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Studies on Taxane Synthesis. II. Syntheses of 3,8,11,11-Tetramethyl-4-oxo- and 4,8,11,11-Tetramethyl-3-oxo-bicyclo[5.3.1]undec-8-enes Corresponding to the A- and B-Rings of Taxane Diterpenes[1]

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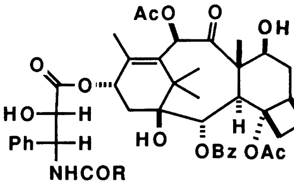
Two types of tetramethylbicyclo[5.3.1]undec-8-enes **2** and **3** were synthesized from α-ionone as a model for taxane synthesis. Introduction of the requisite *cis*-arrangement of substituents at the C-1 and C-7 positions was carried out by catalytic hydrogenation of the α,β-unsaturated ketone **12**. Treatment of the hydroxy ester **27** and **16** with diethyl azodicarboxylate and triphenylphosphine led to regioselective dehydration giving **33** and **43**, respectively. Intramolecular cyclization of **41** and **49** with lithium diisopropylamide followed by reductive desulfurization with Na–Hg produced the eight-membered ring ketones **2** and **3**, respectively, in good yields.

Keywords——tetramethylbicyclo[5.3.1]undec-8-ene; taxane; intramolecular cyclization; eight-membered ring; catalytic hydrogenation; dehydration; Baeyer–Villiger oxidation; Wittig reaction; twelve-membered lactam sulfoxide; sodium-amalgam

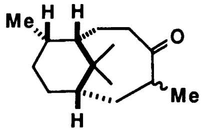
In the preceding paper,[2] we reported the synthesis of the bicyclo[5.3.1]undecane derivative **1** corresponding to the A and B parts of taxane diterpenes based on the strategy for medium-ring ketone formation developed in this laboratory.[3] However, although an α,β-unsaturated keto moiety or its equivalent is present in the A-ring of all of the natural diterpenes, it seemed difficult to introduce any functionality to the A-ring by the procedure used in the previous paper. Thus, we focused our attention on the development of a procedure capable of introducing a double bond into the A-ring of **1**. We now report the syntheses of the bicyclo[5.3.1]undecane derivatives **2** and **3** having a double bond at the C-8 position.

Preparation of the 9α-Hydroxy Ester 16, a Common Intermediate for the Syntheses of the Bicyclo[5.3.1]undecenes 2 and 3

Diketone **6**, possessing the requisite carbon framework and the appropriate functionality for A-ring formation, was chosen as the starting material. The compound **6** has already been synthesized directly from the epoxide **4** prepared from commercially available α-ionone by MeONa treatment, but the yield was only 8.3%.[4a] Thus, an alternate route from **4** was



taxol: $R = C_6H_5$
cephalomannine: $R = CMeCHMe$



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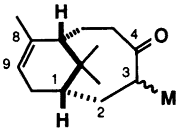

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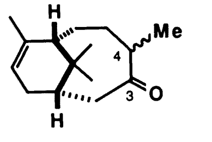


3

Fig. 1

sought. The epoxide **4** was converted into the dienyl ketone **5**[4] by K_2CO_3–MeOH treatment. The double bond in the side chain of **5** could be selectively reduced with NaTeH[5] and the resulting keto allyl alcohol was oxidized with Jones reagent affording the diketone **6** in 62% overall yield. Catalytic hydrogenation of **5** with Raney Ni (W-2, EtOH), PtO_2 (AcOEt) or Pd–C (AcOEt) followed by oxidation also gave **6**, but the yield was less than 35% in every case.

Preferential acetalization of the saturated carbonyl group in **6** took place on ethylene glycol–*p*-toluenesulfonic acid treatment, giving the ketone **7** in nearly quantitative yield. Introduction of a one-carbon unit at the C-1 position[6] in **7** was carried out in the same way as described in the preceding paper.[2] Thus 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation of **7** gave the cross-conjugated dienone **8** (70% yield). Diisopropylamine-induced addition of nitromethane to **8** afforded the Michael adduct **9** in 69% yield, although the reaction was quite slow. Then the nitromethyl group was treated with MeONa and $TiCl_3$[7] and the resultant crude aldehyde was oxidized with Jones reagent to the keto acid **10**, whose esterification followed by reacetallization produced the keto ester **12** *via* **11** in 67.5% overall yield from **9**.

The requisite *cis*-arrangement of substituents at the C-1 and C-7 positions for eight-membered ring formation was induced by catalytic hydrogenation of the α,β-unsaturated ketone. Namely, Pd–C catalyzed hydrogenation of **12** in the presence of sodium acetate[8] in ethyl acetate under $100\,kg/cm^2$ pressure of hydrogen afforded the keto ester **13** as a main product (63.9% yield) along with the isomeric keto ester **14** (5.3% yield), a mixture of the alcohols **15** (10.7% yield) and the 9α-hydroxy ester **16** (13.4% yield). When **13** was treated with MeONa in MeOH, epimerization took place at C-8 giving the more stable isomer **14** in

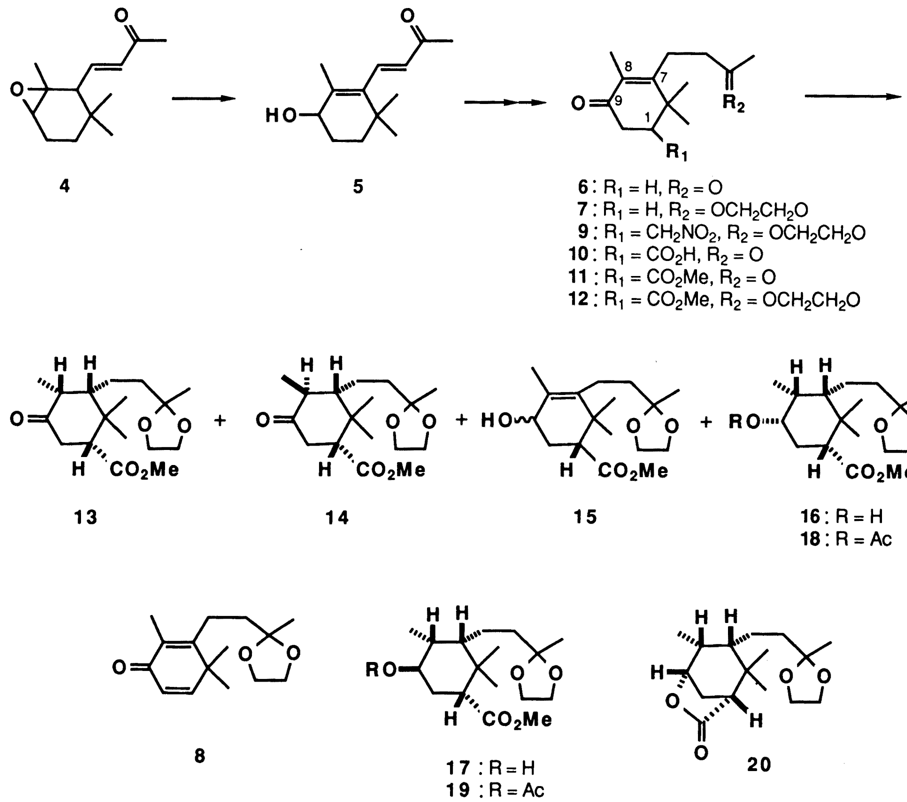


Fig. 2

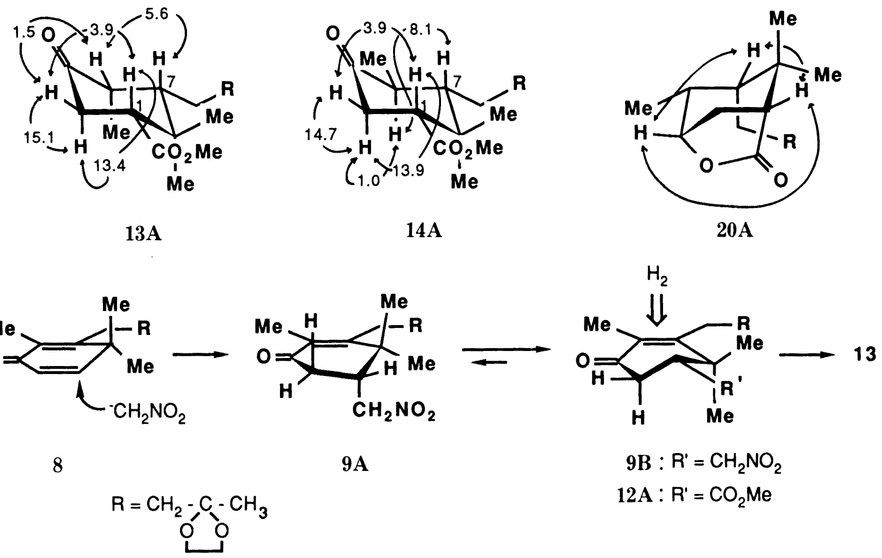


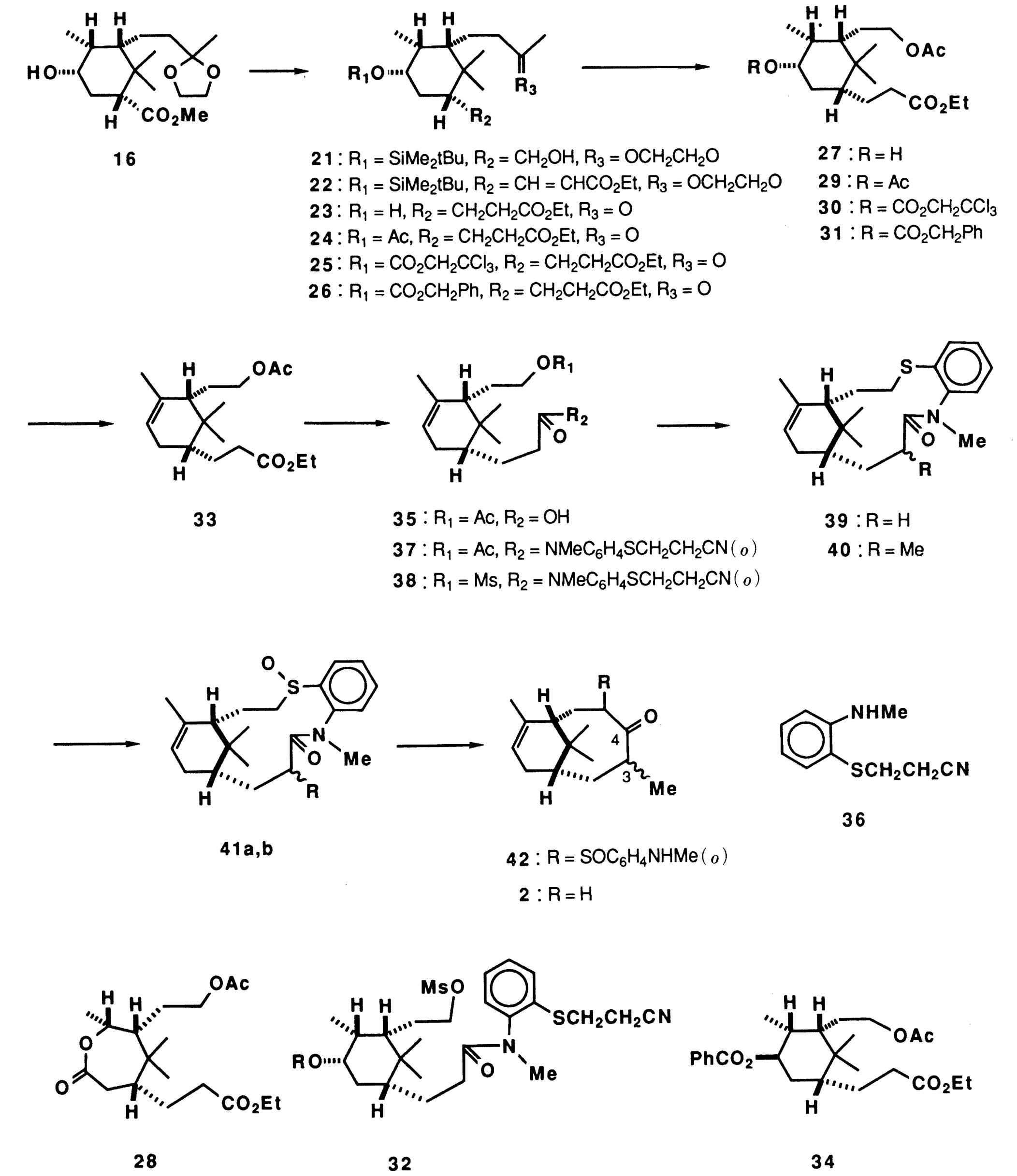
Fig. 3

quantitative yield. The stereostructures of **13** and **14** were deduced by proton nuclear magnetic resonance (^{1}H-NMR) analysis to be **13A** (C-8 Me, axial) and **14A** (C-8 Me, equatorial), respectively. The structure of the former **13** having *cis*-substituents at the C-1 and C-7 positions was finally confirmed by the conversion into the bicyclo[5.3.1]undecenes **2** and **3** as described later. The predominant formation of the 1,7-*cis* compounds **13** and **14** may be rationalized as follows. The initial Michael addition of nitromethane to the cross-conjugated dienone **8** may proceed from the direction perpendicular to the π-system from the less hindered α-side, affording **9A**. However, ring inversion should take place giving the more stable **9B**, in which the nitromethyl group is in the quasi-equatorial position. In the conformer **12A**, the α-side is sterically much more hindered than the β-side due to the presence of the quasi-axial methyl group at the C-11 position and thus catalyst may approach from the β-side giving mainly the 1,7-*cis* compound **13**.

Sodium borohydride ($NaBH_4$) reduction of **13** produced the 9α-hydroxy ester **16** predominantly (84.1% yield) along with a small amount of the 9β-isomer **17** (2.2% yield) ($\alpha:\beta$ ratio, 38 : 1). The configurations of the C-9 hydroxyl groups in **16** and **17** were assigned on the basis of the coupling constant of the C-9 hydrogen of the corresponding acetates **18** (J=4.2, 5.1, 12.2 Hz) and **19** (J=2.2, 2.7, 2.9 Hz). Reduction of **13** even with the sterically demanding potassium tri-*sec*-butylborohydride (K-Selectride) which usually approaches from the equatorial side giving an axial hydroxy group, afforded a mixture of **16** (83.3% yield) and **17** (9.6% yield) in the ratio of 8.7 : 1 demonstrating that the methyl group at C-8 was in the axial position. Moreover, the α-configuration of the C-9 hydroxy group in **16** was confirmed by the conversion into the bicyclic γ-lactone **20**, whose stereostructure was determined by the appearance of a long-range coupling between C-1, C-7 and C-9 hydrogen in the nuclear magnetic resonance (NMR) spectrum.

Synthesis of the Bicyclo[5.3.1]undecene 2

In the next stage, two-carbon elongation of the substituent at C-1 and two-carbon shortening of the substituent at C-7 are required. The Wittig reaction was used for two-carbon elongation. The compound **16** was, after silylation, reduced with $LiAlH_4$, affording the alcohol **21** in nearly quantitative yield. After pyridinium chlorochromate (PCC) oxidation, the resultant aldehyde was converted into the α,β-unsaturated ester **22** in 68% yield by treatment



16

21 : $R_1 = SiMe_2tBu$, $R_2 = CH_2OH$, $R_3 = OCH_2CH_2O$
22 : $R_1 = SiMe_2tBu$, $R_2 = CH = CHCO_2Et$, $R_3 = OCH_2CH_2O$
23 : $R_1 = H$, $R_2 = CH_2CH_2CO_2Et$, $R_3 = O$
24 : $R_1 = Ac$, $R_2 = CH_2CH_2CO_2Et$, $R_3 = O$
25 : $R_1 = CO_2CH_2CCl_3$, $R_2 = CH_2CH_2CO_2Et$, $R_3 = O$
26 : $R_1 = CO_2CH_2Ph$, $R_2 = CH_2CH_2CO_2Et$, $R_3 = O$

27 : R = H
29 : R = Ac
30 : $R = CO_2CH_2CCl_3$
31 : $R = CO_2CH_2Ph$

33

35 : $R_1 = Ac$, $R_2 = OH$
37 : $R_1 = Ac$, $R_2 = NMeC_6H_4SCH_2CH_2CN(o)$
38 : $R_1 = Ms$, $R_2 = NMeC_6H_4SCH_2CH_2CN(o)$

39 : R = H
40 : R = Me

41a,b

42 : $R = SOC_6H_4NHMe(o)$
2 : R = H

36

28

32

34

$SiMe_2tBu$ = *tert*-butyldimethylsilyl

Fig. 4

with (carbethoxymethylene)triphenylphosphorane. The product **22** was hydrogenated with PtO_2 and then hydrolyzed with acid, affording the hydroxy ketone **23** in 81% yield.

Then, the two-carbon shortening was carried out by means of the Baeyer–Villiger oxidation. *m*-Chloroperbenzoic acid (mCPBA, 3 eq) treatment of the hydroxy ketone **23** in 1,2-dichloroethane produced the desired acetate **27** but the yield was only 25%. The starting material **23** (7.5%) and the over-oxidation product (25% yield), whose structure was assigned tentatively as the acetoxy lactone **28**, were also obtained. The corresponding *tert*-butyldimethylsilyl or methoxymethyl ethers prepared from **23** gave similar results. However, the acylated compounds such as the acetate **24**, the 2,2,2-trichloroethyl carbonate **25** and the benzyl carbonate **26** underwent smooth C–C bond cleavage giving the desired acetates **29** (91% yield), **30** (95% yield) and **31** (83% yield), respectively, and the latter two (**30**, **31**) were converted into the hydroxy acetate **27** by reductive deprotection.

The acyl derivatives were converted into the amide mesylate **32** by a series of reactions[2] and subjected to base-induced cyclization to the corresponding twelve-membered lactam sulfide, a key compound for our medium-ring formation strategy. However, every attempt to promote lactam formation failed and only an intractable mixture was obtained. One of the reasons for this failure may be attributed to the unfavorable situation that the conversion of the initially equatorial C-9 hydroxy group into the axial one is necessitated since inversion of the A-ring is essential for the side chains at the C-1 and C-7 positions to be arranged in the *cis*-axial relationship necessary for lactam formation. Thus, conversion of configuration of the C-9 hydroxy group at the stage of **27** was attempted using the Mitsunobu reaction.[9] However, treatment of **27** with diethyl azodicarboxylate and triphenylphosphine in the presence of benzoic acid led to dehydration mainly giving **33** in 88% yield along with the 9β-benzoate **34** in 4.8% yield. This dehydration was found to proceed even in the absence of benzoic acid to produce **33** in 89% yield; another possible dehydration product (Δ^9-isomer) was not detected in any case. It is noteworthy that facile dehydration takes place in **27** under the standard Mitsunobu reaction conditions, although similar dehydration has already been reported in the special case that acidic hydrogen is located in the next position to the hydroxyl group, such as in β-hydroxy esters.[10] The subsequent reactions were undertaken using **33** having a double bond at the C-8 position.

Hydrolysis of the ester **33** followed by reacetylation gave the acid **35**, which on successive treatment with oxalyl chloride and 2-cyanoethyl 2-methylaminophenyl sulfide (**36**)[11] afforded the amide acetate **37** in 88% yield from **33**. Slow addition of **38** obtained from **37** to potassium *tert*-butoxide (*tert*-BuOK) in *tert*-butanol–dioxane at 55—60 °C in the presence of $NaBH_4$ under the same conditions as described for the synthesis of **1**[2] gave the desired lactam sulfide **39**, but the yield was only 16%. Thus the cyclization was examined with various reaction conditions and solvents. The best yield (75—80%) was obtained when the reaction was carried out in *N*,*N*-dimethylformamide (DMF)–dioxane at 100—105 °C and *tert*-BuOK was replaced with anhydrous cesium carbonate (Cs_2CO_3) or, more practically, with anhydrous potassium carbonate (K_2CO_3) (dried over phosphorus pentoxide at 130 °C for 2 h, *in vacuo*). Methylation of **39** with lithium diisopropylamide (LDA)–methyl iodide afforded a single product **40** in 90% yield, and this was oxidized with sodium metaperiodate ($NaIO_4$) producing two stereoisomers **41a** and **41b** due to sulfoxide in quantitative yield (**a**:**b** ratio, 9:7).

The crucial intramolecular cyclization of the isomeric lactam sulfoxides **41a** and **41b** with LDA in tetrahydrofuran (THF) (−78— −10 °C) proceeded quite smoothly to afford the keto sulfoxides **42a** and **42b**, respectively, in nearly quantitative yields. Reductive desulfurization of **42a** and **42b** with Na–Hg in MeOH in the presence of Na_2HPO_4 produced the single ketone as an oil in 52—53% yields. The spectral data (infrared (IR), ^{1}H-NMR, carbon-13 nuclear magnetic resonance (^{13}C-NMR) and mass spectrum (MS)) of this compound are consistent with the structure **2**, although the configuration of the methyl group at the C-3 position remained unknown.

Synthesis of the Bicyclo[5.3.1]undecene 3

The isomeric bicyclo[5.3.1]undecene **3** was synthesized starting from the ester **43** obtained by dehydration of **16** using the Mitsunobu reaction as described in the conversion of **27** into **33**. The ester **43** was converted into the keto acetate **44** in 95% overall yield by three steps ($LiAlH_4$ reduction, acetylation and acidic hydrolysis). In the present synthesis introduction of a one-carbon unit on the carbonyl group in **44** is required. The Wittig reaction using the

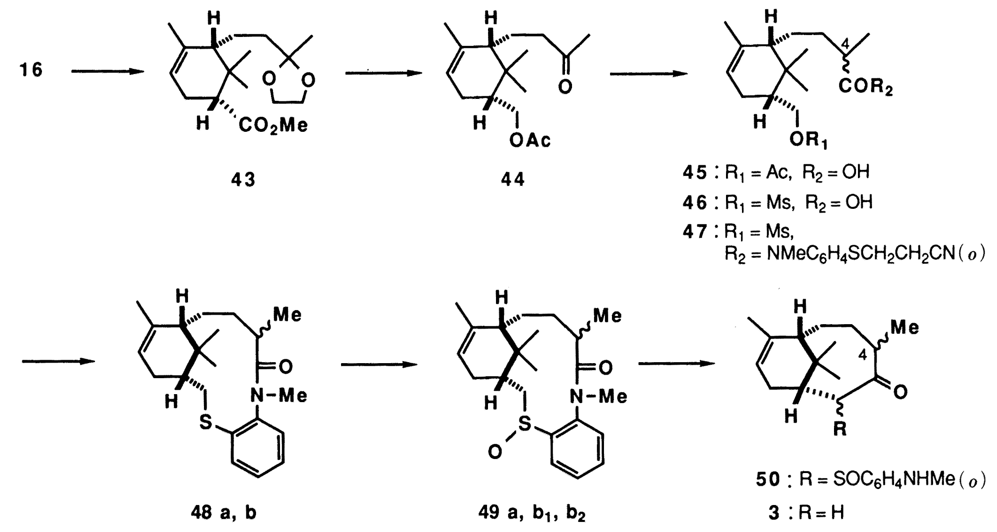


Fig. 5

phosphorane derived from methoxymethyltriphenylphosphonium chloride was found to be quite effective for this purpose. Reacetylation of the alcohol produced by partial hydrolysis of the side chain acetate during the Wittig reaction, acidic hydrolysis of the methyl enol ether and Jones oxidation of the resultant aldehyde afforded the acetoxy acid **45** as an epimeric mixture (1 : 1) at the C-4 position in 70% yield from **44**. Alkaline hydrolysis of **45** followed by mesylation produced **46**, which was converted into the amide mesylate **47** in the same way as described in the synthesis of **37**.

Base-induced removal of the S-protecting group from **47** and subsequent treatment with K_2CO_3 in DMF–dioxane in the presence of $NaBH_4$ afforded the lactam sulfides **48a, b** as an epimeric mixture (**a** : **b** ratio, 2 : 3) in 71% yield although a higher temperature (130—135 °C) was required in the present case than in the formation of **39**. Sodium metaperiodate oxidation of **48a** (less polar) gave the sulfoxide **49a** as a single product in 86% yield but the isomer **48b** (more polar) produced a separable mixture of the sulfoxides **49b**$_1$ (61% yield) and **49b**$_2$ (27% yield), stereoisomers due to the sulfoxide moiety.

On exposure of each of these isomers **49a**, **49b**$_1$ and **49b**$_2$ to LDA in THF (−65 °C, 0.5 h and 0 °C, 4 h), intramolecular cyclization took place forming the eight-membered ring. Namely, LDA treatment of **49a** gave three keto sulfoxides **50a**—**c** in 27% total yield along with 61% yield of the simple epimerization product **49b**$_2$. From **49b**$_1$, a mixture of three keto sulfoxides **50d**—**f** in 65% total yield was obtained and the starting sulfoxide **49b**$_1$ was recovered in 35% yield. On the other hand, LDA treatment of **49b**$_2$ afforded a mixture of three keto sulfoxides **50b, c, g** in 59% total yield. The stereochemistry of these isomers was not investigated further. Reductive desulfurization of the combined keto sulfoxides **50a**—**g** under the same conditions as used in the desulfurization of **42** produced a mixture of the desired bicyclic ketones **3a, b**, stereoisomers at the C-4 position, in 86% yield; these isomers were separable by SiO_2 column chromatography (**a** : **b** ratio, 5 : 3).

Two types of the bicyclo[5.3.1]undecenes **2** and **3** corresponding to the A and B parts of the taxane skeleton were thus synthesized *via* the common intermediate **16**, which clearly demonstrated that a general method for the synthesis of medium-ring ketones developed in this laboratory could be effectively used even in the synthesis of the sterically extremely congested taxane B-ring. Synthesis of the taxane skeleton using the present strategy is now in progress.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were taken on a JEOL FX-60 or GX-400 instrument and ^{13}C-NMR spectra on a JEOL FX-100 in $CDCl_3$ solution with Me_4Si as an internal standard. A JEOL FX-60 instrument was routinely used. IR spectra were measured in CCl_4 solution with a JASCO A-3 spectrometer. Mass spectra were obtained with a Hitachi RMU-6M mass spectrometer and high resolution mass spectra were recorded on a Hitachi M-80 GC-MS spectrometer.

(3*E*)-4-(2,6,6-Trimethyl-3-hydroxy-1-cyclohexen-1-yl)-3-buten-2-one (5)——A mixture of the crude epoxide **4** (27.79 g) prepared from α-ionone (25.00 g, 130.2 mmol) and anhydrous K_2CO_3 (3.40 g) in MeOH (500 ml) was refluxed overnight under nitrogen and the solvent was evaporated off under reduced pressure. The ethereal extract of the residue was washed with brine and dried ($MgSO_4$). Removal of the solvent afforded an oil, which was chromatographed on SiO_2 to give a pale yellow oil **5** (22.19 g, 84.8% yield from α-ionone) from the hexane–AcOEt (9 : 1) eluate. IR cm^{-1}: 3600, 1670. The ^{1}H-NMR spectrum was identical with that described in the literature.[4a)]

4-(2,6,6-Trimethyl-3-oxo-1-cyclohexen-1-yl)butan-2-one (6)——A solution of **5** (2.90 g, 13.9 mmol) in EtOH (30 ml) was added to a black suspension of NaTeH in EtOH prepared from $NaBH_4$ (1.95 g), tellurium (2.67 g), acetic acid (2.7 ml) and EtOH (60 ml) according to the literature.[5)] The whole mixture was stirred for 4 h at room temperature under nitrogen and filtered. The solvent was evaporated off under reduced pressure and a solution of the residue in AcOEt was filtered through a short column packed with SiO_2. Removal of the solvent afforded a yellow oil (2.77 g), which was used in the next oxidation without further purification. ^{1}H-NMR δ: 0.96, 1.02, 1.71 and 2.15 (each 3H, s), 3.8—4.0 (1H, m).

The crude keto allyl alcohol obtained above was treated with Jones reagent (6.3 ml) in acetone for 10 min at 5 °C and 2-propanol (4 ml) was added. Usual work-up of the mixture followed by SiO_2 chromatography using hexane–AcOEt (4 : 1) as an eluent gave **6** (2.13 g, 73.5% overall yield) as a pale yellow oil. IR cm^{-1}: 1720, 1667. ^{1}H-NMR δ: 1.15 (6H, s), 1.73 and 2.18 (each 3H, s), 2.53 (4H, s). MS *m/z*: 208 (M^+), 165 ($M^+ - 43$). High-resolution MS Calcd for $C_{13}H_{20}O_2$ (M^+) *m/z*: 208.1462. Found *m/z*: 208.1472. The IR and ^{1}H-NMR spectra were consistent with those described in the literature.[4a)]

2-Ethylenedioxy-4-(2,6,6-trimethyl-3-oxo-1-cyclohexen-1-yl)butane (7)——A mixture of **6** (4.86 g, 23.4 mmol), ethylene glycol (11.7 ml) and *p*-toluenesulfonic acid (0.12 g) in benzene (120 ml) was refluxed for 2 h with azeotropic removal of water and diluted with ether. The solution was washed with 5% Na_2CO_3 and brine, and dried ($MgSO_4$). Removal of the solvent yielded **7** (5.97 g) as a pale yellow oil, which was used for the next reaction without purification. IR cm^{-1}: 1665. ^{1}H-NMR δ: 1.17 (6H, s), 1.36 and 1.78 (each 3H, s), 3.97 (4H, s). MS *m/z*: 252 (M^+). High-resolution MS Calcd for $C_{15}H_{24}O_3$ (M^+) *m/z*: 252.1724. Found *m/z*: 252.1702.

2-Ethylenedioxy-4-(2,6,6-trimethyl-3-oxo-1,4-cyclohexadien-1-yl)butane (8)——A mixture of the crude ketone **7** (5.97 g) obtained above and DDQ (4.54 g) in benzene (380 ml) was refluxed for 6 d. After further addition of DDQ (2.27 g) and reflux (4 d), the whole mixture was filtered. The filtrate was diluted with Et_2O, washed with 5% Na_2CO_3, dried ($MgSO_4$) and concentrated. SiO_2 chromatography (hexane–AcOEt (9 : 1)) of the residue afforded **8** (4.06 g, 69.5% from **6**) as a colorless oil. IR cm^{-1}: 1663. ^{1}H-NMR δ: 1.25 (6H, s), 1.37 and 1.91 (each 3H, s), 3.99 (4H, s), 6.16 and 6.74 (each 1H, d, $J = 10$ Hz). MS *m/z*: 250 (M^+). High-resolution MS Calcd for $C_{15}H_{22}O_3$ (M^+) *m/z*: 250.1567. Found *m/z*: 250.1536.

2-Ethylenedioxy-4-(2,6,6-trimethyl-5-nitromethyl-3-oxo-1-cyclohexen-1-yl)butane (9)——A mixture of **8** (8.67 g, 34.7 mmol), diisopropylamine (27.2 ml), dimethyl sulfoxide (DMSO) (9 ml) and nitromethane (32.1 ml) was stirred at 75—80 °C (bath temperature) for 36 d in a sealed vessel under nitrogen. The solvent was evaporated off under reduced pressure. An ethereal extract of the residue was washed with water, dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, hexane–AcOEt (4 : 1)) of the resulting oil gave **9** (7.45 g, 69.1% yield) as more polar crystals, which were recrystallized from $CHCl_3$–hexane to afford colorless prisms, mp 94—95 °C. The starting dienone **8** (2.50 g, 28.8% recovery) was obtained as a less polar oil. IR cm^{-1}: 1670. ^{1}H-NMR δ: 1.11, 1.30, 1.36 and 1.81 (each 3H, s), 3.98 (4H, s), 4.12—4.80 (2H, m). *Anal.* Calcd for $C_{16}H_{25}NO_5$: C, 61.76; H, 8.25; N, 4.45. Found: C, 61.74; H, 8.04; N, 4.50.

2,2,4-Trimethyl-5-oxo-3-(3-oxobutyl)cyclohexanecarboxylic Acid (10)——A mixture of aqueous titanium trichloride solution (16%, 30 ml) and $AcONH_4$ (15.90 g) in water (44.6 ml) was added to a stirred solution of **9** (2.40 g, 7.72 mmol) and MeONa (0.56 g) in MeOH (15 ml) on a water bath under nitrogen. The mixture was stirred at room temperature for 20 min, diluted with three volume of water and several drops of concentrated HCl and extracted with $CHCl_3$. The extract was washed with water and brine and dried ($MgSO_4$). Removal of the solvent gave the crude aldehyde (1.61 g, 88.4% yield) as a pale yellow oil, which was oxidized without purification. ^{1}H-NMR δ: 1.24, 1.38, 1.75 and 2.20 (each 3H, s), 9.85 (1H, d, $J = 1.7$ Hz).

A solution of the crude aldehyde (3.89 g) obtained as described above was treated with Jones reagent (19.3 ml) in acetone (194 ml) at 5 °C for 30 min and 2-propanol (19 ml) was added. Usual work-up gave **10** (3.55 g, 85.5% yield), which was esterified without purification. An analytical sample of **10** was obtained by recrystallization from Et_2O–hexane as colorless prisms, mp 108—109 °C. IR cm^{-1}: 1715, 1705, 1670. ^{1}H-NMR δ: 1.23, 1.32, 1.75 and 2.20 (each 3H, s), 10.84 (1H, m). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.38; H, 8.09. Found: C, 66.64; H, 7.99.

Methyl 2,2,4-Trimethyl-5-oxo-3-(3-oxobutyl)-3-cyclohexenecarboxylate (11)——A mixture of the crude keto acid **10** (460 mg), dimethyl sulfate (1.4 ml) and K_2CO_3 (5.8 g) in acetone (57 ml) was refluxed overnight and diluted with water. The mixture was concentrated and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The crude keto ester **11** (470 mg) obtained as colorless prisms could be used for the next acetalization without purification. An analytical sample was obtained by recrystallization from $CHCl_3$–hexane as colorless prisms, mp 68—69 °C. IR cm^{-1}: 1735, 1720, 1670, 1153. ^1H-NMR δ: 1.18, 1.26, 1.76, 2.19 and 3.69 (each 3H, s). *Anal.* Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.55; H, 8.33.

Methyl 3-(3,3-Ethylenedioxybutyl)-2,4,4-trimethyl-5-oxo-3-cyclohexenecarboxylate (12)——A mixture of the crude keto ester **11** (1.69 g), ethylene glycol (4.1 ml) and *p*-toluenesulfonic acid (0.41 g) in benzene (41 ml) was refluxed for 1 h with removal of water using Zeolite A-3. The mixture was diluted with Et_2O, washed with 5% Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated. The resulting oil was chromatographed (SiO_2, hexane–AcOEt (17:3)) to give **12** (1.816 g, 67.5% yield from **9**) as a colorless oil. IR cm^{-1}: 1735, 1670. ^1H-NMR δ: 1.18, 1.28, 1.35, 1.80 and 3.69 (each 3H, s), 3.97 (4H, s). MS *m/z*: 311 ($M^+ + 1$), 195 ($M^+ - 15$). High-resolution MS Calcd for $C_{17}H_{26}O_5$ (M^+) *m/z*: 310.1778. Found *m/z*: 310.1777.

Hydrogenation of 12——A mixture of **12** (2.93 g, 9.45 mmol), anhydrous AcONa (300 mg) and 10% Pd–C (600 mg) in AcOEt (60 ml) was stirred at room temperature for 6 h under 100 kg/cm^2 pressure of hydrogen gas. After filtration, the mixture was concentrated and chromatographed on SiO_2. Elution with hexane–AcOEt (17:3) afforded successively crystalline methyl 3α-(3-ethylenedioxybutyl)-2,2,4β-trimethyl-5-oxocyclohexane-1α-carboxylate (**14**) (156 mg, 5.3% yield) and oily methyl 3α-(3-ethylenedioxybutyl)-2,2,4α-trimethyl-5-oxocyclohexane-1α-carboxylate (**13**) (1884 mg, 63.9% yield). (The polar keto ester **13**) IR cm^{-1}: 1725, 1715. ^1H-NMR (400 MHz) δ: 1.09, 1.12, 1.40 and 3.70 (each 3H, s), 1.14 (3H, d, $J=7.6$ Hz), 2.30 (1H, ddd, $J=1.5$, 3.9, 15.1 Hz, C-6α), 2.57 (1H, ddq, $J=1.5$, 5.6, 7.6 Hz, C-4β), 2.61 (1H, dd, $J=3.9$, 13.4 Hz, C-1β), 2.96 (1H, dd, $J=13.4$, 15.1 Hz, C-6α), 3.9—4.0 (4H, m). MS *m/z*: 311 ($M^+ - 1$). High-resolution MS Calcd for $C_{17}H_{28}O_5$ (M^+) *m/z*: 312.1935. Found *m/z*: 312.1951. (The less polar keto ester **14**) An analytical sample of **14** was obtained by recrystallization from Et_2O–hexane as colorless prisms, mp 66—68 °C. IR cm^{-1}: 1730, 1710. ^1H-NMR (400 MHz) δ: 1.06, 1.10, 1.32 and 3.69 (each 3H, s), 1.10 (3H, d, $J=6.6$ Hz), 2.33 (1H, ddq, $J=1$, 6.6, 8.1 Hz, C-4α), 2.38 (1H, dd, $J=3.9$, 14.7 Hz, C-6β), 2.57 (1H, dd, $J=3.9$, 13.9 Hz, C-1β), 2.80 (1H, ddd, $J=1$, 13.9, 14.7 Hz, C-6α), 3.9—4.0 (4H, m). MS *m/z*: 297 ($M^+ - 15$). *Anal.* Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.02; H, 8.91.

Elution with hexane–AcOEt (7:3) gave a mixture of the alcohols as a less polar oil which contained mainly **15** (317 mg, 10.7% yield) and the polar crystalline hydroxy ester **16** (394 mg, 13.4% yield).

Epimerization of 13 to 14——A mixture of **13** (40 mg) and MeONa (15 mg) in MeOH (3 ml) was stirred at room temperature for 45 h and diluted with AcOEt. The mixture was washed with brine and dried ($MgSO_4$). Removal of the solvent gave crystal (41 mg), whose ^1H-NMR spectrum and *Rf* value on thin layer chromatography (TLC) (SiO_2) were identical with those of **14**.

Reduction of 13 to 16 and 17——1) $NaBH_4$ Reduction: A solution of **13** (156 mg, 0.5 mmol) in MeOH (3 ml) was treated with $NaBH_4$ (38 mg) at −9— −11 °C (bath temperature) and the mixture was stirred at the same temperature for 1 h. Usual work-up and chromatography (SiO_2, hexane–AcOEt (7:3)) yielded less polar methyl 3α-(3-ethylenedioxybutyl)-5β-hydroxy-2,2,4α-trimethylcyclohexane-1α-carboxylate (**17**) (3.5 mg, 2.2% yield) and more polar crystalline methyl 3α-(3-ethylenedioxybutyl)-5α-hydroxy-2,2,4α-trimethylcyclohexane-1α-carboxylate (**16**) (132 mg, 84.1% yield), which was recrystallized from $CHCl_3$–hexane to afford colorless prisms, mp 75—77 °C. (The hydroxy ester **16**) IR cm^{-1}: 3600, 1725. ^1H-NMR δ: 0.89, 1.04, 1.33 and 3.66 (each 3H, s), *ca.* 0.94 (3H, d, $J=$*ca.* 6 Hz), 3.94 (4H, s), 3.8—4.0 (1H, m). MS *m/z*: 299 ($M^+ - 15$). High-resolution MS Calcd for $C_{16}H_{27}O_5$ ($M^+ - 15$) *m/z*: 299.1857. Found *m/z*: 299.1878. *Anal.* Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.65; H, 9.55. (The hydroxy ester **17**, colorless gum) IR cm^{-1}: 3600, 1730. ^1H-NMR δ: 0.87, 1.00, 1.33 and 3.66 (each 3H, s), 0.91 (3H, d, $J=7.3$ Hz), 3.94 (4H, s), 3.7—4.0 (1H, m). MS *m/z*: 315 ($M^+ + 1$). High-resolution MS Calcd for $C_{17}H_{30}O_5$ (M^+) *m/z*: 314.2092. Found *m/z*: 314.2136.

2) K-Selectride Reduction: A solution of 1 M K-Selectride in THF (0.2 ml) was added dropwise to a stirring solution of **13** (31 mg, 0.1 mmol) in THF (2 ml) at −20 °C and the mixture was stirred at the same temperature for 1 h under argon. Saturated aqueous NH_4Cl solution was added and the mixture was extracted with Et_2O. The extract was washed with water, dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 of the resulting oil gave **17** (3 mg, 9.6% yield) and **16** (26 mg, 83.3% yield).

Acetylation of 16 and 17——1) The hydroxy ester **16** (15 mg) was treated with Ac_2O (0.3 ml) in pyridine (0.5 ml) at room temperature for 2 h and the solvent was removed under reduced pressure. SiO_2 chromatography (hexane–AcOEt (4:1)) of the resulting oil gave the acetate **18** (15 mg, 88% yield) as a colorless oil. IR cm^{-1}: 1730. ^1H-NMR (400 MHz) δ: 0.89, 1.02, 1.33, 2.04 and 3.66 (each 3H, s), 0.91 (3H, d, $J=7.3$ Hz), 2.22 (1H, ddq, $J=4.4$, 5.1, 7.3 Hz, C-4β), 2.34 (1H, dd, $J=2.9$, 13.2 Hz, C-1β), 3.9—4.0 (4H, m), 4.78 (1H, ddd, $J=4.2$, 5.1, 12.2 Hz, C-5β). MS *m/z*: 341 ($M^+ - 15$), 296 ($M^+ - 60$). High-resolution MS Calcd for $C_{18}H_{29}O_6$ ($M^+ - 15$) *m/z*: 341.1962. Found *m/z*: 341.1957.

2) The hydroxy ester **17** (3.5 mg) was subjected to acetylation followed by SiO_2 chromatography (hexane–AcOEt (4:1)) in the same way as described for acetylation of **16**, affording the acetate **19** (3.5 mg, 88% yield) as a colorless oil. IR cm^{-1}: 1730. ^1H-NMR (400 MHz) δ: 0.89, 1.05, 1.33, 2.05 and 3.67 (each 3H, s), 0.97 (3H, d, $J=7.8$ Hz), 1.72 (1H,

dddd, $J=1.5$, 2.9, 3.2, 14.9 Hz, C-6β), 1.94 (1H, dddd, $J=1.5$, 1.5, 2.2, 7.8 Hz, C-4β), 2.13 (1H, ddd, $J=2.7$, 13.4, 14.9 Hz, C-6α), 2.62 (1H, dd, $J=3.2$, 13.4 Hz, C-1β), 3.9—3.98 (4H, m), 4.90 (1H, ddd, $J=2.2$, 2.7, 2.9 Hz, C-5α). MS m/z: 341 (M^+-15). High-resolution MS Calcd for $C_{18}H_{29}O_6$ (M^+-15) m/z: 341.1962. Found m/z: 341.1928.

Preparation of the Bicyclic γ-Lactone 20 from 16——A mixture of **16** (34 mg) and KOH (100 mg) in water (1 ml) and EtOH (0.5 ml) was refluxed for 1 h and, after cooling, acidified. The ethereal extract of the mixture was washed with brine, dried ($MgSO_4$) and evaporated to give the hydroxy acid (31 mg) as a caramel. ^{1}H-NMR δ: 0.90 (3H, d, $J=$ 7 Hz), 0.92, 1.08 and 1.34 (each 3H, s), 3.95 (4H, s).

The hydroxy acid (31 mg) obtained above was treated with ethylene glycol (0.5 ml) and p-toluenesulfonic acid (1 mg) in benzene (5 ml) under reflux for 30 min with azeotropic removal of water using Zeolite A-3. The mixture was diluted with Et_2O, washed with 5% Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue (SiO_2, hexane–AcOEt (4:1)) afforded **20** (14 mg, 46% yield) as colorless gum. IR cm^{-1}: 1780. ^{1}H-NMR (400 MHz) δ: 1.00 (3H, d, $J=7.3$ Hz), 1.05, 1.06 and 1.32 (each 3H, s), 1.51 (1H, m, C-3β), 2.14 (1H, ddq, $J=4.9$, 7.1, 7.3 Hz, C-4β), 2.18—2.26 (3H, m), 3.9—4.0 (H4, m), *ca.* 4.64 (1H, m, C-5β). MS m/z: 267 (M^+-15). High-resolution MS Calcd for $C_{15}H_{23}O_4$ (M^+-15) m/z: 267.1595. Found m/z: 267.1571.

Conversion of 16 into the Alcohol 21——The hydroxy ester **16** (1160 mg, 3.69 mmol) was treated with *tert*-butyldimethylsilyl chloride (700 mg) and imidazole (630 mg) in dimethylformamide (23 ml) at room temperature for 13 h. Usual work-up followed by SiO_2 chromatography (hexane–AcOEt (85:1)) afforded the corresponding silyl ether (1580 mg, 100% yeild) as a colorless oil. ^{1}H-NMR δ: 0.03 (6H, s), 0.87 (12H, s), 0.87 (3H, d, $J=7.3$ Hz), 0.98, 1.34 and 3.66 (each 3H, s).

A solution of the silyl ether (1580 mg) in Et_2O (80 ml) was treated with $LiAlH_4$ (280 mg) and the mixture was stirred at 0 °C for 30 min. After usual work-up, the alcohol **21** (1.50 g) was obtained as a colorless oil. ^{1}H-NMR δ: 0.04 (6H, s), 0.70, 0.97 and 1.34 (each 3H, s), 0.89 (9H, s), 0.90 (3H, d, $J=7.9$ Hz), 3.1—3.9 (3H, m), 3.95 (4H, s).

Ethyl (2*E*)-3-(5α-*tert*-Butyldimethylsilyloxy-3β-(3,3-ethylenedioxybutyl)-2,2,4α-trimethylcyclohexan-1α-yl)acrylate (22)——A mixture of the alcohol **21** (1.50 g) obtained above, $AcONa\cdot 3H_2O$ (2.04 g) and PCC (2.48 g) in CH_2Cl_2 (50 ml) was stirred at room temperature for 2.5 h and diluted with Et_2O. The mixture was filtered through Florisil and the filtrate was evaporated to give the aldehyde (1.35 g) as a colorless oil. ^{1}H-NMR δ: 0.04 (6H, s), 0.88 (9H, s), 0.88 (3H, d, $J=7.3$ Hz), 0.93, 1.13 and 1.34 (each 3H, s), 3.45—3.75 (1H, m), 3.95 (4H, s), 9.78 (1H, d, $J=2.3$ Hz).

A mixture of the aldehyde (1.35 g) and (carbethoxymethylene)triphenylphosphorane (2.37 g) in toluene (35 ml) was heated at 100 °C for 16 h under nitrogen. After removal of the solvent, the resulting residue was suspended in hexane–Et_2O (4:1, 100 ml) and filtered. The filtrate was concentrated to give an oil, whose chromatography (SiO_2, hexane–AcOEt (19:1—9:1)) afforded **22** (1181 mg, 68% yield from **16**) as a colorless oil. IR cm^{-1}: 1720, 1645. ^{1}H-NMR δ: 0.03 (6H, s), 0.78 and 1.34 (each 3H, s), 0.84 (3H, d, $J=6.7$ Hz), 0.88 (12H, s), 1.29 (3H, t, $J=7.1$ Hz), 3.35—3.8 (1H, m), 3.95 (4H, s), 4.19 (2H, q, $J=7.1$ Hz), 5.78 (1H, d, $J=15.5$ Hz), 6.95 (1H, dd, $J=8.1$, 15.5 Hz). MS m/z: 412 (M^+-56). High-resolution MS Calcd for $C_{22}H_{39}O_5Si$ (M^+-57) m/z: 411.2564. Found m/z: 411.2564.

Ethyl 3-(5α-Hydroxy-2,2,4α-trimethyl-3α-(3-oxobutyl)cyclohexan-1α-yl)propionate (23)——A mixture of **22** (874 mg, 1.86 mmol) and PtO_2 (90 mg) in AcOEt (44 ml) was stirred at room temperature for 30 min under hydrogen and the mixture was filtered through a short column packed with SiO_2. Removal of the solvent gave the saturated ester (851 mg) as a colorless oil. IR cm^{-1}: 1735. ^{1}H-NMR δ: 0.03 (6H, s), 0.70, 0.91 and 1.34 (each 3H, s), 0.83 (3H, d, $J=$ 7.2 Hz), 0.88 (9H, s), 1.26 (3H, t, $J=7.1$ Hz), 3.3—3.8 (1H, m), 3.94 (4H, s), 4.13 (2H, q, $J=7.1$ Hz). MS m/z: 413 (M^+-57).

A solution of the ester (851 mg) obtained above and p-toluenesulfonic acid (85 mg) in acetone (43 ml) was stirred at room temperature for 5 h under nitrogen. After removal of the solvent, EtOH (43 ml) was added the resulting residue. The mixture was heated at 50 °C for 5 h under nitrogen and concentrated. Chromatography (SiO_2, hexane–AcOEt (7:3)) of the residue afforded **23** (468 mg, 80.7% yield from **22**) as a colorless oil. IR cm^{-1}: 3600, 1730, 1715. ^{1}H-NMR δ: 0.72, 0.93 and 2.16 (each 3H, s), 0.86 (3H, d, $J=7.5$ Hz), 1.25 (3H, t, $J=7.1$ Hz), 3.4—3.75 (1H, m), 4.12 (2H, q, $J=7.1$ Hz). MS m/z: 294 (M^+-18). High-resolution MS Calcd for $C_{18}H_{30}O_3$ (M^+-18) m/z: 294.2194. Found m/z: 294.2224.

Acetylation of 23——The hydroxy ketone **23** (196 mg, 0.63 mmol) was treated with Ac_2O (5 ml) in pyridine (10 ml) at room temperature for 4 h and the solvent was removed under reduced pressure, giving the corresponding acetate **24** (222 mg, 100% yield) as a colorless oil. ^{1}H-NMR δ: 0.74, 0.95, 2.04 and 2.14 (each 3H, s), 0.84 (3H, d, $J=$ 7.3 Hz), 1.25 (3H, t, $J=7.1$ Hz), 4.12 (2H, q, $J=7.1$ Hz), 4.74 (1H, dt, $J=5.3$, 11 Hz).

Preparation of the 2,2,2-Trichloroethyl Carbonate 25——Chloro trichloroethyl carbonate (0.5 ml) was added dropwise to a stirred solution of **23** (383 mg, 1.23 mmol), triethylamine (2 ml) and 4-dimethylaminopyridine (180 mg) in Et_2O (15 ml) and the mixture was stirred at room temperature for 13 h. After dilution with Et_2O, the mixture was washed with dilute HCl, 5% $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Column chromatography of the resulting oil (SiO_2, hexane–AcOEt (17:3)) afforded **25** (472 mg, 78.9% yield) as a pale yellow oil. IR cm^{-1}: 1750, 1735, 1720. ^{1}H-NMR δ: 0.75, 0.96 and 2.15 (each 3H, s), 0.90 (3H, d, $J=7.2$ Hz), 1.26 (3H, t, $J=7.1$ Hz), 4.13 (2H, q, $J=7.1$ Hz), 4.45—4.9 (1H, m), 4.76 (2H, s). MS m/z: 294 ($M^+-93.5$).

Preparation of the Benzyl Carbonate 26——A solution of benzyl chloro carbonate in toluene (30—35%, 1 ml) was added dropwise to a stirred solution of **23** (100 mg, 0.31 mmol) and pyridine (0.4 ml) in THF (5 ml) at −5 °C and the mixture was stirred at room temperature overnight. Usual work-up and subsequent column chromatography (SiO_2) afforded an inseparable mixture of **26** and benzyl alcohol (272 mg) by elution with hexane–AcOEt (4:1) and the starting material **23** (15 mg, 15% recovery) by elution with hexane–AcOEt (7:3). The former (272 mg) was treated with PCC (620 mg) and $AcONa \cdot 3H_2O$ (800 mg) in CH_2Cl_2 (27 ml) at room temperature for 30 min. Usual work-up and SiO_2 chromatography (hexane–AcOEt (4:1)) yielded **26** (97 mg, 67.9% yield) as a colorless oil. IR cm^{-1}: 1730. ^{1}H-NMR δ: 0.73, 0.94 and 2.13 (each 3H, s), 0.86 (3H, d, J=7.3 Hz), 1.25 (3H, t, J=7.1 Hz), 4.12 (2H, q, J=7.1 Hz), 4.3—4.8 (1H, m), 5.13 (2H, s), 7.36 (5H, br). MS m/z: 389 ($M^+ - 57$), 294 ($M^+ - 152$).

The Baeyer–Villiger Oxidation of 23, 24, 25 and 26——General Procedure: A mixture of the keto ester and mCPBA (3 eq) in 1,2-dichloroethane (3 ml/100 mg of mCPBA) was stirred at 55 °C for 44 h in the case of **24** and **26** or for 60 h in the case of **23** and **25**. The mixture was diluted with Et_2O, washed with 5% Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated. The resulting oil was subjected to SiO_2 column chromatography (hexane–AcOEt).

1) In the case of the oxidation of **23** (86.5 mg, 0.28 mmol), elution with hexane–AcOEt (7:3) afforded successively the over-oxidation product **28** (23.5 mg, 24.8% yield) as a colorless oil, the hydroxy acetate **27** (22.5 mg, 24.8% yield) as a colorless oil and the starting material **23** (6.5 mg, 7.5% recovery). (The hydroxy acetate **27**) IR cm^{-1}: 3600, 1735. ^{1}H-NMR δ: 0.71, 0.91 and 2.05 (each 3H, s), 0.90 (3H, d, J=7.3 Hz), 1.26 (3H, t, J=7.1 Hz), 3.4—3.8 (1H, m), 3.8—4.2 (2H, m), 4.13 (2H, q, J=7.1 Hz). MS m/z: 327 ($M^+ + 1$), 316 ($M^+ - 16$). High-resolution MS Calcd for $C_{18}H_{32}O_5$ (M^+) m/z: 328.2247. Found m/z: 328.2209. (The over-oxidation product **28**) ^{1}H-NMR δ: 1.15, 1.20 and 2.05 (each 3H, s), 1.25 (3H, t, J=7.1 Hz), 1.39 (3H, d, J=6.6 Hz), 4.01 (2H, t, J=7.3 Hz), 4.12 (2H, q, J=7.1 Hz), 4.87 (1H, br q, J=6.6 Hz).

2) From the acetate **24** (222 mg, 0.63 mmol), the diacetate **29** (212 mg, 91.2% yield) and the starting material **24** (6 mg, 2.7% recovery) were obtained successively by elution with hexane–AcOEt (17:3). IR cm^{-1}: 1730. ^{1}H-NMR δ: 0.73 and 0.93 (each 3H, s), 0.90 (3H, d, J=7.2 Hz), 1.25 (3H, t, J=7.1 Hz), 2.04 (6H, s), 3.65—4.1 (2H, m), 4.13 (2H, q, J=7.1 Hz), 4.5—4.9 (1H, m). MS m/z: 250 ($M^+ - 120$). High-resolution MS Calcd for $C_{16}H_{26}O_2$ ($M^+ - 120$) m/z: 250.1932. Found m/z: 250.1932.

3) From **25** (453 mg, 0.93 mmol), the acetate **30** (445 mg, 95.1% yield) was obtained as a colorless oil by elution with hexane–AcOEt (9:1). IR cm^{-1}: 1750 (sh), 1735. ^{1}H-NMR δ: 0.74, 0.94 and 2.05 (each 3H, s), 0.95 (3H, d, J=7.3 Hz), 1.26 (3H, t, J=7.1 Hz), 4.13 (2H, q, J=7.1 Hz), 3.75—4.2 (2H, m), 4.4—4.8 (1H, m), 4.76 (2H, s). MS m/z: 310 ($M^+ - C_3H_3Cl_3O_3$), 250 ($M^+ - C_3H_3Cl_3O_3$, CH_3CO_2H).

A mixture of **30** (442 mg, 0.88 mmol) and zinc powder (440 mg) in acetic acid (4.5 ml) was stirred at 50 °C for 5 h under nitrogen and then diluted with AcOEt. Filtration (Celite) of the mixture, concentration of the filtrate and SiO_2 column chromatography (hexane–AcOEt (7:3)) gave **27** (262 mg, 91.0% yield).

4) Oxidation of **26** (97 mg, 0.22 mmol) afforded the acetate **31** (83 mg, 82.6% yield) as a colorless oil and the starting material **26** (2.5 mg, 2.6% recovery) by elution with hexane–AcOEt (17:3). IR cm^{-1}: 1735. ^{1}H-NMR δ: 0.72, 0.92 and 2.04 (each 3H, s), 0.91 (3H, d, J=7.3 Hz), 1.25 (3H, t, J=7.1 Hz), 4.12 (2H, q, J=7.1 Hz), 4.45—4.85 (1H, m), 5.14 (2H, s), 7.36 (5H, s). MS m/z: 311 ($M^+ - C_8H_7O_3$), 250 ($M^+ - C_{10}H_{12}O_5$).

A mixture of **31** (80 mg, 0.17 mmol) and 10% Pd–C (10 mg) in EtOH (4 ml) was stirred at room temperature for 0.5 h under hydrogen, filtered and concentrated. Column chromatography (SiO_2, hexane–AcOEt (7:3)) afforded **27** (51 mg, 89.5% yield).

Ethyl 3-[5α-(2-Acetoxyethyl)-4,6,6-trimethyl-3-cyclohexen-1α-yl]propionate (33) and Ethyl 3-[5α-(2-Acetoxyethyl)-3β-benzoyloxy-4,6,6-trimethylcyclohexan-1α-yl]propionate (34)——1) Diethyl azodicarboxylate (0.70 ml, 4.45 mmol) was added to a stirred solution of the acetate **27** (487 mg, 1.49 mmol), triphenylphosphine (1.17 g, 4.46 mmol) and benzoic acid (273 mg, 2.24 mmol) in THF (20 ml) and the mixture was stirred at room temperature for 15 h under nitrogen. The mixture was diluted with Et_2O, washed with 5% K_2CO_3 solution and brine, and dried ($MgSO_4$). Removal of the solvent followed by SiO_2 column chromatography of the resultant residue afforded **33** (405 mg, 88.0% yield) as a colorless oil by elution with hexane–AcOEt (9:1) and **34** (31 mg, 4.8% yield) as a colorless gum by elution with hexane–AcOEt (4:1). (The acetate **33**) IR cm^{-1}: 1735. ^{1}H-NMR δ: 0.70, 0.97 and 2.05 (each 3H, s), 1.25 (3H, t, J=7.1 Hz), 1.70 (3H, br), 3.75—4.3 (2H, m), 4.12 (2H, q, J=7.1 Hz), 5.2—5.5 (1H, m). MS m/z: 250 ($M^+ - 60$). High-resolution MS Calcd for $C_{16}H_{26}O_2$ m/z: 250.1934. Found m/z: 250.1933. (The benzoate **34**) IR cm^{-1}: 1735, 1715. ^{1}H-NMR δ: 0.79, 1.02 and 1.92 (each 3H, s), 1.03 (3H, d, J=7.2 Hz), 1.17 (3H, t, J=7.1 Hz), 3.8—4.2 (2H, m), 4.05 (2H, q, J=7.1 Hz), 5.0—5.2 (1H, m), 7.25—7.65 (3H, m), 7.9—8.15 (2H, m). MS m/z: 327 ($M^+ - C_6H_5CO$), 310 ($M^+ - C_6H_5CO_2H$). High-resolution MS Calcd for $C_{18}H_{31}O_5$ ($M^+ - C_6H_5CO$) m/z: 327.2169. Found m/z: 327.2157.

2) Diethyl azodicarboxylate (0.95 ml, 6.0 mmol) was added to a stirred solution of **27** (988 mg, 3.01 mmol) and triphenylphosphine (1.58 g, 6.0 mmol) in THF (31 ml) and the mixture was stirred at room temperature for 12 h under nitrogen. Work-up in the same manner as described above and SiO_2 chromatography afforded **33** (832 mg, 89.1% yield).

Conversion of 33 into *N*-Methyl-2′-[(2-cyanoethyl)thio]-3-[3α-(2-acetoxyethyl)-2,2,4-trimethyl-4-cyclohexen-1α-yl]propionanilide (37) *via* 3-[3α-(2-Acetoxyethyl)-2,2,4-trimethyl-4-cyclohexen-1α-yl]propionic Acid (35)——A mixture of **33** (392 mg, 1.26 mmol) and KOH (3.00 g) in EtOH–H_2O (1:2, 30 ml) was stirred at room temperature overnight under nitrogen and then acidified with 3 N HCl. The mixture was saturated with ammonium sulfate, then extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The residue was treated with Ac_2O (10 ml) in pyridine (20 ml) at room temperature overnight and excess Ac_2O was decomposed with ice. Removal of the solvent gave **35** (400 mg) as an oil, which was used for the next reaction without purification. IR cm^{-1}: 1735, 1705. ^{1}H-NMR δ: 0.70, 0.97 and 2.06 (each 3H, s), 1.70 (3H, br), 3.75—4.4 (2H, m), 5.25—5.7 (1H, m).

Oxalyl chloride (1 ml, 11.8 mmol) was added dropwise to a stirred solution of **35** (400 mg) obtained above in benzene (20 ml) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then heated for 1 h at 60 °C. After being cooled, removal of the solvent afforded the corresponding acid chloride as an oil. A solution of the acid chloride in THF (10 ml) was added dropwise to an ice-cooled suspension of **36** (486 mg, 2.53 mmol) and anhydrous K_2CO_3 (700 mg, 5.06 mmol) in THF (25 ml) under nitrogen. The mixture was stirred at 0 °C for 10 min, diluted with AcOEt, washed with brine and dried ($MgSO_4$). The solvent was removed to give a yellow oil, whose SiO_2 column chromatography afforded **37** (503 mg, 87.5% yield from **33**) as a pale yellow oil by elution with hexane–AcOEt (3:2). IR cm^{-1}: 2250, 1735, 1665. ^{1}H-NMR δ: 0.65, 2.04 and 3.18 (each 3H, s), 0.90 and 0.92 (each 1.5H, s), 1.65 (3H, br), 2.5—2.8 (2H, m), 3.0—3.4 (2H, m), 3.6—4.4 (2H, m), 5.1—5.3 (1H, m), 6.8—7.5 (4H, m). MS *m/z*: 456 (M^+). High-resolution MS calcd for $C_{26}H_{36}N_2O_3S$ (M^+) *m/z*: 456.2444. Found *m/z*: 456.2442.

***N*-Methyl-2′-[(2-cyanoethyl)thio]-3-[3α-(2-methanesulfonyloxyethyl)-2,2,4-trimethyl-4-cyclohexen-1α-yl]propionanilide (38)**——The amide acetate **37** (494 mg, 1.08 mmol) was treated with anhydrous K_2CO_3 (1.50 g) in MeOH (24 ml) at 0 °C for 1 h. The mixture was diluted with water, neutralized with dilute HCl and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The resulting gum (490 mg) was used for the next reaction without purification. IR cm^{-1}: 3620, 1655. ^{1}H-NMR δ: 0.65 and 3.18 (each 3H, s), 0.90 and 0.92 (each 1.5H. s), 1.64 (3H, br), 3.05—3.3 (2H, m), 3.3—3.9 (2H, m), 5.0—5.5 (1H, m).

Methanesulfonyl chloride (0.45 ml, 5.8 mmol) was added to a stirred solution of the resultant gum (490 mg) and Et_3N (1.50 ml, 10.8 mmol) in CH_2Cl_2 (24 ml) at 0 °C under nitrogen and the mixture was stirred at 0 °C for 10 min. Excess reagent was decomposed by addition of ice-cold 5% Na_2CO_3 and the mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and concentrated. SiO_2 column chromatography (hexane–AcOEt (2:3)) of the resulting residue afforded **38** (523 mg, 98.4% yield from **37**) as a pale yellow gum. IR cm^{-1}: 1665. ^{1}H-NMR δ: 0.66, 3.01 and 3.18 (each 3H, s), 0.91 and 0.93 (each 1.5H, s), 1.65 (3H, br), 4.0—4.5 (2H, m), 5.10—5.5 (1H, m), 7.1—7.5 (4H, m). MS *m/z*: 279 ($M^+ - 213$).

3,10-Dimethyl-7β,11β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one (39)——(1) Anhydrous Cs_2CO_3 (450 mg, 1.37 mmol) and $NaBH_4$ (55 mg, 1.45 mmol) was dried over P_2O_5 at 130 °C for 2 h under reduced pressure and then DMF–dioxane (1:1, 14 ml) was added. To this suspension, a solution of **38** (134 mg, 0.272 mmol) in dioxane (7 ml) was added slowly at 100—105 °C (bath temperature) with stirring over a period of 20 h under argon, and the mixture was stirred at the same temperature for a further 3 h. After cooling, the mixture was neutralized with dilute HCl, concentrated under reduced pressure and extracted with AcOEt–Et_2O (1:1). The extract was washed with brine, dried ($MgSO_4$) and concentrated. The resulting gum was subjected to SiO_2 column chromatography (hexane–AcOEt (4:1)), affording the crystalline lactam sulfide **39** (68 mg, 72.8% yield). An analytical sample was obtained by recrystallization from $CHCl_3$–hexane. mp 121—123 °C (colorless prisms). IR cm^{-1}: 1655. ^{1}H-NMR δ: 0.39, 0.80 and 3.25 (each 3H, s), 1.66 (3H, d, J = 1 Hz), 4.9—5.3 (1H, m), 6.95—7.4 (3H, m), 7.5—7.8 (1H, m) (methyl signals due to the corresponding rotamer (about 4:1) in the amide group were also observed at 0.87 (s), 1,02 (s) and 3.13 (s)). MS *m/z*: 343 (M^+). High-resolution MS Calcd for $C_{21}H_{29}NOS$ (M^+) *m/z*: 343.1968. Found *m/z*: 343.1964. *Anal.* Calcd for $C_{21}H_{29}NOS$: C, 73.42; H, 8.51; N, 4.08; S, 9.33. Found: C, 73.56; H, 8.60; N, 3.92; S, 9.33.

(2) When a solution of **38** (49 mg, 0.1 mmol) in dioxane (5 ml) was treated with anhydrous Cs_2CO_3 (330 mg, 1.0 mmol) and $NaBH_4$ (40 mg, 1.06 mmol) in DMF–dioxane (1:1, 10 ml) in the same way as described above, 29 mg (84.9% yield) of **39** was obtained.

(3) Treatment of **38** (49 mg) with $NaBH_4$ (40 mg) [anhydrous K_2CO_3 (140 mg, 1.0 mmol) dried over P_2O_5 was used instead of Cs_2CO_3 under the same conditions as in (2)] afforded **39** (25.5 mg, 74.5% yield).

3,5ξ,10-Trimethyl-7β,11β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one (40)——A solution of *n*-butyl lithium in hexane (1.49 mmol) was added dropwise to a stirred solution of **39** (240 mg, 0.70 mmol) and diisopropylamine (0.21 ml, 1.50 mmol) in THF (7 ml) at −78 °C under argon. After 15 min, methyl iodide (0.3 ml) was added. Stirring was continued at −78 °C for 30 min and then at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated. Column chromatography (SiO_2, hexane–AcOEt (17:3)) of the residue afforded **40** (226 mg, 90.4% yield) as a colorless gum. IR cm^{-1}: 1665. ^{1}H-NMR δ: 0.34, 0.80 and 3.25 (each 3H, s), 0.93 (3H, d, J = 5.2 Hz), 1.64 (3H, d, J = 1.2 Hz), 5.0—5.3 (1H, m), 7.0—7.6 (3H, m), 7.7—7.95 (1H, m) (methyl signals due to the corresponding rotamer (about 4:1) in the amide group were also observed at 0.97 (d, J = 6.4 Hz), 1.12 (s), 1.23 (s) and 3.11 (s)). MS *m/z*: 357 (M^+). High-resolution MS Calcd for $C_{22}H_{31}NOS$ (M^+) *m/z*: 357.2124. Found *m/z*: 357.2112.

3,5ξ,10-Trimethyl-7β,11β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one 14-Oxide (41a, b)——$NaIO_4$ (144 mg, 0.67 mmol) was added to a solution of **40** (200 mg, 0.56 mmol) in MeOH–H_2O (4:1, 15 ml). After being stirred at room temperature for 15 h, the mixture was diluted with $CHCl_3$, dried ($MgSO_4$) and filtered. The residue obtained by removal of the solvent was subjected to SiO_2 column chromatography. The fraction eluted with hexane–AcOEt (2 : 3) gave successively the semicrystalline lactam sulfoxides **41a** (117 mg, 56.0% yield) and **41b** (90 mg, 43.1% yield), which were recrystallized from $CHCl_3$–hexane. (The lactam sulfoxide **41a**) mp 203—205 °C (colorless prisms). IR cm^{-1}: 1665, 1040. ^{1}H-NMR δ: 0.34, 0.84 and 3.22 (each 3H, s), 1.15 (3H, d, J=6.5 Hz), 1.66 (3H, br), 5.1—5.4 (1H, m), 7.0—7.25 (1H, m), 7.5—7.8 (2H, m), 8.05—8.3 (1H, m). High-resolution MS Calcd for $C_{22}H_{31}NO_2S$ (M^+) m/z: 373.2074. Found m/z: 373.2087. *Anal.* Calcd for $C_{22}H_{31}NO_2S$: C, 70.73; H, 8.37; N, 3.75; S, 8.58. Found: C, 70.59; H, 8.39; N, 3.70; S, 8.58. (The lactam sulfoxide **41b**) mp 192—194 °C (colorless prisms). IR cm^{-1}: 1665, 1040. ^{1}H-NMR δ: 0.94, 1.04 and 3.22 (each 3H, s), 1.04 (3H, d, J=6 Hz), 1.58 (3H, d, J=1.2 Hz), 5.0—5.35 (1H, m), 7.0—7.3 (1H, m), 7.5—7.8 (2H, m), 7.9—8.2 (1H, m). High-resolution MS Calcd for $C_{22}H_{31}NO_2S$ (M^+) m/z: 373.2074. Found m/z: 373.2092. *Anal.* Calcd for $C_{22}H_{31}NO_2S$: C, 70.73; H, 8.37; N, 3.75; S, 8.58. Found: C, 70.55; H, 8.36; N, 3.73; S, 8.61.

Preparation of 3,8,11,11-Tetramethyl-4-oxobicyclo[5.3.1]undec-8-ene (2) from 41a, b *via* the Keto Sulfoxide 42——(1) A solution of **41a** (56 mg, 0.15 mmol) in THF (3 ml) was added to a stirred solution of LDA (0.68 mmol) in THF (3 ml) at −78 °C under argon. Stirring was continued at the same temperature for 30 min and then at −10 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with $CHCl_3$. The extract was filtered through a short column packed with SiO_2 and the filtrate was concentrated to give the crude keto sulfoxide **42** (53 mg) as a pale yellow oil, which was used for the next desulfurization without purification. IR cm^{-1}: 3280, 1700, 1655.

Pulverized 5% Na–Hg (700 mg) was added portionwise to a suspension of **42** (53 mg) obtained above and Na_2HPO_4 (300 mg) in MeOH–Et_2O (1 : 1, 6 ml) and the mixture was stirred at room temperature for 2 h under nitrogen. The mixture was diluted with Et_2O, washed with 3 N HCl, 5% $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. SiO_2 column chromatography (hexane–AcOEt (49 : 1)) of the resulting residue afforded the colorless oily ketone **2** (17 mg, 51.5% yield from **41a**) as a single product. IR cm^{-1}: 1720 (sh), 1700. ^{1}H-NMR δ: 0.93 (3H, d, J=6.7 Hz), 0.97 (6H, s), 1.68 (3H, d, J=1.9 Hz), 5.4—5.7 (1H, m). ^{13}C-NMR δ: 20.12, 22.96, 26.06 and 34.98 (each CH_3), 26.56, 28.40, 38.67 and 40.34 (each CH_2), 39.64, 42.44 and 47.36 (each CH), 34.28 (–C–), 122.83 (=CH–), 133.59 (=C–), 222.02 (C=O). High-resolution MS Calcd for $C_{15}H_{24}O$ (M^+) m/z: 220.1826. Found m/z: 220.1836.

(2) A solution of **41b** (45 mg, 0.12 mmol) in THF (2.5 ml) was treated with LDA (0.54 mmol) in THF (2.5 ml) under the same conditions as in the case of **41a** and **42** (44 mg) was obtained as a pale yellow oil. IR cm^{-1}: 3280, 1700, 1655.

The crude keto sulfoxide **42** (44 mg) obtained above was reduced with 5% Na–Hg (600 mg) and Na_2HPO_4 (250 mg) in MeOH–Et_2O (1 : 1, 5 ml) in the same way as described above. SiO_2 column chromatography of the crude product yielded the colorless oily ketone (14 mg, 53% yield from **41b**), whose ^{1}H-NMR spectrum and *Rf* value on TLC (SiO_2) were found to be consistent with those of **2** prepared from **41a**.

Methyl 5α-(3,3-Ethylenedioxybutyl)-4,6,6-trimethyl-3-cyclohexene-1α-carboxylate (43)——Diethyl azodicarboxylate (1.28 ml, 8.13 mmol) was added to a stirred solution of **16** (854 mg, 2.72 mmol) and triphenylphosphine (2.14 g, 8.16 mmol) in THF (40 ml) and the mixture was stirred at room temperature for 15 h under nitrogen. The resulting oil obtained by removal of the solvent was chromatographed on SiO_2 using hexane–AcOEt (15 : 1) as an eluent to give **43** (679 mg, 84.3% yield) as a colorless oil. IR cm^{-1}: 1730. ^{1}H-NMR δ: 0.91, 0.99, 1.33 and 3.65 (each 3H, s), 1.69 (3H, br), 3.94 (4H, s), 5.2—5.5 (1H, m). MS m/z: 281 (M^+-15). High-resolution MS Calcd for $C_{15}H_{22}O_4$ ($M^+-C_2H_6$) m/z: 266.1517. Found m/z: 266.1516.

4-(5α-Acetoxymethyl-2,6,6-trimethyl-2-cyclohexen-1α-yl)butan-2-one (44)——An ice-cooled solution of **43** (1.92 g, 6.47 mmol) in Et_2O (96 ml) was treated with $LiAlH_4$ (463 mg) and the mixture was stirred for 20 min on an ice bath. After usual work-up, the crude alcohol (1.73 g) was obtained as a colorless oil. ^{1}H-NMR δ: 0.77, 0.99 and 1.33 (each 3H, s), 1.72 (3H, br), 3.1—3.6 (1H, m), 3.6—3.9 (2H, m), 3.94 (4H, s).

The alcohol (1.73 g) obtained above was treated with Ac_2O (5 ml) in pyridine (10 ml) at room temperature for 1 h and the solvent was removed under reduced pressure to give the acetate (1.94 g) as a colorless oil. ^{1}H-NMR δ: 0.77, 1.00, 1.33 and 2.04 (each 3H, s), 1.71 (3H, br), 3.83 (1H, dd, J=7.5, 10.5 Hz), 3.94 (4H, s), 4.29 (1H, dd, J=3.9, 10.5 Hz), 5.2—5.45 (1H, m).

A solution of the crude acetate (1.94 g) obtained above and p-TsOH (200 mg) in acetone (100 ml) was stirred at room temperature for 2.5 h under nitrogen. Removal of the solvent followed by SiO_2 column chromatography (hexane–AcOEt (17 : 3)) of the resulting residue afforded **44** (1.64 g, 95% yield from **43**) as a colorless oil. IR cm^{-1}: 1735, 1715. ^{1}H-NMR δ: 0.77, 1.01, 2.04 and 2.15 (each 3H, s), 1.68 (3H, br), 3.83 (1H, dd, J=7.7, 10.7 Hz), 4.28 (1H, dd, J=3.9, 10.7 Hz), 5.25—5.6 (1H, m). MS m/z: 248 (M^+-18), 220 (M^+-46).

4-(5α-Acetoxymethyl-2,6,6-trimethyl-2-cyclohexen-1α-yl)-2-methylbutanoic Acid (45)——A solution of n-butyl lithium in hexane (17.0 mmol) was added dropwise to a stirred suspension of methoxymethyltriphenylphosphonium chloride (5.83 g, 17.0 mmol) in THF (85 ml) at 0 °C under argon and the resulting mixture was stirred at room temperature for 1 h. Then, the mixture was cooled to 0 °C and a solution of **44** (1.51 g, 5.65 mmol) in THF (23 ml) was added dropwise. Stirring was continued for 2 h, then saturated aqueous NH_4Cl solution was added at 0 °C. The mixture was diluted with Et_2O, washed with brine, dried ($MgSO_4$) and concentrated. The residue was treated with Ac_2O (22 ml) and pyridine (44 ml) at room temperature for 2 h and the solvent was evaporated off under reduced pressure. A solution of the resulting oil in Et_2O (100 ml) was treated with 60% $HClO_4$ (15 ml) at 0 °C and the mixture was stirred at room temperature for 10 min. The organic layer was separated, washed with 5% $NaHCO_3$ solution and brine, dried ($MgSO_4$) and evaporated. The crude acetoxy aldehyde was obtained as an oil. ^{1}H-NMR δ: 0.77, 1.00 and 2.04 (each 3H, s), 1.13 (3H, d, J=7 Hz), 1.71 (3H, br), 9.63 (1H, d, J=1.7 Hz).

Jones reagent (7.3 ml) was added dropwise to a stirred solution of the crude acetoxy aldehyde obtained above in acetone (110 ml) at 0 °C and the mixture was stirred at room temperature for 30 min. Work-up of the mixture in the usual manner and subsequent SiO_2 column chromatography (hexane–AcOEt (3 : 1)) of the crude product afforded **45** (1.18 g, 70.4% yield) as a colorless oil. IR cm^{-1}: 1735, 1700. ^{1}H-NMR δ: 0.76, 0.99 and 2.04 (each 3H, s), 1.21 (3H, d, J=6.8 Hz), 1.70 (3H, br), 3.82 (1H, dd, J=8, 10.6 Hz), 4.27 (1H, dd, J=3.8, 10.6 Hz), 5.2—5.5 (1H, m). MS m/z: 295 ($M^+ - 1$).

Conversion of 45 into *N*-Methyl-2′-[(2-cyanoethyl)thio]-4-(5α-methanesulfonyloxymethyl-2,6,6-trimethyl-2-cyclohexen-1α-yl)-2-methylbutananilide (47) *via* 46——A mixture of **45** (1.18 g, 3.99 mmol) and NaOH (0.44 g) in MeOH–H_2O (1 : 3, 20 ml) was stirred at 50 °C for 2 h under nitrogen and then cooled to 0 °C. The mixture was acidified with dilute HCl and evaporated to dryness under reduced pressure. The residue was suspended to CH_2Cl_2 (45 ml) and Et_3N (4.7 ml) and cooled to 0 °C. Methanesulfonyl chloride (1.8 ml) was added dropwise to the above stirred mixture. Stirring was continued for 1 h, then excess reagent was decomposed with ice-water. The mixture was acidified with dilute HCl and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give **46** as a colorless oil. ^{1}H-NMR δ: 0.79, 1.01 and 3.00 (each 3H, s), 1.24 (3H, d, J=7 Hz), 1.71 (3H, br), 3.99 (1H, dd, J=8, 9.2 Hz), 4.22 (1H, dd, J=3.6, 9.2 Hz), 5.25—5.4 (1H, m).

A solution of **46** obtained above and oxalyl chloride (7 ml) in benzene (70 ml) was stirred at room temperature for 1 h and then heated at 60 °C for 1 h. Removal of the solvent gave an oil, which was dissolved in THF (50 ml). The solution was added dropwise to a suspension of **36** (2.30 g) and anhydrous K_2CO_3 (3.30 g) in THF (150 ml) at 0 °C. The mixture was stirred at room temperature for 3 h, diluted with water and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The resulting oil was chromatographed on SiO_2 (hexane–AcOEt (1 : 1)) to give a mixture of the amide mesylate **47** (1.15 g, 56.9% yield from **45**) as an oil. ^{1}H-NMR δ: 0.71, 0.76, 0.81 and 0.83 (total 3H, s), 0.87, 0.92 and 0.95 (total 3H, s), 1.00 (0.75H, d, J=6.1 Hz), 1.11 (2.25H, d, J=6.4 Hz), 1.63, 1.64 and 1.72 (total 3H, br), 3.00 and 3.01 (total 3H, s), 3.18, 3.19 and 3.20 (total 3H, s), 3.97 (1H, dd, J=9, 9.2 Hz), 4.39 (1H, dd, J=3.8, 9.2 Hz), 5.1—5.5 (1H, m).

3,5ξ,9-Trimethyl-8β,12β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one (48)——Anhydrous K_2CO_3 (1.10 g, 7.96 mmol) and $NaBH_4$ (300 mg, 7.93 mmol) were dried over P_2O_5 at 130 °C for 2 h *in vacuo* and then DMF (80 ml) was added. A solution of the amides **47** (776 mg, 1.53 mmol) in DMF (31 ml) was added to the above mixture at 130—135 °C with vigorous stirring during a period of 36 h under argon. Heating was continued at the same temperature for a further 4 h, then the mixture was neutralized with dilute HCl, concentrated under reduced pressure and extracted with AcOEt–Et_2O. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The resulting oil was subjected to SiO_2 column chromatography (hexane–AcOEt (17 : 3)) affording the twelve membered lactam sulfides **48a** (121 mg, 26.4% yield) as a less polar colorless gum and **48b** (198 mg, 43.3% yield) as a more polar colorless gum. (Less polar **48a**) IR cm^{-1}: 1655. ^{1}H-NMR δ: 0.89, 1.36 and 3.23 (each 3H, s), 1.13 (3H, d, J=6.7 Hz), 1.54 (3H, d, J=1.7 Hz), 2.72 (1H, dd, J=11.8, 13 Hz), 3.50 (1H, dd, J=6, 13 Hz), 4.8—5.1 (1H, m), 7.0—7.65 (4H, m). MS m/z: 357 (M^+). High-resolution MS Calcd for $C_{22}H_{31}NOS$ (M^+) m/z: 357.2124. Found m/z: 357.2111. (More polar **48b**) IR cm^{-1}: 1650. ^{1}H-NMR δ: 0.79 and 0.92 (each 3H, s), 1.08 (3H, d, J=6.5 Hz), 1.08 (3H, d, J=6.5 Hz), 1.65 (3H, d, J=1.5 Hz), 3.15 (2.5H, s), 3.42 (0.5H, s), 5.15—5.45 (1H, m), 7.0—7.8 (4H, m). MS m/z: 357 (M^+). High-resolution MS Calcd for $C_{22}H_{31}NOS$ (M^+) m/z: 357.2124. Found m/z: 357.2093.

3,5ξ,9-Trimethyl-8β,12β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one 14-Oxide (49)——(1) $NaIO_4$ (130 mg, 0.61 mmol) was added to a stirred solution of **48a** (166 mg, 0.465 mmol) in MeOH–H_2O (4 : 1, 13 ml) at 0 °C. The mixture was stirred at room temperature for 5 h, diluted with water and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated to give an oil, which was subjected to SiO_2 column chromatography. Elution with hexane–AcOEt (1 : 2) afforded **49a** (149 mg, 85.9% yield) as a colorless caramel. IR cm^{-1}: 1660, 1040. ^{1}H-NMR δ: 0.99, 1.23 and 3.37 (each 3H, s), 1.16 (3H, d, J=6.7 Hz), 1.55 (3H, d, J=1.9 Hz), 3.69 (1H, dd, J=12.4, 12.6 Hz), 4.9—5.2 (1H, m), 7.0—7.25 (1H, m), 7.5—7.75 (2H, m), 7.9—8.2 (1H, m). MS m/z: 373 (M^+). High-resolution MS Calcd for $C_{22}H_{31}NO_2S$ (M^+) m/z: 373.2074. Found m/z: 373.2058.

(2) The more polar **48b** (380 mg, 1.06 mmol) was treated with $NaIO_4$ (296 mg, 1.38 mmol) in MeOH–H_2O (4 : 1, 30 ml) in the same way as described in the preparation of **49a**. SiO_2 column chromatography (hexane–AcOEt (2 : 3)) of the crude product afforded **49b$_1$** (243 mg, 61.2% yield) as a less polar colorless caramel and **49b$_2$** (108 mg, 27.2% yield) as a more polar colorless caramel. (Less polar **49b$_1$**) IR cm^{-1}: 1665, 1040. ^{1}H-NMR δ: 0.86, 1.02 and 3.15 (each 3H, s), *ca.* 1.07 (3H, d, J=*ca.* 6.5 Hz), 1.62 (3H, d, J=1.4 Hz), 5.3—5.6 (1H, m), 6.9—7.2 (1H, m), 7.5—7.75 (2H, m), 8.0—8.2 (1H, m). MS m/z: 373 (M^+). High-resolution MS Calcd for $C_{22}H_{31}NO_2S$ (M^+) m/z: 373.2074. Found m/z: 373.2095. (More polar **49b$_2$**) IR cm^{-1}: 1655, 1040. ^{1}H-NMR δ: 1.00, 1.51 and 3.40 (each 3H, s), 1.19 (3H, d, J=6.7 Hz), 1.68 (3H, d, J=1.2 Hz), 5.15—5.4 (1H, m), 7.05—7.3 (1H, m), 7.4—7.7 (2H, m), 7.8—8.1 (1H, m). MS m/z: 373 (M^+). High-resolution MS Calcd for $C_{22}H_{31}NO_2S$ (M^+) m/z: 373.2074. Found m/z: 373.2056.

Intramolecular Acyl Migration of 49 to Give 4,8,11,11-Tetramethyl-2-(2-methylamino)phenylsulfinyl-3-oxobicy-

clo[5.3.1]undec-8-ene (50)——(1) A solution of **49a** (150 mg, 0.402 mmol) in THF (4 ml) was added to a stirred solution of LDA (1.98 mmol) prepared from diisopropylamine (0.28 ml, 2.0 mmol) and *n*-butyl lithium (hexane solution, 1.98 mmol) in THF (8 ml) at −65 °C under argon. The mixture was stirred at −65 °C for 30 min and at 0 °C for 4.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with AcOEt after neutralization with dilute HCl. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The resulting oil was subjected to SiO_2 column chromatography. The first fraction eluted with hexane–AcOEt (17 : 3) afforded **50a** (25 mg, 16.7% yield) as a pale yellow gum. IR cm^{-1}: 3280, 1685. ^{1}H-NMR δ: 0.84 (3H, d, J=6.8 Hz), 0.90 and 1.04 (each 3H, s), 1.71 (3H, d, J=1.3 Hz), 2.86 (3H, d, J=5.2 Hz), 4.78 (1H, d, J=7.8 Hz), 5.45—5.7 (1H, m), 6.0—6.35 (1H, m), 6.45—6.85 (2H, m), 7.0—7.5 (2H, m).

Elution with hexane–AcOEt (3 : 1) gave successively **50b** (7 mg, 4.7% yield) and **50c** (8 mg, 5.3% yield) as a pale yellow gum. (Less polar **50b**) IR cm^{-1}: 3280, 1695. ^{1}H-NMR δ: 0.75 (6H, s), 1.05 (3H, d, J=6.5 Hz), 1.65 (3H, br), 2.89 (3H, d, J=5.2 Hz), 5.27 (1H, d, J=1.2 Hz), 5.2—5.45 (1H, m), 6.5—6.85 (3H, m), 7.1—7.6 (2H, m). (More polar **50c**) IR cm^{-1}: 3280, 1695, 1655. ^{1}H-NMR δ: 0.68 and 0.75 (each 3H, s), 1.15 (3H, d, J=6.8 Hz), 1.64 (3H, br), 2.87 (3H, d, J=5.1 Hz), 5.56 (1H, br), 5.2—5.45 (1H, m), 6.5—6.9 (3H, m), 7.1—7.6 (2H, m).

The last fraction eluted with hexane–AcOEt (2 : 3) afforded **49b**$_2$ (91 mg, 60.7% yield), whose IR and ^{1}H-NMR spectra and *Rf* value on TLC (SiO_2) were identical with those of **49b**$_2$ obtained by oxidation of **48b**.

(2) A solution of **49b**$_1$ (75 mg, 0.20 mmol) in THF (2 ml) was added to a stirred solution of LDA (1.00 mmol) in THF (4 ml) at −65 °C under argon. After being stirred for 30 min, the mixture was stirred at 0 °C for 4 h. Work-up in the same way as described above yielded a pale yellow oil, which was subjected to SiO_2 column chromatography. The first fraction eluted with hexane–AcOEt (17 : 3) afforded a mixture of **50d** and **50e** (9 : 5, 11 mg, 14.7% yield, 22.4% based on the consumed **49b**$_1$) as a solid. (for **50d**) IR cm^{-1}: 3280, 1690. ^{1}H-NMR δ: 0.27 (3H, d, J=6.6 Hz), 1.11 and 1.28 (each 3H, s), 1.58 (3H, d, J=2 Hz), 2.86 (3H, d, J=5.1 Hz), 5.13 (1H, br), 5.2—5.5 (1H, m), 6.4—6.8 (2H, m), 7.0—7.35 (2H, m), 7.4—7.75 (1H, m). (for **50e**) IR cm^{-1}: 3380, 1690. ^{1}H-NMR δ: 0.60 (3H, d, J=6.4 Hz), 1.00 and 1.04 (each 3H, s), 1.58 (3H, d, J=2 Hz), 2.90 (3H, d, J=4.9 Hz), 5.2—5.5 (1H, m), 6.4—6.8 (2H, m), 7.0—7.35 (2H, m), 7.4—7.75 (1H, m).

The second fraction eluted with hexane–AcOEt (3 : 1) gave **50f** (38 mg, 50.7% yield, 77.6% based on the consumed **49b**$_1$) as a colorless oil. IR cm^{-1}: 3320, 1690, 1680 (sh). ^{1}H-NMR δ: *ca.* 0.85 (3H, d, J=*ca.* 7 Hz), 0.92 and 1.03 (each 3H, s), 1.66 (3H, d, J=0.7 Hz), 2.86 (3H, d, J=3.3 Hz), 4.33 (1H, d, J=7.2 Hz), 5.2—5.5 (1H, m), 6.3—6.9 (3H, m), 7.2—7.5 (2H, m).

The third fraction eluted with hexane–AcOEt (2 : 3) yielded the starting sulfoxide **49b**$_1$ (26 mg, 34.7% recovery).

(3) The lactam sulfoxide **49b**$_2$ (150 mg, 0.40 mmol) was exposed to LDA in THF in the same way as described above. The resulting oil obtained by work-up was subjected to SiO_2 column chromatography. Elution with hexane–AcOEt (17 : 3) gave **50g** (10 mg, 6.7% yield) as a pale yellow gum. IR cm^{-1}: 3280, 1685. ^{1}H-NMR δ: 0.06 (3H, d, J=6.8 Hz), 1.01 and 1.07 (each 3H, s), 1.69 (3H, br), 2.86 (3H, d, J=5.2 Hz), 4.61 (1H, d, J=7.1 Hz), 5.2—5.7 (1H, m).

Elution with hexane–AcOEt (3 : 1) afforded successively **50b** (59 mg, 39.3% yield) and **50c** (20 mg, 13.3% yield).

The last fraction eluted with hexane–AcOEt (1 : 2) yielded a mixture of sulfoxides (28 mg).

4,8,11,11-Tetramethyl-3-oxobicyclo[5.3.1]undec-8-ene (3)——Pulverized 5% Na–Hg (2.18 g) was added portionwise to a stirring mixture of **50a—g** (155 mg, 0.416 mmol) and Na_2HPO_4 (800 mg) in MeOH–Et_2O (1 : 1, 18 ml) and the mixture was stirred at room temperature for 2 h under nitrogen. After filtration, the filtrate was diluted with water and extracted with Et_2O. The extract was washed with 3 N HCl, 5% $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. SiO_2 column chromatography (hexane–AcOEt (24 : 1)) of the resulting oil afforded successively the less polar ketone **3a** (49 mg, 53.5% yield) as a colorless oil and the more polar ketone **3b** (29.5 mg, 32.3% yield) as a colorless gum. (Less polar **3a**) IR cm^{-1}: 1720 (sh), 1695. ^{1}H-NMR δ: 0.96 (3H, d, J=6.8 Hz), 0.98 and 1.18 (each 3H, s), 1.62 (3H, d, J=1.6 Hz), 5.25—5.55 (1H, m). High-resolution MS Calcd for $C_{15}H_{24}O$ (M^+) *m/z*: 220.1826. Found *m/z*: 220.1837. (More polar **3b**) IR cm^{-1}: 1735 (sh), 1685. ^{1}H-NMR δ: 0.97 and 1.15 (each 3H, s), 1.04 (3H, d, J=7 Hz), 1.64 (3H, d, J=1.7 Hz), 2.94 (1H, dd, J=2.8, 11.4 Hz), 5.15—5.45 (1H, m). High-resolution MS Calcd for $C_{15}H_{24}O$ (M^+) *m/z*: 220.1826. Found *m/z*: 220.1820.

References and Notes

1) Preliminary communication: Y. Ohtsuka and T. Oishi, *Tetrahedron Lett.*, **27**, 203 (1986).
2) Y. Ohtsuka and T. Oishi, *Chem. Pharm. Bull.*, **36**, 4711 (1988).
3) Y. Ohtsuka and T. Oishi, *Tetrahedron Lett.*, **1979**, 4487; *idem, Chem. Pharm. Bull.*, **31**, 443, 454 (1983).
4) *a*) M. Rosenberger, P. McDougal and J. Bahr, *J. Org. Chem.*, **47**, 2130 (1982); *b*) P. Karrer and C. H. Eugster, *Helv. Chim. Acta*, **34**, 1400 (1951).
5) M. Yamashita, Y. Kato and R. Suemitsu, *Chem. Lett.*, **1980**, 847.
6) In order to avoid confusion, the numbering for the bicyclo[5.3.1]undecane to be synthesized as the final compound has been used for the cyclohexane derivatives in this paper.
7) J. E. McMurry and J. Melton, *J. Org. Chem.*, **38**, 4367 (1973).
8) The hydrogenation in the absence of sodium acetate proceeded rapidly, affording **13** in higher yield, but was not

reproducible.
9) O. Mitsunobu, K. Kato and J. Kimura, *J. Am. Chem. Soc.*, **91**, 6510 (1969); A. K. Bose, B. Lal, W. A. Hoffman III and M. S. Manhas, *Tetrahedron Lett.*, **1973**, 1619.
10) M. Wada, T. Sano and O. Mitsunobu, *Bull. Chem. Soc. Jpn.*, **46**, 2833 (1973); H. Wojciechowska, R. Pawłowicz, R. Andruszkiewicz and J. Grzybowska, *Tetrahedron Lett.*, **1978**, 4063.
11) Y. Ohtsuka, S. Niitsuma, H. Tadokoro, H. Hayashi and T. Oishi, *J. Org. Chem.*, **49**, 2326 (1984).