Tetrahedron Vol 43, No. 23, pp 5499 to 5520, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + 00

MACRORING CONTRACTION METHODOLOGY. 3. TOTAL SYNTHESES OF COSTUNOLIDE AND HAAGEANOLIDE USING TRANSANNULAR [2,3]-WITTIG REARRANGEMENT OF 13-MEMBERED DIALLYLIC ETHERS AS KEY REACTION

TAKASHI TAKAHASHI,* HISAO NEMOTO, YUTAKA KANDA, AND JIRO TSUJI
Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

YOSHIMASA FUKAZAWA AND TOSHIYA OKAJIMA
Department of Chemistry, Faculty of Science, Hiroshima University, Hiroshima 730, Japan

YUTAKA FUJISE
Hamamatsu University School of Medicine 3600, Handa-cho Hamamatsu 431-31, Japan

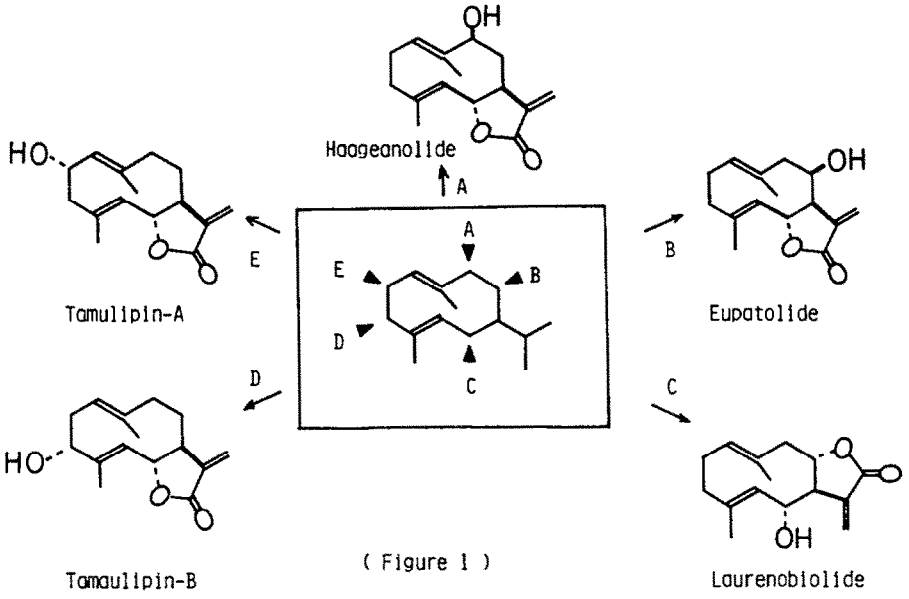
(*Received in USA 7 July* 1987)

Abstract - A new route to construct the carbon skeleton of germacrane sesquiterpenes is described wherein the 13-membered diallylic ethers **12** and **41**, prepared by intramolecular O-alkylation of the bromo alcohol and C-alkylation of the cyanohydrin ether respectively, undergo [2,3]-Wittig rearrangement to give the ten-membered carbocycles. Diastereoselectivity in [2,3]-Wittig rearrangement is discussed based on the MM2 transition structure model using the ab-initio calculations.

INTRODUCTION

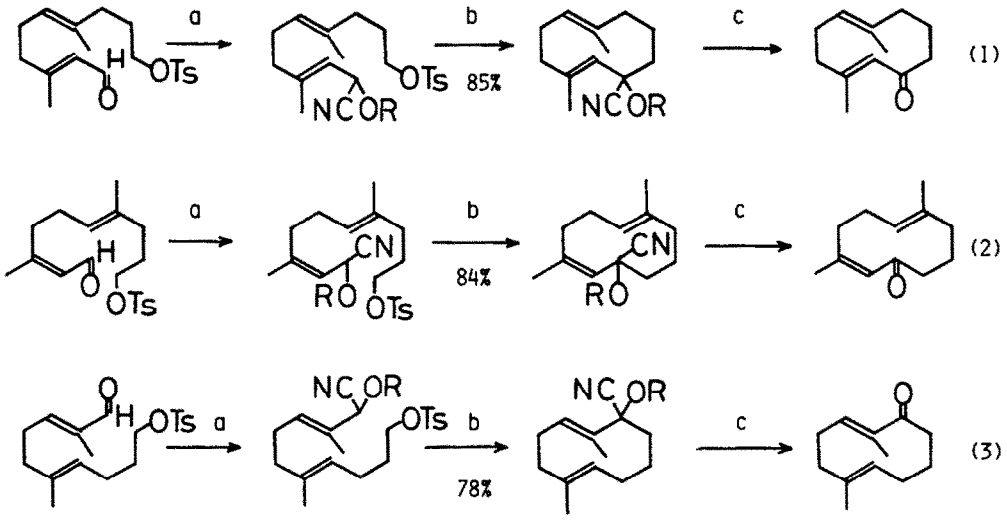
Sesquiterpene lactones constitute an important group of natural products and possess wide-ranging biological activities.[1] Germacrane sesquiterpenes are well known as biogenetic precursors of different skeletal types of sesquiterpenes. Most of germacrane lactones have the nucleophile-sensitive α-methylene-γ-butyrolactone and the chemically and thermally labile (E,E)-1,5-cyclodecadiene system containing oxidized carbon in various positions as shown by A-E in Figure 1. There are four requirements for a general synthetic method for these germacrane lactones ; (1) Direct synthetic method for medium rings. (2) Regio- and stereoselective construction of (E,E)- or (E,Z)-1,5-cyclodecadiene system. (3) Selective introductions of functional groups, substituents and chiral centers at desired positions in ten-membered rings. (4) Efficient synthetic route to α-methylene-γ-butyrolactone. To date, synthetic efforts in this area have mainly focused on the simplest structural members of the family with heavy emphasis on macrocyclization methodology. As the direct approach based on intramolecular carbon-carbon bond formation,[2] cyclizations of the sulfide- and sulfone stabilized carbanion,[3] Ni(0)-promoted coupling reaction of allylic halides,[4] Pd(0)-catalyzed cyclization,[5] Cr(II)-promoted aldehyde addition,[6] $TiCl_4$/Cu-Zn-promoded coupling reaction,[7] Friedel-Crafts acylation,[8] and Wittig reaction[9] have been reported. Another indirect approach such as ring-cleavage of [m,n,0]-bicyclic[10] or [4,4,0,$0^{2,5}$]-tricyclic[11] compounds, and ring-expansions based on Cope,[12] oxy-Cope,[13] and Cope-Claisen[14] rearrangements of normal cyclic compounds are also known. However, most of these methods do not meet all the requirements shown above, especially the selective

formation of the (E,E)-1,5-cyclodecadiene system. Thus the adequate methods to construct germacrane lactones are very few.



(Figure 1)

We have reported a general synthetic method for (E,E)- and (E,Z)-2,6-cyclodecadienone systems by intramolecular alkylation of cyanohydrin ethers (Eq. 1,2,3).[15] These cyclizations have the following characteristic features.[16] (1) The alkylation is irreversible and very rapid, and the cyclized product is stable under basic condition. Therefore this method of cyclization requires short reaction time and no high dilution conditions, and gives a satisfactory yield of the macrocycles. (2) The carbanion acts only as acyl anion equivalent (via alpha attack). The gamma attack and the isomerization of double bonds are not observed. (3) The cyclized products are easily converted to the corresponding E- and Z-enones in high yields



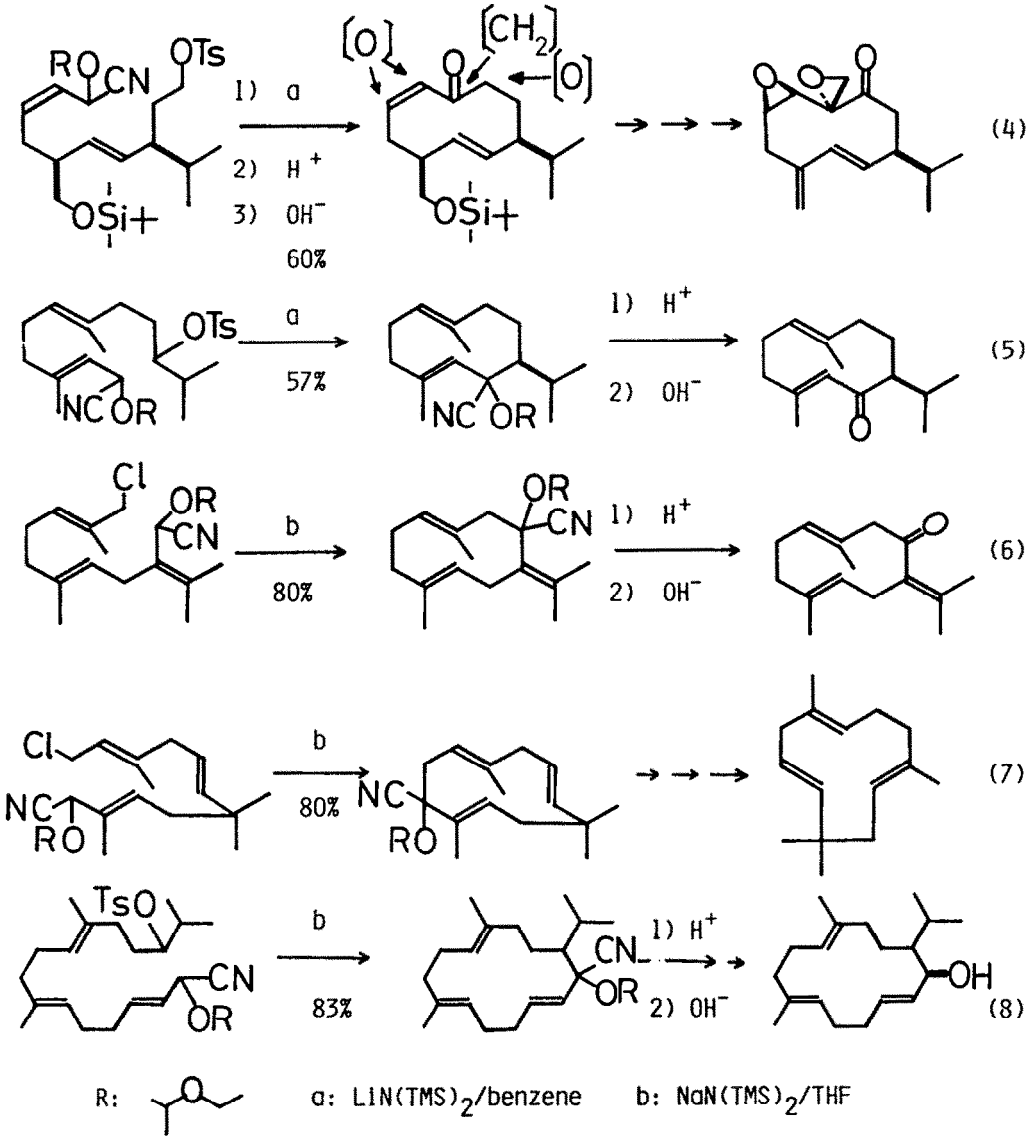
R: 

a: 1) TMSCN/KCN-18-crown-6, 2) $PhCH_2N^+Me_3F^-$, 3) CH_2=CHOR/p-TsOH
b: 1) $NaN(TMS)_2$ in THF, 65°C, c: 1) PPTS/MeOH, 2) 1%$NaHCO_3$aq

(Scheme 1)

with excellent stereoselectivity by mild acid and base treatments. (4) The regioselective introduction of oxidized functional groups at A-E positions in Figure 1 is accessible by choice of the cyclization position. Thus our cyclization is a convenient and efficient route to germacradienes.

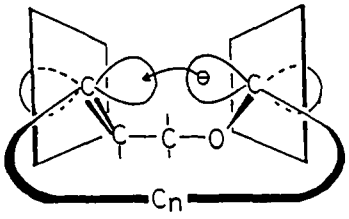
We have applied this cyclization method to the syntheses of periplanone-B (Eq. 4),[17] acoragermacrone (Eq. 5),[18] germacrone (Eq. 6),[19] humulene (Eq. 7),[20] and mukulol (Eq. 8).[18] As shown in the synthesis of periplanone-B, the cyanohydrin ether moiety can be utilized not only for the activation of the carbanion, but also for the stereoselective construction of the Z-enone which was used to introduce two epoxides and α'-carbonyl group. This cyclization is possible in a large scale. Indeed a 60 mmol scale cyclization in the synthesis of periplanone-B, followed by acid and base treatments afforded the Z-enone in 60% overall yield. Cyclizations with the secondary tosylate, as shown in the syntheses of acoragermacrone and mukulol, also proceed smoothly to construct the macrocyclic carbon skeleton and simultaneously induce the asymmetric center at α'-position of the labile enone.



(Scheme 2)

This cyclization, of course, can induce the chiral center, if the secondary tosylate is used in chiral form. Alkylations with the allylic halide, as shown in the syntheses of germacrone and humulene, are very useful to construct the complicated nonconjugated systems and strained molecules.

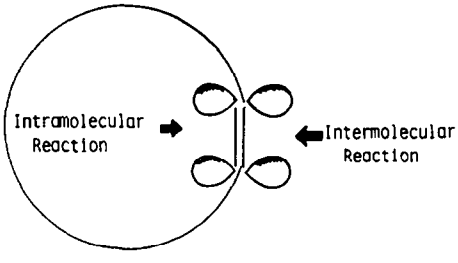
Generally, in the synthesis of natural macrocyclic compounds, the formation of the large ring is always left for the end of the synthesis with expectation that the cyclization proceeds without too much trouble. Indeed, in the previous syntheses of these biologically active germacrane lactones, the α-methylene-γ-butyrolactone moiety and the ten-membered carbon skeleton were constructed separately. Now that the above mentioned powerful cyclization methods are at hand, it is easy to prepare the medium- and large ring compounds similar to the formation of five- and six-membered rings. So, macroring contraction methodology[21] using transannular process (Figure 2), which can simultaneously construct the ten-membered carbon skeleton and the lactone moiety, can be imagined. In this paper, we wish to report the stereoselective syntheses of costunolide (**4**) and haageanolide (**6**) based on the [2,3]-Wittig rearrangement of 13-membered diallylic ethers.[22] A preliminary report[23] has been published, and the details of the studies are presented in this paper.



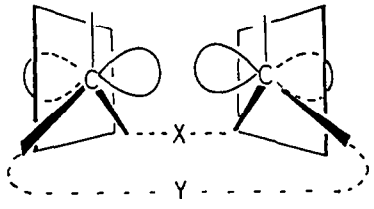
(Figure 2)

RESULTS AND DISCUTSSION

Both inter- and intramolecular reactions on medium- and large-membered rings proceed with high stereoselectivity as a consequence of their conformational properties. This type of stereocontrol might have predictive value in organic syntheses. Before discussing the syntheses of costunolide and haageanolide, we wish at first to clarify important features of macrocyclic stereocontrolled reactions. To minimize transannular nonbonded repulsions, macrocycles have the pi orbitals of the olefin oriented horizontally to the plane of the ring which is significantly different from normal rings in which the sp^2-centers tend to stand perpendicular to the plane of the ring. Therefore the inter- and intramolecular



(Figure 3)

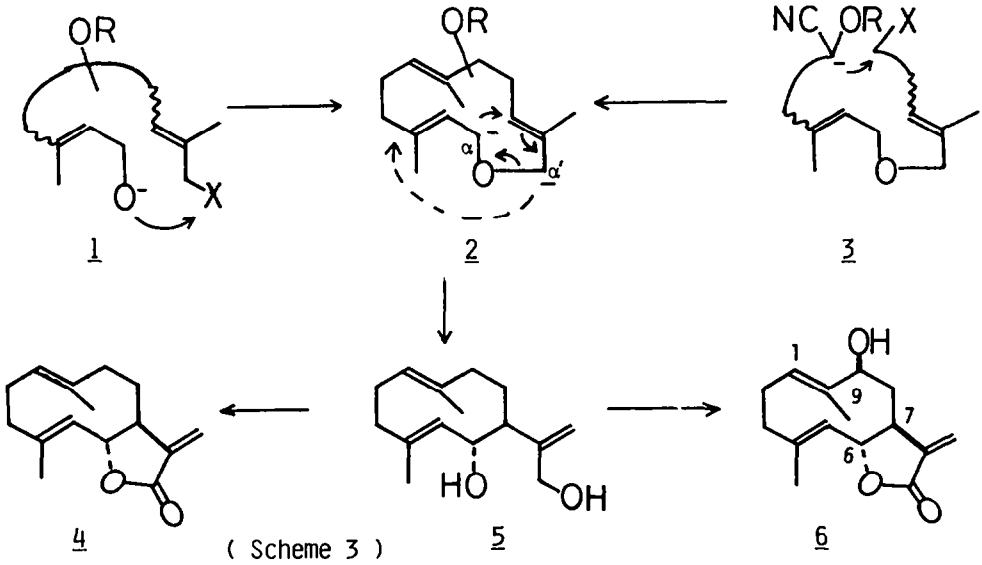


(Figure 4)

reactions should proceed exclusively from the one side as shown in Figure 3. It is also interesting to point out that higher degree of stereochemical control for the approach of a nucleophile toward a electrophile, and a better chemical yield can be envisaged in a transannular process where two centers are held together by two chains (X,Y in Figure 4) in comparison with an intramolecular process having one chain. From these stereoelectronic and entropy points of view, macrocyclic stereocontrolled reactions should give different sense and degree of diastereoselectivity from those in normal five or six membered rings and acyclic systems. Recently Still and co-workers have made important contributions in this field[24] and their work gave us an important idea and stimulated our research.

General Synthetic Strategy for Germacrane Lactones

As outlined in Scheme 3, our pathway to germacrane lactones such as costunolide (4) and haageanolide (6) is a simple one in which the [2,3]-Wittig rearrangement of the 13-membered diallylic ether 2, followed by the allylic oxidation of the resulting isopropenyl group provide the (E,E)-1,5-cyclodecadiene 5 having the secondary allylic alcohol and 3-hydroxy isopropenyl group which are necessary to construct the α-methylene-γ-butyrolactone moiety. The macrocyclic ether 2 is prepared by either intramolecular O-alkylation of the ω-halo alcohol 1 or C-alkylation of the protected cyanohydrin 3. The selective allylic oxidation of the diol 5 affords the γ-butyrolactone via cyclic hemiacetal. Thus the key reaction in our syntheses is the [2,3]-Wittig reaction which necessitates the following four selectivities; (1) the periselectivity ([2,3]-shift vs [1,2] and [1,4]-shifts), (2) the regioselectivity of the allylic anion formation at α-position against α'-position, (3) the trans-stereoselectivity between the newly formed allylic alcohol and isopropenyl group as well as the E-geometry of β,γ-olefin, (4) the remote diastereoselectivity using alkoxy group (the relative stereochemistry among C(6), C(7), and C(9) in the case of haageanolide synthesis).

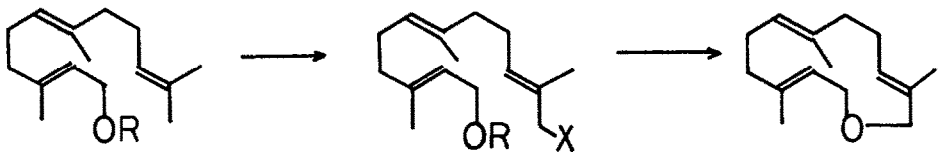


1 2 3 4 5 6

(Scheme 3)

Six Step Synthesis of Costunolide

Synthesis of the macrocyclic (E,E)-diallylic ether 12 is straight forward and summerized in Scheme 4. The allylic oxidation of the farnesyl acetate (8), derived from all-trans farnesol (7) with selenium dioxide (SeO_2)-tert-butyl hydroperoxide (TBHP) gave the allylic alcohol 9 in 34% yield,[25] and 34 % of farnesyl acetate (8) was also recovered. The allylic bromination of 9 with triphenylphosphine and carbon tetrabromide in acetonitrile at 0 °C, followed by methanolysis of the resulting allylic bromide 10 with potassium carbonate afforded the bromo alcohol 11 in 85% overall yield. The macrocyclic ether 12 was synthesized from 11 in 60% yield by using medium dilution condition; a solution of 11 (16.0 mmol) in dry benzene (100 mL) was added dropwise over two hours to a suspension of sodium hydride (30 mmol) and dicyclohexano-18-crown-6 (30.0 mmol) in benzene (200 mL) at 80 °C. Yields of the cyclization were very much dependent upon the amount of crown ether; the use of a catalytic amount of the crown ether gave the lower yield (ca. 20% yield), while its large excess led to polymerization. This O-alkylation is irreversible and the product is stable under the reaction conditions. Therefore this cyclization is clean as in the cyclization of cyanohydrin ether. Recently Marshall used ethylmagnesium bromide as a base for this type of cyclization and obtained a cyclic ether in a high yield.[22]



7: R = H
8: R = Ac

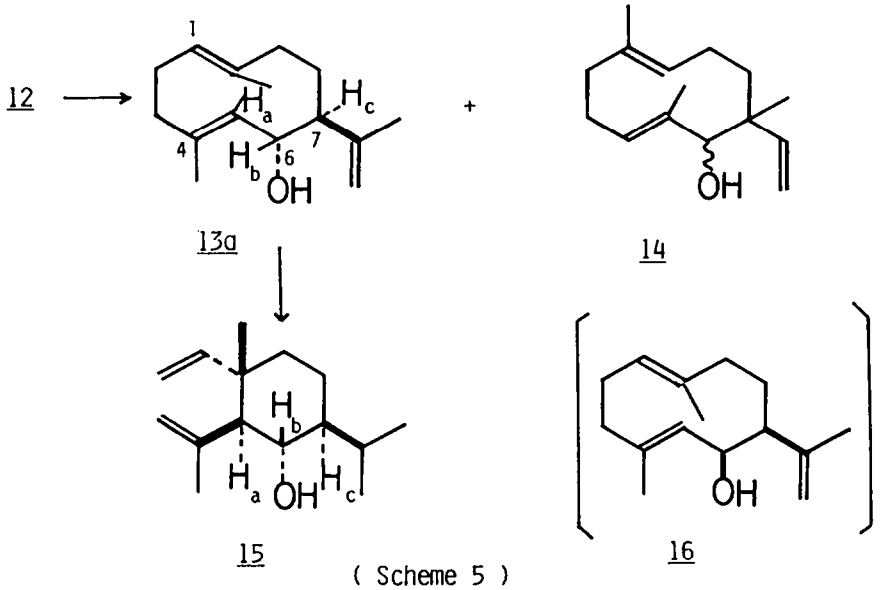
9: X = OH, R = Ac
10: X = Br, R = Ac
11: X = Br, R = H

12

(Scheme 4)

The [2,3]-Wittig rearrangement was carried out in the following way. The ether 12 was metalated in ether with t-butyllithium at -78 °C under nitrogen and the resultant yellow solution was stirred for another 10 hours at -78 °C. Then the reaction mixture was allowed over 30 min to warm to 0 °C and quenched with aqueous ammonium chloride solution. After the usual work-up, a 75 : 25 mixture of the [2,3]-rearrangement products 13 and 14, derived via α- and α'-lithiations respectively, was obtained in 98% yield. None of the [1,2]- or [1,4]-rearrangement products was detected in a crude reaction mixture by HPLC analysis. Thus the periselectivity and the stereoselectivity were excellent. The regioselectivity in this rearrangement, however, was moderate and sensitive to the solvent; the use of tetrahydrofuran (THF) produced a 55 : 45 ratio of 13 to its isomer 14 (total yield of 13 and 14; 95% yield). The use of more polar solvents such as THF/dimethoxyethane (DME), THF/N,N,N'N'-tetramethylethylenediamine (TMEDA), and THF/hexamethylphosphophoramide (HMPA) gave exclusively the regioisomer 14, although its stereochemistry was not determined. None of diastereoisomer of 13 could be detected when the reaction was carried out in THF and ether. The use of less polar media such as n-hexane gave none of rearrangement products, and the starting cyclic ether 12 was recovered. The stereoselectivity in this rearrangement will be discussed later.

The stereostructure of the major product **13a** was established by ^{1}H- and ^{13}C-NMR spectra (see experimental section). The observed coupling constants (d,d, $J_{a,b}$ = 9.4, $J_{b,c}$ = 9.4 Hz) of **13a** indicate the trans stereochemistry between C(6)-hydroxy and C(7)-isopropenyl group by the comparision with 400 MHz ^{1}H-NMR spectrum of an authentic sample.[26] It should be also noted that the ^{1}H-NMR spectra of **13a** and monol[27] having the same trans stereochemistry between C(6)-hydroxy an C(7)-isopropyl group showed H_b as a pair of doublet, whereas the corresponding methine of dilophol[28] having cis stereochemistry between C(6) and C(7)substituents was observed as a broad doublet at 4.57 ppm. Futhermore, the conversion of **13a** to the cyclohexane **15** by the stereoselective Cope-rearrangement[29] (at benzene reflux for six hours; 94% yield) and the observed axial-axial coupling constants ($J_{a,b}$ = 9.4, $J_{b,c}$ = 9.4 Hz) in the product **15** also suggest the trans stereochemistry at C(6) and C(7) substituents and the (4E,10E)-double bond geometry in the [2,3]-Wittig rearrangement product **13a**.



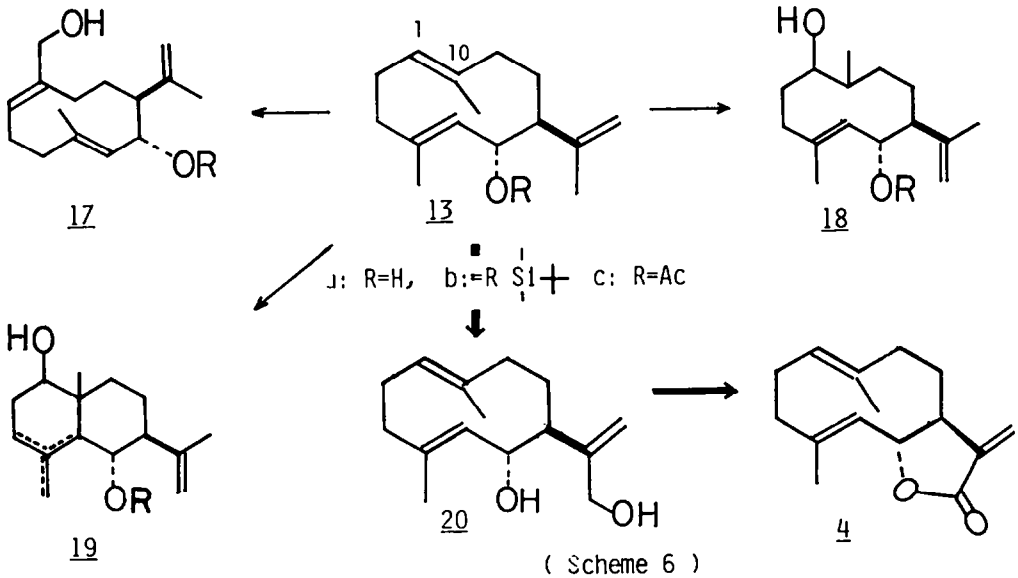
(Scheme 5)

Table 1

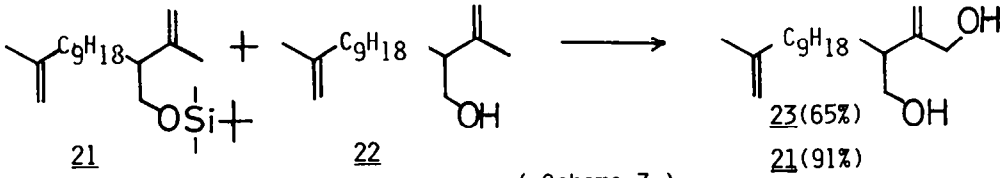
run	Solvent	13 : 14	Yield (%)
1	Hexane	No Reaction	-
2	Ether	75 : 25	98
3	THF	55 : 45	95
4	THF / DME (3 : 1)	10 : 90	-
5	THF / TMEDA (3 : 1)	0 : 100	-
6	THF / HPMA (3 : 1)	0 : 100	-

Conversion of the rearrangement product **13a** to (±)-costunolide **4** requires the regioselective allylic oxidation of the exocyclic isopropenyl group and the formation of the γ-butyrolactone. These transformations seem to be difficult due both

to high reactivity of the trisubstituted C(1,10) double bond in **13a** toward electrophilic reagents and the tendency of 1,5-cyclodecadienes to undergo transannular cyclization. Indeed, oxidation of **13a**, **13b** and **13c** with SeO_2-TBHP gave the C(10)-hydroxymethyl derivative **17**. Hydroboration of **13b** and **13c** both by 9-borabicyclo-[3.3.1]nonane and by disiamylborane followed by oxidation with hydrogen peroxide afforded the alcohol **18** where its stereochemistry was not determined. Epoxidation of **13b** with m-chloroperbenzoic acid gave the transannular reaction product **19** where its stereochemistry was not determined. Thus most electrophilic reagents react with C(1,10)-olefin. Then we have examined the allylic oxidation of the isopropenyl group through allylic lithiation.[30] Treatment of the alcohol **13a** with sec-butyllithium in the presence of TMEDA, oxidation of the resulting lithiated species, followed by work-up with 25% aqueous sodium sulfite (Na_2SO_3) gave the desired diol **20** in 54% yield, and the alcohol **13a** was recovered in 30% yield. No lithiation at C(10)-methyl took place. Interestingly, the lithiation of the siloxy derivative **13b** under the same reaction condition as described above gave the C(10)-hydroxymethyl product **17b**. This directing effect of neighboring hydroxy group on the allylic lithiation is not special in germacrane skeleton and we examined this effect in acyclic system such as **21** and **22** (Scheme 7). A mixture of **21** and **22** was treated in the same way as described above to give the diol **23** in 65% yield and the siloxy derivative **21** was inert in this lithiation. By the observation of such regioselectivity in the lithiation, we next attempted the sequential process for the [2,3]-Wittig rearrangement and the allylic oxidation. Treatment of **12** with sec-butyllithium at -78 °C in ether for 30 mins, followed by addition of TMEDA at -70°C and introduction of oxygen to reaction mixture and final reductive work-up with Na_2SO_3 gave the desired diol **20** in 44% yield and the alcohol **13a** in 21% yield. Oxidation of **20** with manganese dioxide in ether at room temperature for 12 hours gave directly the α-methylene-γ-butyrolactone **4** in 80% yield. Synthetic costunolide



(Scheme 6)

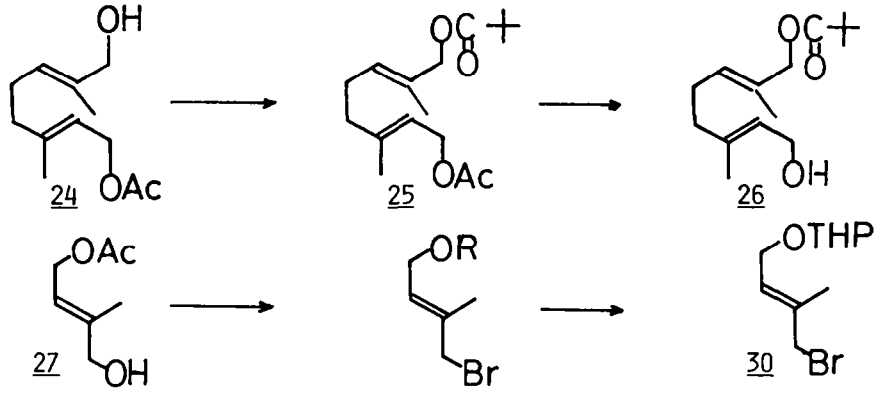


(Scheme 7)

thus prepared was found by ^{1}H-NMR spectrum and TLC to be identical with a sample of natural product supplied by Prof. Kitagawa.[26]

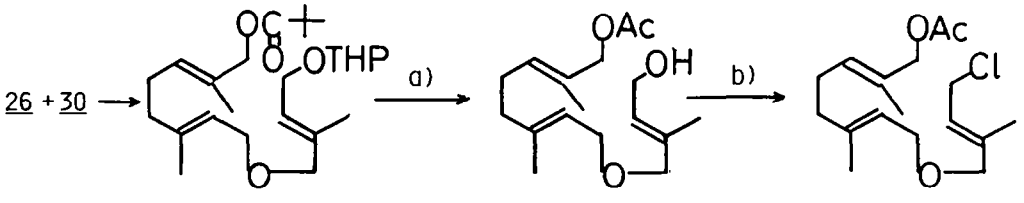
Remote-Stereocontrolled Synthesis of Haageanolide

Our synthesis of haageanolide is based in large part on previous observations that macrocyclic diallylic ethers undergo highly stereoselective [2,3]-Wittig rearrangement to yield the trans stereochemistry between C(6) and C(7) substituents. Differences in the syntheses of haageanolide from that of costunolide are found only in the construction of the macrocylic ether (C-C bond formation or O-alkylation) and additional remote-diastereoselection in [2,3]-Wittig rearrangement. The dienyl segment **26** and the allylic bromide **30** required for these studies were easily prepared from the allylic alcohols **24** and **27**, which were derived from geranyl acetate and 3-methyl-2-butenyl acetate respectively, via allylic oxidation with SeO_2-TBHP,[25] followed by reduction with sodium borohydride. Esterification of the alcohol **24** with trimethylacetyl chloride and selective methanolysis of the acetate **25** with potassium carbonate afforded the dienyl alcohol **26** in 99% yield. The bromide **30** was prepared by the following way. Allylic bromination of the alcohol **27** using triphenylphosphine and carbon tetrabromide, and subsequent basic methanolysis of the resultant acetate **28** gave the alcohol **29** in 53% yield. This alcohol **29** was protected as its tetrahydropyranyl ether **30**.



(Scheme 8) **28**: R = Ac, **29**: R = H

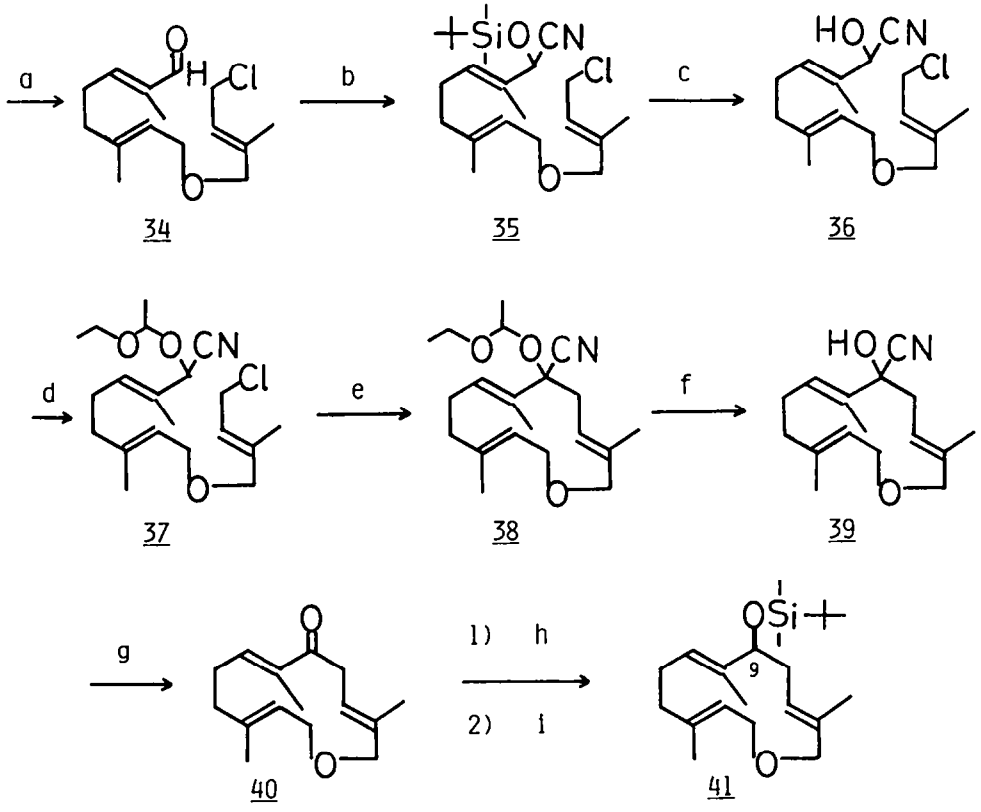
Preparation of the macrocyclic ether **41** is summarised in Schemes 9 and 9'. Intermolecular O-alkylation of the alcohol **26** with the bromide **30** using KOH(39.3 mmol)/Bu_4NI(19.2 mmol)/H_2O(3 mL) at room temperature afforded the ether **31**. Reductive removal of the trimethylacetyl group of the adduct **31** with lithium aluminum hydride, acetylation of the resultant allylic alcohol with acetic anhydride, and acidic mathanolysis of the tetrahydropyranyl ether using pyridinium p-toluenesulfonate gave the alcohol **32** in 57% overall yield from **29**. The allylic chlorination of the alcohol **32** with triphenylphosphine in carbon tetrachloride gave the



a: 1) $LiAlH_4$, 2) Ac_2O/Py, 3) PPTS/MeOH, b: PPh_3/CCl_4

(Scheme 9)

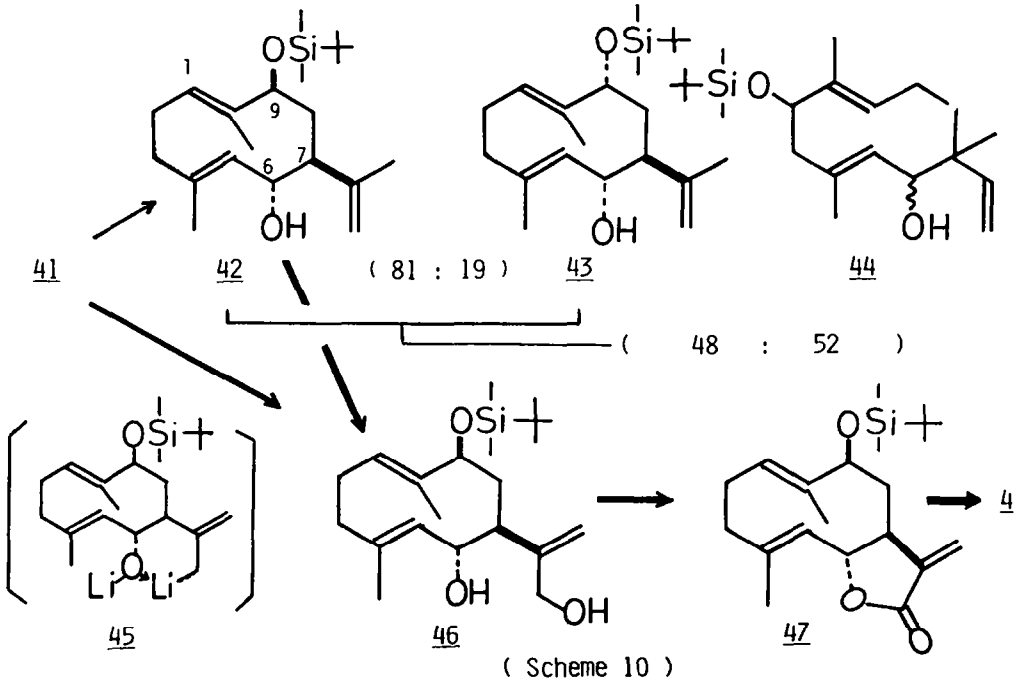
chloride **33** in 98% yield. Basic methanolysis of the acetate **33** followed by oxidation of the resultant allylic alcohol gave the E-enal **34** in 69% overall yield. The enal **34** was transformed into the protected cyanohydrin **36** without isomerization of olefins in three steps. The 1,2-addition of trimethylsilyl cyanide[31] to the enal **34** in the presence of potassium cyanide/dicyclohexyl-18-crown-6 complex, followed by desilylation of the adduct **35** with benzyltrimethylammonium fluoride, and reprotection of the cyanohydrin **36** with ethyl vinyl ether gave the protected cyanohydrin **37** in 95% overall yield. The cyclization was carried out in the following way. The protected cyanohydrin **37** (0.65 mmol) in THF (10 ml) was added, using a Hershberg dropping funnel, over 2 hours at 65°C under nitrogen atmosphere to a solution of sodium bis(trimethylsilyl)amide (3.3 mmol) in THF. The cyclized product **38** was isolated in 80% yield. Acid treatment of the cyclized product **38** with pyridinium p-toluenesulfonate in methanol and vigorous shaking in a separatory funnel with 1% aqueous sodium hydroxide/ether, afforded two phase layers. The trienone **40** was isolated in 99% overall yield and its structure was confirmed by ^{1}H-, ^{13}C-NMR and mass spectra. The reduction of the ketone **40** with diisobutylaluminum hydride and subsequent protection of the allylic alcohol with tert-butyldimethylsilyl chloride gave the ether **41** in 85% yield.



a: 1) K_2CO_3/MeOH, 2) MnO_2, b: Me_3SiCN/KCN-18-crown-6, c: $Me_3(PhCH_2)NF$
d: $CH_2{=}CHOEt$/p-TsOH, e: $NaN(SiMe_3)_2$/THF, f: PPTS/MeOH, g: 2%NaOH
h: $(iso\text{-}Bu)_2AlH$/THF, i: (tert-Bu)Me_2SiCl/DMF / Imidazole
(Scheme 9')

We have examined a directing effect of neighboring C(9)-silyloxy group of the macrocyclic ether **41** on the stereochemistry of the [2,3]-Wittig rearrangement. The ether **41** underwent a remarkably facile rearrangement upon stirring with tert-

butyllithium in ether at -78°C for 24 hours to afford a mixture of **42**, **43** and **44** in over 90% yield where the alcohols **42** and **43** were formed via α-lithiation, while the alcohol **44** was obtained by α'-lithiation. Neither the [1,2]-, [1,4]-rearrangement products nor C(6)-C(7) cis isomers were detected in a crude mixture by ^{1}H-NMR and HPLC analyses. Thus clearly this rearrangement proceeded in a high yield with excellent periselectivity and C(6)-C(7) trans-stereoselectivity. However, the moderate remote-diastereoselectivity (**42**:**43** = 81:19) and the poor regioselectivity (**42**+**43** : **44** = 48 : 52) were observed. Trans-stereochemical assignments at C(6) and C(7) of **42** and **43** were made through the comparision of coupling patterns of the C(6)-proton with those of costunolide, monol[27] and dilophol.[28] Furthermore, the relative stereochemistry including C(9), C(6) and C(7) of **42** and **43** was tentatively assigned by the coupling patterns of C(9)-protons; ^{1}H-NMR **42** 4.54 (br d, J = 9.0 Hz, C(5)), 4.05 (dd, J = 9.0, 9.0 Hz, C(6)), 4.07 (dd, J = 9.0, 2.6 Hz, C(9)); **43** 4.06 (br d, J = 9.4 Hz, C(5)), 4.16 (m, C(9)), 4.05 (dd, 9.4, 9.4 Hz, C(6)). The alcohol **42** was easily converted to (±)-haageanolide (**4**) by the same reaction process described in the synthesis of (±)-costunolide. Treatment of the alcohol **42** with sec-butyllithium in the presence of TMEDA at -70°C in ether, and subsequent introduction of oxygen to lithiated species and reductive work-up with sodium sulfite gave the desired diol **46** in 60% yield. The starting material was also recovered in 30% yield and none of the lithiated products at other methyl groups was detected by HPLC analysis. This regioselective allylic oxidation can be explained by the hydroxy-directed or -assisted lithiation of isopropenyl group as shown in **45**. We also attempted a one-pot process for the [2,3]-Wittig rearrangement and allylic oxidation. Reaction of the macrocyclic ether **41** with sec-butyllithium at -70°C in ether, followed by addition of TMEDA and oxygen to the reaction mixture and final reductive work-up with sodium bisulfite gave the desired diol **46** in 25% yield. The rearrangement products **42** and **44** were obtained in 10% and 47% yields, respectively. With manganese dioxide, the diol **46** was directly converted



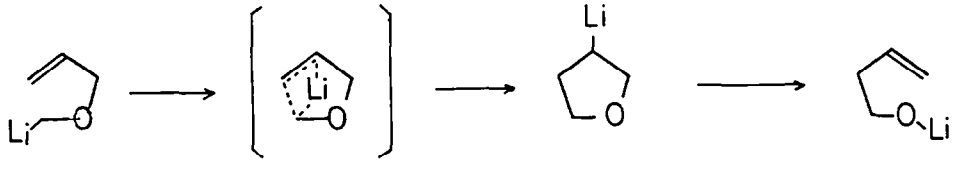
(Scheme 10)

via cyclic hemiacetal into the α-methylene-γ-butyrolactone **47** followed by desilylation of the lactone **47** with tetrabutylammonium fluoride gave (±)-haageanolide (**6**) in 70% overall yield from **46**. The ^{1}H-NMR spectrum of the synthetic haageanolide was identical with those of natural haageanolide and its acetate.[32]

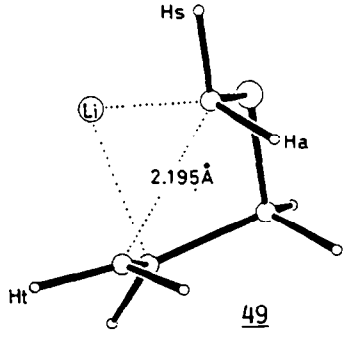
Studies of Transition Structures in Transannular [2,3]-Wittig Rearrangements

Predictions of stereoselectivity in medium ring systems are quite difficult since they have many conformational options. Molecular Mechanics calculations have proven useful in the prediction of the stereoselectivity in macrocyclic systems.[24] The peripheral epoxidation of the 10-membered enone is one of such successful examples where stereoselectivities are predicted from conformational distributions and steric energies of the starting compound.[17] In this case, of course, a small geometrical change between products and the starting compound is essential. Therefore similar approaches cannot be applied to the [2,3]-Wittig rearrangement since there are larger geometrical changes in this reaction. In order to understand (or predict) stereoselectivities in the [2,3]-Wittig rearrangement, geometrical information concerning the transition state models are necessary. So far, three types of envelope transition state model[33,34] for acyclic [2,3]-Wittig rearrangemnts[35] have been proposed. However these qualitative methods are not applicable to the quantitative predictions. The ab-initio quantum mechanical calculations have been used to obtain quantitative informations about the geometry and energetics of the transition state. This method also cannot be applicable directly to the complex molecules such as our synthetic targets, because of the enormous computer time required for such calculations. We used here the MM2 transition structure models[36] based on ab-initio calculations for rationalizing the high degree of trans-stereoselection at C(6) and C(7) in transannular [2,3]-Wittig rearrangements.

For the simple model system, the transition structure **49** in the rearrangement of the (allyloxy)methyllithium **48** to the 3-tetrahydrofuranyllithium **50**[37] (a stepwise

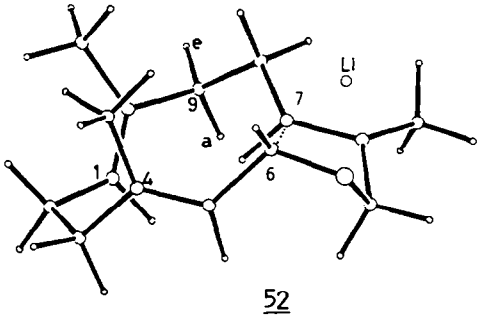


48 **49** (Scheme 11) **50** **51**



49

(Figure 5) The MM2(STO 3G) transition structure **49** for the [2,3]-Wittig rearrangement of (allyloxy)methyllithium **48**



52

(Figure 6) The preferred MM2(STO 3G) transition structure **52** for the transannular [2,3]-Wittig rearrangement of the diallylic ether **12**

mechanism) was obtained by ab-initio calculations with minimal basis set.[38] At present time, we cannot find the concerted transition structure in the [2,3]-Wittig rearrangement of **48** to **51** by ab-initio calculations.[39] The ab-initio transition structure of **49** is shown in Figure 5 and its geometry was used for further analyses by the following reasons; (1) Two reaction processes (**48**-**50** and **50**-**51** in scheme 11) are extremely exothermic.[37] (2) The stereochemical outcome of the reaction can be determined in the transition structures **49**. Then we calculated energies of the transition structure in the [2,3]-Wittig rearrangement of **12** by substituting appropriate hydrogens (H_t, H_a and H_t, H_a respectively) in the ab-initio transition structure shown in Figure 5 for two carbon chains corresponding to the ten-membered ring moeity using MMRS program[40] with 20° degree resolution angle and 2.0 Å ring closure distance. By this program, eight candidates for the transition structure, giving C(6)-C(7) trans-stereoselection in the [2,3]-Wittig rearrangement, were obtained and no candidates for the cis-streoselection was found. The MM2 geometry optimization[41] of eight candidates afforded four transition structures, in which the structure **52** (Figure 6) was the most stable one and has a chair-chair conformation with two-β-methyl groups in the newly forming ten-membered ring. These calculated results are enough to explain the high degree of C(6)-C(7) trans-stereoselection in the rearrangement. Then we calculated energies of the transition structures in the rearrangement of **41** by simply substituting the methoxy group for the C(9)-pseudoequatorial and pseudoaxial hydrogens of the most stable transition structure **52**, since the secondly favored transition structure in the reaction of **12** was 5.7 kcal/mol higher in energy than the MM2 transition structure **52**. The energy difference of the two conformations (C(9)-pseudoequatorial and pseudoaxial methoxy derivatives) was rather small (0.2 kcal/mol). The predominance of the experimental major isomer **42** can be reproduced by this calculation, although the calculated ratio of the pseudoequatorial to the pseudoaxial methoxy derivative (3:2) is much smaller than the experimental value (4:1) at -78°C. The calculated ratio should be improved, when the reliable MM2 parameters for silicon atom can be deduced, since the tert-butyldimethylsiloxy group should be more stereochemically demanding than the methoxy group. Interestingly, the most favorable MM2 transition structure **52** obtained from the ab-initio calculations coincides with the previously proposed structure based on the simple MM2 calculation.

EXPERIMENTAL

IR spectra were recorded on JASCO IRA-2 spectrometer. IR data represent ν_{max} in cm^{-1}. EI-MS were recorded on a JEOL JMS-DX303 mass spectrometer unless otherwise noted. High resolution mass spectra (HRMS) were recorded on a VG ZAB-HF mass spectrometer. ^{1}H-NMR spectra were recorded on a JEOL FX-90Q spectrometer at 90 MHz with tetramethylsilane (TMS) as an internal standard at 0.00 ppm for measurements in $CDCl_3$. ^{1}H-NMR data are shown in ppm (multiplicity, J values, integration). ^{13}C-NMR spectra were recorded on a JEOL FX-90Q spectrometer at 22.5 MHz. A signal for TMS was used as an internal standard in $CDCl_3$. Column chromatography was performed using silica gel (Kanto) 100/200 mesh. TLC was performed using Merck precoated TLC plate 60F 254 (silica gel). Preparative high performance liquid chromatography (HPLC) was performed on Nihonseimitsu NSLC-100 using silica gel (60-5 μm; 7.5 o.d. X 250 mm) column and a RI-detector.

TOTAL SYNTHESIS OF (±)-COSTUNOLIDE (11)

12-Acetoxy-2,6,10-trimethyl-2E,6E,10E-dodecatrien-1-ol (9): A mixture of farnesyl acetate (**8**) (70.0 g, 0.265 mmol), tert-butyl hydroperoxide (TBHP) (123 g, 0.957 mmol, 70% in water), selenium dioxide (SeO_2) (590 mg, 5.30 mmol) and salicylic acid (3.66 g, 26.5 mmol) in methylene chloride (CH_2Cl_2) (200 ml) was

stirred for 13 h at room temperature. The resulting solution was diluted with benzene (200 ml) and evaporated *in vacuo* to remove tert-butanol, H_2O and CH_2Cl_2. The residue was diluted with ether (200 ml), washed with four portions of 10% aqueous potassium hydroxide (KOHaq), followed by 3N hydrochloric acid (HClaq), sodium hydrogen carbonate ($NaHCO_3$aq), brine, dried over magnesium sulfate ($MgSO_4$) and concentrated *in vacuo*. The residue was diluted with acetic acid (AcOH) (100 ml), cooled to 0°C, and dimethyl sulfide (100 ml) was added dropwise slowly to the mixture. The resulting solution was neutralized to pH=7 with several portions of 30% KOHaq (0.95 eq. to AcOH) and sat. $NaHCO_3$aq (0.05 eq. to AcOH). The resulting solution was extracted with three portions of ether/hexane (7/3) and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (elution with hexane/ether 7/1) to give the farnesyl acetate (**8**) (23.6 g, 34% recovered) and the allylic alcohol **9** (25.0 g) in 34% yield. IR (neat) 3400, 2900, 2850, 1740, 1440, 1380, 1360, 1235, 1010, 740 cm^{-1}: ^{1}**H-NMR** 5.39 (m, 1H), 5.33 (br t, J = 7.3 Hz, 1H), 5.09 (br t, J = 6.4 Hz, 1H), 4.56 (br d, J = 7.3 Hz, 2H), 3.96 (br s, 2H), 2.04 (s, 3H), 1.70 (br s, 3H) 1.66 (br s, 3H), 1.60 (br s, 3H): ^{13}**C-NMR** 171.0, 142.0, 135.1, 135.0, 125.4, 123.9, 118.6, 68.5, 61.3, 39.5, 39.4, 26.3, 26.2, 20.8, 16.4, 13.6: **EI-MS** 280(M^+), 119, 107, 93: **HRMS** calc. for $C_{15}H_{20}O_2$ m/e=234.1620, found m/e=234.1628.

1-Bromo-12-acetoxy-2,6,10-trimethyl-2E,6E,10E-dodecatriene (10): To a solution of **9** (3.71 g, 13.2 mmol) and triphenylphosphine (PPh_3) (9.5 g, 17.2 mmol) in dry acetonitrile (40 ml) was added carbon tetrabromide (CBr_4) (5.7 g, 17.2 mmol) portionwise over 15 min with stirring at 0°C and the reaction mixture was stirred for 30 min at 0°C. The resulting mixture was diluted with CH_2Cl_2 (80 ml) and concentrated *in vacuo* to give a brown oil, which was purified by column chromatography on silica gel (elution with hexane/ether 8:1), to give the bromide **10** (4.52 g) in 99% yield; IR (neat) 2900, 1740 cm^{-1}, ^{1}**H-NMR** 5.56 (br t, J = 6.6 Hz, 1H), 5.34 (br t, J = 7.2 Hz, 1H), 5.09 (br t J = 5.7 Hz, 1H), 4.57 (br d J = 7.2 Hz, 2H), 3.95 (br s, 2H), 2.03 (s, 3H), 1.74 (br s, 3H), 1.70 (br s, 3H), 1.59 (br s, 3H) ^{13}**C-NMR** 170.7, 141.8, 134.5, 132.0, 131.0, 124.3, 118.3, 61.3, 41.4, 39.4, 38.8, 26.8, 26.2, 20.9, 16.4, 16.0, 14.6.

1-Bromo-12-hydroxy-2,6,10-trimethyl-2E,6E,10E-dodecatriene (11): A mixture of **10** (4.52 g, 13.2 mmol) and potassium carbonate (450 mg, 3.29 mmol) in dry methanol (60 ml) was stirred for 30 min at 0°C. The resulting mixture was poured into an ice-cold 3N HClaq and extracted with three portions of CH_2Cl_2. The combined extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography on silica gel (elution with hexane/ether 4:1) to give the bromoalcohol **11** (3.41 g, 11.3 mmol) in 86% yield; IR (neat) 3350, 2925, 1440, 1390, 1205, 1000, 605 cm^{-1}: ^{1}**H-NMR** 5.57 (br t, J = 5.8 Hz, 1H), 5.41 (br t, J = 7.2 Hz, 1H), 5.12 (br t, J = 6.6 Hz, 1H), 4.13 (br d, J = 7.2 Hz, 2H), 3.96 (br s, 2H), 1.75 (br s, 3H), 1.67 (br s, 3H), 1.60 (br s, 3H) ^{13}**C-NMR** 139.0, 134.4, 132.0, 131.0, 124.5, 123.7, 59.2, 41.6, 39.5, 38.8, 26.8, 26.4, 16.3, 16.0, 14.6.

1-oxa-3,7,11-trimethyl-3E,7E,11E-cyclotridecatriene (12): A solution of **11** (4.8 g, 16 mmol) in benzene (100 ml) was added dropwise over 2 h to a suspension of sodium hydride (NaH) (1.2 g, 60% in mineral oil, 30 mmol) and dicyclohexano-18-crown-6 (4.95 g, 30 mmol) in benzene (200 ml) at 80°C and the mixture was stirred for 3 h under nitrogen atmosphere. Then the reaction mixture was poured into an ice-cold aqueous ammonium chloride (NH_4Claq) and the aqueous layer was extracted with three portions of hexane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/ether 30:1) to give the ether **12** (2.1 g) in 60% yield; IR (neat) 2900, 2850, 1720, 1660, 1440, 1380, 1250, 1100, 1060, 920, 805 cm^{-1}: ^{1}**H-NMR** (recorded with Bruker WH 400 MHz spectrometer at 400 MHz) 5.24 (ddd, J = 6.2, 6.2, 1.4 Hz, 1H), 5.17 (ddd, J = 5.1, 5.1, 1.1 Hz, 1H), 4.86 (ddd, J = 6.8, 6.8, 1.1 Hz, 1H), 4.09 (dd, J = 6.2, 0.8 Hz, 2H), 3.91 (s, 2H), 1.60 (s, 3H), 1.55 (s, 3H), 1.52 (s, 3H) ^{13}**C-NMR** 135.6, 133.4, 133.3, 125.8, 125.1, 124.4, 77.7, 69.4, 38.8, 38.6, 24.7, 24.2, 15.8, 15.5, 14.0 **MS** (recorded with Varian Mat 312 spectrometer) 220(M^+), 205, 175, 137, 121, 107, 93, 81, 67, 55, 28, 18.

[2,3]-Wittig rearrangement of the cyclic ether 12: To a solution of **12** (254 mg, 1.16 mmol) in dry ether (10 ml) was added tert-butyllithium (5 ml, 6.5 mmol,

1.3 N in pentane) dropwise over 5 min at -78°C and the reaction mixture was stirred for another 10 h at -78°C under nitrogen atmosphere. The resulting mixture was allowed over 30 min to warm to 0°C, poured into an ice-cold NH_4Claq, and extracted with three portions of ether. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a mixture of 1S*,10R*-3,7-dimethyl-10-(2-propenyl)-2E,6E-cyclodecadien-1-ol (**13a**) and 2,6,10-trimethyl-10-vinyl-2E,6E-cyclodecadien-1-ol (**14**), which was purified by column chromatography on silica gel (elution with hexane/ether 20:1-10:1) to give the alcohol **14** (62 mg) in 24% yield, and **13a** (187 mg) in 74% yield; **13a** IR (neat) 3450, 2950, 2870, 1640, 1440, 1385 cm^{-1} ^{1}**H-NMR** (recorded with a JOEL GX-400 spectrometer at 400 MHz) 4.87 (m, 2H), 4.80 (m, 1H), 4.63 (d, J = 9.4 Hz, 1H), 4.08 (dd, J = 9.4, 9.4 Hz, 1H), 1.77 (s, 3H), 1.67 (s, 3H), 1.41 (s, 3H) ^{13}**C-NMR** 149.0, 137.7, 134.3, 132.8, 126.9, 112.6, 69.2, 58.7, 41.4, 39.6, 30.8, 25.8, 19.1, 16.9, 16.4 **MS** 220(M^+), 205, 202, 187: **HRMS** calc. for $C_{15}H_{24}O$ m/e=220.1828, found m/e =220.1839: **14** (mixture of diastereomers) **IR** (neat) 3450, 2920, 2850, 1630, 1440, 905 cm^{-1} ^{1}**H-NMR** 6.09 (dd, J = 11.0, 17.5 Hz, 0.6H), 6.24 (dd, J = 11.9, 18.7 Hz, 0.4H), 5.38-4.70 (m, 2H), 3.78 (br s, 0.6H), 3.67 (br s, 0.4H) **MS** 205($M-CH_3$), 202($M-H_2O$), 187($M-CH_3-H_2O$): **HRMS** calc. for $C_{15}H_{24}O-H_2O$ m/e=205.1593, found m/e =205.1605.

Cope rearrangement of 13a: A solution of **13a** (19.7 mg, 0.09 mmol) in benzene (8 ml) was refluxed with stirring for 6 h under nitrogen atmosphere. The resulting solution was concentrated in vacuo to give an oil, which was purified by column chromatography on silica gel (elution with ether/hexane 1:5) to give 1S*,2S*,3R*,6R*-2,6-bis(2-propenyl)-3-vinyl-3-methyl-cyclohexan-1-ol (**15**; 18.0 mg) in 94% yield. IR (neat) 3400, 2900, 2850, 990, 890 cm^{-1} ^{1}**H-NMR** 5.80 (dd, J = 9.9, 18.1 Hz, 1H), 5.14-470 (m, 6H), 3.58 (dd, J = 9.4, 9.4 Hz, 1H), 1.79 (s, 3H), 1.57 (s, 3H), 1.06 (s, 3H) **MS** 220(M^+), 205, 202, 187: **HRMS** calc. for $C_{15}H_{24}O$ m/e=220.1828, found m/e =220.1826.

1S*,10R*-3,7-dimethyl-10-(2-[1-hydroxy-2-propenyl])-2E,6E-cyclodecadien-1-ol (20): To a mixture of **13a** (26 mg, 0.12 mmol) and N,N,N',N'-tetramethylethylenediamine (TMEDA) (0.089 ml, 0.59 mmol) in tetrahydrofuran (THF) (1.2 ml) was added dropwise sec-butyllithium (0.42 ml, 1.5 M in cyclohexane, 0.59 mmol) at -78 °C under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature over 20 min and stirred for 1 h. After the solution was cooled to -78°C, the nitrogen gas was displaced with oxygen gas. Then the solution was allowed to warm to 0°C, poured into NH_4Claq and extracted with three portions of ethyl acetate. An aqueous solution of 25% sodium sulfide (Na_2SO_3aq) was added to the combined extracts and the two phase layers were stirred vigorously for 24 h at room temperature. After the aqueous layer was extracted with three portions of ethyl acetate, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with ether/hexane 1:1) to give the alcohol **13a** (7.8 mg, 30% recovered) and the diol **20** (15.4 mg) in 54% yield. IR (neat) 3350, 2900, 2850, 1640, 1440, 1380, 1180, 1110, 1010, 900, 720 cm^{-1} ^{1}**H-NMR** 5.16 (br s, 1H), 5.01 (br s, 1H), 4.80 (m, 1H), 4.69 (br d, J = 9.2 Hz, 1H), 4.19 (dd, J = 9.2, 9.2 Hz, 1H), 4.14 (br s, 2H), 1.66 (br s, 3H), 1.40 (br s, 3H) ^{13}**C-NMR** 153.0, 137.9, 134.7, 132.9, 126.7, 112.0, 71.4, 65.1, 55.0, 41.6, 39.5, 32.2, 25.8, 17.0, 16.3.

Sequential process from 12 to 20: To a solution of **12** (27 mg, 0.123 mmol) in ether (1.5 ml) was added dropwise sec-butyllithium (0.42 ml, 1.5 M in cyclohexane, 0.62 mmol) and the solution was stirred for 30 min at -78 °C under nitrogen atmopsphere. After the addition of TMEDA (71 mg, 0.61 mmol)to the solution, the mixture was allowed to warm to room temperature, stirred for 1 h and cooled to -70°C. After the displacement of the nitrogen gas to oxygen gas, the solution was allowed to warm to 0°C, poured into NH_4Claq and extracted with three portions of ethyl acetate. The same reductive work-up and chromatographic purification gave the diol, **20** (12.9 mg, 44% yield) and the alcohols **14** (5.7 mg, 21% yield) and **13a** (7.3 mg, 22% yield).

(±)-Costunolide (11): A suspension of **20** (10.0 mg, 0.042 mmol) and manganese dioxide (MnO_2) (160 mg, 1.84 mmol) in ether (2.0 ml) was stirred for 12 h at room temperature. The reaction mixture was filtered on florisil, and the filtrate was concentrated in vacuo. Column chromatography on silica gel (elution with hexane/ether 2/1) of the residue gave (±)-costunolide (**11**). (7.8 mg) in 80% yield. **mp.** 64-66°C (recrystalized from ether/hexane) **IR** (KBr) 2970, 2920, 2860, 1760,

1660, 1460, 1440, 1385, 1290, 1245, 1190, 1140, 1060, 965, 940, 890, 870, 840, 810, 730, 700, 640, 505 cm^{-1} **^{1}H-NMR** 6.26 (d, J = 3.4 Hz, 1H), 5.52 (d, J = 3.4 Hz, 1H), 4.85 (m, 1H), 4.72 (d, J = 9.8 Hz, 1H), 4.55 (dd, J = 9.8, 8.0 Hz, 1H), 1.71 (d, J = 1.3 Hz, 3H), 1.43 (br s, 3H); **^{13}C-NMR** 170.3, 141.3, 136.9, 127.4, 127.1, 119.5, 81.9, 50.5, 41.1, 39.5, 28.2, 26.2, 17.3, 16.1; TLC, Rf = 0.55 (ether/hexane 2/1): **EI-MS** 232[M^+], 217, 123, 109: **HRMS** calc. for $C_{15}H_{20}O_2$ m/e=232.1464, found m/e=232.1448

TOTAL SYNTHESIS OF (±)-HAAGEANOLIDE (6)

8-Acetoxy-2,6-dimethyl-2E,6E-octadien-1-ol (24) was prepared from geraniol according to the known method (ref. 25).

1-Trimethylacetoxy -2,6-dimethyl-2E,6E-octadien-12-ol (26): To a solution of **24** (41 g, 0.193 mol) in CH_2Cl_2 (100 ml) was added pyridine (18 ml, 0.22 mol) in one portion, then pivaloyl chloride (25 ml, 0.21 mol) dropwise over 20 min at 0°C, and the mixture was stirred for 30 min. The resulting mixture was poured into 3N HClaq and extracted with three portions of hexane/ether (1/1). The combined extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude pivaloyl ester **25**, which was used in the next reaction without further purification. A mixture of the crude oil and potassium carbonate (8.0 g, 57.9 mmol) in dry methanol (100 ml) was stirred for 40 min at 0°C. The resulting mixture was poured into 3N HClaq and extracted with three portions of CH_2Cl_2. The combined extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled under reduced pressure (bp. 160-170°C/0.05 mmHg) to give **26** (48.7 g) in 99% yield; IR (neat) 3400, 2950, 1720 cm^{-1} **^{1}H-NMR** 5.54-5.22 (m, 2H), 4.44 (br s, 2H), 4.13 (br d, J = 6.8 Hz, 2H), 1.65 (br s, 6H), 1.21 (br s, 9H)

4-Acetoxy-2-methyl-2E-buten-1-ol (27): A mixture of prenyl acetate (150 g, 1.167 mol), TBHP (200 g, 1.55 mmol, 70% in water), SeO_2 (2.57 g, 23.4 mmol) and salicylic acid (16 g, 0.117 mol) in CH_2Cl_2 (700 ml) was stirred for 50 h at room temperature. The resulting mixture was diluted with benzene (500 ml) and concentrated *in vacuo* to remove CH_2Cl_2, water and tert-buthyl alcohol. The residue was diluted with hexane/ether (7:3, 500 ml), washed with four portions of 10% KOHaq, 3N HClaq, sat. $NaHCO_3$aq, brine, dried over $MgSO_4$, and concentrated *in vacuo*. To a mixture of the residue and AcOH (100 ml) was added dimethyl sulfide (50 ml) dropwise over 20 min at 0°C and the mixture was stirred for 10 h at room temperature to reduce the excess TBHP. To the resulting solution was added an ice-cold 10% KOHaq (0.95 eq. to AcOH), then sat. $NaHCO_3$aq (0.05 eq. to AcOH) in several portions at 0°C and the resulting mixture was extracted with three portions of ether/hexane (7/3). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a crude mixture of the starting material, desired product and the aldehyde. To a solution of the crude mixture in ethanol (100 ml) was added sodium borohydride ($NaBH_4$) (20 g, 0.53 mol) in some portions and the mixture was stirred for 30 min, quenched with 3N HClaq at 0°C, and extracted with three portions of CH_2Cl_2. The combined extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled under reduced pressure to give prenyl acetate (bp. 75°C/37 mmHg, 68.5 g, 46% recovered) and the alcohol **27** (bp. 140°C/22 mmHg, 50 g) in 30% yield; IR (neat) 3400, 2900, 1740 cm^{-1} **^{1}H-NMR** (recorded with a Hitachi R-24A spectrometer at 60 MHz, CCl_4) 5.50 (br t, J = 7.0 Hz, 1H), 4.53 (br d, J = 7.0 Hz, 2H), 3.90 (br s, 2H), 1.98 (s, 3H), 1.73 (s, 3H).

1-Bromo-2-methyl-2E-buten-4-ol (29): A suspension of **27** (17.0 g, 0.12 mol) and PPh_3 (31.4 g, 0.12 mol) in acetonitrile (70 ml) was added CBr_4 (40 g, 0.12 mol) in several portions and the resulting mixture was stirred for 15 min at 0°C. The mixture was concentrated *in vacuo* and the residue was roughly purified by column chromatography on silica gel (elution with hexane/ether 50/1). A mixture of the crude allyl bromide and potassium carbonate (5.0 g, 36 mmol) was stirred for 30 min at 0°C, poured into 3N HClaq and extracted with three portions of ethyl acetate. The combined extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give an oil, which was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 4/1) to give the bromide **29** (10.4 g) in 53% yield; IR (neat) 3400, 2900 cm^{-1}, **^{1}H-NMR** 5.77 (br t, J = 6.4 Hz, 1H), 4.20 (br d, J = 6.4 Hz, 2H), 3.96 (br s, 2H), 1.80 (br s, 3H).

2-Tetrahydropyranyl ether of 1-bromo-2-methyl-2E-buten-4-ol (30): To a solution

of **29** (6.33 g, 38.4 mmol) in the presence of a catalytic amount of p-toluenesulfonic acid in CH_2Cl_2 (100 ml) was added 2-dihydropyrane (3.5 g, 41.6 mmol) in several portions and the mixture was stirred for 3 h at 0°C. After a catalytic amount of potassium carbonate was added to the solution, the resulting suspension was stirred for 30 min and filtered. The filtrate was concentrated *in vacuo* to give the crude product **30** (9.80 g, 105% yield), which was used for the next reaction without further purification.

2,6,11-Trimethyl-9-oxa-1-pyvaloyloxy-13-[2-tetrahydropyranyloxy]-2E,6E,11E-tridecatriene (31): A mixture of the crude **30** (9.80 g, 40.3 mmol), **26** (10 g, 39.3 mmol), KOH (2.2 g, 39.3 mmol), tetrabutylammonium iodide (7.0 g, 19.2 mmol) and water (3 ml) was stirred for 50 min and diluted with hexane/ether (1/1, 300 ml). The resulting suspension was filtered on celite and the filtrate was concentrated *in vacuo* to give crude **31**, which was used in the next reaction without further purification.

2,6,11-Trimethyl-9-oxa-1-acetoxy-13-hydroxy-2E,6E,11E-tridecatriene (32): To a solution of the crude **31** in dry ether (200 ml) was added lithium aluminum hydride ($LiAlH_4$) (1.5 g, 39.5 mmol) in several portions at 0°C and the resulting suspension was stirred for 30 min to remove the pivaloyl group . To the suspension was added 30% KOHaq dropwise very slowly to quench the excess $LiAlH_4$. After the evolution of hydrogen gas had ceased, the suspension was filtered on celite and the filtrate was concentrated in vacuo. To a solution of the residue in pyridine (40 ml) was added acetic anhydride (5.1 ml, 50 mmol) in several portions and the mixture was stirred for 1 h at 0°C. The resulting solution was poured into 3N HClaq and extracted with three portions of ether/hexane (1/1). The combined extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in dry MeOH and a catalytic amount of pyridinium p-toluenesulfonate (PPTS) was added, the solution was stirred for 3 h at 40°C. The reaction mixture was poured into sat. $NaHCO_3$aq and extracted with three portions of ether/ hexane (1/1). The extracts were washed with brine, dried over $MgSO_4$ and concentreted *in vacuo* to give crude **32**, which was purified by column chromatography on silica gel (elution with hexane/ether 5:1) to give the alcohol **32** (6.49 g) in 57% overall yield from **29**. IR (neat) 3400, 2900, 1740 cm^{-1} ^{1}**H-NMR** 5.64 (br t, J = 6.7 Hz, 1H), 5.44 (m, 1H), 5.36 (br t, J = based on **29**. IR (neat) 3400, 2900, 1740 cm^{-1} ^{1}**H-NMR** 5.64 (br t, J = 6.7 Hz, 1H), 5.44 (m, 1H), 5.36 (br t, J = 7.0 Hz, 1H), 4.44 (br s, 2H), 4.18 (br d, J = 6.7 Hz, 2H), 3.95 (br d, J = 7.0 Hz, 2H), 3.85 (br s, 2H), 2.07 (s, 3H), 1.68 (s, 9H).

2,6,11-Trimethyl-9-oxa-1-acetoxy-13-chloro-2E,6E,11E-tridecatriene (33): A mixture of **32** (2.77 g, 9.35 mmol) and PPh_3 (3.00 g 11.5 mmol) in dry carbon tetrachloride (100 ml) was refluxed with stirring for 12 h. The resulting suspension was diluted with hexane (400 ml) and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane/ether 5:1)to give **33** (2.90 g) in 98.5% yield. IR (neat) 2920, 1740, 785 cm^{-1} ^{1}**H-NMR** 5.70 (br t, J = 7.6 Hz, 1H), 5.44 (m, 1H), 5.36 (br t, J = 7.0 Hz, 1H), 4.44 (br s, 2H), 4.10 (br d, J = 7.6 Hz, 2H), 3.95 (br d, J = 7.0 Hz, 2H), 3.87 (br s, 2H), 2.05 (s, 3H), 1.74 (br s, 3H), 1.66 (br s, 6H).

2,6,11-Trimethyl-9-oxa-13-chloro-2E,6E,11E-tridecatrienal (34): A mixture of **33** (2.90 g, 9.21 mmol) and potassium carbonate (381 mg, 2.76 mmol) in dry methanol (30 ml) was stirred for 30 min at 0°C. The resulting mixture was poured into an ice-cold 3N HClaq and extracted with three portions of CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated *in vacuo*. A suspension of MnO_2 (7.5 g, 86.5 mmol) and the resultant alcohol in dry hexane (50 ml) was stirred for 20 h. The reaction mixture was filtered on florosil and the filtrate was concentrated *in vacuo* to give an oil, which was purified by chromatography on silica gel (elution with hexane/ether 5:1) to give the aldehyde **34** (2.0 g) in 69% yield; IR (neat) 2850, 1680, 1640 cm^{-1} ^{1}**H-NMR** 6.47 (br t, J = 6.8 Hz, 1H), 5.70 (br t, J = 7.5 Hz, 1H), 5.40 (br t, J = 6.4 Hz, 1H), 4.11 (br d, J = 7.5 Hz, 2H), 4.00 (br d, J = 6.4 Hz, 2H), 3.88 (br s, 2H), 2.54 (dt, J = 6.8, 6. 1 Hz, 1H), 2.23 (t, J = 6.1 Hz, 2H), 1.76 (br s, 6H), 1.70 (br s, 3H).

Transformation of the aldehyde 34 to the protected cyanohydrin 37: A mixture of **34** (1.01 g, 3.68 mmol) and trimethylsilyl cyanide (2 g, 20.2 mmol) in the presence a catalytic amount of KCN-dicyclohexyl-18-crown-6 complex was stirred for 30 min at room temperature. The mixture was diluted with THF/H_2O (4 ml/1 ml) and to

the reaction mixture was added a catalytic amount of benzyltrimethylammonium fluoride in one portion. The resulting mixture was stirred for 30 min, poured into brine and extracted with three portions of ether. The extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was diluted with benzene in the presence of a catalytic amount of p-toluenesufonic acid. To the reaction mixture was added ethyl vinyl ether (0.6 ml, 6 mmol) in several portions and the mixture was stirred for 20 min at 0°C. The resulting solution was poured into sat. $NaHCO_3$aq and extracted with three portions of ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (elution with ether/hexane 4:1) to give the protected cyanohydrin **37** (1.31 g) in 95% yield; **IR** (neat) 2970, 2900, 2350 cm^{-1} ^{1}**H-NMR** 5.69 (br t, J = 7.7 Hz, 1H), 5.62 (m, 1H), 5.40 (br t, J = 6.4 Hz, 1H), 4.93 & 4.77 (q, J = 5.6, 5.6 Hz, respectively, 1H), 4.81 & 4.70 (br s, 1H), 4.09 (br d, J = 7.7 Hz, 2H), 3.88 (br d, J = 6.4 Hz, 2H), 3.80-3.30 (m, 2H), 3.80 (br s, 2H), 1.71 (br s, 3H), 1.66 (br s, 3H), 1.33 & 1.30 (d, J = 5.6 & 5.6 Hz, respectively, 3H), 1.21 (t, J = 7.7 Hz, 3H).

Cyclization of 37: A solution of $NaN(SiMe_3)_2$ (3 ml of 1.1 N in benzene, 3.3 mmol) in THF (20 ml) was placed in a two-necked flask (50 ml) equiped with Hershberg dropping funnel and warmed to 65°C under nitrogen. A solution of **37** (243 mg, 0.65 mmol) in THF (10 ml) was introduced to the dropping funnel and added to the base dropwise over 2 h under nitrogen. The resulting brown solution was poured into NH_4Claq and extracted with three portions of ether. The extracts were wsahed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (elution with ether/hexane 10:1) to give the cyclized product **38** (169.8 mg) in 80% yield; **IR** (neat) 2975, 2900 cm^{-1} ^{1}**H-NMR** 5.70 (br t, J = 9.6 Hz, 1H), 5.40-4.90 (m, 1H), 5.20 (br t, J = 7.3 Hz, 1H), 4.88 & 4.81 (q, J = 5.2 & 5.2 Hz, respectively, 1H), 4.16 & 4.08 (br s, 2H), 3.90 (br d, J = 9.6 Hz, 2H), 3.90-3.20 (m, 2H), 2.64 (br d, J = 7.3 Hz, 2H), 1.62 (br s, 6H), 1.56 (br s, 3H), 1.50-1.04 (m, 6H).

6-Oxa-4,9,13-trimethyl-3E,8E,12E-tridecatrien-1-one (40): A mixture of **38** (114.2 mg, 0.34 mmol) and a catalytic amount of PPTS in dry methanol (7 ml) was stirred for 2 h at 40°C. The resulting solution was poured into $NaHCO_3$aq and extracted with three protions of ether. The extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was diluted with ether (15 ml) and a mixture was placed in a separatory funnel (50 ml) and shaken vigorously for 5 min with 1% NaOHaq (15 ml). The aqueous layer was extracted with two portions of ether and the combined organic layers were washed with 3N HClaq, sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (elution with ether/hexane 1:10)to give the 13-membered ether **40** (79 mg) 99% yield; **IR** (neat) 2910, 2850, 1675, 1660 cm^{-1} ^{1}**H-NMR** 6.37 (br t, J = 6.3 Hz, 1H), 5.28 (br t, J = 6.4 Hz, 1H), 5.28 (br t, J = 6.8 Hz, 1H), 4.08 (br d, J = 6.4 Hz, 2H), 3.93 (br s, J = 2H), 3.29 (br d, J = 6.8 Hz, 2H), 2.46 (dt, J = 6.3, 6.0 Hz, 2H), 2.23 (t, J = 6.0 Hz, 2H), 1.74 (d, J = 1.1 Hz, 3H), 1.73 (d, J = 1.1 Hz, 3H), 1.54 (br s, 3H) ^{13}**C-NMR** 201.3, 146.0, 135.8, 135.3, 126.1, 121.3, 78.7, 69.0, 40.3, 38.0, 25.8, 15.0, 14.2, 11.1: **EI-MS** 234[M^+], 166, 121: **HRMS** calc. for $C_{15}H_{22}O_2$ m/e=234.1620, found m/e=234.1628

1-tert-Butyldimethylsiloxy-6-oxa-4,9,13-trimethyl-3E,8E,12E-tridecatriene (41): To a solution of **40** (90 mg, 0.384 mmol) in dry THF (5 ml) was added diisobutylaluminum hydride (2 ml of 1.55 N in pentane, 3.1 mmol) dropwise over 5 min at -78°C, then the mixture was stirred for 5 min and 1 N HClaq was added slowly to quench the excess reducing reagent. The resulting suspension was poured into 1N HClaq and extracted with three portions of ether. The extracts were washed with $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue and imidazole (110 mg, 1.62 mmol) were dissolved in dimethylformamide (5 ml) and to this solution was added t-butyldimethylsilyl chloride (200 mg, 1.32 mmol) in some portions at 0°C, then the mixture was stirred for 1.5 h at room temperature. The resulting solution was poured into 1N HClaq and extracted with three portions of ether. The extracts were washed with $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (elution with ether/hexane 1:10) to give **41** (113.8 mg) in 85% yield; **IR** (neat) 2900, 2850, 1250, 1060 cm^{-1} ^{1}**H-NMR** 5.42-4.86 (m, 3H), 4.12 (m, 1H), 4.08 (br d, J = 6.6 Hz, 2H), 3.88 (br s, 2H), 2.40-1.93 (m, 6H), 1.56 (br s, 9H), 0.88 (s, 9H), 0.03 (s, 3H), 0.00

(s, 3H) **^{13}C-NMR** 136.4, 136.2, 125.9, 123.6, 120.8, 78.6, 77.1, 69.3, 38.3, 33.6, 25.9, 24.4, 18.3, 15.8, 13.9, 10.5, -4.7, -4.9.

[2,3]-Wittig rearangement of 41: To a solution of **41** (62.4 mg, 0.178 mmol) in ether (5 ml) was added t-BuLi (1 ml of 1.9 N in pentane, 1.9 mmol) dropwise over 5 min and the solution was stirred for 24 h at -78°C and allowed to warm to 0°C. The resulting solution was poured into NH_4Claq and extracted with three portions of ether. The extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a mixture of 5-tert-butyldimethylsiloxy-1-hydroxy-3,6,10-trimethyl-10-vinyl-2E,6E-cyclodecadiene (**44**), 6S*,7R*,9S*-9-tert-butyldimethylsiloxy-6-hydroxy-7-(2-propenyl)-4E,10E-cyclodecadiene (**42**), and 6S*,7R*,9R*-9-tert-butyldimethylsiloxy-6-hydroxy-7-(2-propenyl)-4E,10E-cyclodecadiene (**43**). Each isomer was isolated by column chromatography on silica gel. **44** (elution with hexane/ether 32:1, 29.3 mg, 47% yield) **IR** (neat) 3400, 2900, 1440, 905 cm^{-1} **^{1}H-NMR** 6.45-5.88 (m, 1H), 5.51-4.86 (m, 4H), 4.64-3.98 (m, 1H), 3.71 (br s, 1H), 0.90 (br s, 9H), 0.06 (br s, 6H) **42** (elution with hexane/ether 10:1, 21.7 mg, 35% yield) **IR** (neat) 3450, 2950, 2875, 1640, 1440, 1385 cm^{-1} **^{1}H-NMR** 5.18 (br t, J = 7.6 Hz, 1H), 4.88 (m, 2H), 4.54 (br d, J = 9.0 Hz, 1H), 4.07 (dd, J = 9.0, 2.6 Hz, 1H), 4.05 (dd, J = 9.0, 9.0 Hz, 1H), 1.77 (br s, 3H), 1.65 (d, J = 1.3 Hz, 3H), 1.50 (br s, 3H), 0.86 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H) **43** (elution with hexane/ether 16:1, 5.1 mg, 8.2% yield); **IR** (neat) 3450, 2900, 2875, 1640, 1440, 1385 cm^{-1} **^{1}H-NMR** 5.19 (br t, J = 8.1 Hz, 1H), 4.88 (m, 2H), 4.60 (br d, J = 9.4 Hz, 1H), 4.16 (m, 1H), 4.05 (dd, J = 9.4, 9.4 Hz, 1H), 1.76 (br s, 3H), 1.67 (br s, 3H), 1.50 (br s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H)

6S*,7R*,9R*-6-Hydroxy-7-[2-(1-hydroxy-2-propenyl)]-9-tert-butyldimethylsiloxy-4E,10E-cyclodecadiene (46): To a mixture of **42** (40 mg, 0.114 mmol) and TMEDA (0.59 mg, 0.084 mmol) in THF (4 ml) was added sec-butyllithium (0.35 ml of 1.5 M in cyclohexane, 0.455 mmol) dropwise at -78°C under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature over 30 min and stirred for 1 h. After the solution was cooled to -78°C, the nitrogen atmosphere was replaced with oxygen gas. Then the solution was warmed to 0°C, poured into NH_4Claq and extracted with three portions of ethyl acetate. A aqueous solution of 25% sodium sulfite was added to the extracts and two phase layers were stirred vigorously for 24 h at room temperature. After the aqueous layer was extracted with three portions of ethyl acetate, the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with ether/hexane 1/1)to give**42** (12 mg, 30% recovered) and **46** (25 mg) in 60% yield ; IR (neat) 3400, 2950, 2900, 2850, 1640, 1460, 1380, 1250, 1040, 900, 835, 770 cm^{-1}; **^{1}H-NMR** 5.15 (br s, 1H), 5.00 (br s, 1H), 4.95 (m, 1H), 4.55 (d, J = 10.0 Hz, 1H), 4.19 (dd, J = 9.2, 9.2 Hz, 1H), 4.12 (br s, 1H), 4.03 (br d, J = 9.0 Hz, 1H), 1.65 (br s, 3H), 1.42 (br s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H).

Sequential process from the cyclic ether 41 to the diol 46: To a solutio of **41** (40 mg, 0.114 mmol) in ether (4 ml) was added sec-butyllithium (0.38 ml of 1.5 M in cyclohexane, 0.57 mmol) and the solution was stirred for 30 min at -70°C under nitrogen atmosphere. After the addition of TMEDA (0.59 mg, 0.089 mmol) to the solution, the mixture was allowed to warm to room temperature, stirred for 1 h and cooled to -70°C. The nitrogen gas in the flask was replaced with oxygen gas, then the solution was warmed to 0°C. The resulting solution was poured into NH_4Claq and extracted with three portions of ethyl acetate. After the same reductive work-up and chromatographic purification, the diol **46** (15.5 mg, 25% yield), the alcohol **43** (4.0 mg, 10% yield) and **44** (18.8 mg, 47% yield) were obtained.

(±)-Haageanolide (6) : A suspension of **46** (6.0 mg, 0.016 mmol) and MnO_2 (100 mg, 1.15 mmol) in ether (3 ml) was stirred for 72 h at room temperature. The reaction mixture was filtered on florosil and the filtrate was concentrated in vacuo to give the crude **47**, which was used in the next reaction without further reaction. To a solution of the silyl ether **47** in THF (1 ml) was added tetrabutylammonium fluoride (13.0 mg, 0.05 mmol) in one portion and the reaction mixture was stirred for 1 h at room temperature. The resulting solution was poured into brine and extracted with three portions of ether. The extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ether = 2/1) to give (±)-Haageanolide (2.8 mg, 70% yield): IR (KBr) 3400, 2900, 1760, 1665, 1245, 1145, 960, 860 cm^{-1}: **^{1}H-NMR** (pyridine-d_5) 6.34 (d, J = 3.5 Hz, 1H), 5.53 (d, J =

3.5 Hz, 1H), 4.70 (m, 2H), 4.41 (dd, J = 3.1, 10.8 Hz, 1H), 1.68 (br s, 3H), 1.40 (br s, 3H).

Acetylation of (±)-Haageanolide (6) To a solution of (±)-Haageanolide (6) (3.3 mg, 0.014 mmol) in pyridine (1 ml) was added acetic anhydride (3.0 mg, 0.03 mmol) at 0°C and the mixture was stirred for 1 h. The resulting mixture was poured into aqueous solution of copper sulfate and extracted with three portions of ether. The combined extracts were washed with sat. $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with hexane/ether 2/1) to give (±)-9-acetyl Haageanolide (2.8 mg, 69% yield) **mp.** 196-197°C (recrystalized from ethanol); **IR** (KBr) 2900, 1760, 1725, 1665, 1245, 1145, 960, 860 cm^{-1}; **^{1}H-NMR** (recorded with a JEOL GX-270 spectrometer at 270 MHz in pyridine-d_5) 6.37 (d, J = 3.4 Hz,), 5.60 (d, J = 3.4 Hz, 1H), 5.44 (dd, J = 2.7, 10.8 Hz, 1H), 5.20 (m, 1H), 4.72 (m, 2H), 2.82 (m, 1H), 2.06 (s, 3H), 1.63 (br s, 3H), 1.48 (br s, 3H); **EI-MS** 290[M^+], 248, 230, 215.

Ab-initio and MM2 calculation: The calculations for the transition structure (49) were performed with the GAUSSIAN 82 programs and STO-3G basis set. The calculations for the transition structure in the transannular [2,3]-Wittig rearrangement of 12 and 41 was performed by MM2 program. The positions of all the atoms involved in the reacting center were fixed at the ab-initio transition structure 49 except a methyl group attached on it. The remaining atoms were generated using MMRS program with 20° resolution angle and 2.0 Å ring closure distance. Eight initial structures which satisfied these criteria were submitted to the molecular mechanics calculations and four optomized structures were obtained. The four carbon atoms of reacting center were assigned as sp^3 during the MM2 calculations. Lithium atom was eliminated from MM2 optimization cycles.

Acknowledgement

We are grateful to Professor T. Nakai (Tokyo Institute of Technology) and Professor S. Ito (Tohoku University) for helpful discussions on the transition state of [2,3]-Wittig rearrangements. We also thank Dr. Kanda (Hirosima University) for helpful discussion on ab-initio calculations and thank I. Miura (Otsuka Pharmaceutical Co.) and T. Nakata (The Institute of Physical and Chemical Research) for their help in the interprepation of the NMR spectra. The calculations were carried out at the Computer Center of the Institute for Molecular Science.

REFERENCES AND NOTES

1. (a) N. H. Fischer, E. J. Oliver, and H. D. Fischer, Fortschr. Chem. Org. Naturst., 1979, 38, 47.
   (b) J. M. Cassady and S. Matthew, Anticancer Agents Based on Natural Product Models, Academic Press. 1980, 201.
   (c) H. M. R. Hoffmann and R. Jurgen, Angew. Chem. Int. Engl. Ed., 1985, 24, 94.
2. For earlier works on medium- and large-membered ring formation by intramolecular alkylation from this laboratory, cf. (a) T. Takahashi, S. hashiguchi, K. Kasuga, J. Tsuji, J. Am. Chem. Soc. 1978, 100, 7428; (b) T. Takahashi, K. Kasuga, M. Takahashi, J. Tsuji, Ibid. 1979, 101, 5072; (c) T. Takahashi, K. Kasuga, J. Tsuji, Tetrahedron Lett., 1978, 4917 (d) T. Takahashi, T. Nagashima, J. Tsuji, Ibid., 1981, 22, 1359; (e) T. Takahashi, H. Ikeda, J. Tsuji, Ibid., 1981, 22, 1363; (f) T. Takahashi, I. Minami, J. Tsuji, Ibid., 1981, 22, 2651.
3. (a) M. Kodama, Y. Matsuki, and S. Ito, Tetrahedron Lett., 1975, 3065; (b) M. Kodama, Y. Matsuki, and S. Ito, ibid., 1981, 22, 4275; (c) W. G. Dauben, R. K. Saugier, and I. Fleishhauer, J. Org. Chem., 1985, 50, 3767; (d) J. A. Marshall and D. G. Cleary, J. Org. Chem., 1986, 51, 858.

4. (a) W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, and C. Suter, J. Am. Chem. Soc., 1974, 96, 4723; (b) L. Crombie, G. Kneen, and G. Pattenden, J. Chem. Soc. Chem. Commun., 1976, 66.
5. (a) Y. Kitagawa, A. Itoh, S. Hashimoto, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., 1977, 99, 3864; (b) B. M. Trost, R. W. Warner, Ibid., 1983, 105, 5940. (c) N. Miyaura, H. Suginome, A. Suzuki, Tetrahedron Lett., 1984, 25, 761.
6. (a) W. C. Still and D. Mobilio, J. Org. Chem., 1983, 48, 4785; (b) H. Shibuya, K. Ohashi, K. Kawashima, K. Hori, N. Murakami, and I. Kitagawa, Chem. Lett., 1986, 85.
7. (a) J. E. McMurry, J. R. Matz, Ibid, 1982, 24, 2723. (b) J. E. McMurry, D. D. Miller, Tetrahedron Lett., 1983, 24, 1885.
8. (a) T. Kato, T. Kobayashi, and Y. Kitahara, Tetrahedron Lett., 1975, 3299; (b) M. Aoki, Y. Tooyama, T. Uyehara, and T. Kato, Tetrahedron Lett., 1983, 24, 2267.
9. M. A. Tius and A. H. Fauq, J. Am. Chem. Soc., 1986, 108, 1035.
10. (a) J. A. Marshall, W. F. Huffman, and J. A. Ruth, ibid., 1972, 94, 4691; (b) M. Miyashita and A. Yoshikoshi, ibid., 1974, 96, 1917.
11. (a) P. A. Wender and J. C. Lechleiter, ibid., 1980, 102, 6340; (b) J. R. Williams and J. F. Callahan, J. Org. Chem., 1980, 45, 4475, 4479.
12. (a) K. Takeda and I. Horibe, J. Chem. Soc. Perkin Trans. I, 1975, 870; (b) T. C. Jain, C. M. Banks, and J. E. McCloskey, Tetrahedron Lett., 1970, 841; (c) P. A. Grieco and M. Nishizawa, J. Org. Chem., 1977, 42, 1717.
13. (a) W. C. Still, J. Am. Chem. Soc., 1979, 101, 2493; (b) P. A. Wender and D. A. Holt, ibid., 1985, 107, 7771.
14. (a) F. E. Ziegler and J. J. Piwinski, ibid., 1980, 102, 880; (b) S. Raucher, J. E. Burks Jr, K. Hwang, and D. P. Svedberg, ibid., 1981, 103, 1853; (c) S. Raucher, K. W. Chi, K. J. Hwang, J. E. Burks, J. Org. Chem., 1986, 51, 5505.
15. T. Takahashi, H. Nemoto, and J. Tsuji, Tetrahedron Lett., 1983, 24, 2005.
16. The 3-, 4- and 5-membered ring formations by intramolecular alkylation of cyanohydrin ether: G. Stork, J. C. Depezay, and J. d'Angelo, Tetrahedron Lett., 1975, 389; G. Stork and T. Takahashi, J. Am. Chem. Soc., 1977, 99, 1275.
17. T. Takahashi, Y. Kanda, H. Nemoto, K. Kitamura, J. Tsuji, and Y. Fukazawa, J. Org. Chem., 1986, 51, 3393.
18. T. Takahashi, H. Nemoto and J. Tsuji, Tetrahedron Lett., 1983, 24, 3485.
19. T. Takahashi, K. Kitamura, H. Nemoto and J. Tsuji, Ibid., 1983, 24, 3489.
20. T. Takahashi, K. Kitamura and J. Tsuji, Ibid., 1983, 24, 4695.
21. Recently Y. Ohtsuka and T. Oishi reported syntheses of medium-ring ketones by a base-induced intramolecular acyl transfer reaction of 12- and 13- membered lactam sulfoxides; (a) Y. Ohtsuka, S. Niitsuma, H. Tadokoro, T. Hayashi, and T. Oishi, J. Org. Chem., 1984, 49, 2326; (b) Y. Ohtsuka, T. Oishi, Tetrahedron Lett., 1986, 27, 203.
22. A related route involving [2,3]-Wittig rearrangement of 13- and 17-membered diallylic ethers has recently been reported. (a) J. A. Marshall, T. M. Johnson, B. S. DeHoff, J. Org. Chem., 1986, 51, 4316; (b) J. A. Marshall, J. Lebreton, B. S. Drhoff, T. M. Jenson, Tetrahedron Lett., 1987, 28, 723.
23. (a) T. Takahashi, H. Nemoto, Y. Kanda, J. Tsuji, Y. Fujise, J. Org. Chem., 1986, 51, 4315; (b) T. Takahashi, H. Nemoto, Y. Kanda and J. Tsuji, Heterocycles, 1987, 25, 139.
24. (a) W. C. Still, I. Galynker, Tetrahedron, 1981, 37, 3981; (b) W. C. Still, L. J. Macpherson, T. Harada, J. F. Callahan, A.L. Rheingold, ibid., 1984, 40, 2275.

25. M. Umbreit and K. B. Sharpless, J. Am. Chem. Soc., 1977, 99, 5526.
26. Recently I. Kitagawa and H. Shibuya have synthesized the same compound by macrocyclization of the aldehyde allylic bromide promoted by Cr(II) and completed the synthesis of costunolide (14 steps from farnesyl acetate). We are indebted to Professor Kitagawa for providing NMR spectra of this compound and natural costunolide. (See ref. 6b.)
27. F. Bohlmann, C. Zdero, H. Robinson, and R. M. King, Phytochemistry, 1979, 18, 1993.
28. E. Nobuyasu, H. Shirahama, A. Furusaki, K. Suehiro, E. Osawa, R. Ishida, and T. Matsumoto, Chem. Lett., 1984, 459.
29. M. Kodama, S. Yokoo, Y. Matsuki, S. Ito, Tetrahedron Lett., 1979, 1687.
30. Allylic lithiations of the isopropenyl group have been reported; (a) R. J. Crawford, W. F. Erman, and C. D. Broaduss, J. Am. Chem. Soc., 1972, 94, 4298; (b) H. Suemune, G. Iwasaki, K. Ueno, K. Sakai, Chem. Pharm. Bull., 1984, 32, 4632, but directing effects of neighboring hydroxy group on the regioselective allylic lithiation have not been reported.
31. D. A. Evans, J. M. Hoffman, and L. K. Truesdale, J. Am. Chem. Soc., 1973, 95, 5822.
32. W. Kisiel, Phytochemistry, 1978, 17, 1059.
33. (a) B. M. Trost and L. S. Melvin, Jr, "Sulfer Ylides", chapter 7. Academic Press, New York (1975); (b) V. Rautenstrauch, J. C. S., Chem. Commun., 1970, 4. (c) T. Nakai, and K. Mikami, Chem. Rev., 1986, 86, 885.
34. MM2 transition model having oxolane structure has been proposed. We are grateful to Professor T. Nakai and Dr. K. Mikami for giving us a manuscript prior to publication in "Proceeding of the IUPAC Conference on Physical Organic Chemistry" M. Kobayashi ed., Elsevier.
35. (a) J. E. Baldwin, and J. E. Patrick, J. Am. Chem. Soc., 1971, 93, 3556; (b) T. Nakai, K. Mikami and S. Taya, Ibid. 1981, 103, 6492; (c) K. Mikami, Y. Kimura, Y. Kishi, T. Nakai, J. Org. Chem., 1983, 48, 279; (d) D.J. Tsai, M. M. Midland, Ibid. 1984, 48, 1843; (e) J. A. Marshall and T. M. Johnson, Ibid., 1984, 49, 1707.
36. (a) K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, and R. J. Loncharich, Science, 1986, 231, 1108; (b) K. N. Houk, N. G. Rondan, Y. Wu, J. T. Metz, and M. N. Paddon-Row, Tetrahedron, 1984, 40, 2257.
37. Y. Fukazawa, T. Okajima and T. Takahashi to be published.
38. Calculation were performed with GAUSSIAN 82: J. S. Binkley, M. J. Frisch, D. J. Defrees, K. Raghavachari, R. A. Whiteside, H. B. Schlegel, E. M. Fluder, R. Seeger, J. A. Pople, GAUSSIAN 82; Carnegie-Mellon University, Pittsubergh, PA.
39. This result does not prove whether the stepwise mechanisum is, in reality, energetically favored over the concerted mechanisum.
40. Our new version; Y. Fukazawa, S. Usui, Y Shiobara and M. Kodama, Tetrahedron Lett., 1986, 27, 1825, corresponding to the Still's RING MAKER program; W. C. Still in "Current Trends in Organic Synthesis" pp 223-246, H. Nozaki Ed., Pergamon Press (1983) (See ref. 24a).
41. N. L. Allinger, J. Am. Chem. Soc., 1977, 99, 8127.