was isolated as a colorless oil. R_f 0.6 (10:1, petroleum ether/ethyl acetate); $[\alpha]^{18}_D$ +4.3 (*c* 0.35 in $CHCl_3$); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.90 (6H, m), 1.25−1.45 (16H, m, 1.45−1.60 (2H, m), 1.98−2.06 (2H, m), 4.03 (1H, q, J = 6.8), 5.43 (1H, dd, J = 7.2, 15.4), 5.62 (1H, td, J = 6.6, 15.4); *m/z* (CI) 225 ((M − 1)$^+$, 30%), 209 ((M − OH)$^+$, 100%), 141 (72)

Racemic (2*E*)-1-*O*-((*tert*-Butyldiphenylsilyl)oxy)-oct-2-ene-1,4-diol (52). To alkyne **51** (64 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) at rt under an argon atmosphere was added Cp_2ZrHCl (67 mg, 0.23 mmol). Once a homogeneous solution had formed the mixture was cooled to −78 °C, and Et_2Zn (0.20 mL, 0.23 mmol, 1.1M in toluene) was added over 5 min. After warming the solution to 0 °C and stirring for 10 min, hexanal (23 mg, 0.23 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise *via* syringe. The mixture was stirred at 0 °C for 1.5 h and then saturated aqueous NH_4Cl (3 mL) was added. The two layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. The solvent was evaporated at reduced pressure, and the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc (3:1). The product **52** (43 mg, 51%) was isolated as a colorless oil. R_f 0.5 (4:1, petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 6.7), 0.99 (9H, s), 1.22−1.47 (8H, m), 1.35 (1H, d, J = 4.0), 4.10−4.29 (1H, m), 4.44−4.48 (2H, m), 5.61−5.70 (2H, m), 7.28−7.37 (6H, m), 7.59−7.79 (4H, m); MS (EI) *m/z* 379 ((M − OH)$^+$, 35%), 339 ((M − ^{t}Bu)$^+$, 10%), 267 (6), 239 (19), 221 (20), 207 (16), 199 (100).

(6*R*,4*E*)-6-*O*-((*p*-Methoxyphenyl)methyl)-2-methyl-4-undecene-3,6-diol (58) as a 1:1 Mixture of Diastereomers at C-3. To a mixture of *trans*-iodo alkene **40** (181 mg, 0.45 mmol) and 2-methylpropanal (24.3 mL, 0.27 mmol) in DMSO (2 mL) at rt under an argon atmosphere was added $CrCl_2$ (110 mg, 0.89 mmol), containing a catalytic amount of $NiCl_2$ (0.5 wt %, 0.5 mg, 3.86 mmol) in one portion. The dark green solution was stirred at rt for 2 h and quenched by adding saturated aqueous NH_4Cl (3 mL) and $CHCl_3$ (5 mL). The mixture was then extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent evaporated at reduced pressure to give a crude residue which was purified by column chromatography eluting with petroleum ether/EtOAc (3:1). The product **58** (86.4 mg, 100%) was isolated as a 1:1 mixture of diastereomers. R_f 0.4 (10:3, petroleum ether/EtOAc). Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.0; H, 10.0. Found: C, 74.9; H, 10.1; IR (neat) 3443 (br, OH), 1612 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.83−0.97 (9H, m), 1.26−1.80 (9H, m), 3.73 (1H, q, J = 6.0), 3.80 (3H, s), 3.85−3.95 (1H, m), 4.27 (0.5H, d, J_{AB} = 11.5), 4.30 (0.5H, d, J_{AB} = 11.5), 4.51 (0.5H, d, J_{AB} = 11.5), 4.52 (0.5H, d, J_{AB} = 11.5), 5.54 (0.5H, dd, J = 7.3, 15.8), 5.55 (0.5H, dd, J = 7.3, 15.8), 5.65 (0.5H, dd, J = 6.1, 15.6), 5.67 (0.5H, dd, J = 6.1, 15.8), 6.87 (2H, d, J = 8.8), 7.22−7.38 (2H, m); MS (GC:EI, $CF_3C[{=}NSi(CH_3)]OSiMe_3$. CH_3CN) *m/z* 349 ((M − H + $Si(Me_3)_3$ − $(CH_3)_2CH)^+$, 2%), 319 (M − H + $Si(Me_3)_3$ − $(CH_3)_2CH$ − 2 × $CH_3)^+$, 1%), 259 (3), 241 (2), 137 (8), 121 (100); MS (FAB) *m/z* 320 ((M)$^+$, 0.2%), 303 ((M − OH)$^+$, 0.4%), 289 (1), 242 (1.6), 137 (7), 121 (100).

(6*R*,4*E*)-6-*O*-(*tert*-Butyldiphenylsilyl)-2-methyl-4-undecene-3,6-diol (59) as a 2.1:1 Mixture of Diastereomers at C-3. To a mixture of *trans*-iodo alkene **39** (450 mg, 0.92 mmol) and 2-methylpropanal (28 mL, 0.31 mmol) in a mixture of DMSO and DMF (5 mL:3 mL) at rt under an argon atmosphere was added $CrCl_2$ (225 mg, 1.83 mmol), containing a catalytic amount of $NiCl_2$ (0.5 wt %, 1.0 mg, 7.71 mmol) in one portion. The dark green solution was stirred at rt for 1 h and then quenched by adding saturated aqueous NH_4Cl (5 mL) and $CHCl_3$ (6 mL). The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated at reduced pressure to give a crude residue which was purified by column chromatography, eluting with petroleum ether/EtOAc (10:1). The product **59** (136 mg, 100%) was isolated as a 2.1:1 mixture of diastereomers. R_f 0.3 (10:1, petroleum ether/EtOAc); IR (neat) 3420 cm^{-1}; *major isomer*, ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.73−0.88 (9H, m), 1.06 (9H, s), 1.08−1.30 (6H, m), 1.38−1.64 (3H, m), 3.66−3.73 (1H, m), 4.15−4.24 (1H, m), 5.37 (1H, ddd, J = 1.5, 6.5, 15.2), 5.54 (1H, ddd, J = 1.5, 6.8, 15.2), 7.30−7.44 (6H, m), 7.64−7.76 (4H, m). *minor isomer*, ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.73−0.88 (9H, m), 1.05 (9H, s), 1.08−1.30 (6H, m), 1.38−1.64 (3H, m), 3.52−3.58 (1H, m), 4.10−4.18 (1H, m), 5.37 (1H, ddd, J = 1.0, 7.5, 15.8), 5.54 (1H, ddd, J = 1.0, 8.3, 15.8), 7.30−7.44 (6H, m), 7.64−7.76 (4H, m); MS *major isomer*, (GC:EI, $CF_3C[{=}NSi(CH_3)_3]OSiMe_3{\cdot}CH_3CN$) *m/z* 495 ((M − H + $Si(Me_3)_3$ − $CH_3)^+$, 1%), 467 ((M − H + $Si(Me_3)_3$ − $(CH_3)_2CH)^+$, 11%), 453 (M − H + $Si(Me_3)_3$ − ^{t}Bu$^+$, 31%), 439 (4), 381 (7), 271 (100), 211 (18), 199 (95), *minor isomer*, (GC:EI $CF_3C[{=}NSi(CH_3)_3]OSiMe_3{\cdot}CH_3CN$) *m/z* 467 ((M − H + $Si(Me_3)_3$ − $(CH_3)_2CH)^+$, 12%), 453 (M − H + $Si(Me_3)_3$ − ^{t}Bu$^+$, 35%), 439 (5), 381 (7), 271 (100), 211 (17), 199 (95), and 95% pure by gas chromatography; MS (FAB) *m/z* 437 ((M − H)$^+$, 1%), 421 ((M − OH)$^+$, 28%), 339 (6), 239 (10), 199 (56), 135 (100); HRMS *m/z* 421.2918 (calcd for $C_{28}H_{41}OSi$ (M − OH)$^+$ 421.2927).

15-*O*-(*tert*-Butyldiphenylsilyl)halicholactone (60a) and 12-*epi*-15-*O*-(*tert*-butyldiphenylsilyl)halicholactone (60b) as a 2.1 Mixture of Isomers at C-12. To a mixture of *trans*-iodo alkene **39** (155 mg, 0.32 mmol) and 8*S*,9*R*,11*R*-aldehyde **14** (39.4 mg, 0.19 mmol) in DMSO (3 mL) at rt under an argon atmosphere was added $CrCl_2$ (77.4 mg, 0.63 mmol) containing a catalytic amount of $NiCl_2$ (approximately 0.5 wt %, 0.5 mg, 3.87 mmol) in one portion. The dark green solution was stirred at rt for 3 h and then quenched by adding saturated aqueous NH_4Cl (3 mL) and $CHCl_3$ (5 mL). The mixture was then extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$. After the solvent had been evaporated under reduced pressure the crude residue was purified by column chromatography on silica eluting with petroleum ether/EtOAc (7:1 to 5:1) (73% crude yield). By repeating the column chromatography process a total of three times the two diastereomers were sufficiently separated such that the major isomer **60a** (47.0 mg, 44%) was isolated as a colorless oil. The minor isomer **60b** was still contaminated with **60a** (32.0 mg, 30%, **60b**:**60a** 4:1). Data for **60a**. R_f 0.3 (5:1, petroleum ether/ethyl acetate); $[\alpha]^{15}_D$ −43.7 (*c* 0.59 in $CHCl_3$); IR (neat) 3744, 3430 (OH), 2929, 2859, 1738 (s), 1720,

1650, 1496, 1455 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.48 (1H, ddd, J = 5.0, 5.0, 8.5), 0.58 (1H, ddd, J = 5.0, 5.0, 8.5), 0.84 (3H, t, J = 8.0), 0.88−0.98 (2H, m), 1.05 (9H, s), 1.12−1.32 (6H, m), 1.40−1.55 (2H, m), 1.72−1.80 (1H, m), 2.00−2.12 (3H, m), 2.16−2.28 (2H, m), 2.38−2.52 (2H, m), 3.53−3.58 (1H, m), 4.15−4.25 (2H, m), 5.39 (1H, dd, J = 5.0, 15.6), 5.43−5.48 (2H, m), 5.64 (1H, dd, J = 7.5, 15.6), 7.32−7.42 (6H, m), 7.65−7.69 (4H, m); ^{13}C-NMR (125.8 MHz, $CDCl_3$) δ 7.7, 14.0, 19.1, 19.3 (s), 22.5, 22.6, 24.3, 25.3, 26.5, 27.0 (q), 31.7, 33.6, 33.9, 37.9, 73.4, 73.8, 76.0, 124.8, 127.4, 127.5, 129.5, 129.6, 131.1, 134.0, 134.4, 134.6, 134.7, 135.9, 136.0, 174.0 (s, C_1); MS (FAB) m/z 597 ($(M + Na)^+$, 12%), 557 ($(M - OH)^+$, 14%), 301 ($(M - OH - {}^tBuPh_2SiOH)^+$, 199 (100); HRMS m/z 557.3425 (calcd for $C_{36}H_{49}O_3Si$ $[M - OH]^+$ 557.3451). Data for **60b**. R_f 0.4 (5:1, petroleum ether/EtOAc); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.43−0.48 (2H, m), 0.84 (3H, t, J = 6.6), 0.84−0.95 (1H, m), 0.97−1.06 (1H, m), 1.05 (9H, s), 1.12−1.60 (8H, m), 1.72−2.60 (8H, m), 3.36−3.42 (1H, m), 4.05−4.15 (2H, m), 5.39 (1H, dd, J = 6.2, 15.6), 5.43−5.48 (2H, m), 5.51 (1H, dd, J = 7.0, 15.6), 7.32−7.43 (6H, m), 7.64−7.69 (4H, m).

Halicholactone 2.[1a] To a solution of **60a** (34.0 mg, 59.4 mmol) in THF (2 mL) was added TBAF (150 mL, 0.15 mmol, 1.0 M in THF), and the solution was then heated at reflux for 3 h. The volume of solvent was then reduced and the solution directly chromatographed on silica eluting with EtOAc/petroleum ether (10:3). The product **2** (19.6 mg, 99%) was isolated as a colorless oil. R_f 0.4 (10:3, EtOAc/petroleum ether); $[\alpha]^{15}_D$ −91.7 (c 0.29 in $CHCl_3$); IR (neat) 3408 (br), 2930, 2858, 1738 (s,), 1716, 1652 cm^{-1}; ^{1}H-NMR (400 MHz, C_6D_6) δ 0.34 (1H, ddd, J = 5.2, 5.2, 8.9), 0.53 (1H, ddd, J = 5.0, 5.0, 8.9), 0.93 (3H, t, J = 7.0), 0.89−0.96 (1H, m), 1.08−1.15 (1H, m), 1.30−1.69 (12H, m), 1.76−1.84 (1H, m, C*H*H of lactone), 1.94 (1H, ddd, J = 1.2, 6.1, 12.2), 2.12−2.19 (2H, m), 2.36−2.48 (2H, m), 3.60 (1H, dd, J = 3.5, 7.0), 3.98−4.04 (1H, m), 4.35−4.40 (1H, ddd, J = 1.2, 8.0, 12.0), 5.38−5.48 (2H, m), 5.71−5.81 (2H, m); also (500 MHz, $CDCl_3$) δ 0.60 (1H, ddd, J = 5.1, 5.1, 8.5), 0.71 (1H, ddd, J = 5.2, 5.2, 8.8), 0.89 (3H, t, J = 6.9), 1.00−1.06 (1H, m), 1.08−1.13 (1H, m), 1.30−1.45 (6H, m,), 1.47−1.65 (4H, m), 1.94 (1H, dddd, J = 5.9, 12.5, 12.5, 12.5), 2.03−2.10 (2H, m), 2.13−2.16 (1H, m), 2.22−2.32 (2H, m), 2.43−2.52 (2H, m), 3.70 (1H, dd, J = 4.2, 7.4), 4.11 (1H, q, J = 6.2), 4.22 (1H, ddd, J = 1.5, 8.3, 10.6), 5.45−5.50 (2H, m), 5.72−5.80 (2H, m); ^{13}C-NMR (125.8 MHz, $CDCl_3$) δ 8.2, 14.0, 19.5, 22.6, 23.4, 25.0, 25.3, 26.5, 31.7, 33.6, 33.8, 37.2, 72.2, 74.1, 76.1, 124.7, 131.7, 134.0, 134.6, 174.0; MS (FAB) m/z 359 ($(M + Na)^+$, 33%), 337 ($(M + H)^+$, 3%) 319 ($(M - OH)^+$, 100%), 301 ($(M - (OH + H_2O))^+$, 15%), 149 (28); HRMS 319.2276 (calcd for $C_{20}H_{31}O_3$ $(M - OH)^+$ 319.2273).

Alternative Approach to the Preparation of 15-*O*-(*tert*-Butyldiphenylsilyl)halicholactone (60a) and Its C_{12} Isomer (60b). Addition of the Vinyllithium Derivative of 39 to Aldehyde 14. To *trans*-iodo alkene **39** (90.2 mg, 183 mmol) in THF (2 mL) at −78 °C under an argon atmosphere was added *tert*-BuLi (204 mL, 326 mmol, 1.6 M in pentanes) dropwise. The solution was stirred at −78 °C for 30 min, and then aldehyde **14** (31.8 mg, 153 mmol) in THF (3 mL) was added *via* cannula over a 10 min period. After stirring at −78 °C for 30 min the solution was warmed to 0 °C for 5 min. Saturated aqueous NH_4Cl (3 mL) and EtOAc (5 mL) were then added and the two layers separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated at reduced pressure and the residue purified by column chromatography eluting with petroleum ether/EtOAc (5:1). The two isomers **60a** and **60b** were separated from each other but not from unreacted aldehyde **14**. The major isomer **60a** and **14** (23.3 mg in total; 18.2 mg **60a** and 5.1 mg **14**) were isolated together, while the minor isomer **60b** and **14** (16.4 mg in total; 5.7 mg of **60b** and 10.7 mg of **14**) were also isolated together. In addition the alkene resulting from deiodination (38.0 mg, 57%) was recovered. Therefore the addition was diastereoselective, providing a 3:1 ratio of **60a**:**60b** (23.9 mg, 28%) which were contaminated with **14** (15.8 mg, 50%). Data for **60a**, **60b**, and **14** has already been given. Data for alkene. R_f 0.9 (10:1, petroleum ether/ethyl acetate); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.0), 1.07 (9H, s), 1.07−1.30 (6H, m), 1.36−1.55 (2H, m), 4.13 (1H, q, J = 6.4), 4.93−5.02 (2H, m), 5.79 (1H, ddd, J = 6.4, 10.4, 17.0), 7.31−7.44 (6H, m), 7.64−7.07 (4H, m).

Oxidation of Allylic Alcohols 60a and 60b in the Presence of Aldehyde 14. The Recovery of 14. To a mixture of **60a**, **60b**, and **14** (**60a** + **60b**, 23.9 mg, 41.6 mmol; and **14**, 15.8 mg, 75.9 mmol) in CH_2Cl_2 (2 mL) containing powdered 4 Å molecular sieves at rt was added solid PCC (28 mg, 128 mmol) in one portion. The dark green solution was stirred at rt for 30 min and then the volume of solvent reduced before the mixture was placed directly on a silica column, eluting with petroleum ether/EtOAc (5:1). The product **61** (12.8 mg, 54%) and aldehyde **14** (13.7 mg, 87%) were isolated separately. Data for **61**. R_f 0.8 (5:1, petroleum ether/ethyl acetate); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 6.8), 0.93 (1H, ddd, J = 4.2, 6.4, 8.4), 1.08 (9H, s,), 1.10−1.34 (7H, m), 1.42−1.51 (3H, m), 1.71−1.86 (2H, m), 2.06−2.34 (5H, m), 2.47−2.50 (2H, m), 4.27 (1H, ddd, J = 1.3, 8.0, 10.7), 4.35 (1H, q, J = 5.3), 5.46−5.50 (2H, m), 6.16 (1H, dd, J = 1.3, 15.9), 6.73 (1H, dd, J = 5.5, 15.8), 7.30−7.46 (6H, m), 7.56−7.68 (4H, m).

Desilylation of Enone 61. To a solution of **61** (12.8 mg, 22.4 mmol) in THF (0.5 mL) was added TBAF (69 μL, 69 mmol, 1.0 M solution in THF) at rt. After 1 h the solution was concentrated and then placed directly onto a silica column eluting with petroleum ether/EtOAc (3:1). The product **62** (6.2 mg, 81%) was isolated as a colorless oil. R_f 0.4 (3:1, petroleum ether/EtOAc); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 6.8), 0.93 (1H, ddd, J = 4.2, 6.3, 8.3), 1.15−1.80 (12H, m), 1.97−2.30 (6H, m), 2.37−2.50 (2H, m), 4.20 (1H, ddd, J = 1.3, 7.7, 10.7), 4.22−4.35 (1H, m), 5.38−5.42 (2H, m,), 6.36 (1H, dd, J = 1.5, 15.8), 6.79 (1H, dd, J = 5.0, 15.8).

Luche Reduction of Enone 62. To enone **62** (6.2 mg, 18.6 mmol) and $CeCl_3 \cdot (H_2O)_7$ (7.0 mg, 18.6 mmol) in MeOH (1 mL) at rt was added $NaBH_4$ (0.7 mg, 18.6 mmol) in one portion. After 5 min saturated aqueous NH_4Cl (1 mL) was added, and the solution was acidified with 2 N HCl. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated at reduced pressure and the residue purified by column chromatography on silica eluting with EtOAc/petroleum ether (10:3). Compounds **63** and **2** (2.5 mg, 40%) were isolated together as a 1:1 diastereomeric mixture. (We also observed some unreacted starting material by thin layer chromatography which accounts for the low yield in this reaction). The two products (**2** and **63**) had identical R_f values. By subtracting the signals we had observed in the pure spectrum of **2** from the spectrum we now had for the 1:1 mixture of **2** and **63**, the unique and distinguishing signals belonging to **63** could be determined and were as follows. ^{1}H-NMR (400 MHz, C_6D_6) δ 0.30 (1H, m), 0.40 (1H, ddd, J = 4.7, 4.7, 8.6) and 3.47 (1H, dd, J = 2.0, 7.0). The corresponding values for **2** in the mixed spectrum: δ 0.31 (1H, ddd, J = 5.2, 5.2, 8.9), 0.49 (1H, ddd, J = 5.0, 5.0, 8.9), 3.57 (1H, dd, J = 3.5, 7.0, C(12)). The latter values are in better agreement with the published data for *H. okadai* derived halicholactone: δ 0.29 (1H, ddd, J = 5.0, 5.0, 8.0), 0.47 (1H, ddd, J = 5.0, 5.0, 8.0), 3.53 (1H, dd, J = 4.0, 7.0).

15-*O*-(*tert*-Butyldiphenylsilyl)neohalicholactone (64a) and C_{12}-*epi*-15-*O*-(*tert*-Butyldipenylsilyl)neohalicholactone (64b) as A 2.1 Mixture of Isomers at C-12. A mixture of *trans*-iodo alkene **50** (274 mg, 0.56 mmol) and 8*S*,9*R*,11*R*-aldehyde **14** (58.0 mg, 279 mmol) in DMSO (2.5 mL) and DMF (2.5 mL) at rt under an argon atmosphere was added $CrCl_2$ (205 mg, 1.67 mmol) containing a catalytic amount of $NiCl_2$ (approximately 0.5 wt %, 1.0 mg, 7.74 mmol) in one portion. The dark green solution was stirred at rt for 3 h and then quenched by adding saturated aqueous NH_4Cl (5 mL) and $CHCl_3$ (8 mL). The mixture was extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$. After the solvent had been evaporated under reduced pressure, the crude residue was purified on silica eluting with petroleum ether/EtOAc (5:1). The products **64a** and **64b** (97 mg, 61%) were isolated together as a 2:1 mixture. Then 75 mg (of the total 97 mg) of the product mixture was rechromatographed, eluting with petroleum ether/EtOAc (5:1) in an

effort to separate the two diastereomers. The two diastereomers were sufficiently separated such that the major isomer **64a** (44.3 mg) was isolated pure as a colorless oil. The minor isomer **64b** (30.0 mg) was still contaminated with **64a**. Data for **64a**. R_f 0.5 (5:1, petroleum ether/ethyl acetate); $[\alpha]^{25}_D$ −44.6 (*c* 0.50 in $CHCl_3$); IR (neat) 1736 (s), 1650 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.51 (1H, ddd, J = 5.1, 5.1, 8.5), 0.59 (1H, ddd, J = 5.2, 5.2, 8.7), 0.84 (3H, t, J = 7.0), 0.90−0.98 (2H, m), 1.05 (9H, s,), 1.76 (1H, dddd, J = 6.4, 12.1, 12.1, 12.1), 1.87 (2H, pentet, J = 7.2), 2.01−2.12 (3H, m), 2.18−2.32 (4H, m), 2.39−2.48 (2H, m), 3.54−3.59 (1H, m), 4.19−4.24 (2H, m), 5.26−5.30 (1H, m), 5.36−5.41 (1H, m), 5.44−5.48 (3H, m), 5.68 (1H, ddd, J = 1.3, 6.4, 15.6), 7.32−7.42 (6H, m), 7.65−7.69 (4H, m); ^{13}C-NMR (125.8 MHz, $CDCl_3$) δ 7.8, 14.2, 19.1, 19.3 (s), 20.6, 22.6, 25.3, 26.5, 27.0 (q), 33.6, 33.9, 35.9, 73.5 (×2), 76.0, 124.1, 124.8, 127.4, 127.5, 129.5, 129.6, 131.2, 133.5, 133.6, 134.2, 134.4, 134.6, 135.9, 136.0, 174.0 (s, C_1); MS (FAB) *m/z* 595 ($(M + Na)^+$, 40%), 555 ($(M - OH)^+$, 27%), 457 (5), 239 (10), 199 (100); HRMS *m/z* 555.3262 (calcd for $C_{36}H_{47}O_3Si$ $(M - OH)^+$ 555.3294). Data for **64b**; R_f 0.55 (5:1, petroleum ether/ethyl acetate); The ^{1}H-NMR spectrum of **64a**:**64b** (2:1) revealed that only two signals from **64b** were not coincident with the corresponding signals for **64a**; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.39−3.43 (1H, m) and 5.58 (1H, ddd, J = 0.9, 6.7, 15.8) for **64b**, *versus* δ 3.52−3.60 (1H, m) and 5.67 (1H, ddd, J = 1.3, 6.7, 15.2) for **64a**. A pure ^{1}H-NMR spectrum of **64b** was not obtained at this time.

Neohalicholactone (1).[1a] To a solution of pure **64a** (34.0 mg, 61.4 mmol) in THF (2 mL) was added TBAF (123 mL, 123 mmol, 1.0 M in THF), and the solution was then heated at reflux for 3.5 h. After this time a small amount of starting material **64a** was still visible by TLC. However the reaction was worked-up since we did not wish to decompose any product **1**. The volume of solvent was reduced, and the solution was directly chromatographed on silica eluting with EtOAc/petroleum ether (10:3). The product **1** (15.2 mg, 74%) was isolated as a colorless oil, which later solidified on leaving at 0 °C for several hours. A small amount of the product was recrystallized from an EtOAc/hexane mixture (1:5) over 3 days. R_f 0.4 (10:3, EtOAc/petroleum ether); $[\alpha]^{18}_D$ −54.6 (*c* 0.76 in $CHCl_3$); mp 72 °C (literature value[1a] 69−70 °C). By performing a ^{1}H−^{1}H COSY experiment the assignment of all proton signals was possible. ^{1}H-NMR (500 MHz, C_6D_6) δ 0.31 (1H, ddd, J = 5.0, 5.0, 8.6, cyclopropane C(10)*H*), 0.50 (1H, ddd, J = 5.1, 5.1, 8.7, cyclopropane C(10)*H*), 0.89−0.92 (1H, m, cyclopropane C(11)*H*), 0.94 (3H, t, J = 7.5, C(20)$H_3$$CH_2$), 1.02 (1H, d, J = 4.4, C(12)O*H*), 1.06−1.09 (1H, m, cyclopropane C(11)*H*), 1.22 (1H, d, J = 4.2, C(15)O*H*), 1.55−1.64 (2H, m, C(3)H_2), 1.76−1.84 (1H, m, C(4)*H*H), 1.95 (1H, ddd, J = 1.5, 7.2, 13.3, C(7)H*H* of lactone), 2.02 (2H, dpentet, J = 1.3, 7.4, C(19)H_2), 2.11−2.15 (2H, m, C(2)CH_2), 2.18−2.29 (2H, m, C(16)H_2), 2.37−2.43 (2H, m, C(4)H*H* + C(7)*H*H), 3.55−3.59 (1H, m, C(12)*H*OH), 3.99−4.04 (1H, m, C(15)*H*OH), 4.38 (1H, ddd, J = 1.5, 8.3 and 11.0, C(8)*H*OC(O)), 5.41−5.48 (3H, m, lactone olefinics (C5 + C6) and *cis*-C(17)*H*), 5.52−5.55 (1H, m, *cis*-C(18)*H*), 5.71−5.79 (2H, m, 2 × *trans*-C(13 + 14)*H*); also (500 MHz, $CDCl_3$) δ 0.60 (1H, ddd, J = 5.1, 5.1, 8.4, cyclopropane C*H*), 0.71 (1H, ddd, J = 5.2, 5.2, 8.8, cyclopropane C*H*), 0.97 (3H, t, J = 7.5, C$H_3$$CH_2$), 1.00−1.11 (2H, m, 2 × cyclopropane C*H*), 1.60−1.70 (2H, bs, 2 × O*H*), 1.94 (1H, dddd, J = 6.4, 11.9, 11.9, 11.9, C*H* of lactone), 2.03−2.10 (4H, m), 2.13−2.17 (1H, m, C*H*H of lactone), 2.24−2.33 (4H, m), 2.45−2.52 (2H, m), 3.70 (1H, dd, J = 3.8, 7.4, C(12)*H*OH), 4.16−4.19 (1H, m, C(15)*H*OH), 4.23 (1H, ddd, J = 1.4, 8.3, 10.6, C(8)*H*OC(O)), 5.34−5.36 (1H, m, *cis*-C*H*), 5.45−5.50 (2H, m, 2 × *cis*-C*H*), 5.56−5.59 (1H, m, *cis*-C*H*), 5.75−5.80 (2H, m, 2 × *trans*-C*H*). By performing a ^{1}H-^{13}C COSY experiment most of the carbon signals were assigned. ^{13}C-NMR (125.8 MHz, $CDCl_3$) δ 8.2 (C10), 14.2 (C20), 19.5 (C9), 20.7 (C19), 23.4 (C11), 25.3 (C4), 26.4 (C3), 33.6 (C2), 33.8 (C7), 35.2 (C16), 71.5 (C15), 74.2 (C12), 76.1 (C8), 123.7 (C17), 124.7 (C6), 131.8 (C14 or 13), 133.2 (C13 or 14), 134.7 (C18 or C5), 135.3 (C5 or C18), 174.1 (C1); MS (FAB) *m/z* 357 ($(M + Na)^+$, 40%), 317 ($(M - OH)^+$, 100%), 299 ($(M - (OH + H_2O))^+$, 13%), 149 (41), 119 (52), 105 (63); HRMS *m/z* 317.2096 (calcd for $C_{20}H_{29}O_3$ $(M - OH)^+$ 317.2117).[1a]

Neohalicholactone (1) and C_{12}-*epi*-Neohalicholactone (65) from the 2:1 Mixture of 80a and 64b. To a solution of **64a** and **64b** (2:1 mixture, 21.9 mg, 39.5 mmol) in THF (2 mL) was added TBAF (120 mL, 120 mmol, 1.0 M in THF), and the solution was then heated at reflux for 2 h. The volume of solvent was then reduced and the solution directly chromatographed on silica eluting with petroleum ether/EtOAc (10:3). The products **1** and **65** (11.9 mg, 90%) were isolated together in the 2:1 ratio. R_f 0.4 (10:3, EtOAc/petroleum ether). By subtracting the signals we had observed in the pure spectrum of **1** from the spectrum we then acquired from a 2:1 mixture of **1** and **65**, the unique and distinguishing signals belonging to **65** were as follows: ^{1}H-NMR (400 MHz, C_6D_6) δ 0.31 (1H, m), 0.42 (1H, ddd, J = 4.9, 4.9, 8.6) and 3.50 (1H, dd, J = 4.9, 7.0). The corresponding values for **1** in the mixed spectrum: δ 0.31 (1H, ddd, J = 5.2, 5.2, 8.6), 0.51 (1H, ddd, J = 5.2, 5.2, 8.9), 3.57 (1H, dd, J = 3.5, 7.0). The latter values are in better agreement with the published data for *H. okadai* derived neohalicholactone. δ 0.27 (1H, ddd, J = 5.0, 5.0, 8.5), 0.45 (1H, ddd, J = 5.0, 5.0, 8.5), 3.52 (1H, m).

Oxidation of Undesired Isomer 64b to Enone 66. To the C_{12}-isomer **64b** (30.0 mg, 52.4 mmol, containing a small amount of **64a**) and MMO (9.5 mg, 81.2 mmol) in CH_2Cl_2 (1 mL) containing powdered 4 Å molecular sieves was added TPAP (1.0 mg, 2.7 mmol) at rt. After 30 min the mixture was added directly to the top of a silica column eluting with petroleum ether/EtOAc (5:1). The product **66** (27.3 mg, 91%) was isolated as a colorless oil. R_f (5:1, petroleum ether 60:80/ethyl acetate) 0.8; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.3), 0.84−0.96 (2H, m), 1.09 (9H, s,), 1.25−1.33 (2H, m), 1.62−2.38 (10H, m), 2.40−2.60 (2H, m), 4.26 (1H, ddd, J = 1.3, 8.0, 11.3), 4.32−4.42 (1H, m,), 5.16−5.32 (1H, m), 5.35−5.50 (3H, m), 6.20 (1H, dd, J = 1.3, 15.9), 6.75 (1H, dd, J = 5.3, 15.9), 7.31−7.47 (6H, m), 7.60−7.70 (4H, m).

Luche Reduction of Enone 66. To enone **66** (27.3 mg, 47.9 mmol) and $CrCl_2(H_2O)_7$ (17.8 mg, 47.9 mmol) in MeOH (2 mL) at rt was added $NaBH_4$ (1.8 mg, 47.9 mmol) in one portion. After 5 min saturated aqueous NH_4Cl (2 mL) was added, and the solution was acidified with 2 N HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue purified by column chromatography on silica eluting with petroleum ether/EtOAc (10:3). Compounds **64a** and **64b** (15.7 mg, 58%) were isolated together as a 1:3 diastereomeric mixture, where the major isomer (**64b**) possessed the undesired 8*S*,9*R*,11*R*,12*S*,15*R* relative stereochemistry. We also recovered some unreacted starting material **66** (3.3 mg, 12%). Data for **64b**. H-NMR (270 MHz, $CDCl_3$) δ 0.44−0.49 (2H, m), 0.88 (3H, t, J = 7.5), 0.96−1.06 (2H, m), 1.06 (9H, s), 1.77−1.90 (3H, m), 2.00−2.28 (7H, m), 2.40−2.48 (2H, m), 3.41 (1H, t, J = 6.6), 4.10−4.23 (2H, m), 5.22−5.45 (5H, m), 5.58 (1H, ddd, J = 0.9, 6.7, 15.8), 7.34−7.48 (6H, m), 7.64−7.70 (4H, m); MS (FAB) *m/z* 595 ($[M + Na]^+$, 7%), 555 ($[M - OH]^+$, 30%), 457 (6), 299 (5), 253 (5), 239 (11), 199 (100); HRMS *m/z* 555.3282 (calcd for $C_{36}H_{47}O_3Si$ $(M - OH)^+$ 555.3294). The nonsuperimpossible signals belonging to **64a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.51−0.59 (2H, m), 3.54−3.59 (1H, m), 5.64 (1H, ddd, J = 1.3, 6.4, 15.6).

C_{15}-*epi*-15-*O*-(*tert*-Butyldiphenylsilyl)neohalicholactone (68b) and C_{12},C_{15}-*epi*-15-*O*-(*tert*-Butyldipenylsilyl)-neohalicholactone (68a) as a 1:1.3 Mixture of Isomers at C-12. To a mixture of *trans*-iodo alkene (*S*)-**50** (169 mg, 0.35 mmol) and 8*S*,9*R*,11*R*-aldehyde **14** (36.0 mg, 173 mmol) in DMSO (2.0 mL) at rt under an argon atmosphere was added $CrCl_3$ (93 mg, 0.76 mmol) containing a catalytic amount of $NiCl_3$ (approximately 0.5 wt %, 0.5 mg, 3.87 mmol) in one portion. The dark green solution was stirred at rt for 16 h and then quenched by adding saturated aqueous NH_4Cl (3 mL) and $CHCl_3$ (4 mL). The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$. After the solvent had been evaporated under reduced pressure, the crude residue was purified on silica eluting with petroleum ether/EtOAc (5:1). The products **68a** and **68b** (69.3 mg, 70%) were isolated together as a 1.3:1 mixture. This mixture was rechromatographed a further four times, eluting

with petroleum ether/EtOAc (5:1) in an effort to separate the two diastereomers. The two diastereomers were sufficiently separated such that the major isomer **68a** (27.7 mg) was isolated pure as a colorless oil. The minor isomer **68b** (23.5 mg) was still contaminated with 17% of **68a**. Also a 1:1 mixture of **68a**:**68b** (15.7 mg) was isolated. Data for **68a**. R_f 0.6 (5:1, petroleum ether/EtOAc); $[\alpha]^{19}_D$ −50.3 (*c* 0.94 in $CHCl_3$); IR (neat) 1737 (vs) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.45−0.48 (2H, m), 0.87 (3H, t, J 7.3), 0.91−1.06 (2H, m), 1.06 (9H, s), 1.77 (1H, dddd, J = 6.4, 12.5, 12.5, 12.5), 1.87 (2H, pentet, J = 7.3), 2.07−2.35 (7H, m), 2.43−2.51 (2H, m), 3.44 (1H, t, J = 6.4), 4.13−4.21 (2H, m), 5.26−5.48 (5H, m), 5.63 (1H, ddd, J = 1.2, 6.4, 15.6), 7.33−7.44 (6H, m), 7.65−7.69 (4H, m); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 7.5, 14.2, 19.3, 20.3, 20.6, 23.2, 25.2, 26.5, 27.0 (q), 33.6, 33.8, 35.8, 73.5, 74.5, 76.3, 124.0, 124.7, 127.4, 129.5, 129.6, 131.2, 133.6, 134.2, 134.3, 134.6, 135.9, 136.0, 174.2; MS (FAB) *m*/*z* 595 ((M + Na)$^+$, 16%), ((M − 1)$^+$, 3%), 555 ((M − OH)$^+$, 57%), 503 (8), 457 (8), 317 (7), 299 (8), 239 (10), 199 (100); HRMS *m*/*z* 555.3313 (calcd for $C_{36}H_{47}O_3Si$ (M − OH)$^+$ 555.3294). Data for **68b** (contaminated with **68b**). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.52 (1H, ddd, J = 5.2, 5.2 and 8.2), 0.60 (1H, ddd, J = 5.0, 5.0, 8.5), 0.88 (3H, t, J = 7.3), 0.90−0.98 (2H, m), 1.06 (9H, s, ^{t}Bu), 1.72−1.80 (1H, m), 1.87 (2H, pentet, J = 7.3), 2.01−2.12 (3H, m), 2.18−2.35 (4H, m), 2.43−2.50 (2H, m), 3.45−3.41 (1H, m), 4.10−4.21 (2H, m), 5.26−5.41 (2H, m), 5.43−5.48 (3H, m), 5.64 (1H, ddd, J = 1.2, 6.4, 15.6), 7.33−7.44 (6H, m), 7.65−7.69 (4H, m); ^{13}C-NMR (125.8 MHz, $CDCl_3$) δ 7.9, 14.2, 19.1, 19.3 (s), 20.6, 22.7, 25.2, 26.5, 27.0 (q), 33.5, 33.9, 35.9, 73.8, 74.1, 76.0, 124.1, 124.7, 127.4, 127.5, 129.5, 129.6, 131.4, 133.4, 133.8, 134.1, 134.3, 134.6, 135.9, 136.0, 174.0 (s, C_1); MS (FAB) *m*/*z* 595 ((M + Na)$^+$, 29%), 555 ((M − OH)$^+$, 89%), 503 (13), 497 (6), 457 (11), 317 (11), 299 (11), 239 (11), 199 (100). HRMS *m*/*z* 555.3301 (calcd for $C_{36}H_{47}O_3Si$ (M − OH)$^+$ 555.3294).

C_{15}-*epi*-neohalicholactone (67). To a 5:1 mixture of **68b**:**68a** (23.5 mg, 41.1 mmol) in THF (2 mL) was added TBAF (103 mL, 103 mmol, 1.0M in THF), and the solution was then heated at reflux for 5 h. After this time a small amount of starting material was still visible by TLC. However the reaction was worked-up after this time since we did not wish to decompose any product. The volume of solvent was reduced, and the solution was directly chromatographed on silica eluting with EtOAc/petroleum ether (10:3). The product **67** (11.5 mg, 84%) was isolated as a colorless oil which still contained 17% of the C_{12}-isomer **69**. The mixture of **67** (major) and **69** were rechromatographed eluting with petroleum ether/ethyl acetate (1:1). We now isolated some fractions that contained pure **67** (4.3 mg) while many of the fractions were still mixtures of **67** and **69** (6.0 mg). Data for pure **67**. R_f 0.5 (10:3, EtOAc/petroleum ether); $[\alpha]^{20}_D$ −84.9 (*c* 0.43 in $CHCl_3$); IR (neat) 1738 (vs, CO), cm^{-1}. By performing a ^{1}H−^{1}H COSY experiment the assignment of all proton signals was possible. ^{1}H-NMR (500 MHz, C_6D_6) δ 0.27 (1H, ddd, J = 4.9, 4.9, 8.6, cyclopropane C(10)*H*), 0.47 (1H, ddd, J = 5.1, 5.1, 8.8, cyclopropane C(10)*H*), 0.82−0.89 (1H, m, cyclopropane C(11)*H*), 0.89 (3H, t, J = 7.4, C(20)H_3CH$_2$), 1.01−1.07 (1H, m, cyclopropane C(11)*H*), 1.51−1.58 (2H, m, C(3)H_2), 1.73−1.78 (1H, m, C(4)*H*H), 1.90 (1H, ddd, J = 1.4, 7.3, 13.5, C(7)H*H* of lactone), 1.97 (2H, dpentet, J = 1.2 and 7.4, C(19)H_2), 2.06−2.13 (2H, m, C(2)CH_2), 2.18−2.32 (2H, m, C(16)H_2-), 2.31−2.40 (2H, m, C(4)H*H* + C(7)*H*H), 3.54 (1H, dd, J = 2.6, 6.8, C(12)*H*OH), 3.97−4.00 (1H, m, C(15)*H*OH), 4.34 (1H, ddd, J = 1.5, 8.3, 12.2, C(8)*H*OC(O)), 5.35−5.44 (3H, m, *cis*-C(5)*H*, *cis*-C(6)*H*, and *cis*-C(17)*H*), 5.49−5.54 (1H, m, *cis*-C(18)*H*), 5.68−5.71 (2H, m, 2 × *trans*-C(13 + 14)*H*); ^{13}C-NMR (67.8 MHz, $CDCl_3$) 8.2, 14.2, 19.5, 20.7, 23.3, 25.3, 26.5, 33.6, 33.8, 35.2, 71.6, 74.2, 76.1, 123.6, 124.7, 131.9, 133.3, 134.7, 135.4, 174.1 (C_1), and ^{13}C-NMR (125.8 MHz, C_6D_6) δ 7.7, 14.4, 19.5, 21.0, 23.8, 25.6, 26.6, 33.7, 34.1, 35.8, 71.7, 73.5, 76.0, 124.7, 125.1, 132.3, 133.4, 134.6, 134.7, 172.9 (C_1); MS (FAB) *m*/*z* 357 ((M + Na)$^+$, 100%), 317 ((M − OH)$^+$, 93%), 299 ((M − -(OH + H_2O))$^+$, 12%), 259 (18), 165 (42), 149 (70), 123 (71), 109 (74), 105 (94); HRMS *m*/*z* 317.2129 (calcd for $C_{20}H_{29}O_3$ (M − OH)$^+$ 317.2117). The peaks that distinguished **67** from **69** in the ^{1}H-NMR spectrum at 270 MHz: 0.49−0.53 (1H, m), 0.59−0.65 (1H, m), 3.47 (1H, dd, J = 3.7, 6.3). Our data for **67** was consistent with that reported for *L. sinclairii* derived "neohalicholactone".[8]

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Supporting Information Available: Details of experimental work with *O*-silyl protected lactols and the preparation of early intermediates, photocopies of ^{1}H-NMR spectra of compounds not supported by elemental analyses, and 500 MHz and COSY ^{1}H-NMR spectra of **1**, **2**, and **67** (49 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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