Studies on Taxane Synthesis. III. Stereocontrolled Synthesis of a Twelve-Membered Lactam Sulfide as a Precursor of 4,8,11,11-Tetramethyl-3-oxobicyclo[5.3.1]undec-8-ene[1)]

Yasuo OHTSUKA* and Takeshi OISHI*

RIKEN (The Institute of Physical and Chemical Research) Hirosawa, Wako-shi, Saitama 351-01, Japan. *Received October 8, 1990*

Stereocontrolled synthesis of two twelve-membered lactam sulfides 37 and 38 as precursors of 8,11,11-trimethyl-3-oxobicyclo[5.3.1]undec-8-enes constituting the A and B rings of taxane-diterpenes was achieved. The key step involves a Diels–Alder reaction of maleic anhydride and the *E*-diene 18 for introduction of the requisite *cis*-arrangement of substitutions at the C-1 and C-7 positions. The resulting adduct was converted exclusively into the lactone 21b in five steps: 1) hydrolysis, 2) iodo-lactonization, 3) BH_3 reduction, 4) Zn reduction, 5) methylation. The benzyl group of 26 could be selectively removed by heating with Raney Ni (W-2) in EtOH in nearly quantitative yield without hydrogenation of the double bond.

Keywords taxane-type diterpene; stereocontrolled synthesis; Diels–Alder reaction; iodo-lactonization; anhydride; $NaBH_4$ reduction; BH_3 reduction; Raney Ni; selective debenzylation; twelve-membered lactam sulfide

A number of synthetic approaches to taxanes have already been reported[2)] and, recently, Holton and co-workers reported the conversion of (−)-patchoulene oxide into the enantiomer of (−)-taxusin (**1**).[3)] We reported previously syntheses of the bicyclo[5.3.1]undecanes **2**, **3** and **4** constituting the A and B rings of taxane-type diterpenes (*e.g.* **5**)[1)] from α- or β-ionone using a general method for constructing medium-sized ring ketones developed in this laboratory.[4)] Among them, the eight-membered ring ketone **4** was considered to be a potential intermediate for formation of the tricyclo[9.3.1.$0^{3,8}$]pentadecane **6**. However, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation of the cyclohexenone derivative to the corresponding dienone and a Michael addition of nitromethane to the above dienone involved in the previous synthesis of **4** from α-ionone required 4 and 36 d, respectively, and thus development of a more efficient strategy was desirable. The present paper deals with the synthesis of **4** *via* the mesyloxy acid **7** through a small number of steps.

The stereochemistry of two substituents at the C-1 and C-7 positions[5)] in the precursors **9** or **11** should be *cis* for eight-membered B ring formation. The requisite *cis*-

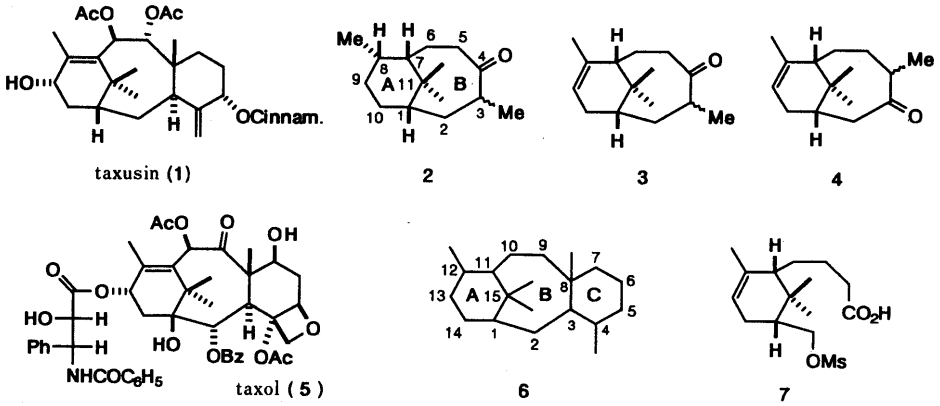

Fig. 1

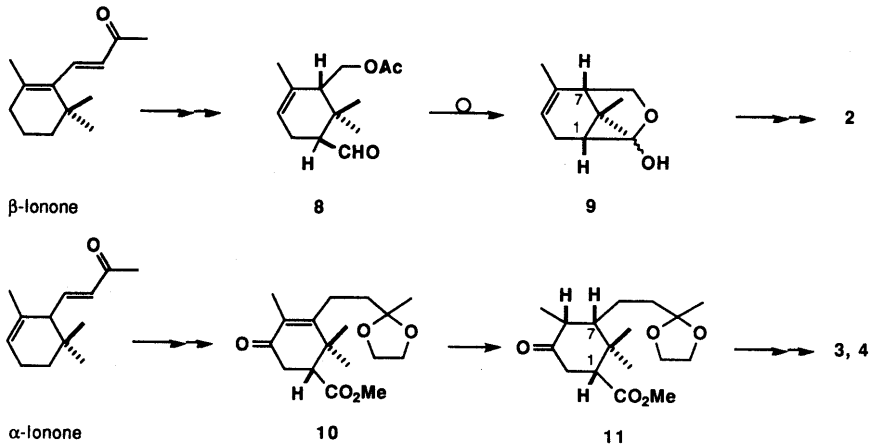

Fig. 2

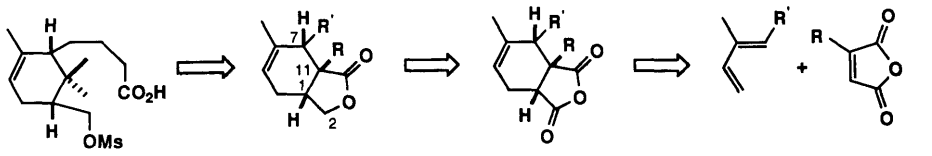

Fig. 3

arrangement of these substituents was effected in the previous synthesis by methanolysis of the acetoxy aldehyde **8** (epimerization at the C-1 position and concomitant formation of the cyclic hemiacetal **9**) or high pressure catalytic hydrogenation of the α,β-unsaturated ketone **10** leading to the ketone **11**, as shown in Fig. 2.[1]

In the present paper, the stereocontrolled synthesis of **7** (or its equivalent) was undertaken by utilizing a Diels–Alder reaction. Our retrosynthesis of **7** is shown in Fig. 3. Since it is known that the intermolecular Diels–Alder reaction generally produces the *endo*-adduct, reaction of the *E*-diene **14** and the anhydride **15** is expected to produce the 1,11,7-all-*cis*-anhydride **13**. The requisite lactone **12b** appears to be obtainable by either introduction of a methyl group into **12a**, which would be obtained from the anhydride **13a**, or selective reduction of the anhydride moiety in **13b**. There should be no difficulty in converting **12b** into **7** containing three substituents of the desired stereochemistry. Based on the above consideration, a Diels–Alder reaction with the *E*-diene **14** and the anhydride **15a**, **b** was carried out.

Diels–Alder Reaction of the *E*-Diene 14 and the Anhydride 15 The *E*-diene **18** corresponding to **14** was prepared from 1,5-pentanediol (**16a**) through 6 steps. Benzyl 5-hydroxypentyl ether (**16b**) obtained by benzylation of **16a** was treated with pyridinium chlorochromate (PCC) and the resulting aldehyde was condensed with (carbethoxyethylidene)triphenylphosphorane to give the α,β-unsaturated ester **17b** in 73% yield. The corresponding alcohol **17a** has been obtained directly from 2-hydroxypyran by the reaction with the same phosphorane but the yield was only 55%.[6] Attempted benzylation of **17a** under the usual conditions (NaH–$PhCH_2Br$–tetrahydrofuran (THF), 0—25 °C) did not produce **17b** but gave only unidentified products. The ester **17b** was subjected to $LiAlH_4$ reduction, PCC oxidation and the Wittig reaction successively to give the *E*-diene **18** in 72% yield.

Treatment of the diene **18** with maleic anhydride (**15a**) in toluene at 100 °C afforded the anhydride **19a** in 83% yield as a single product. Sodium borohydride reduction of **19a** produced a mixture of the desired lactone **21a** and the isomeric lactone **22a** (**21a** : **22a** = 1 : 2) in THF (0 °C).[7] Only **22a** was obtained when *N*,*N*-dimethylformamide (DMF)–toluene was used as the solvent at room temperature. The lactone **21a** could be exclusively prepared from **19a** *via* iodo-lactonization. Alkaline hydrolysis of **19a** with an aqueous $NaHCO_3$ solution followed by iodine (I_2–KI) treatment afforded the iodo lactone **20a**, whose carboxylic acid moiety was reduced with $BH_3 \cdot SMe_2$ complex in $B(OMe)_3$–THF at room temperature. The crude alcohol thus obtained was treated with Zn in refluxing acetic acid to give the desired lactone **21a** in 60—65% overall yield. In this transformation, reduction of **20a** with $BH_3 \cdot SMe_2$ complex afforded a mixture of the alcohol and a small amount of the corresponding aldehyde, which remained unchanged by Zn reduction. The overall yield of **21a** was improved to 78% when $NaBH_4$ (EtOH) was added prior to Zn reduction. Exclusive formation of **21a** from **19a** was in accord with our expectation that the iodo lactone **20a** (**20**-A) would be much more stable than the sterically congested isomeric lactone **27**-A. Introduction of a methyl group into **21a** (lithium diisopropylamide (LDA)–MeI) gave the lactone **21b** in 94% yield.

An alternative preparation of **21b** from citraconic anhydride (**15b**) was also examined. Reaction of **15b** with **18** in toluene (100 °C) provided a 1 : 1 mixture of adducts **19b** and **19c** in 85% yield, but the mixture was inseparable by silica gel (SiO_2) chromatography. When the mixture was treated with $NaBH_4$ in THF at 0 °C, the more hindered carbonyl group in the anhydride[7] was reduced to yield a mixture of γ-lactones **22b** (41% yield) and **23** (43% yield), which could be separated by careful column chromatography on SiO_2. Attempted cleavage of the lactone ring in **22b** with EtSH–$AlCl_3$ to prepare the alcohol **25** *via* the sulfide **24** led only to debenzylation[8] at 0 °C and decomposition at room temperature. Iodo-lactonization of a mixture of **19b**, **c** followed by selective reduction of the liberated carboxylic acid in the same way as described for **19a** produced the lactones **21b** (46% yield) and **23** (14% yield). Formation of **22b** was not detected in this case, either. The yield of **23**, which is expected to be derived from **19c**, was low, which might be ascribed to the sterically congested nature of the intermediary iodo lactone **20**-C (**20c**). In this route, however, separation of the desired lactone **21b** from the isomer **23** is rather difficult and the maximum yield of **21b** is 50% since a 1 : 1 mixture of anhydrides (**19b**, **c**) is used. Thus, the former route *via* the iodo lactone **20a** and the lactone **21a** was adopted for the synthesis of **21b**.

The structures of these lactones **21b**, **22b** and **23** were confirmed by ^{1}H-nuclear magnetic resonance (^{1}H-NMR) analysis (spin-decoupling method) and by conversion of **21b** into the twelve-membered lactam sulfide **37**.

Conversion of Lactone 21b into the Twelve-Membered Lactam Sulfides 37 and 38 The lactone **21b** was readily converted into the acetate **26** by successive treatment with diisobutylaluminum hydride in toluene (−78 °C), hydrazine–NaOH in diethylene glycol and acetic anhydride in pyridine (95% overall yield *via* **25**).

Treatment of **26** under the Pd–C (EtOH) catalyzed reduction conditions, in the expectation of selective debenzylation, gave only the dihydro alcohol **27** in nearly quantitative yield. Attempted debenzylation of **26** with Me_2S–$BF_3 \cdot Et_2O$ (CH_2Cl_2, 0 °C—room temperature)[9] or EtSH–$AlCl_3$ (CH_2Cl_2, 0 °C)[8] also failed. This difficulty

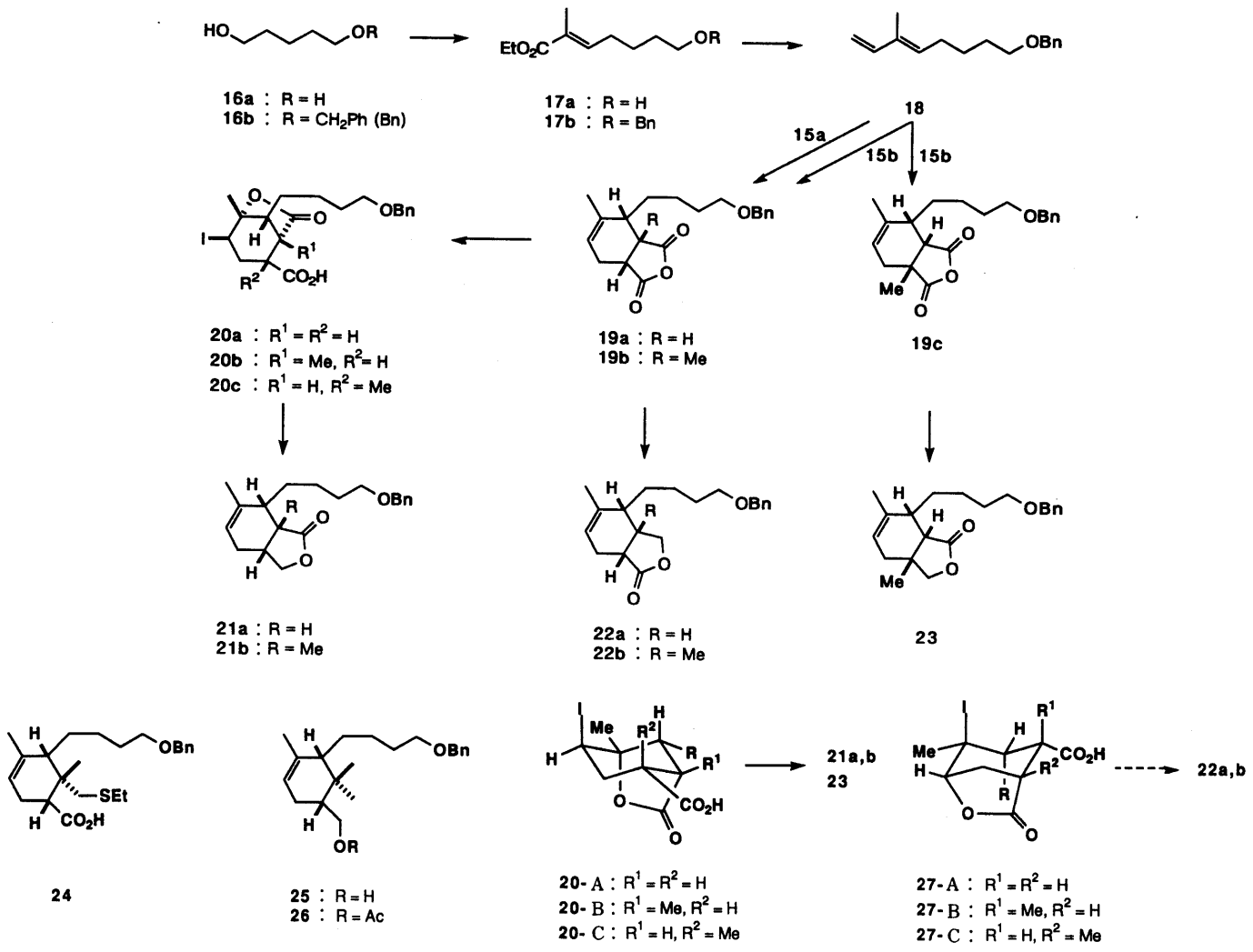

Fig. 4

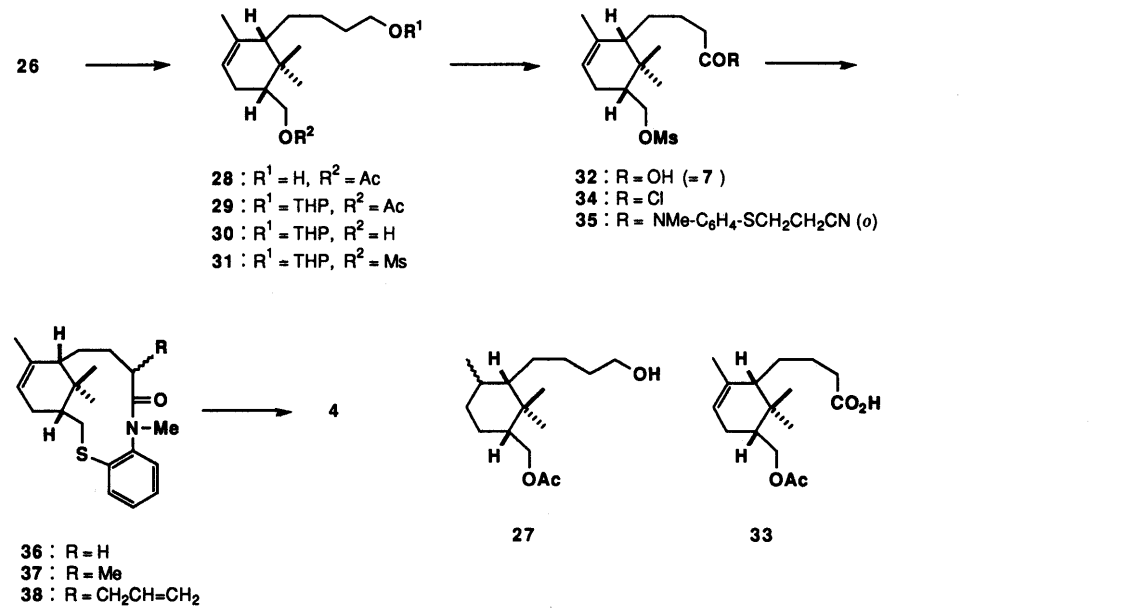

Fig. 5

could be overcome by the use of Raney Ni.[10] When a mixture of **26** with Raney Ni (W-2) in EtOH was refluxed for 7 min under nitrogen, the desired alcohol **28** was obtained in nearly quantitative yield. When heating was prolonged to 1 h, hydrogenation of the double bond took place, producing the dihydro alcohol **27** in about 15% yield

in addition to **28** (80% yield). The alcohol **28** was converted into the acid **32**, the precursor of **4**, in four steps: 1) masking of the primary alcohol with THP, 2) $LiAlH_4$ reduction, 3) mesylation, 4) Jones oxidation (94% overall yield *via* **29**, **30** and **31**). The acid **32** could also be prepared by Jones oxidation of **28** followed by hydrolysis and mesylation, but the yield was 61% from **28** *via* **33**.

The acid **32** was led to the lactam sulfide **36** in essentially the same manner as in the preparation of **4**.[1] 2-Cyanoethyl 2-*N*-methylaminophenyl sulfide was acylated with the acid chloride **34**, prepared from **32** with oxalyl chloride to give the amide **35** in 89% yield. This product was subjected to cyclization at high dilution with anhydrous K_2CO_3 (dried over P_2O_5 at 130 °C *in vacuo*)–$NaBH_4$ in DMF at 130—135 °C to afford the lactam sulfide **36** in 61% yield. No formation of the corresponding dimer was detected. Methylation of **36** with LDA and MeI yielded **37** as a sole product (90% yield), whose physical data (infrared (IR), thin layer chromatography (TLC), ^{1}H-NMR) were consistent with those of the less polar lactam sulfide A among the two isomeric lactam sulfides derived from α-ionone.[1] Treatment of **36** with LDA–allyl bromide also afforded a single isomer **38** in 94% yield, although the stereochemistry of the allyl group remained unknown.

Experimental

Melting point is uncorrected. ^{1}H-NMR spectra were taken on a JEOL FX-60 or GX-400 instrument 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 (MS) were obtained with a Hitachi RMU-6M mass spectrometer and high-resolution MS were recorded on a Hitachi M-80 GC-MS instrument.

Ethyl (2*E*)-7-Benzyloxy-2-methylheptenoate (17b) A solution of 1,5-pentanediol monobenzyl ether (**16b**, 21.60 g, 111.3 mmol) in CH_2Cl_2 (110 ml) was added to a vigorously stirred suspension of PCC (49 g) in CH_2Cl_2 (330 ml) and the mixture was stirred at room temperature. After completion of the reaction (0.5—1.5 h), the mixture was diluted with Et_2O (1.7 l), dried ($MgSO_4$) and filtered through a column packed with Florisil. The filtrate was concentrated to afford the crude aldehyde (19.17 g). ^{1}H-NMR δ: 3.48 (2H, t, J=5.8 Hz), 4.49 (2H, s), 7.31 (5H, s), 9.74 (1H, t, J=1.7 Hz).

A mixture of the aldehyde (19.17 g) obtained above and (carbethoxypropylidene)triphenylphosphorane (54.3 g) in toluene (150 ml) was stirred at 100 °C (bath temperature) for 10 h under nitrogen. After removal of the solvent, the residue was extracted with hexane–Et_2O (4 : 1, 500 ml) and the extract was evaporated to give an oil, chromatography of which on SiO_2 afforded **17b** (22.51 g, 73.3% yield from **16b**) as a colorless oil from the hexane–AcOEt (19 : 1) eluate. ^{1}H-NMR δ: 1.28 (3H, t, J=7.1 Hz), 1.82 (3H, d, J=1.3 Hz), 3.48 (2H, t, J=6 Hz), 4.18 (2H, q, J=7.1 Hz), 4.50 (2H, s), 6.75 (1H, tq, J=1.4, 6.3 Hz), 7.32 (5H, s).

(3*E*)-8-Benzyloxy-3-methyl-1,3-octadiene (18) A solution of **17b** (3.59 g, 13 mmol) in Et_2O (26 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (740 mg) in Et_2O (74 ml) over 10 min on an ice bath and the mixture was stirred for 10 min. Excess of $Na_2SO_4 \cdot 10H_2O$ was added carefully. The mixture was dried ($MgSO_4$) and filtered (Celite), and the filtrate was concentrated to give the allyl alcohol (3.30 g), which was rather unstable and was used immediately for the next oxidation reaction without further purification. ^{1}H-NMR δ: 1.64 (3H, d, J=1.2 Hz), 3.47 (2H, t, J=6.1 Hz), 3.98 (2H, br), 4.50 (2H, s), 7.32 (5H, s).

The allyl alcohol (3.30 g) obrained above was treated with PCC (4.30 g) in CH_2Cl_2 in the same way as for the oxidation of **16b** to give the unsaturated aldehyde (2.86 g). ^{1}H-NMR δ: 1.73 (3H, d, J=1.2 Hz), 3.49 (2H, t, J=5.8 Hz), 4.50 (2H, s), 6.47 (1H, tq, J=1.2, 7.3 Hz), 7.32 (5H, s), 9.38 (1H, s).

A solution of *n*-butyl lithium in hexane (17.6 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium iodide (7.20 g, 17.8 mmol) in THF (72 ml) at −5—0 °C and the orange mixture was stirred for 30 min at room temperature under argon. A solution of the allyl aldehyde (2.86 g) obtained above in THF (40 ml) was added slowly to the stirred solution of the above ylide in THF over 10 min at −13—−15 °C. After 5 min, the mixture was stirred at room temperature for 30 min and the reaction was quenched with saturated aqueous NH_4Cl solution at −5 °C. An ethereal extract of the mixture was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on SiO_2 (hexane–AcOEt (19 : 1)) to afford **18** as a cololess oil (21.6 g, 72.2% from the unsaturated ester). ^{1}H-NMR δ: 1.72 (3H, br), 3.47 (2H, t, J=6.1 Hz), 4.49 (2H, s), 4.8—5.25 (2H, m), 5.48 (1H, br d, J=7.3 Hz), 6.36 (1H, br dd, J=10.5, 17.4 Hz), 7.32 (5H, s).

Diels–Alder Reaction of 18 and the Anhydrides 15a and 15b 1) **15a** (770 mg) was added to a solution of **18** (1.45 g, 6.28 mmol) and hydroquinone (70 mg) in toluene (16 ml) under argon and the container was sealed with a rubber cap. The mixture was stirred at 100 °C (bath temperature) for 15—17 h and then concentrated under reduced pressure to a quarter of the initial volume. The mixture was chromatographed on SiO_2 (hexane–AcOEt (17 : 3)) to afford 3α-(4-benzyloxybutyl)-4-methyl-4-cyclohexene-1α,2α-dicarboxylic anhydride (**19a**, 1.70 g, 82.6% yield from **18**) as a colorless oil. IR: 1845, 1775 cm^{-1}. ^{1}H-NMR δ: 1.77 (3H, br d), 3.2—3.65 (4H, m), 4.50 (2H, s), 5.5—5.8 (1H, m), 7.32 (5H, s). MS *m/z*: 328 (M^+), 237 ($M^+ - 91$). High-resolution MS Calcd for $C_{20}H_{24}O_4$ (M^+) *m/z*: 328.167. Found *m/z*: 328.165.

2) A solution of **18** (460 mg, 2.00 mmol), citraconic anhydride (**15b**, 280 mg, 2.50 mmol) and hydroquinone (46 mg) in toluene (5 ml) was stirred at 100 °C for 67 h in a sealed tube. After removal of the solvent, SiO_2 chromatography (hexane–AcOEt (4 : 1)) of the residue afforded a mixture of 3α-(4-benzyloxybutyl)-1,4-(**19c**) and -2,4-dimethyl-4-cyclohexene-1α,2α-dicarboxylic anhydrides (**19b**) in a ratio of 1 : 1 (582 mg, 85.1% from **18**) as a colorless oil. IR: 1840, 1775 cm^{-1}. ^{1}H-NMR δ: 1.38 and 1.41 (3H each, s), 1.75 (3H, br), 1.82 (3H, d, J=1.8 Hz), 4.47 and 4.51 (2H each, s), 5.4—5.8 (2H, m), 7.31 and 7.32 (5H each, s).

7α-(4-Benzyloxybutyl)-6-methyl-3aβ,4,7β,7aβ-tetrahydrophthalide (21a) *via* the Iodo Lactone 20a A suspension of the anhydride **19a** (3.10 g, 9.45 mmol) in 0.5 M $NaHCO_3$ aqueous solution (57 ml) was boiled for 30 min and allowed to cool to room temperature. To this mixture, $NaHCO_3$ (800 mg) was added and then a solution of I_2 (4.80 g, 2 eq) and KI (9.42 g, 6 eq) in water (57 ml) was added with stirring over 30 min. The reaction mixture was stirred for 3.5 h at room temperature and extracted with $CHCl_3$. The extract was washed with aqueous $Na_2S_2O_3$ solution and brine, dried ($MgSO_4$) and evaporated to give the crude iodo lactone **20a** (4.52 g). IR: 1780, 1715 cm^{-1}.

A solution of **20a** (4.52 g) obtained above in THF–$B(OMe)_3$ (4 : 1, 45 ml) was treated with borane–methylsulfide complex ($BH_3 \cdot Me_2S$, 1.50 ml, *ca.* 2.4 eq) at room temperature for 3 h. An excess of MeOH was added carefully to the ice cooled mixture and the solvent was removed *in vacuo*. The resulting oil was dissolved in MeOH and the solution was evaporated to dryness. The residue was treated with $NaBH_4$ (150 mg) in EtOH (90 ml) for 10 min at room temperature in order to reduce an aldehyde produced to a minor extent. After addition of AcOH (1 ml), the solvent was removed *in vacuo*. A mixture of the residue, IR: 3500, 1780 cm^{-1}, and Zn powder (9.50 g) in AcOH (190 ml) was refluxed for 1 h, cooled to room temperature and filtered. The filtrate was concentrated *in vacuo*. Column chromatography on SiO_2 of the residue afforded **21a** (2.31 g, 77.7% yield from **19a**) as a colorless oil using hexane–AcOEt (4 : 1) as an eluent. IR: 1770 cm^{-1}. ^{1}H-NMR δ: 1.77 (3H, br), 3.3—3.65 (2H, m), 3.87 (1H, dd, J=4.4, 9.0 Hz), *ca.* 4.39 (1H, dd, J=*ca.* 7.3, 9.0 Hz), 4.50 (2H, s), 5.35—5.75 (1H, m), 7.32 (5H, s). MS *m/z*: 314 (M^+), 223 ($M^+ - 91$). High-resolution MS Calcd for $C_{20}H_{26}O_3$ (M^+) *m/z*: 314.188. Found *m/z*: 314.184.

7α-(4-Benzyloxybutyl)-6,7aβ-dimethyl-3aβ,4,7β,7aβ-tetrahydrophthalide (21b) A solution of **21a** (2.31 g, 7.34 mmol) in THF (14.5 ml) was added dropwise to a solution of LDA in THF prepared from iso-Pr_2NH (3.20 ml, 22.86 mmol), a hexane solution of *n*-BuLi (20.56 mmol) and THF (14.5 ml) (−15 °C, 15 min) on a dry ice-acetone bath under Ar. The mixture was stirred for 30 min at −15 °C and then cooled on a dry ice–acetone bath. Methyl iodide (4.4 ml) was added dropwise to the stirred mixture, which was stirred at −78 °C for 30 min and at −15 °C for 30 min. The reaction was quenched with saturated NH_4Cl aqueous solution, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The resulting oil was chromatographed on SiO_2 (hexane–AcOEt (17 : 3)) to afford **21b** (2.27 g, 94.0%) as a colorless oil. IR: 1770 cm^{-1}. ^{1}H-NMR (400 MHz, decoupling) δ: 1.22 (3H, s), 1.83 (3H, d, J=1.4 Hz), 1.93—2.00 (1H, m, 4β-H), 2.07 (1H, dd, J=2.7, 10.0 Hz, 7β-H), 2.35—2.45 (1H, m, 4α-H), 2.4—2.5 (1H, m, 3aβ-H), 3.4—3.7 (2H, m), 3.81 (1H, dd, J=9.0, 9.3 Hz, 3-H), 4.49 (1H, dd, J=9.0, 9.3 Hz, 3-H), 4.48 (2H, s), *ca.* 5.5 (1H, m, 5-H), 7.2—7.4 (5H, m). MS *m/z*: 328 (M^+), 310 ($M^+ - 18$). High-resolution MS Calcd for $C_{21}H_{28}O_3$ (M^+) *m/z*: 328.204. Found *m/z*: 328.203.

$NaBH_4$ Reduction of the Anhydrides 19 1) The anhydride **19a** (33 mg, 0.1 mmol) was treated with an excess of $NaBH_4$ in toluene–DMF (2:1, 1.5 ml) for 17 h at room temperature. The mixture was acidified with diluted HCl and extracted with Et_2O. The extract was washed with water and dried ($MgSO_4$). Removal of the solvent gave an oil (32 mg), whose TLC and ^{1}H-NMR spectrum showed that the product consisted of a mixture of diacid and γ-lactone. Column chromatography (SiO_2) of the residual oil afforded 4α-(4-benzyloxybutyl)-5-methyl-3aβ,4β,7,7aβ-tetrahydrophthalide (**22a**), as a colorless oil (7.5 mg, 23.4%) from the hexane–AcOEt (4:1) eluate. IR: 1775 cm^{-1}. ^{1}H-NMR δ: 1.73 (3H, br), 3.48 (2H, t, J=5.2 Hz), 3.96 (1H, dd, J=6.0, 9.0 Hz), *ca.* 4.30 (1H, dd, J= *ca.* 7.9, 9.0 Hz), 4.50 (2H, s), 5.4—5.75 (1H, m), 7.32 (5H, s). MS *m/z*: 314 (M^+), 223 (M^+-91). High-resolution MS Calcd for $C_{20}H_{26}O_3$ (M^+) *m/z*: 314.188. Found *m/z*: 314.186.

2) The anhydride **19a** (33 mg, 0.1 mmol) was treated with an excess of $NaBH_4$ in THF (1 ml) for 1 h on an ice bath. The mixture was acidified with concentrated HCl (2 drops) and extracted with $CHCl_3$. The extract was filtered through a short column packed with SiO_2 and the filtrate was evaporated to dryness to give an oil (29 mg), whose ^{1}H-NMR and TLC showed that it was a mixture of **21a** and **22a** in a ratio of about 1:2.

3) A mixture of **19b** and **19c** (1:1, 292 mg, 0.855 mmol) was treated with $NaBH_4$ (50 mg) in THF (5 ml) at 0 °C for 30 min and at room temperature for 1.5 h. After addition of 6 N HCl (1 ml) on an ice both, the reaction mixture was stirred for 10 min at room temperature, diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The resulting oil was chromatographed on SiO_2 using hexane–AcOEt (17:3) as an eluent to afford successively 7α-(4-benzyloxybutyl)-3aβ,6-dimethyl-3aβ,4,7β,7aβ-tetrahydrophthalide (**23**) (120 mg, 42.8%) as a less polar colorless oil and 4α-(4-benzyloxybutyl)-3aβ,5-dimethyl-3aβ,4β,7,7aβ-tetrahydrophthalide (**22b**) (114 mg, 40.5%) as a more polar colorless oil. (The less polar **23**) IR: 1775 cm^{-1}. ^{1}H-NMR (400 MHz, decoupling) δ: 1.16 (3H, s, 3aβ-Me), 1.73 (3H, br, 6-Me), *ca.* 1.87 and *ca.* 2.19 (1H each, m, 4-H_2), *ca.* 2.32 (1H, m, 7β-H), 2.41 (1H, d, J=5.6 Hz, 7aβ-H), 3.45—3.55 (2H, m), 3.87 and 3.91 (1H each, d, J=8.5 Hz, 3-H_2), 4.51 (2H, s), 5.4—5.5 (1H, m, 5-H), 7.34 (3H, s), 7.35 (2H, s). MS *m/z*: 328 (M^+), 237 (M^+-91). High-resolution MS Calcd for $C_{21}H_{28}O_3$ (M^+) *m/z*: 328.204. Found *m/z*: 328.204. (The more polar **22b**) IR: 1775 cm^{-1}. ^{1}H-NMR (400 MHz, decoupling) δ: 1.16 (3H, s, 3aβ-Me), 1.78 (3H, br, 5-Me), 2.35 (1H, dd, J=5.1, 9.0 Hz, 7aβ-H), 2.4—2.45 (2H, m, 7-H_2), 3.4—3.47 (2H, m), 4.00 and 4.25 (1H each, d, J=9.4 Hz, 3-H_2), 4.49 (2H, s), *ca.* 5.41 (1H, m, 6-H), *ca.* 7.33 (5H, m). MS *m/z*: 328 (M^+), 237 (M^+-91). High-resolution MS Calcd for $C_{21}H_{28}O_3$ (M^+) *m/z*: 328.204. Found *m/z*: 328.202.

Conversion of a Mixture of 19c and 19b into 23 and 21b *via* the Iodo Lactones A mixture of **19c** and **19b** (1:1, 342 mg, 1 mmol) obtained from **18** and citraconic anhydride (**15b**) was treated successively with 0.5 M $NaHCO_3$ aqueous solution (6 ml) and a solution of I_2 (508 mg, 2 eq)–KI (996 mg, 6 eq) in water (6 ml) in the same way as described for the preparation of **21a**. Work-up of the reaction mixture afforded a mixture of iodo lactones (506 mg) as a colorless oil. IR: 3500, 1775, 1720 (sh) cm^{-1}. ^{1}H-NMR δ: 1.26 and 1.71 (3H each, s), 1.59 (6H, s), 3.25—3.65 (4H, m), 4.3—4.5 (2H, m, –CH–I), 4.50 and 4.52 (2H each, s), 7.32 and 7.33 (5H each, s).

A part (352 mg) of the above mixture of iodo lactones was dissolved in THF–$B(OMe)_3$ (4:1, 3.5 ml) and the solution was treated with $BH_3\cdot Me_2S$ (0.12 ml) for 13 h at room temperature. An excess of MeOH was added carefully and the solvent was removed to give an oily mixture of lactones (342 mg). IR: 3630, 3400, 1775 cm^{-1}.

A mixture of the resulting lactones and Zn powder (700 mg) in AcOH (17 ml) was refluxed for 2.5 h with vigorous stirring, filtered through Celite and concentrated under reduced pressure. Column chromatography (SiO_2) of the residue afforded successively **23** (38 mg, 16.6% from the mixture of anhydrides) and **21b** (92 mg, 40.2% from the mixture of anhydrides) from the hexane–AcOEt (17:3) eluate and the unidentified lactone (55.5 mg) as colorless oil from the hexane–AcOEt (2:1) eluate. IR: 3600, 1780 cm^{-1}. ^{1}H-NMR δ: 1.13 (3H, s), 1.70 (3H, br), 3.35—3.7 (2H, m), 3.8—4.3 (1H, m), 4.51 (2H, s), 7.32 (5H, s).

6α-(4-Benzyloxybutyl)-4α-hydroxymethyl-1,5,5-trimethylcyclohexene (25) and Its Acetate (26) A solution of diisobutylaluminum hydride in toluene (1 M solution, 7 ml) was added dropwise to a stirred solution of **21b** (1.54 g, 4.69 mmol) in toluene (47 ml) on a dry ice–acetone bath under Ar, and the mixture was stirred for 10 min. After addition of saturated NH_4Cl aqueous solution (15 ml), the mixture was stirred at room temperature for 10 min and then 5% H_2SO_4 (15 ml) was added on an ice bath. The mixture was stirred for 10 min, diluted with water and extracted with Et_2O–AcOEt. The extract was washed with $NaHCO_3$ aqueous solution and brine, and dried ($MgSO_4$). Removal of the solvent gave the cyclic hemiacetal (1.62 g) as a colorless oil, which was used for the next reduction without further purification.

A mixture of the cyclic hemiacetal (1.62 g) obtained above, 80% hydrazine hydrate (3.1 ml) and NaOH (1.84 g) in diethylene glycol (23 ml) was heated at 110°C (bath temperature) for 1 h with vigorous stirring under N_2. Then, the temperature was raised gradually to 210 °C (bath temperature) during 1—1.5 h with removal of water and excess hydrazine, and maintained for 2.5 h at 210 °C. After cooling, the mixture was diluted with water and extracted with Et_2O. The extract was washed with water, dried ($MgSO_4$) and evaporated to dryness to afford an oil (1.60 g), which was chromatographed on SiO_2 (hexane–AcOEt (4:1)) to provide the alcohol **25** (1.37 g, 92.1%) as a colorless oil. IR: 3620 cm^{-1}. ^{1}H-NMR δ: 0.74 and 0.97 (3H each, s), 1.70 (3H, br), 3.40 (1H, dd, J=8.1, 10.5 Hz), 3.3—3.65 (3H, m), 3.83 (1H, dd, J=4.1, 10.5 Hz), 4.50 (2H, s), 5.2—5.5 (1H, m), 7.32 (5H, s). MS *m/z*: 316 (M^+), 298 (M^+-18). High-resolution MS Calcd for $C_{21}H_{32}O_2$ (M^+) *m/z*: 316.240. Found *m/z*: 316.239.

The alcohol **25** (1.30 g, 4.13 mmol) was treated with Ac_2O (14 ml) and pyridine (28 ml) for 2 h at room temperature and the solvent was removed under reduced pressure. Column chromatography (SiO_2, hexane–AcOEt (19:1)) of the residue afforded **26** (1.41 g, 95.4%) as a colorless oil. IR: 1735 cm^{-1}. ^{1}H-NMR δ: 0.76, 0.98 and 2.03 (3H each, s), 1.69 (3H, br), 3.2—3.65 (2H, m), 3.85 (1H, dd, J=8.1, 10.6 Hz), 4.25 (1H, dd, J=3.8, 10.6 Hz), 4.50 (2H, s), 5.15—5.55 (1H, m), 7.32 (5H, s). MS *m/z*: 298 (M^+-60). High-resolution MS Calcd for $C_{21}H_{30}O$ ($M^+-CH_3CO_2H$) *m/z*: 298.229. Found *m/z*: 298.226.

4α-Acetoxymethyl-6α-(4-hydroxybutyl)-1,5,5-trimethylcyclohexene (28) Commercially available Raney Ni W-2 (16 ml, Aldrich Chemical Co.) was washed by suspension in distilled water and decantation until the washings were neutral to litmus and then the washing process was repeated three times with 99.5% EtOH (20 ml). A mixture of **26** (5.17 g, 14.4 mmol) and Raney Ni obtained above in 99.5% EtOH (100 ml) was refluxed for 7 min with vigorous stirring under N_2, then cooled rapidly below 20 °C and filtered through Celite. The filtrate was concentrated and the residual oil was dissolved in AcOEt. The mixture was passed through a short column packed with SiO_2. Removal of the solvent gave **28** (3.90 g, 100.7%) as a colorless oil, which was used for the next reaction without purification. An analytical sample was obtained by SiO_2 column chromatography (hexane–AcOEt (3:1)). IR: 3620, 1735 cm^{-1}. ^{1}H-NMR δ: 0.77, 0.99 and 2.04 (3H each, s), 1.70 (3H, br), 3.4—3.9 (2H, m), *ca.* 3.85 (1H, dd, J=8.0, 10.7 Hz), 4.23 (1H, dd, J=3.9, 10.7 Hz), 5.15—5.45 (1H, m). MS *m/z*: 268 (M^+), 208 (M^+-60). High-resolution MS Calcd for $C_{16}H_{28}O_3$ (M^+) *m/z*: 268.204. Found *m/z*: 268.199.

4-(5α-Acetoxymethyl-2,6,6-trimethyl-2-cyclohexen-1α-yl)butyl Tetrahydropyranyl Ether (29) A mixture of crude **28** (3.41 g) obtained by debenzylation of **26** (4.56 g, 12.73 mmol), dihydropyran (3 ml) and pyridinium *p*-toluenesulfonate (315 mg) in CH_2Cl_2 (50 ml) was stirred at room temperature for 1 h and diluted with Et_2O. The solution was washed with aqueous Na_2CO_3 solution and brine, dried ($MgSO_4$), and concentrated. SiO_2 column chromatography (hexane–AcOEt (9:1)) of the resulting oil provided **29** (4.47 g, 99.7% from **26**) as a colorless oil. IR: 1735 cm^{-1}. ^{1}H-NMR δ: 0.77, 0.99 and 2.04 (3H each, s), 1.69 (3H, br), 3.15—4.1 (5H, m), 4.26 (1H, dd, J=3.7, 9.7 Hz), 4.57 (1H, br), 5.15—5.45 (1H, m). MS *m/z*: 352 (M^+), 292 (M^+-60). High-resolution MS Calcd for $C_{21}H_{36}O_4$ (M^+) *m/z*: 352.261. Found *m/z*: 352.259.

4-(5α-Methanesulfonyloxymethyl-2,6,6-trimethyl-2-cyclohexen-1α-yl)-butanoic Acid (32) *via* 30 and 31 The acetoxy ether **29** (4.42 g, 12.54 mmol) was treated with $LiAlH_4$ (940 mg) in Et_2O (80 ml) for 10 min at 0 °C. Usual work-up of the mixture provided **30** (3.88 g) as a colorless oil. IR: 3620 cm^{-1}. ^{1}H-NMR δ: 0.76 and 0.98 (3H each, s), 1.68 (3H, br), 3.1—4.0 (6H, m), 4.57 (1H, br), 5.15—5.45 (1H, m). MS *m/z*: 310 (M^+), 292 (M^+-18).

Methanesulfonyl chloride (4.8 ml) was added dropwise to a stirred solution of **30** (3.88 g) obtained above and Et_3N (10.9 ml) in CH_2Cl_2 (129 ml) at 0 °C for 1 h. Work-up of the mixture in the usual manner gave **31** (5.44 g) as an oil. ^{1}H-NMR δ: 0.79, 1.01 and 3.00 (3H each, s), 1.70 (3H, br).

Jones reagent (27 ml) was added dropwise to a stirred solution of crude **31** (5.44 g) obtained above in acetone (220 ml) at 0 °C and stirring was continued for 1 h at room temperature. Work-up of the mixture in the usual manner and subsequent SiO_2 column chromatography (hexane–AcOEt (3:1)) afforded **32** (3.75 g, 94.0% from **29**) as a colorless gum. IR: 1705, 1175 cm^{-1}. ^{1}H-NMR δ: 0.79, 1.01 and 3.00 (3H, each, s), 1.72 (3H, br), 4.00 (1H, dd, J=8.1, 9.3 Hz), 4.39 (1H, dd, J=3.5, 9.3 Hz),

5.2—5.5 (1H, m). MS *m/z*: 318 (M^+), 303 (M^+-15), 222 (M^+-96). High-resolution MS Calcd for $C_{15}H_{26}O_5S$ (M^+) *m/z*: 318.150. Found *m/z*: 318.148.

4-(5α-Acetoxymethyl-2,6,6-trimethyl-2-cyclohexen-1α-yl)-butanoic Acid (33) The crude acetoxy alcohol **28** (1.03 g) prepared from **26** (1.41 g, 3.94 mmol) was oxidized with Jones reagent (10 ml) in acetone (80 ml) at room temperature for 30 min. Usual work-up of the reaction mixture and subsequent SiO_2 column chromatography (hexane–AcOEt (7 : 3)) afforded **33** (924 mg, 83.2% from **26**) as a colorless oil. IR: 1735, 1705 cm^{-1}. ^{1}H-NMR δ: 0.77, 0.99 and 2.04 (3H each, s), 1.71 (3H, br), 3.84 (1H, dd, J=8.0, 10.7 Hz), 4.26 (1H, dd, J=3.8, 10.7 Hz), 5.2—5.5 (1H, m). MS *m/z*: 282 (M^+), 222 (M^+-60). High-resolution MS Calcd for $C_{16}H_{26}O_4$ (M^+) *m/z*: 282.183. Found *m/z*: 282.184.

Conversion of 33 into 32 A solution of **33** (663 mg, 2.35 mmol) in MeOH–H_2O (1 : 3, 12 ml) was stirred with NaOH (260 mg) at room temperature overnight. The mixture was acidified with concentrated HCl and then concentrated. The residue was suspended in toluene and the solvent was evaporated off. The resulting residue was treated with methanesulfonyl chloride (1 ml) in CH_2Cl_2 (24 ml) in the presence of Et_3N (2.8 ml) at 0 °C for 1 h. The mixture was poured into ice, acidified, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure affording an oil. Column chromatography (SiO_2) (hexane–AcOEt (3 : 1)) gave **32** (547 mg, 73.2%) as a colorless gum.

***N*-Methyl-2'-[(2-cyanoethyl)thio]-4-(5α-methanesulfonyloxymethyl-2,6,6-trimethyl-2-cyclohexen-1α-yl)butananilide (35)** A solution of **32** (1.45 g, 4.60 mmol) and oxalyl chloride (2.3 ml) in benzene (23 ml) was stirred at room temperature for 1 h and then at 60 °C for 1 h. Removal of the solvent afforded the corresponding acid chloride **34** as a colorless oil, which was dissolved in THF (46 ml). The solution was added dropwise to a stirred mixture of 2-cyanoethyl (2-methylamino)phenyl sulfide (1.75 g) and anhydrous K_2CO_3 (2.52 g) in THF (90 ml) at 0 °C under Ar and stirring was continued for 30 min. The mixture was diluted with water and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (SiO_2, hexane–AcOEt (1 : 1)) of the resulting oil gave **35** (2.00 g, 89.2%) as a pale yellow caramel. IR ($CHCl_3$): 2240, 1650 (sh), 1645 cm^{-1}. ^{1}H-NMR δ: 0.76, 0.94, 2.99 and 3.18 (3H each, s), 1.66 (3H, br), 2.5—2.85 (2H, m), 3.0—3.4 (2H, m), 3.7—4.6 (2H, m), 5.1—5.4 (1H, m), 7.0—7.5 (2H, m). MS (FD-MS) *m/z*: 492 (M^+).

3,9-Dimethyl-8β,12β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one (36) Anhydrous K_2CO_3 (4.40 g) and $NaBH_4$ (1.20 g) were dried over P_2O_5 at 130 °C for 2 h under reduced pressure and then DMF (318 ml) was added. To the stirred mixture, a solution of **35** (3.13 g, 6.36 mmol) in DMF (40 ml) was added over 48 h at 130 °C under Ar, and after complete addition stirring was continued for 5 h. The mixture was neutralized with diluted HCl, concentrated under reduced pressure, diluted with water and extracted with Et_2O–AcOEt (1 : 1). The extract was washed with aqueous Na_2CO_3 solution and brine, dried ($MgSO_4$), and concentrated. Column chromatography (SiO_2, hexane–AcOEt (3 : 1)) of the resulting residue afforded crystalline **36** (1.32 g, 60.6%), which was recrystallized from $CHCl_3$–hexane to give colorless prisms, mp 140—142 °C. IR: 1650 cm^{-1}. ^{1}H-NMR δ: 0.90, 1.35 and 3.24 (3H, each, s), 1.54 (3H, br), 2.75 (1H, dd, J=11.0, 12.9 Hz), 3.42 (1H, dd, J=6.7, 12.9 Hz), 4.85—5.1 (1H, m), 6.95—7.7 (4H, m). MS *m/z*: 343 (M^+), 328 (M^+-15). High-resolution MS Calcd for $C_{21}H_{29}NOS$ (M^+) *m/z*: 343.197. Found *m/z*: 343.194. *Anal.* Calcd for $C_{21}H_{29}NOS$: C, 73.42; H, 8.51; N, 4.08; S, 9.33. Found: C, 73.53; H, 8.52; N, 4.13; S, 9.32.

3,5ξ,9-Trimethyl-8β,12β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one (37) A solution of *n*-BuLi in hexane (1.55 M, 2.50 ml) was added dropwise to a stirred solution of **36** (686 mg, 2.00 mmol) and diisopropylamine (0.70 ml, 5 mmol) in THF (20 ml) at −78 °C under Ar, and after 20 min methyl iodide (0.8 ml) was added. Stirring was continued for 30 min at −78 °C and for 30 min at −10 °C. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and the solvent was removed. Column chromatography on SiO_2 (hexane–AcOEt (9 : 1)) of the crude product afforded **37** (645 mg, 90.3%) as a colorless gum, whose IR and ^{1}H-NMR spectra and *Rf* values of TLC were identical with those of the less polar lactam sulfide A prepared from α-ionone.[1)]

5ξ-Allyl-3,9-dimethyl-8β,12β-dimethylmethano-14-thia-3-aza-1,2-benzo-1,9-cyclotetradecadien-4-one (38) According to the above procedure, the anion prepared from **36** (1.03 g, 3.00 mmol) and LDA (4.6 mmol) was treated with allyl bromide (1.30 ml). The crude product was chromatographed (SiO_2, hexane–AcOEt (9 : 1)) to give the allyl lactam sulfide **38** (1.07 g, 93.5%) as a pale yellow gum. IR: 1650 cm^{-1}. ^{1}H-NMR δ: 0.90, 1.41 and 3.23 (3H each, s), 1.54 (3H, br), 2.66 (1H, t, J=12.7 Hz), 3.58 (1H, dd, J=4.7, 12.7 Hz), 4.85—5.4 (3H, m), 5.4—6.0 (1H, m), 7.0—7.6 (4H, m). MS *m/z*: 383 (M^+), 368 (M^+-15). High-resolution MS Calcd for $C_{24}H_{33}NOS$ (M^+) *m/z*: 383.228. Found *m/z*: 383.229.

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