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Studies on Taxane Synthesis. I. Synthesis of 3,8,11,11-Tetramethyl-4-oxobicyclo[5.3.1]undecane as a Model for Taxane Synthesis

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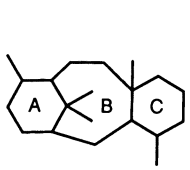
The bicyclo[5.3.1]undecanone **5** corresponding to the A and B rings in taxane diterpenes was synthesized from β-ionone. Reduction of the tosylhydrazone **11** with catecholborane afforded the trisubstituted olefin **12** having *trans* substituents at the C-1 and C-7 positions. The requisite *cis*-arrangement of these substituents for eight-membered ring formation was induced by epimerization of the aldehyde **13** to give the bicyclic hemiacetal **14**. The lithium diisopropylamide-promoted intramolecular cyclization of the twelve-membered lactam sulfoxide **32** proceeded quite smoothly, affording the eight-membered keto sulfoxide **33** in quantitative yield.

Keywords——taxane; eight-membered ring; intramolecular cyclization; twelve-membered lactam sulfoxide; β-ionone; epimerization; tosylhydrazone; catecholborane; Michael addition; bicyclo[5.3.1]undecane

The taxanes, a group of naturally occurring diterpenes isolated from various species of *Taxus*, possess a unique tricyclo[9.3.1.$0^{3,8}$]pentadecane structure (**1**) involving a sterically congested eight-membered B-ring.[1] Among them, taxol (**2**) and cephalomannine (**3**) were recently found to exhibit antileukemic and antitumor activities.[2]

The crucial step in the synthesis of **1** is obviously in the construction of the eight-membered B-ring, and several approaches based on fragmentation,[3a] rearrangement,[3b] intramolecular Diels–Alder reaction[3c] or direct ring closure[3d] have been reported. Recently, we developed an efficient general method for the construction of medium-ring ketones based on the intramolecular cyclization of large-membered lactam sulfoxides or sulfones[4] and this method was successfully applied for the total syntheses of caryophyllene and isocaryophyllene, possessing a bicyclo[7.2.0]undecane ring system.[5] We now report a series of model experiments aimed at examining whether our new strategy can be applied for the construction of the sterically extremely congested eight-membered taxane B-ring having a functionality for C-ring formation.

Initially, we intended the synthesis of the bicyclo[5.3.1]undecane derivative **4** having a keto group on the eight-membered B-ring. In our strategy for eight-membered ketone



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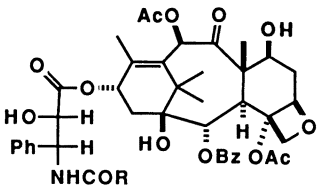
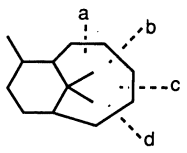


taxol (**2**): R = C_6H_5
cephalomannine (**3**): R = CMeCHMe



4: alkyl and carbonyl groups in B ring

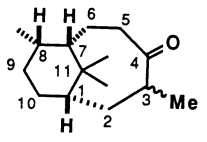


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Fig. 1

formation, a key intermediate is a twelve-membered lactam sulfoxide or sulfone. However, in the present cases, the oxidation-labile tetrasubstituted double bond is present in the A-ring of the natural products and thus the preferential oxidation of sulfide to sulfone is presumed to be difficult, while oxidation to sulfoxide does take place without any difficulty. Therefore, the pathway which proceeds *via* lactam sulfoxides was chosen.

As a route for the synthesis of compounds having a bicyclo[5.3.1]undecane skeleton **4**, eight variants can be formulated (Fig. 2). Among them, the routes 1, 2, 4 and 7 are eliminated since the keto groups in the products are located inadequately for the subsequent C-ring formation. The routes 5 and 6 should also be avoided for the following reasons. In the previous paper,[4] it was shown that the intramolecular cyclization of lactam sulfoxides proceeded smoothly only when an alkyl group was present α to the lactam carbonyl group.

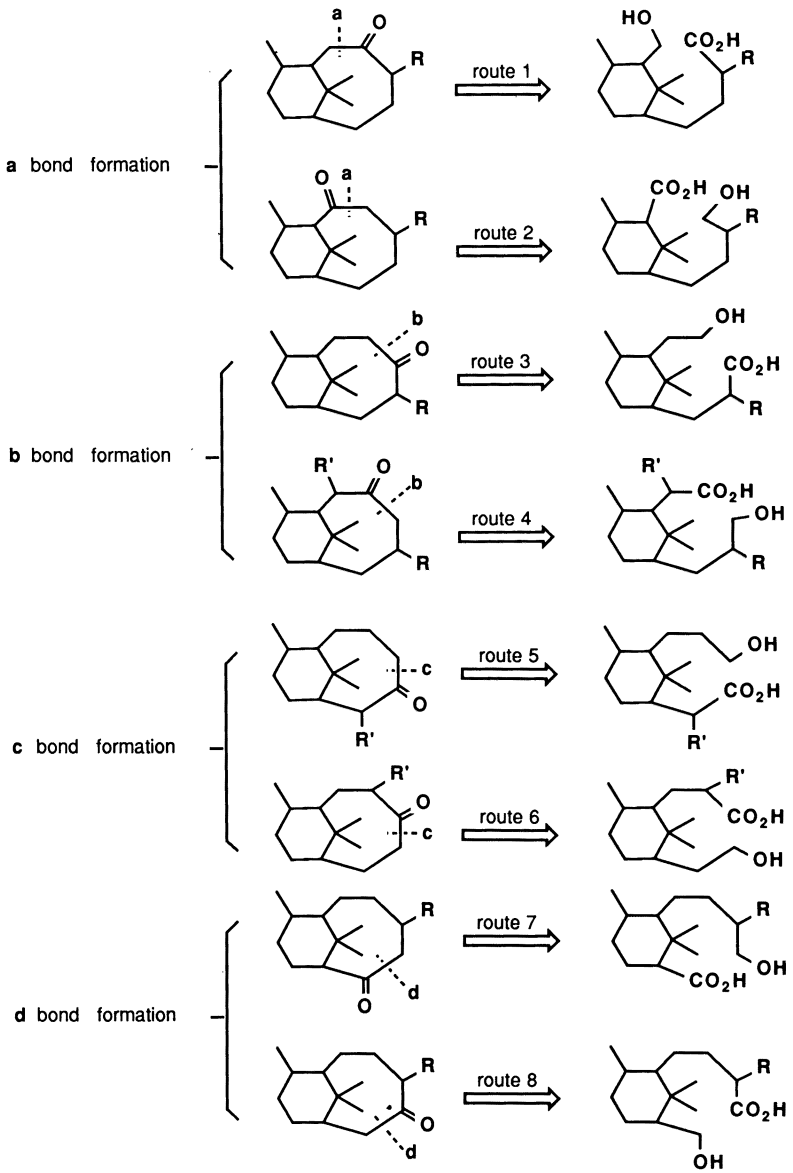

Fig. 2

According to this limitation, only the ketones having an unnecessary alkyl group on the C-2 or C-5 position can be prepared by the routes 5 or 6, respectively, while alkyl groups in the ketones prepared by the routes 3 and 8 are situated in positions where they can be used directly for formation of the C-ring provided they are properly functionalized. In the present paper the synthesis of the 3-methyl-4-oxo compound **5** by the route 3 is described and in the following paper the synthesis of the 4-alkyl-8-en-3-oxo derivative of **4** by the route 8 will be reported.

The acetate **7**, easily prepared from β-ionone (**6**) by selective ozonolysis of the side chain,[6] $NaBH_4$ reduction and acetylation of the resulting primary alcohol (55% overall yield), was chosen as the starting material and subjected successively to SeO_2 oxidation and Jones oxidation, affording the keto acetate **8** (73% yield). To introduce a functional group at the C-1 position,[7] **8** was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to the cross-conjugated dienone **9**, which was subjected to base-catalyzed Michael addition. However, addition of carbanions derived from 1,3-dithiane, methyl methylsulfinylmethyl sulfide, ethyl ethylsulfinylmethyl sulfide, methyl phenyl sulfide, methyl phenyl sulfoxide or methyl phenyl sulfone to the C-1 position in **9** under various conditions did not take place. The desired addition product was obtained only when nitromethane was used, although the reaction was quite slow. Namely, when **9** was treated with nitromethane in the presence of diisopropylamine in dimethyl sulfoxide (DMSO) at 65 °C for 20 d, the nitro acetate **10** was obtained in 88% yield along with a small amount of the starting dienone **9** (9% yield). When the reaction was carried out at 110 °C in a sealed tube, it proceeded more rapidly, but side reactions also took place, diminishing the yield appreciably (53%).

The tetrasubstituted α,β-unsaturated ketone in **10** was then converted into the trisubstituted olefin **12** in 95.3% yield by reduction of the corresponding tosylhydrazone **11** with catecholborane. The substituents at the C-1 and C-7 positions in **12** can be assigned as *trans* since it is presumed that the reducing agent approaches the C=N double bond of the tosylhydrazone **11** from the less hindered α-side producing the diimine ii *via* i, and then double bond migration, nitrogen gas extrusion and intramolecular hydride transfer take place concomitantly, affording *trans* **12** as shown in Fig. 5. The nitromethyl group in **12** was then converted into an aldehyde by MeONa and $TiCl_3$ treatment[8] producing **13**. In order that the eight-membered ring formation might be achieved at a later stage, substituents as the C-1 and C-7 positions should be *cis*. Therefore, base-induced epimerization of the formyl group in **13** was examined at this stage. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (benzene, 80 °C) treatment of **13** led only to the recovery of the starting material, and lithium diisopropylamide (LDA) (tetrahydrofuran (THF), −10 °C) treatment gave a complex mixture. Quite unexpectedly, however, treatment of **13** with MeONa in MeOH afforded the bicyclic hemiacetal

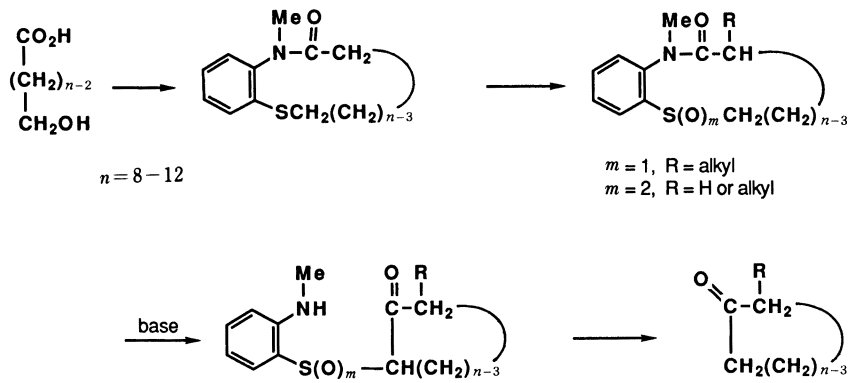

Fig. 3

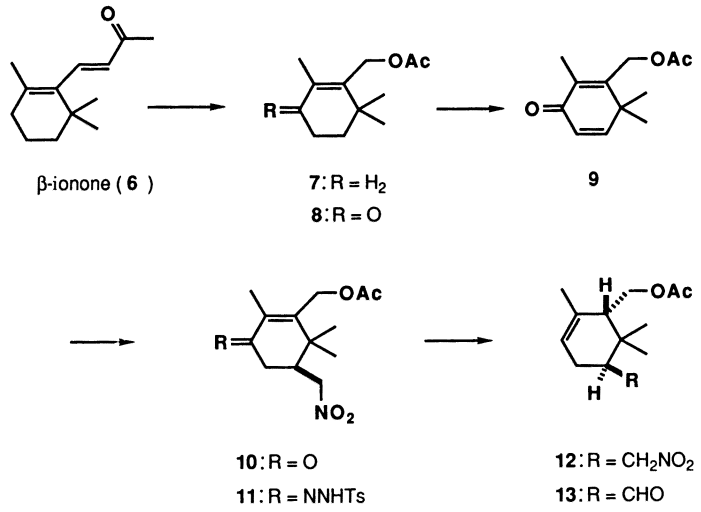

Fig. 4

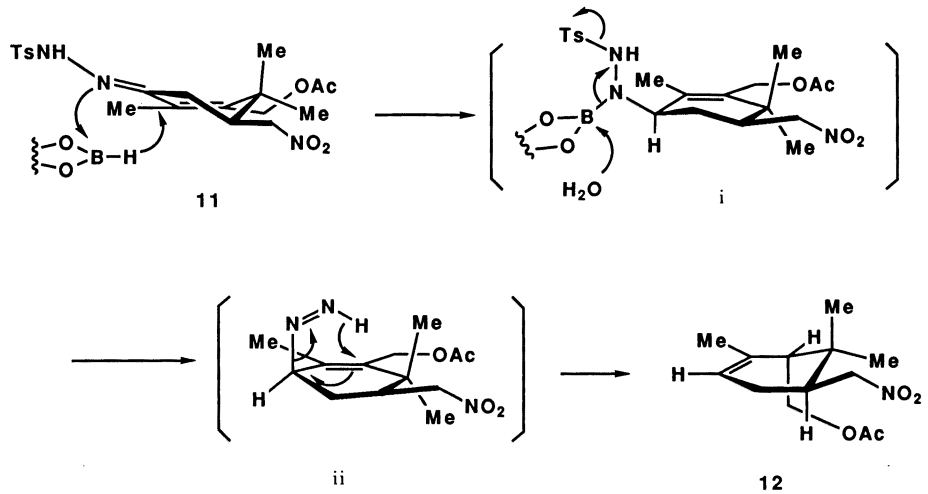

Fig. 5

14. Sodium borohydride reduction of **14** followed by acetylation produced the *cis* diacetate **15**. On the other hand, direct lithium aluminum hydride reduction of the aldehyde **13** followed by acetylation yielded the isomeric diacetate **16**. Therefore, the substituents at C-1 and C-7 in **16** should be assigned as *trans*, which clearly shows that the above stereochemical assumption leading to **12** from **11** is correct. Initial methanolysis of the acetate in **13** by MeONa–MeOH and the subsequent intramolecular attack of the resulting alkoxide anion on the nearby C-1 hydrogen atom may account for this unique epimerization of the formyl group. The fact that the hydrolysis of the acetate is essential for the initiation of the reaction is supported by the following observations; 1) an attempt at epimerization under anhydrous conditions using DBU failed, and 2) even when the pivalate **17** or the methoxymethyl ether **18** were treated with *tert*-BuOK (or KH)–THF or MeONa–MeOH, respectively, epimerization did not take place. These compounds are known to resist hydrolysis under the above specific conditions.

Next, the bicyclic hemiacetal **14** was treated with (carbethoxymethylene)triphenylphos-

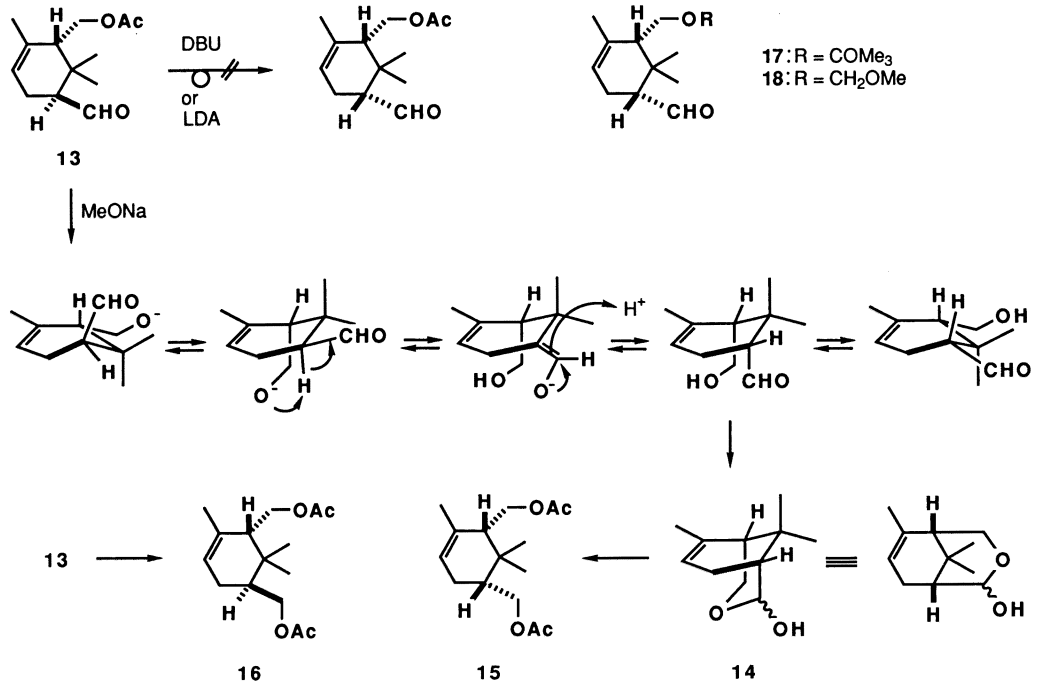

Fig. 6

phorane, affording the unsaturated ester **19**. However, an attempted selective hydrogenation of the α,β-unsaturated ester of **19** to **20** with NaTeH,[9] or lithium tri-*sec*-butylborohydride (L-Selectride)–*tert*-BuOH[10] was unsuccessful. Only the starting **19** was recovered unchanged. Thus, **19** was converted by catalytic hydrogenation into the fully saturated compound **21**, which was still expected to serve as a model compound in testing the crucial B-ring formation. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **21** showed that substituents at the C-7 and C-8 positions of **21** could be assigned as *cis* from the small coupling constant ($J_{7,8}$ = 4.6 Hz). One-carbon elongation of the C-7 side chain in **21** was then carried out. Mesylation followed by NaCN treatment (DMSO, 100 °C) yielded the cyanide **22** (45% yield from **21**) along with the elimination product **23** (45% yield from **21**). Selective reduction of **22** with $LiBH_4$ afforded the alcohol **24** in quantitative yield.

Then, the tetrahydropyranyl ether **25** derived from **24** was treated successively with diisobutylaluminum hydride, $NaBH_4$ and Ac_2O to give an acetate, whose acidic hydrolysis followed by Jones oxidation afforded the acetoxy acid **26** in 46% yield. The acetoxy acid **26** was converted, *via* the acetate **28**, into the amide tosylate **29** by amidation (i, $(COCl)_2$, ii **27**), hydrolysis (K_2CO_3–MeOH) and tosylation (*p*-TsCl–pyridine). Slow addition of a dioxane solution of **29** into a mixture of *tert*-BuOK in *tert*-BuOH brought about retro-Michael reaction of the cyanoethyl protecting group liberating sulfide anion, which attacked the tosylate intramolecularly, producing the twelve-membered lactam sulfide **30** in 26% yield from **26**. Formation of the corresponding dimer or polymer was not detected in this reaction. Here, an alkyl group should be introduced to the position of the lactam carbonyl group to promote the subsequent cyclization to the eight-membered ketone. In the present model experiment, the methyl group was introduced in order to simplify the subsequent step. Peracid oxidation of **31** gave the lactam sulfoxide **32** in 91% yield.

The LDA-promoted intramolecular cyclization of the lactam sulfoxide **32** proceeded quite smoothly affording the eight-membered keto sulfoxide **33** in quantitative yield. Re-

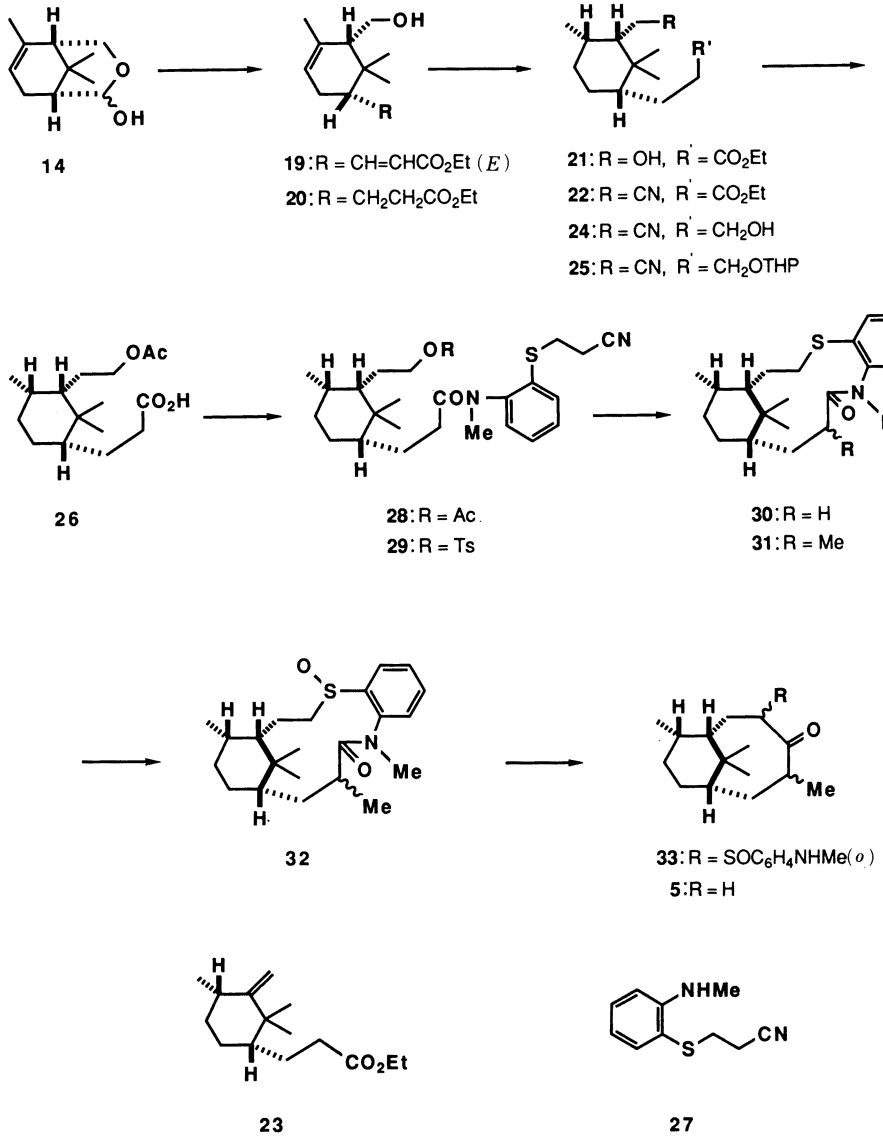

Fig. 7

ductive removal of the methylaminophenylsulfinyl group of **33** with Na–Hg in MeOH in the presence of Na_2HPO_4 produced the desired bicyclic ketone **5** in 68% yield as a sole product but the stereochemistry at the C-3 position remained unknown. The analytical and spectral data including ^{13}C-nuclear magnetic resonance (^{13}C-NMR) were consistent with the proposed structure.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were taken on a JEOL FX-60, FX-90, 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. Infrared (IR) spectra were measured in CCl_4 solution with a JASCO A-3 spectrometer. Mass spectra (MS) were obtained with a Hitachi RMU-6M mass spectrometer and high resolution mass spectra were recorded on a Hitachi M-80 GC-MS spectrometer.

2-Acetoxymethyl-1,3,3-trimethylcyclohexene (7)——β-Ionone (**6**) was subjected to partial ozonolysis according to the procedure reported by Müller and Hoffmann.[6] A solution of **6** (23.65 g, 123.2 mmol) in MeOH was treated with ozone at −27 °C until the starting material was no longer detectable (about 4 h). After removal of an excess of ozone at the same temperature, $NaBH_4$ (22 g) was added portionwise to the stirred solution below 10 °C. The solvent was evaporated off under reduced pressure from the mixture, and the residue was dissolved in Et_2O–H_2O. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated. The resulting oily alcohol (21.81 g) was subjected to the next acetylation without purification. ^{1}H-NMR δ: 1.04 (6H, s), 1.75 (3H, br), 4.14 (2H, s).

The crude alcohol (21.81 g) obtained above was treated with acetic anhydride (120 ml) in pyridine (240 ml) in the presence of 4-dimethylaminopyridine (100 mg) for 3 d at room temperature and then concentrated under reduced pressure. SiO_2 column chromatography (hexane–AcOEt (19 : 1)) of the resulting oil afforded **7** (13.30 g, 55.1% yield from **6**) as a pale yellow oil. IR cm^{-1}: 1735. ^{1}H-NMR δ: 0.99 (6H, s), 1.67 (3H, br), 2.05 (3H, s).

2-Acetoxymethyl-1,3,3-trimethyl-6-oxocyclohexene (8)——A mixture of **7** (9.03 g, 46.1 mmol) and SeO_2 (5.21 g) in dioxane (145 ml) was refluxed for 45 min and, after cooling, filtered through a short column packed with SiO_2. The solvent was evaporated off under reduced pressure. Jones reagent (14.7 ml) was added dropwise to a stirred solution of the resulting oil in acetone (245 ml) at 0 °C and stirring was continued for 5 min. After addition of 2-propanol (12 ml), usual work-up of the mixture and subsequent SiO_2 column chromatography (hexane–AcOEt (9 : 1)) afforded **8** (7.09 g, 73.3%) as a yellow oil. IR cm^{-1}: 1740, 1675. ^{1}H-NMR δ: 1.18 (6H, s), 1.81 and 2.09 (each 3H, s), 4.74 (2H, s). MS *m/z*: 210 (M^+). High-resolution MS Calcd for $C_{12}H_{18}O_3$ (M^+) *m/z*: 210.1256. Found *m/z*: 210.1279.

2-Acetoxymethyl-1,3,3-trimethyl-6-oxo-1,4-cyclohexadiene (9)——2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ, 7.07 g) was added to a solution of **8** (8.65 g, 41.2 mmol) in benzene (290 ml) and the mixture was refluxed for 3 d with stirring. More DDQ (4.02 g) was added and reflux was continued for 3 d. The precipitate was filtered off and the filtrate was diluted with Et_2O. The solution was washed with aqueous Na_2CO_3 solution, water and brine, and dried ($MgSO_4$). Removal of the solvent gave an oil, which was subjected to SiO_2 column chromatography. Elution with hexane–AcOEt (9 : 1—4 : 1) afforded successively **9** (7.48 g, 87.3%) as a pale yellow oil and the starting keto acetate **8** (0.83 g). IR cm^{-1}: 1740, 1660. ^{1}H-NMR δ: 1.26 (6H, s), 1.94 and 2.09 (each 3H, s), 4.84 (2H, s), 6.22 and 6.78 (each 1H, d, J = 10 Hz). MS *m/z*: 208 (M^+). High-resolution MS Calcd for $C_{12}H_{16}O_3$ (M^+) *m/z*: 208.1099. Found *m/z*: 208.1116.

2-Acetoxymethyl-1,3,3-trimethyl-4-nitromethyl-6-oxocyclohexene (10)——i) Diisopropylamine (31.5 ml) and nitromethane (39 ml) were added to a solution of **9** (11.86 g, 57 mmol) in DMSO (17.5 ml) and the mixture was stirred for 20 d at 65 °C under nitrogen. Excess nitromethane and diisopropylamine were removed under reduced pressure from the mixture and the residue was extracted with Et_2O–AcOEt (3 : 1). The extract was washed with water, dried ($MgSO_4$), and concentrated to give an oil, which was subjected to SiO_2 column chromatography. The fraction eluted with hexane–AcOEt (4 : 1—7 : 3) afforded **10** (13.55 g, 88.3%) as crystals, which were recrystallized from $CHCl_3$–hexane to yield colorless prisms, mp 74—75 °C. IR cm^{-1}: 1740, 1680, 1375. ^{1}H-NMR δ: 1.13, 1.30 and 2.10 (each 3H, s), 1.85 (3H, br), 4.23 (1H, dd, J = 8.8, 12.5 Hz), 4.67 (1H, dd, J = 4.2, 12.5 Hz), 4.76 (2H, s). *Anal.* Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.90; H, 7.19; N, 5.02.

The starting dienone **9** (1.04 g, 8.8%) was recovered from the fraction eluted with hexane–AcOEt (4 : 1).

ii) In a sealed tube, a mixture of **9** (7.43 g, 35.7 mmol), DMSO (11 ml), diisopropylamine (20 ml) and nitromethane (24.5 ml) was stirred for 3 d at 110 °C under nitrogen. The same work-up as described above and subsequent SiO_2 chromatography gave **10** (5.10 g, 53.1%) and the starting dienone **9** (1.81 g, 24.4%).

6α-Acetoxymethyl-1,5,5-trimethyl-4β-nitromethylcyclohexene (12)——A mixture of **10** (4.785 g, 17.8 mmol) and *p*-toluenesulfonylhydrazide (4.02 g, 1.2 eq) in EtOH (15 ml) was stirred for 1 h at 65 °C under nitrogen. Removal of the solvent afforded **11** as yellow crystals (10.20 g), which were subjected to the next reductive degradation without purification. IR cm^{-1}: 3200, 1740, 1165. ^{1}H-NMR δ: 1.00, 1.18, 2.05 and 2.44 (each 3H, s), 1.88 (3H, br), 4.15 (1H, dd, J = 7.8, 14.4 Hz), 4.68 (2H, s), 4.75 (1H, dd, J = 4.8, 14.4 Hz), 7.33 and 7.87 (each 2H, d, J = 8.4 Hz).

Catecholborane (3.66 ml, 34.1 mmol) was added dropwise to a stirred solution of **11** (10.20 g) obtained above in $CHCl_3$ (20 ml) at 0 °C, and the mixture was stirred for 2 h at room temperature under nitrogen. After careful addition of $AcONa \cdot 3H_2O$ (11.44 g, 84.1 mmol) with stirring, the mixture was refluxed for 2 h under nitrogen. The precipitate was filtered off and washed with $CHCl_3$. The solvent of the combined filtrate and extract was evaporated to give a yellow oil. SiO_2 column chromatography (hexane–AcOEt (9 : 1)) of the oil gave **12** (4.325 g, 95.3% from **10**) as a colorless oil. IR cm^{-1}: 2850, 1740. ^{1}H-NMR δ: 0.88, 1.05 and 2.05 (each 3H, s), 1.75 (3H, br), 3.7—4.5 (2H, m), 4.21 (1H, dd, J = 1.4, 11.5 Hz), 4.54 (1H, dd, J = 4.8, 11.5 Hz), 5.3—5.6 (1H, m). MS *m/z*: 256 ($M^+ + 1$), 195 ($M^+ - 60$). High-resolution MS Calcd for $C_{13}H_{21}NO_4$ (M^+) *m/z*: 255.1469. Found *m/z*: 255.1431.

Preparation of 6α-Acetoxymethyl-4β-formyl-1,5,5-trimethylcyclohexene (13)——Sodium methoxide (96%, 540 mg, 9.6 mmol) was dissolved in a solution of **12** (2.170 g, 8.51 mmol) in MeOH (15 ml) under nitrogen. To this solution, a mixture of aqueous $TiCl_3$ solution (16%, 36 ml) and $AcONH_4$ (18.70 g) in water (15 ml) was added rapidly with stirring on a water bath (bath temperature, 15 °C) and stirring was continued for 30 min under nitrogen. The reaction mixture was diluted with 1% HCl (about 300 ml) and extracted with AcOEt–Et_2O (1 : 1). The extract was washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The crude aldehyde **13** (1.38 g) was obtained as a pale yellow oil, which was used in the next reaction without purification. IR cm^{-1}: 2900, 1740,

1720. ^{1}H-NMR δ: 1.00, 1.20 and 2.04 (each 3H, s), 1.74 (3H, br), 3.7—4.5 (2H, m), 5.3—5.6 (1H, m), 9.85 (1H, d, J = 2 Hz).

The Bicyclic Hemiacetal of 4α-Formyl-6α-hydroxymethyl-1,5,5-trimethylcyclohexene (14)——A solution of the crude aldehyde **13** (1.38 g) prepared from **12** (2.170 g) in MeOH (12 ml) was treated with MeONa (690 mg) and the mixture was stirred for 15 h at room temperature. The solvent was evaporated off from the mixture. After addition of an excess of diluted HCl, the mixture was extracted with AcOEt. The extract was washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. SiO_2 column chromatography (hexane–AcOEt (4 : 1)) of the resulting solid gave **14** (761 mg, 48.5% from **12**) as colorless crystals, which were recrystallized from $CHCl_3$–hexane to give colorless prisms, mp 49—50 °C. Thin layer chromatography (TLC, SiO_2) of the product afforded single spot with various solvent systems, but the ^{1}H-NMR spectrum showed that **14** was a diastereomeric mixture (about 5 : 2) in $CDCl_3$ solution. IR cm^{-1}: 3600, 3400. ^{1}H-NMR (signals due to a major component) δ: 1.00 and 1.15 (each 3H, s), 1.71 (3H, br), 3.51 (1H, dd, J = 1, 11.3 Hz), 4.00 (1H, dd, J = 1.5, 11.3 Hz), 5.21 (1H, br), 5.4—5.7 (1H, m); (signals due to a minor component) δ: 0.93 and 1.35 (each 3H, s), 1.67 (3H, br), 3.2—4.3 (2H, m), 5.06 (1H, br), 5.4—5.7 (1H, m). *Anal.* Calcd for $C_{11}H_8O_2$: C, 72.49; H, 9.96. Found: C, 72.28; H, 10.18.

4α,6α-Bisacetoxymethyl-1,5,5-trimethylcyclohexene (15)——The bicyclic hemiacetal **14** (168 mg) was treated with $NaBH_4$ (70 mg) in EtOH (5 ml) for 15 h at room temperature. Usual work-up of the mixture afforded a diol (177 mg) as a colorless oil. ^{1}H-NMR (90 MHz) δ: 0.85 and 1.08 (each 3H, s), 1.80 (3H, br), 3.43 (1H, dd, J = 8, 10.4 Hz), 3.6—4.0 (1H, m), 5.56 (1H, br d, J = 3.3 Hz). A part of the crude diol (18 mg) obtained above was acetylated with Ac_2O (0.5 ml) in pyridine (1 ml) (1 h, room temperature). Removal of the solvent gave an oil, whose SiO_2 column chromatography (hexane–AcOEt (19 : 1)) afforded **15** (23 mg) as a colorless oil. IR cm^{-1}: 1740. ^{1}H-NMR (90 MHz) δ: 0.80 and 1.10 (each 3H, s), 1.71 (3H, br), 2.05 (6H, s), 3.75—4.1 (1H, m), 4.15—4.4 (3H, m), 5.4—5.6 (1H, m). MS m/z: 268 (M^+), 208 ($M^+ - 60$). High-resolution MS Calcd for $C_{13}H_{20}O_2$ ($M^+ - 60$) m/z: 208.1461. Found m/z: 208.1428.

4β,6α-Bisacetoxymethyl-1,5,5-trimethylcyclohexene (16)——A solution of the crude aldehyde **13** (28 mg) prepared from **12** (38 mg) in THF (2 ml) was treated with $LiAlH_4$ (15 mg) for 15 min on an ice bath. Usual work-up of the mixture gave a diol (24 mg) as a colorless gum. ^{1}H-NMR (90 MHz) δ: 0.82 and 1.10 (each 3H, s), 1.73 (3H, br), 3.37 (1H, dd, J = 7.5, 10.3 Hz), 3.6—3.95 (1H, m), 5.62 (1H, br d, J = 3.8 Hz). The crude diol (24 mg) obtained above was treated with Ac_2O (0.8 ml) in pyridine (1.5 ml) (1 h, room temperature). The mixture was concentrated under reduced pressure. SiO_2 column chromatography (hexane–AcOEt (19 : 1)) of the resulting gum afforded **16** (30 mg) as a colorless oil. IR cm^{-1}: 1740. ^{1}H-NMR (90 MHz) δ: 0.88, 1.04, 2.04 and 2.05 (each 3H, s), 1.74 (3H, d, J = 1.3 Hz), 3.7—4.0 (1H, m), 4.05—4.4 (3H, m), 5.4—5.55 (1H, m). MS m/z: 208 ($M^+ - 60$). High-resolution MS Calcd for $C_{12}H_{16}O_3$ ($M^+ - 60$) m/z: 208.1098. Found m/z: 208.1083.

Ethyl (2*E*)-3-(5α-Hydroxymethyl-4,6,6-trimethyl-3-cyclohexen-1α-yl)acrylate (19)——A mixture of **14** (2.52 g, 13.8 mmol) and (carbethoxymethylene)triphenylphosphorane (14.48 g) in toluene (50 ml) was stirred for 24 h at 100 °C under argon. After cooling, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on SiO_2 (hexane–AcOEt (4 : 1)), affording **19** (2.45 g, 70.5%) as a colorless oil. IR cm^{-1}: 3620, 1715, 1645. ^{1}H-NMR δ: 0.87 and 1.02 (each 3H, s), 1.29 (3H, t, J = 7.1 Hz), 1.81 (3H, br), 3.7—4.0 (2H, m), 4.19 (2H, q, J = 7.1 Hz), 5.4—5.6 (1H, m), 5.81 (1H, d, J = 15.4 Hz), 6.98 (1H, dd, J = 8, 15.4 Hz). MS m/z: 220 ($M^+ - 28$), 222 ($M^+ - 30$), 207 ($M^+ - 45$).

Ethyl 3-(3α-Hydroxymethyl-2,2,4α-trimethylcyclohexan-1α-yl)propionate (21)——A solution of **19** (2.45 g, 9.72 mmol) in AcOEt (50 ml) was stirred for 2 h at room temperature in the presence of PtO_2 (1.16 g) under hydrogen. The filtrate of the mixture was concentrated to give an oil, which was subjected to SiO_2 column chromatography. Elution with hexane–AcOEt (9 : 1) afforded **21** (2.42 g, 97.3%) as a colorless oil. IR cm^{-1}: 3620, 1715. ^{1}H-NMR (400 MHz) δ: 0.73 and 1.00 (each 3H, s), 0.95 (3H, d, J = 7.6 Hz), 1.28 (3H, t, J = 7.1 Hz), 1.40 (1H, ddd, J = 4.2, 4.6, 10 Hz; 7β-H), 2.21 (1H, ddd, J = 7.2, 8.9, 15.6 Hz, C<u>H</u>$_2$CO$_2$), 2.41 (1H, ddd, J = 5.4, 9.4, 15.6 Hz, C<u>H</u>$_2$CO$_2$), 3.64 (1H, dd, J = 10, 10.5 Hz, C<u>H</u>$_2$OH), 3.91 (1H, dd, J = 4.2, 10.5 Hz, C<u>H</u>$_2$OH), 4.13 (2H, q, J = 7.1 Hz).

Ethyl 3-(3α-Cyanomethyl-2,2,4α-trimethylcyclohexan-1α-yl)propionate (22)——Methanesulfonyl chloride (1.1 ml) was added dropwise to a stirred solution of **21** (628 mg, 2.45 mmol) and Et_3N (3.4 ml) in CH_2Cl_2 (22 ml) at 0 °C, and stirring was continued for 20 min at 0 °C. Usual work-up of the reaction mixture gave the crude mesylate (820 mg, 100%) as a colorless oil, which was used for the next reaction without purification. ^{1}H-NMR δ: 0.77, 1.03 and 3.01 (each 3H, s), 0.97 (3H, d, J = 7 Hz), 1.26 (3H, t, J = 7.1 Hz), 4.13 (2H, q, J = 7.1 Hz), 4.30 (1H, d, J = 10.2 Hz), 4.50 (1H, dd, J = 4.8, 10.2 Hz).

A mixture of the crude mesylate (820 mg) obtained above and NaCN (635 mg) in DMSO (22 ml) was stirred for 7 h at 100—105 °C under nitrogen and, after cooling, diluted with water. The ethereal extract of the mixture was washed with water, dried ($MgSO_4$), and concentrated. The resulting oil was chromatographed on SiO_2. Elution with hexane–AcOEt (19 : 1) afforded ethyl 3-(3-methylene-2,2,4α-trimethylcyclohexan-1α-yl)propionate (**23**) (235 mg, 44.8% from **21**) as a colorless oil which tended to color at room temperature. ^{1}H-NMR δ: 1.02 (3H, d, J = 6.7 Hz), 1.08 and 1.17 (each 3H, s), 1.25 (3H, t, J = 7.1 Hz), 4.11 (2H, q, J = 7.1 Hz), 4.71 and 4.74 (each 1H, s). MS m/z: 238 (M^+), 223 ($M^+ - 15$). High-resolution MS Calcd for $C_{15}H_{26}O_2$ (M^+) m/z: 238.1932. Found m/z: 238.1943.

Elution with hexane–AcOEt (9 : 1) afforded **22** (290 mg, 44.6% from **21**) as a colorless oil. IR cm^{-1}: 2230, 1730.

^{1}H-NMR δ: 0.72 and 0.96 (each 3H, s), 0.96 (3H, d, J=7.3 Hz), 1.26 (3H, t, J=7.1 Hz), 2.19 (1H, d, J=16.6 Hz), 2.65 (1H, dd, J=5.5, 16.6 Hz), 4.13 (2H, q, J=7.1 Hz). MS m/z: 250 (M^+-15), 178 (M^+-87). High-resolution MS Calcd for $C_{16}H_{27}NO_2$ (M^+) m/z: 265.2040. Found m/z: 265.2017.

The intermediary mesylate (29 mg, 3.5%) was recovered from the last fraction eluted with hexane–AcOEt (4 : 1).

3-(3α-Cyanomethyl-2,2,4α-trimethylcyclohexan-1α-yl)propan-1-ol (24)——A mixture of **22** (290 mg, 1.09 mmol) and excess $LiBH_4$ (700 mg) in Et_2O (40 ml) was refluxed for 3 h with stirring. The mixture was poured into ice-water, acidified with diluted HCl, and extracted with Et_2O–AcOEt (1 : 1). The extract was washed with aqueous $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Removal of the solvent afforded **24** (240 mg) as a colorless oil, which was used for the next reaction without purification. IR cm^{-1}: 3610, 2230. ^{1}H-NMR δ: 0.70 and 0.94 (each 3H, s), 0.96 (3H, d, J=7.3 Hz), 2.19 (1H, d, J=16.4 Hz), 2.64 (1H, dd, J=5.5, 16.4 Hz), 3.64 (2H, t, J=6.1 Hz).

The Tetrahydropyranyl Ether 25 of 24——The crude alcohol **24** (240 mg) prepared from **22** (290 mg) was treated with dihydropyran (1 ml) and pyridinium *p*-toluenesulfonate (56 mg) in CH_2Cl_2 (15 ml) for 13 h at room temperature. The mixture was diluted with Et_2O, washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The resulting oil was subjected to SiO_2 column chromatography, affording **25** (321 mg, 95.5% from **22**) as a colorless oil by elution with hexane–AcOEt (19 : 1). ^{1}H-NMR δ: 0.69 and 0.93 (each 3H, s), 0.96 (3H, d, J= 7.1 Hz), 4.56 (1H, br).

3-[3α-(2-Acetoxyethyl)-2,2,4α-trimethylcyclohexan-1α-yl]propionic Acid (26)——A solution of diisobutylaluminum hydride in hexane (1.76 M, 0.40 ml) was added to a solution of **25** (180 mg, 0.586 mmol) in toluene (6 ml) at −78 °C under argon. The mixture was stirred for 30 min at −78 °C and then for 1 h at room temperature. Saturated aqueous NH_4Cl solution (2 ml) and 5% H_2SO_4 (2 ml) were added successively to the reaction mixture with stirring at 0 °C, and stirring was continued for 10 min at room temperature. The mixture was diluted with ice-water and extracted with Et_2O–AcOEt (1 : 1). The extract was washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and filtered through a short column packed with SiO_2. The solvent of the filtrate was removed to give the aldehyde (185 mg) as a colorless oil, which was used immediately for the next reaction without purification. ^{1}H-NMR δ: 0.73 and 0.90 (each 3H, s), 0.90 (3H, d, J=6.6 Hz), 4.57 (1H, br), 9.72 (1H, dd, J=1.9, 3.7 Hz).

The crude aldehyde (185 mg) obtained above was treated with $LiAlH_4$ (44 mg) in Et_2O (10 ml) at −15 °C for 30 min followed by successive addition of water (2 drops) and 3 N NaOH (3 drops). The mixture was stirred for 10 min at room temperature, diluted with Et_2O, dried ($MgSO_4$), and filtered using Celite. Removal of the solvent yielded an alcohol (176 mg) as a colorless oil. ^{1}H-NMR δ: 0.71 and 0.91 (each 3H, s), 0.91 (3H, d, J=7.1 Hz), 4.57 (1H, br).

Treatment of the resulting alcohol (176 mg) with Ac_2O (1.5 ml) in pyridine (3 ml) (room temperature, 1 h) afforded the acetate (179 mg) as a colorless oil. ^{1}H-NMR δ: 0.71, 0.90 and 2.04 (each 3H, s), 0.91 (3H, d, J=6.8 Hz), 4.56 (1H, br).

A solution of the acetate (179 mg) obtained above in EtOH (6 ml) was stirred for 3 h at room temperature in the presence of *p*-TsOH (20 mg), and concentrated under reduced pressure. The extract of the residue with AcOEt was washed with aqueous Na_2CO_3 solution and brine, dried ($MgSO_4$), and concentrated. SiO_2 column chromatography (hexane–AcOEt (3 : 1)) of the resulting oil gave an acetoxy alcohol (74 mg, 46.7% from **25**) as a colorless oil. IR cm^{-1}: 3610, 1735. ^{1}H-NMR δ: 0.71, 0.91 and 2.05 (each 3H, s), 0.91 (3H, d, J=7 Hz), 3.64 (2H, br t, J=5.8 Hz), 3.8—4.4 (2H, m). MS m/z: 252 (M^+-18), 210 (M^+-60). High-resolution MS Calcd for $C_{16}H_{30}O_3$ (M^+-H_2O) m/z: 252.2088. Found m/z: 252.2092.

The acetoxy alcohol (70 mg, 0.26 mmol) was treated with Jones reagent (0.3 ml) in acetone (4 ml) at room temperature for 30 min. Usual work-up of the mixture afforded **26** (80 mg) as a colorless oil, which was subjected to the next amidation without purification. IR cm^{-1}: 1735, 1705. ^{1}H-NMR δ: 0.73, 0.93 and 2.05 (each 3H, s), 0.92 (3H, d, J=7 Hz), 3.65—4.45 (2H, m).

***N*-Methyl-2′-[(2-cyanoethyl)thio]-3-[3α-(2-acetoxyethyl)-2,2,4α-trimethylcyclohexan-1α-yl]propionanilide (28)**——A mixture of **26** (80 mg) obtained above and oxalyl chloride (0.1 ml) in benzene (1.5 ml) was stirred for 1 h at room temperature and then heated for 1 h at 60 °C. The solvent and excess oxalyl chloride were removed under reduced pressure to give an acid chloride as an oil, which was dissolved in THF (2 ml). This solution was added dropwise to a stirred suspension of 2-cyanoethyl 2-(methylamino)phenyl sulfide (**27**) (98 mg) and anhydrous K_2CO_3 (176 mg) in THF (4 ml) at 0 °C under nitrogen and stirring was continued for 10 min at 0 °C. The mixture was poured into ice and extracted with Et_2O–AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. SiO_2 column chromatography (hexane–AcOEt (3 : 2)) of the resulting oil gave **28** (108 mg, 91% from the acetoxy alcohol) as a colorless gum. IR cm^{-1}: 1735, 1660. ^{1}H-NMR δ: 0.68, 2.03 and 3.18 (each 3H, s), 0.86 and 0.89 (each 1.5H, s), 0.86 (3H, d, J=7 Hz), 2.5—2.85 (2H, m), 3.1—3.4 (2H, m), 3.8—4.4 (2H, m), 7.1—7.6 (4H, m). MS m/z: 458 (M^+), 443 (M^+-15). High-resolution MS Calcd for $C_{25}H_{35}N_2O_3S$ (M^+-CH_3) m/z: 443.2366. Found m/z: 443.2349.

***N*-Methyl-2′-[(2-cyanoethyl)thio]-3-[3α-(2-*p*-toluenesulfonyloxyethyl)-2,2,4α-trimethylcyclohexan-1α-yl]propionanilide (29)**——A mixture of acetoxy amide **28** (99 mg, 0.22 mmol) and K_2CO_3 (300 mg) in MeOH (5 ml) was stirred for 1.5 h at 0 °C under nitrogen, and then diluted with water. The extract with $CHCl_3$ of the mixture was washed with brine, dried ($MgSO_4$), and concentrated to give a hydroxy amide (99 mg) as a colorless oil. IR cm^{-1}: 3600, 1660. ^{1}H-NMR δ: 0.68 and 3.18 (each 3H, s), 0.85 (3H, d, J=7 Hz), 0.86 and 0.89 (each 1.5H, s), 3.59 (2H, t, J=

7.5 Hz).

The hydroxy amide (99 mg) obtained above was treated with *p*-toluenesulfonyl chloride (82 mg) in pyridine (2 ml) for 12 h in refrigerator. Usual work-up of the mixture and subsequent column chromatography on SiO_2 (hexane–AcOEt (3 : 2)) gave **29** (111 mg, 90.1% from **28**) as a colorless gum. IR cm^{-1}: 1660, 1370, 1175. ^{1}H-NMR δ: 0.62, 2.44 and 3.18 (each 3H, s), 0.75 (3H, d, J=6.5 Hz), 0.78 and 0.81 (each 1.5H, s), 2.5—2.9 (2H, m), 3.0—3.4 (2H, m), 7.1—7.5 (4H, m), 7.21 and 7.78 (each 2H, d, J=8.4 Hz).

3,10α-Dimethyl-7β,11β-dimethylmethano-14-thia-3-aza-1,2-benzocyclotetradecen-4-one (30)——A solution of **29** (19 mg, 0.033 mmol) in degassed dioxane (3 ml) was added slowly to a stirred mixture of *tert*-BuOK (97%, 20 mg) in DMF–dioxane (1 : 1, 10 ml) at 65—70 °C over 7 h under nitrogen and, after complete addition, the mixture was stirred for 1 h at the same temperature. The mixture was neutralized with dilute HCl and then concentrated. The ethereal extract of the residue 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 (4 : 1) afforded **30** (3 mg, 26%) as colorless prisms ($CHCl_3$–hexane), mp 152—160 °C. IR cm^{-1}: 1650. ^{1}H-NMR δ: 0.23 (3H, br), 0.88 and 3.26 (each 3H, s), 0.81 (3H, d, J=6.6 Hz), 6.9—7.5 (3H, m), 7.6—7.9 (1H, m). MS *m/z*: 345 (M^+), 330 (M^+-15). High-resolution MS Calcd for $C_{21}H_{31}NOS$ (M^+) *m/z*: 345.2126. Found *m/z*: 345.2141. *Anal.* Calcd for $C_{21}H_{31}NOS$: C, 72.99; H, 9.04; N, 4.09. Found: C, 72.80; H, 9.02; N, 4.09.

The second fraction eluted with hexane–AcOEt (3 : 2) gave the starting amide **29** (7.5 mg, 39.5%).

3,5ξ,10α-Trimethyl-7β-,11β-dimethylmethano-14-thia-3-aza-1,2-benzocyclotetradecen-4-one (31)——A solution of butyl lithium in hexane (1.45 M, 0.46 ml, 0.67 mmol) was added dropwise to a stirred solution of **30** (23 mg, 0.067 mmol) and diisopropylamine (0.093 ml, 0.66 mmol) in THF (1 ml) at −78 °C under argon. After 5 min, methyl iodide (0.2 ml) was added, and the mixture was stirred for 0.5 h at −78 °C and for 1 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. SiO_2 column chromatography (hexane–AcOEt (17 : 3)) of the resulting oil gave **31** (21 mg, 87.8%) as a colorless gum. This product is a mixture of two stereoisomers (3 : 2), which were inseparable by SiO_2 column chromatography and TLC (SiO_2). IR cm^{-1}: 1650. ^{1}H-NMR (major component) δ: 0.24, 0.96 and 3.25 (each 3H, s), 0.80 (3H, d, J=6.6 Hz), 1.19 (3H, d, J=6.3 Hz), 6.9—7.45 (3H, m), 7.6—7.9 (1H, m); (minor component) δ: 0.24, 0.88 and 3.20 (each 3H, s), 0.49 (3H, d, J=6.7 Hz), 1.32 (3H, d, J=6.6 Hz), 6.9—7.45 (3H, m), 7.6—7.9 (1H, m). MS *m/z*: 359 (M^+), 344 (M^+-15). High-resolution MS Calcd for $C_{22}H_{33}NOS$ (M^+) *m/z*: 359.2280. Found *m/z*: 359.2250.

3,5ξ,10α-Trimethyl-7β,11β-dimethylmethano-14-thia-3-aza-1,2-benzocyclotetradecen-4-one 14-Oxide (32)——The lactam sulfide **31** (20 mg, 0.056 mmol) was treated with *m*-chloroperbenzoic acid (85%, 13 mg, 0.064 mmol) in CH_2Cl_2 (2 ml) for 10 min at 0 °C. The reaction mixture was diluted with Et_2O, washed with aqueous K_2CO_3 solution and brine, dried ($MgSO_4$), and concentrated. SiO_2 column chromatography (hexane–AcOEt (1 : 1)) of the resulting oil gave a 3 : 2 mixture of lactam sulfoxides **32** (19 mg, 90.9%) as a colorless caramel, which was inseparable by column chromatography and TLC (SiO_2). IR cm^{-1}: 1660, 1035. ^{1}H-NMR (major component) δ: 0.19, 0.97 and 3.32 (each 3H, s), 0.86 (3H, d, J=6.6 Hz), 1.19 (3H, d, J=6.5 Hz), 6.9—7.25 (1H, m), 7.45—7.8 (2H, m), 8.0—8.35 (1H, m); (minor component) δ: 0.19, 0.91 and 3.29 (each 3H, s), 0.52 (3H, d, J=6.7 Hz), 1.33 (3H, d, J=6.5 Hz), 6.9—7.25 (1H, m), 7.45—7.8 (2H, m), 8.0—8.35 (1H, m). MS *m/z*: 375 (M^+), 359 (M^+-16). High-resolution MS Calcd for $C_{22}H_{33}NO_2S$ (M^+) *m/z*: 375.2231. Found *m/z*: 375.2252.

Preparation of 3,8α,11,11-Tetramethyl-4-oxobicyclo[5.3.1]undecane (5) from 32 *via* 33——A solution of **32** (15 mg, 0.04 mmol) in THF (1 ml) containing hexamethylphosphoramide (0.067 ml) was added dropwise to a solution of LDA (0.70 mmol) prepared from diisopropylamine (0.10 ml) and *n*-butyl lithium (1.45 M hexane solution, 0.483 ml) in THF (1.5 ml) at −78 °C under argon. The mixture was stirred for 0.5 h at −78 °C and then for 1 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl solution at −78 °C and the mixture was neutralized with dilute HCl. The ethereal extract of the mixture was washed with brine, dried ($MgSO_4$) and filtered through a short column packed with SiO_2. The solvent was removed to give **33** (15 mg) as a pale yellow oil, which was used in the next desulfurization without purification. IR cm^{-1}: 3300, 1725, 1700. ^{1}H-NMR δ: 2.89 (3H, d, J=5.1 Hz), 5.36 (1H, dd, J=2.7, 12.4 Hz).

Pulverized 5% Na–Hg (370 mg) was added to a suspension of **33** (15 mg) obtained above and Na_2HPO_4 (150 mg) in MeOH (2 ml) at 0 °C, and the mixture was stirred for 1 h at room temperature under nitrogen. Further Na_2HPO_4 (100 mg) and Na–Hg (250 mg) were added and stirring was continued for 0.5 h at room temperature. The mixture was diluted with Et_2O, washed with cold 3 N HCl and brine, dried ($MgSO_4$), and concentrated. The resulting oil was subjected to SiO_2 column chromatography (hexane–AcOEt (49 : 1)), affording **5** (6 mg, 67.6% from **32**) as a colorless oil. IR cm^{-1}: 1725 (sh), 1695. ^{1}H-NMR δ: 0.88 and 1.08 (each 3H, s), 0.96 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=6.8 Hz), 2.7—3.3 (3H, m). ^{13}C-NMR δ: 19.26, 20.12, 27.84 and 34.58 (each $-CH_3$), 26.04, 27.33, 30.76, 42.38 and 43.32 (each $-\dot{C}H_2$), 30.14, 40.43, 43.32 and 46.32 (each $-\dot{C}H$), 35.44 ($-\dot{C}-$), 223.68 (C=O). MS *m/z*: 222 (M^+), 207 (M^+-15). High-resolution MS Calcd for $C_{15}H_{26}O$ (M^+) *m/z*: 222.1982. Found *m/z*: 222.1978.

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