STUDIES ON ENANTIOSELECTIVE SYNTHESIS OF BIOACTIVE TERPENOIDS

TSUTOMU INOKUCHI

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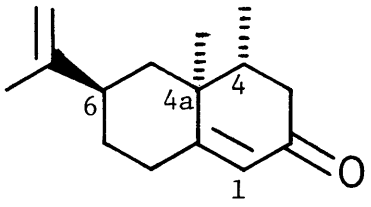
CONTENTS

CHAPTER 1

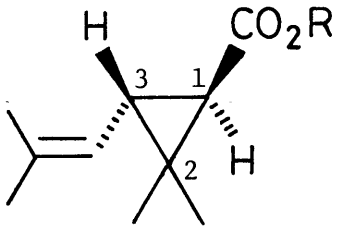
INTRODUCTION AND GENERAL SUMMARY

Today, much attention has been paid to the practical synthetic method which can provide only a desired enantiomer,[1] implicating practical utilization in the field of industrial organic chemistry, since the biological activity of one enantiomer often differs completely from that of its mirror image.[2] In general, the desired enantiomer can be supplied by one of either following four recipes: (1) optical resolution by using the so-called "mesotrick", [1c,3] (2) asymmetric synthesis under in-vitro conditions,[1c,4] (3) microbiological/enzymatic method,[5] (4) use of the "chiral pool" of optically pure natural products.[1,6] From the viewpoint of the overall efficiency and the optical purity of products together with the availability as natural resources, the methods based on the last concept are considered to be the most attractive strategy. A variety of examples which employ an appropriate chiral substances as a starting material have already been reported.[7] However, the author has been much interested in extending this general approach through a description of the syntheses of valuable terpenoids, i.e., nootkatone (1), methyl trans- and cis-chrysanthemates (2a, 3a), and rose oxide (4), starting with (-)-β-pinene, (+)- and (-)-carvones, and (+)-pulegone.

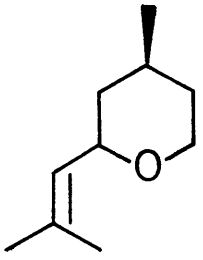
(+)-Nootkatone (1) is a typical eremophilanoid isolated originally from the heartwood of Alaska yellow cedar



1



2a, R = Me
b, R = H



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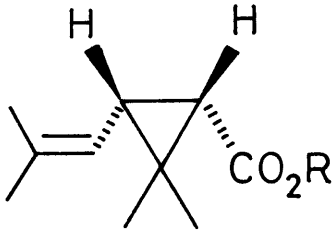


3a, R = Me
b, R = H

(Chamaecyparis nootkatensis).[8] Afterward, MacLeod found the same ketone in the peel oil of grapefruit (Citrus paradisi) as the constituent that most powerfully contributes to grapefruit flavor and determined the chemical structure of (+)-nootkatone as 1.[9,10] (+)-Nootkatone (1) has a fresh, green, sour, fruity character resembling that of grapefruit, with a threshold of 0.8 ppm.[11] However, its optical antipode, (-)-nootkatone, has no fruity character at all and its threshfold value is about 600 ppm. Thus, only the (+)-enantiomer of this ketone possesses the

intrinsic scent of grapefruit peel oil.[12] This fact has stimulated selective synthetic efforts toward (+)-enantiomer.[13,14]

Chrysanthemic acid, [2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropane-1-carboxylic acid], constitutes an acid component of pyrethroidal insecticides,[15] which are more active to the insects and less toxic to mammals. A priori, there exist four optical isomers originated from two asymmetric carbon atoms at the C(1) and C(3) positions. Relative insecticidal activities of the synthetic pyrethroids derived from these optical isomers are shown as 1R-trans>1R-cis>>1S-trans>1S-cis.[16] Thus, their physiological activity is closely associated with the (1R)-configuration, and practical routes to optically active 2 and 3 are being the subject of intensive investigations.[17]

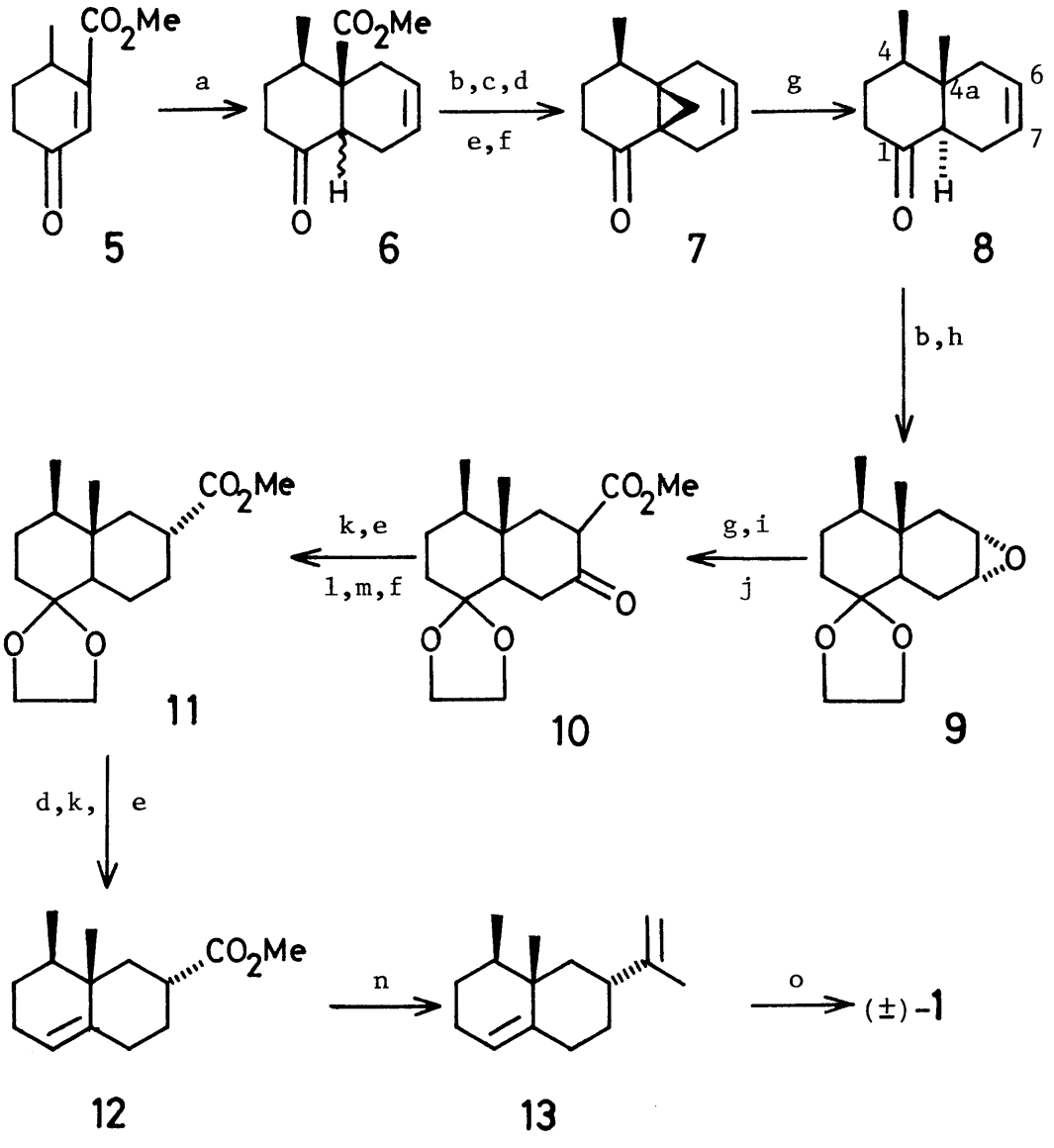
Incidentally, the electroorganic reaction has currently been recognized as a powerful tool in synthetic organic chemistry.[18] Owing to its both non-polluting and energy-saving nature, the electrochemical method has made significant contributions to the production of adiponitrile,[19a] tetraalkyl lead,[19b] and other fine chemicals.[20] Especially noteworthy is the utilization of electrolytic procedure to the preparation of chiral building blocks from the source of natural origin, and this approach, if successful, will be a powerful tool in the

chiral synthesis of biologically active compounds. The auhtor has been much interested in introducing such electrochemical method to the asymmetric synthesis of methyl chrysanthemates (2a, 3a) and rose oxide (4),[21] and has endeavored to develop novel, useful, and selective reaction for carbon-carbon bond cleavage reaction by means of the electrooxidation procedure.

This thesis discloses novel synthetic approaches to nootkatone (1) in the first two chapters, while the synthetic applications of the electrochemical oxidation to chiral methyl trans- and cis-chrysanthemates (2a, 3a) and (+)-rose oxide (4) constitute the successive two chapters.

The following Chapter 2 is concerned with synthetic efforts on (±)-nootkatone (1) and (±)-valencene (13).[22] The synthetic pathway is outlined in Scheme 1-I. The bicyclic carbon framework is constructed by the Diels-Alder reaction of methyl 6-methyl-3-oxo-1-cyclohexene-1-carboxylate (5) with butadiene. The adduct 6 is converted to 4β,4aβ-dimethyloctalone 8 via the reductive ring opening of the cyclopropyl ketone 7. Regioselective functionalization of the C(6)-C(7) double bond of 8 is achieved by the following series of reactions: (1) epoxidation, (2) reduction of the oxirane ring, (3) subsequent oxidation of the resulting hydroxyl group, and (4) methoxycarbonylation, giving methyl 7-oxodecalin-6-carboxylate 10. The ketone 10 is readily

Scheme 1-I

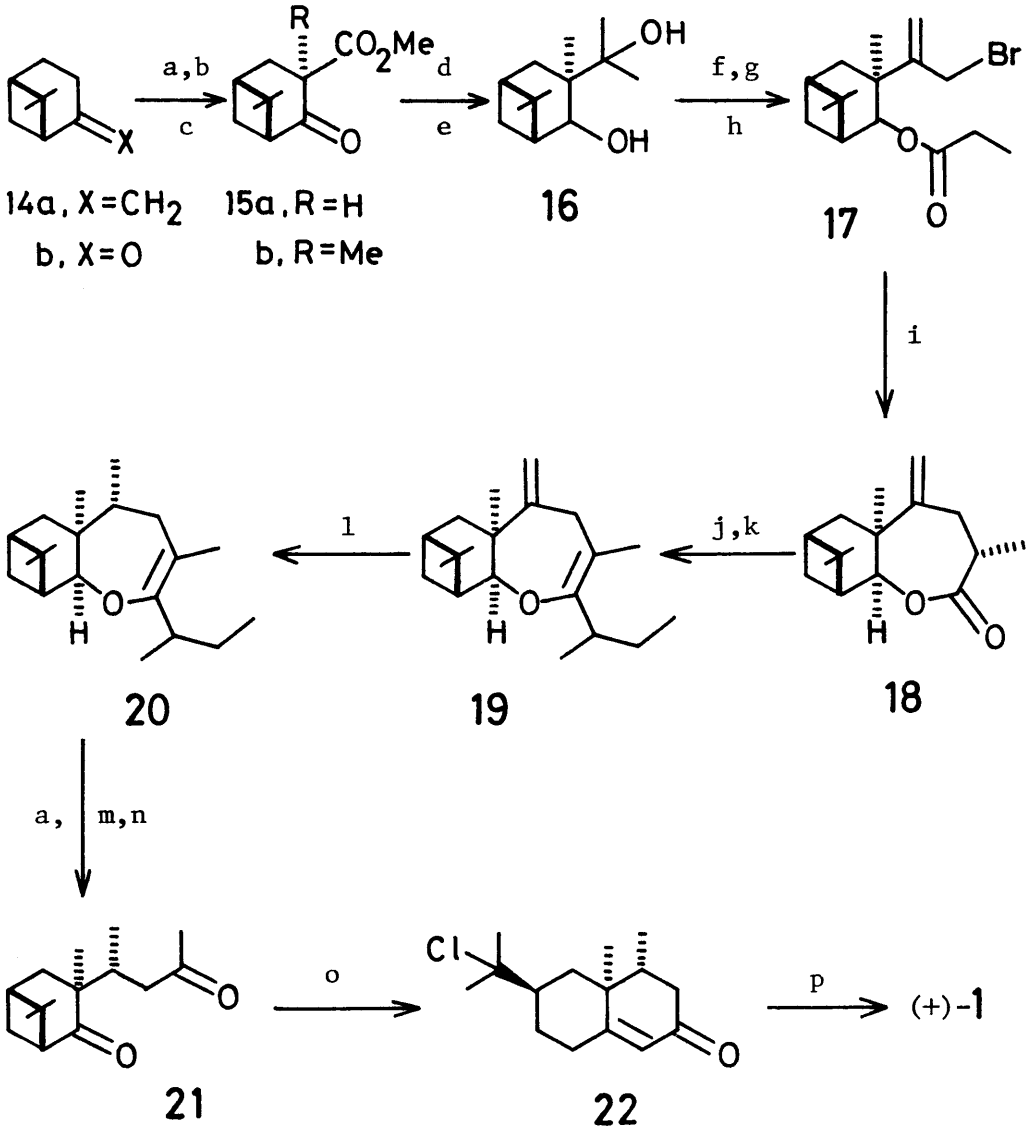


a) butadiene, 150-160°; b) $(CH_2OH)_2/H^+$; c) $LiAlH_4$; d) aq. $HClO_4$; e) MsCl-Py; f) MeONa; g) Li/liq. NH_3; h) m-CPBA; i) PCC; j) $CO(OMe)_2/NaH$; k) $NaBH_4$; l) DBU; m) H_2/PtO_2; n) $(Ph)_3P=CH_2$; o) $CrO_3.(Py)_2$

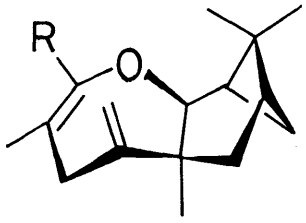
reduced to methyl decalin-6α-carboxylate 11, a precursor of 12. Finally, the ester group of 12 is transformed into the α-isopropenyl function of (±)-13 whose allylic oxidation yields the desired (±)-1.

In Chapter 3, the author describes a stereocontrolled synthesis of (+)-enantiomer of nootkatone 1, the natural form, starting from (-)-β-pinene (14a) (Scheme 1-II). The bridged dimethylmethylene portion of 14a is transformed into the 6α-isopropenyl moiety of the target 1. 6,6-Dimethylbicyclo[3.1.1]-heptan-2-one (nopinone, 14b) derived by oxidation of 14a is converted into 15b by methoxycarbonylation and subsequent methylation. This alkylation is found to proceed exclusively at the opposite site of the dimethylmethylene bridge of 15a. Elongation of the side chain of 15b through the Grignard reaction and the intramolecular alkylation leads to the lactone 18. Construction of vicinal, cis-dimethyl group of the nootkatone structure, which is the highlight of the present synthesis, is achieved cleanly by lithium metal reduction of the exo-methylene group of the enol ether 19 derived from 18. High stereoselectivity of the reduction may be attributed to the participation of a lithium bidentate chelate complex B.[23] Oxidative cleavage of 20 and subsequent oxidation gives the 1,5-

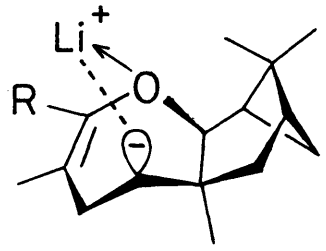
Scheme 1-II



a) O_3-Me_2S; b) $CO(OMe)_2$/NaH; c) MeI/K_2CO_3; d) $NaBH_4$; e) MeMgI; f) $(EtCO)_2O$/Py; g) $SOCl_2$; h) NBS; i) Lithium N-Cyclohexyl-isopropylamide; j) sec-BuLi; k) DHP/PPTS; l) Li/liq. $EtNH_2$; m) $LiAlH_4$; n) PCC; o) HCl/AcOH; p) Al_2O_3



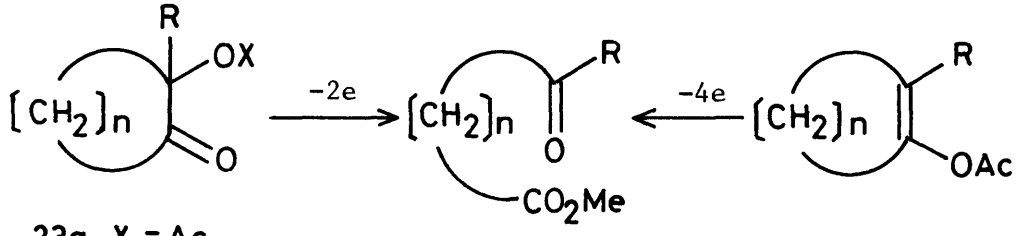
A



B

diketone 21 which is transformed into (+)-1 by cyclization with hydrogen chloride followed by dehydrochlorination of 22.

In Chapter 4, the author describes a novel electrochemical access to acyclic keto esters 24 from 2-oxycycloalkanones 23 or cycloalkanone enol acetates 25. Electrolysis of 23 in methanol



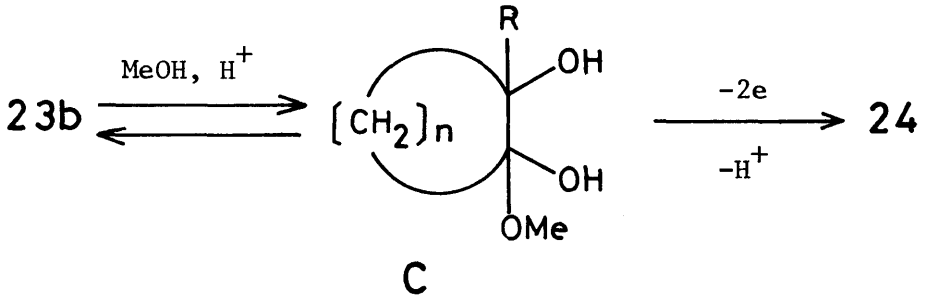
23a, X = Ac
b, X = H

24

25

using lithium perchlorate as a supporting electrolyte induces cleanly a cleavage of carbon-carbon bond to give 24. Similar electrolysis of 25 in MeOH-AcOH (10/1) provides 24 in satisfactory yields. A dramatic effect of supporting electrolyte is observed in this cleavage reaction: strong electrolytes such as $LiClO_4$, $LiBF_4$, and CF_3COOLi are effective for the present

purpose, whereas ammonium salts are less. These findings suggest that the reaction may proceed through the cleavage of 1,2-diol moiety of intermediary hemiacetal C which may be equilibrated to 23b under the electrolysis conditions.[24]

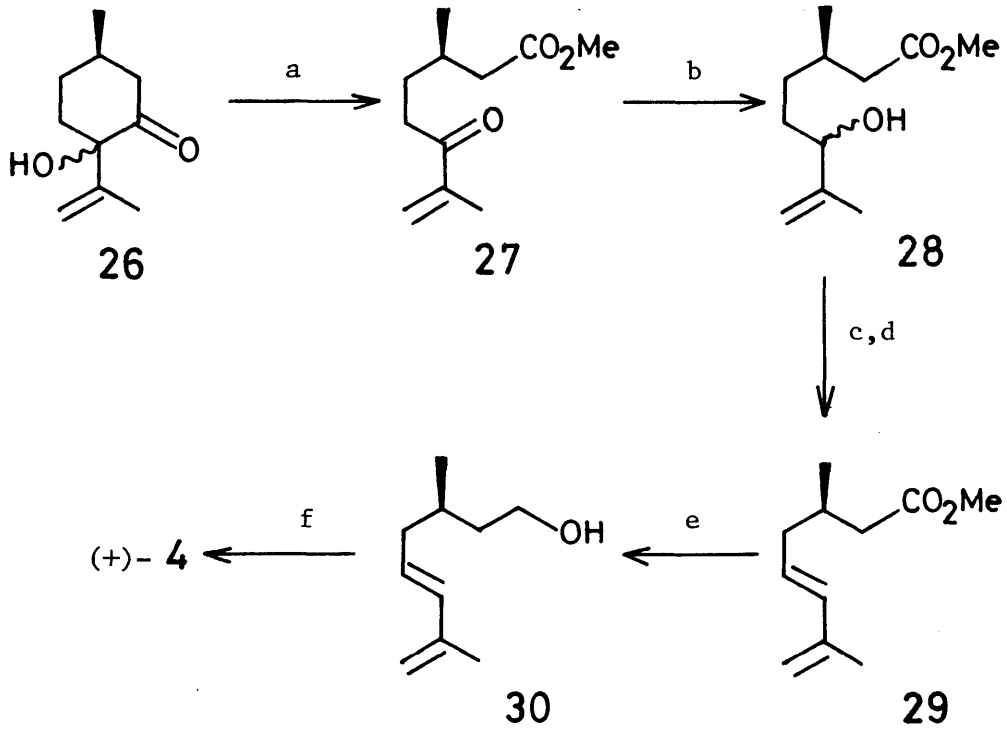


C

Synthetic utility of the electrochemical procedure has been further exemplified by the synthesis of (+)-rose oxide (4), an important ingredient of rose [25a] and geranium [25b] oil. The synthesis of 4 is summarized in Scheme 1-III. Electrolysis of 2-hydroxyketone 26 in methanol affords the key intermediate 27. Subsequent conversion of 27 into 4 via the diene 29 proceeds smoothly under mild reaction conditions.

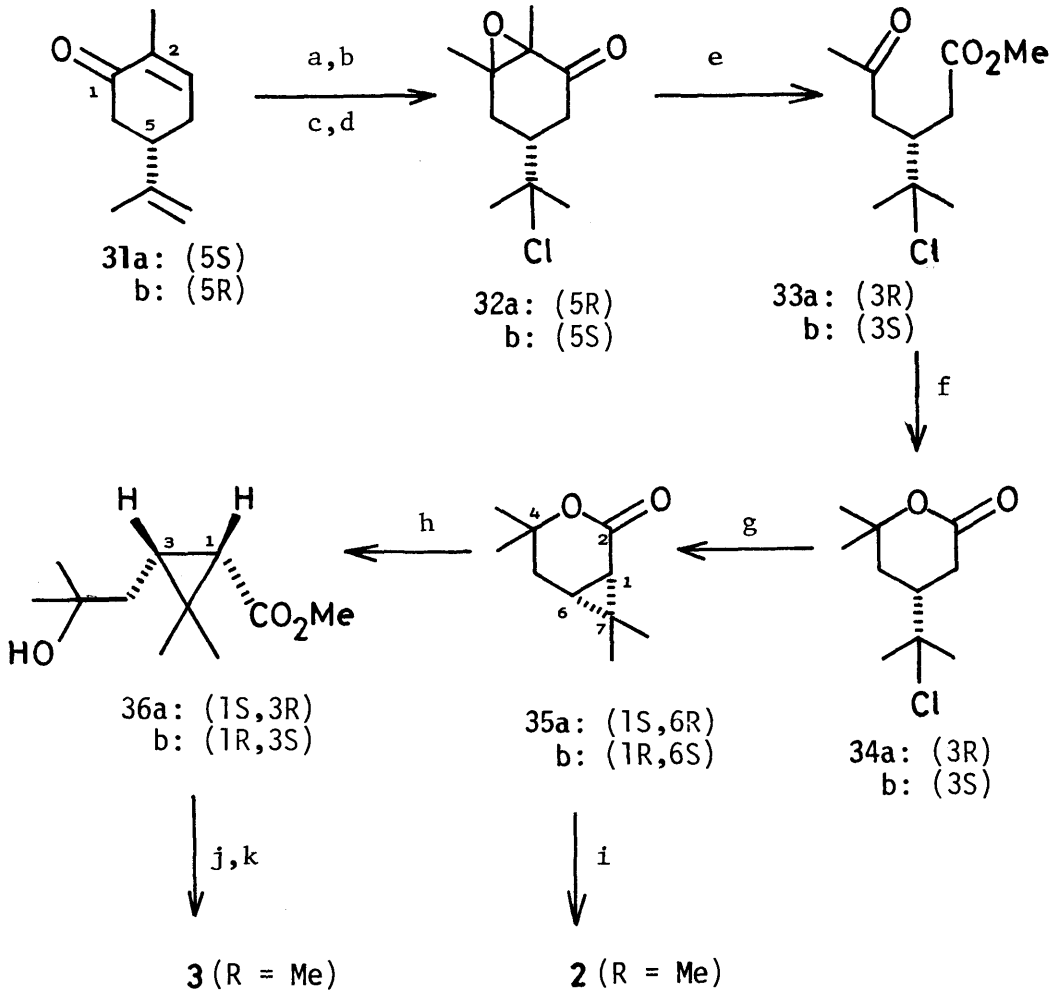
The electrolytic procedure to the concurrent cleavage at the C(1)-C(2) and C(2)-C(3) bonds of 2,3-epoxy ketone is described in Chapter 5, in which chiral methyl trans- and cis-chrysanthemates (2a, 3a) are synthesized from (+)- and (-)-carvones (31) as outlined in Scheme 1-IV. Electrooxidative cleavage of 32 is carried out in a MeOH-AcOEt (7/1)-0.047 M $LiClO_4$-(Pt) system to

Scheme 1-III



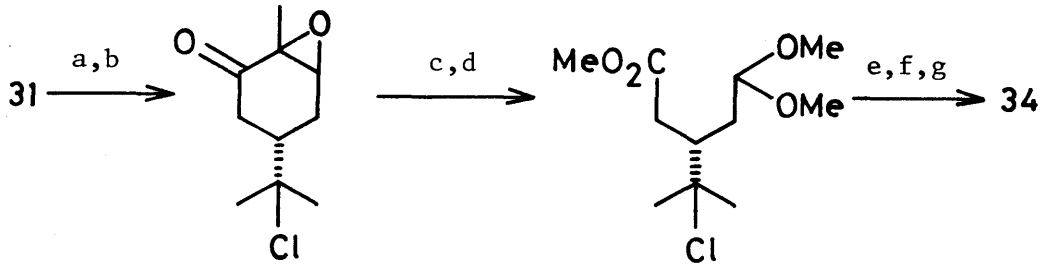
a) -2e, MeOH-$LiClO_4$-(Pt); (b) $NaBH_4$; (c) MsCl;
d) DBU; e) $LiAlH_4$; f) 30% H_2SO_4

Scheme 1-IV



a) MeLi; b) CrO_3/H_2SO_4; c) dry HCl; d) H_2O_2-NaOH; e) -4e, MeOH-AcOEt (7:1)-$LiClO_4$-(Pt); f) MeMgI; g) $LiN(\underline{i}\text{-}C_3H_7)_2$; h) aq. KOH; CH_2N_2; i) NaOH, 230-235°; CH_2N_2; j) $POCl_3$/Py; k) $RhCl_3.3H_2O$, isopropanol

give methyl (3R)- and (3S)-3-(1-chloro-1-methylethyl)-5-oxohexanoates (33). The keto ester 33 is converted into 4,4,7,7-tetramethyl-3-oxabicylo[4.1.0]heptan-2-one (dihydrochrysanthemolactone, 35) by methylation and subsequent cyclization of 34 with base. Treatment of 35 with sodium hydroxide at 230-235° followed by esterification with diazomethane brings about concomitant dehydration and epimerization at the C(1) position to give the desired trans-isomer 2a.[26] The cis-isomer 3a can be obtained from 35 by hydrolysis followed by dehydration. An alternative route to the δ-lactone 34 via the acetal ester 38, prepared by the electrochemical cleavage of 37, is also investigated as shown below:



37a: (5S)
b: (5R)

38a: (3S)
b: (3R)

a) dry HCl; b) H_2O_2-NaOH; c) MeOH-H_2SO_4 (or $HClO_4$); d) -4e, MeOH-$LiClO_4$-(Pt); e) MeLi; MeOH-p-TsOH; f) HCl-AcOH; g) CrO_3-H_2SO_4

In conclusion, the author summarized his contributions as follows: (1) The novel access to eremophilane skeleton is explored by means of the Diels-Alder reaction of methyl 6-methyl-3-oxo-2-cyclohexene-1-carboxylate with butadiene which proceeds through a transition state with the endo-selectivity. The diene adduct is smoothly transformed into (±)-nootkatone and (±)-valencene.

(2) The naturally occuring (+)-nootkatone is stereoselectively synthesized from (-)-β-pinene, in which the cyclohexane ring and the bridged dimethylmethylene group are utilized for preparing the bicyclic framework and 6α-isopropenyl appendage of the target molecule, respectively. Synthesis of vicinal, two methyl groups, characteristic structural feature of eremophilanes, is achieved with correct configuration by the following two operations: (a) introduction of methyl group from the opposite site of the bridged dimethylmethylene group and (b) stereocontrolled reduction of exo-methylene group assisted by the coordination effect of oxygen atom to the lithium metal.

(3) A new electrooxidative cleavage reaction of the C(1)-C(2) bond of 2-oxycycloalkanones and C-C double bond of cycloalkanone enol acetates has been explored. Utility of the reaction in producing oxoalkanoates is exemplified by a straightforward synthesis of (+)-rose oxide from pulegone oxide.

The role of strong electrolytes is studied in detail and a new concept on the cleavage mechanism is now available. The concurrent cleavave at the C(1)-C(2) and C(2)-C(3) bonds of 2,3-epoxycycloalkanones to give the corresponding oxoalkanoates is also investigated.

(4) A facile synthesis of chiral methyl chrysanthemates is described. The key step of the synthesis consists in the electrooxidative cleavage of 2,3-epoxy ketone. The method comprises a new route to (1S,6R)- and (1R,6S)-4,4,7,7-tetramethyl-3-oxabicyclo[4.1.0]heptan-2-ones, common intermediates for both trans- and cis-chrysanthemates, from (+)- and (-)-carvone, respectively.

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Instrumentation.

Infrared data were obtained using a JASCO IRA-1 grating spectrometer and calibrated against the 906, 1601, and 3027 cm^{-1} bands of polystyrene. Nuclear magnetic resonance spectra were determined with a Hitachi R-24 (60 MHz) or JEOL FX-100 (100 MHz for proton and 25.05 MHz for carbon-13), using tetramethylsilane as an internal standard, and the signals are expressed in parts per million downfield from the standard (δ = 0). Optical rotations were measured with a JASCO DIP-140 digital polarimeter in chloroform. Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus. Analytical and preparative gas-liquid phase chromatography was performed on a Yanaco Gas Chromatograph, Model GCG-550T or G-80, using thermal conductivity detectors and hydrogen carrier gas. High performance liquid chromatography was carried out by a Waters 6000A solvent deliverly system and a Waters differential refractometer, Model R-401 detector. Product percentages were caluculated from peak area ratio without correction. Medium-pressure liquid chromatography was performed with a Kyowa-seimitsu KHD-90 solvent pump, fittings, and tubings using Merck silica gel PF-254 as the stationary phase.

General Reaction Procedures.

All reactions, unless otherwise specified, were conducted under a nitrogen or argon atomosphere. Liquid reagents were

transferred *via* dry hypodermic syringe and added through a rubber septa wired onto the reaction flask from which a steady stream of inert gas was flowing. Organic extracts of the reaction mixture were dried over anhydrous sodium sulfate. The dried extracts were concentrated by evaporation with a rotary evaporator evacuated at 20-40 mm by a water aspirator. Column chromatography, unless otherwise noted, was carried out using a Wako C-200 (silica gel).

Analytical Procedure and Data Presentation.

Analytical thin layer chromatography was performed on Merck, pre-coated, silica gel 60 F-254 or glass plates covered with a Merck PF-254 of 0.2-0.3 mm thick. Melting points and boiling points are given without correction. IR data are reported in wavenumber (cm^{-1}) and major absorptions are compiled. Unless otherwise indicated, ^{1}H NMR spectra were recorded at 60 MHz in deuterochloroform and indicated in the form: δ-value of signal (peak multiplicity, coupling constant (if any), integrated number of protons, and structural assignment). Microanalyses were performed in this laboratory using a Yanaco Microdetermining Apparatus for Elements, Model MU-2.

Abbreviations.

The following abbreviations will be used in the Experimental Sections: brine = saturated aqueous sodium chloride, ether =

diethyl ether, HMPA = hexamethylphosphoric triamide, DBU = diazabicylo[5.4.0]undec-7-ene, sec-BuLi = sec-butyllithium, t-BuOH = tert-butyl alcohol, MCPBA = m-chloroperbenzoic acid, NBS = N-bromosuccinimide, LDA = lithium diisopropylamide, DME = 1,2-dimethoxyethane, DMF = N,N-dimethylformamide, DMSO = dimethylsulfoxide, MsCl = methanesulfonyl chloride, TsOH = p-toluenesulfonic acid, PPTS = pyridinium p-toluenesulfonate, PCC = pyridinium chlorochromate, THF = tetrahydrofuran, NMR = nuclear magnetic resonance (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, d,t = doublet of triplet, etc.), IR = infrared, mp = melting point, bp = boiling point, GLC = gas-liquid phase chromatography (R_t = retention time), HPLC = high performance liquid chromatography, tlc = thin layer chromatography (R_f = mobility relative to the solvent front), Calcd = elemental analysis.

CHAPTER 2

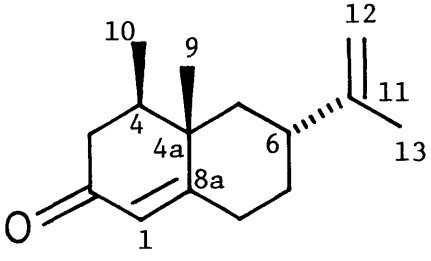
SYNTHESIS OF (±)-NOOTKATONE

ABSTRACT

Syntheses of (±)-nootkatone (1) and (±)-valencene (18b) are described. The bicyclic carbon framework is constructed by the Diels-Alder reaction of methyl 6-methyl-3-oxo-1-cyclohexene-1-carboxylate (2b) and butadiene. The adduct 3b is converted into 4β,4aβ-dimethyloctalone 8 via the reductive ring opening of the cyclopropyl ketone 7. Regioselective functionalization of the C(6)-C(7) double bond of 8 is achieved by the following four steps: (1) epoxidation, (2) reduction of the oxirane ring, (3) subsequent oxidation of the resulting hydroxyl group, and (4) methoxycarbonylation, giving methyl 7-oxodecalin-6-carboxylate 14a. The ketone 14a is reduced to methyl decalin-6α-carboxylate 16b, a precursor of 18a. Finally, the ester group of 18a is successfully transformed into the α-isopropenyl appendage of (±)-18b whose allylic oxidation yields the desired (±)-1.

INTRODUCTION

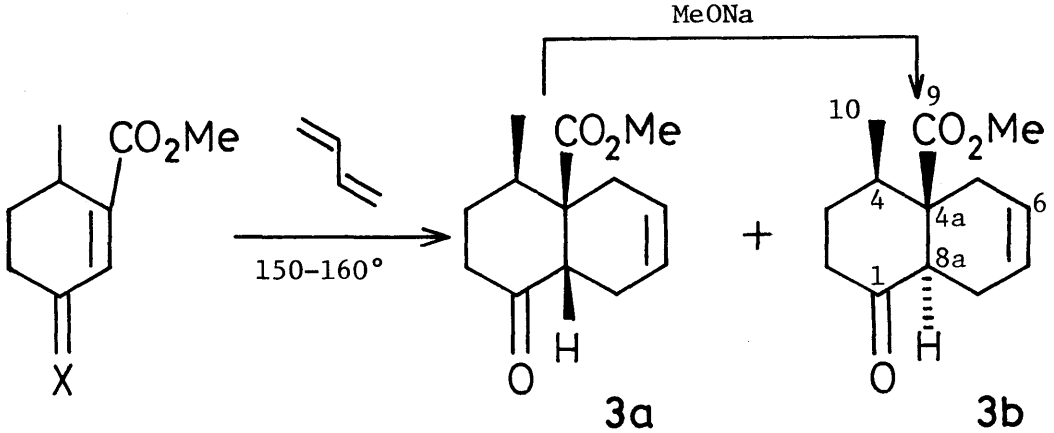
The major problem in the synthesis of nootkatone (1)[1] is need to obtain only the isomer with the right configuration about C(4)β,C(4a)β dimethyl groups. Previous synthetic methods utilizing the Robinson annulation technique[1f-h,j] are notorious for being unselective in this respect, although some measure of a control can be exercised by a cyclopentenone annulation procedure[11] for producing the rearranged moiety of the eremophilane structure. We have now disclosed a new stereoselective synthesis of 1 on the basis of the endo-rule selectivity of the Diels-Alder reaction[2] of **2b** with butadiene.



1

2.1. SYNTHESIS OF (±)-NOOTKATONE AND (±)-VALENCENE

The Diels-Alder reaction of 2b, derived from 2a,[3] with butadiene took place at 150-160° in a sealed tube to give a mixture of 3a (11%) and 3b (45%), the structures of which had been proved as follows. Treatment of 3a with sodium methoxide gave 3b in a quantitative yield. Furthermore, the cis configuration of the C(4) methyl and C(4a) methoxycarbonyl groups was based on the NMR data: thus, the assignment of the



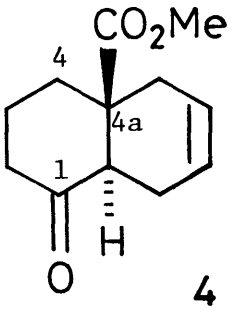


Table 2-1. The ^{13}C NMR chemical shifts [a] of substituted decalin and octalin derivatives

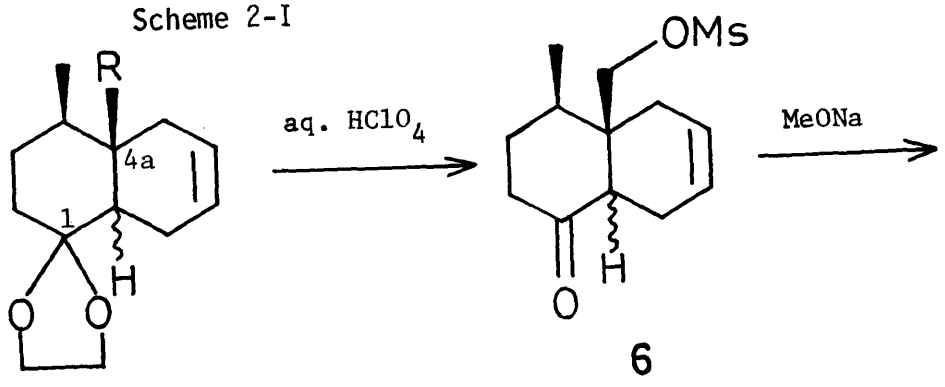
Compound [b]	Carbon NO															
	1	2	3	4	4a	5	6	7	8	8a	9	10	11	OMe	$-(OCH_2)_2-$	
3a	210.5	36.0	30.1	33.6	52.7	30.1	125.5*	123.3*	22.8	45.7	174.8	15.7		51.9		
3b	208.7	40.0	30.9	40.2	53.8	34.6	125.6*	124.6*	23.2	50.6	173.1	16.0		51.6		
4	208.5	40.4	22.2	36.1	50.6	36.2	126.8*	124.4*	23.2	50.9	175.1			52.0		
8	212.0	39.5	31.2	42.2	39.8	41.5	124.9*	124.3*	21.7	53.1	11.9	14.6				
10	110.0	35.7	28.3	42.8	36.1	41.3	125.7*	124.6*	21.4	47.8	11.9	15.0			64.0	65.4
11	110.0	35.9	19.5	40.7	33.6	43.4	126.1*	124.7*	21.4	47.0	18.2				64.0	65.5
12	110.0	35.5	28.0	42.6	34.9	39.7	52.7*	50.3*	20.2	42.9	13.2	15.1			64.0	65.3
13a	110.5	35.8	28.2*	42.5	37.7	33.7	28.4*	66.0	27.1	44.7	11.5	14.8			64.0	65.2
13b	109.3	35.6	28.3	42.1	37.1	39.1	37.7*	211.8	36.4*	50.9	11.7	15.3			64.1	65.4
14a	109.4	35.5	28.1	42.4	36.4	38.2	95.7	171.5	25.4	47.0	11.8	15.3	173.1	51.3	64.1	65.5
15	109.7	35.5	28.3	42.6	36.1	40.0	128.2	138.7	22.4	46.9	11.8	15.2	167.9	51.4	64.0	65.5
16a	109.9	35.9	28.2	37.4	38.1	41.2	52.7	26.3	16.8	43.0	12.5	14.9	176.4	51.4	64.3	65.4
16b	110.0	35.8	28.4*	38.9	37.7	42.5	51.9	28.9*	19.0	42.6	12.7	14.8	176.7	51.4	64.2	65.3
17a	212.0	40.8	31.3	38.6	41.4	41.2	57.2	27.8	19.8	42.5	11.7	14.5	176.3	51.7		
17b	71.9	34.1	25.2*	39.2	36.5	42.7	48.6	29.3	25.7*	43.1	15.1	14.3	176.9	51.5		

[a] The chemical shifts are shown in δ values (ppm) relative to internal Me_4Si. [b] For the numbering systems, see numbers on the structures. * These pairs of shifts may be interchanged since the assignments are ambiguous.

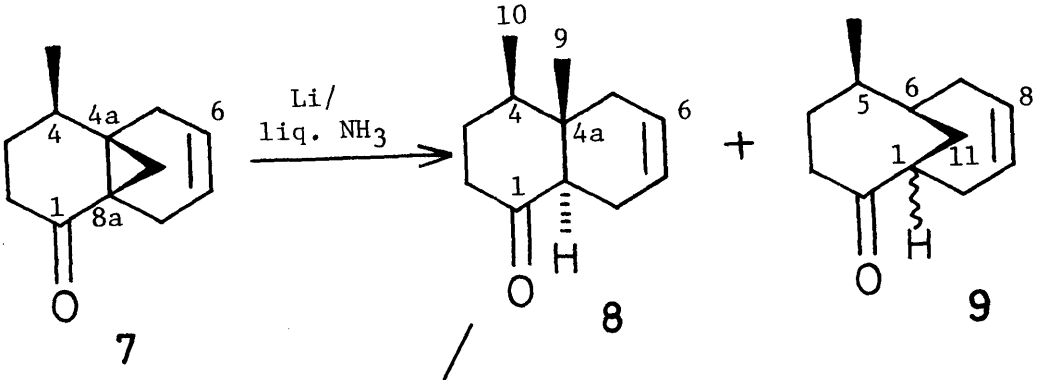
C(4) methyl group was made by comparison of the NMR data of **3b** and an octalin **4** which lacks the C(4) methyl group of **3b**. All the ^{13}C NMR chemical shifts of the related decalin and octalin derivatives are listed in Table 2-1. The chemical shifts of C(2) (δ 40.0) and C(8a) (δ 50.6) carbons of **3b** are close to those of C(2) (δ 40.4) and C(8a) (δ 50.9) of **4**, suggesting absence of the γ-effect[4] between the C(4) methyl and C(2) and C(8a) carbons of **3b** due to the equatorial conformation of the C(4) methyl group. On the other hand, the steric compression shift of the C(9) carbon (δ 173.1) of **3b** appears at 2.0 ppm higher fields than the value (δ 175.1) of **4**. The stereochemistry of **3b** was fully confirmed by the following transformation to ($\pm$)-**1**.

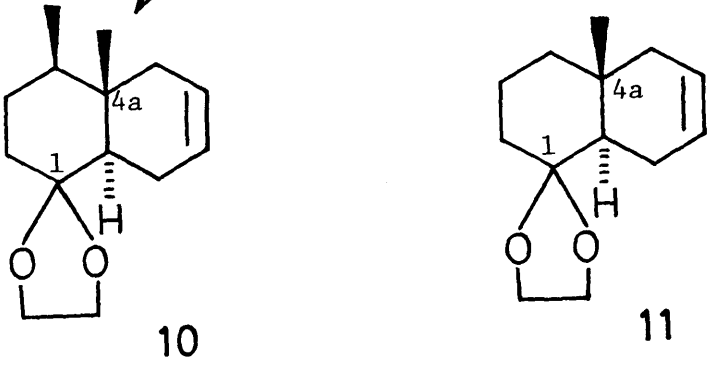
We first examined the conversion of **3b** into **8** according to the known procedures: (1) reduction of the ester group with lithium aluminum hydride, (2) oxidation of the hydroxymethyl group to formyl group, and (3) subsequent Wolff-Kishner reduction.[5] Difficulties were encountered, however, in performing the final reduction step. The generation of the methyl group was accomplished by the alternative approach: the reductive ring opening of the fused cyclopropane **7**[6] (Scheme 2-I). Thus, the acetalization of **3b**[7] was followed by the reduction of **5a** with lithium aluminum hydride to provide **5b** in 86% yield (from **3b**). Methanesulfonylation of **5b** to produce **5c**

Scheme 2-I



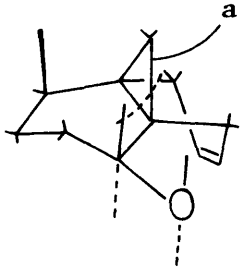
5a, R = CO_2Me
b, R = CH_2OH
c, R = CH_2OMs
d, R = CHO



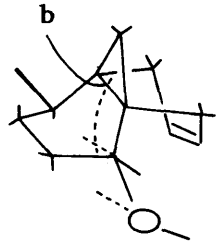


and subsequent hydrolysis of 5c with perchloric acid afforded 6 in 95% yield (from 5b). The cyclopropane 7 was generated by the smooth cyclization of 6 with sodium methoxide (84% yield).[8] The regioselective reductive cleavage of the cyclopropane 7 with lithium metal in liquid ammonia gave a mixture of 8[9] as the major product (83%) and a small amount of 9 (10%). The distribution of the reduction products may depend on the preferential conformation of transition states 7a and 7b (Chart 2-I). Thus, either bond a of 7a or b of 7b, both of which are parallel to the carbonyl π-orbitals, could be opened by electron transfer from lithium.[10] It appears that the present reduction

Chart 2-I



7a

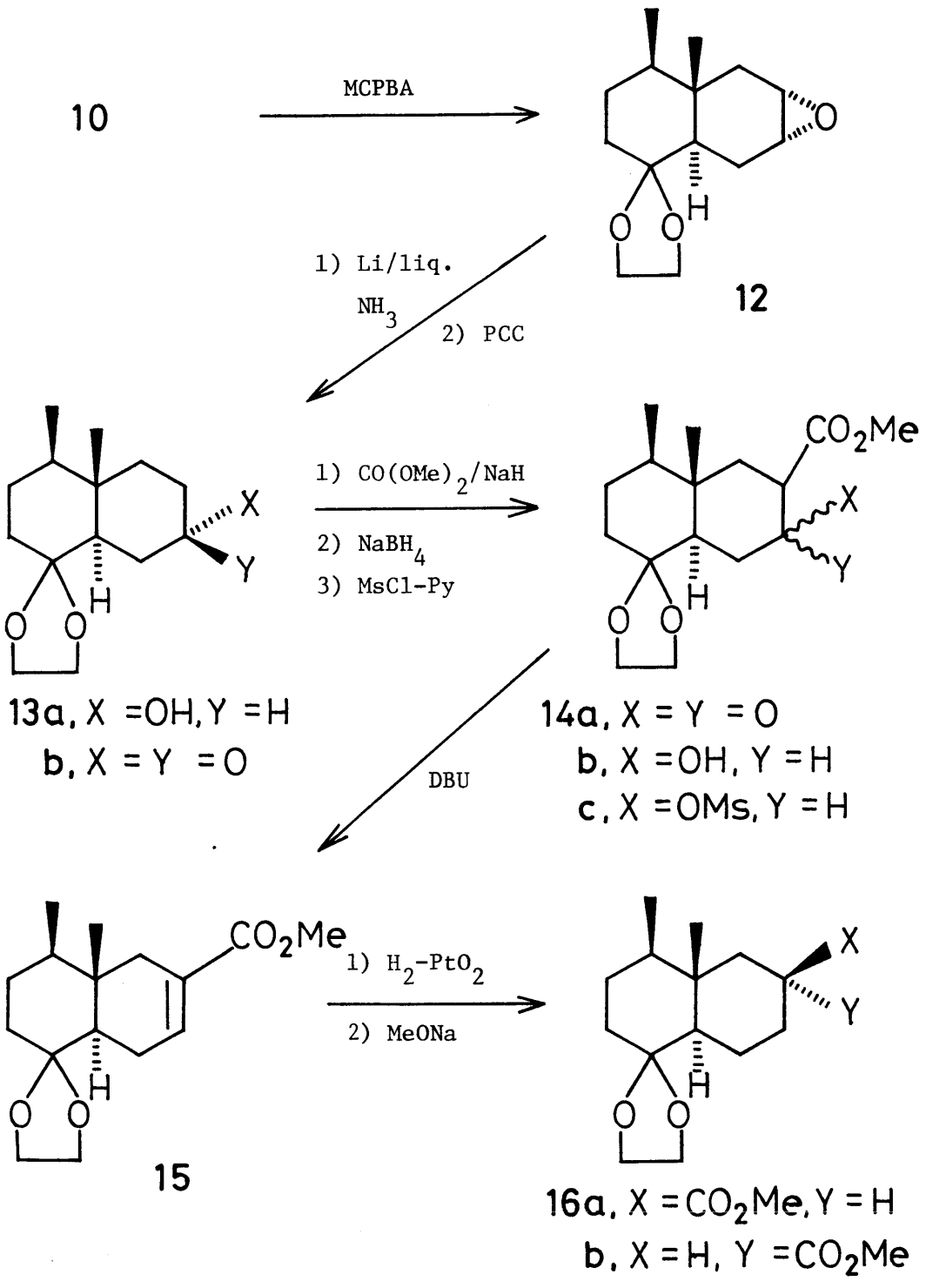


7b

preferentially takes place through the conformation **7a**. The marked upfield shift of the C(9) carbon of **10** at δ 11.9 in ^{13}C NMR spectra, in sharp contrast to that of **11**[11] at δ 18.2, can be rationally interpreted to assign the stereochemistry of **10**, compatible with the calculated values of Crew's substituents increments parameter.[6,12]

The introduction of an isopropenyl function in **1** and **18b** was the next and the remaining task for our synthesis. The conversion of **10** to **16b** (Scheme 2-II) was attempted as follows. Epoxidation of **10** with m-chloroperbenzoic acid at $-60 \sim 10^{o}$ gave the corresponding 6α,7α-epoxide **12** in 94% yield. Regioselective cleavage of the oxirane ring at the C(6) position of **12** with lithium metal in liquid ammonia afforded the 7α-alcohol **13a** in 96% yield. Thus, the reduction strictly followed the axial ring opening rule.[13] Oxidation of **13a** with pyridinium chlorochromate (PCC)[14] gave the ketone **13b** and subsequent methoxycarbonylation at the C(6) position of **13b** with sodium hydride in dimethyl carbonate gave the corresponding keto ester **14a**[15] in 81% yield (from **13a**). The completely enolized form of **14a** was characterized by two singlets at δ 95.7 and δ 171.5 ppm due to the C(6) and C(7) carbons in ^{13}C NMR spectra[16] (Table 2-1). Reduction of **14a** with sodium borohydride yielded a mixture of epimeric alcohols **14b** in 82% yield and subsequent dehydration of

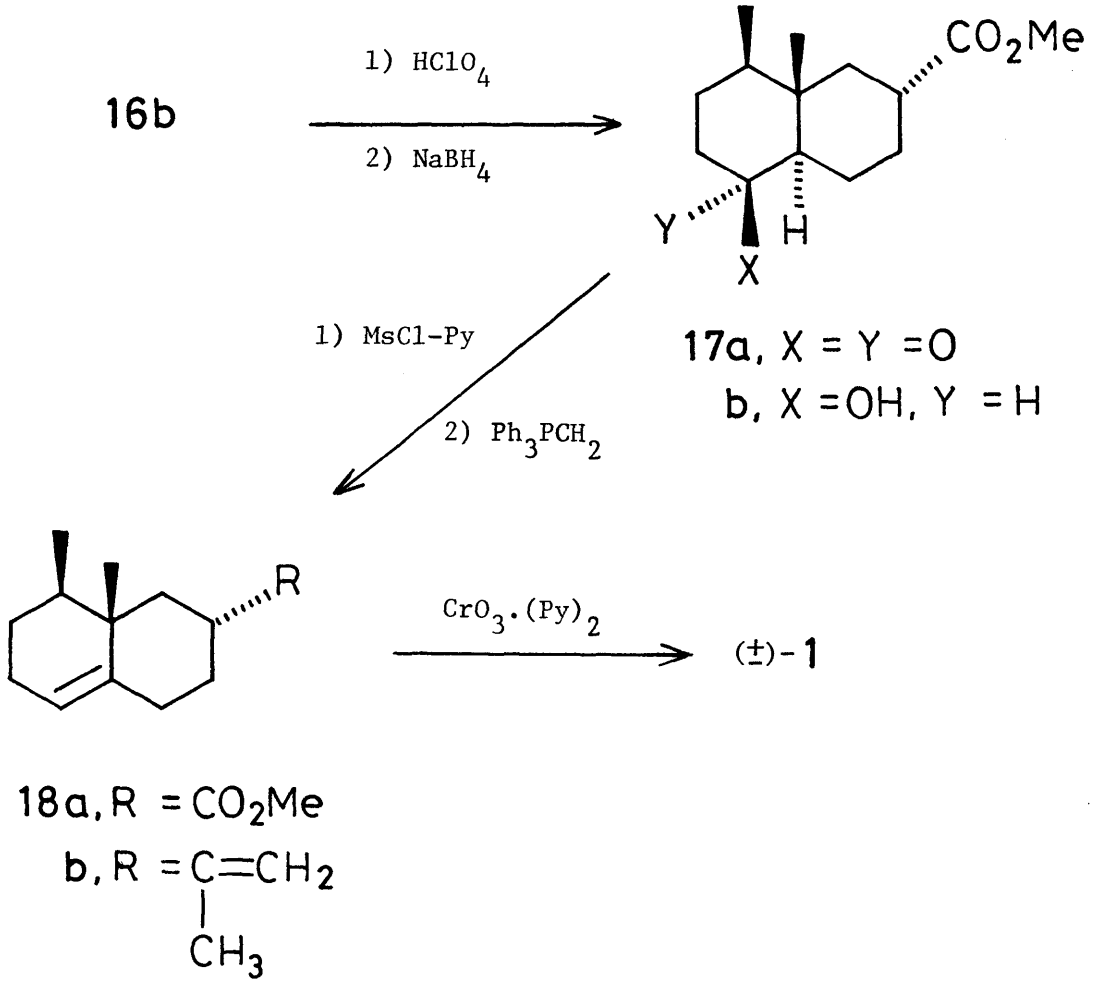
Scheme 2-II


10
MCPBA
12
1) Li/liq. NH3
2) PCC
1) CO(OMe)2/NaH
2) NaBH4
3) MsCl-Py
13a, X =OH, Y =H
b, X = Y =O
14a, X = Y =O
b, X =OH, Y =H
c, X =OMs, Y =H
DBU
15
1) H2-PtO2
2) MeONa
16a, X =CO2Me, Y =H
b, X =H, Y =CO2Me

14b via the corresponding mesylates 14c afforded α,β-unsaturated ester 15 in 64% yield (from 14b).[17] Catalytic hydrogenation of 15 over platinum oxide gave the desired 6β-methoxycarbonyl 16a in 98% yield by the preferential attack of hydrogen from the α-side of the molecule. The ^{13}C NMR spectra of 16a indicated the homogeneity of the product. The β-configuration was confirmed by its conversion into the thermodynamically favorable 6α-isomer 16b by treatment with sodium methoxide in methanol at 85-90° (93% yield).[18]

The final version of the present synthesis was carried out by the ester ⟶ isopropenyl transformation using Wittig olefination process.[19] Thus, hydrolysis of the ethylene acetal of 16b with perchloric acid and subsequent reduction of 17a with sodium borohydride provided 1β-alcohol 17b in 95% yield (from 16b). Dehydration of the hydroxyl group of 17b with methanesulfonyl chloride afforded 18a (73% yield). Reaction of 18a with an excess of salt-free methylenetriphenylphosphorane in tetrahydrofuran under refluxing conditions afforded the desired (±)-valencene 18b[20] in 76% yield. The allylic oxidation of 18b with a slurry of anhydrous chromium trioxide-pyridine complex[21] in dichloromethane furnished (±)-1 in 80% yield (Scheme 2-III).

Scheme 2-III


16b
1) HClO4
2) NaBH4
CO2Me
Y
H
X
17a, X = Y = O
b, X = OH, Y = H
1) MsCl-Py
2) Ph3PCH2
R
CrO3·(Py)2
(±)-1
18a, R = CO2Me
b, R = C=CH2
CH3

2.2. EXPERIMETNAL SECTION

The boiling points are indicated by an air-bath temperature without correction and the melting points are uncorrected. IR spectra were obtained with a JASCO IRA-1 grating spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-24 (60 MHz) and ^{13}C NMR spectra were obtained with a JEOL FX-100 (25.05 MHz). Samples were dissolved in $CDCl_3$ and the chemical shifts are expressed in δ values (ppm) relative to Me_4Si as an internal standard. Elemental analyses were performed in our laboratory. After the desired reaction period, unless otherwise noted, the mixture was poured into a separatory funnel with benzene-AcOEt (1/1) and brine. The organic layer was separated and washed with brine. The extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator.

Methyl 6-Methyl-3-oxo-1-cyclohexene-1-carboxylate (2b). A solution of 2a[22] (1.79 g, 12 mmol) and SeO_2 (1.92 g, 17 mmol) in dioxane (10 ml) was heated to 85° for 20 h and to 100° for 3 h. The precipitate was filtered and washed with benzene. The combined filtrates were concentrated and the residue was dissolved in CH_2Cl_2 (20 ml). To this solution was added dropwise

a chromium trioxide solution[23] with vigorous stirring over 30 min at 0°. The mixture was filtered and the filtrate was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (SiO_2, hexane-AcOEt 2/1) to give 928 mg (46%) of **2b**: bp 132-133° (9 mm); IR (neat) 1722 (ester C=O), 1683 (C=O), 1620 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.23 (d, $\underline{J}$ = 7 Hz, 3H, CH_3), 1.63-2.27 (m, 2H, CH_2), 2.35 (t, $\underline{J}$ = 2 Hz, 2H, $COCH_2$), 2.65-3.20 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 6.42 (s, 1H, HC=C). Found: C, 64.13; H, 7.35. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19.

Methyl 1,3,4,5,8,8aβ-Hexahydro-4β-methyl-1-oxonaphthalene-4aβ(2H)-carboxylate (**3a**) and Methyl 1,3,4,5,8,8aα-Hexahydro-4β-methyl-1-oxonaphthalene-4aβ(2H)-carboxylate (**3b**). A mixture of **2b** (2.95 g, 17.5 mmol), 1,3-butadiene (2.3 g, 41.0 mmol), and 2,5-di-$\underline{t}$-butylhydroquinone (50 mg) in benzene (10 ml) was heated at 150-160° for 3 days in a sealed tube. The mixture was extracted with hot MeOH and the extract was filtered. The concentrated filtrate was distilled at 80-90° (3 mm) to afford an unchanged **2b** (1.14 g). The residue in the flask was purified by column chromatography (SiO_2, hexane-AcOEt 2/1) to give 263 mg (11% yield based on recovered **2b**, R_f 0.75) of **3a** and 1.08 g (45%, R_f 0.68) of **3b**. **3a**: mp 84-85° (from hexane); IR (Nujol) 3027, 1720 (ester C=O), 1714 (C=O), 1653 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ

1.12 (d, $\underline{J}$ = 7 Hz, 3H, CH_3), 1.70-2.60 (m, 9H, CH_2, CH), 3.00-3.40 (m, 1H, COCH), 3.69 (s, 3H, OCH_3), 5.55 (m, 2H, HC=C). Found: C, 70.38; H, 8.32. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. **3b**: mp 88-89° (from hexane); IR (Nujol) 3018, 1721 (ester C=O), 1698 (C=O), 1655 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.94 (d, $\underline{J}$ = 6.5 Hz, 3H, CH_3), 1.68-2.50 (m, 9H, CH_2, CH), 2.69-3.10 (m, 1H, COCH), 3.59 (s, 3H, OCH_3), 5.60 (m, 2H, HC=C). Found: C, 70.36; H, 8.32. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16.

Conversion of **3a** into **3b**. A mixture of **3a** (32 mg) and MeONa (10 mg) in MeOH (0.5 ml) was stirred at room temperature for 24 h. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 3/1) gave 32 mg (100%) of **3b** as solids.

Methyl 1,1-Ethylenedioxy-1,3,4,5,8,8a-hexahydro-4β-methylnaphthalene-4aβ(2H)-carboxylate (**5a**). A mixture of **3b** (420 mg, 1.89 mmol), ethylene glycol (2.3 g, 37.0 mmol), and $\underline{p}$-TsOH (50 mg) in benzene (40 ml) was heated to reflux for 24 h in a Dean-Stark apparatus. The reaction was quenched with aqueous 5% $NaHCO_3$. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 3/1) gave 466 mg (92%) of **5a**: bp 61-63° (0.01 mm); IR (neat) 3022, 1727 (ester C=O), 1664 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.92-1.05 (m, 3H, CH_3), 1.35-2.85 (m, 10H, CH_2, CH), 3.62-3.80 (m, 3H, OCH_3), 3.95 (br, 4H, CH_2O), 5.49-5.88 (m, 2H, HC=C). Found: C, 67.57; H, 8.49. Calcd for $C_{15}H_{22}O_4$: C, 67.65;

H, 8.33.

3,4,4a,5,8,8a-Hexahydro-4aβ-hydroxymethyl-4β-methyl-1(2H)-naphthalenone Ethylene Acetal (5b). To a suspension of $LiAlH_4$ (50 mg, 1.32 mmol) in THF (2 ml) was added a solution of 5a (115 mg, 0.43 mmol) in THF (2 ml) at 0°. After stirring at room temperature for 10 h, the reaction was quenched with AcOEt and aqueous 5% $NaHCO_3$. Extraction with ether followed by washing, drying (Na_2SO_4), and evaporation of the solvent gave 95 mg (93%) of 5b: bp 57-59.5° (0.005 mm); IR (neat) 3450 (OH), 3021, 1660 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.79-1.09 (m, 3H, CH_3), 1.18-2.64 (m, 10H, CH_2, CH), 3.59 (brs, 1H, OH), 3.00-3.70 (m, 2H, CH_2O), 3.78-4.10 (m, 4H, CH_2O), 5.60 (brs, 2H, HC=C). Found: C, 70.68; H, 9.41. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30.

3,4,4a,5,8,8a-Hexahydro-4β-methyl-4aβ-methylsulfonyloxymethyl-1(2H)-naphthalenone Ethylene Acetal (5c). A mixture of 5b (386 mg, 1.62 mmol), MsCl (592 mg, 5.2 mmol), and pyridine (2.5 ml) was stirred at 0° for 2 h and at room temperature for 3 h, and the reaction was quenched with aqueous 5% $NaHCO_3$. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 4/1) gave 500 mg (97%) of 5c: IR(neat) 3028, 1671 (C=C), 1175 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 7 Hz, 3H, CH_3), 1.40-2.59 (m, 10H, CH_2, CH), 3.01 (s, 3H, SO_2CH_3), 3.93 (s, 4H, CH_2O), 4.29 (m, 2H, CH_2O), 5.63 (brs, 2H, HC=C). Found: C,

57.11; H, 7.79. Calcd for $C_{15}H_{24}O_5S$: C, 56.95; H, 7.65.

3,4,4a,5,8,8a-Hexahydro-4β-methyl-4aβ-methylsulfonyloxymethyl-1(2H)-naphthalenone (6). A solution of 5c (90 mg, 0.28 mmol) and 70% $HClO_4$ (90 mg) in THF (3 ml) and H_2O (1.5 ml) was stirred at 0° for 1 h and at room temperature for 10 h. The reaction was quenched with aqueous $NaHCO_3$ and the mixture was extracted with benzene-AcOEt (1/1). The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 4/1) gave 76 mg (98%) of 6: IR (neat) 3033, 1710 (C=O), 1656 (C=C), 1177 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.92-1.34 (m, 3H, CH_3), 1.57-2.78 (m, 10H, CH_2, CH), 2.93, 3.02 (s, 3H, SO_2CH_3), 4.18 (s, 2H, CH_2O), 5.64 (m, 2H, HC=C). Found: C, 57.30; H, 7.66. Calcd for $C_{13}H_{20}O_4S$: C, 57.34; H, 7.40.

3,4,4a,5,8,8a-Hexahydro-4aβ,8aβ-methano-4β-methyl-1(2H)-naphthalenone (7). To a solution of 6 (257 mg, 0.95 mmol) in MeOH (2 ml) was added a solution of MeONa (254 mg, 4.7 mmol) in MeOH (2.5 ml) at 0°. After stirring at room temperature for 24 h, the mixture was poured onto dilute HCl and crushed ice. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 139 mg (84%) of 7: bp 40.5-42.0° (0.02 mm); IR (neat) 3079, 3030, 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.76-2.83 (m, 11H, CH_2, CH), 1.05 (d, J = 6 Hz, 3H, CH_3), 5.49-5.53 (m, 2H, HC=C). Found: C, 81.84; H, 9.03. Calcd for

$C_{12}H_{16}O$: C, 81.77; H, 9.15.

3,4,4a,5,8,8aα-Hexahydro-4β,4aβ-dimethyl-1(2H)-naphthalenone (8) and 5,6-cis-5-Methylbicyclo[4.4.1]undec-8-en-2-one (9). To a blue solution of Li (84 mg, 12.1 mmol) in liquid NH_3 (ca. 30 ml) was added a solution of 7 (245 mg, 1.39 mmol) and t-BuOH (104 mg, 1.39 mmol) in DME (4 ml) at -70°. The mixture was stirred at -70° for 1.5 h and the reaction was quenched with NH_4Cl (500 mg). Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 2/1) gave 202 mg (83%) of 8 (R_f 0.8) and 24 mg (10%) of 9 (R_f 0.5). 8: bp 38.0-39.5° (0.02 mm); IR (neat) 3025, 1711 (C=O), 1658 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.63 (s, 3H, CH_3), 0.91 (d, J = 6 Hz, 3H, CH_3), 1.53-2.56 (m, 10H, CH_2, CH), 5.63 (m, 2H, HC=C). Found: C, 80.94; H, 10.27. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18.

9: mp 91-95°; IR(Nujol) 3019, 1698 (C=O), 1656 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.93 (m, 3H, CH_3), 1.05-2.56 (m, 13H, CH_2, CH), 5.65 (m, 2H, HC=C). Found: C, 80.94; H, 9.94. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18.

3,4,4a,5,8,8aα-Hexahydro-4β,4aβ-dimethyl-1(2H)-naphthalenone Ethylene Acetal (10). Similar acetalization of 8 (131 mg, 0.73 mmol) as described for the preparation of 5a gave 158 mg (97%) of 10: bp 73-75° (0.03 mm); IR (neat) 3020, 1559 (C=C), 1159, 1092, 1040, 985, 897 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81

(s, 3H, CH_3), 0.84 (d, J = 6 Hz, 3H, CH_3), 1.10-2.44 (m, 10H, CH_2, CH), 3.72-4.04 (m, 4H, CH_2O), 5.61 (brs, 2H, HC=C). Found: C, 75.64; H, 10.03. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97.

6α,7α-Epoxy-4β,4aβ-dimethyl-3,4,4a,5,6,7,8,8aα-octahydro-1(2H)-naphthalenone Ethylene Acetal (12). To a solution of MCPBA (324 mg, 1.88 mmol) in CH_2Cl_2 (10 ml) was added a solution of **10** (320 mg, 1.44 mmol) in CH_2Cl_2 (10 ml) at -60°. After 1 h, the mixture was allowed to be warmed to 10° during 5 h, at which temperature it was stirred for 2 h. The mixture was filtered and the filtrate was washed with aqueous 20% KOH and aqueous $NaHCO_3$. Concentration followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 332 mg (97%) of **12**: bp 119-121° (2 mm); IR (neat) 1297, 1277, 1197, 1162, 1150, 1085, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H, CH_3), 0.79 (d, J = 6 Hz, 3H, CH_3), 1.05-2.22 (m, 10H, CH_2, CH), 2.80-3.11 (m, 2H, CH-O), 3.51-3.96 (m, 4H, CH_2O). Found: C, 70.65; H, 9.47. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30.

7α-Hydroxy-4β,4aβ-dimethyl-3,4,4a,5,6,7,8,8aα-octahydro-1(2H)-naphthalenone Ethylene Acetal (13a). To a blue solution of Li (55 mg, 7.93 mmol) in liquid NH_3 (45 ml) was added a solution of **12** (350 mg, 1.47 mmol) in THF (5 ml) at -70°. The mixture was stirred at -70° for 3 h and at -33° for 1.5 h and then the reaction was quenched with NH_4Cl. Extractive workup followed by

column chromatography (SiO_2, hexane-AcOEt 3/1) gave 340 mg (96%) of **13a**: bp 157-159° (0.03 mm); IR (neat) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 0.80 (m, 3H, CH_3), 0.82 (s, 3H, CH_3), 1.00-2.10 (m, 12H, CH_2, CH), 3.17 (br, 1H, OH), 3.54-4.00 (m, 4H, CH_2O), 4.11 (m, 1H, CH-O). Found: C, 69.87; H, 10.17. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07.

1,1-Ethylenedioxy-4β,4aβ-dimethyl-1,2,3,4,4a,5,8,8aα-octahydro-7(6H)-naphthalenone (**13b**). To a suspension of PCC (1.06 g, 3.96 mmol) and AcONa (550 mg, 6.7 mmol) in CH_2Cl_2 (15 ml) was added a solution of **13a** (320 mg, 1.33 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature for 3 h and diluted with ether. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 3/1) gave 294 mg (93%) of **13b**: mp 59-61°; IR (Nujol) 1705 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.91 (m, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.12-2.14 (m, 8H, CH_2, CH), 2.15-2.57 (m, 4H, CH_2CO), 3.57-4.10 (m, 4H, CH_2O). Found: C, 70.63; H, 9.11. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30.

Methyl 1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1,1-ethylenedioxy-4β,4aβ-dimethyl-7-oxonaphthalene-6-carboxylate (**14a**). A mixture of **13b** (340 mg, 1.43 mmol) and NaH (65 mg, 2.71 mmol) in dimethyl carbonate (2 ml) was heated to reflux for 3 h. The reaction was quenched with aqueous 5% $NaHCO_3$ and the mixture was extracted with benzene-AcOEt (1/1). The usual workup followed by column

chromatography (SiO_2, hexane-AcOEt 3/1) gave 369 mg (87%) of **14a**: mp 99-103°; IR (Nujol) 1655 (ester C=O), 1621 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.78 (s, 3H, CH_3), 0.89 (m, 3H, CH_3), 1.05-2.00 (m, 6H, CH_2, CH), 2.04-2.48 (m, 4H, CH_2), 3.72 (s, 3H, OCH_3), 3.80-4.12 (m, 4H, CH_2O), 12.11 (s, 1H, OH). Found: C, 64.93; H, 8.31. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16.

Methyl 1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1,1-ethylenedioxy-7-hydroxy-4β,4aβ-dimethylnaphthalene-6-carboxylate (**14b**). To a solution of **14a** (462 mg, 1.58 mmol) in MeOH (25 ml) was added a solution of $NaBH_4$ (59 mg, 1.56 mmol) in H_2O (1 ml) at 0°. The mixture was stirred at room temperature for 12 h and then poured into aqueous $NaHCO_3$. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 1/1) gave 381 mg (82%) of **14b**: bp 143-145° (0.025 mm); IR (neat) 3500 (OH), 1740 (ester C=O), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.71, 0.90 (s, 3H, CH_3), 0.81 (m, 3H, CH_3), 1.05-2.60 (m, 11H, CH_2, CH), 2.90 (br, 1H, OH), 3.46-4.40 (m, 5H, CH_2O, CH-O), 3.66 (s, 3H, OCH_3). Found: C, 64.69; H, 8.79. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78.

Methyl 1,1-Ethylenedioxy-4β,4aβ-dimethyl-1,2,3,4,4a,5,8,8aα-octahydronaphthalene-6-carboxylate (**15**). A mixture of **14b** (438 mg, 1.47 mmol), Et_3N (1.04 g, 2.94 mmol), and MsCl (337 mg, 2.94 mmol) in ether (10 ml) was stirred at 0° for 2 h and at room temperature for 1 h. The reaction was quenched with aqueous

$NaHCO_3$. Extractive workup gave 480 mg (87%) of **14c**: mp 123-125°. Without further purification, the mesylate **14c** (460 mg, 1.22 mmol) was treated with DBU (1.36 g, 8.93 mmol) in benzene (20 ml) at reflux for 12 h. Evaporation of the solvent followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 255 mg (74%) of **15**: mp 79-81°; IR (Nujol) 1718 (ester C=O), 1650 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H, CH_3), 0.93 (m, 3H, CH_3), 1.10-2.55 (m, 10H, CH_2, CH), 3.70 (s, 3H, OCH_3), 3.90 (m, 4H, CH_2O), 6.95 (m, 1H, HC=C). Found: C, 68.50; H, 8.89. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63.

Methyl 1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1,1-ethylenedioxy-4β,4aβ-dimethylnaphthalene-6β-carboxylate (**16a**). A mixture of **15** (123 mg, 0.44 mmol) and PtO_2 (40 mg) in AcOEt (7 ml) was treated with excess H_2 at room temperature for 4 days. The mixture was freed from the catalyst by filtration and the filtrate was concentrated *in vacuo* to give 122 mg (98%) of **16a**: bp 110-111° (0.017 mm); IR (neat) 1730 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 0.72 (s, 3H, CH_3), 0.82 (m, 3H, CH_3), 1.00-2.70 (m, 13H, CH_2, CH), 3.67 (s, 3H, OCH_3), 3.86 (m, 4H, CH_2O). Found: C, 70.52; H, 9.46. Calcd for $C_{16}H_{26}O_4$: C, 70.56; H, 9.30.

Epimerization of **16a** to **16b**. **16a** (110 mg, 0.39 mmol) was heated with MeONa (540 mg) in MeOH (6 ml) at 85-90° for 12 h. The mixture was poured into aqueous 5% tartaric acid and

extracted with AcOEt-benzene (1/1). The crude product obtained after the usual workup was treated with excess CH_2N_2 to give 102 mg (93%) of **16b**: bp 121-123° (0.015 mm); IR (neat) 1730 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 0.86 (m, 3H, CH_3), 0.87 (s, 3H, CH_3), 1.10-2.75 (m, 13H, CH_2, CH), 3.64 (s, 3H, OCH_3), 4.87 (m, 4H, CH_2O). Found: C, 70.65; H, 9.51. Calcd for $C_{16}H_{26}O_4$: C,70.56; H, 9.30.

Methyl 1,2,3,4,4a,5,6,7,8,8aα-Decahydro-4β,4aβ-dimethyl-1-oxonaphthalene-6α-carboxylate (17a). Similar hydrolysis of **16b** (122 mg, 0.43 mmol) with 70% $HClO_4$ as described for the preparation of 6 gave 101 mg (98%) of **17a**: mp 68-69°; IR (Nujol) 1725 (ester C=O), 1705 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.66 (s, 3H, CH_3), 0.90 (d, J = 6 Hz, 3H, CH_3), 1.10-2.80 (m, 13H, CH_2, CH), 3.65 (s, 3H, OCH_3). Found: C, 70.52; H, 9.46. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30.

Methyl 1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1β-hydroxy-4β,4aβ-dimethylnaphthalene-6α-carboxylate (17b). To a solution of **17a** (217 mg, 0.91 mmol) in MeOH (10 ml) was added a solution of $NaBH_4$ (35 mg, 0.92 mmol) in H_2O (0.5 ml). The mixture was stirred at room temperature for 3 h, and the reaction was quenched with aqueous 10% AcOH. Extraction with AcOEt-benzene (1/1) followed by washing, drying (Na_2SO_4), and column chromatography (SiO_2, hexane-AcOEt 3/1) of the crude product gave 213 mg (97%) of **17b**:

bp 93-94° (0.005 mm); IR (neat) 3480, 3400 (OH), 1730, 1715 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 0.81 (m, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.00-2.85 (m, 13H, CH_2, CH), 1.68 (brs, 1H, OH), 3.63 (s, 3H, OCH_3), 3.67 (m, 1H, CH-O). Found: C, 69.91; H, 10.08. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07.

Methyl 4β,4aβ-Dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalene-6α-carboxylate (18a). To a solution of **17b** (213 mg, 0.89 mmol) and Et_3N (629 mg, 6.22 mmol) in ether (10 ml) was added MsCl (203 mg, 1.77 mmol) at 0°. The mixture was stirred at room temperature for 12 h, and the reaction was quenched with aqueous $NaHCO_3$. The mixture was worked up in the usual manner and the crude product was heated to reflux with DBU (946 mg, 6.21 mmol) in benzene (3 ml) for 12 h. Evaporation of the solvent followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 144 mg (73%) of **18a**: bp 74-76° (0.015 mm); IR (neat) 1725 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 0.85 (m, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.10-2.60 (m, 12H, CH_2, CH), 3.64 (s, 3H, OCH_3), 5.35 (m, 1H, HC=C); ^{13}C NMR ($CDCl_3$) δ 15.5 (q, C-10), 18.0 (q, C-9), 25.8 (t), 27.2 (t), 30.4 (t), 31.7 (t), 37.5 (s, C-4a), 39.7 (d), 40.8 (d), 41.9 (t, C-5), 51.4 (q, OCH_3), 121.0 (d, C-1), 141.6 (s, C-8a), 176.4 (s, COO). Found: C, 75.57; H, 9.97. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97.

(±)-Valencene (18b). To a solution of **18a** (110 mg, 0.5

mmol) in THF (5 ml) was added a salt-free methylenetriphenylphosphorane prepared from methyltriphenylphosphonium bromide (715 mg, 2.0 mmol) and $NaNH_2$ (200 mg, 5.13 mmol) in THF (4 ml). The mixture was heated at reflux for 12 h. Extractive workup followed by column chromatography (SiO_2, hexane-ether 15/1) gave 78 mg (76%) of **18b**: bp 116-118° (14 mm) [lit.[1h] 73-75° (0.03 mm)]; IR (neat) 3050, 3010, 1670, 1645 (C=C), 1455, 1440, 1385, 1361, 985, 850, 890, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (m, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.10-2.30 (m, 12H, CH_2, CH), 1.71 (brs, 3H, CH_3), 4.65 (brs, 2H, H_2C=C), 5.30 (m, 1H, HC=C); ^{13}C NMR ($CDCl_3$) δ 15.7 (q, C-10), 18.4 (q, C-9), 20.8 (q, C-13), 25.9 (t), 27.2 (t), 32.8 (t), 33.2 (t), 37.9 (s, C-4a), 41.0 (d), 41.1 (d), 45.0 (t, C-5), 108.3 (t, C-12), 120.1 (d, C-1), 143.1 (s, C-8a), 150.6 (s, C-11).

(±)-Nootkatone (1). To a solution of **18b** (42 mg, 0.21 mmol) in CH_2Cl_2 (5 ml) was added a slurry of CrO_3.(pyridine)$_2$ complex (553 mg, 3.09 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature for 12 h, and the reaction was quenched with aqueous tartaric acid. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 3/1) furnished 36 mg (80%) of **1**: mp 42-43° (lit.[1f] 44-45°), crystallized from petroleum ether (boiling range: 30-70°) at -70°; IR (Nujol) 3080, 3010, 1670 (C=O), 1620 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.96 (d, *J* =

6 Hz, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.22-2.63 (m, 10H, CH_2, CH), 1.74 (brs, 3H, CH_3), 4.71 (brs, 2H, H_2C=C), 5.73 (brs, 1H, HC=C); ^{13}C NMR ($CDCl_3$) δ 14.9 (q, C-10), 16.8 (q, C-9), 20.8 (q, C-13), 31.7 (t, C-7), 33.1 (t, C-8), 39.3 (s, C-4a), 40.4 (d, C-4), 40.5 (d, C-6), 42.1 (t, C-3), 43.9 (t, C-5), 109.2 (t, C-12), 124.7 (d, C-1), 149.0 (s, C-11), 170.4 (s, C-8a), 199.5 (s, C-2). Except for the optical rotation, the physical data (IR, ^1H NMR, and TLC analyses) of the product 1 were identical in all respects with those of the authentic sample.[24]

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CHAPTER 3

SYNTHESIS OF (+)-NOOTKATONE

ABSTRACT

The (+)-nootkatone (1) is stereoselectively derived from (-)-β-pinene (5a). The present synthesis is characterized by the following two features: (1) stereocontrolled introduction of the C(4a) methyl group and (2) selective formation of vicinal, cis-dimethyl groups. The methylation of the β-keto ester 6a prepared from 5a proceeds at the opposite side of the dimethylmethylene bridge to give 4. Lithium metal reduction of the exo-methylene 3 gives 17a. The formation of the cis-dimethyl isomer 17a can be explained by assuming the participation of a lithium bidentate chelate intermediate. The compound 3 is accessible from 4 by elongation of the side chain through the Grignard reaction and the intramolecular alkylation. The conversion of 17a into (+)-1 is accomplished by (1) ozonolysis, (2) oxidation of 19, giving the 1,5-diketone 2, and (3) cyclization of 2 with hydrogen chloride followed by dehydrochlorination.

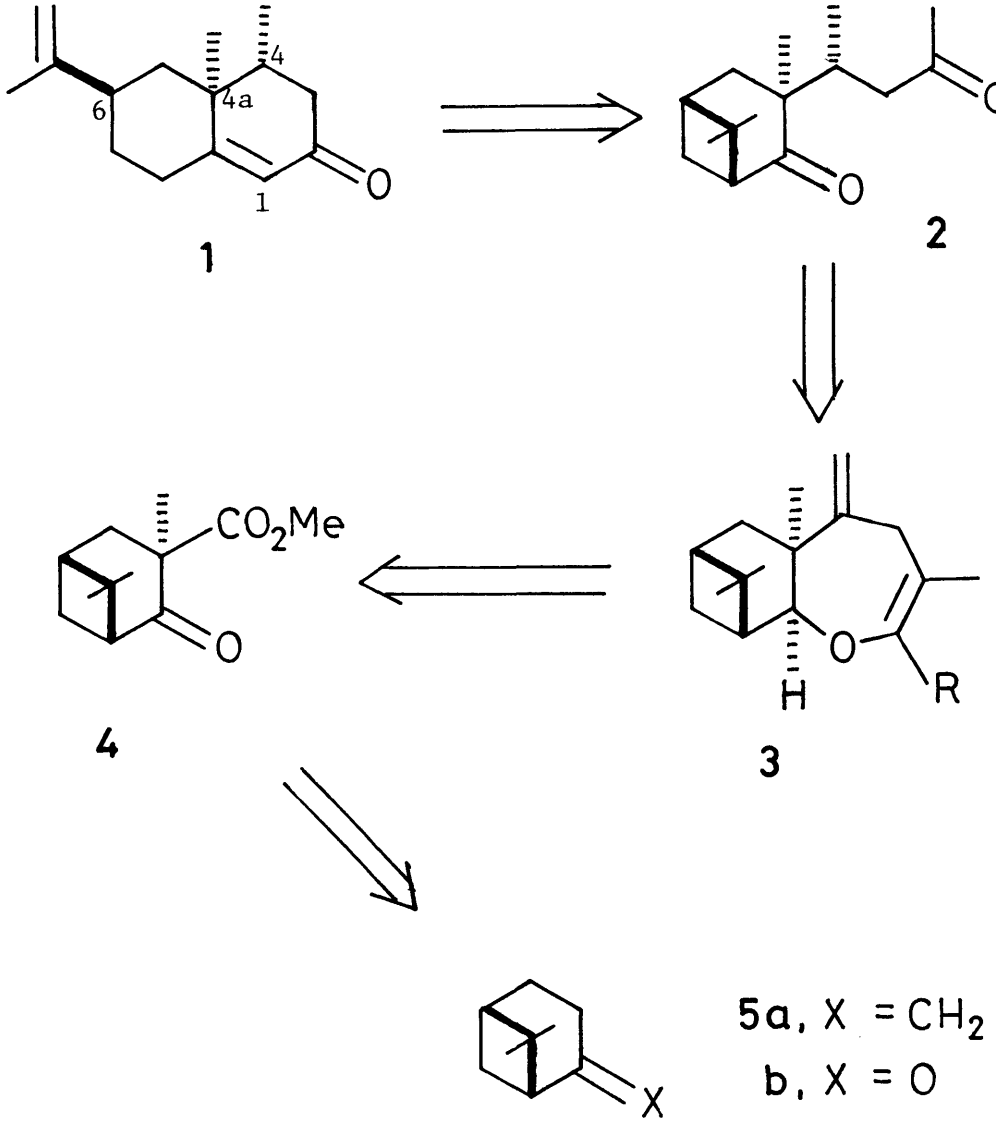
INTRODUCTION

Only the (+)-enantiomer, a natural form of nootkatone 1,[1] possesses a characteristic flavor of grapefruit.[2] Stereoselective synthesis of the (+)-isomer has not yet been accomplished, although several attempts have been reported by using chiral monoterpenes.[3-5] Although (-)-β-pinene (5a) is used as a starting material for introducing the 6β-isopropenyl group of 1 *via* ring cleavage of the cyclobutane,[5a] it was shown to be still difficult to achieve the desired configurations of the isopropenyl and two methyl groups. Recently, Yoshikoshi and his co-workers have devised a partial solution to this problem. Thus, the conjugate addition of allylsilanes to ethylidenenopinone gave a 4:1 mixture of the *cis*- and *trans*-dimethyl isomers at the C(4) and C(4a) positions of 1.[6] We have now established a highly stereocontrolled synthesis of (+)-1 starting from 5a.

Our synthetic plan in the present study is outlined in Scheme 3-I. In order to satisfy the stereochemical requirements in construction of the framework of 1, the following major problems had to be solved: (a) stereocontrolled synthesis of 4 from 5a through 5b and (b) stereoselective reduction of the *exo*-methylene group of 3 to vicinal, *cis*-disposed two methyl groups.

The major strategy for the present synthesis also involves the transformation of the keto ester 4 into 3 and the efficient conversion of 2 to the target molecule 1.

Scheme 3-I

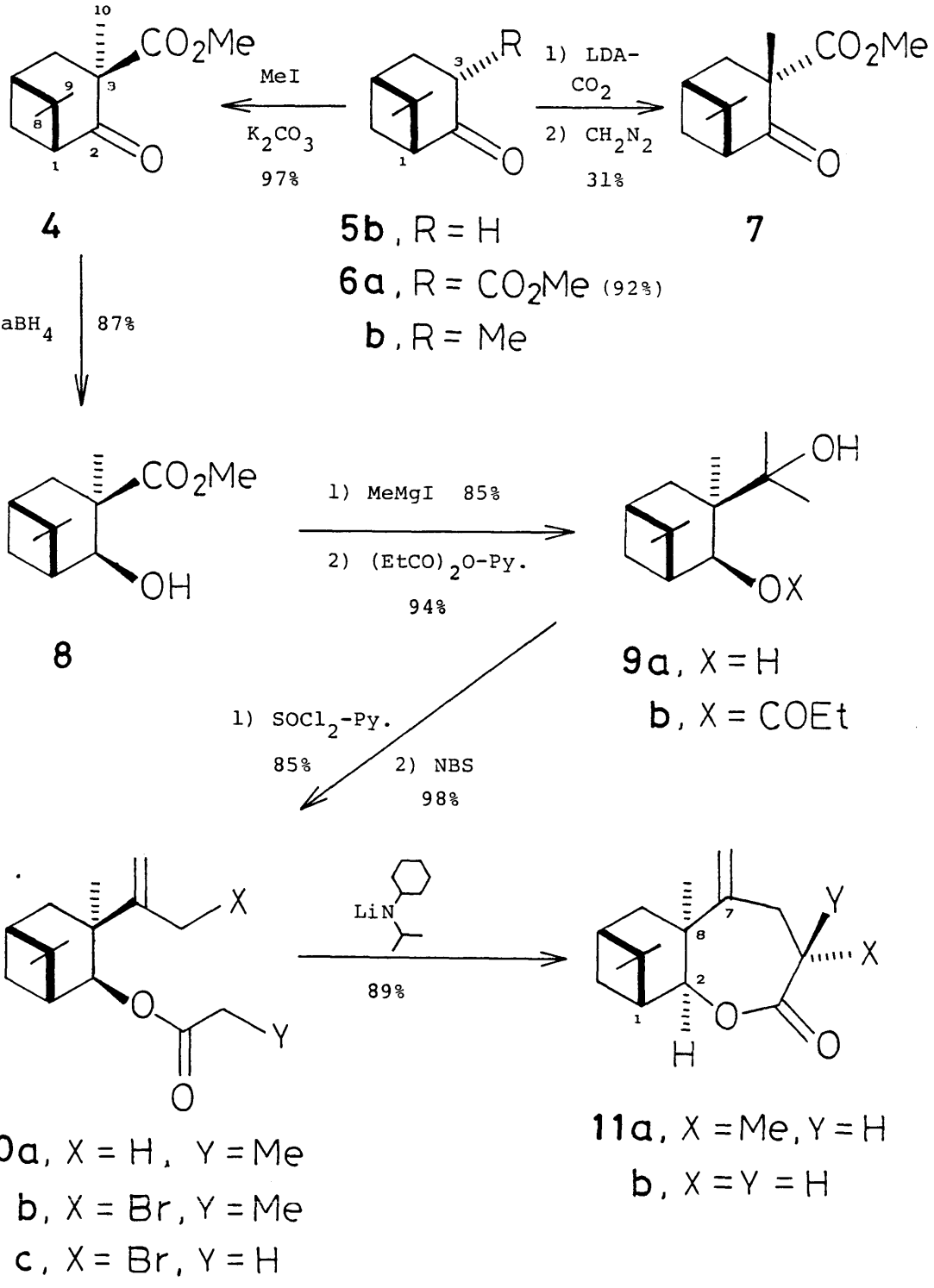


3.1 SYNTHESIS OF (+)-NOOTKATONE FROM (-)-β-PINENE

Starting with nopinone (5b)[5a,7] obtained by ozonolysis of (-)-β-pinene (5a), the keto ester 4 was prepared as follows. On heating at reflux with sodium hydride in dimethyl carbonate, 5b was converted into 6a, whose alkylation by means of methyl iodide and potassium carbonate in acetone afforded 4 as a sole product (89% yield from 5b). The stereochemistry of the C(3) methyl group of 4[8] was corroborated by the comparison with its stereoisomer 7, which was prepared from 3-methylnopinone (6b)[9] by successive treatment with lithium diisopropylamide (LDA) and then carbon dioxide at -10^{o}, followed by esterification with diazomethane. The homogeneities of the products 4 and 7 were indicated by TLC and ^{1}H and ^{13}C NMR analyses. The rigorous stereoselectivities obtained in these alkylations at the C(3) positions of 6a and 6b may be ascribed to the constraint caused by the dimethylmethylene bridge.

Subsequently, we examined the conversion of 4 into 11a by means of the intramolecular alkylation of 10b. Stereoselective reduction of 4 was achieved on treatment with sodium borohydride in methanol, giving 8 as the result of preferential attack of hydride from the sterically less hindered α-side of the molecule.[9a] The hydroxy ester 8 was alkylated with an excess

Scheme 3-II

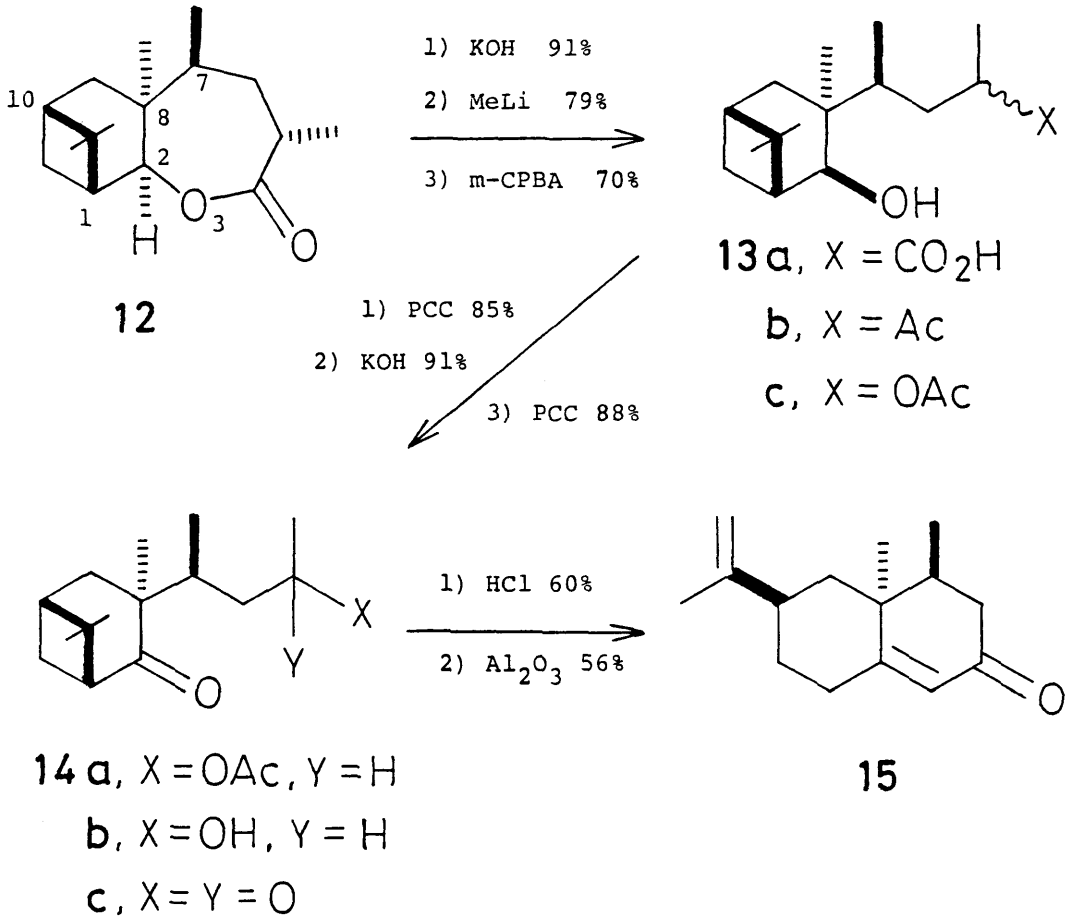

CO2Me
MeI
K2CO3
97%
R
1) LDA-
CO2
2) CH2N2
31%
4
5b, R = H
6a, R = CO2Me (92%)
b, R = Me
7
NaBH4
87%
8
1) MeMgI 85%
2) (EtCO)2O-Py.
94%
OH
OX
9a, X = H
b, X = COEt
1) SOCl2-Py.
85%
2) NBS
98%
X
Y
LiN
89%
10a, X = H, Y = Me
b, X = Br, Y = Me
c, X = Br, Y = H
11a, X = Me, Y = H
b, X = Y = H

methylmagnesium iodide to give the diol 9a in 74% yield (from 4). Esterification of 9a with propionic anhydride in pyridine and subsequent dehydration of 9b with thionyl chloride-pyridine gave 10a in 75% yield (from 9a). On heating with N-bromosuccinimide (NBS) in carbon tetrachloride, 10a was converted into the allylic bromide 10b in 98% yield. The intramolecular cyclization of 10b to the seven-membered lactone 11a was effected by lithium N-cyclohexylisopropylamide in tetrahydrofuran-hexamethylphosphoric triamide (HMPA) at -50^{o} in 89% yield. Meanwhile, the reaction of 10c, which lacks methyl group at the α-position of carbonyl function, with same base resulted in the corresponding 11b in poor yield (10-15%; Scheme 3-II).

We originally considered that a steric effect caused by the C(8) angular methyl group of 11a could result in the vicinal, α-C(7)-methyl group[10] through the catalytic hydrogenation of the adjoining exo-methylene group. Hydrogenation of 11a over platinum dioxide, however, afforded exclusively the β-C(7)-methyl product 12 in 97% yield. The ^{1}H and ^{13}C NMR spectra of 12 indicated the homogeneity of the product. The assigned configuration of the C(7) methyl group was further confirmed by its conversion into the known 1,5-diketone 14c [6](Scheme 3-III).

Hydrolysis of 12 followed by methylation with methyllithium gave the methyl ketone 13b. Baeyer-Villiger oxidation of 13b with

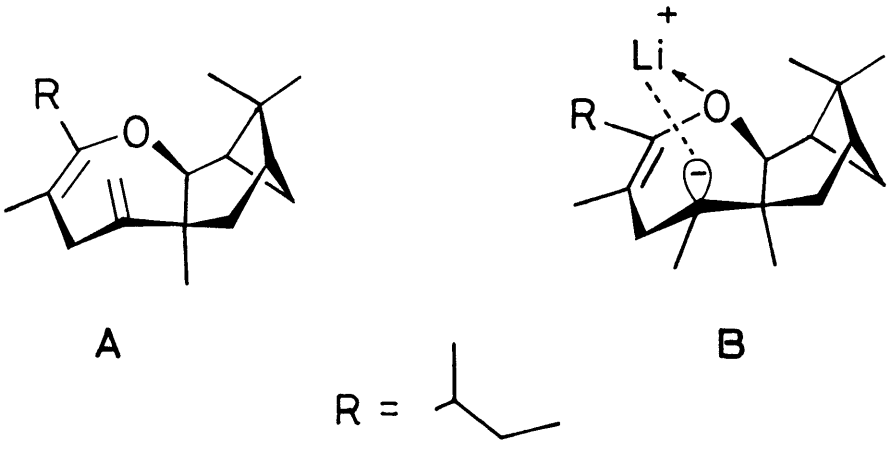
Scheme 3-III


10
7
8
2
1
H
O3
O
12
1) KOH 91%
2) MeLi 79%
3) m-CPBA 70%
OH
X
13a, X = CO2H
b, X = Ac
c, X = OAc
1) PCC 85%
2) KOH 91%
3) PCC 88%
X
Y
O
14a, X = OAc, Y = H
b, X = OH, Y = H
c, X = Y = O
1) HCl 60%
2) Al2O3 56%
O
15

m-chloroperbenzoic acid (MCPBA) afforded 13c in 50% yield (from 12). The compound 13c was converted into 14c in 68% yields by successive treatment with (i) pyridinium chlorochromate (PCC)[11] in dichloromethane, (ii) aqueous potassium hydroxide in methanol, and (iii) again PCC. (+)-4-Epinootkatone (15) was prepared from 14c by intramolecular aldol cyclization[6] with hydrogen chloride in acetic acid followed by dehydrochlorination with an activated alumina at 60° in 35% yield.

Apparently, the formation of the lactone 12 may be attributed to the steric hindrance caused by the bridged dimethylmethylene substituent in the catalytic hydrogenation. This disappointing result turned our attention to different approach. We looked for the other possibility to construct α-C(7)-methyl group by lithium metal reduction of the exo-methylene 3. Inspection of the model suggests that the preferential conformation of the enol ether 3 can be drawn as A and hence the thermodynamically controlled reduction of the exo-methylene group should lead to a quasiequatorial 7-methyl group.[12] Furthermore, as depicted in B, the intermediary lithiated carbanion may be stabilized by the chelation with oxygen,[13] which can affect the stereochemical outcome of the protonation process in the expected way (Chart 3-I). These hypotheses require the enol ether 3 which was prepared from 11a as follows.

Chart 3-I



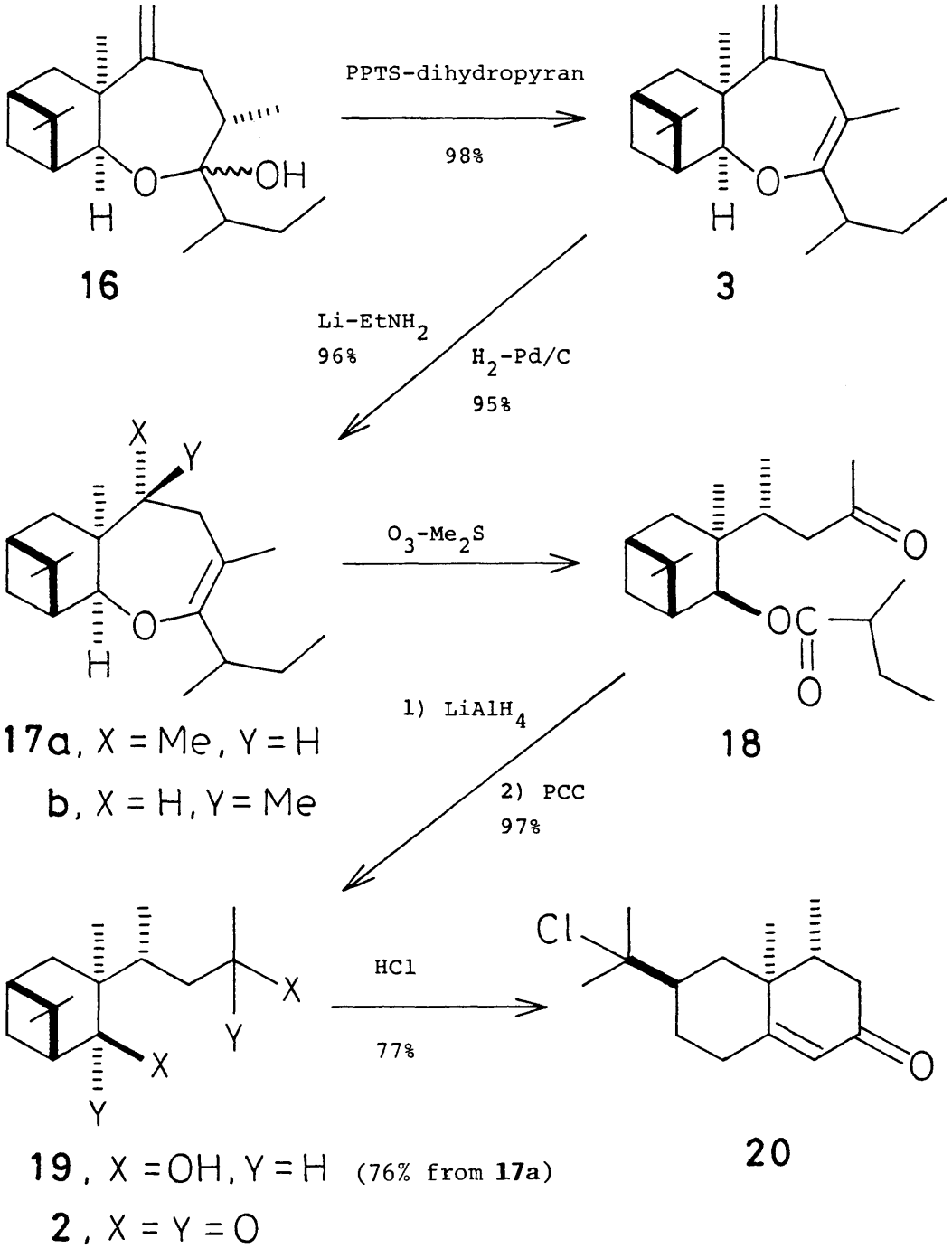
A B

R =

On treatment with an equimolar sec-butyllithium at -78°, 11a was converted into the lactol 16 in 96% yield. Dehydration of 16 was carried out on treatment with pyridinium p-toluenesulfonate (PPTS)[16] in the presence of dihydropyran to give the enol ether 3 in 98% yield. In this reaction it is essential to remove the liberated water with dipyranyl ether due to extreme lability of 3 in the acidic media.

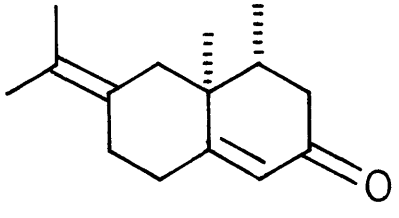
Reduction of 3 with an excess lithium metal dissolved in liquid ethylamine at 0-5° produced 17a in 96% yield. In sharp contrast to the dissolving metal reduction, catalytic hydrogenation of 3 over 10% palladium on carbon afforded 17b in 95% yield.[16] The structural assignment of 17a was carried out by

Scheme 3-IV


PPTS-dihydropyran
98%
16
3
Li-EtNH2
96%
H2-Pd/C
95%
X
Y
O3-Me2S
17a, X = Me, Y = H
b, X = H, Y = Me
18
1) LiAlH4
2) PCC
97%
HCl
77%
Cl
19, X = OH, Y = H (76% from 17a)
2, X = Y = O
20

its conversion to the known diketone 2.[6] Thus, the enolic double bond of 17a was cleaved by ozonolysis and subsequent workup with dimethyl sulfide to afford 18. Reduction of the keto ester 18 with lithium aluminum hydride and subsequent oxidation of 19 with PCC yielded the desired 2 in 74% yield (from 17a), whose IR and ^{1}H NMR spectra were identical with those of an authentic specimen.[17]

Finally, the ketone 2 was converted into (+)-1 in an analogous way as the preparation of its C(4) isomer 15. Thus, cyclization of 2 by the action of hydrogen chloride in acetic acid was attended by the cleavage of cyclobutane ring, giving the hydrogen chloride adduct 20, and subsequent dehydrochlorination of 20 with an activated alumina at 60° in hexane[6,18] furnished the desired (+)-1 along with its C(6) isopropylidene isomer 21 in 54% yield (from 2). The ratio of 1/21 was determined by high performance liquid chromatography (HPLC) to be 91:9 (Scheme 3-IV).



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3.2. EXPERIMENTAL SECTION

The melting points are uncorrected, and the boiling points are indicated without correction by the air-bath temperature. ^1H NMR spectra were obtained on a Hitachi R-24 (60 MHz) or a JEOL FX-100 (100 MHz). Samples were dissolved in $CDCl_3$, and the chemical shifts values are expressed in δ values relative to Me_4Si as an internal standard. Optical rotations were taken on a JASCO DIP-140 digital polarimeter in $CHCl_3$.

Materials. Commerically available (-)-β-pinene (5a) was converted into nopinone [5b: $[\alpha]^{17}_D$ +17.4° (neat)] by the reported procedure.[9]

Methyl (1R,5R)-6,6-Dimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (6a). A suspension of 5b (600 mg, 4.34 mmol) and NaH (209 mg, 8.7 mmol) in dimethyl carbonate (2 ml) was heated to 80-90° for 5 h. The reaction was quenched with aqueous 10% HCl, and the mixture was extracted with benzene-AcOEt (1/1). The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane-AcOEt 7/1) to give 720 mg (92%) of 6a: bp 117° (12.5 mm); $[\alpha]^{20}_D$ +24.4° (c 1.9); IR (neat) 1745 (ester C=O), 1713 (C=O), 1650, 1615 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.89, 0.96 (s, 3H, CH_3),

1.05-2.75 (m, 6H, CH_2, CH), 1.35 (s, 3H, CH_3), 3.35-4.25 (m, $COCHCO_2$), 3.77, 3.79 (s, 3H, OCH_3), 11.90 (brs, C=COH). Found: C, 67.42; H, 8.26. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22.

Methyl (1R,3R,5R)-3,6,6-Trimethyl-2-oxobicyclo[3.1.1]-heptane-3-carboxylate (4). To a suspension of **6a** (2.0 g, 10.2 mmol) and K_2CO_3 (7.4 g, 53.5 mmol) in acetone (70 ml) was added MeI (1.74 g, 12.3 mmol).[19] The mixture was stirred at room temperature for 1 h and was heated to reflux for 24 h, and the solids were filtered off. The filtrate was concentrated and the residue was purified by column chromatography (SiO_2, hexane-AcOEt 5/1) to give 2.07 g (97%) of 4: mp 41-42°; $[\alpha]^{19}_D$ +31.8° (c 1.4); IR (Nujol) 1728 (ester C=O), 1704 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 0.97, 1.35, 1.68 (s, 9H, CH_3), 1.78 (d, J = 11 Hz, 1H, CH_2), 1.96 (d,d, J = 15, 4 Hz, 1H, CH_2), 2.16-2.86 (m, 4H, CH_2, CH), 3.76 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 21.7 (q, C-9), 26.5 (t, C-7), 26.7 (q, C-8), 29.9 (q, C-10), 34.2 (t, C-4), 41.1 (d, C-5), 42.7 (s, C-6), 52.7 (q, OCH_3), 52.9 (d, C-1), 58.7 (d, C-1), 173.8 (s, CO_2), 211.1 (s, C-2). Found: C, 68.39; H, 8.54. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63.

Methyl (1R,3S,5R)-3,6,6-Trimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (7). To a solution of $(i\text{-}C_3H_7)_2NLi$ prepared from a hexane solution of 1.5 M BuLi (0.8 ml, 1.2 mmol) and $(i\text{-}C_3H_7)_2NH$ (133.5 mg, 1.32 mmol) in THF (3 ml) was added a solution of **6b**

(100 mg, 0.66 mmol) in THF (2 ml) at -70°. After stirring at -70° for 1 h and at -10° for 1 h, the mixture was treated with excess gaseous CO_2 for 1 h, and the reaction was quenched with aqueous 5% HCl. Extractive workup followed by esterification of the crude product with CH_2N_2 gave 62 mg (62%) of (1R,3R,5R)-3-methylnopinone [5a] (R_f 0.7, hexane-AcOEt 7/1) and 43 mg (31%) of 7 (R_f 0.48). 7: bp 92-93° (3 mm); $[\alpha]^{20}_D$ +152.5° (c 1.5); IR (neat) 1738 (ester C=O), 1715 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 0.77, 1.35, 1.44 (s, 9H, CH_3), 1.47 (d, t, J = 15, 1.5 Hz, 1H, CH_2), 2.10-2.60 (m, 2H, CH_2), 2.71 (t, J = 5 Hz, 1H, CH), 2.98 (d,d, J = 14, 5 Hz, 1H, CHCO), 3.71 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 22.4 (q, C-9, C-10), 25.0 (t, C-7), 26.4 (q, C-8), 34.7 (t, C-4), 41.2 (d, C-5), 45.6 (s, C-6), 52.4 (s, C-3), 53.0 (q, OCH_3), 58.5 (d, C-1), 175.0 (s, COO), 209.9 (s, C-2). Found: C, 68.50; H, 8.55. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63.

Methyl (1R,2S,3R,5R)-2-Hydroxy-3,6,6-trimethylbicyclo-[3.1.1]heptane-3-carboxylate (8). To a solution of 4 (210 mg, 1.0 mmol) in MeOH (2 ml) was added a solution of $NaBH_4$ (73 mg, 1.9 mmol) in H_2O (0.5 ml) at 5°. The mixture was stirred at room temperature for 12 h, and the reaction was quenched with aqueous 10% AcOH. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 185 mg (87%) of 8: bp 72-73° (0.015 mm); $[\alpha]^{25}_D$ +27.5° (c 2.1); IR (neat) 3520 (OH), 1725, 1700 cm^{-1}

(ester C=O); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.99, 1.23, 1.54 (s, 9H, CH_3), 1.20-2.32 (m, 5H, CH_2, CH), 2.98 (d, J = 14 Hz, 1H, CH), 3.10 (br, 1H, OH), 3.76 (s, 3H, OCH_3), 4.10 (d, J = 4 Hz, 1H, CH-O). Found: C, 67.92; H, 9.42. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50.

(1R,2S,3R,5R)-3-(1-Hydroxy-1-methylethyl)-3,6,6-trimethylbicylo[3.1.1]heptan-2-ol (9a). To a solution of MeMgI prepared from MeI (6.5 g, 45.8 mmol) and Mg (1.0 g, 41.2 mmol) in ether (45 ml) was added a solution of 8 (1.95 g, 9.19 mmol) in ether (10 ml) at 0-5°. After the mixture was heated at 35-40° for 12 h, most of the solvent was removed by distillation. The mixture was heated at 75-80° for 24 h, and the reaction was quenched with aqueous 10% NH_4Cl. Extraction with benzene-AcOEt (1/1) followed by washing, drying (Na_2SO_4), concentration, and purification by column chromatography (SiO_2, hexane-AcOEt 3/1) of the crude product gave 1.66 g (85%) of 9a: mp 98-99° (from hexane); $[\alpha]^{26}_D$ +25.9° (c 1.64); IR (Nujol) 3230 cm^{-1} (OH); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.21 (s, 3H, CH_3), 1.25 (s, 9H, CH_3), 1.30-2.27 (m, 5H, CH_2, CH), 1.46 (s, 3H, CH_3), 2.54 (d, J = 14 Hz, 1H, CH), 3.57 (brs, 1H, OH), 4.27 (d, J = 4 Hz, 1H, CH-O), 4.70 (br, 1H, OH). Found: C, 73.75; H, 11.33. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39.

(1R,2S,3R,5R)-3-(1-Hydroxy-1-methylethyl)-3,6,6-trimethylbicyclo[3.1.1]hept-2-yl Propionate (9b). A solution of 9a (6.2

g, 29.2 mmol) and propionic anhydride (11.4 g, 87.6 mmol) in pyridine (24 ml) was heated at 100° for 8 h. The mixture was poured into cold aqueous 5% $NaHCO_3$ and extracted with benzene-AcOEt (1/1). The usual workup gave 7.4 g (94%) of **9b**: bp 85° (0.0075 mm); $[\alpha]^{26}_D$ +49.5° (c 1.7); IR (neat) 3560 (OH), 1735 cm^{-1} (ester C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 0.90-2.45 (m, 10H, CH_3, CH_2, CH), 1.17 (s, 3H, CH_3), 1.21 (s, 6H, CH_3), 1.24, 1.34 (s, 6H, CH_3), 2.67 (d, $\underline{J}$ = 14 Hz, 1H, CH), 3.45 (brs, 1H, OH), 5.42 (d, $\underline{J}$ = 4 Hz, 1H, CH-O). Found: C, 71.70; H, 10.57. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52.

(1R,2S,3S,5R)-3,6,6-Trimethyl-3-(1-methylethenyl)bicyclo-[3.1.1]hept-2-yl Propionate (10a). To a solution of **9b** (6.2 g, 23.1 mmol) in pyridine (20 ml) was added $SOCl_2$ (4.9 g, 41.3 mmol) at -10°. After stirring at -10° for 3 h and at room temperature for 5 h, the mixture was poured into cold water and extracted with benzene-AcOEt (1/1). The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 10/1) gave 4.9 g (85%) of **10a**: bp 76-77° (0.015 mm); $[\alpha]^{25}_D$ +5.8° (c 1.66); IR (neat) 3070, 1725 (ester C=O), 1635 (C=C), 882 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.93, 1.19, 1.41, 1.67 (s, 12H, CH_3), 0.90-2.45 (m, 7H, CH_2, CH), 1.08 (t, $\underline{J}$ = 8 Hz, 3H, CH_3), 2.65 (d, $\underline{J}$ = 14 Hz, 1H, CH), 4.87, 5.00 (brs, 2H, H_2C=C), 5.26 (d, $\underline{J}$ = 4 Hz, 1H, CH-O); ^{13}C NMR ($CDCl_3$) δ 9.0 (q), 21.0 (q), 23.4 (q), 24.6 (t), 27.0 (q), 28.4

(t), 34.4 (t), 36.3 (q), 38.4 (s), 40.3 (s), 41.3 (d), 45.9 (d), 81.1 (d), 109.5 (t), 148.9 (s), 173.0 (s). Found: C, 76.91; 10.40. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47.

(1R,2S,3S,5R)-3-[(1-Bromomethyl)ethenyl]-3,6,6-trimethyl-bicyclo[3.1.1]hept-2-yl Propionate (10b). A suspension of 10a (1.03 g, 4.11 mmol) and NBS (808 mg, 4.54 mmol) in CCl_4 (15 ml) was gently heated to reflux for 15 h. Concentration in vacuo followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 1.32 g (98%) of 10b: bp 102° (0.015 mm); $[\alpha]^{17}_D$ -60.1° (c 1.9); IR (neat) 3080, 1726 (ester C=O), 1630 cm^{-1} (C=C); ^1H NMR (60 MHz, $CDCl_3$) δ 0.89, 1.19, 1.56 (s, 9H, CH_3), 1.07 (t, J = 7.5 Hz, 3H, CH_3), 1.10-2.75 (m, 8H, CH_2, CH), 3.71, 4.01 (d, J = 11 Hz, 2H, CH_2Br), 5.35 (d, J = 4 Hz, 1H, CH-O), 5.48, 5.56 (brs, 2H, H_2C=C); ^{13}C NMR ($CDCl_3$) δ 8.9 (q), 23.3 (q), 24.5 (t), 26.8 (q), 28.2 (t), 33.2 (t), 34.5 (t), 36.5 (d), 38.0 (s), 41.1 (d), 41.1 (s), 45.6 (d), 81.2 (d), 117.0 (t), 150.0 (s), 173.1 (s). Found: C, 58.24; H, 7.68. Calcd for $C_{16}H_{25}BrO_2$: C, 58.36; H, 7.65.

(1R,2S,5S,8S,10R)-5,8,11,11-Tetramethyl-7-methylene-3-oxatricyclo[8.1.1.$0^{2,8}$]dodecan-4-one (11a). To a solution of lithium N-isopropylcyclohexylamide prepared from a hexane solution of 1.6 M BuLi (3.0 ml, 4.8 mmol) and N-isopropylcyclohexylamine (690 mg, 4.86 mmol) in THF (30 ml) was added a solution of 10b (692 mg, 2.1 mmol) in THF (5 ml) at -70°.

After the mixture was stirred at -50° for 30 min, HMPA (2.5 ml) was added and the mixture was warmed gradually to room temperature over about 2 h. The reaction was quenched with cold aqueous 10% NH_4Cl, and the mixture was extracted with benzene-AcOEt (1/1). The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 470 mg (89%) of **11a**: mp 114-115° (from hexane); $[\alpha]^{22}_D$ -29° (c 0.9); IR (Nujol) 3080, 1730 (lactone C=O), 1635 (C=C), 905 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96, 1.24, 1.51 (s, 9H, CH_3), 1.10-3.16 (m, 9H, CH_2, CH), 1.20 (d, J = 6 Hz, 3H, CH_3), 4.63 (d, J = 4 Hz, 1H, CH-O), 5.07, 5.15 (brs, 2H, H_2C=C); ^{13}C NMR ($CDCl_3$) δ 16.4 (q), 23.1 (q), 24.5 (t), 26.6 (q), 34.3 (q), 34.6 (d), 34.7 (t), 38.1 (s), 39.9 (s), 40.5 (t), 41.2 (d), 46.5 (d), 87.1 (d), 113.4 (t), 147.3 (s), 176.2 (s). Found: C, 77.23; H, 9.92. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74.

(1R,2S,5S,7S,8S,10R)-5,7,8,11,11-Pentamethyl-3-oxatricyclo-[8.1.1.$0^{2,8}$]dodecan-4-one (12). A suspension of **11a** (130 mg, 0.52 mmol) and PtO_2 (30 mg) in AcOEt (5 ml) was treated with excess H_2 at room temperature for 15 h. The mixture was freed from the catalyst and the filtrate was concentrated in vacuo to give 127 mg (97%) of **12**: mp 113-114° (from hexane); $[\alpha]^{24}_D$ +4.1° (c 1.08); IR (Nujol) 1720 cm^{-1} (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 1.13, 1.27, 1.48 (s, 9H, CH_3), 1.20-3.08 (m, 10H, CH_2, CH), 1.19,

1.32 (d, $\underline{J}$ = 6 Hz, 6H, CH_3), 4.74 (d, $\underline{J}$ = 4 Hz, 1H, CH-O); ^{13}C NMR ($CDCl_3$) δ 17.6 (q), 20.7 (q), 21.9 (q), 25.2 (t), 28.0 (q), 32.8 (d), 35.0 (t), 36.5 (t), 36.9 (s), 37.4 (q), 37.9 (s), 42.1 (d), 42.1 (d), 46.6 (d), 87.6 (d), 177.3 (s). Found: C, 76.65; H, 10.66. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47.

(4S)-4-[(1R,2S,3S,5R)-2-Hydroxy-3,6,6-trimethylbicyclo-[3.1.1]hept-2-yl]-2-methylpentanoic Acid (13a). Hydrolysis of 12 (127 mg, 0.5 mmol) in a mixed solvent of MeOH (5 ml) and H_2O (0.5 ml) containing KOH (360 mg, 6.4 mmol) was carried out at 65-70° for 14 h. The mixture was acidified with aqueous 5% HCl and extracted with benzene-AcOEt (1/1). The usual workup gave 124 mg (91%) of 13a: $[\alpha]^{24}_D$ -14.5° (c 1.2); IR (neat) 3600-2500 (COOH), 3420 (OH), 1705 cm^{-1} (COO); ^1H NMR (60 MHz, $CDCl_3$) δ 0.97, 1.08, 1.20 (s, 9H, CH_3), 1.20-2.85 (m, 10H, CH_2, CH), 1.07, 1.21 (d, $\underline{J}$ = 6 Hz, 6H, CH_3), 3.82 (m, 1H, CH-O), 6.44 (br, 2H, OH, COOH). Attempts at further purification for a satisfactory elemental analysis were unsuccessful.

(1R,2S,3S,5R)-3-[(1S)-1,3-Dimethyl-4-oxopentyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (13b). To a solution of 13a (70 mg, 0.26 mmol) in ether (3ml) was added an ethereal 1.05 M MeLi solution (1.25 ml, 1.3 mmol) at 0°. After stirring at room temperature, the reaction was quenched with cold aqueous 10% NH_4Cl, and the mixture was extracted with ether. The usual

worup followed by column chromatography (SiO_2, hexane-AcOEt 7/1) gave 55 mg (79%) of **13b**: bp 95-96° (0.03 mm); $[\alpha]^{29}_D$ +11.4° (c 1.6); IR (neat) 3460 (OH), 1704 cm^{-1} (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 0.97-1.21 (m, 15H, CH_3), 1.10-2.90 (m, 11H, CH_2, CH, OH), 2.13, 2.14 (s, 3H, $COCH_3$), 3.92 (m, 1H, CH-O). Found: C, 76.67; H, 11.36. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35.

(1R,2S,3S,5R)-3-[(1S)-3-Acetoxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (13c). A solution of **13b** (55 mg, 0.21 mmol) and MCPBA (108 mg, 0.63 mmol) in $CDCl_3$ (3 ml) was stirred at 5-10° for 36 h. The mixture was diluted with CH_2Cl_2. The organic layer was washed with aqueous 5% $NaHCO_3$, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane-AcOEt 5/1) to give 41 mg (70%) of **13c**: bp 102-103° (0.03 mm); $[\alpha]^{30}_D$ -14.1° (c 1.13); IR (neat) 3470, 3370 (OH), 1735, 1708 cm^{-1} (ester C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 0.91-1.31 (m, 15H, CH_3), 1.10-2.45 (m, 9H, CH_2, CH), 2.03 (s, 3H, $COCH_3$), 3.69 (brs, 1H, OH), 3.98 (d, *J* = 4 Hz, 1H, CH-O), 4.77-5.31 (m, 1H, CH-O). Found: C, 72.58; H, 10.63. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71.

(1R,3S,5R)-3-[(1S)-3-Acetoxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (14a). To a suspension of PCC (200 mg, 0.93 mmol) and AcONa (82 mg, 1.0 mmol) in CH_2Cl_2 (5 ml) was added a solution of **13c** (44 mg, 0.16 mmol) in CH_2Cl_2 at 0-5°. After

stirring at 5° for 30 min and at room temperature for 2 h, the mixture was diluted with ether. A precipitate was filtered off by passing through a pad of silica gel. The filtrate was concentrated and the residue was purified by column chromatography (SiO_2, hexane-AcOEt 4/1) to give 38 mg (85%) of **14a**: bp 85-86° (0.01 mm); $[\alpha]^{29}_D$ -15.6° (c 1.05); IR (neat) 1735 (ester C=O), 1700 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 0.89 (s, 3H, CH_3), 1.15-2.66 (m, 12H, CH_2, CH), 1.19-1.34 (m, 9H, CH_3), 2.02, 2.04 (s, 3H, $COCH_3$), 4.82-5.18 (m, 1H, CH-O). Found: C, 72.63; H, 10.11. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06.

(1R,3S,5R)-3-[(1S)-3-Hydroxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (**14b**). Similar hydrolysis of **14a** (36 mg, 0.123 mmol) as described for the prepration of **13a** gave 30 mg (91%) of **14b**: bp 85-86° (0.05 mm); $[\alpha]^{18}_D$ -31.5° (c 0.7); IR (neat) 3395 (OH), 1695 cm^{-1} (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 0.90 (s; 3H, CH_3), 1.07-1.35 (m, 6H, CH_3), 1.28, 1.32 (s, 6H, CH_3), 1.40-2.72 (m, 10H, CH_2, CH, OH), 3.66-4.10 (m, 1H, CH-O). Found: C, 75.56; H, 10.96. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99.

(1R,3S,5R)-3-[(1S)-1-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (**14c**). Similar oxidation of **14b** (30 mg, 0.13 mmol) with PCC as described for the preparation of **14a** gave 27 mg (88%) of **14c**: mp 106-107° (lit. [6] 106-107°); $[\alpha]^{30}_D$

+22° (c 1.1); IR ($CHCl_3$) 1697 cm^{-1} (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 0.92 (s, 3H, CH_3), 1.16 (d, $\underline{J}$ = 6.5 Hz, 3H, CH_3), 1.25 (m, 1H, CH), 1.30, 1.33 (s, 6H, CH_3), 1.80-2.85 (m, 8H, CH_2, CH), 2.16 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 16.5 (q), 22.6 (q), 26.2 (t), 26.6 (q), 27.0 (q), 30.4 (q), 36.2 (t), 37.0 (d), 41.9 (d), 42.9 (s), 45.6 (s), 47.7 (t), 60.0 (d), 208.3 (s), 218.2 (s). IR and ^1H NMR spectral data were identical with those of an authentic specimen.[17]

(4S,4aS,6R)-4,4a,5,6,7,8-Hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-2(3H)-naphthalenone (4-epinootkatone, 15). Into a solution of **14c** (44 mg, 0.19 mmol) in AcOH (10 ml) was passed dry gaseous HCl at room temperature for 2 h. After stirring at room temperature for 24 h, the mixture was poured into cold water. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 28 mg (60%) of 4-epinootkatone hydrochloride: bp 98-101° (0.025 mm) [lit.[6] 135-145° (0.2 mm)]; $[\alpha]^{17}_D$ +82.2° (c 0.68); ^{13}C NMR ($CDCl_3$) δ 15.8 (q), 24.6 (q), 29.0 (t), 30.3 (q), 30.7 (q), 32.5 (t), 36.2 (t), 39.2 (d), 39.4 (s), 42.4 (t), 45.2 (d), 73.8 (s), 123.4 (d), 167.1 (s), 199.2 (s). A suspension of 4-epinootkatone hydrochloride (27 mg, 0.106 mmol) and an activated alumina 300 (450 mg) in hexane (2 ml) was heated at 60° for 24 h. The solid was filtered off and the filtrate was concentrated. The residue was purified by column

chromatography (SiO_2, hexane-AcOEt 4/1) to give 13 mg (56%) of **15** which was identical by spectral comparison with those of the reported ones[6]: bp 111-113° (1.5 mm); $[\alpha]^{16}_D$ +83° (c 0.28) (lit.[6] +85°); ^{13}C NMR ($CDCl_3$) δ 15.8 (q), 21.0 (q), 24.5 (q), 32.7 (t), 33.0 (t), 39.1 (d), 39.6 (s), 39.7 (s), 40.0 (d), 42.4 (t), 109.3 (t), 123.5 (d), 148.9 (s), 168.2 (s), 199.4 (s).

(1R,2S,5S,8S,10R)-5,8,11,11-Tetramethyl-7-methylene-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.$0^{2,8}$]dodecan-4-ol (**16**). To a solution of **11a** (186 mg, 0.75 mmol) in THF (7 ml) was added a hexane solution of 1.0 M sec-BuLi (0.78 ml, 0.78 mmol) at -78°. The mixture was stirred at -78° for 45 min, and the reaction was quenched with cold aqueous 10% NH_4Cl. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 7/1) gave 219 mg (96%) of **16**: bp 145-146° (0.025 mm); $[\alpha]^{17}_D$ +12.4° (c 1.4); IR (neat) 3480 (OH), 3080, 1669 (C=O), 1624 (C=C), 885 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.76-1.29 (m, 9H, CH_3), 0.98, 1.21, 1.39 (s, 9H, CH_3), 1.30-3.18 (m, 13H, CH_2, CH, OH), 4.05 (m, 1H, CH-O), 4.97, 5.19 (brs, 2H, H_2C=C). Found: C, 78.48; H, 11.17. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18.

(1R,2S,8S,10R)-5,8,11,11-Tetramethyl-7-methylene-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.$0^{2,8}$]dodec-4-ene (**3**). A solution of **16** (108 mg, 0.35 mmol), dihydropyran (460 mg, 5.5 mmol), and PPTS (5 mg) in CH_2Cl_2 (7 ml) was stirred at room

temperature for 5 h. The reaction was quenched with cold aqueous 5% $NaHCO_3$. Extraction with benzene-AcOEt (1/1) followed by washing, drying (Na_2SO_4), concentration in vacuo, and column chromatograpghy (SiO_2, hexane) gave 99.5 mg (98%) of **3**: bp 81-82° (0.02 mm); $[\alpha]^{18}_D$ -37.5° (c 0.94); IR (neat) 3080, 1680 (C=C), 1628 (C=C), 900 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.83 (t, 3H, CH_3), 0.88 (d, J = 6 Hz, 3H, CH_3), 0.94, 1.24, 1.42 (s, 9H, CH_3), 1.10-3.38 (m, 11H, CH_2, CH), 1.58 (s, 3H, CH_3C=C), 3.88 (d, J = 4.5 Hz, 1H, CH-O), 4.89, 4.99 (brs, 2H, H_2C=C). Found: C, 83.35; H, 11.26. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18.

(1R,2S,7R,8S,10R)-5,7,8,11,11-Pentamethyl-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.$0^{2,8}$]dodec-4-ene (**17a**). To a blue solution of Li (80 mg, 11.4 mmol) in $EtNH_2$ (ca. 12 ml) was added a solution of **3** (156 mg, 0.54 mmol) and t-BuOH (400 mg, 5.41 mmol) in THF (2 ml) at -30°. After the mixture was stirred at -30° for 30 min, additional Li (120 mg, 17.1 mmol) was added. The mixture was stirred at -20 to -10° for 2 h and then allowed to stand at room temperature until most of the $EtNH_2$ was removed. The residue was poured into ice-water and the mixture was extracted benzene-AcOEt (1/1). The usual workup followed by column chromatography (SiO_2, hexane) gave 151 mg (96%) of **17a**: bp 95-96° (0.03 mm); $[\alpha]^{18}_D$ -37.5° (c 0.94); IR (neat) 1682 (C=C), 1457, 1386, 1229, 1080, 1010 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.86

(d, $\underline{J}$ = 6 Hz, 3H, CH_3), 0.99 (t, 3H, CH_3), 0.99, 1.09, 1.23 (s, 9H, CH_3), 1.10-2.95 (m, 12H, CH_2, CH), 1.50 (s, 3H, CH_3C=C), 3.72 (d, $\underline{J}$ = 4 Hz, 1H, CH-O). Found: C, 82.89; H, 11.90. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80.

(1R,2S,7S,8S,10R)-5,7,8,11,11-Pentamethyl-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.$0^{2,8}$]dodec-4-ene (17b). A mixture of 3 (50 mg, 0.17 mmol) and 10% Pd on carbon (30 mg) in AcOEt (5 ml) was treated with excess H_2 gas at room temperature for 12 h. The catalyst was filtered off and the filtrate was concentrated to give 48 mg (95%) of **17b**: bp 84-86° (0.02 mm); $[\alpha]^{15}_D$ -17.0° (c 0.83); IR (neat) 1672 (C=C), 1455, 1225, 1135, 1076, 1015 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.80 (t, 3H, CH_3), 0.87 (d, $\underline{J}$ = 6.5 Hz, 3H, CH_3), 0.91 (d, $\underline{J}$ = 6.5 Hz, 3H, CH_3), 1.10, 1.21, 1.34 (s, 9H, CH_3), 1.15-3.03 (m, 12H, CH_2, CH), 1.52 (s, 3H, CH_3C=C), 3.93 (m, 1H, CH-O). Found: C, 82.80; H, 11.91. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80.

(1R,2S,3S,5R)-3-[(1R)-1-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]hept-2-yl 2-Methylbutyrate (18). Into a solution of **17a** (131 mg, 0.45 mmol) in CH_2Cl_2 (10 ml) and MeOH (4 ml) was passed excess ozone at -78° for 1 h. After the excess ozone was removed by bubbling through with N_2 gas for 30 min, dimethyl sulfide (280 mg, 4.5 mmol) was added. The mixture was stirred at -70° for 1 h and at room temperature for 12 h. Removal of the

solvent followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 109 mg (75%) of **18** (R_f 0.51, Merck F 254, hexane-AcOEt 5/1) and 31 mg of unidentified compound (R_f 0.34). **18**: bp 82-83° (0.02 mm); $[\alpha]^{26}_D$ +34° (c 1.5); IR (neat) 1720 (ester C=O), 1705 cm^{-1} (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 0.82 (t, 3H, CH_3), 0.87 (d, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.06 (d, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.18 (s, 6H, CH_3), 1.20-3.00 (m, 12H, CH_2, CH), 2.06 (s, 3H, $COCH_3$), 3.14 (d, $\underline{J}$ = 4 Hz, 1H, CH-O). Found: C, 74.22; H, 10.68. Calcd for $C_{20}H_{34}O_3$: C, 74.49;, 10.63.

(1R,2S,3S,5R)-3-[(1R)-3-Hydroxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (**19**). To a suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in ether (2 ml) was added a solution of **18** (109 mg, 0.34 mmol) and 31 mg of the unidentified compound obtained above in ether (5 ml) at 0°. The mixture was stirred at 2-5° for 1 h and at room temperature for 2 h, and the reaction was quenched with AcOEt and aqueous 5% $NaHCO_3$. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 2/1) gave 82 mg (76% yield from **17a**) of **19**: mp 96-97°; $[\alpha]^{19}_D$ +27° (c 1.1); IR (Nujol) 3350 (OH), 3280 (OH), 1458, 1136, 1031 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.94 (d, $\underline{J}$ = 7 Hz, 3H, CH_3), 1.04, 1.11 (s, 6H, CH_3), 1.17 (d, $\underline{J}$ = 7 Hz, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.20-2.40 (m, 9H, CH_2, CH), 2.87 (brs, 2H, OH), 3.66-3.98 (m, 1H, CH-O), 4.08 (d, $\underline{J}$ = 4 Hz, 1H, CH-O). Found: C, 74.75; H, 11.55. Calcd

for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74.

(1R,3S,5R)-3-[(1R)-1-Methyl-3-oxobutyl]-3,6,6-trimethyl-bicyclo[3.1.1]heptan-2-one (2). To a suspension of PCC (410 mg, 1.9 mmol) and AcONa (312 mg, 3.5 mmol) in CH_2Cl_2 (7 ml) was added a solution of 19 (65 mg, 0.27 mmol) in CH_2Cl_2 (3 ml) at 0-5°. After stirring at 0-5° for 1 h and at room temperature for 3 h, the mixture was diluted with ether. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 3/1) gave 62 mg (97%) of 2: bp 74-75° (0.025 mm) [lit. [6] 100° (0.1 mm)]; $[\alpha]^{15}_D$ +94° (c 0.5) (lit. [6] +120°); IR ($CHCl_3$) 1710, 1698 cm^{-1} (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 0.92 (d, J = 7 Hz, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.26, 1.32 (s, 6H, CH_3), 1.62-2.90 (m, 8H, CH_2, CH), 2.15 (s, 3H, $COCH_3$), 3.72 (d,d, J = 17, 4 Hz, 1H, COCH); ^{13}C NMR ($CDCl_3$) δ 16.4 (q), 22.7 (q), 24.9 (q), 25.9 (t), 26.4 (q), 30.4 (q), 35.3 (d), 37.0 (t), 41.8 (d), 42.8 (s), 44.8 (s), 47.4 (t), 59.6 (d), 208.3 (s), 219.9 (s). IR and ^1H NMR spectral data were identical with those of the authentic specimen.[17]

(4R, 4aS,6R)-4,4a,5,6,7,8-Hexahydro-6-(1-chloro-1-methyl-ethyl)-4,4a-dimethyl-2(3H)-naphthalenone (20). A solution of 2 (87.8 mg, 0.37 mmol) in AcOH (8 ml) was treated with excess gaseous HCl at room temperature for 24 h. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 73 mg (77%) of 20: mp 84-85° (lit. [6] 84-85.5°); $[\alpha]^{16}_D$ +159.5° (c

0.43) (lit. [5b] +146°, [6] +160°); ^{13}C NMR ($CDCl_3$) δ 15.0 (q), 16.9 (q), 28.1 (t), 30.1 (q), 30.5 (q), 32.6 (t), 39.1 (s), 40.0 (t), 40.4 (d), 42.0 (t), 45.3 (d), 73.7 (s), 124.5 (s), 170.0 (d), 199.0 (s).

(+)-Nootkatone (1). A suspension of **20** (60.4 mg, 0.237 mmol) and an activated alumina 300 (300 mg) in hexane (2 ml) was heated to 60° for 24 h. The precipitates were filtered off and the filtrate was concentrated. The residue was purified by column chromatography (SiO_2, hexane-AcOEt 4/1) to give 39.5 mg (76%) of oil which was shown to be a mixture of (+)-**1** and isonootkatone (**21**) (91:9) by HPLC analysis. The analysis together with their separation were carried out by HPLC (Waters Associates Model 6000A solvent deliverly systems and a Waters Associates Differential Refractometer R-401 detecter, column; μ-Porasil 7.8 mm x 30 cm; hexane-AcOEt 10/1, 1.5 ml/min at room temperature). Analytical sample of (+)-**1** was obtained by the preparative HPLC (R_t 28.8 min): mp 29-30° (from petroleum ether of boiling range 30-70°) (lit. [1a] 36-37°, [4b] 28-30°); $[\alpha]_D^{15}$ +184° (c 0.94) (lit. [1a] +195.5°, [6] +188°). IR, ^1H NMR, and ^{13}C NMR [20] spectral data were identical with those of the authentic sample of (+)-**1**.[21]

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CHAPTER 4

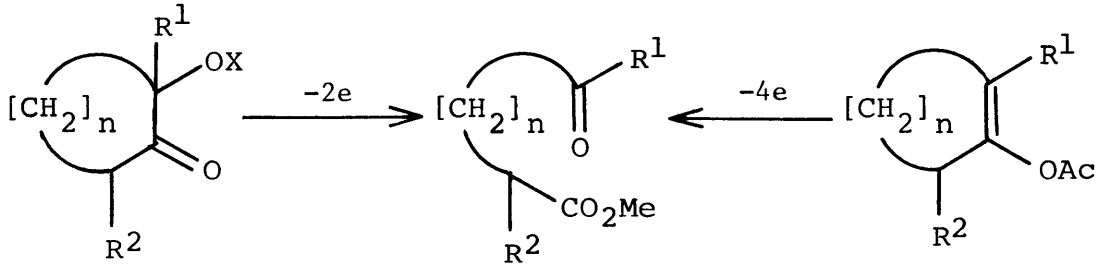
ELECTROOXIDATIVE CLEAVAGE OF CARBON-CARBON LINKAGES

ABSTRACT

A methodology is described for the synthesis of acyclic oxoalkanoates 2 by electrooxidative cleavage of carbon-carbon bonds of 2-oxycycloalkan-1-ols 1 or cycloalkanone enol acetates 3. The reactions smoothly proceed in a MeOH (or MeOH-AcOH)-0.23 M $LiClO_4$-(Pt) system to afford the corresponding keto esters 2. Strong supporting electrolytes such as $LiClO_4$, $LiBF_4$, and CF_3COOLi are extremely effective for the present purpose, whereas ammonium salts such as Et_4NOTs and Et_4NClO_4 are less. The formation of 2 from 1 or 3 is rationalized by assuming the oxidative cleavage of 1,2-diol moiety of an intermediary hemiacetal which is probably produced by the action of an electrochemically generated acid-catalyst under the electrolysis conditions. Synthetic utility of the procedure is exemplified by the facile synthesis of (+)-rose oxide (17).

INTRODUCTION

Oxidative cleavage at the C(1)-C(2) bond of 2-oxy-1-cycloalkanones 1 and cycloalkanone enol acetates 3 is of interest as a possible means of obtaining keto esters 2.[1] Hitherto, the cleavage of carbon-carbon bond of 1 has been carried out by using lead tetraacetate,[2] sodium periodate,[3] and perbenzoic acid.[4] Instead of these chemical methods, we have been interested in preparing 2 from 1 or 3 by electrolysis. Electrochemical carbon-carbon bond cleavage reactions have been investigated on 1,2-diols,[5,6] 2-amino-1-ols,[6] and 1,2-diamines.[7] On the other hand, the electrochemical oxidation of the enol acetates 3 in acetic acid has been shown to give the corresponding α-acetoxy-[8a] and α,β-unsaturated ketones.[8b] We



1a, X = Ac
b, X = H
c, X = Me

2

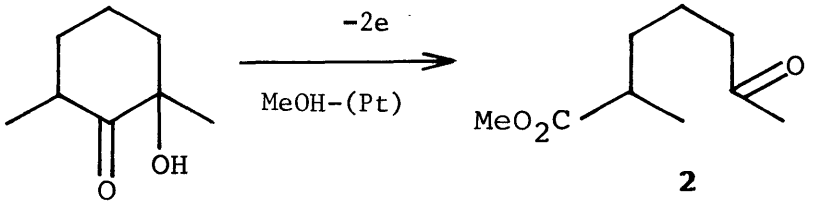
3

disclosed here a novel procedure of the electrooxidative cleavage of carbon-carbon bonds at the C(1)-C(2) position of 1[9] and 3, which can open a significant route to some chiral building blocks.

4.1a. PREPARATION OF OXOALKANOATES FROM 2-OXYCYCLOALKANONES

The electrooxidative cleavage of the carbon-carbon bond of 2-hydroxy ketone **1b** (n = 3, $R^1 = R^2$ = Me) was carried in methanol using 0.23 M $LiClO_4$ as a supporting electrolyte. Passage of 4.2 F/mol of electricity at a constant applied voltage of 20 V (anode potential: 2.00-2.05 V vs. Ag/0.1 M AgCl) afforded the desired **2** (n = 3, $R^1 = R^2$ = Me) in 83% yield. The electrolyses with ammonium salt such as Et_4NOTs and Et_4NClO_4 instead of $LiClO_4$ met with some difficulties in producing the desired **2**, and most of the electrolyses resulted in the recovery of **1b** (Table 4-1). It is likely that dissociation of $LiClO_4$ as a strong electrolyte would provide a stable solvated perchlorate ion along with a lithium cation in methanol, in contrast to the formation of solvated ion pairs from the ammonium salts.[10] If the dissociated perchlorate ion is oriented to the surface of the anode, one might expect the outer Helmholtz layer to act as an acid catalyst.[11] Other lithium salts derived from strong acids

Table 4.1. Electrolysis of **1b** with Various Electrolytes



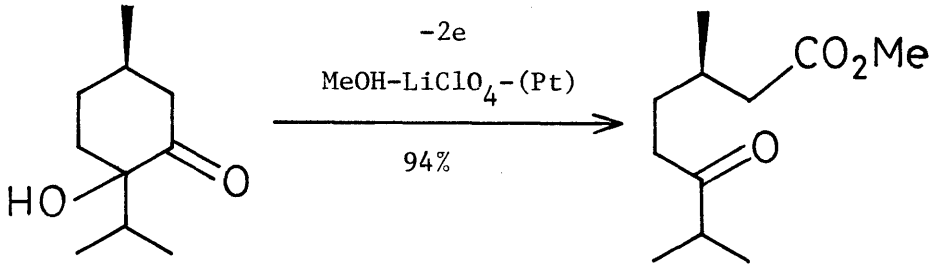
1b **2**

	Electrolyte				
	$LiClO_4$	$LiBF_4$	CF_3CO_2Li	Et_4NOTs	Et_4NClO_4
electricity (F/mol)	4.2	7.4	6.9	5.9	2.7
yield of **2** (%)	83	88	80	recovery	recovery

and bases, i.e., $LiBF_4$ and CF_3CO_2Li can be used for the present purpose. Thus, the electrolysis of 1b (n = 3, R^1 = R^2 = Me) with these electrolytes afforded the corresponding cleavaged products 2 in 80-88% yields.

As shown in Table 4-2, most of the electrolysis of 1 in a MeOH-$LiClO_4$-(Pt) system required 4.2-7.5 F/mol of electricity for the 100% conversion reaction. However, employment of an acidic solvent system consisted of MeOH-AcOH (10/1 V/V) improved the current efficiency as shwon in entry 3. The method could successfully be applied for the preparation of keto ester 5, an enantiomer of (-)-6-oxo-6,7-dihydrocitronellic acid: a constituent of Reunion germanium oil (Pelargonium graveolens).[12] Thus, the electrolysis of 4 was carried out in a MeOH-$LiClO_4$-(Pt) system to give 5 in 94% yield (entry 8).

Scheme 4-I



4 5

Table 4.2. Conditions and Results of Electrooxidative Cleavage of 2-Oxycycloalkanones [a]

entry	Substrate Compd	n	R^1	R^2	Current mA/cm^2	Electricity F/mol	Product (Yield, %)
1	**1b**	3	Me	Me	10.0-15.0	4.2	**2** (83)
2	**1a**	3	Me	H	5.3-11.3	4.5	**2** (82)
3	**1b**	3	Me	Me	4.7-11.3	2.9	**2** (93)[b]
4	**1a**	2	$n\text{-}C_5H_{11}$	H	5.3-11.3	5.5	**2** (82)
5	**1b**	3	$n\text{-}C_5H_{11}$	H	6.3-13.3	5.3	**2** (97)
6	**1b**	4	$n\text{-}C_5H_{11}$	H	6.2-15.5	5.2	**2** (94)
7	**1b**	9	Me	H	5.6-17.5	7.5	**2** (94)
8	**4**				11.0-15.0	5.0	**5** (94)
9	**9**				10.0-11.3	4.8	**10** (84)

a) Unless otherwise noted, electrolyses were carried out in a MeOH-0.23 M $LiClO_4$-(Pt) system under a constant applied voltage of 20 V with platinum electrodes (3 cm^2).

b) Carried out in a mixed solution of MeOH-AcOH (10/1).

4.1b. ELECTROOXIDATIVE CLEAVAGE OF CYCLOALKANONE ENOL ACETATES

The elelctrolysis of enol acetates 3 has been shown to give α-acetoxy- and α,β-unsaturated ketones,[8] but there is no report on the oxidative cleavage of 3. We have found that the enol acetates 3 represent excellent precursors for the electrosynthesis of the oxoalkanoates 2. The electrolysis of 3 (n = 3, R^1 = R^2 = Me) in a MeOH-$LiClO_4$-(Pt) system gave the desired 2 (n = 3, R^1 = R^2 = Me) in poor yield (25%, Table 4-3, entry 1), whereas the electrolysis in a mixed solvent of MeOH-AcOH (10/1 V/V) brought about the improved yield of 2 (up to 72%, entry 2). Other results are shown in Table 4-3.

The product distribution obtained by the electrolysis of 3 (n = 3, R^1 = R^2 = Me) is shown in Figure 4-1. The electrolysis afforded a mixture of 1c (n = 3, R^1 = R^2 = Me, 18%), 6 (14%), 7 (4%), and 2 (n = 3, R^1 = R^2 = Me, 40%) at the stage when 2 F/mol of electricity has been passed. However, prolonged electrolysis increased the yield of 2 (n = 3, R^1 = R^2 = Me) in contrast to the decrease of 1c (n = 3, R^1 = R^2 = Me) and 6. Appararently, the compound 1c (n = 3, R^1 = R^2 = Me) is considered to be the precursors of 2. The formation of 7 and 8 can be explained by assuming the cleavage of double bond of 6.

Table 4-3. Conditions and Results of Electrooxidative Cleavage of Enol Acetates [a]

entry	Substrate **3** n	R^1	R^2	Electricity F/mol	Temp., °C	Yield [b] of **2** (%)
1	3	Me	Me	7.2	24-26	25 [c]
2	3	Me	Me	6.7	2-3	72
3	2	$n\text{-}C_5H_{11}$	H	6.6	2-3	75
4	3	$n\text{-}C_5H_{11}$	H	7.4	2-3	79
5	3	$n\text{-}C_5H_{11}$	H	7.2	2-3	75

a) Unless otherwise noted, electrolyses were carried out in MeOH-AcOH (10/1) solution of 0.23 M $LiClO_4$ under a constant applied voltage of 20 V with platinum electrode (3 cm^2) in a divided cell. b) Based on isolated products in complete conversion of the substrates. c) Electrolyzed in MeOH.

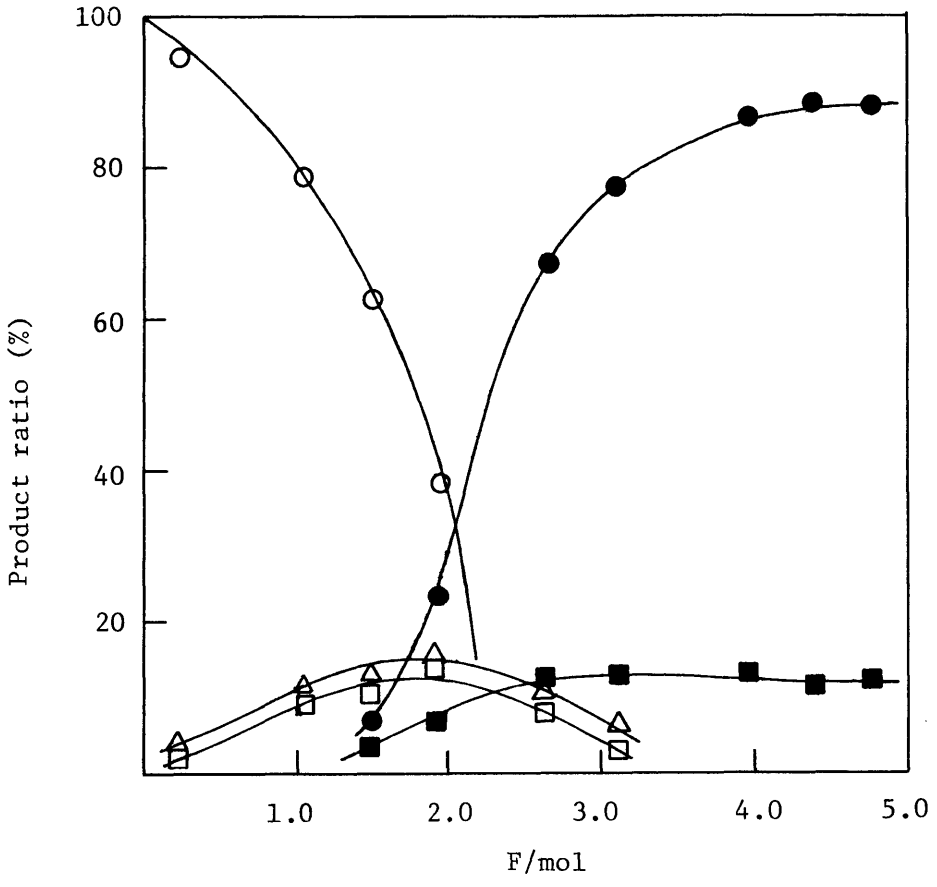
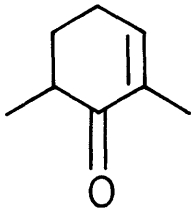
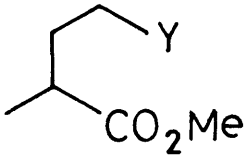


Figure 4-1. Relation between consumed electricity and yields of oxidized products. Reaction conditions are the same as described in Table 4-2. Experimental points are given for **3** (○), **1c** (△), **6** (□), **2** (●), and **7** + **8** (■) (n = 3, R^1 = R^2 = Me).



6

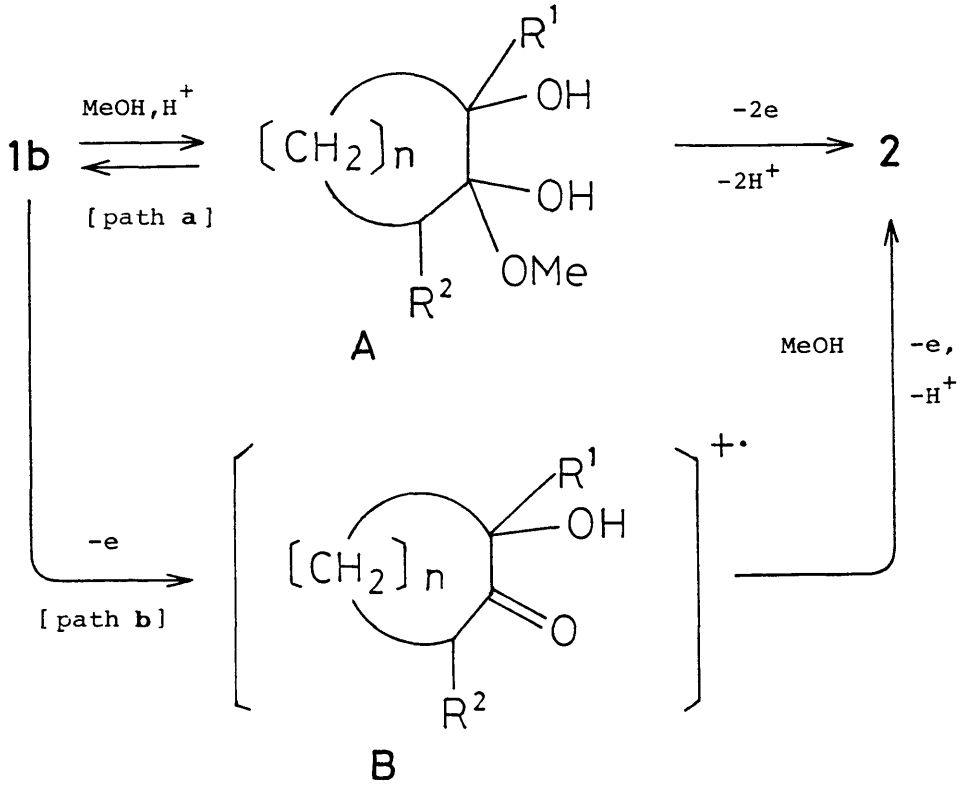


7, Y = CHO

8, Y = CO_2Me

A plausible reaction path for the formation of 2 from 1 is depicted in Scheme 4-II. The employment of a strong electrolyte such as $LiClO_4$ is essential for the formation of 2. Dissociation of $LiClO_4$ would provide a stable solvated perchlorate ion, being oriented to the anode, which act as an acid catalyst. Consequently, the formation of the hemiacetal A [path a] would be expected to occur by an acid-catalyzed equilibration near the

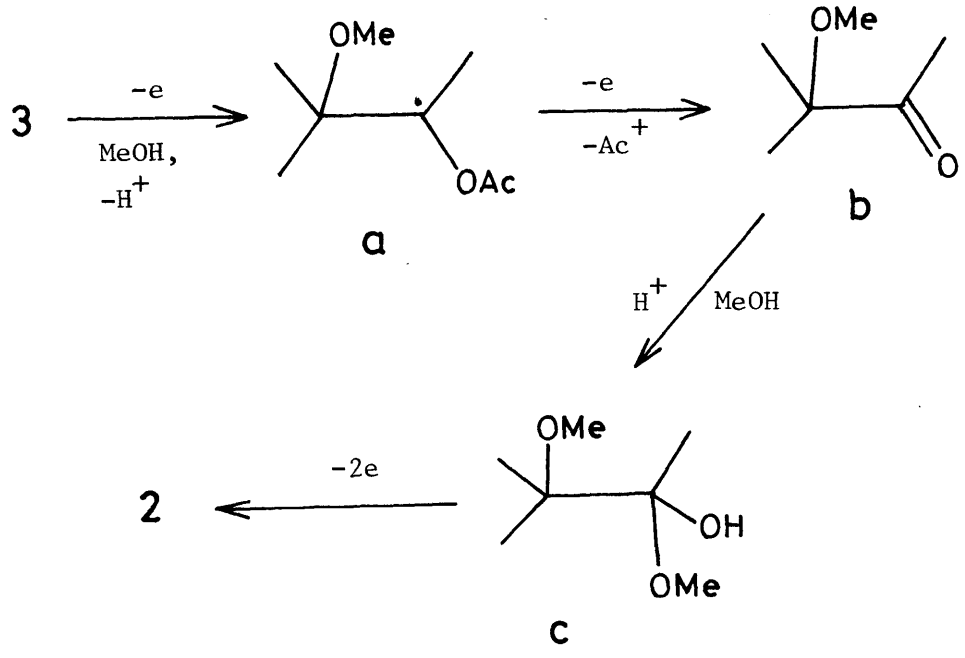
Scheme 4-II



acidic anode in a MeOH-0.23 M $LiClO_4$-(Pt) system. The formation of **2** can readily be rationalized by assuming electrooxidative cleavage of the 1,2-diol moiety of **A**. This process (**A**⟶**2**) occurs more readily than the direct oxidation of the carbonyl group of **1b** [path b].[13]

A variety of the enol acetates **3** are oxidized in a AcOH-Et_4NOTs-(C) system, giving principally α-acetoxy- and α,β-unsaturated ketones.[8] In contrast, the electrolysis of **3** in a MeOH-AcOH (10/1)-$LiClO_4$-(Pt) system affords the cleavage product **2**, exclusively. A plausible mechanism for the formation of **2** in the latter electrolysis system is shown in Scheme 4-III. The intermediate **b** would be produced by the oxidation of radical intermediate **a**, which arises from nucleophilic attack of methanol to a cation radical intermediate derived by one electron discharge of **3** on the anode. Acutally, the electrolysis of **3** (n = 3, R^1 = R^2 = Me) provided the methoxylated **1c** (n = 3, R^1 = R^2 = Me) as an initial reaction product. In analogy with the case of 2-hydroxy ketone **1b**, the hemiacetal **c** produced by acid-catalyzed equilibration with **b** in methanol would undergo further two-electron oxidation to provide the cleavage product **2**.

Scheme 4-III



4.2. SYNTHESIS OF (+)-ROSE OXIDE

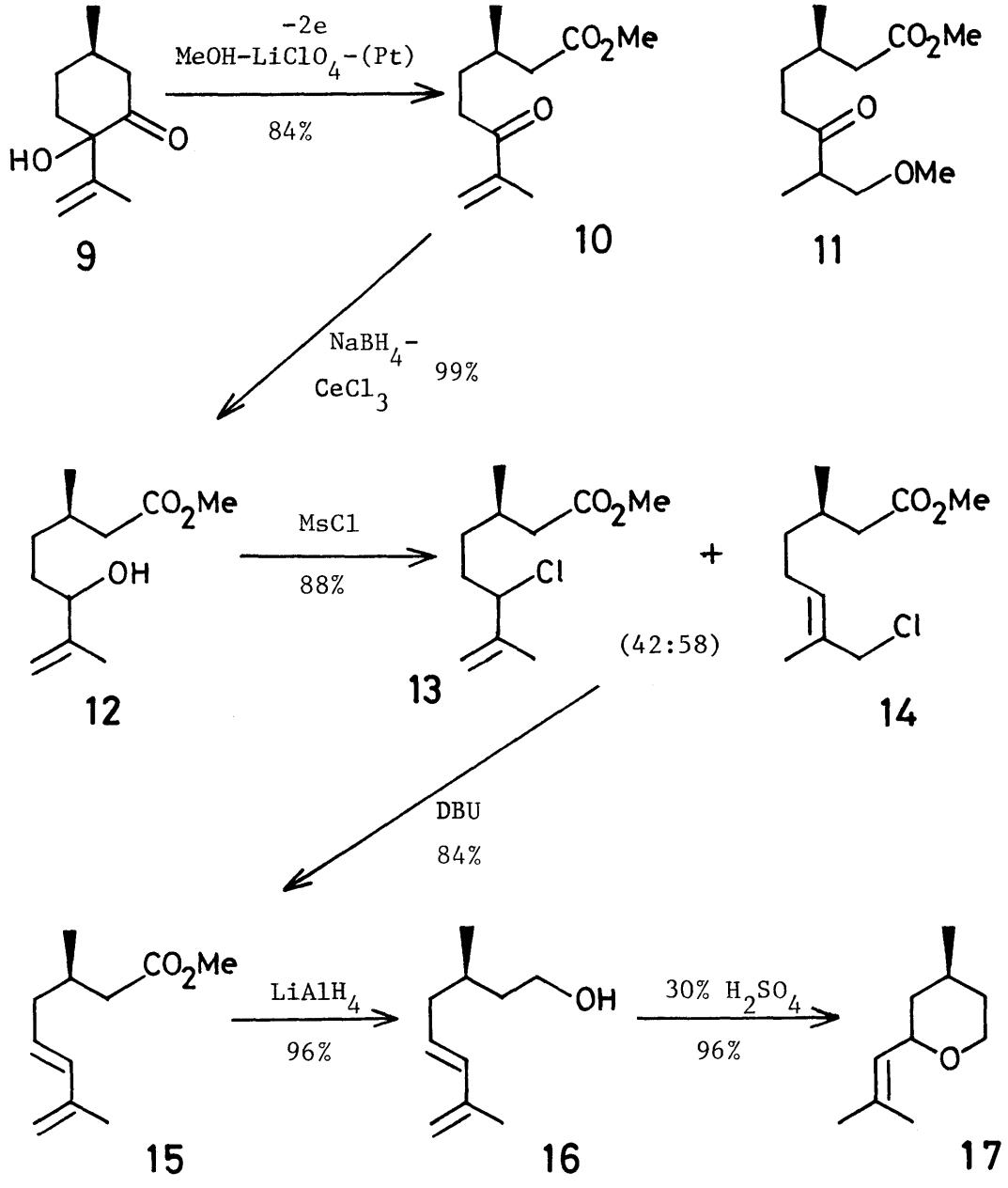
We were stimulated to explore the versatility of the electrolytic cleavage procedure in an attempt to prepare chiral building block **10** for (+)-rose oxide synthesis from readily available natural products. Rose oxide (**17**) is a valuable base material in perfumary [14] and occurs naturally as an ingredient of Bulgarian rose oil[15] and geranium oil.[16] The synthetic pathway leading to (+)-**17**[17] from **9** is outlined in Scheme 4-IV.

The electrooxidative cleavage of **9**, prepared from pulegone oxide,[18] was carried out in a similar manner as the electrolysis of **1**. Thus, the electrolysis of **9** under a constant applied voltage of 20 V with platinum electrodes at 8-10^{o} afforded the desired chiral keto ester **10** in 84% yield. While, the similar electrolysis at 30-33^{o} provided a mixture of **10** (64%) and the methoxylated **11** (23%).

The conversion of the keto ester **10** into (+)-**17** through the diene intermediate **15** was conducted as follows. Reduction of **10** with sodium borohydride in the presence of ceric(III) chloride [19] gave the allyl alcohol **12**, smoothly. Chlorination of **12** with methanesulfonyl chloride in N,N-dimethylformamide (DMF) followed by dehydrochlorination of a mixture of **13** and **14** on treatment with diazabicyclo[5.4.0]undec-7-ene (DBU) [20] at 100^{o} gave the diene **15** in 74% yield, which was in turn reduced with lithium

aluminum hydride (LAH) to the diene alcohol **16**. Cyclization of **16** with 30% sulfuric acid[21] at 17-18° resulted in a 9:1 mixture of (+)-cis- and (+)-trans-rose oxide **17** in 92% yield (from **15**).

Scheme 4-IV


-2e
MeOH-LiClO4-(Pt)
84%
HO
O
CO2Me
O
9
10
11
OMe
NaBH4-
CeCl3
99%
CO2Me
OH
MsCl
88%
CO2Me
Cl
+
(42:58)
CO2Me
Cl
12
13
14
DBU
84%
CO2Me
LiAlH4
96%
OH
30% H2SO4
96%
O
15
16
17

4.3. EXPERIMENTAL SECTION

Melting points are uncorrected and boiling points are indicated by an air-bath temperature without correction. Unless otherwise noted, ^{1}H NMR spectra were determined at 60 MHz with a Hitachi R-24 spectrometer. ^{13}C NMR spectra were recorded with a JEOL FX-100 (25.05 MHz) spectrometer. Optical rotations were taken on a JASCO DIP-140 digital polarimeter with chloroform as a solvent. Elemental analyses were performed in our laboratory.

Materials. Enol acetates 3 were prepared by the method of Bedoukian.[22] According to the reported procedures,[23] 2-hydroxy ketones **1b** were obtained by (1) epoxidation of 3 with monoperphthalic acid in CH_2Cl_2, (2) acid-catalyzed rearrangement of the corresponding epoxide on treatment with acetic acid, giving 2-acetoxy ketones 1a, and (3) alkaline hydrolysis of **1a**. (5R)-2-Hydroxy-2-isopropenyl-5-methylcyclohexanone (9) was prepared by the reported procedure.[18]

Electrolysis Apparatus.[24] A modified H-type two compartment cell (100 ml volume) was used. The anode compartment fitted with a drying tube ($CaCl_2$), a thermometer, and a magnetic stirring bar was divided from the cathode by 1.8 cm diameter glass-frits plate (No 5G). Two platinum electrodes (3 cm^2) were placed paralled to each other 3 cm apart. Regulated dc power was supplied by a

Metronix Model 543B instrument. The integration of the current was carried out by accumulating the amount of electric current recorded on the time-current diagrams.

General Procedure for Electrolysis of 2-Oxycycloalkaonones 1. A solution of 1a (n = 3, R^1 = Me, R^2 = H; 85 mg, 0.5 mmol) and $LiClO_4$ (500 mg) in MeOH (20 ml) was charged into the anode compartment. Into the cathode compartment was charged a solution of $LiClO_4$ (200 mg) in MeOH (16 ml). The mixture was electrolyzed under a constant applied voltage of 20 V at a current of 5.3-11.3 mA/cm^2 at 20-25°. After 4.5 F/mol of electricity was passed, the mixture was concentrated and the residue was taken up in benzene-AcOEt (1/1). The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane-AcOEt 10/1) to give 65 mg (82%) of 2 (n = 3, R^1 = Me, R^2 = H).

Details of the reaction conditions and results are given in Table 4-2 and the physical properties along with spectral data of the electrolysis products are listed in Table 4-4.

General Procedure for Electrolysis of Enol Acetates 3. A solution of $LiClO_4$ (700 mg) in MeOH-AcOH (10/1, 36 ml) was added to both compartments of a divided electrolsis cell. To the anode compartment was added 3 (n = 3, R^1 = R^2 = Me, 128 mg, 0.76 mmol), and the mixture was electrolyzed under a constant applied voltage

of 20 V at a current of 2.2-12.0 mA/cm^2. After 6.7 F/mol of electricity was passed, the solution in the anode compartment was concentrated, neutralized with aqueous 5% $NaHCO_3$, and extracted with hexane-ether (1/1). The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 10/1) gave 94 mg (72%) of 2 (n = 3, $R^1 = R^2$ = Me).

The constituents (Figure 4-1) of the reaction mixture after 2 F/mol of electricity had been passed were separated by preparative GLC (Silicon GE, 10% SE-30 coated on 80-100 mesh Chamelite, 4 mm x 4 m, 120^o, H_2 at 20 ml/min). Retention times and spectral data of the constituents are as follows.

2,6-Dimethyl-2-cyclohexenone (6): R_t = 4.4 min; IR (neat) 1670 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 1.02 (d, J = 7 Hz, 3H, CH_3), 1.20-2.55 (m, 5H, CH_2, CH), 1.79 (m, 3H, CH_3), 6.70 (m, 1H, HC=C).

2-Methoxy-2,6-dimethylcyclohexanone (1c, n = 3, $R^1 = R^2$ = Me): R_t = 4.5 min; IR (neat) 2812, 1700 (C = O), 1170, 1080, 1015, 994 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.17 (d, J = 7 Hz, 3H, CH_3), 1.10-2.40 (m, 7H, CH_2, CH), 1.21 (s, 3H, CH_3), 3.14 (s, 3H, OCH_3).

Methyl 2-Methyl-5-oxopentanoate (7): R_t = 10.4 min; IR (neat) 2720, 1730 (ester C=O), 1720 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 1.20 (d, J = 7.5 Hz, 3H, CH_3), 1.72-2.10 (m, 2H, CH_2),

2.40-2.65 (m, 3H, CH_2, CH), 3.68 (s, 3H, OCH_3), 9.76 (t, J = 1 Hz, 1H, CHO).

Dimethyl 2-Methylglutarate (8): R_t = 17 min; IR (neat) 1745 cm^{-1} (ester C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 1.19 (d, J = 7 Hz, 3H, CH_3), 1.70-2.64 (m, 5H, CH_2, CH), 3.68 (s, 6H, OCH_3).

Methyl (3R)-6-Hydroxy-3,7-dimethyl-7-octenoate (12). To a solution of 10 (60 mg, 0.3 mmol) and aqueous 0.4 M $CeCl_3.7H_2O$ (0.75 ml, 0.3 mmol) in MeOH (2 ml) was added $NaBH_4$ (11.4 mg, 0.3 mmol) at 0°. The mixture was stirred at room temperature for 5 min, and the reaction was quenched with aqueous 10% AcOH. Extraction with AcOEt-benzene (1/1) followed by washing, drying (Na_2SO_4), and concentration in vacuo gave 59.4 mg (99%) of 12: bp 95-97° (2 mm); $[\alpha]^{10}_D$ +8.8° (c 1.6); IR (neat) 3440 (OH), 3070, 1735 (ester C=O), 1640 (C=C), 1199, 1088, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6 Hz, 3H, CH_3), 1.10-2.43 (m, 8H, CH_2, CH, OH), 1.71 (brs, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.05 (t, J = 6 Hz, 1H, CH-O), 4.85-4.93 (m, 2H, H_2C=C). Found: C, 65.92; H, 10.29. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07.

Methyl (3R)-6-Chloro-3,7-dimethyl-7-octenoate (13) and Methyl (3R)-8-Chloro-3,7-dimethyl-6-octenoate (14). To a solution of 12 (95 mg, 0.48 mmol) and Et_3N (220 mg, 1.92 mmol) in DMF (3 ml) was added MsCl (97 mg, 0.96 mmol) at 0°. After stirring at 45-50° for 8 h, the mixture was poured into cold

aqueous 5% $NaHCO_3$ and extracted with benzene-AcOEt (1/1). The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 10/1) gave 91 mg (88%) of a 42:58 mixture of 13 and 14: bp 117-119° (16 mm); $[\alpha]^{17}_D$ +11.1° (c 0.97); IR (neat) 3075, 1735 (ester C=O), 1640 (C=C), 1284, 1198, 1170, 1085, 1006, 904 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6 Hz, 3H, CH_3), 1.10-2.40 (m, CH_2, CH), 1.72, 1.79 (brs, 3H, CH_3), 3.63 (s, 3H, OCH_3), 3.99 (s, CH_2Cl), 4.32 (t, J = 7 Hz, CHCl), 4.85, 4.96 (m, H_2C=C), 5.46 (t, J = 7 Hz, HC=C). Found: C, 60.75; H, 8.75. Calcd for $C_{11}H_{19}ClO_2$: C, 60.41; H, 8.76.

Methyl (3R,5E)-3,7-Dimethyl-5,7-octadienoate (15). A solution of 13 and 14 (30 mg, 0.14 mmol) in DBU (43 mg, 0.28 mmol) was heated at 100° for 3 min. The mixture was extracted with ether-benzene (1/1) and the extract was worked up in the usual manner. The crude product was purified by column chromatography (SiO_2, hexane-ether 10/1) to give 21 mg (84%) of 15: bp 104-106° (16 mm); $[\alpha]^{17}_D$ +19.8° (c 0.83); IR (neat) 3055, 3010, 1735 (ester C=O), 1605 (C=C), 1245, 1198, 1150, 1012, 962, 880 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96 (d, J = 6 Hz, 3H, CH_3), 1.83 (t, J = 1 Hz, 3H, CH_3), 1.60-2.50 (m, 5H, CH_2, CH), 3.64 (s, 3H, OCH_3), 4.88 (brs, 2H, H_2C=C), 5.61 (d,t, J = 15, 7 Hz, 1H, HC=C), 6.15 (d, J = 15 Hz, 1H, HC=C); ^{13}C NMR ($CDCl_3$) δ 18.7 (q), 19.8 (q), 30.7 (d), 40.0 (t), 41.0 (t), 51.4 (q), 114.8 (t),

128.1 (d), 134.9 (d), 142.0 (s), 173.6 (s). Found: C, 72.56; H, 10.15. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95.

(3R,5E)-3,7-Dimethylocta-5,7-dien-1-ol (16). To a suspension of $LiAlH_4$ (21 mg, 0.55 mmol) in THF (4 ml) was added a solution of 15 (50 mg, 0.27 mmol) in THF (1 ml). After stirring at room temperature for 1 h, the reaction was quenched with AcOEt and cold aqueous 5% $NaHCO_3$. Extractive workup followed by column chromatography (SiO_2, hexane-ether 5/1) gave 40 mg (96%) of 16: bp 131-133° (16 mm) [lit. [21] 100° (4 mm)]; $[\alpha]^{17}_D$ +6.7° (c 0.9); IR (neat) 3300 (OH), 3065, 3010, 1372, 1050, 1372, 1050, 960, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 6 Hz, 3H, CH_3), 1.10-2.35 (m, 6H, CH_2, CH, OH), 1.84 (brs, 3H, CH_3), 3.67 (t, J = 6.5 Hz, 2H, CH_2O), 4.85 (brs, 2H, H_2C=C), 5.60 (d,t, J = 15, 7.5 Hz, 1H, HC=C), 6.16 (d, J = 15 Hz, 1H, HC=C).

(+)-Rose Oxide (17). A solution of 16 (50 mg, 0.32 mmol) in 30% H_2SO_4 (1 ml) was stirred at 17-18° for 4 h. Extractive workup followed by column chromatography (SiO_2, hexane-ether 10/1) furnished 48 mg (96%) of a mixture of cis- and trans-17. The ratio of cis/trans of the product was determined to be 9:1 by GLC [Silicon GE SE-30, 10%. 4 mm x 6 m column, H_2 at 15 ml/min, 140°, R_t (min): 8.1 (cis-17), 9.1 (trans-17)]: bp 68-70° (15 mm) [lit. [21] 72-73° (15 mm)]; $[\alpha]^{29}_D$ +39° (c 0.9) (lit. [17] +38.1°); IR (neat) 1440, 1375, 1252, 1172, 1162, 1088, 1072, 1041, 975,

879, 840 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.93 (d, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.00-2.70 (m, 5H, CH_2, CH), 1.70, 1.73 (d, $\underline{J}$ = 1.5 Hz, 6H, CH_3C=C), 3.69 (t,d, $\underline{J}$ = 12, 3 Hz, 1H, CH-O), 3.90-4.14 (m, 2H, CH_2O), 5.24 (d,t, $\underline{J}$ = 8, 1.5 Hz, 1H, HC=C).

Table 4-4. Physical Properties of the Electolysis Products.

Compound	bp (°/mm) [mp (°)]	IR (cm^{-1})[a]	^1H NMR (δ ppm)[b]
2 (n = 3, R^1 = Me, R^2 = H)	110-112°/19 (lit.[25] 140-142°/8)	1735 1710	1.35-1.70 (m, 4H, CH_2), 2.00-2.55 (m, 4H, $COCH_2$), 2.08 (s, 3H, $COCH_3$), 3.61 (s, 3H, OCH_3)
2 (n = 3, R^1 = R^2 = Me	98-100°/6 (lit.[26] 106-107°/11)	1735 1715	1.15 (d, $\underline{J}$ = 6.5 Hz, 3H, CH_3), 1.15-1.70 (m, 4H, CH_2), 2.12 (s, 3H, $COCH_3$), 2.15-2.55 (m, 3H, $COCH_2$, COCH), 3.68 (s, 3H, OCH_3)
2 (n = 2, R^1 = n-C_5H_{11}, R^2 = H)	128-130°/19 (lit.[27] 135-142°/10)	1740 1714	0.88 (m, 3H, CH_3), 1.05-2.05 (m, 8H, CH_2), 2.10-2.55 (m, 6H, $COCH_2$), 3.62 (s, 3H, OCH_3)
2 (n = 3, R^1 = n-C_5H_{11}, R^2 = H)[c]	133-135°/19	1738 1710	0.91 (m, 3H, CH_3), 1.05-1.79 (m, 10H, CH_2), 2.10-2.45 (m, 6H, $COCH_2$), 3.61 (s, 3H, OCH_3)
2 (n = 4, R^1 = n-C_5H_{11}, R^2 = H)[d]	139-141°/19	1739 1711	0.89 (m, 3H, CH_3), 1.05-1.83 (m, 12H, CH_2), 2.11-2.39 (m, 6H, $COCH_2$), 3.58 (s, 3H, OCH_3)

Table 4-4, continued

2 (n = 9, R^1 = Me, R^2 = H)	[29.0-30.5°] (lit.[28] 32.6-33.2°)	1735[e] 1718	1.25 (brs, 16H, CH_2), 2.11 (s, 3H, $COCH_3$), 2.15-2.50 (m, 4H, $COCH_2$), 3.63 (s, 3H, OCH_3)
5[f]	87-89°/3	1739 1710	0.94 (d, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.09 (d, $\underline{J}$ = 7 Hz, 6H, CH_3), 1.10-2.05 (m, 3H, CH_2, CH), 2.12-2.72 (m, 5H, $COCH_2$, COCH), 3.67 (s, 3H, OCH_3)
10[g]	82-84°/2	3100 1735 1675 1630	0.93 (d, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.35-1.95 (m, 3H, CH_2, CH), 1.43 (d, $\underline{J}$ = 1 Hz, 3H, CH_3), 1.98-2.25 (m, 2H, $COCH_2$), 2.36-2.86 (m, 2H, $COCH_2$), 3.57 (s, 3H, OCH_3), 5.65, 5.85 (brs, 2H, $H_2C{=}C$)
11[h]	139-141°/19	1735 1710	0.93 (d, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.06 (d, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.20-2.08 (m, 3H, CH_2, CH), 2.23 (d,d, $\underline{J}$ = 8, 6 Hz, 2H, $COCH_2$), 2.51 (t, $\underline{J}$ = 7 Hz, 2H, $COCH_2$), 2.64-3.00 (m, 1H, COCH), 3.28-3.51 (m, 2H, CH_2O), 3.30 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3)

Footnotes for Table 4-4

[a] Neat unless otherwise stated.

[b] Determined in $CDCl_3$ at 60 MHz.

[c] Found: C, 67.46; H, 10.54. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35.

[d] Found: C, 68.59; H, 10.76. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59.

[e] Nujol.

[f] $[\alpha]^{11}_D$ +9.7° (c 1.3, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 18.3 (q, 2C), 19.5 (q), 30.0 (d), 30.3 (t), 37.8 (t), 40.8 (d), 41.4 (t), 51.4 (q), 173.2 (s), 214.2 (s). Found: C, 65.93; H, 10.25. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07.

[g] $[\alpha]^{10}_D$ +95° (c 0.95, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 17.6 (q), 19.7 (q), 30.1 (d), 31.1 (t), 35.0 (t), 41.4 (t), 51.3 (q), 124.3 (t), 144.4 (s), 173.2 (s), 201.5 (s). Found: C, 66.51; H, 9.36. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15.

[h] $[\alpha]^{10}_D$ +9.1° (c 0.66, $CHCl_3$). Found: C, 62.60; H, 9.76. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63.

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CHAPTER 5

SYNTHESIS

OF

CHIRAL METHYL CHRYSANTHEMATES

ABSTRACT

Syntheses of optically active methyl trans- and cis-chrysanthemates 1 and 26 starting with (+)- and (-)-carvones (7) are described. The key step consists in the electrochemical concurrent cleavage of carbon-carbon bond of α,β-epoxy ketones 5 and 6, giving the corresponding oxoalkanoates 3 and 4. Subsequent methylation of 3 with methylmagnesium iodide and geminal dimethylation of 4 with methyllithium followed by oxidation with chromic acid gives the same δ-lactone 2. Cyclization of 2 with base leads to dihydrochrysanthemolactone 23 which is in turn dehydrated either to the desired 1 by heating with sodium hydroxide or to 26 by treatment with phosphorus oxychloride after hydrolysis.

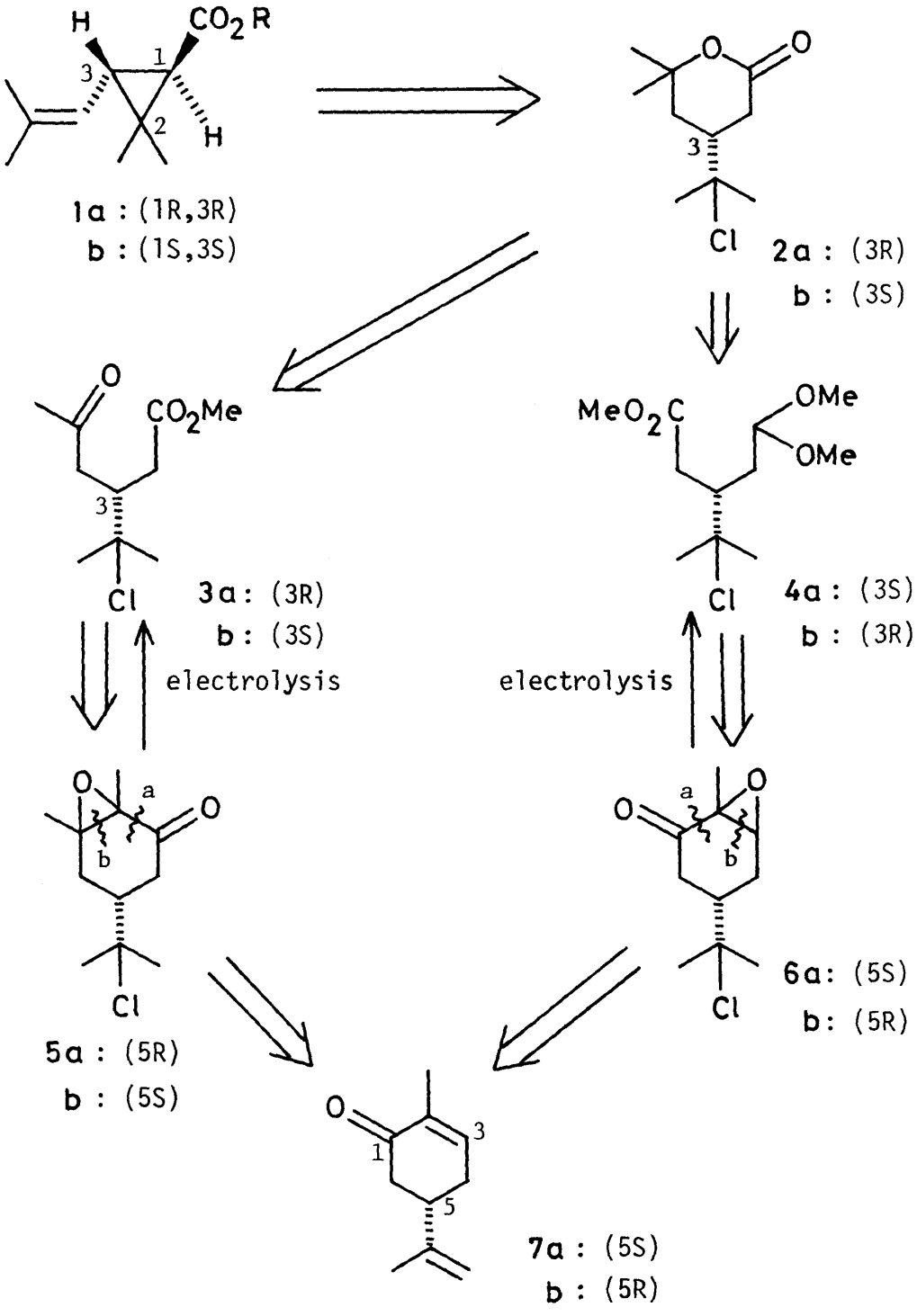
INTRODUCTION

The use of chiral synthons derived from the suitable precursors of natural origin has been of current interest for the synthesis of chiral, biologically active compounds.[1] The synthesis of chiral trans- and cis-chrysanthemic acids 1 and 26 (R = H) is one of the key subjects in insecticide chemistry.[2] Actually, several attempts at the enantioselective synthesis of 1 (R = H) have been tried by i) asymmetric synthesis of the cyclopropane ring by using chiral copper chelate complexes,[3] ii) optical resolution of racemic acids 1 with chiral amines,[4] and iii) use of readily available natural monoterpenes such as (+)-Δ^3-carene[5] and (-)-β-pinene as a chiral template.[6] Among these procedures, the methods based on the last concept are considered to be most attractive strategy in terms of producing the acids 1 (R = H) with high optical purity. However, the reported methods dealing with the conversion of (+)-Δ^3-carene to 1 are disadvantageous due to long sequence of reactions and lower overall yields. We have described an enantioselective synthesis of methyl trans-(3R)-1a (R = Me) and cis-(3R)-26a (R = Me) via a novel electrolytic concurrent cleavage reaction of the α,β-epoxy ketone 5a and 6a derived from (+)-carvone (7a). Similarly, trans-(3S)-1b (R = Me) and cis-(3S)-26b (R = Me) was also

prepared from (-)-carvone (**7b**). The structural formulas shown in the following schemes are depicted as enantiomers starting from (5S)-**7a**.

The synthetic design for the target molecule **1** from **7** is outlined in Scheme 5-I wherein the C(5) carbon of **7** is incorporated intact into the requisite C(3) position of **1**. The crucial step in this approach is the double cleavage of carbon-carbon bond at the postions **a** and **b** of **5** and **6** for preparing the keto esters **3** and **4**. The key intermediate **2**, a precursor of the target, may be easily obtained by either methylation at the terminal acetyl group of **3** or geminal methylation of the ester group of **4**. The merit of the present approach, therefore, depends upon the success of electrooxidative carbon-carbon bond cleavage of α,β-epoxy ketones **5** and **6**.[7]

Scheme 5-I


H
CO2R
1
2
3
1a : (1R,3R)
b : (1S,3S)
O
O
3
Cl
2a : (3R)
b : (3S)
MeO2C
OMe
OMe
4a : (3S)
b : (3R)
electrolysis
O
CO2Me
3a : (3R)
b : (3S)
electrolysis
a
b
5a : (5R)
b : (5S)
6a : (5S)
b : (5R)
1
3
5
7a : (5S)
b : (5R)

5.1. SYNTHESIS OF METHYL TRANS- AND CIS-CHRYSANTHEMATES FROM (+)- AND (-)-CARVONES

Both enantiomer of α,β -epoxy ketones 5 were independently prepared from **7a** and **7b** (Scheme 5-II). Thus, methylation of 7 was followed by oxidation with chromic acid [8] to give the enone 9. The desired 5 was obtained in 63-64% overall yields (from 7) by hydrochlorination of 9 and subsequent epoxidation of 10 with alkaline hydrogen peroxide. The epoxy ketones 6 were smoothly prepared from 7 by hydrochlorination [9] and subsequent epoxidation [10] in ca. 75% yield.

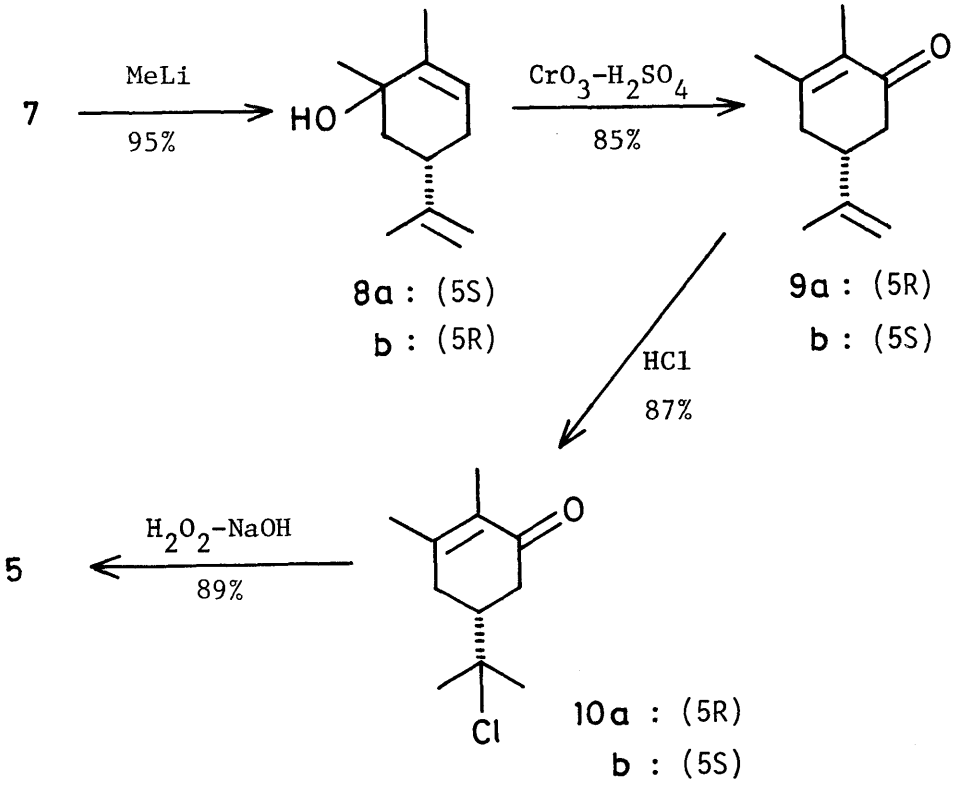
The electrolysis of **5a** was carried out in a MeOH- or MeOH-AcOEt (7/1)-0.047 M $LiClO_4$-(Pt) system at a constant current of 30 mA/cm^2 under an applied voltage of 6.0-7.0 V (anode potential: 2.10-2.23 V vs. Ag/0.1 M AgCl). As shown in entry 1 (Table 5-1), the passage of 45 F/mol of electricity in methanol yielded the desried **3a** in 90% yield. The employment of a co-solvent system consisted of MeOH-AcOEt (7/1) improved the current efficiency strikingly (entry 2). The significant improvement of the current efficiency in the co-solvent system may be the result of increased solubility of 5 in the solution. The results from the electrolysis of **5b** utilizing equal amounts of electricity (entries 3 and 4) demonstrate that the co-solvent system is

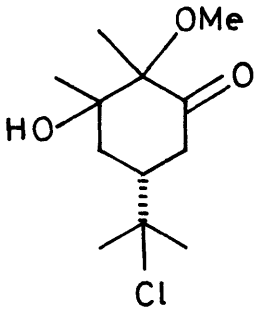
Table 5-1. Conditions and Results of Electrochemical Cleavage of **5**, **11**, **12**, **14**, and **15** [a]

entry	substrate	solvent [b]	electrolyte	current mA/cm^2	electricity F/mol [c]	product, yield [d] (%)
1	**5a**	A	$LiClO_4$	27-30	45	**3a** (90)
2	**5a**	B	$LiClO_4$	30	12	**3a** (87)
3	**5b**	A	$LiClO_4$	30	12	**3b** (52) + **5b** (32)
4	**5b**	B	$LiClO_4$	30	12	**3b** (86)
5	**5a**	B	$LiBF_4$	30	28	**3a** (85)
6	**5b**	B	CF_3CO_2Li	30	27	**3b** (16) + **5b** (68)
7	**5b**	A	Et_4NOTs	6-7	23	**5b** (28) + **11b** (46) + **12b** (15) [e]
8	**11b**	A	$LiClO_4$	30	8	**3b** (94)
9	**12b**	A	$LiClO_4$	30	6	**3b** (96)
10	**14a**	A	$LiClO_4$	20	10	**4a** (87)
11	**15a**	A	$LiClO_4$	20	10	**4a** (87)
12	**15b**	A	H_2SO_4	8	5	**4b** (20) + **18b** (44) [f]

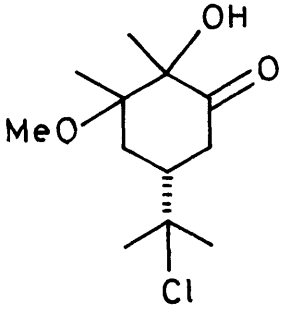
[a] Unless otherwise noted, electrolyses were carried out under an applied voltage of 6.5-11.5 V (entries 1-6) or at 3.0-6.0 V (entries 8-12) with platinum electrodes (3 cm^2) in an undivided cell. [b] Solvents: A = MeOH, B = MeOH-AcOEt (7/1). [c] Faradays/mol during the preparative run. [d] Based on isolated products in complete conversion of 0.5-3.5 mmol of the substrates. [e] Carried out in a divided cell under a constant applied voltage of 20 V. [f] Carried out with carbon electrodes.

Scheme 5-II





11a: (5R)
b: (5S)



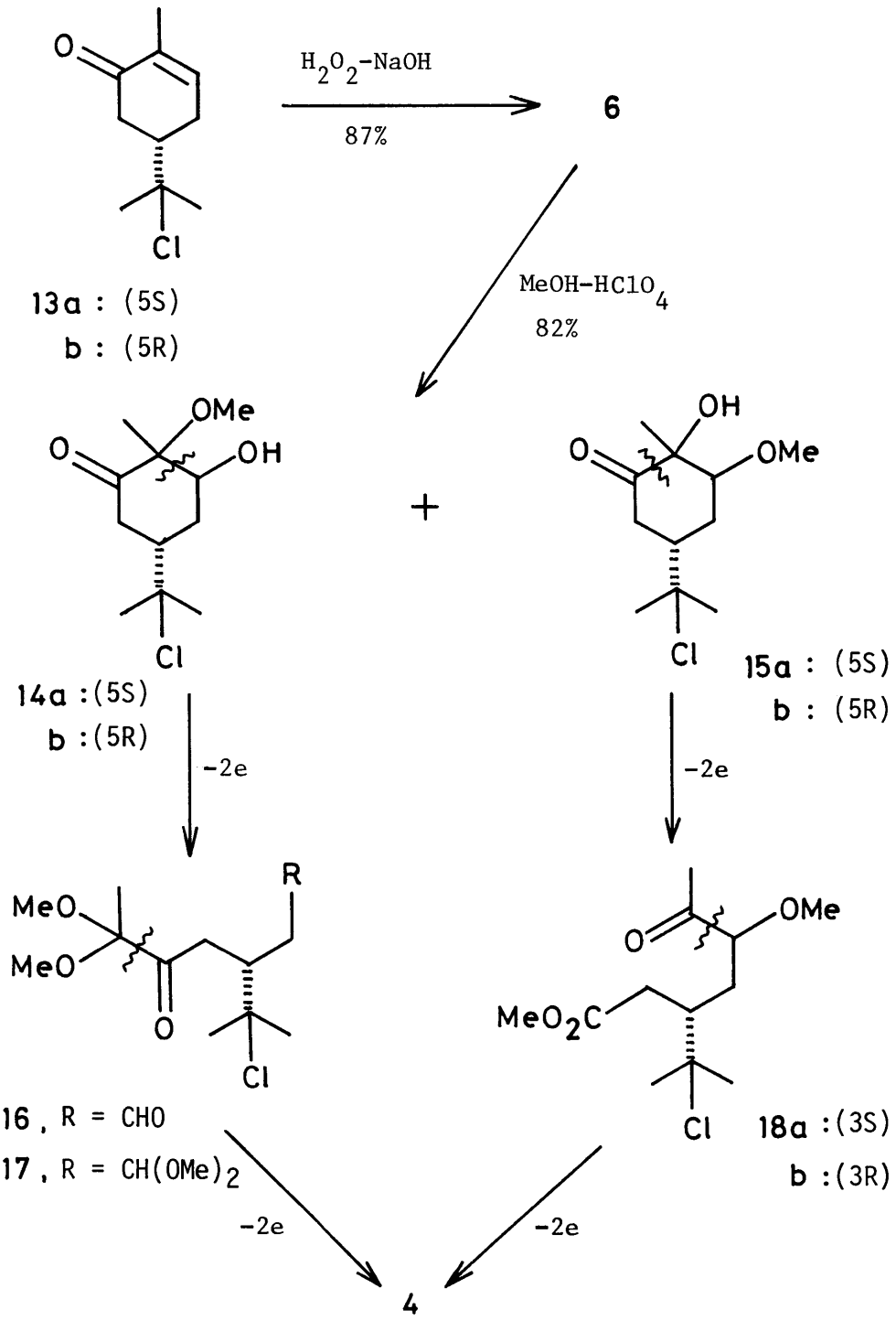
12a : (5R)
b : (5S)

favorable for producing **3b**.

Particularly noteworthy is the effect of the supporting electrolyte. In the preceding Chapter 4, we discussed the role of strong electrolytes, i.e., $LiClO_4$, $LiBF_4$, and CF_3CO_2Li, in methanol in the electrooxidative cleavage of carbon-carbon bonds of 2-oxycycloalkanones.[11] A similar effect of strong electrolytes was observed in the cleavage reaction of the α,β-epoxycycloalkanone system. As shown in entries 1, 2, 4, and 5, use of $LiClO_4$ or $LiBF_4$ as a supporting electrolyte facilitated the formation of **3**. While, lithium trifluoroacetate was less effective in producing **3b** (entry 6). In contrast, the electrolysis of **5b** with Et_4NOTs produced the epoxy ring opening products **11b** (46%) and **12b** (15%) together with the starting material **5b** (28%) (entry 7). However, the electrolysis of **11b** and **12b** with $LiClO_4$ in the same way as the case of **5b** afforded **3b** in 94-97% yields (entries 8 and 9).

Cleavage of the carbon-carbon bond of the compounds **11b** and **12b** in a MeOH-$LiClO_4$-(Pt) system occurs with less electricity than the electrolysis of **5b**, suggesting that the electrochemical cleavage reaction can easily proceed after the opening of the oxirane ring of **5b** by an acid-catalyzed methanolysis near the surface of the anode. The electrooxidative carbon-carbon bond cleavage of **6**, which lacks the C(3) methyl group of **5**, did not

Scheme 5-III


H2O2-NaOH
87%
6
MeOH-HClO4
82%
13a : (5S)
b : (5R)
14a : (5S)
b : (5R)
15a : (5S)
b : (5R)
-2e
-2e
16 , R = CHO
17 , R = CH(OMe)2
18a : (3S)
b : (3R)
-2e
-2e
4

proceed under the same electrolysis conditions used for **5**. However, the electrolysis of **14a** and **15a**, prepared by an acid-catalyzed hydrolysis of **6a**, in MeOH-$LiClO_4$-(Pt) system gave the desired **4a** in 87% yield (Scheme 5-III).

The profiles of the product ratios in relation to passed electricity in the electrolysis of **14b** and **15b** are shown in Figures 5-1 and 5-2, respectively. Figure 5-1 reveals that the yield of **16b** [13] (anode potential: 2.25-2.35 V vs. Ag/0.1 M AgCl) reached a maximum when ca. 2.5 F/mol of electricity was passed in the oxidation of **14b** at the anode potential of 2.00-2.15 V vs. Ag/0.1 M AgCl. The potential gap between **14b** and **16b** (ca. 0.20-0.25 V) can facilitate the accumulation of the intermediate **16b** in the initial electrolysis stage. In contrast, cleavage of carbon-carbon bonds of **15b** suppresses the accumulation of **18b** in the media due to the proximity of their oxidation potentials (**15b**: 2.00-2.10 V; **18b**: 2.00-2.15 V vs. Ag/0.1 M AgCl) as shown in Figure 5-2. On the other hand, the electrolysis of **15b** with sulfuric acid in methanol afforded **18b** as a major product (44%) along with a small amount of **4b** (20%) (entry 12).

The last stage of the synthesis were accomplished in a manner as described in Scheme 5-IV. Treatment of enatiomers (3R)-**3a** and (3S)-**3b** with methylmagnesium iodide at -20^{o} afforded 82% yield of (3R)-δ-lactone **2a** and 83% yield of (3S)-δ-lactone

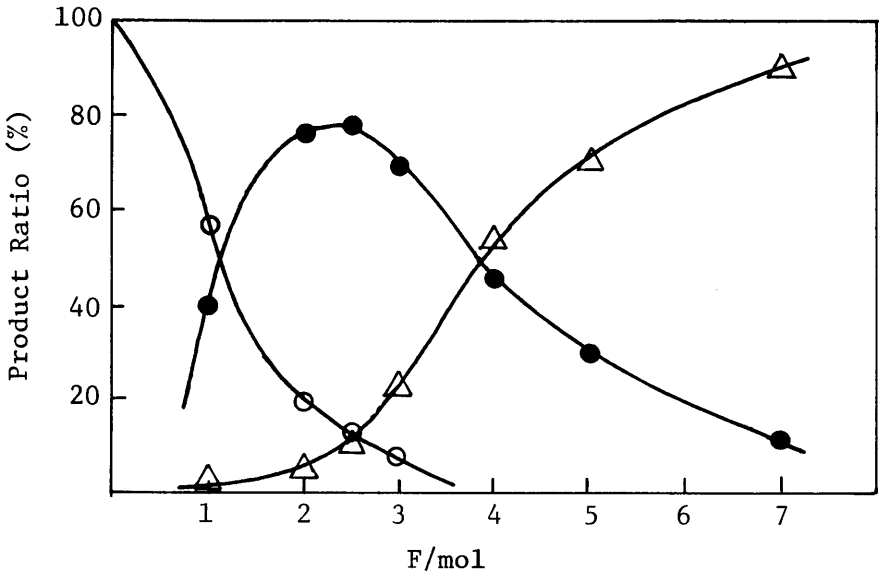


Figure 5-1. Plots of product ratio of the electrooxidation of **14b** (○) against passed electricity (F/mol) at a current of 20 mA/cm^2. Experimental points are given for **16b** (●) and **4b** (△).

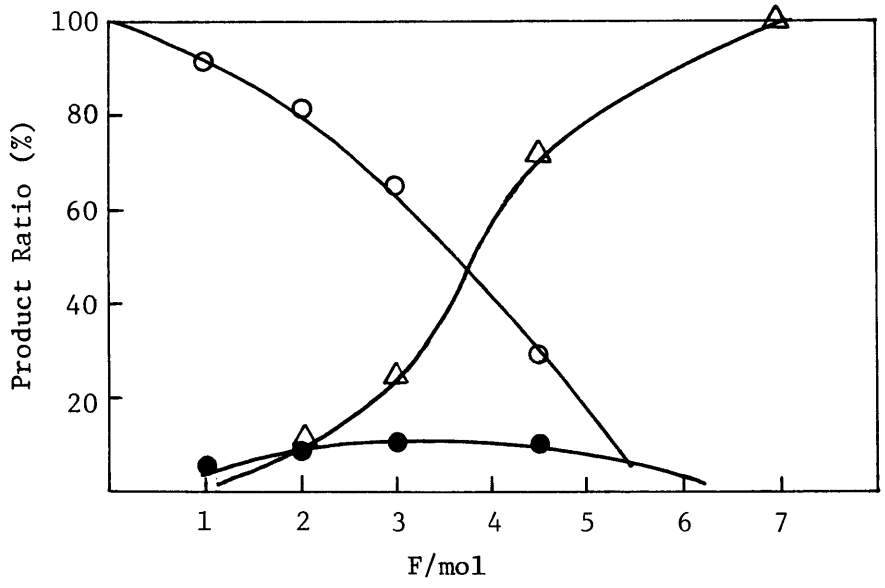
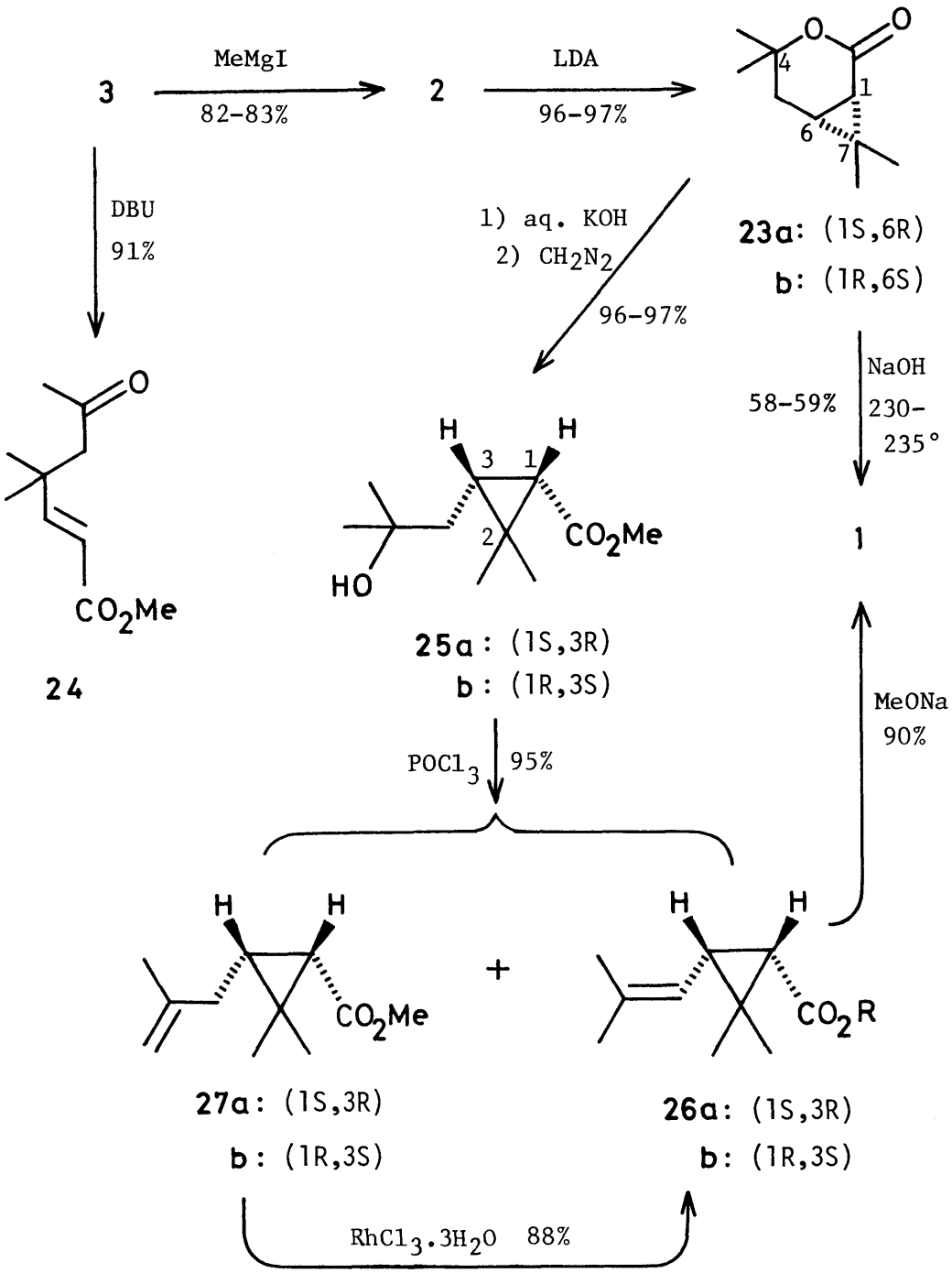


Figure 5-2. Plots of product ratio of the electrooxidation of **15b** (○) against passed electricity (F/mol) at a current of 4 mA/cm^2. Experimental points are given for **18b** (●) and **4b** (△).

2b, respectively. However, the reaction of 3 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene gave the enone 24, exclusively. The latter reaction may proceed by initial formation of cyclopropane ring with DBU followed by ring opening with the same base.[14] Cyclization of δ-lactone 2 with lithium diisopropylamide yielded (1S,6R)-23a (97%) and (1R,6S)-23b (96%). The direct conversion of the lactone 23 into the desired trans-isomers 1 (R = Me) was carried out according to the reported procedure.[5c] Thus, heating of 23a and 23b with sodium hydroxide at 230-235° in diethylene glycol and subsequent esterification of the reaction products with diazomethane gave (1R,3R)-1a (R = Me, 58%) and (1S,3S)-1b (R = Me, 59%) together with a small amount of 26 (R = Me, 8%) and 27 (7%).

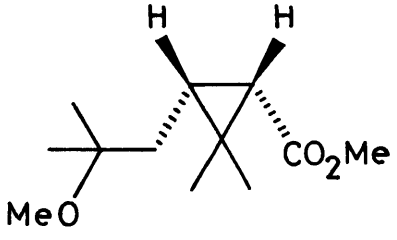
An alternative route to the δ-lactone 2 from the acetal ester 4 was examined (Scheme 5-V). Methylation of enantiomer (3S)-4a and (3R)-4b with methyllithium at -60 to -35° was followed by acidic workup in methanol to give the pyranyl ether 19. Hydrolysis of 19 and subsequent oxidation of the lactol 20 with chromic acid gave 2 (51% overall yields from 4a and 4b, respectively). A second route to 2 involves hydrolysis of (3S)-4a and (3R)-4b to give the somewhat unstable aldehyde 21 which was in turn oxidized with chromic acid to 22. The half-ester 22 was alkylated with methyllithium to afford 4 in 51% overall

Scheme 5-IV


3
MeMgI
82–83%
2
LDA
96–97%
DBU
91%
1) aq. KOH
2) CH_2N_2
96–97%
23a: (1S,6R)
b: (1R,6S)
58–59%
NaOH
230–235°
1
24
25a: (1S,3R)
b: (1R,3S)
$POCl_3$
95%
MeONa
90%
27a: (1S,3R)
b: (1R,3S)
26a: (1S,3R)
b: (1R,3S)
$RhCl_3.3H_2O$ 88%

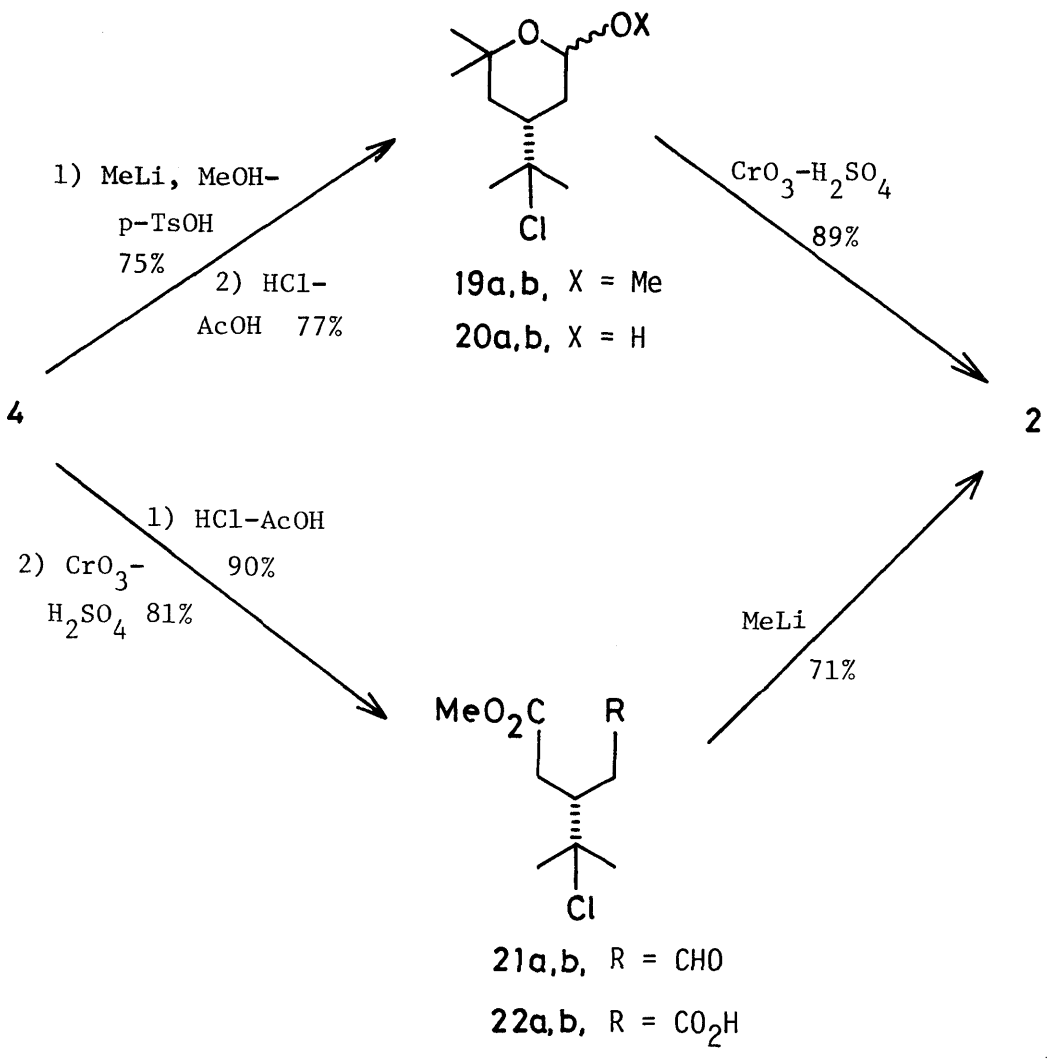
yields.

As shown in Scheme 5-IV, methyl (+)- and (-)-cis-chrysanthemates 26 (R = Me) were prepared from (1R,6S)- and (1S,6R)-23. Hydrolysis of 23 with potassium hydroxide in methanol and subsequent esterification with diazomethane afforded 25 which was in turn dehydrated with phosphorus oxychloride in hexamethylphosphoric triamide (HMPA)[15] to give a 1:2 mixture of 26 (R = Me) and 27 in 91% yield (from 23). Isomerization of the double bond of 27 was carried out on treatment of the mixture of 26 (R = Me) and 27 with rhodium trichloride as a catalyst[16] at 100° in isopropanol to give 26 (R = Me) in 88% yield. HPLC analysis of the products revealed that both (+)- and (-)-26 (R = Me) are contaminated with less than 4% of their corresponding trans-isomer (1S,3S)- and (1R,3R)-1 (R = Me), respectively. However, the same treatment of a 1:2 mixture of 26b (R = Me) and 27 in methanol resulted in a 47:53 mixture of 26b (R = Me) and 28b in 98% yield. The cis-isomer 26 (R = Me) can be smoothly converted into the corresponding trans-isomer 1 (R = Me) on treatment with sodium methoxide.[5a,d]



28a : (1S,3R)
b : (1R,3S)

Scheme 5-V


1) MeLi, MeOH-
p-TsOH
75%
2) HCl-
AcOH 77%
19a,b, X = Me
20a,b, X = H
CrO_3-H_2SO_4
89%
4
2
1) HCl-AcOH
90%
2) CrO_3-
H_2SO_4 81%
MeLi
71%
MeO_2C R
Cl
21a,b, R = CHO
22a,b, R = CO_2H

5.2. EXPERIMENTAL SECTION

Melting points are uncorrected and boiling points are indicated by an air-bath temperature without correction. Unless otherwise noted, ^{1}H NMR spectra were determined at 60 MHz with a Hitachi R-24 spectrometer and ^{13}C NMR spectra were recorded with a JEOL FX-100 (25.05 MHz) spectrometer. The chemical shift values are expressed in δ values relative to Me_4Si as an internal standard. Optical rotations were taken on a JASCO DIP-140 digital porarimeter with chloroform as a solvent.

Electrolysis Apparatus. An undivided cell was equipped with a gas lead pipe, a stirring bar, a thermometer, and two platinum foil electrodes (3 cm^2) being placed parallel to each other 4 mm apart. The vessel was immersed in an ice-water bath at 2-5°.

(5R)-5-Isopropenyl-2,3-dimethyl-2-cyclohexenone (9a). To a solution of 7a [17] (2.0 g, 13.3 mmol) in ether (10 ml) was added an ethereal 1.1 M MeLi (13.2 ml, 14.5 mmol) at -30°. The mixture was stirred at 0° for 1 h, and the reaction was quenched with cold 10% NH_4Cl. Extraction with ether followed by washing with brine, dring (Na_2SO_4), and evaporation of the solvent gave 2.1 g (95%) of (5S)-8a. Without further purification, this material was dissolved in ether (39 ml) and to this solution was added a solution of CrO_3 (3.4 g, 34 mmol) in 5% H_2SO_4 (34 ml) at 0°. The

mixture was stirred at 0^{o} for 1 h and diluted with water. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was distilled at 74^{o} (10 mm) to give 1.85 g (85%) of (5R)-9a whose analytical sample (R_t 4.5 min) was obtained by preparative GLC (Silicon GE SE-30, 10%. 3 mm x 4 m. carrier gas H_2 at 42 ml/min, 145^{o}); $[\alpha]^{26}_{D}$ -104.5^{o} (c 2.1); IR (neat) 3055, 1662 (C=O), 1650 (C=C), 1635 (C=C), 889 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (brs, 6H, CH_3), 1.94 (s, 3H, CH_3), 2.10-2.85 (m, 5H, CH_2, CH), 4.73 (brs, 2H, H_2C=C). Found: C, 80.26; H, 9.67. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82.

Similarly, (5S)-9b was obtained in 81% yield from 7b: bp 74^{o} (10 mm); $[\alpha]^{26}_{D}$ $+103.5^{o}$ (c 2.1). Found: C, 80.49; H, 9.76. Calcd for $C_{11}H_{16}O$: C, 80.44; C, 9.82.

(5R)-5-(1-Chloro-1-methylethyl)-2,3-dimethyl-2-cyclohexenone (10a). Into a solution of (5R)-9a (58 mg, 0.35 mmol) in ether (6 ml) was passed dry gaseous HCl at $0-5^{o}$ for 4 h. The mixture was poured into cold aqueous $NaHCO_3$ and extracted with ether. The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 62 mg (87%) of (5R)-10a: bp $130-132^{o}$ (4 mm); $[\alpha]^{23}_{D}$ -103.3^{o} (c 1.0); IR (neat) 1665 (C=O), 1638 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 6H, CH_3Cl), 1.76, 1.95 (s, 6H, CH_3), 1.95-2.85 (m, 5H, CH_2, CH). Found: C, 65.98; H, 8.63. Calcd for $C_{11}H_{17}ClO$: C, 65.83; H, 8.54.

Similarly, (5S)-10b was obtained in 87% yield from (5S)-9b: bp 119-121° (2.5 mm); $[\alpha]^{21}_{D}$ +103.5° (c 1.3). Found: C, 65.65; H, 8.49. Calcd for $C_{11}H_{17}ClO$: C, 65.83; H, 8.54.

(5R)-5-(1-Chloro-1-methylethyl)-2,3-epoxy-2,3-dimethylcyclohexanone (5a). To a solution of (5R)-10a (46 mg, 0.23 mmol) and aqueous 6 M NaOH (0.021 ml) in MeOH (5 ml) was added 30% H_2O_2 (0.07 ml). The mixture was stirred at 2-5° for 2 h and at room temperature for 1 h. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 7/1) gave 44 mg (89%) of (5R)-5a: mp 109-110° (from hexane); $[\alpha]^{25}_{D}$ +49° (c 1.7); IR (Nujol) 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.42, 1.47, 1.52, 1.59 (s, 12H, CH_3), 1.20-2.75 (m, 5H, CH_2, CH); ^{13}C NMR ($CDCl_3$) δ 11.5 (q), 19.4 (q), 30.5 (q), 30.7 (q), 31.7 (t), 38.6 (t), 39.8 (d), 63.4 (s), 64.3 (s), 72.4 (s), 205.6 (s). Found: C, 61.18; H, 7.97. Calcd for $C_{11}H_{17}ClO_2$: C, 60.97; H, 7.91.

Similarly, (5S)-5b was obtained in 89% yield from (5S)-10b: mp 109-110° (from hexane); $[\alpha]^{25}_{D}$ -49.2° (c 1.8). Found: C, 61.13; H, 8.07. Calcd for $C_{11}H_{17}ClO_2$: C, 60.97; H, 7.91.

(5S)-5-(1-Chloro-1-methylethyl)-2,3-epoxy-2-methylcyclohexanone (6a). Similar epoxidation of 13a [9] ($[\alpha]^{30}_{D}$ +43.1° (c 4.22), 138 mg, 0.74 mmol) as described for the preparation of 5a gave 130 mg (87%) of 6a: mp 73.5° (from hexane); $[\alpha]^{23}_{D}$ -64.2° (c 3.8); IR (Nujol) 1700 (C=O), 1370, 1235, 1112, 884, 810 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.20-2.80 (m, 5H, CH_2, CH), 1.40, 1.53, 1.59 (s, 9H, CH_3), 3.48 (m, 1H, CH-O). Found: C, 59.43; H, 7.35. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.46.

Similarly, (5R)-**6b** was obtained in 87% yield from **13b** [9] ($[\alpha]_D^{30}$ -43° (c 3.73)): mp 73.5-74.0° (from hexane); $[\alpha]_D^{19}$ +64.5° (c 4.0). Found: C, 59.53; H, 7.60. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.46.

(5S)-5-(1-Chloro-1-methylethyl)-3-hydroxy-2-methoxy-2-methylcyclohexanone (**14a**) and (5S)-5-(1-Chloro-1-methylethyl)-2-hydroxy-3-methoxy-2-methylcyclohexanone (**15a**). A mixture of **6a** (200 mg, 0.99 mmol) and 70% $HClO_4$ (0.1 ml) in MeOH (3 ml) was stirred at room temperature for 12 h. The reaction was quenched with aqueous $NaHCO_3$ and the mixture was extracted with benzene-AcOEt (1/1). The usual workup gave 190 mg (82%) of a mixture of **14a** and **15a** (R_f 0.32, Merck F254, hexane-AcOEt 2/1).

Separation of **14a** and **15a** via Their Tetrahydropyranyl Ethers. A solution of **14a** and **15a** (209 mg, 0.89 mmol), dihydropyran (209 mg, 2.5 mmol), and PPTS (10 mg) in CH_2Cl_2 (2 ml) was stirred at room temperature for 12 h. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 176 mg (62%) of the THP ether of **14a** (R_f 0.65 and 0.55) and 68.6 mg (24%) of the THP ether of **15a** (R_f 0.4). Subsequent hydrolysis of the each THP ether with PPTS by stirring in EtOH at 60° for 10

h gave 14a (90%) and 15a (85%), respectively. 14a: bp 94-95° (0.02 mm); $[\alpha]^{23}_{D}$ -17.5° (c 3.3); IR (neat) 3460 (OH), 2814, 1715 (C=O), 1395, 1377, 1150, 1125, 1075, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H, CH_3), 1.55 (s, 6H, CH_3), 1.65-2.65 (m, 5H, CH_2, CH), 2.37 (brs, 1H, OH), 3.12 (s, 3H, OCH_3), 4.03 (m, 1H, CH-O). Found: C, 56.45; H, 8.31. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.16.

15a: bp 77-78° (0.02 mm); $[\alpha]^{29}_{D}$ -61.5° (c 4.2); IR (neat) 3460 (OH), 1708 (C=O), 1382, 1364, 1135, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.50-2.70 (m, 5H, CH_2, CH), 1.57, 1.60 (s, 6H, CH_3), 3.05-3.35 (m, 1H, CH-O), 3.50 (s, 3H, OCH_3), 3.96 (br, 1H, OH). Found: C, 56.39; H, 8.33. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.16.

Similarly, 14b and 15b were obtained in 45 and 16% yields from 6b. 14b: bp 94-95° (0.02 mm); $[\alpha]^{27}_{D}$ +17.4° (c 2.32). Found: C, 56.45; H, 8.21. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.16.

15b: bp 77-78° (0.02 mm); $[\alpha]^{20}_{D}$ +62.6° (c 3.1). Found: C, 56.42; H, 8.26. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.16.

(5S)-5-(1-Chloro-1-methylethyl)-3-hydroxy-2-methoxy-2,3-dimethylcyclohexanone (11b) and (5S)-5-(1-Chloro-1-methylethyl)-2-hydroxy-3-methoxy-2,3-dimethylcyclohexanone (12b). A similar acid-catalyzed methanolysis of 5b as described above gave a

mixture of **11b** (39%) and **12b** (55%). **11b**: bp 91-93° (0.04 mm); $[\alpha]^{17}_{D}$ -3.6° (c 1.7); IR (neat) 3430 (OH), 2820, 1717 (C=O), 1370, 1040, 915, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22, 1.30, 1.58, 1.59 (s, 12H, CH_3), 1.50-2.76 (m, 6H, CH_2, CH, OH), 3.12 (s, 3H, OCH_3). Found: 58.08; H, 8.74. Calcd for $C_{12}H_{21}ClO_3$: C, 57.94; H, 8.51.

12b: mp 53.0-54.0° (from hexane); $[\alpha]^{17}_{D}$ -4.36° (c 0.9); IR (Nujol) 3440, 3320 (OH), 1712 (C=O), 1372, 1148, 1038, 798 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10, 1.41, 1.57, 1.61 (s, 12H, CH_3), 1.50-2.22 (m, 3H, CH_2, CH), 2.55-2.76 (m, 2H, CH_2CO), 3.41 (s, 3H, OCH_3), 3.96 (s, 1H, OH). Found: C, 58.18; H, 8.61. Calcd for $C_{12}H_{21}ClO_3$: C, 57.94; H, 8.51.

General Procedure for Electrolysis of α,β-Epoxycyclohexanone Analogues. A solution of (5R)-**5a** (750 mg, 3.46 mmol) in MeOH (14 ml) and AcOEt (2 ml) containing $LiClO_4$ (80 mg) as a supporting electrolyte was electrolyzed under a constant current of 30 mA/cm^2 (applied voltage: 6.0-8.0 V; cell voltage: 2.10-2.23 V vs. Ag/0.1 M AgCl) at 2-5°. After 12 F/mol of electricity was passed, the mixture was concentrated and the residue was taken up in benzene-AcOEt (1/1). The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 6/1) gave 665 mg (87%) of (3R)-**3a**: bp 71-73° (2.5 mm); $[\alpha]^{17}_{D}$ +4.28° (c 1.1); IR (neat) 1739 (ester C=O), 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$)

δ 1.59 (s, 6H, CH_3), 2.05-3.10 (m, 5H, CH_2, CH), 2.21 (s, 3H, $COCH_3$), 3.67 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 30.0 (q), 30.7 (q), 31.2 (q), 36.3 (t), 42.0 (d), 45.6 (t), 51.8 (q), 73.3 (s), 170.3 (s), 206.6 (s). Found: C, 54.59; H, 7.82. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.77.

Similarly, (3S)-3b was obtained in 88% yield by the electrolysis of (5S)-5b: bp 71-73° (2.5 mm); $[\alpha]^{10}_D$ -4.24° (c 1.7). Found: C, 54.60; H, 7.75. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.77.

Details of the reaction conditions and results are given in Table 5-1 and physical properties along with spectral data of the electrolysis products are as follows.

Methyl (3S)-3-(1-Chloro-1-methylethyl)-5,5-dimethoxypentanoate (4a): bp 78-79° (0.02 mm); $[\alpha]^{29}_D$ -0.6° (c 3.04); IR (neat) 2804, 1732 (ester C=O), 1432, 1385, 1369, 1192, 1152, 1110, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25-2.70 (m, 5H, CH_2, CH), 1.57 (s, 6H, CH_3), 3.30 (s, 6H, OCH_3), 3.68 (s, 3H, OCH_3), 4.41 (t, J = 6 Hz, 1H, CH-O); ^{13}C NMR ($CDCl_3$) δ 30.5 (q), 30.8 (q), 35.0 (t), 36.5 (t), 43.5 (d), 51.7 (q), 52.8 (q), 53.7 (q), 74.0 (s), 104.0 (d), 173.5 (s). Found: C, 52.25; H, 8.23. Calcd for $C_{11}H_{21}ClO_4$: C, 52.28; H, 8.38.

(3R)-4b: bp 78-79° (0.02 mm); $[\alpha]^{29}_D$ +0.6° (c 2.4). Found: C, 52.52; H, 8.48. Calcd for $C_{11}H_{21}ClO_4$: C, 52.28; H, 8.38.

(5R)-5-(1-Chloro-1-methylethyl)-2,2,7,7-tetramethyoxy-heptan-3-one (17b): bp 95-98° (0.03 mm); $[\alpha]^{28}_{D}$ -1.1° (c 1.8); IR (neat) 2810, 1710 (C=O), 1370, 1125, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10-3.00 (m, 5H, CH_2, CH), 1.37 (s, 3H, CH_3), 1.50, 1.55 (s, 6H, CH_3), 3.20, 3.22, 3.24, 3.29 (s, 12H, OCH_3), 4.32 (t, J = 6 Hz, 1H, CH-O). Found: C, 54.22; H, 8.87. Calcd for $C_{14}H_{27}ClO_5$: C, 54.10; H, 8.76.

Methyl (3R)-3-(1-Chloro-1-methylethyl)-5-methoxy-6-oxo-heptanoate (18b): bp 75-78° (0.02 mm); $[\alpha]^{28}_{D}$ -44.2° (c 1.7); IR (neat) 2810, 1735 (ester C=O), 1708 (C=O), 1435, 1374, 1108, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25-2.75 (m, 5H, CH_2, CH), 1.57 (s, 6H, CH_3), 2.17 (s, 3H, $COCH_3$), 3.34 (s, 3H, OCH_3), 3.61 (d,d, J = 12, 4 Hz, 1H, CH-O), 3.68 (s, 3H, OCH_3). Found: C, 54.61; H, 8.17. Calcd for $C_{12}H_{21}ClO_4$: C, 54.44; H, 8.00.

(3R)-3-(1-Chloro-1-methylethyl)-5-methylhexan-5-olide (2a). To a solution of (3R)-3a (100 mg, 0.45 mmol) in ether (5 ml) was added a solution of MeMgI, prepared from MeI (160 mg, 1.13 mmol) and Mg (22 mg, 0.9 mmol) in ether (3 ml), at -20°. The mixture was stirred at -20° for 20 min, and the reaction was quenched with aqueous NH_4Cl. Extraction with benzene-AcOEt (1/1) followed by washing, drying (Na_2SO_4), concentration, and purification by column chromatography (SiO_2, hexane-AcOEt 6/1) gave 76 mg (82%) of (3R)-2a: mp 86-87° (from hexane); $[\alpha]^{20}_{D}$ +15° (c 1.5); IR

(Nujol) 1718 cm^{-1} (lactone C=O); ^1H NMR ($CDCl_3$) δ 1.25-2.85 (m, 5H, CH_2, CH), 1.39, 1.48 (s, 6H, CH_3), 1.57, 1.59 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 27.4 (q), 29.9 (q), 30.4 (q), 30.8 (q), 31.6 (t), 36.2 (t), 41.1 (d), 71.5 (s), 81.1 (s), 170.7 (s). Found: C, 58.80; H, 8.59. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.37.

Similarly, (3S)-2b was obtained in 83% yield from (3S)-3b: mp 86-87° (from hexane); $[\alpha]^{17}_D$ -15.2° (c 1.3). Found: C, 58.80; H, 8.50. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.37.

Methyl (E)-4,4-Dimethyl-6-oxo-2-heptenoate (24). A solution of 3a (136 mg, 0.62 mmol) and DBU (240 mg, 1.56 mmol) in toluene (3 ml) was heated at 110° for 5 h. Concentration followed by column chromatography (SiO_2, hexane-AcOEt 4/1) gave 103 mg (91%) of 24: bp 102-103° (23 mm); IR (neat) 1720 (ester C=O), 1704 (C=O), 1650 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.16 (s, 6H, CH_3), 2.09 (s, 3H, $COCH_3$), 2.52 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 5.75 (d, J = 16 Hz, 1H, HC=C), 7.05 (d, J = 16 Hz, 1H, HC=C). Found: C, 65.11; H, 8.75. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75.

(1S,6R)-4,4,7,7-Tetramethyl-3-oxabicyclo[4.1.0]heptan-2-one (Dihydrochrysanthemolactone, 23a). To a solution of (3R)-2a (36.4 mg, 0.18 mmol) in THF (3 ml) was added a solution of LDA prepared from a hexane solution of 1.6 M BuLi (0.28 ml, 0.45 mmol) and (i-C_3H_7)$_2$NH (46.5 mg, 0.46 mmol) in THF (4 ml). The mixture was stirred at -78° for 5 min and at room temperature for

1 h, and the reaction was quenched with dilute aqueous HCl. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 3/1) gave 29 mg (97%) of (1S,6R)-23a: mp 82-83° (from hexane) (lit.[5b] 82-83°); $[\alpha]^{25}_D$ -77.3° (c 1.4) (lit.[5b] -72°, [5c] -77.24°); ^{13}C NMR ($CDCl_3$) δ 15.9 (q), 22.7 (d), 24.4 (q), 26.2 (s), 27.1 (q), 27.3 (d), 28.9 (q), 30.2 (t), 83.2 (s), 170.9 (s).

Similarly, (1R,6S)-23b was obtained in 96% yield from (3S)-2b: mp 82-83° (from hexane) (lit.[5a] 83°); $[\alpha]^{22}_D$ +77.6° (c 1.8) (lit.[5a] +77°).

Methyl (+)-trans-Chrysanthemate [(1R,3R)-1a, R = Me]. Direct dehydration of the lactone 23 was performed according to the method by Dev and Sobti.[5c] A mixture of (1S,6R)-23a (100 mg, 0.6 mmol) and NaOH (109 mg, 2.7 mmol) in diethylene glycol (3 ml) was heated to 230-235° for 7 h. The mixture was diluted with ether, and poured onto dilute HCl and crushed ice. Extractive workup and esterification of the products with CH_2N_2 in ether gave 79 mg (73%) of a mixture of (1R,3R)-1a (R = Me, 79.2%), (1S,3R)-27a (9.8%), and (1S,3R)-26a (R = Me, 11%). The analysis together with their separation was carried out by HPLC (column: μ-Poracil, 7.8 mm x 30 cm; hexane-AcOEt 80/1, 1.5 ml/min at room temperature). 1a (R = Me, R_t 16.8 min): bp 97-99° (10 mm)[lit.[5c] 120-125° (5 mm)]; $[\alpha]^{23}_D$ +20.7° (c 1.1) (lit.[18] +20.74°,[5c]

+13.27°); ^{13}C NMR ($CDCl_3$) δ 18.5 (q), 20.4 (q), 22.2 (q), 25.5 (q), 28.6 (s), 32.8 (d), 34.7 (d), 51.4 (q), 121.1 (d), 135.5 (s), 173.0 (s). IR and ^1H NMR spectral data were identical with those reported.[19]

Similarly, (-)-trans isomer (1S,3S)-**1b** (R = Me) was obtained in 59% yield from (1R,6S)-**23b**: bp 98-99° (10 mm); $[\alpha]^{22}_D$ -20.8° (c 1.0) [lit.[20] -19° (EtOH)].

(4R)-4-(1-Chloro-1-methylethyl)-2-methoxy-6,6-dimethyltetrahydropyran (**19a**). To a solution of **4a** (700 mg, 2.77 mmol) in ether (8 ml) was added an ethereal 0.95 M MeLi (6.9 ml, 6.6 mmol) at -60°. The mixture was warmed gradually to -35° over about 30 min, and the reaction was quenched with aqueous NH_4Cl. The mixture was worked up in the usual manner and the crude product was dissolved in MeOH (3 ml) containing p-TsOH (3 mg). Stirring was continued at room temperature for 1 h. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 460 mg (75%) of **19a**: bp 88-89° (4 mm); IR (neat) 1370, 1198, 1122, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-2.40 (m, 5H, CH_2, CH), 1.24, 1.31, 1.36 (s, 6H, CH_3), 1.54 (s, 6H, CH_3), 3.37, 3.46 (s, 3H, OCH_3), 4.47-4.82 (m, 1H, CH-O). Found: C, 59.86; H, 9.46. Calcd for $C_{11}H_{21}ClO_2$: 59.85; H, 9.59.

Similarly, (4S)-**19b** was obtained in 75% yield from **4b**: bp 88-89° (4 mm). Found: C, 59.92; H, 9.42. Calcd for $C_{11}H_{21}ClO_2$:

C, 59.85; H, 9.59.

Conversion of 19a to 2a. A mixture of 19a (190 mg, 0.86 mmol), AcOH (81 ml), H_2O (0.5 ml), 5% HCl (0.2 ml) was stirred at room temperature for 10 h. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 2/1) gave 137 mg (77%) of 20a: bp 78-80° (0.025 mm); IR (neat) 3370 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.00-2.60 (m, 5H, CH_2, CH), 1.24, 1.33 (s, 6H, CH_3), 1.57 (s, 6H, CH_3), 3.95 (br, 1H, OH), 4.73-5.45 (m, 1H, CH-O). The lactol 20a (137 mg, 0.66 mmol) in ether (4 ml) was treated with a solution of CrO_3 (198 mg, 1.98 mmol) in 5% H_2SO_4 (2.0 ml) at 0°. Stirring was continued at 0° for 30 min and at room temperature for 30 min. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 5/1) gave 120 mg (89%) of 2a: mp 86-87°; $[\alpha]^{26}_D$ +15.5° (c 2.44).

Similarly, 2b was obtained in 68% yield from 19b: mp 86-87°; $[\alpha]^{21}_D$ -15.3° (c 0.75).

Methyl hydrogen (3S)-3-(1-Chloro-1-methylethyl)glutarate (22a). A mixture of 4a (510 mg, 2.02 mmol), AcOH (3 ml), H_2O (1.5 ml), and 5% HCl (0.3 ml) was stirred at 2-5° for 45 min. The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 10/1) gave 376 mg (90%) of 21a: $[\alpha]^{28}_D$ -3.7° (c 1.9); IR (neat) 2710, 1730 (ester C=O), 1715 (C=O), 1435, 1375, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (s, 6H, CH_3), 2.05-3.10 (m, 5H, CH_2, CH),

3.66 (s, 3H, OCH_3), 9.74 (t, $\underline{J}$ = 1 Hz, 1H, CHO). The aldehyde **21a** (220 mg, 1.06 mmol) in ether (5 ml) was treated with CrO_3 (320 mg, 3.2 mmol) in 5% H_2SO_4 (3.2 ml) at 4-5°. Stirring was continued at 4-5° for 2 h. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 1/1) gave 192 mg (81%) of **22a**: $[\alpha]^{29}_D$ +1.6° (c 1.8); IR (neat) 3600-2600 (COOH), 1730 (ester C=O), 1708 (C=O), 1370, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (s, 6H, CH_3), 2.63-3.00 (m, 5H, CH_2, CH), 3.65 (s, 3H, OCH_3), 8.40 (br, 1H, COOH). Found: C, 48.68; H, 6.91. Calcd for $C_9H_{15}ClO_4$: C, 48.55; H, 6.79.

Similarly, **22b** was obtained in 80% yield from **4b** <u>via</u> **21b** ($[\alpha]^{19}_D$ +3.5° (c 3.14)): $[\alpha]^{29}_D$ -1.29 (c 2.2). Found: 48.76; H, 6.97. Calcd for $C_9H_{15}ClO_4$: C, 48.55; H, 6.79.

<u>Conversion of **22a** to **2a**</u>. To an ethereal 0.68 M MeLi (5.9 ml, 4.0 mmol) was added a solution of **22a** (90 mg, 0.4 mmol) in ether (2 ml) at -70°. After stirring at -70° for 20 min, the mixture was warmed gradually to -30° over about 40 min and the reaction was quenched with 10% NH_4Cl. Extractive workup followed by column chromatography (SiO_2, hexane-AcOEt 1/1) gave 58 mg (71%) of **2a**: mp 86-87°; $[\alpha]^{26}_D$ +15.3° (c 3.2).

Similarly, **2b** was obtained in 70% yield from **22b**: mp 86-87°; $[\alpha]^{26}_D$ -15.3° (c 2.5).

<u>Methyl (1R,3S)-3-(2-Hydroxy-2-methylpropyl)-2,2-dimethyl-</u>

cyclopropane-1-carboxylate (25b). A mixture of (1R,6S)-23b (145 mg, 0.86 mmol) and KOH (110 mg, 1.96 mmol) in MeOH (2 ml) and H_2O (0.6 ml) was stirred at 40-45° for 48 h. The whole was acidified with cold 5% HCl and extracted with benzene-AcOEt (1/1). The extract was worked up in the usual manner and the crude product was treated with excess CH_2N_2 in ether. Concentration in vacuo followed by column chromatography (SiO_2, hexane-AcOEt 3/1) gave 167 mg (97%) of (1R,3S)-25b: bp 84-86° (1.5 mm) [lit.[5h] 110° (1 mm)]; $[\alpha]^{23}_D$ -21.5° (c 1.9) (lit.[5h] -16.3°); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 25.0 (s), 28.7, 28.85, 28.93, 29.4 (2C), 36.7 (t), 51.1 (q), 70.8 (s), 172.7 (s).

Similarly, (1S,3R)-25a was obtained in 96% yield from (1S,6R)-23a: bp 85-87° (1.5 mm)[lit.[5f] 105° (3.5 mm)]; $[\alpha]^{23}_D$ +21.0° (c 2.1) (lit.[5f] +16.2°).

Methyl (+)-cis-Chrysanthemate [(1R,3S)-26b, R = Me]. To a solution of (1R,3S)-25b (180 mg, 0.9 mmol) in HMPA (1.5 ml) was added $POCl_3$ (500 mg, 3.3 mmol). After stirring at 50° for 1 h, pyridine (530 mg, 6.7 mmol) was added and the whole was heated at 50° for 1 h, at 75° for 30 min, and at 100° for 45 min. The mixture was poured into cold aqueous $NaHCO_3$ and extracted with benzene-AcOEt (1/1). The usual workup followed by column chromatography (SiO_2, hexane-AcOEt 10/1) gave 156 mg (95%) of a 1:2 mixture of (1R,3S)-26b (R = Me) and (1R,3S)-27b. The

analytical sample of (1R,3S)-**27b** was obtained by preparative GLC (Silicon GE, 10% coated on 80-100 mesh Chamelite, 4 mm x 6 m, 130°, carrier gas H_2 at 15 ml/min, R_t 7.8 min): bp 96-98° (10 mm); $[\alpha]^{18}_D$ -42.1° (c 0.65); IR (neat) 3070, 1728 (ester C=O), 1648 (C=C), 1437, 1378, 1200, 1168, 1130, 1088, 885, 852 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16-1.59 (m, 2H, CH), 1.17 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.75 (brs, 3H, $CH_3C=C$), 2.38 (d, $\underline{J}$ = 7 Hz, 2H, CH_2), 3.62 (s, 3H, OCH_3), 4.74 (m, 2, $H_2C=C$); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 23.1 (q), 25.5 (s), 28.4 (q), 29.0 (d), 31.0 (t), 32.1 (d), 51.0 (q), 109.3 (t), 145.6 (s), 172.3 (s). Found: C, 72.46; H, 9.87. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Without separation of the double bond isomers, the above mixture was dissolved in isopropanol (1.7 ml) containing $RhCl_3.3H_2O$ (3 mg, 0.01 mmol) and the whole was heated at 90-95° for 12 h. Concentration <u>in vacuo</u> followed by column chromatography (SiO_2, hexane-AcOEt 10/1) gave 153 mg (98%) of (1R,3S)-**26b** (R = Me) contaminated with 4% of (1R,3S)-**27b** and 6% of unidentified compounds. Analytical sample of (1R,3S)-**26b** (R = Me) was obtained by preparative HPLC (R_t 15.2 min) under the same conditions for the purification of **1** (R = Me): bp 95-97° (10 mm) [lit.[5h] 105° (10 mm)]; $[\alpha]^{21}_D$ +59.8° (c 1.2)(lit.[5h] +41°); ^{13}C NMR ($CDCl_3$) δ 14.8 (q), 18.3 (q), 25.9 (q), 26.4 (s), 28.8 (q), 31.0 (d), 32.3 (d), 51.0 (q), 118.1 (d), 134.6 (s), 171.6 (s). IR and ^1H NMR spectral data were identical

with those reported.[19]

Similarly, the (-)-cis-isomer (1S,3R)-**26a** (R = Me) was obtained in 83% yield from (1S,3R)-**25a**: bp 95-97° (10 mm); $[\alpha]^{21}_{D}$ -59.1° (c 1.8) (lit.[5e] -41.5°).

The treatment of a 2:1 mixture of **27b** and **26b** (R = Me) with $RhCl_3.3H_2O$ in MeOH gave a 47:53 mixture of **26b** (R = Me) and **28b** in 98% yield. An analytical sample of **28b** was obtained by preparative GLC (Silicon GE, 10% coated on 80-100 mesh Chamelite, 4 mm x 4 m, 120°, H_2 at 30 ml/min, R_t 11.6 min): bp 111-113° (9 mm); $[\alpha]^{18}_{D}$ -16.1° (c 0.7); IR (neat) 2804, 1723 (ester C=O), 1435, 1378, 1219, 1170, 1139, 1128, 1080, 847 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 6H, CH_3), 1.16 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.20-1.56 (m, 2H, CH), 1.70 (d,d, $\underline{J}$ = 6, 3 Hz, 2H, CH_2), 3.17 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 24.7 (q), 25.0 (q), 25.1 (q), 28.6, 28.9, 29.0, 32.7 (t), 49.1 (q), 50.9 (q), 74.6 (s), 172.5 (s). Found: C, 67.26; H, 10.37. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35.

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