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New Synthetic Routes to (±)-Perhydrohistrionicotoxin. Stereoselective Synthesis of (6*S**, 7*S**, 8*S**)-7-Butyl-8-hydroxy-1-azaspiro[5.5]-undecan-2-one and Its (6*R**)-Isomer

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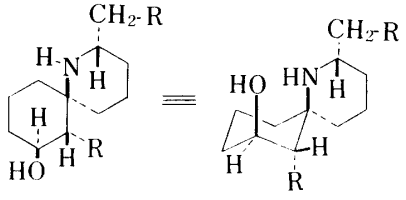
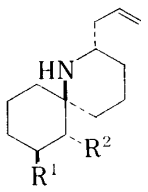
A highly stereoselective synthesis of (6*S**,7*S**,8*S**)-7-butyl-8-hydroxy-1-azaspiro[5.5]-undecan-2-one (**6**), a key intermediate for (±)-perhydrohistrionicotoxin synthesis, from the Diels-Alder cycloadduct of 1,3-bis(trimethylsiloxy)-2-methyl-1,3-butadiene (**15**) and ethyl 3-acetoxy-1-cyclohexene-1-carboxylate is described. This key intermediate and its stereoisomer, (6*R**,7*S**,8*S**)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (**7**), were stereoselectively synthesized by means of a conjugate addition reaction using 1-(3-*tert*-butyldimethylsiloxy-1-cyclohexen-1-yl)-ethanone and $BuCu \cdot AlCl_3$ as the key step.

Keywords——perhydrohistrionicotoxin; (6*S**,7*S**,8*S**)-7-butyl-8-hydroxy-1-azaspiro-[5.5]undecan-2-one; (6*R**,7*S**,8*S**)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one; butylcopper-aluminum trichloride complex; X-ray analysis

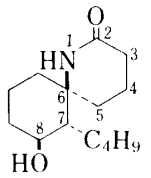
Extensive studies by Witkop, Daly, and their co-workers on the toxic skin alkaloids of Neotropical poison-dart frogs of *Dendrobates* have resulted in the isolation and characterization of many novel alkaloids with a spiropiperidine framework, and these alkaloids were termed histrionicotoxins.[1–8] The structures and the stereochemistries at C-2, C-6, C-7, and C-8 of histrionicotoxin (**1**) and of isodihydrohistrionicotoxin have been elucidated by X-ray diffraction analyses of their single crystals.[2,3] Although the term "histrionicotoxins" had been restricted to the C_{19}-alkaloids (C_5- and C_4-side chains at C-2 and C-7 positions, respectively), nowadays histrionicotoxins also include lower homologues such as alkaloid 235A (**2**), and desoxy derivatives such as alkaloid 219A (**3**).[5,6]



1 : R = $-CH=CH-C\equiv CH$
4 : R = $-(CH_2)_2-CH=CH_2$
5 : R = $-(CH_2)_3-CH_3$



2 : R^1 = OH, R^2 = $-CH=CH_2$
3 : R^1 = H, R^2 = $-CH_2-CH=CH_2$



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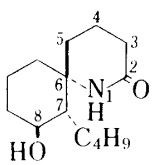

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Chart 1

Histrionicotoxins have proven to be useful pharmacological tools because of their ability to antagonize the conductance after acetylcholine activation of nicotinic receptors in muscle.[2,9-11] Simple 1-azaspiropiperidine derivatives have also been reported to show analgetic, antipyretic, and antiphlogistic activity.[12] The difficulty of isolation of substantial amounts of histrionicotoxins from natural sources, the unique 1-azaspiropiperidine structure of the bases, and the significant neurophysiological activity make histrionicotoxins attractive synthetic targets. Although (±)-octahydrohistrionicotoxin (**4**), one of the natural bases, has been synthesized,[13] the principal alkaloid histrionicotoxin (**1**) has resisted synthetic efforts to date due to the lability of the *cis*-enyne side chains. It has been suggested that the biological activity is not associated with the unsaturated side chains of histrionicotoxin, because perhydrohistrionicotoxin (**5**), which is not a natural alkaloid, still retains comparable biological activity.[11]

Although a fairly large number of stereoselective or nonstereocontrolled synthetic methods for simple 1-azaspiro[5.5]undecanes have been developed by many groups,[14] stereoselective synthetic routes to the ring system which allow for the incorporation of functionality, are rather limited.[13,15-17]

In this paper we present details of our stereoselective synthesis of the racemic lactam (**6**)[15] by two routes,[18] which illustrate the utility of the Diels–Alder reaction using 1,3-bis(trimethylsiloxy)-2-methyl-1,3-butadiene[19] and of the conjugate addition reaction with an equimolar mixture of butylcopper and aluminum trichloride[20] in solving stereochemical problems. Synthesis of the lactam (**6**) consititutes a formal total synthesis of perhydrohistrionicotoxin (**5**), since **6** has been transformed into **5** by Kishi,[13,17a] and Corey.[17c] Recently, the *O*-formate of **6** has also been converted into **5** by Evans.[17d] For the purpose of pharmacological studies on structure-activity relationships, we also synthesized a stereoisomeric lactam (**7**) and details of this synthesis are also presented.

Results and Discussion

Synthesis of the 1-Azaspirocycle *via* the Diels–Alder Cycloadduct

The first synthetic route to the target lactam (**6**) is based on the assumption that the three chiral centers in the lactam (**6**) would be formed stereoselectively in the first step of the synthesis by the Diels–Alder reaction of an α,β-unsaturated ester and oxygenated 1,3-butadienes as shown in the reaction sequence **8**+**9**→**10**→**11**→**6**. On the basis of the above considerations, we synthesized the lactam (**6**) as follows.

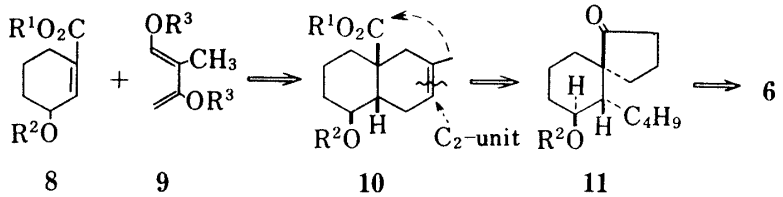
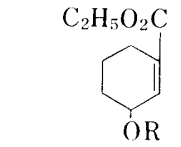
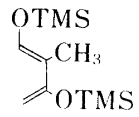


Chart 2

The Diels–Alder reaction of the enoate (**12**) with 1,3-bis(trimethylsiloxy)-2-methyl-1,3-butadiene (**15**)[19] in a sealed glass tube at 170°C (2 days) and then at 190°C (3 days) followed by hydrolysis with 5% aqueous hydrochloric acid yielded an inseparable mixture of the enones (**16**) in 72% yield.[21] Under the same reaction condition, the Diels–Alder reaction of the diene (**15**) with the enoate (**13**) or (**14**) did not yield any cycloadduct. Thioacetalization of a mixture of the enones (**16**) afforded two crystalline thioacetals (**17**) and (**18**) in an 85: 15 ratio after column chromatographic separation. Eivdence for the assignment of the β-acetoxy group in **17** was obtained by its conversion to the lactone (**21**) through the following sequence



12 : R = Ac
13 : R = Si<
14 : R = Bu^t



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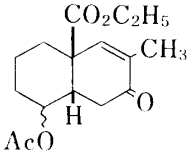

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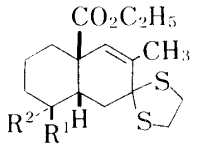
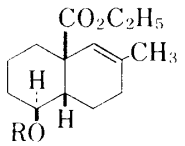
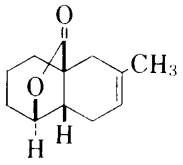


17 : R^1 = OAc, R^2 = H
18 : R^1 = H, R^2 = OAc



19 : R = Ac
20 : R = H



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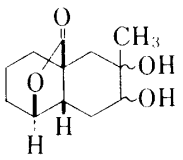

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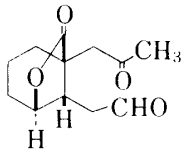


23

Chart 3

of steps (**17**→**19**→**20**→**21**). The acetoxy group in the minor thioacetal (**18**), therefore, was assigned the undesired α-configuration (*vide infra*).

The acetate (**19**), obtained by desulfurization of the major thioacetal (**17**) with Raney W-2 nickel, was hydrolyzed with aqueous potassium hydroxide to yield the hydroxy ester (**20**). Treatment of **20** with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene gave the lactone (**21**) with migration of the double bond in 89% yield. Oxidation of **21** with osmium tetroxide[20] furnished the crystalline glycol (**22**) in 74% yield and subsequent treatment with periodic acid[22] in a 3: 2 mixture of tetrahydrofuran (THF) and water at −50°C for 25 min yielded the rather unstable keto aldehyde (**23**) in 98% overall yield.

With the keto aldehyde (**23**) in hand, the next step was chemoselective two-carbon homologation at the aldehyde group. This was effectively accomplished by the Witting procedure. Thus, reaction of **23** with 1.12 equivalents of triphenylphosphine ethylidene proceeded smoothly to afford the keto lactone (**24**) as a single isolable product in 59% yield after quenching with a mixture of methanol and THF (1: 1). To achieve the Wittig reaction in a chemoselective manner, it was essential to add a solution of the ylide to the keto aldehyde at −40——50°C with vigorous stirring. In this reaction, quenching with an aqueous ammonium chloride gave only small amounts of **24**.

Catalytic hydrogenation of **24** at atmospheric pressure over platinum dioxide yielded the butyl compound (**25**). Since our initial attempts to spirocyclize **25** to the diketone (**26**) were unsuccessful, the following reactions were undertaken. Methoxycarbonylation of **25** according to the method of Whitlock[23] yielded the ester (**27**) in 83% yield. Successive treatments of **27** with sodium borohydride in methanol at −30——40°C, methanesulfonyl chloride-pyridine at 4°C, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-triethylamine at 4—7°C, and then hydrogenation over platinum dioxide at atmospheric pressure yielded the ester (**28**) in 97% overall yield.

The Dieckmann condensation of **28** with potassium hydride in THF[24] provided the spirane (**29**) in 75% yield. Although attempts to remove the methoxycarbonyl group in **29**

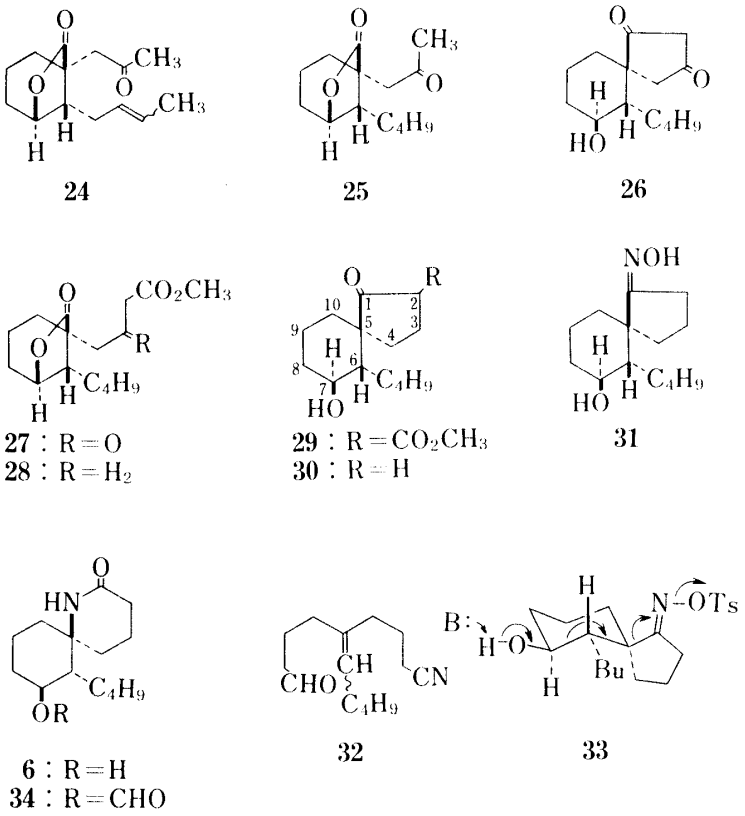


Chart 4

with dimethylsulfoxide–sodium chloride[25] or sulfuric acid–THF–water[15d,e] were unsuccessful, treatment of **29** in refluxing xylene with 1,4-diazabicyclo[2.2.2]octane (Dabco) by the procedure of Miles[26] gave the ketone (**30**) in 67% yield. Oximation of **30** by a standard procedure furnished the oxime (**31**), whose melting point and spectra data were in good accord with those reported by Corey.[15d,17c] The Beckmann rearrangement of **31** with *p*-toluenesulfonyl chloride–pyridine afforded the desired lactam (**6**) and the cyano aldehyde (**32**) as a by-product in 25% and 23% yields, respectively. The synthesized lactam (**6**) was identical with an authentic sample kindly provided by Professor Evans by IR (in KBr), ^{1}H-NMR (in $CDCl_3$, 200 MHz), and TLC. The by-product (**32**) might have been formed from a presumed intermediate (**33**) by a Grob-type fragmentation.[27]

Since the racemic lactam (**6**) and its *O*-formate (**34**) have been converted into (±)-perhydrohistrionicotoxin (**5**) in a straight-forward way by Kishi,[13,17a] Corey,[17b,c] and Evans,[17d] the present stereoselective synthesis of **6** constitutes a new formal synthesis of racemic perhydrohistrionicotoxin.

Synthesis of 1-Azaspirocycle *via* the Conjugate Adduct using BuCu·$AlCl_3$

(a) **Synthesis of (6*S**, 7*S**, 8*S**)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one**——The second approach to the target (**6**) for perhydrohistrionicotoxin synthesis involves the successful 1,4-addition reaction of a γ-oxygenated-α,β-unsaturated ketone (**35**) with a new reagent BuCu·$AlCl_3$[20] to a butyrated ketone (**36**) as a key step in the sequence **35**→**36**→**37**→**6**.

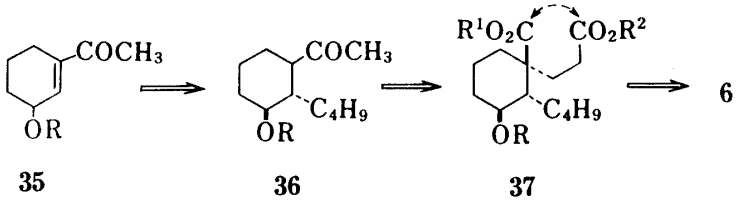
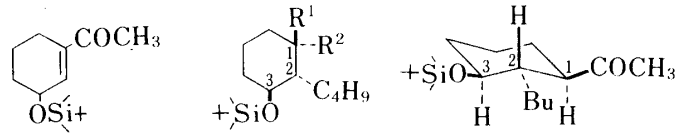
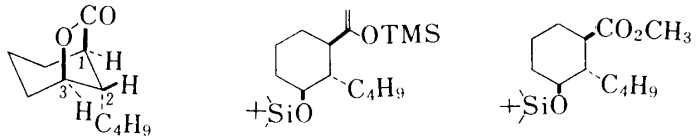


Chart 5

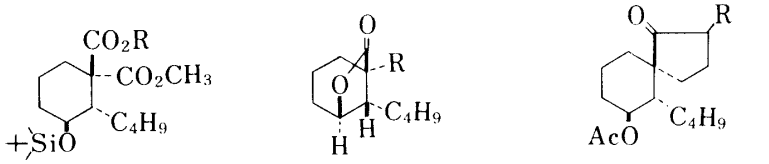
The synthesis of **6** was initiated with a conjugate addition of *γ-tert*-butyldimethylsiloxy-α,β-enone (**38**) with organometallics. Although ordinary organocopper (I) reagents such as homocuprates (R_2CuLi) are probably the best known organometallics for the conjugate addition reaction of various types of α,β-unsaturated carbonyl compounds,[28] it is well recognized that γ-oxygenated-α,β-unsaturated carbonyl compounds are inert[20] with these reagents susceptible to serious undesired side reactions.[20a,b,28a,29] In fact, treatment of **38** with ordinary organocopper (I) reagents such as Bu_2CuLi and BuCu(CN)Li gave a mixture of the adducts (**39**) and (**40**) in less than 9% yield. On the other hand, treatment of **38** with $BuCu \cdot AlCl_3$[20] furnished the adducts (**39**) and (**40**) in 77±3% and 7% yields, respectively, after column chromatographic separation. Recently, Yamamoto and his co-workers also obtained a comparable result using $BuCu \cdot BF_3$.[30] On treatment of **40** with KH in THF–hexamethylphosphoric triamide, an equilibrium mixture of **39** and **40** in a 3:5 ratio was obtained. This result indicated that the two products are epimeric at C-1.



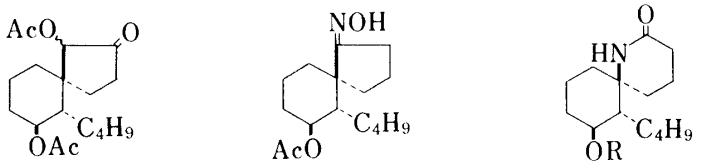
38 **39** : R^1=Ac, R^2=H; **40** : R^1=H, R^2=Ac **39-A**



41 **42** **43**



44 : R=H; **45** : R=CH_3; **46** : R=CH_2CH_3 **47** : R=CO_2CH_3; **48** : R=CHO; **49** : R=$(CH_2)_2CO_2CH_3$ **50** : R=H; **51** : R=OAc



52 **53** **54** : R=Ac; **6** : R=H

Chart 6

The stereochemistry of the major adduct (**39**) was assigned on the basis of the following evidence. The ^{1}H-NMR spectrum of **39** revealed two axial proton signals at δ 3.42 (J=10, 10, 4.5 Hz) and at δ 2.25 (J=10.2, 10.2, 3.5 Hz) assignable to the C-3 and the C-1 positions, respectively. Two large splittings (J=10 and 10 Hz) of the signal at δ 3.42 indicated that the protons at the C-3 and the C-2 positions are both axial. Two large coupling constants (J=10.2 and 10.2 Hz) of the C-1 proton also showed that the C-1 and the C-2 protons are both axial. Consequently, the configurations of all substituents at the C-1, the C-2, and the C-3 positions were assigned as equatorial,[32] as shown in **39-A**. Furthermore, the stereochemical assignment

of the α-butyl group in **39** was based on a spin-decoupling experiment at the signal due to the C-3 proton at δ 4.63 (triplet, J=4.5 Hz) of the lactone (**41**) which was derived from **39**.[31,32]

Enol silylation[33] of **39** by a conventional method yielded a rather labile compound (**42**), which, without purification, was successively treated with ozone at −70°C and diazomethane to furnish the ester (**43**) in 96% overall yield. Carboxylation of **43** by successive treatments with LDA and carbon dioxide yielded the labile acid (**44**), which on reaction with diazomethane or diazoethane furnished the diester (**45**) or (**46**) in 95% or 80% yield, respectively. The stereochemistry of the carboxy group in **44** was inferred from the fact that the diesters (**45**) and (**46**) both gave the same lactone (**47**) in high yield on exposure to 5% hydrochloric acid.

Reduction of **47** with diisobutylaluminum hydride followed by oxidation with pyridinium chlorochromate gave the aldehyde (**48**). The Wadsworth-Emmons reaction of **48** with the sodium salt of trimethyl phosphonoacetate, and subsequent catalytic hydrogenation over platinum dioxide affoded the lactone ester (**49**) in 74% yield. Spirocyclization of **49** was achieved by using the modified acyloin condensation according to the method of Bloomfield.[31] Thus, treatment of **49** with sodium in the presence of chlorotrimethylsilane, and successive treatments with 5% hydrochloric acid and then acetic anhydride–pyridine gave a mixture of spiranes. Column chromatographic separation afforded the acetoxy ketones (**50**), (**51**), and (**52**) in 16%, 44%, and 17% yields, respectively. Although **51** is a separable 5:6 mixture due to the stereochemistry of the acetoxy group adjacent to the ketone function, the undesired product (**52**) was an inseparable 1:1 mixture judging from the ^{1}H-NMR spectrum. The compounds (**51**) was readily converted to the ketone (**50**) by reduction with zinc in boiling acetic acid.

Oximation of **50** gave the oxime (**53**), which on treatment with p-toluenesulfonyl chlroide in pyridine afforded the lactam (**54**). Finally, hydrolysis of the acetoxy group in **54** was effected with sodium methoxide in methanol to furnish the target lactam (**6**), which was identical with an authentic sample provided by Evans.[15b] Stereoselective synthesis of **6** by the present procedure constitutes a new formal synthesis of (±)-perhydrohistrionicotoxin.

(b) **Synthesis of (6*R**, 7*S**, 8*S**)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one**——It is well known that the stereostructures of natural or synthetic products play an important role in biological activity. For this reason the synthesis of stereoisomers of natural histrionicotoxins appeared to be of considerable significance. Stereoselective synthesis of 2,7-epi-perhydrohistrionicotoxin (**55**) and the 7-epi-lactam (**56**) has already been reported by Corey[16a] and Speckamp.[16b] The 6-epi-lactam (**7**), a promising intermediate for 6-epi-perhydrohistrionicotoxin, was synthesized for the purpose of pharmacological study on the structure–activity relationship by the route outlined below.

The ester (**57**), obtained by an acidic hydrolysis of **43**, was reacted with 2,3-dihydrofuran in the presence of a catalytic amount of pyridinium p-toluenesulfonate[35] to give the ester (**58**) in 95% yield. Successive treatments of **58** with potassium hexamethyldisilazane, allyl bromide, and then 5% hydrochloric acid gave the allylated product (**59**). The β-configuration of the allyl group in **59**, thus the α-configuration of the methoxycarbonyl group, was presumed from the analogy with the carboxylation reaction of **43** (**43**→**44**). At this stage of the study, we anticipated that the *cis*-relationship of the C-1 methoxycarbonyl group and the C-3 hydroxy group would be chemically determinable by lactone formation. The compound (**59**) gave the lactone (**60**) on being refluxed in toluene or benzene in the presence of a catalytic amount of p-toluenesulfonic acid, suggesting the *cis*-relationship of these two functions. This result, therefore, caused some confusion in the stereochemical assignments of **59** at this stage. On the other hand, the ^{1}H-NMR spectrum of **60** suggested the correct stereostructure of **60**. Thus, the signal due to the C-3 proton was observed at δ 4.57 as a doublet (J=3.7 Hz) indicating the β-axial configuration of the C-2 proton.[32] Consequently, the relative configuration of the C-1 allyl group and the C-2 butyl group was assignable as *trans*. The unambiguous *trans* relationship of the C-1 methoxycarbonyl group and the C-3 hydroxy group in **59** was ultimately

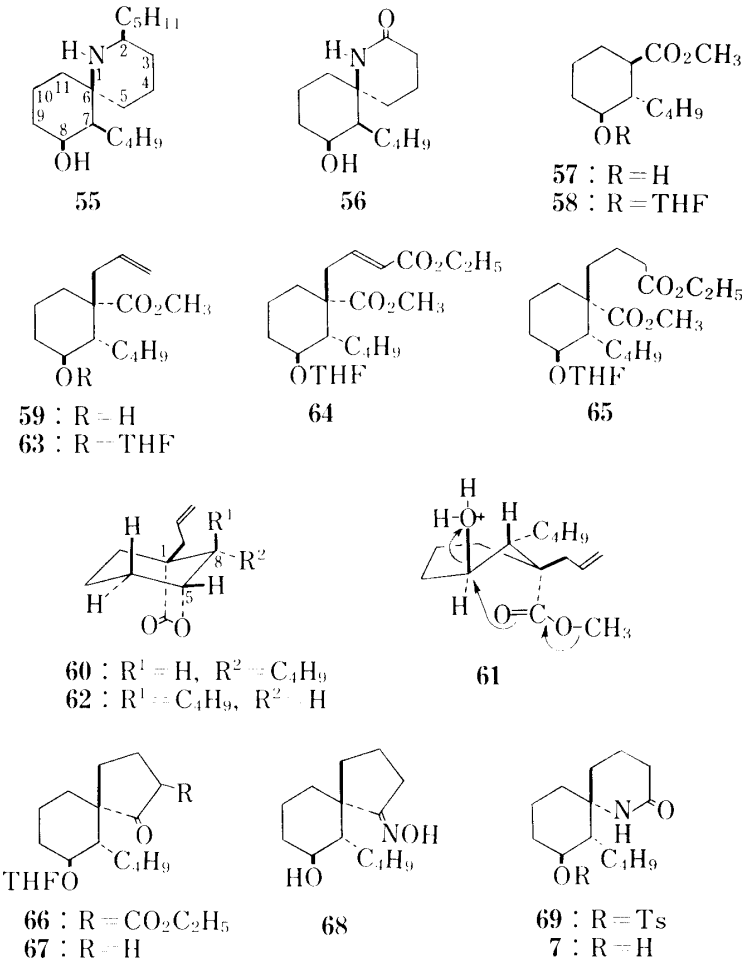


Chart 7

established by an X-ray analysis of the compound (**69**) (*vide infra*) derived from **59**. This type of unusual lactone formation has been observed by Danishefsky in their studies on vernolepin and vernomenin[36] and the lactone (**60**) is presumably formed *via* the intermediate (**61**).

Allylation of **57** as described for **58** and subsequent quenching with aqueous ammonium chloride gave an isomeric lactone (**62**) in low yield together with a substantial amount of (1*R**, 2*S**, 3*S**)-2-butyl-3-hydroxy-1-(*N*,*N*-diisopropyl)cyclohexanecarboxamide as a by-product. The ^{1}H-NMR spectrum of **62** revealed a signal assignable to the C-3 proton at δ 4.71 as a triplet (J=3.7 Hz), suggesting the stereostructure of **62**. This result indicated that allylation of **57** took place at least in part from the same side as that of the butyl substituent.

The tetrahydrofuranyl ether (**63**) was allowed to react with osmium tetroxide-sodium periodate[22] and the resulting labile aldehyde was treated with the sodium salt of triethyl phosphonoacetate to furnish the enoate (**64**) in 76% yield. The (*E*)-configuration of a double bond in **64** was inferred from the large coupling constant (J=*ca.* 16 Hz) between the two olefinic protons.

The diester (**65**), obtained by catalytic hydrogenation of **64**, was treated with KH in THF to give the spirane (**66**) in 85% yield, and this was decarboxylated with dimethylsulfoxide–lithium chloride–sodium bicarbonate–water (300: 2: 1: 100) to furnish the ketone (**67**). Although the ketone (**67**) reacted sluggishly under ordinary oximation conditions, forcing conditions in a sealed glass tube at 170°C yielded the oxime (**68**), mp 56°C, with concomitant hydrolysis of the tetrahydrofuranyl group. The Beckmann rearrangement of **68** with *p*-toluenesulfonyl chloride–pyridine gave the lactam (**69**), mp 164—165°C, as a sole isolable product.

TABLE I. Atomic Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B or β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N (1)	0.1605(2)	0.5407(2)	0.1479(1)	169(3)	109(2)	46(1)	34(2)	7(1)	15(1)
C (2)	0.2536(3)	0.5465(2)	0.0777(1)	193(4)	105(2)	53(1)	46(2)	15(2)	24(1)
C (3)	0.4342(3)	0.5908(2)	0.1262(2)	200(4)	158(3)	73(2)	53(3)	29(2)	38(2)
C (4)	0.4890(3)	0.6738(2)	0.2446(2)	179(4)	116(2)	88(2)	30(2)	6(2)	18(2)
C (5)	0.3950(3)	0.5995(2)	0.3164(2)	187(4)	112(2)	56(1)	39(2)	−4(2)	8(1)
C (6)	0.2121(2)	0.5793(2)	0.2731(1)	184(3)	95(2)	43(1)	49(2)	0(2)	4(1)
C (7)	0.1175(2)	0.4665(2)	0.3239(1)	181(3)	101(2)	39(1)	61(2)	14(2)	7(1)
C (8)	−0.0603(3)	0.4610(2)	0.2972(1)	192(4)	116(2)	46(1)	63(2)	19(2)	11(1)
C (9)	−0.0881(3)	0.5922(2)	0.3367(2)	228(4)	148(3)	79(2)	107(3)	28(2)	2(2)
C (10)	−0.0037(3)	0.6995(2)	0.2815(2)	278(5)	116(2)	80(2)	104(3)	4(2)	−2(2)
C (11)	0.1753(3)	0.7114(2)	0.3072(2)	241(5)	95(2)	72(2)	63(3)	5(2)	3(1)
O (12)	0.1924(2)	0.5154(2)	−0.0263(1)	219(3)	182(2)	52(1)	59(2)	22(1)	26(1)
C (13)	0.1416(2)	0.3290(2)	0.2912(1)	183(3)	92(2)	55(1)	49(2)	26(2)	10(1)
C (14)	0.1916(3)	0.2631(2)	0.3924(2)	273(5)	114(2)	70(2)	83(3)	30(2)	22(2)
C (15)	0.2141(3)	0.1280(2)	0.3654(2)	220(4)	108(2)	88(2)	58(3)	21(2)	21(2)
C (16)	0.2578(4)	0.0670(2)	0.4688(2)	434(8)	121(3)	106(2)	85(4)	2(4)	39(2)
O (17)	−0.1367(2)	0.3594(1)	0.3581(1)	180(2)	148(2)	52(1)	60(2)	28(1)	20(1)
S (18)	−0.3152(1)	0.2684(1)	0.3028(0)	179(1)	167(1)	70(0)	63(1)	38(1)	25(0)
O (19)	−0.3584(2)	0.2055(2)	0.3909(1)	254(4)	246(3)	91(1)	50(3)	87(2)	46(2)
O (20)	−0.4113(2)	0.3456(2)	0.2474(1)	200(3)	186(2)	116(2)	97(2)	15(2)	18(2)
C (21)	−0.2974(2)	0.1486(2)	0.1997(2)	162(3)	120(2)	66(1)	35(2)	25(2)	28(1)
C (22)	−0.2660(3)	0.0329(2)	0.2286(2)	216(4)	141(3)	82(2)	45(3)	29(2)	47(2)
C (23)	−0.2433(3)	−0.0579(2)	0.1501(2)	233(5)	118(2)	118(2)	56(3)	24(3)	20(2)
C (24)	−0.2488(3)	−0.0364(2)	0.0422(2)	201(4)	132(3)	102(2)	26(3)	22(2)	−3(2)
C (25)	−0.2827(3)	0.0794(3)	0.0141(2)	269(5)	166(3)	63(2)	24(3)	28(2)	14(2)
C (26)	−0.3075(3)	0.1721(2)	0.0906(2)	233(4)	130(2)	68(2)	45(3)	21(2)	29(2)
C (27)	−0.2225(4)	−0.1373(3)	−0.0423(3)	280(7)	232(5)	156(3)	44(5)	41(4)	−69(3)
H (1)	0.0625(26)	0.5149(20)	0.1192(18)	5.55(50)					
H (3 A)	0.4671(30)	0.5035(23)	0.1283(20)	7.05(60)					
H (3 B)	0.4789(28)	0.6392(22)	0.0793(19)	6.04(53)					
H (4 A)	0.4776(27)	0.7590(22)	0.2471(18)	6.12(54)					
H (4 B)	0.6053(24)	0.6865(18)	0.2800(16)	4.80(45)					
H (5 A)	0.4231(26)	0.6418(20)	0.3903(17)	5.20(47)					
H (5 B)	0.4132(24)	0.5139(18)	0.3249(15)	4.39(42)					
H (7)	0.1596(21)	0.4942(17)	0.4064(14)	3.42(37)					
H (8)	−0.1110(23)	0.4302(17)	0.2192(15)	4.07(41)					
H (9 A)	−0.2046(29)	0.5832(22)	0.3165(19)	6.38(55)					
H (9 B)	−0.0448(27)	0.6125(21)	0.4190(18)	5.92(52)					
H (10 A)	−0.0596(27)	0.6765(20)	0.2063(17)	5.59(50)					
H (10 B)	−0.0122(29)	0.7826(22)	0.3128(19)	6.63(58)					
H (11 A)	0.2255(23)	0.7398(18)	0.3862(15)	4.12(41)					
H (11 B)	0.2342(26)	0.7774(20)	0.2755(17)	5.38(49)					
H (13 A)	0.0496(22)	0.2699(17)	0.2384(15)	3.80(39)					
H (13 B)	0.2181(25)	0.3324(19)	0.2484(16)	4.82(45)					
H (14 A)	0.2982(28)	0.3258(22)	0.4399(18)	5.92(51)					
H (14 B)	0.1223(33)	0.2573(24)	0.4316(21)	8.21(69)					
H (15 A)	0.1125(30)	0.0698(22)	0.2996(18)	6.83(59)					
H (15 B)	0.3036(31)	0.1388(23)	0.3248(20)	7.50(63)					
H (16 A)	0.2665(35)	−0.0260(25)	0.4595(22)	8.84(73)					
H (16 B)	0.3424(33)	0.1167(26)	0.5245(21)	8.53(71)					
H (16 C)	0.1839(45)	0.0478(32)	0.5045(28)	12.20(99)					
H (22)	−0.2634(32)	0.0229(24)	0.3002(20)	7.50(63)					
H (23)	−0.2161(31)	−0.1411(23)	0.1641(20)	7.35(62)					
H (25)	−0.2832(32)	0.0998(24)	−0.0528(21)	7.69(64)					
H (26)	−0.3356(31)	0.2554(23)	0.0656(20)	7.18(62)					
H (27 A)	−0.3112(38)	−0.1867(28)	−0.0914(24)	10.08(80)					
H (27 B)	−0.1433(38)	−0.0974(29)	−0.0777(26)	9.88(79)					
H (27 C)	−0.1348(44)	−0.1718(33)	−0.0209(28)	12.70(99)					

The values of β are multiplied by 10^4.
The temperature factors are expressed by the formula: $T=1/\exp(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)$.

TABLE II. Bond Angles (degree) and Their Estimated Standard Deviations

Bond	Angle	Bond	Angle
C(2)-N(1)-C(6)	128.07(15)	C(2)-N(1)-H(1)	116.75(169)
C(6)-N(1)-H(1)	115.15(169)	N(1)-C(2)-C(3)	118.84(14)
N(1)-C(2)-O(12)	120.79(21)	C(3)-C(2)-O(12)	120.37(22)
C(2)-C(3)-C(4)	113.06(22)	C(2)-C(3)-H(3A)	105.10(123)
C(2)-C(3)-H(3B)	108.44(140)	C(4)-C(3)-H(3A)	109.66(127)
C(4)-C(3)-H(3B)	109.65(126)	H(3A)-C(3)-H(3B)	110.87(228)
C(3)-C(4)-C(5)	108.55(16)	C(3)-C(4)-H(4A)	113.97(131)
C(3)-C(4)-H(4B)	111.16(120)	C(5)-C(4)-H(4A)	110.00(160)
C(5)-C(4)-H(4B)	107.54(123)	H(4A)-C(4)-H(4B)	105.43(170)
C(4)-C(5)-C(6)	112.58(19)	C(4)-C(5)-H(5A)	114.21(132)
C(4)-C(5)-H(5B)	113.83(133)	C(6)-C(5)-H(5A)	104.85(151)
C(6)-C(5)-H(5B)	108.84(111)	H(5A)-C(5)-H(5B)	101.62(177)
N(1)-C(6)-C(5)	109.26(16)	N(1)-C(6)-C(7)	109.04(13)
N(1)-C(6)-C(11)	109.27(17)	C(5)-C(6)-C(7)	110.23(16)
C(5)-C(6)-C(11)	109.16(15)	C(7)-C(6)-C(11)	109.88(17)
C(6)-C(7)-C(8)	110.60(16)	C(6)-C(7)-C(13)	113.90(15)
C(6)-C(7)-H(7)	106.04(100)	C(8)-C(7)-C(13)	112.27(14)
C(8)-C(7)-H(7)	105.25(117)	C(13)-C(7)-H(7)	108.18(115)
C(7)-C(8)-C(9)	113.47(16)	C(7)-C(8)-O(17)	106.47(16)
C(7)-C(8)-H(8)	110.27(135)	C(9)-C(8)-O(17)	108.07(18)
C(9)-C(8)-H(8)	110.92(126)	O(17)-C(8)-H(8)	107.33(111)
C(8)-C(9)-C(10)	109.41(22)	C(8)-C(9)-H(9A)	109.98(130)
C(8)-C(9)-H(9B)	106.68(145)	C(10)-C(9)-H(9A)	109.55(144)
C(10)-C(9)-H(9B)	111.87(125)	H(9A)-C(9)-H(9B)	109.30(206)
C(9)-C(10)-C(11)	110.67(20)	C(9)-C(10)-H(10A)	105.26(133)
C(9)-C(10)-H(10B)	108.57(158)	C(11)-C(10)-H(10A)	115.18(164)
C(11)-C(10)-H(10B)	106.81(144)	H(10A)-C(10)-H(10B)	110.24(202)
C(6)-C(11)-C(10)	113.99(15)	C(6)-C(11)-H(11A)	106.46(129)
C(6)-C(11)-H(11B)	107.85(149)	C(10)-C(11)-H(11A)	110.09(134)
C(10)-C(11)-H(11B)	114.36(142)	H(11A)-C(11)-H(11B)	103.28(157)
C(7)-C(13)-C(14)	113.49(13)	C(7)-C(13)-H(13A)	112.14(128)
C(7)-C(13)-H(13B)	112.61(122)	C(14)-C(13)-H(13A)	109.47(119)
C(14)-C(13)-H(13B)	108.72(129)	H(13A)-C(13)-H(13B)	99.49(163)
C(13)-C(14)-C(15)	115.81(19)	C(13)-C(14)-H(14A)	105.21(137)
C(13)-C(14)-H(14B)	110.21(185)	C(15)-C(14)-H(14A)	108.28(151)
C(15)-C(14)-H(14B)	108.65(172)	H(14A)-C(14)-H(14B)	108.40(202)
C(14)-C(15)-C(16)	112.94(20)	C(14)-C(15)-H(15A)	107.81(148)
C(14)-C(15)-H(15B)	107.30(138)	C(16)-C(15)-H(15A)	116.50(132)
C(16)-C(15)-H(15B)	110.41(146)	H(15A)-C(15)-H(15B)	100.90(189)
C(15)-C(16)-H(16A)	119.32(155)	C(15)-C(16)-H(16B)	116.33(181)
C(15)-C(16)-H(16C)	115.98(246)	H(16A)-C(16)-H(16B)	107.54(243)
H(16A)-C(16)-H(16C)	92.83(299)	H(16B)-C(16)-H(16C)	101.13(270)
C(8)-O(17)-S(18)	119.65(11)	O(17)-S(18)-O(19)	104.28(8)
O(17)-S(18)-O(20)	109.65(10)	O(17)-S(18)-C(21)	104.14(9)
O(19)-S(18)-O(20)	119.94(12)	O(19)-S(18)-C(21)	109.22(13)
O(20)-S(18)-C(21)	108.45(9)	S(18)-C(21)-C(22)	119.72(19)
S(18)-C(21)-C(26)	120.44(18)	C(22)-C(21)-C(26)	119.78(22)
C(21)-C(22)-C(23)	120.10(23)	C(21)-C(22)-H(22)	115.28(179)
C(23)-C(22)-H(22)	124.62(180)	C(22)-C(23)-C(24)	121.65(22)
C(22)-C(23)-H(23)	125.58(150)	C(24)-C(23)-H(23)	112.70(153)
C(23)-C(24)-C(25)	117.51(23)	C(23)-C(24)-C(27)	120.64(24)
C(25)-C(24)-C(27)	121.83(25)	C(24)-C(25)-C(26)	122.31(24)
C(24)-C(25)-H(25)	121.16(186)	C(26)-C(25)-H(25)	116.42(182)
C(21)-C(26)-C(25)	118.63(23)	C(21)-C(26)-H(26)	121.56(148)
C(25)-C(26)-H(26)	119.79(148)	C(24)-C(27)-H(27A)	113.80(245)
C(24)-C(27)-H(27B)	112.18(183)	C(24)-C(27)-H(27C)	119.17(199)
H(27A)-C(27)-H(27B)	111.76(281)	H(27A)-C(27)-H(27C)	119.79(294)
H(27B)-C(27)-H(27C)	72.45(308)		

Confirmation of the structure of **69** was obtained by a single-crystal X-ray analysis (see Fig. 1 and "Experimental"). Finally, removal of the *p*-toluenesulfonyl group in **69** was achieved by using sodium-naphthalene in THF[37] to afford (6*R**, 7*S**, 8*S**)-7-butyl-8-hydroxy-1-azaspiro-[5.5]undecan-2-one (**7**), mp 163°C, in 90% yield.

In conclusion, we have synthesized the lactam (**6**), a key intermediate for (±)-perhydrohistrionicotoxin synthesis, and the isomeric lactam (**7**) in a stereoselective manner. The present synthetic methods provide new routes for the synthesis of other spirocyclic natural products.

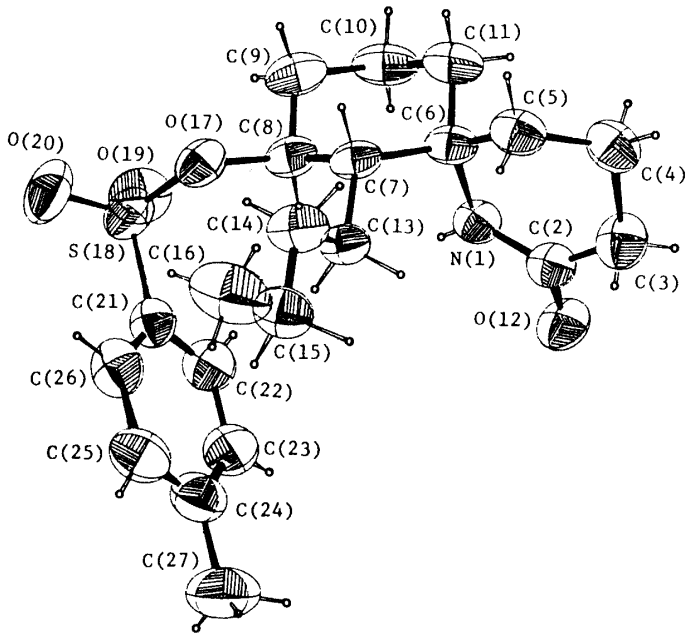


Fig. 1. Computer-generated Perspective Drawing of **69**

TABLE III. Bond Distances (Å) and Their Estimated Standard Deviations

Bond	Dist.	Bond	Dist.	Bond	Dist.
N(1)-C(2)	1.331(3)	N(1)-C(6)	1.486(2)	N(1)-H(1)	0.817(20)
C(2)-C(3)	1.499(3)	C(2)-O(12)	1.243(2)	C(3)-C(4)	1.519(3)
C(3)-H(3A)	1.031(27)	C(3)-H(3B)	0.910(25)	C(4)-C(5)	1.509(4)
C(4)-H(4A)	0.923(25)	C(4)-H(4B)	0.988(20)	C(5)-C(6)	1.534(3)
C(5)-H(5A)	0.918(20)	C(5)-H(5B)	0.965(21)	C(6)-C(7)	1.556(3)
C(6)-C(11)	1.540(3)	C(7)-C(8)	1.518(3)	C(7)-C(13)	1.536(3)
C(7)-H(7)	0.983(16)	C(8)-C(9)	1.509(3)	C(8)-O(17)	1.492(2)
C(8)-H(8)	0.944(17)	C(9)-C(10)	1.513(3)	C(9)-H(9A)	0.981(26)
C(9)-H(9B)	0.978(21)	C(10)-C(11)	1.513(4)	C(10)-H(10A)	0.917(19)
C(10)-H(10B)	0.943(25)	C(11)-H(11A)	0.952(17)	C(11)-H(11B)	0.940(22)
C(13)-C(14)	1.527(3)	C(13)-H(13A)	0.937(14)	C(13)-H(13B)	0.952(24)
C(14)-C(15)	1.494(3)	C(14)-H(14A)	1.004(19)	C(14)-H(14B)	0.865(31)
C(15)-C(16)	1.508(3)	C(15)-H(15A)	1.054(19)	C(15)-H(15B)	1.027(29)
C(16)-H(16A)	0.995(28)	C(16)-H(16B)	0.887(22)	C(16)-H(16C)	0.870(41)
O(17)-S(18)	1.569(2)	S(18)-O(19)	1.417(2)	S(18)-O(20)	1.432(2)
S(18)-C(21)	1.754(2)	C(21)-C(22)	1.379(3)	C(21)-C(26)	1.387(4)
C(22)-C(23)	1.370(4)	C(22)-H(22)	0.901(26)	C(23)-C(24)	1.372(4)
C(23)-H(23)	0.986(27)	C(24)-C(25)	1.386(4)	C(24)-C(27)	1.505(4)
C(25)-C(26)	1.376(4)	C(25)-H(25)	0.878(27)	C(26)-H(26)	1.028(26)
C(27)-H(27A)	0.868(24)	C(27)-H(27B)	0.949(35)	C(27)-H(27C)	0.934(41)
C(27)-H(27A)	0.868(24)				

Experimental

General Methods——All reactions were performed under an atmosphere of argon. Tetrahydrofuran was freshly distilled from lithium aluminum hydride. All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. The evaporative bulb-to-bulb distillations were done by using a Büchi Kugelrohrofen apparatus at the temperature and pressure indicated. All IR spectra were recorded on a Shimadzu Model IR-400 spectrometer. Nominal and accurate mass spectra were recorded on a Jeol JMS-01SG-2 mass spectrometer equipped with a direct inlet system. All proton magnetic resonance spectra (^{1}H-NMR) were recorded in $CDCl_3$ on one of the following spectrometers: Jeol PMX-60, Varian A-60, Jeol FX-100, Varian HA-100D, Jeol FX-200, and Nicolet NT-360. Chemical shifts are quoted in parts per million down-field from internal tetramethylsilane (s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m=multiplet). Elemental analyses were carried out by the Microanalytical Center of Kyoto University. For column chromatographies, silica gel (Mallinckrodt, 100 mesh) or alumina (Merck, aluminum oxide 90, activity II—III) was employed.

The Diels-Alder Reaction of 1,3-Bis(trimethylsiloxy)-2-methyl-1,3-butadiene (15) and Ethyl 3-Acetoxy-1-cyclohexene-1-carboxylate (12)——A mixture of the enoate (**12**)[20a] (27.7 g, 0.131 mol) and the diene (**15**)[19] (48.1 g, 0.197 mol) in 65 ml of mesitylene was heated in a sealed glass tube at 170°C for 48 h and then at 190°C for 72 h. After cooling, the solvent was removed on a rotary evaporator to leave a yellow oily residue. The residue was taken up in 10 ml of THF and 40 ml of 5% HCl, and the mixture was heated at 40°C for 30 min. The major portion of the solvent was removed under reduced pressure, and then the residual oil was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, and concentrated to leave a yellow oily residue. Silica gel column chromatographic separation eluted with $CHCl_3$ gave an inseparable epimeric mixture of the enone (**16**) (27.9 g, 72% yield based on the consumed enoate (**12**)) and the recovered enoate (**12**) (6.5 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726, 1677. MS *m/z* Calcd for $C_{16}H_{22}O_5$: 294.1467. Found: 294.1466.

Thioacetalization of 16——To a solution of **16** (1.285 g, 4.4 mmol) in 15 ml of CH_2Cl_2 were added 2.5 ml of 1,2-ethanedithiol and 3 ml of 47% ethereal solution of boron trifluoride etherate, and the mixture was allowed to stand at ambient temperature for 7 h. The usual work-up led to a yellow oil which was chromatographed on a silica gel column. Elution with $CHCl_3$ gave 196 mg (12.1% yield) of **18** followed by 1.374 g (85% yield) of **17**. **18**: Recrystallization from hexane–ether (1: 1) produced colorless needles. mp 106°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.95 (3H, d, J=1 Hz, vinyl $C\underline{H}_3$), 2.05 (3H, s, $COC\underline{H}_3$), 3.35 (4H, m, $SC\underline{H}_2C\underline{H}_2S$), 4.19 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.05 (1H, m, $\underline{H}$–Ç–OAc), 5.38 (1H, m, olefinic H). MS *m/z* Calcd for $C_{18}H_{26}O_4S_2$: 370.1271. Found: 370.1269. **17**: Recrystallization from hexane–ether (9: 1) gave co orless crystals. mp 83°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.94 (3H, d, J=1 Hz, vinyl $C\underline{H}_3$), 1.97 (3H, s, $COC\underline{H}_3$), 3.33 (4H, m, $SC\underline{H}_2C\underline{H}_2S$), 4.13 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.85 (1H, m, $\underline{H}$–Ç–OAc), 5.19 (1H, m, olefinic H). MS *m/z* Calcd for $C_{18}H_{26}O_4S_2$: 370.1271. Found: 370.1263.

Ethyl (1*S,4a*S**,8a*S**)-1-Acetoxy-6-methyl-1,2,3,4,4a,7,8,8a-octahydro-4a-naphthalenecarboxylate (19)**——Raney W-2 nickel (50 g) was added to a solution of **17** (4.56 g, 12.3 mmol) in 30 ml of dry THF, and the mixture was stirred at ambient temperature for 3 h. The mixture was acidified with 5% HCl under ice-cooling and then filtered. The filtrate was concentrated under reduced pressure to leave an oily residue. The residue was purified by silica gel column chromatography with $CHCl_3$ to give **19** (1.26 g, 37% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.68 (3H, m, vinyl $C\underline{H}_3$), 2.01 (3H, s, $COC\underline{H}_3$), 4.11 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.70 (1H, m, $\underline{H}$–Ç–OAc), 5.18 (1H, m, olefinic H). MS *m/z* Calcd for $C_{16}H_{24}O_4$: 280.1674. Found: 280.1664.

Ethyl (1*S,4a*S**,8a*S**)-1-Hydroxy-6-methyl-1,2,3,4,4a,7,8,8a-octahydro-4a-naphthalenecarboxylate (20)**——A solution of **19** (341 mg, 1.22 mmol) in 3 ml of ethanol was treated with KOH (152 mg, 2.7 mmol) in 0.6 ml of water at 50°C for 4 h with stirring. After cooling, the solution was acidified with 5% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over $MgSO_4$, and concentrated to yield a colorless oil. Silica gel column chromatographic purification with $CHCl_3$ gave **20** (282 mg, 97% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1714. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.70 (3H, m, vinyl $C\underline{H}_3$), 2.40 (1H, s, O$\underline{H}$), 3.52 (1H, m, C$\underline{H}$–OH), 4.15 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.22 (1H, m, olefinic H). MS *m/z* Calcd for $C_{14}H_{22}O_3$: 238.1568. Found: 238.1567.

(1*S,4a*S**,8a*S**)-6-Methyl-1,2,3,4,4a,5,8,8a-octahydro-4a,1-naphthalenecarbolactone (21)**——*p*-Toluenesulfonic acid (57 mg) was added to a solution of **20** (1.27 g, 5.34 mmol) in 16 ml of toluene, and the mixture was heated under reflux for 8 h. The solution was washed successively with 5% sodium bicarbonate, water, 5% HCl, and water, dried over $MgSO_4$, and concentrated to leave **21** (914 mg, 89% yield) as a colorless crystalline mass. Recrystallization from hexane gave colorless prisms, mp 54°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, m, vinyl $C\underline{H}_3$), 4.75 (1H, m, O–Ç–$\underline{H}$), 5.37 (1H, m, olefinic H). MS *m/z* Calcd for $C_{12}H_{16}O_2$: 192.1149. Found: 192.1148.

(1*S,4a*S**,8a*S**)-6-Methyl-6,7-dihydroxyperhydro-4a,1-naphthalenecarbolactone (22)**——A solution of *N*-methylmorpholine-4-oxide (733 mg, 6.85 mmol) in 3 ml of water and a solution of OsO_4 (19 mg, 0.1 mmol) in 2 ml of *tert*-BuOH were added to a solution of **21** (822 mg, 4.28 mmol) in 7 ml of acetone, and the solution was stirred at ambient temperature for 4 h. A solution of sodium hydrogen sulfite (1.3 g) in 4 ml of water was then added and the mixture was stirred for 30 min. Magnesium silicate (1.5 g) was added with stirring, and the mixture was filtered. The filtrate was extracted with ethyl acetate and the extract was washed with saturated brine, dried over $MgSO_4$, and concentrated to leave a semisolid. Recrystallization from CH_2Cl_2–hexane (1: 3) gave **22** (715 mg, 74% yield) as colorless prisms. mp 123—124°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1770. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, s, $C\underline{H}_3$), 2.85 (1H, broad s, O$\underline{H}$), 3.30 (1H, broad s, O$\underline{H}$), 3.73 (1H, t, J=3 Hz, $\underline{H}$–Ç–OH), 4.73 (1H, m, $\underline{H}$–Ç–O). MS *m/z* Calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1213.

(1*S,5*S**,8*S**)-1-Acetonyl-8-formylmethyl-6-oxabicyclo[3.2.1]octan-7-one (23)**——A solution of HIO_4–$2H_2O$ (741 mg, 3.25 mmol) in 1.5 ml of water was added to a solution of **22** (490 mg, 2.17 mmol) in 10 ml of dry THF (with stirring at −50°C, and the mixture was stirred for 25 min at the same temperature. After removal of the solvent at 0°C under reduced pressure, the residual oil was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to leave the rather labile aldehyde **23** (480 mg, 98% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1773, 1723. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s, $COC\underline{H}_3$), 4.77 (1H, m, $\underline{H}$–Ç–O), 9.73 (1H, s, C$\underline{H}$O). MS *m/z* Calcd for $C_{12}H_{16}O_4$: 224.1049. Found: 224.1052.

(1*S,5*S**,8*S**)-1-Acetonyl-8-(2-butenyl)-6-oxabicyclo[3.2.1]octan-7-one (24)**——A solution of triphenylphosphine ethylidene (2.40 mmol in a mixture of THF (2.6 ml) and dimethylsulfoxide (3.4 ml) was added dropwise to a solution of **23** (480 mg, 2.14 mmol) in 12 ml of THF with vigorous stirring at −50°C, and the mixture was further stirred for 30 min. Then 8 ml of methanol–THF (1: 1) was added at −50°C with stirring, and the whole was extracted with ether. The extract was successively washed with 5% HCl and water, dried over $MgSO_4$, and concentrated to yield a colorless oil. Purification by silica gel column chromatography with $CHCl_3$ gave **24** (298 mg, 59% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1723. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, m, vinyl $C\underline{H}_3$), 2.11 (3H, s, $COC\underline{H}_3$), 4.65 (1H, m, $\underline{H}$–Ç–O), 5.10—5.80 (2H, m, olefinic protons). MS *m/e* Calcd for $C_{14}H_{20}O_3$: 236.1410. Found: 236.1405.

(1*S,5*S**,8*S**)-1-Acetonyl-8-butyl-6-oxabicyclo[3.2.1]octan-7-one (25)**——The lactone (**24**) (1.1 g, 4.66 mmol) in 5 ml of methanol was catalytically hydrogenated over $PtO_2 \cdot 2H_2O$ (50 mg) at atmospheric pressure by a conventional procedure. The residual oil obtained from the filtrate by evaporation of the solvent was dissolved in $CHCl_3$ and the solution was filtered through a short silica gel column. Removal of the solvent yielded **25** (1.07 g, 97% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1766, 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, tripletoid, m, $C\underline{H}_3$), 2.10 (3H, s, $COC\underline{H}_3$), 4.63 (1H, m, $\underline{H}$–Ç–O). MS *m/z* Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1564.

(1*S,5*S**,8*S**)-8-Butyl-1-(2-oxo-3-methoxycarbonylpropyl)-6-oxabicyclo[3.2.1]octan-7-one(27)**——According to the procedure of Whitlock,[23] a solution of **25** (217 mg, 0.912 mmol) in 10 ml (18.24 mmol) of 1.8 M methylmagnesium carbonate in *N*,*N*-dimethylformamide was heated at 125—130°C for 4 h. After cooling, the solution was acidified with 5% HCl and extracted with ether. The extract was washed with 5% sodium bicarbonate and the aqueous layer was acidified with 5% HCl, and then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine, dried over $MgSO_4$, and concentrated to leave a colorless oil. The oil in 5 ml of ether was methylated with etherial diazomethane and the product was purified by silica gel column chromatography with $CHCl_3$–hexane (4: 1) to yield **27** (232 mg, 86% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1723. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, tripletoid m, $C\underline{H}_3$), 2.73 (2H, s, $C\underline{H}_2$–CO–$CH_2CO_2CH_3$), 3.47 (2H, s, CH_2CO–$C\underline{H}_2$–CO_2CH_3), 3.73 (3H, s, $CO_2C\underline{H}_3$), 4.67 (1H, m, $\underline{H}$–Ç–O). MS *m/z* Calcd for $C_{16}H_{24}O_5$: 296.1623. Found: 296.1632.

(1*S,5*S**,8*S**)-8-Butyl-1-(3-methoxycarbonylpropyl)-6-oxabicyclo[3.2.1]octan-7-one(28)**——The compound (**28**) was obtained in 97% overall yield from **27** by the following four successive reactions.

(a) Sodium borohydride (15 mg, 0.338 mmol) was added to a solution of **27** (100 mg, 0.338 mmol) in 4 ml of methanol with stirring at −30——40°C, and the mixture was stirred at −30°C for 1.5 h. The mixture was acidified with 5% HCl at 0°C, and the solvent was evaporated off *in vacuo* to leave an oily residue. The residue was extracted with $CHCl_3$, washed successively with 5% sodium bicarbonate and water, dried over $MgSO_4$, and concentrated to leave an oily residue (101 mg) which was used for the next step without purification.

(b) Triethylamine (0.2 ml) and methanesulfonyl chloride (0.1 ml) were added to a solution of the above residue (101 mg) in 5 ml of benzene (0.1 ml) under stirring, and the mixture was stirred at the same temperature for 2 h. The mixture was made basic with 5% sodium bicarbonate and extracted with ether. The ether extract was successively washed with 5% sodium bicarbonate, 5% HCl, and water, dried over $MgSO_4$, and concentrated to leave the mesylate (127 mg, 99% yield) as a colorless oil. The product was immediately used for the next step.

(c) Next, 0.2 ml of triethylamine and 0.075 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were added to the above mesylate (127 mg, 0.336 mmol) in 3 ml of benzene at 4°C, and the mixture was stirred at 4—7°C for 2 h. After acidification with 5% HCl at 0°C, the mixture was extracted with ether. The ether extract

was successively washed with 5% HCl and water, dried over $MgSO_4$, and concentrated to leave an α,β-unsaturated ester (93 mg, 98% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1766, 1720, 1660. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, tripletoid m, C<u>H</u>$_3$), 3.70 (3H, s, $CO_2C\underline{H}_3$), 4.63 (1H, m, <u>H</u>–Ç–O), 5.83 (1H, d, J=16 Hz, olefinic H), 6.38 (1H, t of d, J=7.5 and 16 Hz, olefinic H). MS m/z Calcd for $C_{16}H_{24}O_4$: 280.1674. Found: 280.1677.

(d) The above enoate (93 mg, 0.33 mmol) in 12 ml of methanol was catalytically hydrogenated over $PtO_2\cdot 2H_2O$ (10 mg) at atmospheric pressure by a conventional procedure. The residual oil obtained from the filtrate by evaporation of the solvent was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated brine, dried over $MgSO_4$, and concentrated to leave **28** (93 mg, 99% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1762, 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, tripletoid m, C<u>H</u>$_3$), 2.30 (2H, m, C<u>H</u>$_2$CO$_2$CH$_3$), 3.63 (3H, s, OC<u>H</u>$_3$), 4.61 (1H, m, <u>H</u>–Ç–O). MS m/z Calcd for $C_{16}H_{26}O_4$: 282.1829. Found: 282.1818.

(5*S,6*S**,7*S**)-2-Methoxycarbonyl-6-butyl-7-hydroxyspiro[4.5]decan-1-one (29)**——A solution of **28** (200 mg, 0.71 mmol) in 3 ml of dry THF was added dropwise to a suspension of potassium hydride (176 mg, 4.4 mmol) in 4 ml of dry THF at 0°C, and the mixture was stirred at the same temperature for 4 h. The excess potassium hydride was decomposed with saturated aqueous ammonium chloride at −70°C with vigorous stirring. The solution was acidified with 5% HCl, and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave an oily residue. The residue was purified by silica gel column chromatography with hexane–$CHCl_3$ (1: 5) to give **29** (150 mg, 75% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1745 (shoulder), 1722. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, tripletoid m, C<u>H</u>$_3$), 3.68 (3H, s, OC<u>H</u>$_3$). MS m/z Calcd for $C_{16}H_{26}O_4$: 282.1829. Found: 282.1829.

(5*S,6*S**,7*S**)-6-Butyl-7-hydroxyspiro[4.5]decan-1-one (30)**——A mixture of **29** (30 mg, 0.106 mmol), 1,4-diazabicyclo[2.2.2]octane (119 mg, 1.06 mmol), and xylene (0.4 ml) was heated for 2 h at 110°C, then cooled. The solvent was evaporated off *in vacuo* to leave an oily residue which was purified by silica gel column chromatography with $CHCl_3$ to yield **30** (16 mg, 67% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, tripletoid m, C<u>H</u>$_3$), 3.37 (1H, m, <u>H</u>–Ç–OH). MS m/z Calcd for $C_{14}H_{24}O_2$: 224.1776. Found: 224.1774.

(5*S,6*S**,7S*)-6-Butyl-7-hydroxy-1-hydroxyiminospiro[4.5]decane (31)**——A mixture of **30** (10 mg, 0.046 mmol), sodium acetate (38 mg, 0.467 mmol), hydroxylamine hydrochloride (32.5 mg, 0.467 mmol), ethanol (3 ml), and water (1 ml) was heated under reflux for 3 h. The solvent mixture was evaporated off *in vacuo*, and the residual oil was extracted with $CHCl_3$. The extract was washed successively with 5% sodium bicarbonate and water, dried over $MgSO_4$, and concentrated to yield a semisolid. Recrystallization from a mixture of ether–hexane (1: 1) gave **31** (10.4 mg, 93% yield) as colorless crystals, mp 129—130°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3260, 3130, 2935, 1700, 1460, 1381, 1350, 1275, 1186, 1172, 1142, 1130, 1083, 1070, 1014, 990, 970, 950, 933, 909. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, tripletoid m, C<u>H</u>$_3$), 2.55 (2H, m, C<u>H</u>$_2$–C=N), 3.74 (1H, m, <u>H</u>–Ç–O). MS m/z Calcd for $C_{14}H_{25}NO_2$: 239.1885. Found: 239.1855. Nominal MS m/z 239 (M^+), 222, 221, 204, 189, 182, 168, 165, 164, 112 (base peak). The spectral data for **31** were in good accord with those reported by Corey.[15e]

(6*S,7*S**,8*S**)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (6) and 8-Formyl-5-(1-pentenyl)octanenitrile (32)**——A solution of **31** (49 mg, 0.21 mmol) in 2 ml of dry pyridine was treated portionwise with 80 mg (0.21 mmol) of *p*-toluenesulfonyl chloride with stirring at 0°C, and stirring was continued for 17 h at 0°C. Next, 5 ml of 5% sodium bicarbonate was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was successively washed with 5% sodium bicarbonate, water, 5% HCl, and then water, dried over $MgSO_4$, and concentrated to leave 42 mg of a colorless oil. The oil was chromatographed on a silica gel column; elution with $CHCl_3$ gave 10 mg (23% yield) of **32** and further elution gave 12 mg (25% yield) of **6**. **32**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250, 1724. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, tripletoid m, C<u>H</u>$_3$), 5.17 (1H, m, olefinic <u>H</u>), 9.60 (1H, t, J=1.5 Hz, C<u>H</u>O). MS m/z Calcd for $C_{14}H_{23}NO$: 221.1780. Found: 221.1787. **6**: Recrystallized from ether to give colorless prisms, mp 141—142°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3230, 1626. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, C<u>H</u>$_3$), 2.04—2.48 (2H, m, C<u>H</u>$_2$–CO), 4.04 (1H, m, <u>H</u>–Ç–O), 8.32 (1H, broad s, N<u>H</u>). MS m/z Calcd for $C_{14}H_{25}NO_2$: 239.1883. Found: 239.1881. The compound (**6**) was identical with an authentic sample provided by Professor Evans.[15b]

1-[(1*R,2*S**,3*S**)-2-Butyl-3-*tert*-butyldimethylsiloxycyclohexyl]ethanone (39) and Its (1*S**)-Isomer (40) from 1-(3-*tert*-Butyldimethylsiloxy-1-cyclohexen-1-yl)ethanone (38) and BuCu·AlCl$_3$**——To a suspension of CuI ((0.8 g, 4.2 mmol) in dry ether (5 ml) at −40°C was added dropwise 2.5 ml (3.94 mmol) of 1.56 M BuLi in hexane at −40°C with stirring, and the mixture was stirred for 20 min. Then a solution of $AlCl_3$ (533 mg, 4 mmol) in 3 ml of dry ether was added at −70°C with stirring, and the whole was stirred at the same temperature for 1 h. The enone (**38**) (200 mg, 0.79 mmol) in 3 ml of dry ether was added dropwise to the above mixture at −70°C with stirring and the temperature was allowed to rise to −25°C. The mixture was poured into an ice-cooled saturated solution of ammonium chloride. The inorganic precipitates were filtered off, and the filtrate was extracted with ether. The usual work-up of the etherial solution gave an oily residue which was chromatographed on a silica gel column. Elution with hexane–$CHCl_3$ (1: 4) gave 17 mg (7% yield) of **40** and further elution gave 190 mg (77% yield) of **39**. **39**: Kugelrohr distillation, bath temperature 11°C (3 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1703, 842. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.88 (9H, s, SiBu^t),

2.15 (3H, s, $COCH_3$), 3.42 (1H, m, H-C-O). *Anal.* Calcd for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61. Found: C, 69.38; H, 11.58. **40**: Kugelrohr distillation, bath temperature 120°C (1 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1699, 840. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiBu^t$), 2.08 (3H, s, $COCH_3$), 2.98 (1H, m, CO-CH-), 4.00 (1H, m, -O-C-H). MS *m/z* Calcd for $C_{18}H_{36}O_2Si$: 312.2485. Found: 312.2488.

Equilibration of 40 with Potassium Hydride——A solution of **40** (50 mg, 0.16 mmol) in 1 ml of a mixture of THF–hexamethylphosphoric triamide (9: 1) was added to a stirred suspension of potassium hydride (30 mg, 0.75 mmol) in 2 ml of dry THF at −50°C. The temperature of the mixture was allowed to rise to 20°C and stirring was continued for 2.5 h. The solution was acidified with 5% HCl at −30°C and extracted with ether. The extract was successively washed with 5% HCl, water, 5% sodium bicarbonate, dried over $MgSO_4$, and concentrated to leave an oily residue. Silica gel column chromatographic separation with $CHCl_3$ gave recovered **40** (25 mg, 50% yield) and then **39** (15 mg, 30% yield). Both **39** and **40** were identified by IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$) and TLC comparisons with authentic samples.

Methyl (1*R,2*S**,3*S**)-2-Butyl-3-*tert*-butyldimethylsiloxy-1-cyclohexanecarboxylate (43)**——A solution of **39** (2.8 g, 9 mmol) in 5 ml of THF was added to a stirred solution of lithium diisopropylamide (12.6 mmol) in 20 ml of dry THF at −70°C, and the mixture was stirred for 15 min. The temperature of the mixture was allowed to rise to −40°C, and the mixture was stirred at the same temperature for 30 min, then cooled to −70°C. Next, 0.7 ml (5.4 mmol) of triethylamine and 2.1 ml (17.1 mmol) of trimethylchlorosilane were added at −70°C under stirring, the temperature was gradually raised to −10°C. Saturated aqueous sodium bicarbonate (10 ml) was added dropwise to the above mixture at −70°C with stirring. The major portion of the solvent was removed under reduced pressure and the concentrate was extracted with pentane–ether (1: 1). The extract was successively washed with cold 5% HCl, water, 5% sodium bicarbonate, and then water, dried over $MgSO_4$, and concentrated to leave **42** (3.446 g) as a colorless, rather labile oil. The oil (**42**) (3.446 g, 9 mmol) in 50 ml of dry hexane was oxidized with ozone at −70°C with stirring. The usual work-up led to a colorless oily carboxylic acid (2.8 g), which was methylated with ethereal diazomethane. Silica gel column chromatographic purification gave 2.83 g (96% yield) of **43** as a colorless oil. Kugelrohr distillation, bath temperature 130°C (2 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiBu^t$), 2.20 (1H, m, H-C-CO_2CH_3), 3.39 (1H, m, H-C-OSi), 3.66 (3H, s, CO_2CH_3). *Anal.* Calcd for $C_{18}H_{36}O_3Si$: C, 65.85; H, 10.97. Found: C, 65.69; H, 11.12.

Dimethyl (2*S,3*S**)-2-Butyl-3-*tert*-butyldimethylsiloxy-1,1-cyclohexanedicarboxylate (45)**——A solution of **43** (210 mg, 0.64 mmol) in 3 ml of dry THF was added dropwise to a stirred solution of diisopropylamide (2.5 mmol) in 3 ml of dry THF at −70°C, and the temperature was allowed to rise to −40°C. After stirring for a further 1 h at −40°C, CO_2 was bubbled through the mixture at −70°C. To the above mixture, 1 ml of saturated ammonium chloride, 5 ml of 5% HCl, and then excess ethereal diazomethane were successively added with stirring at −30°C. The solution was extracted with ether and the extract was successively washed with 5% HCl, water, and then 5% sodium bicarbonate, dried over $MgSO_4$, and concentrated to leave a colorless oil. The oil was purified by silica gel column chromatography with hexane–ether (1: 9) to give **45** (234 mg, 95% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiBu^t$), 3.72 (6H, s, $CO_2CH_3 \times 2$). MS *m/z* Calcd for $C_{20}H_{38}O_5Si$: 386.2488. Found: 386.2493.

Ethyl Methyl (1*R,2*S**,3*S**)-2-Butyl-3-*tert*-butyldimethylsiloxy-1,1-cyclohexanedicarboxylate (46)**——The diester (**46**) was prepared from **43** in a 80% yield by a procedure similar to the preparation of **45** but using diazoethane instead of diazomethane. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiBu^t$), 3.72 (3H, s, CO_2CH_3), 4.16 (2H, q, J=7 Hz, $CO_2CH_2CH_3$). MS *m/z* Calcd for $C_{21}H_{40}O_5Si$: 400.2642. Found: 400.2637.

(1*R,5*S**,8*S**)-8-Butyl-1-methoxycarbonyl-6-oxabicyclo[3.2.1]octan-7-one (47)**——A mixture of **45** (264 mg, 0.684 mmol), methanol (4 ml), and 5% HCl (0.4 ml) was heated at 50°C for 2 h. After evaporation of the solvent *in vacuo*, the residual oil was extracted with ether. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil. Purification of the oil by alumina column chromatography with $CHCl_3$ gave **47** (145 mg, 86% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775, 1734. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, tripletoid m, CH_3), 3.76 (3H, s, CO_2CH_3), 4.70 (1H, m, H-C-O). MS *m/z* Calcd for $C_{13}H_{20}O_4$: 240.1359. Found: 240.1354.

(1*R,5*S**,8*S**)-8-Butyl-1-formyl-6-oxabicyclo[3.2.1]octan-7-one (48)**——Diisobutylaluminum hydride (11.2 ml, 11.2 mmol in hexane) was added dropwise to a solution of **47** (677 mg, 2.8 mmol) in 30 ml of hexane–toluene (4: 1) with stirring at −70°C and the mixture was stirred at the same temperature for 3 h. Then, 30 ml of 3 M aqueous NaOH was added to the mixture with vigorous stirring, the whole was allowed to warm to ambient temperature, and stirring was continued for 2 h. After acidification with 5% HCl, the solution was extracted with $CHCl_3$. The extract was washed with saturated brine, dried over $MgSO_4$ and concentrated to leave a colorless oil, which was used for the next oxidation step. Pyridinium chlorochromate (1.5 g) was added portionwise to the above oil (670 mg) in 10 ml of CH_2Cl_2 and the mixture was stirred for 48 h at ambient temperature. The mixture was filtered through a short silica gel column and the column was eluted with $CHCl_3$. Evaporation of the solvent *in vacuo* left **48** (220 mg, 42% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1769, 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7 Hz, CH_3), 4.80 (1H, t, J=4.5 Hz, H-C-O), 9.62 (1H, s, CHO). The compound (**48**) was used immediately for the next step due to its instability.

(1*S,5*S**,8*S**)-8-Butyl-1-(2-methoxycarbonylethyl)-6-oxabicyclo[3.2.1]octan-7-one (49)**——The compound (**49**) was derived from **48** by the following two reaction sequences: (a) Trimethyl phosphonoacetate (910 mg, 5 mmol) in 5 ml of ether was added dropwise with stirring to a suspension of sodium hydride (120 mg, 5 mmol) in 20 ml of benzene–ether (1: 1) at 0°C, and the mixture was stirred at 5°C for 1 h. The sodium salt solution of trimethyl phosphonoacetate was added to the aldehyde (**48**) (210 mg, 1 mmol) in 10 ml of benzene–ether (1: 1) with stirring at 0°C, and the mixture was stirred at this temperature for 2 h. Saturated ammonium chloride solution was added to the mixture with stirring at −40°C and the solution was acidified with 5% HCl at 0°C. The solution was extracted with ether and the extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oily enoate (220 mg).

(b) The above enoate (220 mg) in 10 ml of methanol was catalytically hydrogenated over $PtO_2 \cdot 2H_2O$ (30 mg) at atmospheric pressure by a conventional procedure. The residual oil obtained from the filtrate by evaporation of the solvent was purified by silica gel column chromatography with hexane–$CHCl_3$ (1: 7) to give **49** (198 mg, 74% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1763, 1732. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, tripletoid m, C<u>H</u>$_3$), 3.66 (3H, s, COC<u>H</u>$_3$), 4.66 (1H, m, <u>H</u>–C–O). MS *m/z* Calcd for $C_{15}H_{24}O_4$: 268.1674. Found: 268.1675.

(5*S,6*S**,7*S**)-7-Acetoxy-6-butylspiro[4.5]decan-1-one (50), (5*S**,6*S**,7*S**)-2,7-Diacetoxy-6-butylspiro[4.5]decan-1-one (51), and (5*S**,6*S**,7*S**)-1,7-Diacetoxy-6-butylspiro[4.5]decan-2-one (52)**——A solution of **49** (90 mg, 0.373 mmol) in a mixture of toluene (3 ml) and trimethylchlorosilane (0.48 ml, 3.73 mmol) was added dropwise to a refluxing suspension of sodium (86 mg, 3.37 mmol) in 5 ml of toluene with vigorous stirring, and the mixture was refluxed for 1 h. After cooling, the suspension was filtered and the filtrate was concentrated *in vacuo* to leave a colorless oil (138 mg) which was immediately used for the next step. To the above oil (138 mg) in 5 ml of THF was added 0.25 ml of 5% HCl with stirring at 0°C, and the mixture was stirred for 15 min. The solution was concentrated at ambient temperature *in vacuo* and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil (90 mg). The above oil (90 mg) was dissolved in 10 ml of $CHCl_3$, and 0.5 ml of pyridine, 0.5 ml of acetic anhydride, and 10 mg of 4-dimethylaminopyridine were added with stirring at 0°C. The mixture was stirred at ambient temperature for 5 h, then the usual work-up led to a colorless oil (76 mg) which was chromatographed on a silica gel column. Elution with $CHCl_3$ provided successively **50**, **51** (a separable epimeric mixture), and **52** (an inseparable epimeric mixture). **50**: a colorless oil (14 mg, 16% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, C<u>H</u>$_3$), 2.01 (3H, s, COC<u>H</u>$_3$), 4.61 (1H, m, <u>H</u>–C–O). MS *m/z* Calcd for $C_{16}H_{26}O_3$: 266.1879. Found: 266.1878. **51a** (one of the epimers at the C-2 position): a colorless oil (22 mg, 20% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, tripletoid m, C<u>H</u>$_3$), 2.00 and 2.08 (each 3H, s, COC<u>H</u>$_3$ × 2), 4.53 (1H, m, <u>H</u>–C–O), 4.96 (1H, t, J = 9 Hz, –CO–C(<u>H</u>)–OAc). MS *m/z* Calcd for $C_{18}H_{28}O_5$: 324.1934. Found: 324.1926. **51b** (the other C-2 epimer): a colorless oil (26 mg, 24% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, tripletoid m, C<u>H</u>$_3$), 2.01 and 2.10 (each 3H, s, COC<u>H</u>$_3$ × 2), 4.55 (1H, m, <u>H</u>–C–O), 5.25 (1H, t, J = 8 Hz, –CO–C(<u>H</u>)–OAc). MS *m/z* Calcd for $C_{18}H_{28}O_5$: 324.1934. Found: 324.1940. **52** (an inseparable epimeric 1: 1 mixture): a colorless oil (18 mg, 17% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1729. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, tripletoid m, C<u>H</u>$_3$), 1.97, 2.00, 2.10, 2.13 (each 1.5H, s, COC<u>H</u>$_3$ × 2), 4.73 (1H, m, <u>H</u>–C–O), 5.02, 5.33 (each 0.5H, s, –CO–C(<u>H</u>)–OAc). MS *m/z* Calcd for $C_{18}H_{28}O_5$: 324.1934. Found: 324.1939.

Zinc-Acetic Acid Reduction of 51a——A mixture of **51a** (10 mg, 0.15 mmol), acetic acid (2 ml), zinc dust (800 mg), and ammonium chloride (0.5 g) was heated with stirring under reflux for 8 h. The major portion of the solvent was removed under reduced pressure. Ether was added to the residue and the suspension was filtered. The filtrate was successively washed with water, 5% sodium bicarbonate, 5% HCl, and water, dried over $MgSO_4$, and concentrated to leave an oil. Silica gel column chromatographic separation of the oil with $CHCl_3$ furnished **50** (5 mg, 87% based on the consumed starting material) and 3 mg of the starting material. The compound (**50**) was found to be identical with an authentic sample by IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$), TLC, and GLC comparisons.

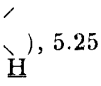
(5*S,6*S**,7*S**)-7-Acetoxy-6-butyl-1-hydroxyiminospiro[4.5]decane (53)**——A mixture of **50** (45 mg, 0.17 mmol), sodium acetate (554 mg, 6.76 mmol), hydroxylamine hydrochloride (470 mg, 6.76 mmol), ethanol (7 ml), and water (4 ml) was heated in a sealed glass tube at 110°C for 66 h. After cooling, the mixture was made basic with 5% sodium bicarbonate and extracted with $CHCl_3$. The extract was washed with 5% sodium bicarbonate and then water, dried over $MgSO_4$, and concentrated to leave a colorless oil. The oil was chromatographed on a silica gel column with $CHCl_3$–hexane (4: 1) to yield **53** (40 mg, 84% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 3280, 1722. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, tripletoid m, C<u>H</u>$_3$), 2.00 (3H, s, COC<u>H</u>$_3$), 2.16—2.73 (2H, m, –C<u>H</u>$_2$–C=N), 4.61 (1H, m, <u>H</u>–C–O). MS *m/z* Calcd for $C_{16}H_{27}NO_3$: 281.1988. Found: 281.1988.

(6*S,7*S**,8*S**)-8-Acetoxy-7-butyl-1-azaspiro[5.5]undecan-2-one (54)**——At ambient temperature, 10 mg of 4-dimethylaminopyridine and 81 mg (0.426 mmol) of *p*-toluenesulfonyl chloride were added to a solution of **53** (40 mg, 0.142 mmol) in 0.5 ml of pyridine with stirring, and the mixture was stirred for 3 h. The usual work-up of the reaction mixture led to a yellow oil which was chromatographed on a silica gel column with

acetone–$CHCl_3$ (1: 9) to yield a crystalline mass. Recrystallization from hexane–ether (1: 1) gave **54** (13 mg, 33% yield) as colorless prisms, mp 153—154°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1724, 1645. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, C<u>H</u>$_3$), 2.08 (3H, s, COC<u>H</u>$_3$), 2.32 (2H, m, C<u>H</u>$_2$CO), 4.90 (1H, m, <u>H</u>–Ç–OAc), 6.02 (1H, broad s, N<u>H</u>). MS *m/z* Calcd for $C_{16}H_{27}NO_3$: 281.1988. Found: 281.1987.

(6*S,7*S**,8*S**)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (6)**——A solution of methanolic sodium methoxide [prepared from 7.8 mg (0.34 mmol) of sodium and 1.2 ml of dry methanol] was added to a solution of **54** (16 mg, 0.057 mmol) in 2 ml of dry methanol, and the mixture was refluxed for 1 h, then cooled. The solvent was evaporated off under reduced pressure and the residual oil was extracted with $CHCl_3$. The extract was washed with 5% HCl and then water, dried over $MgSO_4$, and concentrated to leave a crystalline mass. Recrystallization from ether gave **6** (11 mg, 81% yield) as colorless crystals, mp 142—144°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200, 2925, 2860, 1635, 1450, 1404, 1377, 1342, 1304, 1276, 1223, 1180, 1164, 1154, 1140, 1115, 1096, 1068, 1021, 1005, 998, 976, 941, 930, 917, 890, 827, 803, 786, 721, 690. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, C<u>H</u>$_3$), 2.04—2.48 (2H, m, C<u>H</u>$_2$CO), 2.76 (1H, broad s, O<u>H</u>), 4.04 (1H, m, <u>H</u>–Ç–O), 8.12 (1H, broad s, N<u>H</u>). The compound (**6**) thus obtained was identical with an authentic sample provided by Professor Evans.

Methyl (1*R,2*S**,3*S**)-2-Butyl-3-hydroxy-1-cyclohexanecarboxylate (57)**——A mixture of **43** (1.28 g, 3.9 mmol), THF (3 ml), methanol (10 ml), 5% HCl (2 ml), and water (2 ml) was stirred at ambient temperature for 4 h. The major portion of the solvent was evaporated off under reduced pressure and the residual oil was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil. Kugelrohr distillation at 125°C (1 mmHg) gave **57** (810 mg, 97% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, tripletoid m, C<u>H</u>$_3$), 2.20 (3<u>H</u>, m, H–Ç–CO_2C<u>H</u>$_3$), 3.45 (1H, m, <u>H</u>–Ç–OH), 3.71 (3H, s, OC<u>H</u>$_3$). MS *m/z* Calcd for $C_{12}H_{22}O_3$: 214.1570. Found: 214.1573.

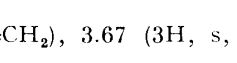
Methyl (1*S,2*S**,3*S**)-2-Butyl-3-(2-tetrahydrofuranyloxy)-1-cyclohexanecarboxylate (58)**——To a solution of **57** (666 mg, 3.1 mmol) in 5 ml of $CHCl_3$ were added 1.3 ml (17.2 mmol) of 2,3-dihydrofuran and 5 mg of pyridinium *p*-toluenesulfonate with stirring at 0°C, and the mixture was stirred for 2 h. The solution was made basic with 5% sodium bicarbonate and extracted with ether. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil which was purified by alumina column chromatography with ether to give **58** (836 mg, 95% yield). Kugelrohr distillation at 115°C (2 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, tripletoid m, C<u>H</u>$_3$), 3.67 (3H, s, OC<u>H</u>$_3$), 3.87 (3H, m, ), 5.25 (1H, m,  –). *Anal.* Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.58; H, 10.10.

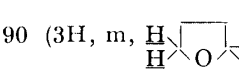
Methyl (1*R,2*S**,3*S**)-2-Butyl-3-hydroxy-1-(2-propenyl)-1-cyclohexanecarboxylate (59)**——Hexamethyldisilazane (4.6 ml, 22 mmol) was added dropwise to a suspension of potassium hydride (0.82 g, 20.9 mmol) in 17 ml of THF with stirring at ambient temperature. The mixture was stirred for 30 min, then **58** (845 mg, 2.98 mmol) in 10 ml of THF was added dropwise to the mixture with stirring and the whole was stirred for 1 h at ambient temperature. Allyl bromide (2.6 ml, 30 mmol) and then hexamethylphosphoric triamide (1 ml) were added dropwise with stirring to the above mixture at −10°C. The reaction mixture was stirred for 13 h at ambient temperature, then poured into saturated aqueous ammonium chloride solution with vigorous stirring and the major portion of the solvent was removed under reduced pressure. The residual aqueous solution was extracted with ether and the extract was successively washed with cold 1% HCl, 5% sodium bicarbonate, and water, dried over $MgSO_4$, and concentrated to leave an oil. The oil in a mixture of THF (25 ml) and 1% HCl (5 ml) was stirred at ambient temperature for 3 h. After removal of THF under reduced pressure at 0°C, the residual aqueous solution was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil which was chromatographed on a silica gel column with hexane–$CHCl_3$ (1: 20) to give **59** (491 mg, 65% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 3425, 1720, 1643. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, C<u>H</u>$_3$), 2.58 (2H, m, C<u>H</u>$_2$–CH=C<u>H</u>$_2$), 3.66 (3H, s, OC<u>H</u>$_3$), 3.90 (1H, m, <u>H</u>–C–O), 4.85—6.15 (3H, m, C<u>H</u>=C<u>H</u>$_2$). Nominal MS *m/z* 254 (M^+), 236, 222, 196 (base peak), 177. MS *m/z* Calcd for $C_{15}H_{26}O_3$: 254.1880. Found: 254.1875.

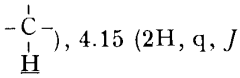
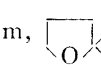
(1*R,5*R**,8*S**)-8-Butyl-1-(2-propenyl)-6-oxabicyclo[3.2.1]octan-7-one (60)**——*p*-Toluenesulfonic acid (50 mg) was added to a solution of **59** (505 mg, 1.99 mmol) in 5 ml of benzene, and the solution was heated under reflux for 13 h. The solution was cooled, then 50 ml of $CHCl_3$–ether (1: 4) was added and the organic layer was washed successively with 5% sodium bicarbonate, 5% HCl, and water, dried over $MgSO_4$, and concentrated to leave an oily residue which was chromatographed on a silica gel column with hexane–$CHCl_3$ (3: 7) to yield **60** (270 mg, 61% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1766. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, tripletoid m, C<u>H</u>$_3$), 2.34 (2H, m, C<u>H</u>$_2$–CH=C<u>H</u>$_2$), 4.57 (1H, d, J=3.7 Hz, <u>H</u>–Ç–O), 5.00—6.00 (3H, m, C<u>H</u>=C<u>H</u>$_2$). MS *m/z* Calcd for $C_{14}H_{22}O_2$: 222.1619. Found: 222.1619.

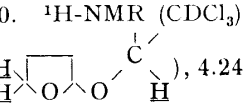
(1*S,5*S**,8*S**)-8-Butyl-1-(2-propenyl)-6-oxabicyclo[3.2.1]octan-7-one (62)**——A solution of **57** (55 mg, 0.26 mmol) in 1 ml of THF was added dropwise to a solution of lithium diisopropylamide (1 mmol) in 1 ml of dry THF at −70°C with stirring, and the temperature of the solution was allowed to rise to −40°C. Stirring was continued for 2 h at −40°C. Allyl bromide (0.1 ml, 12 mmol) was added to the solution at −70°C with stirring and the mixture was stirred for 2 h at −40°C. Saturated ammonium chloride solution (3 ml)

was added to the solution at −40°C with stirring and the solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over $MgSO_4$, and concentrated to leave an oil, which was chromatographed on silica gel column with $CHCl_3$ to give **62** (14 mg, 25% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1761. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, tripletoid m, C$\underline{H}_3$), 4.71 (1H, t, J=4.7 Hz, $\underline{H}$–C(–O)), 4.92—5.98 (3H, m, C$\underline{H}$=C$\underline{H}_2$). MS *m/z* Calcd for $C_{14}H_{22}O_2$: 222.1619. Found: 222.1615.

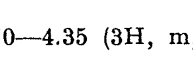
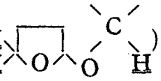
Methyl (1*R,2*S**,3*S**)-2-Butyl-1-(2-propenyl)-3-(2-tetrahydrofuranyloxy)-1-cyclohexanecarboxylate (63)**——To a stirred solution of **59** (40 mg, 0.16 mmol) in 1.5 ml of $CHCl_3$ were added 0.12 ml (1.6 mmol) of 2,3-dihydrofuran and 5 mg of pyridinium *p*-toluenesulfonate at 0°C, and the mixture was stirred for 1 h. The mixture was made basic with saturated sodium bicarbonate solution and then extracted with ether. The extract was successively washed with 5% sodium bicarbonate and water, dried over $MgSO_4$, and concentrated to give an oil, which was purified by alumina column chromatography with hexane to yield **63** (47 mg, 92% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (tripletoid m, C$\underline{H}_3$), 2.60 (2H, m, C$\underline{H}_2$–C$\underline{H}$=C$\underline{H}_2$), 3.67 (3H, s, OC$\underline{H}_3$), 3.88 (3H, m, ), 5.27 (1H, m, ), 4.80—5.85 (3H, m, C$\underline{H}$=C$\underline{H}_2$). MS *m/z* Calcd for $C_{19}H_{32}O_4$: 324.2298. Found: 324.2292.

Methyl (1*R,2*S**,3*S**)-2-Butyl-1-(3-ethoxycarbonyl-2-propenyl)-3-(2-tetrahydrofuranyloxy)-1-cyclohexanecarboxylate (64)**——The enoate (**64**) was obtained from **63** by the following two successive reactions. (a) A stirred solution of **63** (1.4 g, 4.32 mmol) in a mixture of 25 ml of THF and 10 ml of water was treated withr 930 mg (8.64 mmol) of *N*-methylmorpholine *N*-oxide and 67 mg (0.26 mmol) of osmium tetroxide, and the mixture was stirred for 15 min. Sodium periodate (1.85 g, 8.64 mmol) was added to the mixture in portions with stirring, and stirring was continued for a further 3.5 h at amibient temperature. The solution was acidified with 5% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over $MgSO_4$, and concentrated to leave an oily unstable aldehyde which was immediately used for the next step without purification. (b) Triethyl phosphonoacetate (5.16 g, 23 mmol) in 15 ml of dry ether was added dropwise to a suspension of sodium hydride (0.52 g, 21.6 mmol) in 5 ml of dry ether with stirring at 0°C, and the mixture was stirred for 1 h. The sodium salt solution of triethyl phosphonoacetate was added with stirring at 0°C to the aldehyde prepared as described above in 10 ml of ether, and the mixture was stirred for 15 min. The usual work-up led to a colorless oil which was chromatographed on a silica gel column with $CHCl_3$ to yield **64** (1.3 g, 76% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1713, 1655. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, tripletoid m, C$\underline{H}_3$), 1.27 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.72 (2H, m, C$\underline{H}_2$–CH=CH_2), 3.67 (3H, s, OC$\underline{H}_3$), 3.90 (3H, m, ), 4.19 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.24 (1H, m, ), 5.81 (1H, m, CH=C$\underline{H}$–$CO_2C_2H_5$), 6.45—7.15 (1H, m, C$\underline{H}$=CH–$CO_2C_2H_5$). MS *m/z* Calcd for $C_{22}H_{36}O_6$: 396.2510. Found: 396.2510.

Methyl (1*R,2*S**,3*S**)-2-Butyl-1-(3-ethoxycarbonylpropyl)-3-(2-tetrahydrofuranyloxy)-1-cyclohexanecarboxylate (65)**——The enoate (**64**) (1.3 g, 3.3 mmol) in 20 ml of ethanol was catalytically hydrogenated over $PtO_2 \cdot 2H_2O$ (100 mg) at atmospheric pressure by a conventional procedure. The residual oil obtained from the filtrate by evaporation of the solvent was dissolved in $CHCl_3$ and the solution was filtered through a silica gel column to obtain **65** (1.28 g, 98% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1721. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid, m, C$\underline{H}_3$), 1.26 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 3.67 (3H, s, $CO_2C\underline{H}_3$), 3.82 (3H, m, ), 4.15 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.25 (1H, m, ). MS *m/z* Calcd for $C_{22}H_{38}O_6$: 398.2667. Found: 398.2662.

(5*R,6*S**,7*S**)-6-Butyl-2-ethoxycarbonyl-7-(2-tetrahydrofuranyloxy)spiro[4.5]decan-1-one (66)**——A solution of **65** (1 g, 2.5 mmol) in 10 ml of dry THF was added dropwise to a stirred suspension of potassium hydride (160 mg, 4 mmol) in 8 ml of dry THF at −10°C, and the mixture was stirred at −5°C for 2.5 h. The excess reagent was decomposed with saturated ammonium chloride solution (2 ml) at −70°C with stirring, and the mixture was acidified with 5% HCl. The mixture was extracted with $CHCl_3$, and the extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil. Silica gel column chromatographic purification of the oil with $CHCl_3$ gave **66** (800 mg, 87% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1744, 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, tripletoid m, C$\underline{H}_3$), 1.30 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 3.90 (3H, m, ), 4.24 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.29 (1H, m, ). MS *m/z* Calcd for $C_{21}H_{34}O_5$: 366.2405. Found: 366.2395.

(5*R,6*S**,7*S**)-6-Butyl-8-(2-tetrahydrofuranyloxy)spiro[4.5]decan-1-one (67)**——A mixture of **66** (100 mg, 0.27 mmol), dimethyl sulfoxide (3 ml), water (1 ml), lithium chloride (20 mg), and sodium bicarbonate (10 mg) was heated with stirring at 150°C (bath temperature) for 3 h, then cooled. Ice-water (10 ml) was added to the mixture and the mixture was extracted with ether. The extract was washed with saturated brine, dried over $MgSO_4$, and concentrated to leave a colorless oil. Silica gel column chromatographic purification

of the residual oil with $CHCl_3$ gave **67** (74 mg, 92% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1723. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, C<u>H</u>$_3$), 3.70—4.35 (3H, m, ), 5.30 (1H, m, ). MS *m/z* Calcd for $C_{18}H_{30}O_3$: 294.2195. Found: 294.2201.

(5R*,6S*,7S*)-6-Butyl-7-hydroxy-1-hydroxyiminospiro[4.5]decane (68)——A mixture of **67** (85 mg, 0.28 mmol), sodium acetate (500 mg, 6.1 mmol), hydroxylamine hydrochloride (390 mg, 5.6 mmol), methanol (10 ml) and water (1 ml) was heated in a sealed tube at 170°C for 36 h, then cooled. The major portion of the solvent was removed under reduced pressure. The residual oil was extracted with $CHCl_3$ and the extract was washed with 5% sodium bicarbonate and then water, dried over $MgSO_4$, and concentrated to leave a colorless oil. The residual oil was chromatographed on a silica gel column with $CHCl_3$–acetone (9: 1) to yield a crystalline mass. Recrystallization from ether gave **68** (60 mg, 87% yield) as colorless crystals, mp 56°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3300. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, C<u>H</u>$_3$), 2.53 (2H, m, C<u>H</u>$_2$–C=NOH), 4.13 (1H, m, <u>H</u>–C–O), 8.77 (1H, s, C=NO<u>H</u>). MS *m/z* Calcd for $C_{14}H_{25}NO_2$: 239.1886. Found: 239.1886.

(6*R,7*S**,8*S**)-7-Butyl-8-(4-methylphenylsulfonyloxy)-1-azaspiro[5.5]undecan-2-one (69)**——A stirred solution of **68** (57 mg, 0.24 mmol) in 0.2 ml of dry pyridine was treated with 91 mg (0.24 mmol) of *p*-toluenesulfonyl chloride at 0°C, and the mixture was stirred at the same temperature for 20 h. The usual work-up of the mixture led to a yellow oily residue which was purified by preparative TLC (silica gel PF_{254}, Merck) with $CHCl_3$–acetone (9: 1). Recrystallization from acetone gave **69** (35 mg, 38% yield) as colorless prisms, mp 164—165°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400—3200, 1649. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, tripletoid m, C<u>H</u>$_3$), 2.35 (2H, m, HN–CO–C<u>H</u>$_2$), 4.70 (1H, m, <u>H</u>–C–O), 6.90 (1H, broad s, N<u>H</u>), 7.37 (2H, d, J=9 Hz, aromatic protons), 7.88 (2H, d, J=9 Hz, aromatic protons). MS *m/z* Calcd for $C_{21}H_{31}NO_4S$: 393.1973. Found: 393.1978.

X-Ray Analysis of 69——Single crystals of the compound (**69**) were prepared by slow crystallization from acetone. The crystals were triclinic, space group P$\bar{1}$ with the unit cell dimensions a=8.873(1), b=10.499(1), c=12.391(2) Å, α=96.44(1), β=103.77(1), γ=104.63(1)°, and D_{calcd}=1.216 g·cm^{-3} for Z=2 ($C_{21}H_{31}NO_4S$, mol wt 393.20). A crystal with dimensions of 0.26×0.33×0.48 mm was used for data collection. The intensity data were measured on a Rigaku AFC-5 diffractometer with Ni-filtered monochromated Cu$K\alpha$ radiation (λ=1.54178 Å), using the ω-2θ scan method at an ω scan speed of 2° min^{-1}. Three standard reflections were measured every 50 reflections to monitor intensity fluctuations. Absorption corrections were not applied (μ=15.10 cm^{-1}). A total of 3158 reflection data were collected for θ<60°, of which 3060 reflections were considered to be usable (F_o>2σ(F_o)). The structure was solved by the direct method using MULTAN 78 program, and was refined by the full-matrix least-squares method, minimizing the function $\Sigma w(F_o-F_o)^2$ with $w=\sigma^{-2}$. The last cycles of refinement, which included anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms, converged the discrepancy factors R and R_w to 0.048 and 0.074, respectively. The final difference map has no peaks greater than ±0.2 eÅ^{-3}. All computations were performed on a FACOM M200 computer in the Data Processing Center of Kyoto University, using the KPAX system for X-ray structure analysis.

(6*R,7*S**,8*S**)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (7)**——A solution of sodium-naphthalene[37] (1 mmol in 1 ml of THF) was added to a stirred solution of **69** (8 mg, 0.02 mmol) in 0.2 ml of dry THF at ambient temperature, and the mixture was stirred for 20 min. The mixture was acidified with 5% HCl (2 ml) at 0°C and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil which was purified by silica gel column chromatography with $CHCl_3$–acetone (19: 1). Recrystallization from ether gave **7** (4.7 mg, 90% yield) as colorless crystals, mp 163°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1641. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, tripletoid m, C<u>H</u>$_3$), 2.33 (2H, m, C<u>H</u>$_2$–CONH), 3.51 (1H, m, <u>H</u>–C–O), 5.82 (1H, broad s, N<u>H</u>). MS *m/z* Calcd for $C_{14}H_{25}NO_2$: 239.1885. Found: 239.1886.

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