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크로토니테논에 대한 합성방법*1

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A Synthetic Approach towards Crotonitenone*1

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要 約

천연물 중 casbene-type diterpenoid의 하나인 crotonitenone의 합성이 시도되었다. 합성 방법으로는 crotonitenone의 각 부분을 먼저 합성하여 이들을 합하는 방법(convergent method)을 적용하였으며, 각 부분이 최종 물질에 적합한 sterochemistry를 갖게 하기 위하여 시작물질로는 chiron으로 S-(-)-citronellol과 1S-chrysanthemic acid를 사용하였다. 환구조를 형성하는데 중요한 역할을 할 TBDMS protecting group이 붙은 phosphonium salt(synthon A)가 고압반응으로부터 고수율(70%)로 생성되었다. 또한, 중요한 반응으로서 synthon A와 hydroxy lactone(synthon B)과의 Witting reaction이 성공적으로 이루어졌다. 그러나, TBDMS protecting group의 존재하에 이중 치환된 이중결합(disubstituted double bond)과 삼중치환된 것과의 선택적인 환원의 어려움으로 인하여 최종 물질의 합성방법이 재고되었으며 이에 대해 간단히 논하였다.

Keywords: Casbene-type diterpenoid, crotonitenone, citronellol, chrysanthemic acid, wittig reaction

1. INTRODUCTION

Crotonitenone 1, a first novel oxygenated casbene-type diterpenoid, was isolated from the twigs and leaves of ***Croton nitens*** (***Euphorbiaceae***) (Barke ***et al***, 1981: Commissiong ***et al***, 1986). Its structure as well as its absolute stereochemistry was established by means of spectroscopic, chemical, and X-ray methods. More recently, agrostistachin 2 was isolated from a chloroform extract of the twigs of ***Agrostistachys hookeri*** (Choi ***et al***, 1986). It also displayed significant ***in vitro*** activity against the P-388 lymphocytic leukemia. Since the isolation of crotonitenone and agrostistachin, ethanol extraction of the stem of ***Croton nepetaefolius*** afforded large amounts of a casbane-type diterpenoid 3(Moura ***et al***, 1990). The cyclopropane moiety of 3 has an antipodal relationship to that of 1 and 2. It is noteworthy that these three compounds, crotonitenone 1, agrostistachin 2 and a similar compound 3 shown in Figure are the only identified oxygenated casbane derivatives so far.

Although compounds of the macrocyclic diter-

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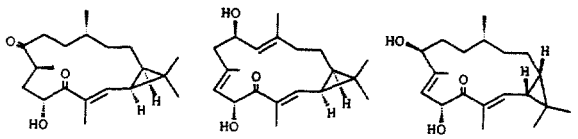


Fig. 1. Crotonitenone 1, agrostistachin 2 and unnamed compound 3.

penes were the first diterpenes to be isolated from the ***Ephorbiaceae*** (Dublyanskaya, 1937). little interest has been shown in them compared with other classes of compounds such as phorbols. Its co-occurrance, however, with the tri- and tetra-cyclic diterpenes in the ***Euphorbiaceae*** family suggests that they may arise from a common biosynthetic source and play important biogenetic roles in the plants. And also because of their novel structure and their relationship to casbene, which is the progenitor of a great many interesting diterpenes, casbene derived diterpenes represent an exciting new class of natural products.

Besides its novel characteristics as mentioned above, crotonitenone consists of an α'-hydroxy at C-5, α, β-unsaturated cis-cyclopropyl enone and the C-7 and C-11 chiral methyl substituted moiety. The compound, therefore, was chosen as a synthetic target molecule. In this report the synthesis of component fragments of crotonitenone is described and also their elaborations toward the final product are mentioned shortly.

2. MATERIALS & METHODS

2.1 General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Triethyamine (Et_3N), methylene chloride (CH_2Cl_2) and diisopropylamine (i-Pr_2NH) were distilled from calcium hydride (CaH_2) prior to use. Methanol (MeOH) was distilled from magnesium. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. (-)-(1S)-Chrysanthemic acid was obtained from Sumitomo Chemical Company. Lithium aluminum hydride (LAH) was purchased as a 95% pure powder from Alfa Chemical Company. Potassium t-butoxide (t-BuOK) was purchased as a 95% pure solid from Aldrich Chemical Company.

All reactions were conducted under a nitrogen atmosphere unless otherwise noted. A cold bath (-78 ℃) was prepared by suspending solid carbon dioxide with acetone in a Dewer flask. All liquids added to a nitrogen atmosphere were added via syringe through a rubber septum. Upon workup, solvents were evaporated by using a Büchi rotary evaporator, followed by high vacuum unless otherwise indicated.

Purifications were carried out under flash silica gel column chromatography (Silica Gel 60, particle size 0.040~0.063mm, 230~400mesh ASTM, VWR Scientific Co.) in various glass columns depending on the sample amount. Boiling points and melting points (Pyrex capillary) were uncorrected. Optical activity was measured only for the optically pure compounds using a Perkin-Elmer 241 polarimeter. IR spectra were recorded with a Perkin-Elmer Model 281 infrared recording spectrophotometer.

^1H NMR spectra were recorded at 400 MHz and 500 MHz and ^{13}C-NMR spectra at 100.60 MHz and 125.76 MHz on Bruker AM-400 and Bruker-500 spectrometers, respectively. Chemical shifts were expressed in ppm downfield from tetramethylsilane (TMS) using chloroform as an internal standard (7.25 ppm for ^1H and 77.0 ppm for ^{13}C). Significant ^1H NMR data were tabulated in the order of multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; m, multiplet, etc), number of protons, coupling constants in Hertz. All NMR spectra were recorded using $CDCl_3$ as the solvent. Spectral data and yields were reported for compounds which were chromatographically homogeneous.

Further purification was often applied to analytical samples. Mass spectral data were tabulated as *m/z* (intensity expressed as percent of total ion current). High resolution mass spectra (HRMS) were determined on a Kratos MS-50 high resolution mass spectrometer. Low resolution mass spectra (LRMS) were determined on an AEI-MS-12 mass spectrometer.

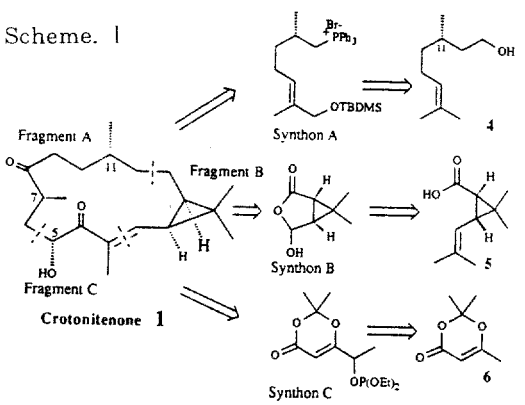
2.2 3S,3,7-Dimethyl-6-octenoic acid(7)

Into a solution of 62*ml* of 40% aqueous H_2SO_4 at 0℃ was added slowly CrO_3 (13g, 0.13mol) in a portion over 10min. A 1000*ml* three-neck round-bottomed flask equipped with a mechanical stirrer and an additional funnel was charged with the alcohol 4(10g, 0.064mol) and 250mL of acetone. The solution was mechanically stirred and the prepared CrO_3 solution was added slowly via an additional funnel over 20 min at 0℃ until the solution was persist the purple color for 30min. The liquid was transferred into a 1,000*ml* round-bottomed flask and dark precipitate was washed with 100*ml* of diethyl ether. The combined solutions were condensed using a rotary evaporator and redissolved in 150*ml* of diethyl ether. The solution was transferred into a separatory funnel and washed with 3×150*ml* of 1 N NaOH. The combined aqueous layers were acidified to pH 1 with concentrated H_2SO_4 at 0℃. The acidified solution was washed with 3×200*ml* of diethyl ether in a separatory funnel. The combined ether extracts were washed with saturated brine (3×100*ml*) and dried over anhydrous $MgSO_4$. The resulting solution was condensed using a rotary evaporator to afford 7.0g(64%) of the acid 7 as a clear oil.

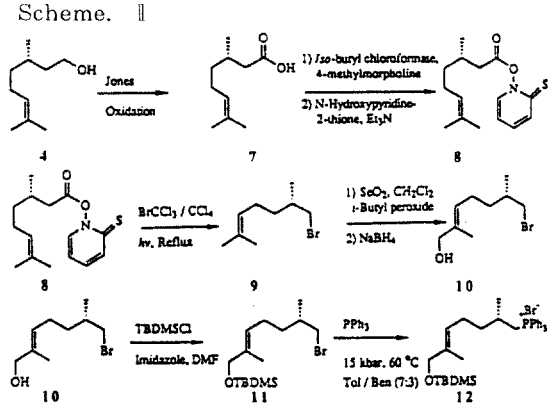
2.3. 2S-1-Bromo-2,6-dimethyl-5-heptene(9)

To a solution of the acid 7 (5.0g, 29.4mmol) in 200 mL of THF at -20℃ under nitrogen were added 3.3*ml* (30mmol) of 4-methylmorpholine and 3.89*ml*(30mmol) of isobutyl chloroformate. The reaction solution was stirred for 10min. The reaction flask was wrapped in aluminum foil and then 20*ml* of THF solution containing 5.55g (50mmol) of N-hydroxypyridine-2-thione and 7*ml* (50mmol) of Et_3N was added. The reaction mixture was allowed to warm to room temperature over 12h. The mixture was filtered under reduced pressure and the yellow precipitate was washed with diethyl ether until it became white. The ether was added to the filtrate, which was transferred to an aluminum wrapped round-bottomed flask and concentrated using a rotary evaporator. The resulting yellow oil was purified using flash chromatography on a foil wrapped glass column using CH_2Cl_2 eluent. The yellow band fraction was collected in a foil wrapped 1,000*ml* round-bottomed flask and condensed using a rotary evaporator and a high vacuum pump to give 8.12g of the thio pyridine

Scheme. I



Scheme. II

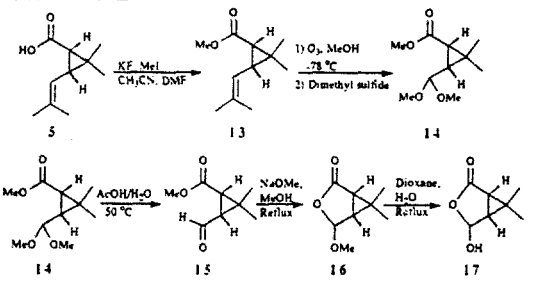


ester 8 as a viscous yellow oil. Without further characterization, the ester 8 was dissolved in 450*ml* of CCl_4 and 50*ml*(63mmol) of $BrCCl_3$. The reaction flask was equipped with a reflux condenser, purged with nitrogen and brought to reflux. When reflux was achieved, the solution was irradiated with an external 250watt tungsten lamp. Irradiation was continued for 30min until the solution stayed clear. The lamp was removed and the solution was allowed to cool to room temperature. The solution was condensed using a rotary evaporator and the residue was purified by flash column chromatography using pure hexane as eluent. The main fraction gave 3.5g(58%) of the bromide 9 as a clear oil.

2.4 2S-1-Bromo-2,6-dimethyl-7-hydroxy-5E-heptene(10)

To a solution of SeO_2 (0.55g, 5.0mmol) in 100 mL of CH_2Cl_2 was added 15.1*ml* of 70% aqueous *t*-BuOOH. The mixture was allowed to stir for 30min and a solution of the bromide 9(1.02g, 5.0mmol) in 5*ml* of CH_2Cl_2 was added. The solution was stirred for an additional 8h. 20*ml* of benzene was added and the mixture was condensed to 20*ml* using a rotary evaporator. To the concentrate 800*ml* of diethyl ether was added and the mixture was transferred to a separatory funnel. The organic layer was washed with 3×50*ml* of 10% KOH(w/w), 2×50*ml* of water and 50*ml* of saturated brine. The ether fraction was dried over anhydrous $MgSO_4$, filtered, and condensed using a rotary evaporator to give a crude oil. The oil was dissolved into 50*ml* of MeOH and 5g of $NaBH_4$ was slowly added in portions with care. After one hour, water was added to quench excess $NaBH_4$ and the mixture was condensed using a rotary evaporator to give an oil. The oil was redissolved in 50*ml* of diethyl ether and washed with 2×20*ml* of the saturated brine. The ether layer was dried over anhydrous $MgSO_4$ and condensed using a rotary evaporator. The crude oil was purified by flash column chromatography with 15% EtOAc in hexane as

Scheme. Ⅲ



eluent. The major fraction afforded 0.45g(47%) of the alcohol 10 as a viscous oil.

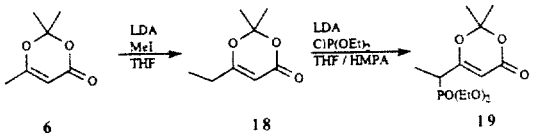
2.5. 2S-1-Bromo-7-(t-butyldimethyl)siloxy-2,6-dimethyl-5E-heptene(11)

To a solution of the allylic alcohol 10(1.9g, 8.6 mmol) and 1.17g(17.2mmol) of imidazole in 15 *ml* of DMF was added 1.42g(9.5mmol) of TBDMSCl in one portion. The mixture was stirred for 2 h at room temperature. The mixture was transferred in a separatory funnel and 30*ml* of water was added. The aqueous layer was extracted three times with 20*ml* of diethyl ether. The combined ether solutions were washed successively with 10*ml* of 1N HCl, 2× 10*ml* of $NaHCO_3$, and 20*ml* of saturated brine. The ether solution was dried over anhydrous $MgSO_4$ and condensed using a rotary evaporator to give colorless oil, which was purified by flash column chromatography with 5% EtOAc in hexane as eluent. Upon concentration of the major fraction, it afforded 2.0g(86%) of the protected bromide 11 as a colorless oil.

2.6 7-(t-Butyldimethyl)siloxy-2,6-dimethyl-5E-heptene-triphenylphosphonium bromide(12)

To a solution of the protected bromide 11(1.5 g, 4.6mmol) in 4*ml* of toluene/benzene (7:3, v/v) was added 12g 4.6mmol) of PPh3. The solution was transferred to a 12cm× 1cm Teflon tube (wall thickness=0.02 cm) clamped at both ends and pressurized to 15-Kbar(1.5GPa) hydrostatic pressure for 72 h at 60℃. The reaction was

Scheme. Ⅳ



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cooled to room temperature prior to release the pressure. The resulting viscous oil was transferred into a 500*ml* round-bottomed flask and condensed using a rotary evaporator and a high-vacuum pump (0.5torr). To the resulting oil 10 *ml* of dry hexanes was added to wash out the remaining starting materials. The hexane solution was removed via a syringe. The remaining hexanes in the flask were evaporated by means of a high vacuum pump. Another 10*ml* portion of dry hexanes was added again and processed the same manner. This step was repeated until the residue formed white foams. To the remaining foams was added 10*ml* of benzene and frozen at -78℃. By applying high vacuum at -78℃, benzene was evaporated away slowly warming to room temperature overnight to give 1.9g(70.4%) of the phosphonium salt 12 as a white hygroscopic sticky solid.

2.7 1S-cis/trans-Methylchrysanthemate (13)

To a solution of the chrysanthemic acid 5(80 g, 0.48mol, (-)-trans 68.9%, (-)-cis 16.2%, (+)-trans 11.8% (+)-cis 3.1%) in 600*ml* of acetonitrile and 200*ml* of DMF were added anhydrous potassium fluoride(55g, 0.96mol) and methyl iodide(55*ml*, 0.80mol). The mixture was stirred at room temperature for 24 h and was concentrated to become a thick white mixture using a rotary evaporator. The resulting mixture was transferred to a separatory funnel and 300*ml* of diethyl ether was added and the solution was washed with 400*ml* of saturated aqueous sodium bicarbonate solution. The aqueous layer was back-washed with 2×250*ml* of diethyl ether. The ethereal extracts were combined and washed again with 200*ml* of the saturated aqueous sodium bicarbonate solution then 2×300*ml* of the saturated brine. The ether fraction was dried over anhydrous magnesium sulfate and concentrated using a rotary evaporator to afford 80g of a clear oil which was distilled at 211~214 ℃ (atm pressure) to give 77 g(88%) of the ester 13 as a colorless oil.

2.8 (1S,3R)-cis-6,6-Dimethyl-4-hydroxy-3-oxabicyclo[3.1.0]hexan-2-one (Hydroxy lactone, 17)

In a 1000*ml* round-bottomed flask compound 13(75g) was dissolved into 600*ml* of MeOH and cooled to -78℃. Ozone was generated into the solution until the solution turned pale blue. This blue solution was spared with O_2 for 20 min to remove excess ozone in the reaction solution and 80*ml* of dimethyl sulfide was added. The resulting solution was stirred and allowed to come to room temperature over 12h. The solution was condensed using a rotary evaporator and 400*ml* of CH_2Cl_2 was added. The solution was then washed with 100*ml* of saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator to give a clear oil 14. To the oil 14, 400*ml* of distilled water was added and 160*ml* of glacial acetic acid. The mixture was stirred and warmed to 80℃ for 20min. then allowed to stand at room temperature. The mixture was transferred to a separatory funnel and extracted with 3×250*ml* of diethyl ether. The combined ether extracts were washed with 4×300*ml* of water, 3×300*ml* of the saturated aqueous $NaHCO_3$ and 2×300*ml* of brine. The resulting ether solution was dried over anhydrous $MgSO_4$ and condensed using a rotary evaporator to give 62g of 15 as a crude clear oil. Without further purification, the crude oil was used in the following isomerization and cyclization reaction.

To the NaOMe solution in MeOH was added 15 (62g, 370mmol) in one portion. The mixture was refluxed for 3h. After cooling down to room

temperature, the resulting light yellow solution was concentrated under reduced pressure. The concentrated oil was cooled in an ice-water bath and 165*ml* of 3 N-HCl solution was added slowly so as not to exceed the temperature of the solution above 10℃. The mixture was transferred to a separatory funnel and extracted with 2×200*ml* of diethyl ether. The combined ether layer was washed with 100*ml* each of water, saturated aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous $MgSO_4$ and condensed using a rotary evaporator to give 54g of a viscous yellow oil 16. To the viscous yellow oil(54g) were added 260*ml* of water and 130*ml* of dioxane and the mixture was allowed to reflux for 2h. The solvents were removed using a rotary evaporator and the thick oil was dissolved in 400*ml* of EtOAc. The solution was dried over anhydrous $MgSO_4$ then condensed using a rotary evaporator. The resulting material was crystallized from 30*ml* of CH_2Cl_2 to give 25g of the hydroxy lactone 17 as light yellow needles.

2.9 6-(1-(Diethylphosphino)ethyl)-2, 2-dimethyl-1,3-dioxen-4-one(19)

To a solution of LDA (9.5mmol) in THF (75 *ml*) at -78℃ under N_2 was added a solution of 18 (1.4g, 8.9mmol) in HMPA (1.75*ml*, 10 mmol). The solution was allowed to stand for fifteen mintes and diethyl chlorophosphite (1.45*ml*, 10mmol) was added via syringe. The solution was allowed to warm to room temperature over 12h and was cooled to 0℃ (ice bath). Saturated aqueous sodium bicarbonate solution (3*ml*) and 30% aqueous H_2O_2(3*ml*) were added and the solution was allowed to stand for twenty minutes. The mixture was concentrated using a rotary evaporator. The resulting bi-phasic mixture was transferred to a separatory funnel and partitioned between diethyl ether and water. The ether was washed with saturated brine and dried over anhydrous magnesium sulfate. The organic extracts were concentrated using a rotary evaporator to give 1.60g of a yellow oil, which was purified by flash chromatography (ethyl acetate) to afford 0.68g(26%) of 19 as a colorless oil.

Wittig reaction of 12 and 17 to give 20. To a stirred solution of phosphonium salt 12(1.5g, 2.5mmol) in 15*ml* of THF at 0℃ under nitrogen was added 7.1*ml*(2.5mmol) of LDA dropwise via a syringe and formed an ylide. The mixture was stirred at 0℃ for 30 min. To a solution of the hydroxy lactone 17(353mg, 2.5 mmol) in 3*ml* of THF at - 78℃ under nitrogen was added 7.1*ml* (2.5mmol) of LDA. The solution was stirred for 20 min and condensed using a high-vacuum pump to give white solids, which were redissolved in 5*ml* of THF and added into the ylide solution. The mixture was stirred for 1h at 0℃ and warmed to room temperature over 3 h. To the solution was added 15*ml* of water and condensed using a rotary evaporator. The resulting thick oil was taken into 20*ml* of EtOAc, transferred to a separatory funnel, and washed with 20*ml* of 1N HCl, 10*ml* of water, 20*ml* of saturated aqueous $NaHCO_3$ and 2×20*ml* of saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and condensed using a rotary evaporator. The resulting oil was subjected to flash column chromatography using 25% EtOAc in hexane as eluent. The main fraction was collected and concentrated to yield 320mg(40%) of the carboxylic acid 20 as a colorless oil: $[\alpha]_D^{25}$ - 54.5.25° (c 2.2, $CHCl_3$): IR (thin film) 3020, 2960, 2890, 1710, 1460, 1440, 1370, 1270, 1240, 1140, 1070, 850cm^{-1}; ^1H-NMR(500MHz, $CDCl_3$) δ 0.04(s, 6H), 0.88(s, 9H), 0.94(d, 3H, J= 6.65Hz), 1.18(s, 3H), 1.23 s, 3H), 1.32~1.37(m, 1H), 1.66(s, 3H), 1.91~2.0(m, 3H), 2. 45~2.49(m, 1H), 3. 98(s, 2H), 5.30(t, 1H, J = 10.35Hz), 5.37(br, t, 1H, J = 7.5Hz), and 5.58(t, 1H, J = 10.35Hz); ^{13}C NMR(125.76MHz, $CDCl_3$) δ 13.42, 14.71, 18.43, 21.12, 25.53, 25.63, 25.96, 27.67, 28.79, 31.28, 31.95, 32.38, 37.30, 68.69, 121.69, 124.75, 134.27, and 138.89.

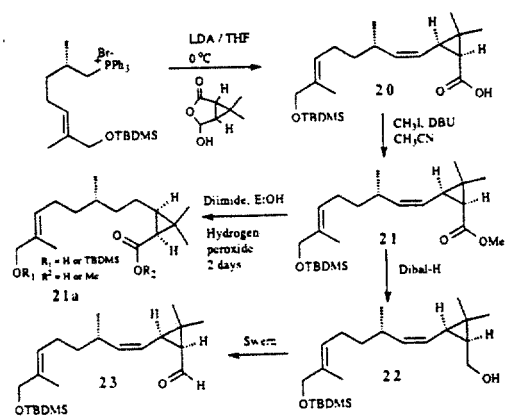
2.10 *cis*-2,2-Dimethyl-3-[1-(t-Butyldimethyl)siloxy-2,6-dimethyl-2E,7Z-octene]-1-cyclopropanecarboxylic Acid Methyl ester(21)

To the solution of the acid 20(200mg, 0.53mmol) in 15*ml* of CH_3CN at room temperature under nitrogen were successively added 0.1 *ml* (0.6mmol) of DBU and 0.05*ml* (0.8mmol) of CH_3I via a syringe. The mixture was stirred for 12h at room temperature and condensed using a rotary evaporator. Ten *ml* of EtOAc was added to the resulting oil and the solution transferred to a separatory funnel and washed successively with 7*ml* of water, 10*ml* of saturated aqueous $NaHCO_3$ and 20*ml* of saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and condensed using a rotary evaporator to afford 1.68g(80%) of methyl ester 21 as a clear oil.

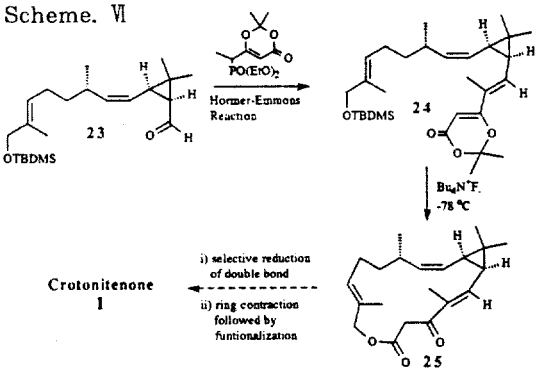
2.11 *cis*-2,2-Dimethyl-3-[1-(t-Buthyldimethyl)siloxy-2,6-dimethyl-2E,7Z-octene]-1-hydroxymethylcyclopropane (22)

To a stirred solution of methylester 21(1.5g, 1.3mmol) in 15*ml* of hexane at 0℃ under nitrogen was added 2.5*ml* (2.5mmol) of 1 M Dibal-H in hexane. After 10 min, 10*ml* of saturated aqueous ammonium chloride and 20*ml* of diethyl

Scheme. V



Scheme. VI



ether were added and the mixture was stirred for additional 30min. The white slurry solution was filtered through a glass-filter packed with celite and the glass-filter was thoroughly washed with 30*ml* of diethyl etsher. The ethereal extracts were transferred to a separatory funnel and washed with 10*ml* of 1N HCl, saturated aqueous $NaHCO_3$, and saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and condensed using a rotary evaporator to give 1.78g of clear oil, which was purified by flash column chromatography(25% ethyl acetate in hexane) to yield 1.0g(85%) of alcohol 22 as a clear oil.

3. RESULTS & DISCUSSION

3.1 Retrosynthetic Analysis of Crotonitenone and formation of Fragments A, B, and C

Because of its efficiency and flexibility, the convergent method has been chosen in this synthetic approach. Retrosynthetic analysis of the molecule revealed that three fragments were necessary for the target molecule and each fragment was envisaged as shown in Scheme I. Fragment A was envisioned to come from (-)-(S)-citronellol 4, since optically pure citronellol can provide desired chiral center at C-11 of crotonitenone. Elaboration of (-)-(S)-citronellol would lead to synthon A which can be functionalized for a Wittig couping with synthon B. Among many possible functional groups,

TBDMS group in the synthon A was recognized as an convenient group for the formation of ring closure. Synthon B has been regarded for the fragment B, which could be transformed from optically pure 1S-chrysanthemic acid 5. The final portion of the molecule requires the introduction of a tri-substituted trans double bond. For the part of this fragment was selected the phosphonate reagent synthon C, since it can be transformed from the compound 6.

3.2 Synthesis of the citronellol fragment

As a part of convergent approach to crotonitenoe, (S)-citronellol 4 was selected (Valentine *et al*, 1976; Corey *et al*, 1976) as a synthon for a piece A, shown in Scheme I. In order to use (S)-citronellol (10-carbons) as a piece in this synthetic route, one carbon atom at C-1 of (S)-citronellol should be replaced by other functional group. This critical step was achieved by the halogenative decarboxylation, which was previously examined(Barton *et al*, 1986) and established by Dauben *et al*(1989).

The first step in this route was the oxidation of the alcohol 4 to its acid 7 in 64% yield by means of Jones reagent(Bowers *et al*, 1953). The overall process is shown in Scheme II. In situ esterification with isobutyl chloroformate and transesterification with N-hydroxypyridine afforded the thiohydroxamic ester 8 in 67% yield. The halogenative decarboxylation of the thiohydroxamic ester 8 was carried out by irradiation with a tungsten lamp under reflux condition for 30 min to give the bromide 9 in 58% yield. The allylic oxidation of the bromoalkene 9 to give α,β - unsaturated carbonyl compound can be effectively achieved by using selenium dioxide(Jerussi, 1970; Umbreit & Sharpless, 1977). The high selectivity of E-allylic alcohol or aldehyde was established by the favoured transition state of selenium dioxide(Bhalerao & Rapoport, 1971; Woggon *et al*, 1980) to the less substituted side of the molecule. The crude oxidized product was followed by reduction with sodium borohydride to give completely the hydroxy compound 10 in 47% yield. Subsequent protection of the alcohol 10 with *t*-butyldimethylsilylchloride and imidazole in dimethyl formamide gave the protected bromide 11 in 86 % yield. The treatment of 11 with triphenylphosphine under 15 Kbar hydrostatic pressure at 60℃ gave the phosphonium salt 12, which is somewhat difficult to handle under normal condition because of its relatively high solubility in solvents. Fortunately, the compound 12 was obtained as a white foam in over 70 % yield. Because of its high hygroscopicity, it was freshly-made for the next Wittig reaction.

3.3 Synthesis of Synthons for Cyclopropane Moiety

The required hydroxy lactone 17, which is shown in Scheme III was prepared in five steps from readily available a mixture of *cis, trans*-(S)-chrysanthemic acid 5. The treatment of 5 with potassium fluoride and methyl iodide in acetonitrile gave its methyl ester 13, which was purified by distillation in 88% yield. The ozonolysis of 13 in methanol at -78℃, followed by the reduction of the ozonide with dimethyl sulfide yielded a mixture of the *cis*,- and *trans*-isomers of the dimethyl acetal 14. Without purification, these were hydrolyzed in aqueous acetic acid to give the aldehyde 15. Subsequent treatment of the aldehyde 15 in refluxing 1.25M sodium methoxide in methanol for 3h afforded the methoxy lactone 16. Hydrolysis of the crude lactone 16 was then achieved by refluxing in aqueous dioxane to yield the hydroxy lactone 17 which was then crystalized from methylene chloride(Martel, 1973; Montellano & Dinizo, 1978). The overall yield from 5 to 17 was 36.7%.

3.4 Synthesis of phosphonate for fragment C

It begins with 6, which is readily available from the reaction of diketene and acetone. γ-Methylation of this compound was achieved by

treatment with lithium diisopropyl amide (LDA) and methyl iodide in THF. Addition of hexamethyl phosporous triamide(HMPA) to this reaction resulted in α-methylation. Deprotonation of 18 with LDA in THF/HMPA, followed by the addition of diisopropyl phosphite gave the phosphinite. This phosphinite was oxidized during workup, with $H_2O_2/NaHCO_3$, to produce the phosphonate 19, which is shown in Scheme IV. The yield for the conversion of 6 to 19 was low(20%). Since 6 can be synthesized on large scale (100g) and only small quantities of 19 were needed(1~5g), no attempt has been made to increase the yield.

3.5 Convergence of Synthon A and B

Coupling of the piece A and B was a primary concern to be success for the convergent synthesis of crotonitenone. A Wittig reaction was selected as a first candidate (Scheme V). The standard Wittig reaction of 1 equiv. of 12 and 17 with 1 equiv. of base, however, yielded low production (20~25% based on the phosphonium salt 12) of the desired compound 20. Small amount of starting materials(15~20%) and polar viscous oil material (unidentified, 40~50 %) were recovered from flash column chromatography. Reactions at the various temperature and different reaction times as well as different amount of ratio were tested, but showed similar result. This result suggests that acidic protons of the hydroxy lactone, such as a proton of the hydroxy group and methine protons of the cyclopropane ring, participate to neutralize the phosphorous ylide, and the hydroxy lactone itself being decomposed. Under the various reaction condition, the compound 20 was being produced in 35~40% yield. And the acid 20 was used for further reactions.

3.6 Further Elaboration of the Intermediates and Synthetic plan to Crotonitenone

In this synthetic studies, the disubstituted double bond, which was generated from the Wittig reaction between 12 and 17, should be reduced to the corresponding saturated analogue, with the trisubstituted olefin group being intact. For the selective reduction of less-substituted double bond, diimide hydrazine was regarded as one of the well known selective reducing agents in these cases. Upon treatment of diimide, the compound 20 and the methyl ester 21, which was made from the free acid with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and methyl iodide in acetonitrile. After workup, these products were chromatographed and its fractions were analyzed by gas chromatography. By closely looking at each fraction with proton NMR spectroscopy, it turned out that five products were produced in this reaction. Those as well as the desired product 21a were recognized as deprotected products at R_1 and/or R_2 site, confirmed by the measurement of the NMR intensities for the corresponding peaks. This result suggested that some of TBDMS group and tri-substituted double bond can not survive in diimide solution for 2 days, which was also recognized in the previous results(Harris, 1991).

Since TBDMS group will provide a facile ring closure, this protecting group is necessary to keep itself on the protection site. Because of its deprotection under the reduction condition, however, some kind of different approach ought to be considered for the reduction of the double bond. Unfortunatly, the selective reduction of double bonds with TBDMS group has not been reported so far. As a result of this difficulty, decision has been made to change the reaction procedure, which are being under investigation, as shown in Scheme V and VI The methyl ester is reduced to alcohol 22 followed by Swern oxidation to give corresponding aldehyde 23. The next step will be a reaction for the coupling product 24 by Hormer-Emmons reaction with TBDMS protected aldehyde 23 and synthon C which is already available. At this stage or after the ring contraction selective disubstitut-

ed double bond will be reduced to generate desired ring framework to crotonitenone. Oxidations or fuctionalizations of the ring skeleton will give a natural product, crotonitenone, 1.

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18. Supplementary material available: ^{1}H and ^{13}C-NMR data for the compounds 7, 9, 10, 11, 12, 13, 17, 19, 20, 21, and 22. This material can be ordered from the author
19. Optically pure (-)-(S)-citronellol was graciously supplied by IFF: $[\alpha]_D^{22}$ -5.28° (neat) $[\alpha]_D^{22}$ -5.30° (neat)