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Synthetic Studies Towards the Total Synthesis of Olivin: Synthesis of a Fully Functionalized Alkyne Appropriate for the Benzannulation Reaction

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Abstract

A synthetic strategy for the synthesis of olivin has been developed which features a benzannulation reaction of a Fischer carbene complex in the assembly of the tricyclic core of the molecule containing the acyclic carbohydrate side chain and the phenol functions differentiated. In this work, a synthesis of a key alkyne is developed to be used in a benzannulation reaction that constructs the B-ring of olivin. This alkyne incorporates four of the five asymmetric centers in the aglycone of olivin. The synthesis of this alkyne begins with the exclusively syn selective Mukaiyama aldol reaction of 2-trimethylsiloxyfuran with the 2S,3R-dihydroxybutanal protected as its acetonide. Conjugate addition of a vinyl cuprate to the butenolide obtained from this reaction gives a single stereoisomer of an intermediate that has all of the chiral centers of the acyclic carbohydrate side chain. The final carbon in the alkyne is introduced by a Corey-Fuchs reaction which is used to install the alkyne function. The synthesis of the alkyne is accomplished in 15 steps (6 % overall yield) and can provide gram quantities of material. Initial evaluation of the key benzannulation step was performed with alkyne **45** and carbene complex **44** which demonstrates the viability of a synthetic strategy that employs the reaction of an aryl Fischer carbene complex with a complex alkyne containing the functionality needed for the synthesis of olivin.

Keywords; Mukaiyama aldol, conjugate addition, Corey-Fuchs reaction, 2-trimethylsiloxyfuran

INTRODUCTION

The aureolic acids consist of the olivomycins, the chromomycins and the mithramycins, all of which are clinically active antitumor antibiotics and potent inhibitors of DNA-dependent RNA polymerase.[1] Studies on the structure-activity relationships of these compounds have thus far focused on chromomycin A_3 **1**. It is currently believed that **1** binds as an octahedral 2:1 drug-Mg^{2+} dimer complex in the minor grove of DNA in GC rich regions.[2] Recently it has been

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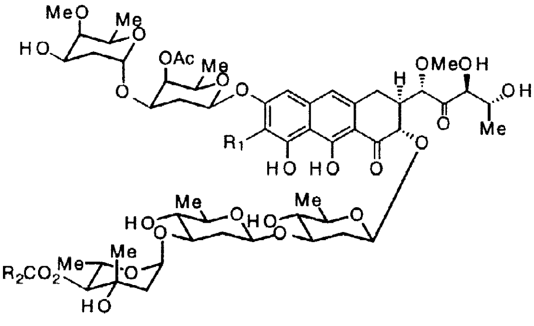
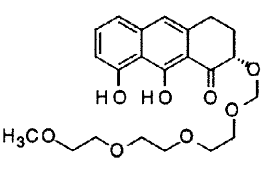
shown that the closely related mithramycin inhibits transcription of the c-myc protooncogene by binding to a GC rich promoter region and blocking gene transcription.[3] More recently, studies by Kahne *et al.* have shown that the trisaccharide moiety is critical for stable dimer formation in methanol solution while the disaccharide and acyclic side chains appear to play less important roles.[4] Interestingly, the less hindered chromomycin A_3 aglycone forms a 1:1 drug-Mg^{2+} complex.[5] In addition, Kahne has shown that a simplified TEG-chromophore conjugate **3** forms a 2:1 complex with Mg^{2+} which interacts with DNA.[6] While active against a variety of tumors, the aureolic acids often do not discriminate between cancerous and non-cancerous cells resulting in painful side effects such as anemia and internal bleeding thereby limiting their application as drugs.[1]



1 Chromomycin A_3, $R_1 = R_2 = CH_3$
2 Olivomycin A, R_1 = H, R_2 = *i*-Pr



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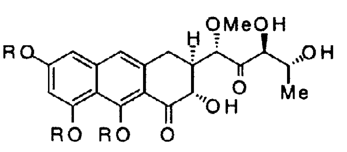
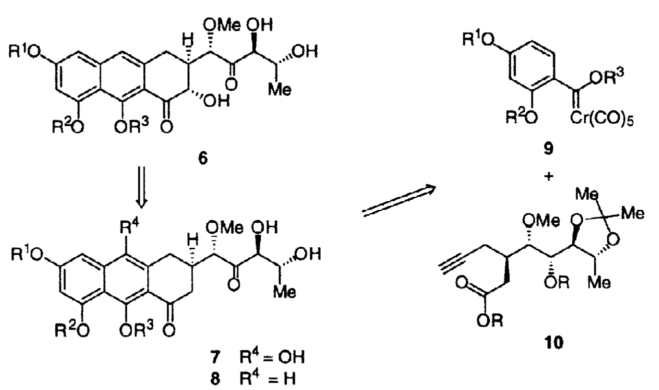
Olivomycin A **2** and it's aglycone, olivin **4** have been the focus of much of the synthetic effort in this field. In addition to studies aimed at synthesizing the oxygenated naphthalene nucleus[1,7] and the acyclic carbohydrate side chain,[8] four total syntheses of olivin **4** and it's methylated analog, tri-*O*-methylolivin **5** have appeared in the literature: Weinreb's synthesis of (±)-**5**,[9] Franck's synthesis of (+)-**5**,[10] and Roush's two synthesis of (+)-**4**.[11] In addition Roush has made substantial progress towards the total synthesis of (+)-**2**.[12]



4 R = H
5 R = Me

Our interest in the synthesis of the aureolic acid aglycones derives from our previous work on the benzannulation reaction of Fischer carbene complexes with alkynes as a general method for the synthesis of a variety of highly substituted phenols and naphthols.[13] This methodology appeared to us to be amenable to the synthesis of the aureolic acid aglycones since the anthrone portion of these molecules could be synthesized in a highly convergent manner from an aryl carbene complex **9**, and a fully functionalized alkyne **10.** In addition, due to the generality of the benzannulation reaction, many types of olivin analogs could be synthesized using this methodology since many kinds of functionality on both the carbene complex and the alkyne are tolerated by the benzannulation reaction. Previous model studies from our laboratories have shown that the hydroxyl group in an olivin tricyclic core (R^4 in **7**) could be removed via its triflate using a Pd-catalyzed procedure that had been developed for this purpose.[7a] While this model study showed the viability of our strategy towards **3**, an efficient synthesis to give gram quantities of a highly functionalized alkyne **10** was still needed. Therefore, we present our recent work directed towards this goal.

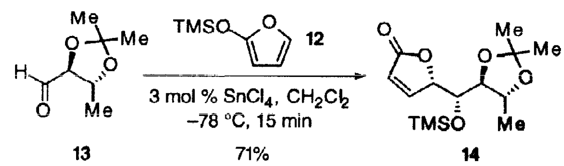


RESULTS AND DISCUSSION

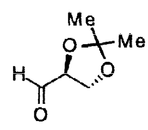
An Attempt to Synthesize the Fully Functionalized Olivin Alkyne **10** using a Suárez-type Lactol Fragmentation.

Our approach to alkyne **10** begins with a diastereoselective Mukaiyama aldol reaction between 2-trimethylsiloxyfuran **12** and aldehyde **13**[14] to give butenolide **14** as a single diastereomer in 71 % yield (eq. 1). The precedent for this reaction is the work by Casiraghi who published *syn* selective Mukaiyama reactions between **12** and D- and L glyceraldehyde, D- and L serinal and their imines.[15] In addition, Jefford has shown that the steric bulk of the aldehyde side chain does not affect the *syn* selectivity of Lewis acid catalyzed Mukaiyama reactions of **12** with hexanal, phenylacetaldehyde, isobutyraldehyde and pivaldehyde.[16] This precedent leads us to expect that the relative stereochemistry of **14** will be that shown in equation (1) and this was indeed found to be the case as discussed below.

Since the TMS group in **14** would probably not survive further manipulations, it was removed using HF·pyridine[17] to give **16** (Scheme I). The use of other desilylating reagents (TBAF, HCl, K_2CO_3) led to substantial epimerization at C-4. Even using HF·pyridine, a small amount of epimerization occurs at this center as an 80 % yield of **16** is obtained in addition to a 5 % yield of **16a**. Alcohols **16** and **16a** are easily separated by flash chromatography, and give levorotation ($[\alpha]_D$ = -45 °) and dextrorotation ($[\alpha]_D$ = +86 °) respectively. This result is consistent with the observations of Casiraghi that, regardless of the tail substituent at C-4, 2,3-



(1)



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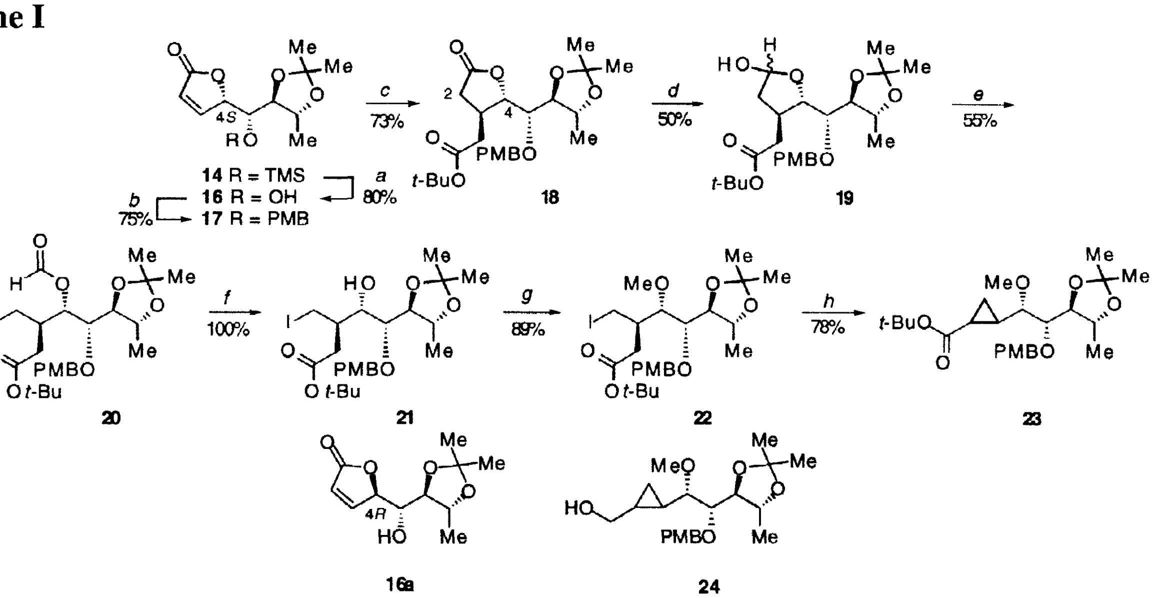
unsaturated γ-lactones having an *S* configuration at C-4 always are levorotatory while those with an *R* configuration at C-4 always are dextrorotatory, thus providing further structural and stereochemical proof for **16** and **16a**.[15]

Protection of the alcohol in **16** proved to be problematic due to steric hindrance as well as the easy epimerization of the hydrogen at C-4. It was eventually found that using the *p*-methoxybenzyl trichoroacetimidate[18] and 10 mol % CSA in CH_2Cl_2 gave **17** in 75% yield. The use of other acid catalysts (PPTS, $BF_3{\cdot}Et_2O$, and TfOH) either causes epimerization of C-4 or leds to poor conversions. The only drawbacks of this imidate/CSA procedure are long reaction times (69 h), and some epimerization at C-4 is seen when the reaction is run on a larger scale than reported in the experimental section. Introduction of the *tert*-butyl acetyl group as the 5th contiguous stereocenter is accomplished via a diastereoselective Michael addition of the anion of *tert*-butyl acetate in THF at -78 °C, to give **18** as a single diastereomer. While the stereochemistry of the conjugate addition was not rigorously proven at this point, ample

Scheme I



^{a} HF·pyridine, pyridine, 0 °C, 10 min. ^{b} $Cl_3CC(NH)OCH_2C_6H_4$-*p*-OCH_3, 10 mol % (±)-CSA, CH_2Cl_2, 25 °C , 69 h. ^{c} LDA, *tert*-butyl acetate, THF, -78 °C, 30 min; **17**, THF, -78 °C, 15 min. ^{d} 1.3 equiv. DIBAL, Et_2O, -78 °C, 1.75 h. ^{e} $PhI(OAc)_2$, I_2, *hν*, cyclohexane, 25 °C, 1 h. ^{f} $KHCO_3$, MeOH, H_2O, 25 °C, 5 h. ^{g} Me_3OBF_4, Proton Sponge, CH_2Cl_2, 25 °C, 18 h. ^{h} Trimethylsilylacetylene, *n*-BuLi/hex, THF, 0 °C; **23**, THF, HMPA, -20 °C to 0 °C, 1.25 h.

literature precedent shows that a variety of nucleophiles undergo conjugate addition anti to the side chain substituent at C-4 in γ-lactones such as **17**.[19]

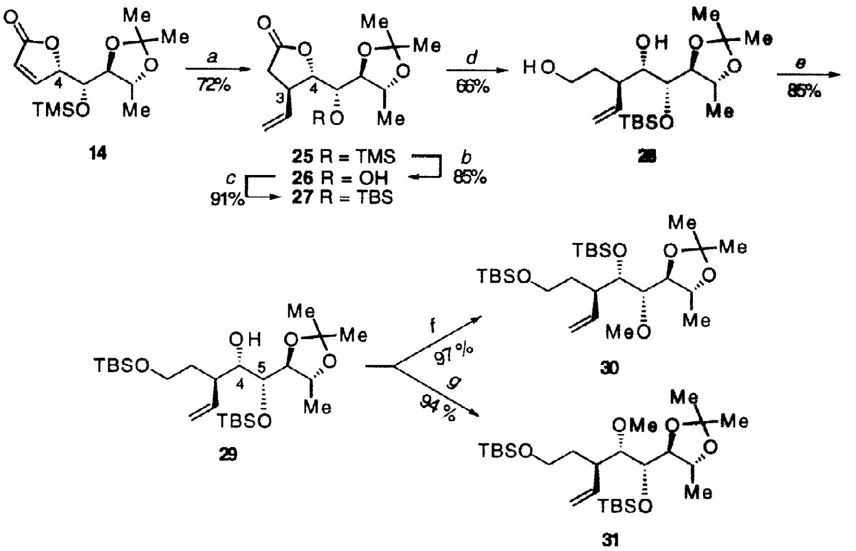
Lactone **18** may be chemoselectively reduced to lactol **19** as a 1:1 mixture of epimers at C-1 in 50 % (unoptimized) yield with DIBAL-H in Et_2O, leaving the *tert*-butyl ester moiety intact. All attempts to olefinate the keto isomer lactol **19** using standard Wittig and Horner-Emmons reagents failed, possibly because **19** only exists in the lactol form. We felt that opening of the lactol in **19** could be carried out using a Suárez-type fragmentation[20] to produce a secondary hydroxyl group at C-4 and an electrophilic center at C-2 where an acetylene group could be attached. According to this plan, lactol **19** undergoes Suárez lactol fragmentation ($PhI(OAc)_2$, I_2, *hν*, cyclohexane), to give iodoformate **20** in 55 % yield. Hydrolysis of the formate moiety is accomplished using $KHCO_3$, MeOH/H_2O to give **21** (quantitative yield), and the hydroacyl group in **21** is methylated using Meerwein's salt/Proton Sponge[21] to give **22** in 89 % yield. Methylations using NaH/CH_3I or Ag_2O/CH_3I appear to give a 5-membered ring lactone and a 4-membered ring oxetane, resulting from intramolecular attack of the alcohol on the *tert*-butyl ester and the primary iodide respectively.

Unfortunately, excess lithium trimethylsilylacetylide in THF/HMPA[22] fails to give S_N2 type displacement at the primary iodide in **22**. Instead cyclopropane **23** is produced in 78 % yield by abstraction of a proton alpha to the ester moiety of **22** to give the ester enolate, followed by intramolecular displacement of the iodide. In addition to ^1H NMR, IR and mass spectroscopy which confirm the structure of **23**, the 75 MHz ^1H-coupled ^{13}C NMR spectrum of **23** clearly shows three aliphatic carbon resonances (δ 15.3 (t, $J_{C\text{-}H}$ = 163.1 Hz), δ 17.3 (d, $J_{C\text{-}H}$ = 166.6 Hz), and δ 22.6 (d, $J_{C\text{-}H}$ = 163.0 Hz)) where the $J_{C\text{-}H}$ coupling constants indicate that these aliphatic resonances must be cyclopropyl carbons. Substitution of the iodide in **22** for an acetylene using a SmI_2-mediated radical addition gives a complicated mixture of products that were not characterized.[23] Finally, several attempted openings of **23** with lithium trimethylsilylacetylide at the least substituted position of the cyclopropane gives a compound whose ^1H NMR, IR and ^{13}C NMR spectra are consistent with alcohol **24**. To our knowledge, the opening of singly activated (one-electron withdrawing group) cyclopropanes of type **23** with nucleophiles has not been published. The nucleophilic opening of doubly activated cyclopropanes however is known.[24]

The Synthesis of the Fully Functionalized Olivin Alkyne **10**

Since we were unable to use the Suárez fragmentation route to synthesize alkyne **10**, we opted to explore a more straightforward strategy that is presented in Schemes II-IV. Due to epimerization problems at C-4 in **16**, we decided to attempt a nucleophilic conjugate addition to butenolide **14**. We decided not to use the anion of *tert*-butyl acetate in this reaction, as in Scheme I, since we felt the that the resulting *tert*-butyl ester would not be stable to reducing conditions that we anticipated using to open up the resulting lactone at a later stage in the synthesis. Using a vinyl group as the nucleophile appeared to be a good choice since this moiety could be converted to a *tert*-butyl acetyl group via hydroboration, oxidation to the carboxylic acid and esterification.

Scheme II



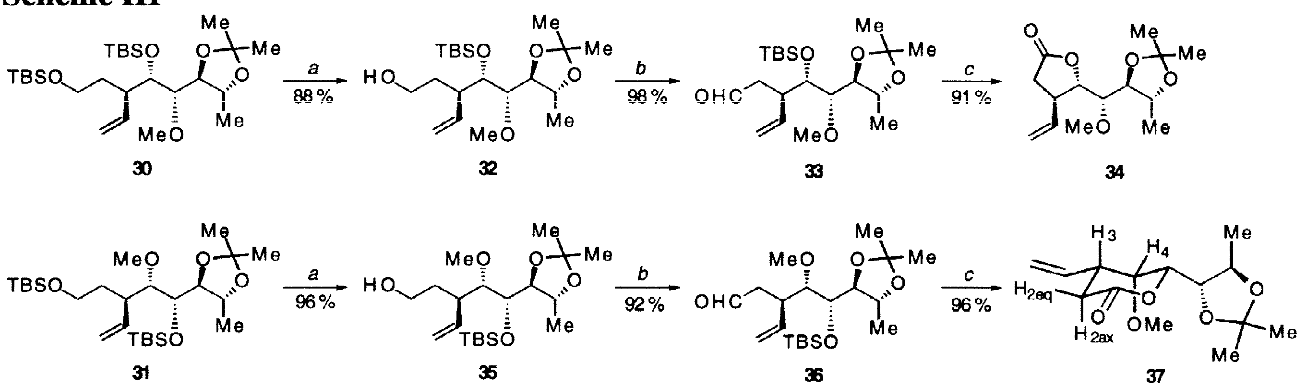
[a] (vinyl)2Cu(CN)Li2, Et2O, -78 °C, 30 min. [b] HF·pyridine, THF, 0 °C, 30 min. [c] TBSOTf, 2,6-lutidine, CH2Cl2, 25 °C, 72 h. [d] LiBH4, Et2O, 0 to 25 °C, 3.5 h. [e] TBSCl, Et3N, cat. DMAP, CH2Cl2, 25 °C, 14 h. [f] NaH, CH3I, THF/DMF (4/1), 0 to 25 °C, 14 h. [g] Me3OBF4, Proton Sponge, CH2Cl2, 25 °C, 20 h.

After unsuccessfully trying a number of vinyl cuprate reagents (vinyl-MgBr/10 mol % $CuBr_2$·Me_2S, $(vinyl)_2CuLi$, $(vinyl)_2CuLi$/TMSCl), we found that the more reactive higher-order vinyl cuprate $(vinyl)_2Cu(CN)Li_2$[25] gives an excellent yield of lactone **25** as a single diastereomer (Scheme II). Surprisingly, the TMS ether remains intact in the presence of $(vinyl)_2Cu(CN)Li_2$, an important point since conjugate additions of all vinyl cuprate reagents to alcohol **16** failed. As in the case of the conjugate addition of lithium *tert*-butyl acetate to **17**, literature precedent exists which suggests that nucleophiles should add to **14** opposite to the C-4 side chain to give the stereochemistry depicted in **25**.[20] Removal of the TMS moiety was accomplished using HF·pyridine[18a] to give **26** in 85 % yield as an off-white solid. Numerous attempts to grow suitable crystals in order to confirm the absolute stereochemistry of **26** by X-ray diffraction failed, however simple 1-D ^{1}H NMR decoupling experiments showed the coupling constant of the protons at C-3 and C-4 to be J = 8.8 Hz, which suggests but does not confirm a *trans* relationship. Attempts to form the PMB ether of **26** using the PMB-trichloroacetimidate[19] using a number of protic and Lewis acids (TfOH, PPTS, CSA, BF_3·OEt_2) gave poor conversions to the corresponding PMB ether, and basic conditions (NaH/PMBCl) lead to decomposition. However, the alcohol of **26** may be protected as it's TBS ether (TBSOTf/2,6-lutidine)[26] to give **27** in excellent yield (91 %). Overall, the procedure outlined above which converts **14** to **27** is much more efficient than the procedure which converts **14** to **17** since epimerization problems are eliminated by doing the vinyl cuprate addition to **14** first, and there are no problems with reaction scale-up as seen in the conversion of alcohol **16** to PMB ether **17**.

Given the problems encountered attempting to olefinate lactol **19**, lactone **27** was reduced to diol **28** with $LiBH_4$ in Et_2O in 66 % yield. The use of $LiAlH_4$ in this reduction gives both **28** (20 % yield) as well as the triol which results from loss of the TBS group (29 % yield).

Selective protection of the primary hydroxyl group with TBSCl/Et_3N/catalytic DMAP[27] gives **29** in 85 % yield and methylation of the secondary hydroxyl group of **29** with NaH/CH_3I gives an excellent yield (97 %) of a compound that we at first assumed to be **31**. In fact the compound obtained from this reaction is **30** where the TBS ether has migrated from the C-5 to the C-4 hydroxyl group and the C-5 hydroxyl is methylated. This silyl migration was proven as follows (Scheme III): deprotection of the primary TBS ether in the presence of a secondary TBS ether using HF·pyridine[18a] gives alcohol **32** (88 % yield), Swern oxidation[28] produces aldehyde **33** (96 % yield), removal of the secondary TBS group with excess TBAF, and oxidation of the resulting lactol with PCC/NaOAc[29] gives the 5-membered ring lactone **34** (91 % yield, two steps). That the expected six-membered ring lactone derived from **30** did not form was proven by the lactone carbonyl IR stretch of 1782 cm^{-1} for **34**. We found it surprising that the TBS migration from the C-5 to the C-4 hydroxyl group was complete and that a mixture of products was not obtained.

Scheme III



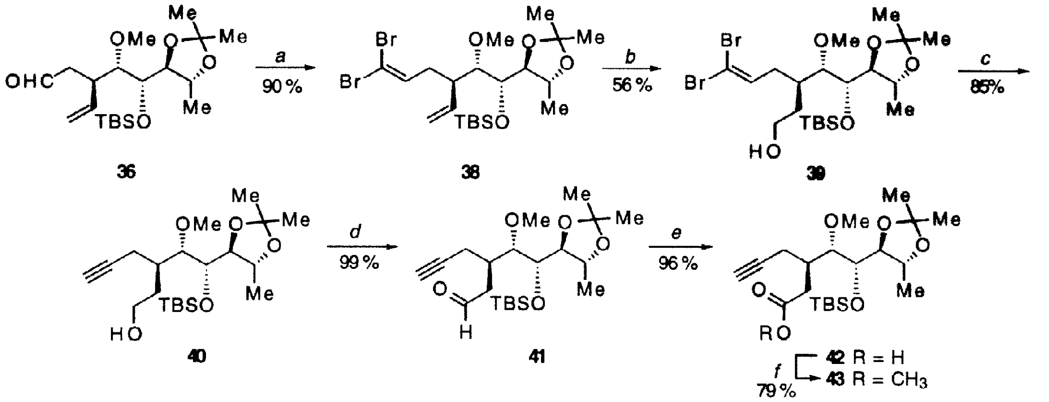
^{a} HF·pyridine, THF, 0 to 25 °C, 3 h. ^{b} DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 15 min; Et_3N, -78 to 25 °C, 2 h. ^{c} TBAF, THF, 25 °C, 1.3 h; PCC, NaOAc, CH_2Cl_2, 25 °C, 15 h.

Fortunately, methylation without TBS migration occurred by using Me_3OBF_4/Proton Sponge[22] to give **31** in 94 % yield (Scheme II). The structure of **31** and its absolute stereochemistry were determined by converting it to lactone **37** via the same sequence used to convert **30** to lactone **34** (Scheme V - HF·pyridine desilylation, Swern oxidation, TBAF desilylation and PCC oxidation). Lactone **37** has practically identical spectroscopic characteristics to the corresponding cyclohexyl acetal of **37** which was synthesized by Roush in his synthesis of (+)-olivin.[12b] In particular, **37** has a 6-membered ring lactone carbonyl stretch at 1748 cm^{-1}. The 500 MHz ^1H NMR ($CDCl_3$) spectrum shows a large diaxial coupling between H_{2ax} (d, 2.70) and H_3 (d, 2.60-2.68) of J = 12.5 Hz, and this data taken together with the fact that H_4 appears as a triplet is only consistent with the structure and stereochemistry of **37**.

The final steps to the olivin alkyne **10** were completed as follows (Scheme IV). Aldehyde **36** is converted to the dibromoolefin **38** in 90 % yield using the procedure of Corey and Fuchs.[30] Treatment of **38** with *n*-BuLi gives the corresponding enyne which fails to undergo regioselective hydroboration/oxidation at the terminal olefin even using 9-BBN which is known to preferentially hydroborate olefins in the presence of acetylenes.[31] A regioselective hydroboration/oxidation of the terminal olefin of **38** is possible however using excess

BH_3·THF/basic H_2O_2 to give alcohol **39** in 56 % yield. Presumably the monosubstituted olefin is more reactive to BH_3·THF than the more hindered and deactivated trisubstituted dibromoolefin. Other more hindered hydroboration agents (Sia_2BH, 9-BBN) were also tried in attempts to give higher yields of **39**, but instead they gave lower product yields and more complex product mixtures.

Scheme IV

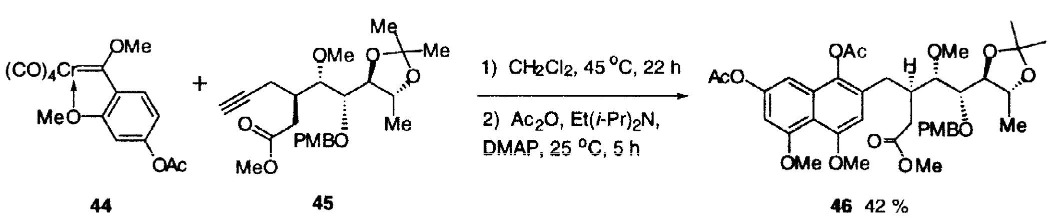


[a] CBr_4, Ph_3P, CH_2Cl_2, CH_2Cl_2, 25 °C, 35 min. [b] 2.0 equiv. BH_3·THF, THF, -15 °C, 26 h; CH_3OH; 3 N NaOH; 30 % H_2O_2, 25 °C, 2 h. [c] 3 equiv. *n*-BuLi/hexanes, THF, - 78 °C, 1 h; 25 °C, 1 h. [d] Dess-Martin periodinane, CH_2Cl_2, 25 °C, 1.25 h. [e] $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 25 °C, 1.5 h. [f] CH_2N_2, Et_2O, 0 °C, 15 min.

Alcohol **39** may then be converted to alcohol **40** in excellent yield (85 %) using the conditions of Corey and Fuchs.[31] Oxidation of alcohol **40** to acid **42** is best accomplished in a two-step procedure by first oxidizing **40** to aldehyde **41** using the Dess-Martin periodinane (99 % yield),[32] and oxidizing **41** to carboxylic acid **42** using buffered $NaClO_2$/2-methyl-2-butene[33] in practically quantitative yield (96 %). Esterification of **42** to the methyl ester **43** is accomplished using CH_2N_2 (79 % yield) which completes the synthesis of the fully functionalized olivin alkyne **10**. Using the procedures presented above, gram quantities of acid **42**.

In a preliminary study on the benzannulation of the alkynes of the general structure **10**, the reaction of carbene complex **44**[36] with the methyl ester **45** was carried out in methylene chloride and after the reaction was complete the phenol product was acetylated[37] to give the desired penta-substituted naphthalene **46** which contains all of the carbons of olivin. Four other minor products were observed for this reaction but the identity of these compounds has not yet been determined. It is known that the success of the benzannulation reaction can be highly dependent on the reaction conditions and on the substituents on the carbene complex and on the alkyne.[13,36]

Scheme V



In one case of a highly oxygenated alkyne, the reaction failed to give any of the normal phenol product but this seems to be related to the presence of methoxy groups in the 2 and 5-positions of the aryl ring of the carbene complex.[38] It is likely that once the minor products of the reaction of carbene complex **44** with alkyne **45** are determined, improved yields of the naphthalene **46** from this reaction will be possible with proper choice of reaction conditions.[36]

CONCLUSION

We have presented a stereoselective route to alkyne **43**, a key intermediate in our approach towards the total synthesis of olivin **4** using the benzannulation reaction. The synthesis starts with commercially available 2-trimethylsiloxyfuran **12** and the threonine derived aldehyde **13** and requires 15 steps (overall yield of 6 %). The synthesis of **43** features a completely diastereoselective Mukaiyama reaction between **12** and aldehyde **13** which establishes 4 of the 5 stereocenters in **43**, a diastereoselective vinyl cuprate addtion with $(vinyl)_2Cu(CN)Li_2$ which establishes the fifth stereocenter in **43**, and a regioselective hydroboration/oxidation of **38** with BH_3·THF which distinguishes the two differentially substituted olefins of **38** to give alcohol **39**. Preliminary studies of the reaction of alkyne **45** with carbene complex **44** demonstrates that the benzannulation reaction of highly functionalized alkyne of the type **10** will provide for a viable approach to the synthesis of olivin.

EXPERIMENTAL SECTION

General Information. The atmosphere under which synthetic reagents were combined was argon. Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Prior to use, tetrahydrofuran and diethyl ether were distilled from Na/benzophenone ketyl, methylene chloride, pyridine, triethylamine, 2,6-lutidine and diisopropylamine were distilled from CaH_2, and N,N'-dimethylformamide was stirred for 12 h over BaO, decanted and distilled under reduced pressure.[34] All of the above compounds were stored under N_2 after distillation. Hexamethylphosphoramide was distilled under reduced pressure onto activated 4Å molecular sieves and stored under Ar. All other reagents obtained from commercial suppliers were used as received. Flash chromatography was carried out according to Still[35] using 230-240 mesh silica gel. Routine ^1H NMR spectra were recorded on a DS 1000 (Chicago built) 500 MHz spectrometer, a 400 MHz Varian XL spectrometer or a General Electric QE 300 MHz spectrometer with tetramethylsilane (δ 0.0) as an internal reference. Routine ^{13}C NMR spectra were recorded on General Electric QE-300 spectrometer at 75 MHz with the central peak of the $CDCl_3$ triplet (δ 77.0) as an internal reference. Infrared spectra were recorded on a Nicolet 20SXB FTIR spectrometer. Low-resolution mass spectra were recorded on a Finnigan 1015 instrument, and high-resolution mass spectra were recorded on a VG 70-250 mass spectrometer. Elemental Analyses were performed by Galbraith Inc, Knoxville, TN.

TMS Butenolide 14. To 14.98 g (104 mmol) of aldehyde **13**[15a], 11.7 mL (10.87 g, 69.3 mmol) of 2-trimethylsiloxyfuran **12**, and 200 mL of CH_2Cl_2 at -78 °C was added 0.24 mL (534 mg, 2.05 mmol) of freshly distilled $SnCl_4$. After stirring at -78 °C for 15 min, the mixture was poured into 300 mL of brine and diluted with 400 mL of Et_2O. The layers were separated, and the organics were washed with 300 mL of H_2O, 300 mL brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/CH_2Cl_2/Et_2O (10/1/1 to 2/1/1), gave 14.85 g (49.43 mmol, a 71 % yield) of **14** as a clear oil which solidifies to a wax in a -20 °C freezer. Rf = 0.18 (4/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = -63.5° (*c.* 0.0026, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.16 (s, 9 H), 1.35 (s, 3 H), 1.37 (d, *J* = 6.0 Hz, 3 H), 1.42 (s, 3 H), 3.65-3.75 (m, 2 H), 4.01 (pent, *J* = 6.0 Hz, 1 H), 5.05-5.11 (m, 1 H), 6.12 (dd, *J* = 2.0, 6.0 Hz, 1 H), 7.49 (dd, *J* = 1.0, 6.0 Hz, 1 H); IR (NaCl, thin film, cm^{-1}): 2986m, 1760s, 1300m, 1253s, 1162s, 1148m, 1094s, 1061s, 1039m, 907m, 845s; ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.5, 19.8, 26.8, 27.2, 75.5, 76.4, 81.4, 85.1, 108.7, 122.2, 153.7, 172.5.

Hydroxy Butenolides 16 and 16a. HF·pyridine (5 mL) was added dropwise to 5.0 g (16.64 mmol) of **14** in 75 mL of pyridine at 0 °C. After stirring at 0 °C for 10 min, the reaction was carefully quenching by slowly adding 200 mL saturated aqueous $NaHCO_3$. After pouring into 200 mL of H_2O and extraction with 6 x 75 mL of Et_2O, the combined organics were washed with 1 x 200 mL of brine, dried over $MgSO_4$, filtered and evaporated to leave an oil. Excess pyridine was removed by evaporating the oil with 3 x 100 mL of benzene. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (2/1/1 to 1/1/1), gave 3.03 g (13.28 mmol, an 80 % yield) of **16** as a white solid (mp 87-91 °C) after removal of solvents in addition to 200 mg (0.88 mmol, a 5 % yield) of **16a** as a white solid. **16**: Rf = 0.11 (1/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = -45.2° (*c.* 0.002, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 3 H), 1.39 (d, *J* = 6.0 Hz, 3 H), 1.42 (s, 3 H), 2.86 (d, *J* = 7.0 Hz, 1 H - OH, exchanges with D_2O), 3.32-3.40 (m, 2 H), 4.10 (pent, *J* = 6.0 Hz, 1 H), 5.23 (t, *J* = 1.5 Hz, 1 H), 6.12 (dd, *J* = 2.0, 6.0 Hz, 1 H), 7.54 (dd, *J* = 1.5, 6.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 27.3, 27.8, 74.2, 77.5, 81.5, 85.3, 109.3, 122.5, 155.1, 173.8; IR ($CHCl_3$ solution, cm^{-1}): 3610-3425brw, 2988e, 2879w, 1755s, 1373w, 1096w; MS (EI) *m/z* (relative intensity) 213 (M - CH_3, 42), 171 (12), 153 (11), 145 (9), 115 (53), 101 (19), 97 (10), 84 (14), 83 (12), 69(11), 59 (100); HRMS (EI) calcd for $C_{10}H_{13}O_5$ (M^+ - CH_3) 213.0763, found 213.0767. **16a**: Rf = 0.14 (1/1/1 hexanes/ CH_2Cl_2/Et_2O); mp 86-89 °C; $[\alpha]_D$ = 86.4° (*c* 0.003); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (d, *J* = 6.0 Hz, 3 H), 1.40 (s, 3 H), 1.42 (s, 3 H), 2.80 (d, *J* = 4.5 Hz, 1 H - OH, exchanges with D_2O), 3.57 (t, *J* = 7.5 Hz, 1 H), 3.98-4.06 (m, 1 H), 4.15 (pent, *J* = 6.0 Hz, 1 H), 5.18-5.26 (m, 1 H),6.18 (dd, *J* = 2.0, 6.0 Hz, 1 H), 7.58 (dd, *J* = 1.5, 6.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 26.8, 27.3, 72.0, 76.4, 81.4, 84.2, 109.0, 122.9, 153.5, 173.3; IR ($CHCl_3$ solution, cm^{-1}): 3610-3430brw, 2988w, 2879w, 1759s, 1375w, 1092w, 902w; MS (EI) *m/z* (relative intensity) 213 (M^+ - CH_3, 51), 153 (14), 115 (38), 101 (22), 84 (17), 83 (18), 69(15), 59(100); HRMS (EI) calcd for $C_{10}H_{13}O_5$ (M^+ - CH_3) 213.076 3, found 213.0765.

PMB Butenolide 17. To 21 mg (0.71 mmol) of 80 % NaH/mineral oil in 10 mL of Et_2O at room temperature was added 0.88 mL (975 mg, 7.05 mmol) of *p*-methoxybenzyl alcohol in drops over 3 min. After stirring at room temperature for 30 min, the reaction mixture was cooled to 0 °C and 0.71 mL (1.02 g, 7.05 mmol) of Cl_3CCN was added dropwise. After slowly warming to room temperature over 4 h, the resulting orange solution was evaporated to an oil, dissolved in 10 mL of hexanes/3 drops of CH_3OH, filtered through Celite and evaporated to a yellow oil to give to the crude trichloroacetimidate. To this oil were added 20 mL of CH_2Cl_2, 805 mg (3.53 mmol) of **16**, 82 mg (0.35 mmol) of (±)-camphor sulfonic acid and the resulting solution was stirred at room temperature. The reaction was most conveniently followed by ^{1}H NMR by monitoring the disappearance of the δ 7.54 (dd, 1 H) for **16** and the appearance of the δ 7.45 (dd, 1 H) for **17**. After 69 h, the reaction mixture was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted with 3 x 30 mL of Et_2O, and the combined organics were washed with 1 x 50 mL of H_2O, 1 x 50 mL of brine, dried over $MgSO_4$, filtered and evaporated to a while solid. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (4/1/1 to 2/1/1), gave 1.17 g (3.36 mmol, a 95 % yield) of a white solid. ^{1}H NMR indicated contamination by a polymeric material (d, 6.1 br s; d, 6.6 br s). Repeated flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (4/1/1 to 2/1/1), gave 923 mg (2.65 mmol, a 75 % yield) of **17** as a colorless oil. Rf = 0.14 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 3 H), 1.32 (d, J = 6.0 Hz, 3 H - partially obscured by the s at δ 1.31), 1.39 (s, 3 H), 3.49 (q, J = 4.6 Hz, 1 H), 3.71 (t, J = 8.0 Hz, 1 H), 3.80 (s, 3H), 3.87-3.95 (m, 1 H), 4.51 (AB quartet, J = 11.0 Hz, 2 H), 5.16-5.22 (m, 1 H), 6.10 (dd, J = 1.7, 6.0 Hz, 1 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 7.45 (dd, J = 1.7, 6.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 26.8, 27.3, 55.3, 74.5, 80.5, 80.7, 85.0, 102.2, 108.8, 113.9, 122.0, 128.9, 130.0, 153.4, 159.6, 172.8; IR (NaCl plate, thin film, cm^{-1}): 2985m, 2933m, 1750s, 1612m, 1513s, 1248s, 1162m, 1078s, 1033s, 822m; MS (EI) *m/z* (relative intensity) 348 (M^+, 5), 333 (M^+ - CH_3, 20), 290 (25), 207 (15), 166 (90), 153 (40), 137 (85), 121 (100); HRMS (EI) calcd for $C_{19}H_{24}O_6$ 348.1573, found 348.1548.

PMB *tert*-butoxyacetyl Lactone 18. To 1.95 mL (1.40 g, 13.88 mmol) of di-isopropylamine in 25 mL of THF at -78 °C was added 5.55 mL (13.88 mmol) of a 2.50 M solution of *n*-BuLi/hexanes in drops over 5 min. After stirring at -78 °C for 15 min, 1.88 mL (1.61 g, 13.88 mmol) of *tert*-butyl acetate was added in drops over 3 min. After 30 min at -78 °C, a pre-cooled -78 °C solution of 1.21 g (3.47 mmol) of **17** in 8 mL of THF was added in drops via cannula over 5 min. After 15 min at -78 °C, the reaction mixture was poured into 100 mL of brine, extracted with 1 x 100 mL of Et_2O, and the organics were washed with 1 x 100 mL of H_2O, 1 x 100 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (4/1/1 to 2/1/1), gave 1.18 g (2.54 mmol, a 73 % yield) of **18** as a off white wax. Rf = 0.29 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, J = 5.7 Hz, 3 H), 12.37 (s, 3 H), 1.39 (s, 3 H), 1.45 (s, 9 H), 2.09-2.17 (m, 1 H), 2.34-2.42 (m, 2 H), 2.68-2.76 (m, 2 H), 3.65 (dd, J = 2.0, 8.0 Hz, 1 H), 3.78 (q, J = 7.2 Hz, 2 H), 3.81 (s, 3 H), 4.38-4.44 (m, 1 H), 4.65 (AB quartet, J = 11.4 Hz, 2 H), 6.87 (d, J = 8.9 Hz, 2 H), 7.22 (d, J = 8.9 Hz, 2 H); IR (NaCl plate, thin film, cm^{-1}): 2981w, 2935w, 1775m, 1725s, 1611w, 1514m, 1369m, 1250m, 1172m, 1156m, 1032m, 826m; MS (EI) *m/z* (relative intensity): 464 (M^+, 5), 449 (M^+- CH_3, 10), 407 (5), 349 (100), HRMS (EI) calcd for $C_{25}H_{36}O_8$ 464.2410, found 464.2408.

PMB *tert*-butoxyacetyl Lactol 19. To a -78 °C solution of 961 mg (2.07 mmol) of **18** in 30 mL of Et_2O was added 2.69 mL (2.69 mmol) of a 1.0 M solution of DIBAL/hexanes in drops over 5 min. After stirring at -78 °C for 1.75 h, TLC indicated that no starting material remained. The reaction mixture was quenched with 10 mL of a saturated aqueous Rochelle's salt solution, warmed to room temperature and stirred at room temperature for 30 min until the organic layer was clear. After extraction with 3 x 50 mL of Et_2O, the combined organics were washed with 1 x 100 mL brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (4/1/1 to 1/1/1) gave 480 mg (1.03 mmol, a 50 % yield) of **19** (1:1 mixture of diastereomers by ^1H NMR) as a colorless oil. Rf = 0.25 (1/1/1 hexanes/ CH_2Cl_2/Et_2O); IR (NaCl, thin film, cm^{-1}): 3520-3340brw, 2981m, 2934m, 1726s, 1613w, 1515s, 1368m, 1250s, 1152s, 1037m, 978w, 824w; MS (EI) *m/z* (relative intensity) 466 (M+, 2), 448 (M+ - H_2O, 20), 392 (60), 351 (20), 334 (40), 248 (25), 183 (60), 145 (80), 121 (100).

***tert*-Butoxyacetyl formyl Iodide 20.** In a 250 mL single-neck round-bottom flash were combined 471 mg (1.01 mmol) of **19** in 100 mL of cyclohexane, 358 mg (1.11 mmol) of $PhI(OAc)_2$, and 260 mg (1.01 mmol) of I_2. The flask was fitted with a water-cooled reflux condenser, degassed by bubbling Ar through it with vigorous stirring for 15 min, and irradiated with a 250 Watt sun lamp for 1 h. The reaction mixture was poured into a separatory funnel containing 50 mL Et_2O, 50 mL of saturated aqueous $NaHCO_3$, 50 mL of saturated aqueous $Na_2S_2O_3$, and extracted. The aqueous layer was washed with 1 x 50 mL of Et_2O, and the combined organics were washed with 1 x 100 mL of brine, dried over $MgSO_4$, filtered and evaporated to a red oil. Flash chromatography on silica gel, eluting with hexanes/CH_2Cl_2/Et_2O (10/1/1 to 2/1/1), gave 329 mg (0.56 mmol, a 55 % yield) of **20** as a clear oil. Rf = 0.54 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.0 Hz, 3 H), 1.36 (s, 3 H), 1.39 (s, 3 H), 1.46 (s, 9 H), 2.34-2.42 (m, 1 H), 2.52-2.60 (m, 2 H), 3.11-3.19 (m, 1 H), 3.52 (dd, *J* = 2.9, 10.2 Hz, 1 H), 3.61 (t, *J* = 7.6 Hz, 1 H), 3.68 (dd, *J* = 5.2, 7.6 Hz, 1 H), 3.81 (s, 3 H), 3.95-4.02 (m, 1 H), 4.59 (AB quartet, *J* = 10.8 Hz, 2 H), 5.10-5.16 (m, 1 H), 6.87 (d, *J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 7.9 Hz, 2 H), 8.10 (s, 1 H); IR (NaCl plate, thin film, cm^{-1}): 2980w, 2935w, 1728s, 1609w, 1515m, 1368m, 1249s, 1165s, 1038m.

***tert*-Butoxyacetyl hydroxy Iodide 21.** To 329 mg (0.56 mmol) of **20** in 14 mL of CH_3OH and 5.5 mL of H_2O was added 334 mg (3.33 mmol) of $KHCO_3$. After stirring at room temperature for 5 h, the reaction mixture was poured into 50 mL of brine, extracted with 3 x 25 mL of Et_2O, and the combined organics were washed with 1 x 50 mL of H_2O, 1 x 50 mL of brine, dried over $MgSO_4$, filtered and evaporated to give 315 mg (0.56 mmol, a quantitative yield) of **21** as a colorless oil which was pure by 400 MHz ^1H NMR. Rf = 0.44 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, *J* = 6.0 Hz, 3 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 1.45 (s, 9 H), 1.89-1.94 (m, 1 H - OH, exchanges with D_2O), 2.29-2.37 (m, 2 H), 2.78 (d, *J* = 7.8 Hz, 1 H), 3.50 (dd, *J* = 3.2, 9.9 Hz, 1 H), 3.55-3.65 (m, 3 H), 3.74-3.79 (m, 1 H), 3.80 (s, 3 H), 4.00-4.06 (m, 1 H), 4.62 (AB quartet, *J* = 11.0 Hz, 2 H), 6.89 (d, *J* = 6.7 Hz, 2 H), 7.27 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3, 18.9, 26.9, 27.2, 28.1, 29.7, 37.1, 38.9, 55.3, 72.0, 73.5, 75.1, 78.0, 80.9, 82.3, 108.5, 114.0, 129.2, 130.0, 171.1; IR (NaCl plate, thin film, cm^{-1}): 3600-3400brw, 2980m, 2934m, 2911w, 2875w, 1726s, 1612m, 1515s, 1456m, 1386s, 1251s, 1155s, 1036s, 849m; MS (EI) m/z (relative intensity) 564 (M+, 3), 549 (M+ - CH_3, 3), 535 (5), 508 (40), 432 (15), 410 (5), 366 (70), 310 (30), 296 (20), 243 (35), 225 (25), 207 (75), 167 (45), 148 (85), 137 (100).

***tert*-Butoxyacetyl methoxy Iodide 22.** To 36 mg (0.064 mmol) of **21** in 3 mL of THF was added 65 mg (0.30 mmol) of Proton Sponge followed by 38 mg (0.26 mmol) of $(CH_3)_3O^+BF_4^-$. After stirring at room temperature for 15 h, TLC indicated that some starting material remained. An additional 65 mg (0.30 mmol) of Proton Sponge and 38 mg (0.26 mmol) of $(CH_3)_3O^+BF_4^-$ were added and this mixture was stirred an additional 2 h until TLC indicated that all starting material had been consumed. After pouring into brine and extraction with 2 x 10 mL of Et_2O, the combined organics were washed with 1 x 20 mL of 0.5 N HCl, 1 x 20 mL of H_2O, 1 x 20 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (10/1/1), gave 33 mg (0.057 mmol, an 89 % yield) of **22** as a colorless oil. Rf = 0.41 (4/1/1 hexanes/ CH_2Cl_2/Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, J = 6.0 Hz, 3 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 1.45 (s, 9 H), 2.23-2.30 (m, 1 H), 2.41 (d, J = 6.7, 16.1 Hz, 1 H), 2.50 (dd, J = 6.8, 16.1 Hz, 1 H), 3.30-3.38 (m, 2 H), 3.50-3.54 (m, 1 H), 3.53 (s, 3 h), 3.57 (dd, J = 4.4, 7.6 Hz, 1 H), 3.66 (t, J = 7.6 Hz, 1 H), 3.77 (s, 3 H), 4.04 (pent, J = 6.7 Hz, 1 H), 4.56 (AB quartet, J = 10.7 Hz, 2 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 1.0, 10.7, 19.4, 26.9, 27.2, 28.1, 29.7, 37.5, 39.3, 55.3, 61.4, 74.3, 75.6, 80.8, 81.0, 82.9, 108.1, 113.8, 120.8, 129.9, 171.3; IR (NaCl plate, thin film, cm^{-1}): 2979m, 2934m, 2906m, 2835w, 1727s, 1613w, 1515s, 1456w, 1368s, 1303w, 1250s, 1179s, 1161s, 1084s, 1065s, 1037m, 847w, 822w; MS (EI) m/z (relative intensity) 578 (M^+, 1), 563 (M^+ - CH_3, 2), 521 (10), 465 (5), 366 (5), 313 (5), 257 (20), 129 (20), 121 (100).

Cyclopropane 23. To a 0 °C solution of 0.08 mL (56 mg, 0.57 mmol) of trimethylsilylacetylene and 1 mL of THF was added 40 mL (0.086 mmol) of a 2.53 M solution of *n*-BuLi/hexanes. After stirring at 0 °C for 30 min, this solution was added to a -20 °C solution of 33 mg (0.057 mmol) of **22**, 2 mL of HMPA and 0.5 mL of THF in drops via a cannula. After stirring at -20 °C for 15 min and 0 °C for 1 h, the reaction mixture was quenched with 5 mL of H_2O, and extracted with 3 x 10 mL of Et_2O. The combined organics were washed with 2 x 20 mL of H_2O, 1 x 20 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (4/1/1 to 2/1/1), gave 20 mg (0.044 mmol, a 78 % yield) of **23** as a colorless oil. Rf = 0.13 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 1.03-1.07 (m, 1 H), 1.27 (d, J = 5.9 Hz, 3 H), 1.32 (s, 3 H), 1.36 (s, 3 H), 1.37-1.47 (complex m, 2 H - partially obscured by the d 1.42 singlet), 1.42 (s, 9 H), 1.69-1.75 (m, 1 H), 2.86 (dd, J = 2.1, 8.4 Hz, 1 H), 3.44 (s, 3 H), 3.51 (dd, J = 1.9, 7.7 Hz, 1 H), 3.74 (t, J = 7.7 Hz, 1 H), 3.77 (s, 3 H), 3.83 (pent, J = 6.1 Hz, 1 H), 4.54 (AB quartet, J = 10.7 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3 (t, $J_{C\text{-}H}$ = 163.1 Hz), 17.3 (d, $J_{C\text{-}H}$ = 166.6 Hz), 19.6 (q, $J_{C\text{-}H}$ = 126.3 Hz), 22.6 (d, $J_{C\text{-}H}$ = 163.0 Hz), 27.0, 27.3, 28.1, 28.2, 55.2, 58.3, 75.0, 75.8, 80.4, 80.7, 82.5, 82.8, 107.8, 113.7, 129.8, 130.2, 172.8; IR (NaCl plate, thin film, cm^{-1}): 2980m, 2935w, 2909w, 2837w, 1720s, 1613w, 1515m, 1457w, 1368m 1250s, 1214w, 1173m, 1152s, 1087s, 1058m, 853w, 824w; MS (EI) m/z (relative intensity) 450 (M^+, 10), 435 (M^+ - CH_3, 10), 393 (45), 335 (35), 218 (15), 207 (30), 185 (100).

Cyclopropane alcohol 24. To a 0 °C solution of 0.06 mL of trimethylsilylacetylene in 1 mL of THF was added 60 mL (0.13 mmol) of a 2.53 M solution of n-BuLi/hexanes. After stirring at 0 °C for 15 min, this solution was added via cannula to a room temperature solution of 20 mg (0.044 mmol) of **23**, 2 mL of HMPA, and 0.5 mL of THF. The reaction mixture immediately becomes dark red and then black after several minutes. After stirring at room temperature for 4 h, the dark solution is quenched with 5 mL of H_2O, extracted with 3 x 25 mL of Et_2O, and the combined organics were washed with 3 x 50 mL of H_2O, 1 x 40 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (4/1/1 to 2/1/1) gave 8 mg (0.021 mmol, a 48 % yield) of **24** as a light yellow oil. Rf = 0.45 (1/1/1 hexanes/ CH_2Cl_2/Et_2O); $_1$H NMR (500 MHz, $CDCl_3$): δ 0.82-0.90 (m, 2 H), 1.03 -1.08 (m, 1 H), 1.30 (d, J = 6.0 Hz, 3 H), 1.36 (s, 3 H), 1.41 (s, 3 H), 1.42-1.47 (m, 1 H), 1.50-1.56 (m, 1 H), 2.53 (d, J = 26.9 Hz, 1 H), 2.79 (dd, J = 4.4, 9.3 Hz, 1 H), 3.46 (s, 3 H), 3.57 (dd, J = 4.4, 7.8 Hz, 1 H), 3.70 (t, J = 7.7 Hz, 1 H), 3.77 (s, 3 H), 3.99 (s, 1 H - OH, exchanges with D_2O), 4.07 (pent, J = 6.3 Hz, 1 H), 4.69 (AB quartet, J = 10.9 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.9, 17.8, 19.4, 26.1, 26.6, 27.2, 55.3, 58.6, 71.5, 72.5, 74.8, 75.7, 81.0, 83.0, 85.9, 108.6, 113.8, 130.0, 130.2; IR (NaCl plate, thin film, cm^{-1}): 3381w, 3283w, 2985w, 2931w, 1617w, 1514m, 1380w, 1249s, 1174m, 1083s, 1036m.

TMS Vinyl Lactone 25. To 1.67 mL (2.54 g, 23.74 mmol) of vinyl bromide and 45 mL of Et_2O at -78 °C was added 27.9 mL (47.48 mmol) of a 1.7 M solution of *t*-BuLi/pentanes dropwise over 8 min. After stirring at -78 °C for 20 min and 0 °C for 30 min, the resulting yellow solution was added to a -78 °C slurry of 1.06 g (11.87 mmol) of CuCN (previously dried by evaporating *in vacuo* with 3 x 5 mL of toluene) and 45 mL of Et_2O. The resulting yellow slurry was stirred at -78 °C for 10 min, 0 °C for 15 min where the slurry turns green, recooled to -78 °C where a solution of 2.74 g (9.13 mmol) of butenolide **14** and 10 mL of Et_2O was added via cannula over 5 min. After stirring at -78 °C for 30 min, the reaction mixture was quenched with 50 mL of 10 % aqueous NH_4OH and warmed to room temperature. The layers were separated, the blue aqueous layer extracted with 3 x 75 mL of Et_2O, and the combined organics were washed with 200 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (4/1/1 to 2/1/1), gave 2.15 g (6.55 mmol, a 72 % yield) of **25** as a colorless oil. Rf = 0.38 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = +23.5° (*c*. 0.00304, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.19 (s, 9 H), 1.35 (s, 3 H), 1.35 (d, J = 6.0 Hz, 3 H, overlaps with singlet at δ 1.35), 1.38 (s, 3 H), 2.40 (dd, J = 8.1, 17.6 Hz, 1 H), 2.72 (dd, J = 9.0, 17.6 Hz, 1 H), 3.06 (m, 1H), 3.70 (t, J = 7.1 Hz, 1 H), 3.73 (m, 1 H), 4.03 (pent, J = 6.3 Hz, 1 H), 4.35 (m, 1H), 5.12-5.18 (m, 1 H), 5.16 (d, J = 6.3 Hz, 1 H), 5.72-5.82 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.8, 20.1, 27.0, 27.2, 34.9, 40.2, 74.1, 75.7, 81.6, 84.8, 108.5, 117.4, 136.3, 175.4; IR (NaCl, thin film, cm^{-1}): 2985w, 2870w, 1786s, 1379w, 1253m, 1209m, 1168m, 1133w, 1059w, 888w, 843s; MS (EI) m/z (relative intensity) 328 (M^+, 10), 313 (M^+ - CH_3, 20), 255 (10), 214 (20), 185 (10), 173 (20), 159 (20), 143 (20), 128 (25), 116 (45), 115 (100).

Vinyl Lactone 26. To 3.36 g (10.23 mmol) of **25** in 100 mL of THF at 0 °C was added 3.0 mL of HF·pyridine. After 30 min at 0 °C TLC showed that no starting material remained. The reaction mixture was carefully quenched via dropwise addition of 100 mL of a saturated $NaHCO_3$ solution, extracted with 4 x 50 mL of Et_2O, and the combined organics were washed with 1 x 200 mL of brine, dried over $MgSO_4$, filtered and stripped of solvent to give 2.23 g (8.70 mmol, an 85 % yield) of **26** as a while solid (mp 122-124 °C) which was pure by 400 MHz ^{1}H NMR. Rf = 0.10 (1/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = +49.7° (*c* 0.003, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3 H), 1.39 (d, J = 6.1 Hz, 3 H), 1.41 (s, 3 H), 1.78 (d, J = 10.5 Hz, 1 H - OH, exchanges with D_2O), 2.50 (dd, J = 10.9, 17.5 Hz, 1 H - H2a), 2.76 (dd, J = 8.6, 17.6 Hz, 1 H - H2b), 3.30 (pent, J = 8.8 Hz, 1 H - H3), 3.55-3.63 (m, 2 H - H6 and H7), 4.12 (pent, J

= 6.4 Hz, 1 H - H5), 4.46 (d, J = 8.8 Hz, 1 H - H4), 5.19-5.25 (m, 2 H), 5.75 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 26.9, 27.4, 35.2, 40.8, 71.5, 76.7, 81.3, 83.3, 108.6, 118.7, 135.2, 176.2; IR (NaCl, thin film, cm^{-1}): 3420w, 2985w, 2870w, 1771s, 1370w, 1214m, 1167m, 1048m, 1018m, 930w, 856w; MS (EI) *m/z* (relative intensity) 241 (M^+ - CH_3, 100), 199 (40), 149 (35), 115 (95), 83 (20), 59 (80); Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.91; H, 7.87.

TBS Lactone 27 To 2.20 g (8.58 mmol) of **26** in 80 mL of CH_2Cl_2at 0 °C was added 4.02 mL (3.69 g, 34.48 mmol) of 2,6-lutidine and 3.96 mL (4.58 g, 17.25 mmol) of TBSOTf and the resulting solution was allowed to warm to room temperature. After 72 h at room temperature, the reaction mixture was quenched with 50 mL of a saturated $NaHCO_3$ solution, extracted with 2 x 100 mL of Et_2O, and the combined organics were washed with 2 x 100 mL of 1 N aqueous HCl, 1 x 100 mL of H_2O, 2 x 100 mL of brine, dried over $MgSO_4$, filtered and evaporated to a yellow oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (10/1/1 to 1/1/1), gave 2.91 g (7.85 mmol, a 91 % yield) of **27** as a colorless oil. Rf = 0.71 (1/1 hexanes/ethyl acetate); $[\alpha]_D$ = +12.7° (*c*. 0.045, CH2Cl2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.13 (s, 3 H), 0.15 (s, 3 H), 0.90 (s, 9 H), 1.36 (d, J = 6.0 Hz, 3 H), 1.36 (s, 3 H, overlaps with doublet at δ 1.36), 1.37 (s, 3 H), 2.39 (dd, J = 8.2, 17.7 Hz, 1 H), 2.73 (dd, J = 9.3, 17.7 Hz, 1 H), 3.15-3.23 (m, 1 H), 3.69 (t, J = 7.0 Hz, 1 H), 3.81 (dd, J = 2.8, 6.7 Hz, 1 H), 4.08 (pent, J = 6.4 Hz, 1 H), 4.30 (dd, J = 2.8, 6.7 Hz, 1 H), 5.13 (br s, 1 H), 5.15 (d, J = 9.6 Hz, 1 H), 5.72-5.82 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.1, -3.6, 18.2, 20.2, 25.6, 25.8, 27.0, 27.2, 34.8, 39.5, 73.2, 75.2, 82.1, 85.1, 117.2, 136.7, 175.4; IR (NaCl, thin film, cm^{-1}): 2955w, 2933m, 2858w, 1786s, 1379w, 1255m, 1209m, 1170m, 1092br w, 839m, 778w; MS (EI) m/z (relative intensity) 370 (M^+, 1), 355 (M^+ - CH_3, 30), 313 (20), 297 (15), 269 (5), 255 (100); Anal. Calcd for $C_{19}H_{34}O_5Si$: C, 61.58; H, 9.25. Found: C, 61.85; H, 9.53.

Diol 28. To 180 mg (7.83 mmol) of 95 % $LiBH_4$ in 60 mL of Et_2O at 0 °C was added 2.90 g (7.83 mmol) of **27** in 20 mL of Et_2O dropwise via a cannula. The reaction mixture was warmed to room temperature and additional portions of 50 mg (2.18 mmol) of $LiBH_4$ were added after 1.5 h, and 2.5 h. After a total of 3 1/2 h, the reaction mixture was quenched with 5 mL of ethyl acetate, and stirred with 50 mL of a saturated aqueous Rochelle's salt solution at room temperature until the organic/aqueous layers cleared. After extraction with 3 x 50 mL of Et_2O, the combined organics were washed with 1 x 100 mL of brine, dried over Na_2SO_4, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ethyl acetate (2/1 to 1/1), gave 1.93 g (5.15 mmol, a 66 % yield) of **28** as a colorless oil. Rf = 0.34 (1/1 hexanes/ethyl acetate); $[\alpha]_D$ = -6.7° (*c*. 0.0038, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.14 (s, 6 H), 0.92 (s, 9 H), 1.32 (d, J = 6.0 Hz, 3 H), 1.37 (s, 3 H), 1.38 (s, 3 H), 1.55-1.65 (complex m, 2 H), 2.01-2.09 (m, 1 H), 2.32-2.40 (m, 1 H), 2.92 (d, J = 10.3 Hz, 1 H - OH, exchanges with D_2O), 3.43 (t, J = 9.5 Hz, 1 H), 3.56-3.60 (m, 1 H, exchanges with D_2O), 3.61-3.65 (m, 1 H), 3.70 (pent, J = 4.9 Hz, 1 H), 3.91 (d, J = 4.0 Hz, 1 H), 3.99 (pent, J = 6.7 Hz, 1 H), 5.07 (d, J = 17.5 Hz, 1 H), 5.10 (d, J = 10.6 Hz, 1 H), 5.52-5.62 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.0, -3.6, 18.2, 19.5, 26.1, 27.1, 27.2, 34.6, 45.4, 61.1, 71.8, 73.3, 73.7, 84.3, 108.2, 117.0, 139.5; IR (NaCl, thin film, cm^{-1}): 3550-3380br m, 2959s, 2927 s, 2857s, 1462w, 1378m, 1255m, 1085-1052brm, 918 w, 859m, 777m; MS (EI) m/z (relative intensity) 359 (M^+ - CH_3, 10), 299 (5), 259 (15), 241 (20), 231 (35), 215 (10), 201 (20), 187 (20), 171 (15), 145 (65), 115 (50), 75 (100); Anal. Calcd for $C_{19}H_{38}O_5Si$: C, 60.92; H, 10.22. Found: C, 60.83; H, 10.33.

TBS Alcohol 29. Diol **28** (1.93 g, 5.15 mmol), 815 mg (5.41 mmol) of TBSCl, 0.79 mL (573 mg, 5.67 mmol) of Et_3N, a few crystals of DMAP and 60 mL of CH_2Cl_2 were combined and stirred at room temperature. After 14 h, the reaction mixture was poured into 100 mL of brine, extracted with 2 x 100 mL of Et_2O, and the combined organics were washed with 1 x 100 mL of 1 N aqueous HCl, 1 x 100 mL of H_2O, 1 x 100 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (20/1/1 to 10/1/1), gave 2.13 g (4.36 mmol, an 85 % yield) of **29** as a colorless oil. Rf = 0.31 (10/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = -5.3° (*c.* 0.0028, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.13 (s, 6 H), 0.89 (s, 9 H), 0.92 (s, 9 H), 1.25 (m, 1 H), 1.33 (d, *J* = 6.0 Hz, 3 H), 1.38 (s, 3 H), 1.39 (s, 3 H), 2.08-2.16 (complex m, 1 H), 2.39 (dq, *J* = 3.0, 10.1 Hz, 1 H), 2.67 (d, *J* = 8.9 Hz, 1 H - OH, exchanges with D_2O), 3.39 (dt, *J* = 1.6, 9.0 Hz, 1 H), 3.53-3.59 (m, 1 H), 3.67 (sextet, *J* = 6.8 Hz, 2 H), 3.96 (dd, *J* = 1.8, 4.8 Hz, 1 H), 4.03 (pent, *J* = 6.2 Hz, 1 H), 5.06 (dd, *J* = 1.9, 17.2 Hz, 1 H), 5.12 (dd, *J* = 1.9, 10.4 Hz, 1 H), 5.52 (ddd, *J* = 1.9, 10.4, 17.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3, -4.0, -3.6, 18.3, 19.7, 26.0, 26.1, 27.1, 27.2, 29.7, 33.2, 43.9, 60.6, 72.0, 73.5, 84.1, 107.9, 111.8, 117.1, 139.2; IR (NaCl, thin film, cm^{-1}): 3541w, 2956s, 2930s, 2897m, 2858s, 1469w, 1379m, 1256s, 1089br s, 1004w, 917w, 832s, 776s; MS (EI) m/z (relative intensity) 475 (M^+ - CH_3, 4), 431 (5), 415 (2), 373 (20), 315 (10), 299 (10), 241 (45), 232 (40), 171 (30), 149 (30), 115 (50), 97 (45), 75 (100); Anal. Calcd for $C_{25}H_{52}O_5Si_2$: C, 61.42; H, 10.72. Found: C, 61.18; H, 10.32.

TBS Methyl Ether 30. To a 0 °C solution of 2.12 g (4.34 mmol) of **29** and 80 mL of THF was added 20 mL of DMF, 2.70 mL (6.16 g, 43.4 mmol) of CH_3I, and 434 mg (10.84 mmol) of a 60 % NaH/mineral oil dispersion. After stirring at room temperature for 16 h, the reaction mixture was carefully quenched by adding 25 mL of a saturated aqueous NH_4Cl solution, extracted with 2 x 100 mL of Et_2O, and the combined organics were washed with 2 x 100 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (20/1/1), gave 2.12 g (4.22 mmol, a 97 % yield) of **30** as a colorless oil. Rf = 0.52 (10/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = -7.8° (*c.* 0.0020, CH2Cl2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.06 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 9 H), 0.92 (s, 9 H), 1.33 (d, *J* = 6.1 Hz, 3 H), 1.39 (br s, 6 H), 1.48-1.54 (m, 1 H), 1.75-1.83 (m, 1 H), 2.42-2.46 (m, 1 H), 3.33 (t, *J* = 5.6 Hz, 1 H), 3.46 (s, 3 H), 3.46-3.54 (m, 1 H), 3.65 (pent, *J* = 4.4 Hz, 2 H), 3.74 (t, *J* = 6.0 Hz, 1 H), 4.15 (pent, *J* = 6.8 Hz, 1 H), 4.99 (d, *J* = 17.3 Hz, 1 H), 5.05 (d, *J* = 9.6 Hz, 1 H), 5.72-5.82 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3, -4.1, -3.9, 1.0, 18.3, 19.0, 26.0, 26.3, 26.9, 27.4, 29.7, 31.6, 43.6, 60.7, 60.8, 74.2, 76.1, 81.2, 82.7, 107.7, 115.8, 140.3; IR (NaCl, thin film, cm^{-1}): 2955s, 2929s, 2858s, 1463m, 1366m, 1256s, 1125-1038br s, 857s, 836s, 775s; MS (EI) *m/z* (relative intensity) 487 (M^+- CH_3, 10), 445 (5), 387 (25), 355 (35), 281 (15), 243 (100).

Hydroxy Methyl Ether 32. To a 0 °C solution of 2.12 g (4.22 mmol) of **30** in 45 mL of THF was added 2.4 mL of HF·pyridine. After 3 h, TLC showed the disappearance of starting material. The reaction mixture was carefully quenched with 100 mL of a saturated aqueous $NaHCO_3$ solution, extracted with 3 x 100 mL of Et_2O, and the combined organics were dried over Na_2SO_4, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (2/1/1 to 1/1/1), gave 1.45 g (3.73 mmol, an 88 % yield) of **32** as a colorless oil. Rf = 0.21 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = -11.4° (*c*. 0.00272, CH2Cl2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 3 H), 0.10 (s, 3 H), 0.93 (s, 9 H), 1.34 (d, *J* = 5.9 Hz, 3 H), 1.38 (s, 3 H), 1.40 (s, 3 H), 1.60-1.66 (m, 1 H), 1.67-1.75 (br m, 1 H - OH, exchanges with D_2O), 1.83-1.89 (m, 1 H), 2.42-2.50 (m, 1 H), 3.31 (t, *J* = 6.4 Hz, 1 H), 3.46 (s, 3 H), 3.59 (dt, *J* = 2.4, 8.2 Hz, 1 H), 3.65 (m, 2 H), 3.70 (sextet, *J* = 5.4 Hz, 1 H), 4.14 (m, 1 H), 5.05 (d, *J* = 15.4 Hz, 1 H), 5.08 (d, *J* = 10.2 Hz, 1 H), 5.82 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.0, -3.9, 18.4, 19.0, 26.2, 26.8, 27.4, 29.9, 31.9, 44.2, 60.9, 74.7, 81.4, 83.0, 108.0, 116.0, 140.5; IR (NaCl, thin film, cm^{-1}): 3520-3350br m, 2955s, 2931s, 2857s, 1473m, 1369m, 1252s, 1120-1036br s, 916m, 860m, 833s, 775s; MS (EI) *m/z* (relative intensity) 373 (M^+ - CH_3, 10), 303 (5), 273 (30), 241 (35), 229 (95), 215 (20), 183 (30), 171 (100).

Aldehyde Methyl Ether 33. To a -78 °C solution of 0.37 mL (519 mg, 4.09 mmol) of oxalyl chloride and 25 mL of CH_2Cl_2 was added 0.58 mL (639 mg, 8.18 mmol) of DMSO. After stirring at -78 °C for 10 min, a solution of 1.44 g (3.72 mmol) of **32** in 20 mL of CH_2Cl_2 was added dropwise via a cannula. After stirring at -78 °C for 15 min, 2.59 mL (1.88 g, 18.6 mmol) of Et_3N was added, the reaction mixture was stirred at -78 °C for 5 min, and allowed to warm to room temperature over 1 h. After partitioning between 50 mL CH_2Cl_2 and 50 mL brine and further extraction of the aqueous layer with 2 x 50 mL of CH_2Cl_2, the combined organics were dried over $MgSO_4$, filtered and evaporated to an oily yellow solid. This solid was dissolved in 5 mL of Et_2O and filtered through a pipette containing glass wool. The resulting yellow solution was evaporated to give 1.41 g (3.65 mmol, a 98 % yield) of **33** as a light yellow oil which was pure by 500 MHz ^1H NMR. Rf = 0.63 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); $[\alpha]_D$ = +4.6° (*c*. 0.00657, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 0.07 (s, 3 H), 0.09 (s, 3 H), 0.93 (s, 9 H), 1.34 (d, *J* = 6.0 Hz, 3 H), 1.35 (s, 3 H), 1.37 (s, 3 H), 2.50 (dd, *J* = 5.8, 16.0 Hz, 1 H), 2.75 (dd, *J* = 5.3, 16.1 Hz, 1 H), 2.97-3.05 (m, 1 H), 3.20 (dd, *J* = 4.0,7.5 Hz, 1 H), 3.43 (s, 3 H), 3.66 (t, *J* = 6.5 Hz, 1 H), 3.79 (t, *J* = 7.0 Hz, 1 H), 4.09 (pent, *J* = 6.5 Hz, 1 H), 5.07 (d, *J* = 10.2 Hz, 1 H), 5.08 (d, *J* = 17.2 Hz, 1 H), 5.80-5.90 (complex m, 1 H), 9.70 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.0, 1.0, 18.4, 19.1, 26.2, 26.9, 27.3, 29.7, 41.6, 43.8, 60.8, 75.4, 75.7, 80.9, 83.6, 116.6, 139.2, 202.4; IR (NaCl, thin film, cm^{-1}): 2954s, 2931s, 2858s, 2714w, 1727s, 1473w, 1379m, 1255s, 1152-1054br s, 920w, 837s, 776s; MS (EI) *m/z* (relative intensity): 371 (M^+ - CH_3, 15), 303 (10), 271 (30), 239 (75), 227 (100).

Lactone 34. To a room temperature solution of 35 mg (0.089 mmol) of **33** and 5 mL of THF was added 1.3 mL (1.34 mmol) of a 1.0 M solution of TBAF/THF. After stirring at room temperature for 1.3 h, the reaction mixture was partitioned between 10 mL H_2O and 10 mL CH_2Cl_2, extracted and the combined organics were dried over $MgSO_4$, filtered and evaporated to a yellow oil. This oil was dissolved in 8 mL of CH_2Cl_2 and 51 mg (0.623 mmol) of NaOAc followed by 192 mg (0.891 mmol) of PCC were added. After stirring at room temperature 15 h, the brown mixture was filtered through Celite and evaporated to a brown oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O, gave 22 mg (0.081 mmol, a 91 % yield) of **34** as an orange oil. Rf = 0.54 (2/1/1 hexanes CH_2Cl_2/Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 3 H), 1.38 (d, *J* = 6.2 Hz, 3 H - overlaps with the singlet at δ 1.37), 1.39 (s, 3 H), 2.40 (dd, *J* = 9.0, 17.4 Hz, 1 H), 2.75 (dd, *J* = 8.8, 17.5 Hz, 1 H), 3.15 (pent, *J* = 8.4 Hz, 1 H), 3.27 (dd, *J* = 1.4, 7.6 Hz, 1 H), 3.53 (s, 3 H), 3.72 (t, *J* = 7.7 Hz, 1 H), 4.10 (pent, *J* = 6.3

Hz, 1 H), 4.36 (dd, J = 1.4, 7.6 Hz, 1 H), 5.17 (d, J = 10.1 Hz, 1 H), 5.19 (d, J = 17.1 Hz, 1 H), 5.72-5.80 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 26.9, 27.2, 35.1, 41.1, 61.5, 75.7, 81.0, 81.3, 83.9, 108.3, 118.1, 136.0, 175.4; IR (NaCl, thin film, cm^{-1}): 2984m, 2932w, 2913w, 2898w, 1782s, 1378w, 1210m, 1163m, 1084m, 1068m, 1033w; MS (EI) m/z (relative intensity): 270 (M^+, 2), 255 (M^+ - CH_3, 35), 195 (5), 167 (3), 156 (20), 135 (5), 115 (100).

TBS Methyl Ether 31. To a room temperature solution of 4.28 g (8.76 mmol) of **29** and 100 mL of CH_2Cl_2 was added 7.52 g (35.0 mmol) of Proton Sponge followed by 5.17 g (35.0 mmol) of Me_3OBF_4. The resulting orange slurry was stirred at room temperature for 18 h, after which an additional 1.5 g (7.00 mmol) of Proton Sponge and 1.0 g (6.76 mmol) of Me_3OBF_4 were added. After stirring for an additional 2 h, TLC indicated that all starting material had been consumed. The reaction mixture was diluted with 300 mL of Et_2O, washed with 2 x 200 mL of 1 N HCl, 1 x 200 mL of H_2O, 1 x 200 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/CH_2Cl_2/Et_2O (20/1/1 to 10/1/1) gave 4.12 g (8.19 mmol, a 94 % yield) of **31** as a colorless oil. Rf = 0.53 (10/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (s, 6 H), 0.11 (s, 6 H), 0.89 (s, 9 H), 0.91 (s, 9 H), 1.32 (d, J = 6.0 Hz, 3 H), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.44-1.53 (m, 1 H), 1.79-1.86 (m, 1 H), 2.45-2.53 (br m, 1 H), 3.05 (t, J = 5.6 Hz, 1 H), 3.41 (s, 3 H), 3.46-3.53 (complex m, 1 H), 3.59-3.64 (m, 1 H), 3.69 (dd, J = 4.5, 6.9 Hz, 1 H), 3.91 (t, J = 5.4 Hz, 1 H), 4.13 (pent, J = 6.4 Hz, 1 H), 5.00 (d, J = 16.7 Hz, 1 H), 5.02 (d, J = 9.6 Hz, 1 H), 5.62-5.71 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3 (2 carbons), -3.8 (2 carbons), 18.3, 20.0, 26.0, 26.2, 27.2, 27.3, 31.3, 42.1, 60.6, 61.1, 73.1, 73.4, 75.2, 82.3, 85.7, 107.8, 116.0, 140.3; IR (thin film, cm^{-1}): 2955s, 2931s, 2895m, 2858s, 1472w, 1463w, 1377w, 1254m, 1097s, 900w, 834s, 776s; MS (EI) *m/z* (relative intensity): 487 (M^+ - CH_3, 10), 445 (5), 3.87 (25), 355 (35), 281 (15), 243 (100).

Hydroxy Methyl Ether 35. To a 0 °C solution of 4.10 g (8.15 mmol) of **31** and 80 mL of THF was added 4.1 mL of HF·pyridine. After stirring at room temperature for 3 h, the reaction mixture was carefully quenched by slowly added 200 mL of a saturated $NaHCO_3$ solution, extracted with 5 x 50 mL of Et_2O, and the combined organics were dried over Na_2SO_4, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (2/1/1 to 1/1/1) gave 3.03 g (7.80 mmol, a 96 % yield) of **35** as a colorless oil. Rf = 0.20 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 1.33 (d, J = 6.1 Hz, 3 H), 1.37 (s, 3 H), 1.38 (s, 3 H), 1.60-1.68 (m, 1 H), 1.82-1.91 (m, 2 H - 1 H exchanges with D_2O, OH proton), 2.48-2.55 (m, 1 H), 3.08 (t, J = 5.6 Hz, 1 H), 3.44 (s, 3 H), 3.53-3.59 (m, 1 H), 3.63 (t, J = 6.3 Hz, 1 H), 3.68 (sept, J = 5.5 Hz, 1 H), 3.88 (t, J = 5.9 Hz, 1 H), 4.12 (pent, J = 6.5 Hz, 1 H), 5.05 (d, J = 10.1 Hz, 1 H), 5.06 (d, J = 17.1 Hz, 1 H), 5.72-5.81 (complex m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -3.8, 18.3, 20.0, 26.2, 27.1, 27.4, 32.2, 43.0, 60.7, 61.1, 73.6, 74.1, 82.6, 85.9, 108.2, 116.0, 140.3; IR (thin film, cm^{-1}): 3537-3323brw, 3069w, 2974m, 2954s, 2858m, 1472w, 1462w, 1378w, 1253m, 1120m, 1084s, 1052s, 835s, 776m; MS (EI) *m/z* (relative intensity) 388 (M^+, 5), 373 (M^+ - CH_3, 15), 331 (20), 313 (10), 299(10), 273 (20), 259 (10), 241 (70), 215 (55), 201 (30), 187 (65), 187 (65), 167 (25), 145 (100).

Aldehyde Methyl Ether 36. To a -78 °C solution of 0.75 mL (1.08 g, 8.54 mmol) of $(COCl)_2$ and 40 mL of CH_2Cl_2 was added 1.21 mL (1.33 g, 17.07 mmol) of DMSO in drops. After stirring at -78 °C for 10 min, a solution of 3.0 g (7.72 mmol) of **35** and 35 mL of CH_2Cl_2

was added dropwise via a cannula. After 20 min at -78 °C, 5.41 mL (3.93 g, 38.8 mmol) of Et_3N was added and the reaction mixture was allowed to warm to room temperature over 1.5 h. After pouring into 100 mL brine and extraction with 3 x 75 mL of CH_2Cl_2, the combined organics were washed with 1 x 150 mL of brine, dried over $MgSO_4$, filtered and evaporated to a yellow slurry. Filtration of this slurry through a glass wool plug using Et_2O as solvent gave 2.74 g (7.09 mmol, a 92 % yield) of **36** as a yellow oil which was pure by 500 MHz ^{1}H NMR spectroscopy. Rf = 0.63 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 1.34 (d, J = 6.0 Hz, 3 H), 1.35 (s, 3 H), 1.39 (s, 3 H), 2.47 (td, J = 15.8, 6.9 Hz, 1 H), 2.54-2.61 (m, 1 H), 3.05 (pent, J = 7.1 Hz, 1 H), 3.15 (dd, J = 4.4, 7.0 Hz, 1 H), 3.37 (s, 3 H), 3.66 (t, J = 6.8 Hz, 1 H), 3.80 (dd, J = 4.1, 6.8 Hz, 1 H), 4.08 (pent, J = 6.2 Hz, 1 H), 5.06 (d, J = 10.1 Hz, 1 H), 5.09 (d, J = 17.5 Hz, 1 H), 5.71-5.81 (complex m, 1 H), 9.59 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -3.5, -3.4, 18.4, 20.5, 26.2, 27.4, 27.7, 40.8, 45.4, 60.3, 73.9, 75.4, 82.7, 84.9, 108.6, 116.6, 138.9, 201.5; IR (thin film, cm^{-1}): 3080w, 2981m, 2932s, 2896m, 2858m, 2730w, 1726s, 1472w, 1378m, 1254s, 1118m, 1086s, 1054m, 919w, 836s, 776m; MS (EI) m/z (relative intensity): 371 (M^+ - CH_3, 25), 271 (60), 259 (25), 239 (90), 227 (20), 215 (70), 201 (55), 185 (60), 145 (55), 127 (100).

Lactone 37. To a room temperature solution of 90 mg (0.23 mmol) of **36** and 12 mL of THF was added 3.49 mL (3.49 mmol) of a 1.0 M solution of TBAF/THF. After 1.5 h, the reaction mixture was partitioned between 20 mL of H_2O and 20 mL of CH_2Cl_2/Et_2O and extracted. The aqueous layer was washed with 1 x 20 mL of CH_2Cl_2 and the combined organics were dried over $MgSO_4$, filtered and evaporated to an oil. This oil was dissolved in 15 mL of CH_2Cl_2, and 134 mg NaOAc (1.63 mmol) followed by 502 mg of PCC (2.33 mmol) were added. After stirring at room temperature for 15 h, the brown mixture was filtered through Celite, and the filtrate was evaporated to give a brown oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (2/1/1 to 1/1/1), gave 61 mg (0.22 mmol, a 96 % yield) of **37** a light yellow oil. Rf = 0.36 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 3 H), 1.42 (s, 3 H), 1.43 (d, J = 6.1 Hz, 3 H), 2.52 (dd, J = 4.4, 16.2 Hz, 1 H - H_{2eq}), 2.60-2.68 (m, 1 H - H_3), 2.70 (dd, J = 12.5, 16.2 Hz, 1 H - H_{2ax}), 3.51 (s, 3 H), 3.65 (br t, 1 H - H_4), 3.77 (t, J = 8.2 Hz, 1 H), 4.10 (pent, J = 6.9 Hz, 1 H), 4.13 (d, J = 9.2 Hz, 1 H), 5.13 (d, J = 18.2 Hz, 1 H), 5.14 (d, J = 9.4 Hz, 1 H), 5.82-5.89 (complex m, 1 H); ^{1}H NMR (300 MHz, C_6D_6): δ 1.28 (s, 3 H), 1.34 (s, 3 H), 1.47 (d, J = 5.9 Hz, 3 H), 1.84-1.95 (m. 1 H - H_3), 2.24 (dd, J = 6.0, 17.9 Hz, 1 H - H_{2eq}), 2.59 (dd, J = 12.8, 17.8 Hz, 1 H - H_{2ax}), 3.25 (s, 3 H), 3.35 (br s, 1 H), 3.63 (dd, J = 1.0, 8.9 Hz, 1 H), 3.82 (t, J = 8.9 Hz, 1 H), 4.05 (pent, J = 7.0 Hz, 1 H), 4.74 (d, J = 17.3 Hz, 1 H), 4.84 (d, J = 10.3 Hz, 1 H), 5.42-5.55 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.9, 27.3, 30.4, 40.8, 61.3, 75.1, 77.0, 78.0, 84.2, 108.7, 116.7, 137.0, 169.0; IR (thin film, cm^{-1}): 3082w, 2985w, 2935w, 2889w, 1748s, 1453w, 1371w, 1229m, 1173m, 1087s, 1057m; MS (EI) m/z (relative intensity) 270 M^+ (8), 255 (100), 212 (7), 181 (12), 153 (13), 135 (18), 115 (100), 97 (64), 84 (42), 69 (43), 59 (90).

Dibromodiene 38. To a 0 °C solution of 4.52 g (13.66 mmol) of CBr_4 and 60 mL of CH_2Cl_2 was added 7.17 g (27.32 mmol) of Ph_3P followed by a solution of 2.64 g (6.83 mmol) of **36** and 35 mL of CH_2Cl_2 in drops via a cannula. After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with 200 mL hexanes, filtered through Celite and evaporated to give an orange solid. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (20/1/1), gave 3.33 g (6.14 mmol, a 90 % yield) of **38** as a colorless oil. Rf = 0.50 (10/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 1.33 (d, J = 6.1 Hz, 3 H), 1.36 (s, 3 H), 1.38 (s, 3 H), 2.15-2.23 (m, 1 H), 2.38-2.45 (m, 1 H), 2.45-2.50 (m, 1 H), 3.10 (t, J = 5.6 Hz, 1 H), 3.43 (s, 3 H), 3.64 (t, J = 6.6 Hz, 1 H), 3.84 (t, J = 5.7 Hz, 1 H), 4.09 (pent, J = 6.4 Hz, 1 H), 5.03 (d, J = 17.4 Hz, 1 H), 5.06 (d, J = 10.4 Hz, 1 H), 5.64-5.73 (complex m, 1 H), 6.33 (t, J = 7.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -3.7, -3.6, 18.3, 20.2, 26.1, 27.2, 27.5, 33.4, 44.8, 60.7, 73.6, 74.7, 82.6, 84.8, 88.8, 108.3, 116.7, 137.3, 139.1; IR (thin film, cm^{-1}): 3078w, 2980m, 2954m, 2932s, 2896m, 2857m, 1472w, 1377m, 1253s, 1119s, 1087s. 1053s, 919w, 836s, 776s; MS (EI) m/z (relative intensity): 542 (M^+, 1), 527 ($M^+ - CH_3$, 10), 485 (10), 427 (35), 395 (40), 321 (20), 283 (35), 259 (60), 241 (25), 215 (90), 201 (90), 185 (90), 143 (65), 115 (100).

Dibromoalcohol 39. To a -15 °C solution of 3.27 g (6.03 mmol) of **38** and 80 mL of THF was added 12.06 mL (12.06 mmol) of a 1.0 M solution of BH_3·THF via a syringe. After stirring at -15 °C for 11 h, 4 mL of CH_3OH was added followed by the simultaneous addition of 15 mL of 3 M NaOH and 15 mL of 30 % H_2O_2, and the resulting mixture was stirred at room temperature for 2 h. After pouring into 100 mL of brine and extraction with 3 x 100 mL of Et_2O, the combined organics were dried over Na_2SO_4, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (2/1/1), gave 1.90 g (3.39 mmol, a 56% yield) of **39** as a viscous clear oil. Rf = 0.28 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (s, 3 H), 0.14 (s, 3 H), 0.92 (s, 9 H), 1.34 (d, J = 6.0 Hz, 3 H), 1.38 (br s, 6 H), 1.60-1.77 (m, 3 H - one H exchanges with D_2O - OH proton), 1.96-2.05 (br m, 1 H), 2.17 (pent, J = 7.7 Hz, 1 H), 2.23-2.30 (m, 1 H), 3.12 (dd, J = 2.8, 7.2 Hz, 1 H), 3.43 (s, 3 H), 3.54 (dd, J = 6.0, 7.2 Hz, 1 H), 3.67-3.76, (m, 2 H), 3.83 (t, J = 5.8 Hz, 1 H), 4.10 (pent, J = 7.0 Hz, 1 H), 6.43 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$); δ -3.9, -3.7, 18.2, 19.9, 26.2, 27.0, 27.2, 32.8, 34.5, 36.0, 60.5, 61.3, 73.7, 74.5, 83.6, 84.1, 89.1, 108.2, 137.9; IR (thin film, cm^{-1}): 3521-3300brw, 2980w, 2954m, 2931s, 2897m, 2856m, 1472w, 1377w, 1253m, 1118m, 1084s, 1049m, 836s, 777s; MS (EI) m/z (relative intensity) 547 M^+ - 15 (1.0, ^{81}Br), 545 (2.0, ^{81}Br, ^{79}Br), 543 (1.0, ^{79}Br), 515 (1.0, ^{81}Br), 473 (3, ^{81}Br), 415 (12, ^{81}Br), 357 (8, ^{81}Br), 271 (12, ^{81}Br), 215 (32), 199 (30), 198 (37), 196 (20), 107 (45), 105 (35), 145 (95), 115 (100), 89 (97), 75 (98), 73 (92), 59 (95).

Alcohol 40. To a -78 °C solution of 1.85 g (3.30 mmol) of **39** and 60 mL of THF was added 4.23 mL (10.56 mmol) of a 2.5 M solution of n-BuLi/hexanes in drops. After stirring at -78 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for 1 h. After quenching with 5 mL of a saturated aqueous NH_4Cl solution and extraction with 3 x 50 mL of Et_2O, the combined organics were dried over Na_2SO_4, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/CH_2Cl_2/Et_2O (2/1/1 to 1/1/1), gave 1.12 g (2.80 mmol, an 85 % yield) of **40** a colorless oil. Rf = 0.11 (2/1/1 hexanes/CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.35 (d, J = 6.0 Hz, 3 H), 1.38 (br s, 6 H) 1.61 (t, J = 6.2 Hz, 1 H - OH proton, exchanges with D_2O); 1.80 (m, 2 H), 1.96 (t, J = 2.6 Hz, 1 H), 2.07 (m, 1 H), 2.38 (m, 2 H), 3.19 (t, J = 5.3 Hz, 1 H), 3.44 (s, 3 H), 3.64 (t, J = 6.8 Hz, 1 H), 3.74 (m, 2 H), 3.90 (t, J = 5.8 Hz, 1 H), 4.10 (pent, J = 6.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -3.8, -3.6, 18.4, 18.5, 20.2, 26.3, 27.3, 27.4, 33.9, 36.4, 60.8, 69.8, 73.5, 75.1, 83.1, 83.6, 108.4; IR (NaCl, thin film, cm^{-1}): 3585-3425brw, 3310w, 2951m, 2932s, 2858m, 1473w, 1463w, 1378w, 1254m, 1087s, 837s, 777m; MS (EI) *m/z* (relative intensity) 385 M+ - 15 (3), 285 (11), 253 (100), 145 (55), 115 (64), 97 (81), 89 (46), 75 (47), 73 (72), 59 (55).

Aldehyde 41. To room temperature solution of 1.32 g (3.10 mmol) of the Dess-Martin periodinane[33] and 40 mL of CH_2Cl_2 was added 1.08 g (2.70 mmol) of **40** and 20 mL of CH_2Cl_2 in drops via a cannula. After stirring at room temperature for 1.25 h, the reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$, containing 50 mL H_2O and 10 g $Na_2S_2O_3$ and stirred vigorously until both the organic and aqueous layers became clear (~ 5 min). The organic layer was separated, the aqueous layer extracted with 2 x 50 mL of CH_2Cl_2, and the combined organics were washed with 1 x 100 mL saturated aqueous $NaHCO_3$, 1 x 100 mL H_2O, dried over $MgSO_4$, filtered and evaporated to give 1.07 g (2.68 mmol, a 99 % yield) of **41**, as a light yellow oil which was pure by 500 MHz ^{1}H NMR. Rf = 0.40 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz): δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.92 (s, 9 H), 1.33 (d, *J* = 6.0 Hz, 3 H), 1.375 (s, 3 H), 1.381 (s, 3 H), 1.98 (t, *J* = 2.2 Hz, 1 H), 2.45 (m, 2 H), 2.53 (m, 1 H), 2.73 (dd, *J* = 6.2, 16.8 Hz, 1 H), 2.77 (dd, *J* = 6.2, 16.8 Hz, 1 H), 3.17 (t, *J* = 5.9 Hz, 1 H), 3.41 (s, 3 H), 3.61 (t, *J* = 5.8 Hz, 1 H), 3.88 (t, *J* = 5.5 Hz, 1 H), 4.11 (pent, *J* = 6.9 Hz, 1 H), 9.74 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -3.9, -3.8, 18.3, 18.8, 19.9, 26.3, 27.2, 27.4, 34.1, 45.0, 60.6, 70.7, 73.1, 74.5, 82.4, 82.9, 83.2, 108.3, 201.4; IR (thin film, cm^{-1}): 3309w, 3282w, 2984m, 2955s, 2913s, 2885m, 2858m, 1725s, 1461w, 1377w, 1254s, 1085s, 837s, 777s; MS (EI) *m/z* (relative intensity) 383 M^+- 15, (8), 283 (22), 251 (38), 139 (50), 115 (70), 89 (70), 75 (59), 73 (98), 59 (100).

Carboxylic acid 42. To a room temperature solution of 1.04 g (2.61 mmol) **41**, 10 mL of 2-methyl-2-butene and 40 mL of *tert*-butanol was added a solution of 1.18 g (10.44 mmol) of 80 % $NaClO_2$, 626 mg (5.22 mmol) of NaH_2PO_4, and 20 mL of H_2O. After stirring at room temperature for 1.5 h, 50 mL of H_2O was added, the resulting mixture was extracted with 3 x 50 mL of Et_2O. The combined organics were dried over Na_2SO_4, filtered and evaporated to give 1.04 g (2.51 mmol, a 96 % yield) of **42** as a cloudy, colorless oil which was pure by 500 MHz ^{1}H NMR except for a small amount of *tert*-butanol (δ 1.27 s). $[\alpha]_D$ = -6.2° (*c*. 0.0193, $CHCl_3$), Rf = 0.57 (1/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.33 (d, *J* = 6.0 Hz, 3 H), 1.38 (br s, 6 H), 1.99 (br t, *J* = 2.4 Hz, 1 H), 2.36-2.50 (m, 3 H), 2.67 (dd, *J* = 6.8, 17.1 Hz, 1 H), 2.72 (dd, *J* = 6.4, 17.4 Hz, 1 H), 3.21 (t, *J* = 5.5 Hz, 1 H), 3.44 (s, 3 H), 3.65 (t, *J* = 6.7 Hz, 1 H), 3.91 (t, *J* = 5.3 Hz, 1 H), 4.12 (pent, *J* = 6.6 Hz, 1 H) (No carboxylic acid proton visible); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.1, -4.0, 18.6, 19.6, 26.0, 27.1, 27.2, 31.2, 34.6, 35.9, 60.7, 70.4, 73.0, 74.1, 82.1, 82.4, 82.7, 108.3, 177.9; IR (thin film, cm^{-1}): 3350-2700brw, 3310w, 3273w, 2983m, 2955s, 2932s, 2897m, 2858m, 1735m, 1709s, 1463w, 1379m, 1254m, 1169-1059brs, 837s, 777m; MS (EI) *m/z* (relative intensity) 399 M^+- 15 (12), 299 (20), 267 (98), 215 (34), 201 (29), 105 (27), 145 (92), 123 (47), 115 (100), 89 (73), 75 (92), 73 (92), 59 (99).

Methyl Ester 43 A 0 °C solution of CH_2N_2 in Et_2O was generated by adding 701 mg (6.80 mmol) of $MeN(NO)CONH_2$ to a 0 °C mixture of 15 mL Et_2O and 10 mL of 40 % aqueous KOH, stirring at 0 °C for 45 min, isolating the yellow organic layer in a separatory funnel and drying over solid KOH pellets. This CH_2N_2/Et_2O solution was added to a 0 °C solution of 94 mg (0.23 mmol) of **42** and 10 mL of Et_2O. After 15 min, the excess CH_2N_2 was destroyed by adding 3 mL of a 3:1 mixture of glacial acetic acid/H_2O. The resulting solution was extracted with 2 x 15 mL of a saturated aqueous $NaHCO_3$, 1 x 15 mL of H_2O, 1 x 15 mL of brine, dried over $MgSO_4$, filtered and evaporated to an oil. Flash chromatography on silica gel, eluting with hexanes/ CH_2Cl_2/Et_2O (10/1/1), gave 78 mg (0.18 mmol, a 79 % yield) of **43** as a light yellow oil. Rf = 0.70 (2/1/1 hexanes/ CH_2Cl_2/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.33 (d, J = 6.1 Hz, 3 H), 1.38 (br s, 6 H), 1.97 (br t, J = 2.4 Hz, 1 H), 2.36-2.46 (m, 3 H), 2.62 (d, J = 6.0 Hz, 2 H), 3.17 (t, J = 5.3 Hz, 1 H), 3.43 (s, 3 H), 3.63-3.68 (m, 1 H), 3.66 (s, 3 H - overlaps with the m at δ 3.63-3.68), 3.91 (t, J = 5.4 Hz, 1 H), 4.12 (pent, J = 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.1, -4.0, 18.1, 18.5, 19.7, 26.1, 27.1, 27.2, 34.8, 36.2, 51.6, 60.7, 70.2, 73.1, 74.0, 82.3, 82.5, 83.8, 108.0, 173.0; IR (thin film, cm^{-1}): 3307w, 3271w, 2983w, 2954m, 2930s, 2895w, 2857m, 1738s, 1472w, 1369w, 1254s, 1213m, 1162m, 1118m, 1087s, 1059m, 836s, 777m; MS (EI) *m/z* (relative intensity) 413 (19), 353 (38), 313 (90), 282 (88), 281 (100), 221 (92), 206 (85), 201 (920, 185 (93), 169 (97), 147 (92), 141 (95), 115 (85), 109 (100), 97 (86), 89 (92), 75 (91), 73 (94), 59 (88).

Benzannulation of Carbene Complex 44 with Alkyne 45. Alkyne **45** was prepared from **17** via the procedures outlined in Schemes II - IV. A solution of 37 mg of complex **44**[36] (0.100 mmol) and 45 mg of alkyne **45** (0.104 mmol) in 0.20 mL of methylene chloride was deoxygenated by the freeze-thaw method (-196 °/25 °C, 3 cycles) in a 10 mL heavy-walled test-tube that was modified with a threaded teflon high vacuum stopcock. The flask was back-filled with argon at room temperature, sealed and then heated at 45 °C for 22 h. To this was added 3 mL of methylene chloride, 0.02 mL of acetic anhydride, 0.04 mL of ethyl(diisopropyl)amine, a few crystals of 4-dimethylamino pyridine. After 5 hours at room temperature the reaction mixture was diluted with ether and poured into brine. The aqueous layer was extracted with ether and the combined ether layer was washed twice with 1N HCl, once with $NaHCO_3$ and once with brine. Analysis by TLC indicated the presence of five mobile compounds with a solvent mixture of ether/methylene chloride/hexane. Development with phosphomolybdic acid revealed that the most prominate compound was also the most polar with R_f = 0.22. Isolation of this compound by silica gel chromatography gave 30 mg (42 %) of a yellow-white solid which was identified as the naphthalene **46**. Spectral data for **46**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.0 Hz, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 2.18 (dd, J = 16.0, 3.0 Hz, 1H), 2.34 (s, 3H), 2.42 (d, J = 6.8 Hz, 1H), 2.46 (s, 3H), 2.67 (m, 2H), 2.82 (d, J = 9.0 Hz, 1H), 3.37 (m, 1H), 3.53 (br s, 3H), 3.54 (s, 3H), 3.73 (m, 1H), 3.79 (s, 3H), 3.89 (m, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 4.18 (m, 1H), 4.69 (ABq, J = 10.4 Hz, 2 H), 6.60 (d, J = 2.1 Hz, 1H), 6.70 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 1.9 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H); IR (thin film, cm^{-1}): 2934w, 1765m, 1734m, 1611w, 1586m, 1513w, 1376m, 1249m, 1208s, 1142m, 1112m, 1082m, 1039m: ^{13}C NMR ($CDCl_3$) δ 19.4, 20.7, 21.2, 22.6, 27.0, 27.4, 29.7, 34.7, 37.6, 51.2, 55.3, 56.6, 57.1, 61.2, 74.6, 74.8, 80.9, 82.6, 84.1, 102.1, 104.7, 108.0, 108.5, 113.9, 129.6, 130.4, 130.5, 130.6, 138.6, 150.0, 155.4, 158.8, 159.5, 168.9, 169.4, 173.3; MS (EI) *m/z* (relative intensity) 712 M^+ (1.5), 670 (10), 549 (10), 518 (5), 491 (5), 373 (20), 275 (10), 232 (30), 121 (100), 77 (15); HRMS (EI) calcd for $C_{38}H_{48}O_{13}$ 712.3095, found 712.3132.

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