Preparation of Bicyclo[3.3.1]nonane-2,4-dione Derivatives

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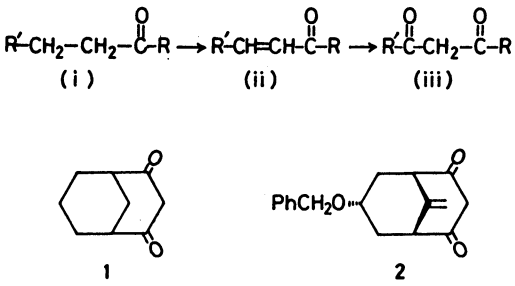
Bicyclo[3.3.1]nonane-2,4-dione and 7-*endo*-benzyloxy-9-methylenebicyclo[3.3.1]nonane-2,4-dione were prepared starting from bicyclo[3.3.1]nonan-2-one and 7-*endo*-benzyloxybicyclo[3.3.1]nonane-2,9-dione, respectively. The key reaction was the NCS oxidation of the 2,2-ethylenedioxy-4-phenylthiobicyclo[3.3.1]nonanes, derived from the corresponding bicyclo[3.3.1]non-3-en-2-ones.

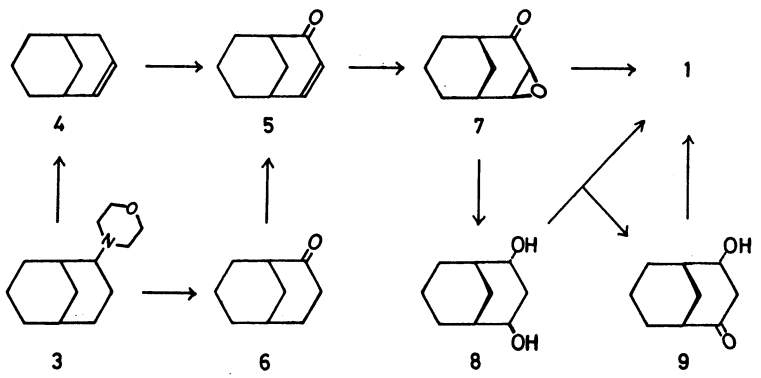
In the course of our study on the synthesis of the taxane framework,[1] we investigated the preparation of bicyclo[3.3.1]nonane-2,4-dione derivatives. Such systems had been reported by several workers,[2] but methodologies had limited application to the preparation of poly functionalized bicyclic derivatives. We chose the transformation from a ketone(**i**) to a 1,3-diketone(**iii**) via an α,β-unsaturated ketone(**ii**) (Scheme 1) because carbonyl compounds are easy to prepare and several efficient methods to their transformation have recently been developed. However, as shown later, there exists clear differences in a bicyclic ring system as compared to an acyclic or a monocyclic one; especially, the conformation of the ring is frequently fixed in the former system and the methods applicable to the latter are not always suitable in the bicyclic system. In this report, we wish to describe our results concerning the preparation of bicyclo[3.3.1]nonane-2,4-dione (**1**) and 7-*endo*-benzyloxy-9-methylenebicyclo-[3.3.1]nonane-2,4-dione (**2**) starting from bicyclo[3.3.1]-nonan-2-ones via α,β-unsaturated carbonyl compounds. The bicyclic diketone **1** have been successfully converted to the 3β-trinortaxane derivative.[1]



Scheme 1.

A. Bicyclo[3.3.1]nonane-2,4-dione (1). As the parent bicyclo[3.3.1]nonane-2,4-dione (**1**) had been unknown, our initial efforts were focused on the preparation of **1**. The reaction of a cyclohexanone enamine with acrylaldehyde[3] or acryloyl chloride[4] is one of the useful methods for constructing a bicyclo[3.3.1]-nonane framework. Schaefer and co-workers[5] prepared bicyclo[3.3.1]non-3-en-2-one (**5**) via **4** by starting from the amine **3** derived from the reaction of 1-morpholinocyclohexene and acrylaldehyde followed by Wolff-Kishner reduction. We followed the reaction and could improve the total yield up to 28% (lit,[5] 23%) by changing the oxidizing agent of the nitrogen from H_2O_2 to purified *m*-chloroperbenzoic acid (MCPBA). However, the yield was still low and a short-step synthesis of **5** was then examined. When **3** was oxidized with $Hg(OAc)_2$[6] in 5% acetic acid in water bicyclo-[3.3.1]nonan-2-one (**6**) was obtained in 61% yield after the hydrolysis of the iminium salt produced. A usual bromination-dehydrobromination[7] smoothly afforded the desired enone **5** in 88% yield.

A direct oxidation of the enone **5** with H_2O_2 or with *t*-butyl hydroperoxide catalyzed by Pd(II)[8] resulted in the recovery of the starting enone. The reaction of the epoxy ketone **7**, prepared by treating **5** with alkaline H_2O_2 in methanol, with tetrakis(triphenylphosphine)-palladium and 1,2-bis(trimethylphosphino)ethane[9] in



Scheme 2.

toluene gave a target diketone **1** but in only 20% yield with several concomitant. Although the above two procedures[8,9] have been found to be effective to acyclic or monocyclic analogues, the present results were considered to be due to a facile β-elimination of the axial hydroxyl (or corresponding oxygen) group. Lithium aluminium hydride reduction of **7** afforded a 2-*endo*,4-*exo*-diol **8**, one hydroxyl of which was equatorial and the other axial. As the axial hydroxyl group is known to be liable to oxidation with Cr(VI) and the equatorial hydroxyl is less eliminable, the oxidation of **8** would proceed via an equatorial hydroxy ketone **9**. Among various chromium reagents, chromium etherate[10] at low temperature was proved to be most suitable to afford **1**. Treatment of the diol **8** with an equimolar amount of $CrO_3 \cdot Et_2O$ in dichloromethane over Celite at −60—−40 °C gave **1** in 30% yield accompanied with **9** (34%) and the starting diol (20%). The equatorial hydroxy ketone **9** was also converted to **1** under the same conditions in 50% yield with 41% recovery.

The structure of **1** was confirmed to be β-diketones by the typical behavior of the absorption maximum in the UV spectra: λ_{max} at 255 nm (log ε=4.13) in ethanol shifted to 281 nm (4.31) with the addition of a base. The IR spectra of **1** in KBr (1625 and 1590 cm^{-1}) and in chloroform (1730sh, 1705, 1630sh, and 1600br cm^{-1}) suggest that the β-diketone **1** exists in a monoketo monoenol form when it is solid, but in a mixture of a monoketo monoenol and a diketo forms in solution.

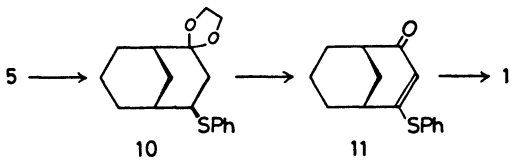
Recently, Fetizon and co-workers[11] reported the preparation of bicyclo[3.3.1]nonane-2,4-dione derivatives under a similar reaction sequences in a comparable yield.

Although the target β-diketone **1** was obtained, the low overall yield and complexity at the last oxidation stage of the reaction sequences required us to search for other approaches. We utilized a sulfur group in place of the oxygen since the sulfur group is easy to introduce to an enone[12,13] and since the sulfur is less apt to eliminate that an alkoxyl group under acidic conditions. The sulfide may be converted into a ketone by the oxidation either to a corresponding sulfoxide followed by a Pummerer rearrangement[14] or to a chloro sulfide followed by hydrolysis.[15] Heating a mixture of the enone **5**, ethylene glycol, and thiophenol in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) afforded a 4-phenylthio acetal **10** in good yield. The treatment of **10** with 1.05 equimolar amount of *N*-chlorosuccinimide (NCS) in purified (dried) carbon tetrachloride[13] at room temperature gave a new spot on TLC in 3 h, but filtration of the mixture through a silica-gel column gave two spots. The R_f value of the second was identical with that of a vinyl sulfide **11**. It was suggested that the initially formed intermediate was hydrolyzed with the water present in the column. Thus, the NCS oxidation of **10** under the addition of water resulted in one-pot conversion of **10** into **11**. The subsequent hydrolysis of the vinyl sulfide **11** into **1** was quantitatively accomplished under either acidic or basic conditions (see Experimental).

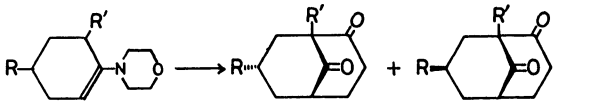
In the present method, **1** was obtained in 40% overall yield from the amine **3**.

B. 7-Benzyloxy-9-methylenebicyclo[3.3.1]nonane-2,4-dione(2). The successful preparation of **1** prompted us next to examine whether this method is applicable to a more functionalized bicyclo[3.3.1]nonan-2-one. The starting ketone chosen was 7-substituted 2,9-dione (e.g., **15**), which has functional groups at both rings and the bridged carbon. **15** can be prepared by the reaction of 4-benzyloxy-1-morpholinocyclohexene with acryloyl chloride.[4] The stereochemistry of the 7-substituent had been proven only in the case of 4-*t*-butyl-6-methyl-1-morpholinocyclohexene(**12**); the major isomer (**13b**/**13a**=4/1) was subjected to X-ray crystal analysis to establish the syn relation between the *t*-butyl group and the bridge C=O group.[16] We used 4-benzyloxy-1-morpholinocyclohexene(**14**) as a starting material. After a reexamination of several reaction conditions,[6,18,19] we found that the addition of hydroquinone to the procedure reported by Aredova and co-workers[19] improved the yield up to 80%. From an ^1H NMR study, **15** was found to consist of two stereoisomers (**15a**/**15b**=2.2/1.0). The characteristic features of the two isomers in ^1H NMR spectra are the shape of the signal of C_7-H — a broad singlet at δ=3.72 in **15a** and a triplet of triplet at 3.89 (J=10.8 and 5.4 Hz) in **15b**, and that of the benzylic protons — an AB quartet at 4.20 and 4.50 with J=11.6 Hz in **15a** and a sharp singlet at 4.50 in **15b**. These properties suggested that the benzyloxyl group of the major isomer **15a** was anti to the bridged C=O group and existed in axial in contrast to the *t*-butyl group of **13b**. This was unequivocally confirmed by an X-ray crystal analysis[20] of **20a** (vide infra).

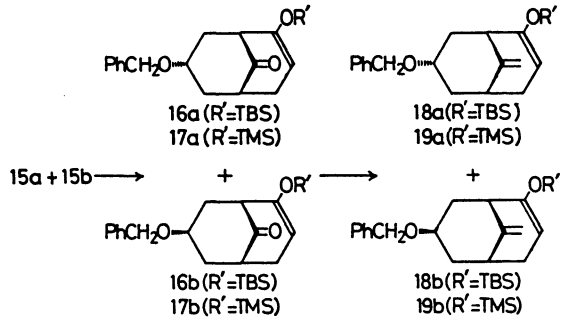
As the β-diketones **15** was unstable to alkali, the enolizable C_2-carbonyl group was protected by treating **15a** and **15b** with t-butyldimethylsilyl or trimethylsilyl triflate as silyl enol ether **16** (R′=SiBu^{t}Me$_2$; TBS) or **17**



Scheme 3.



Scheme 4.



Scheme 5.

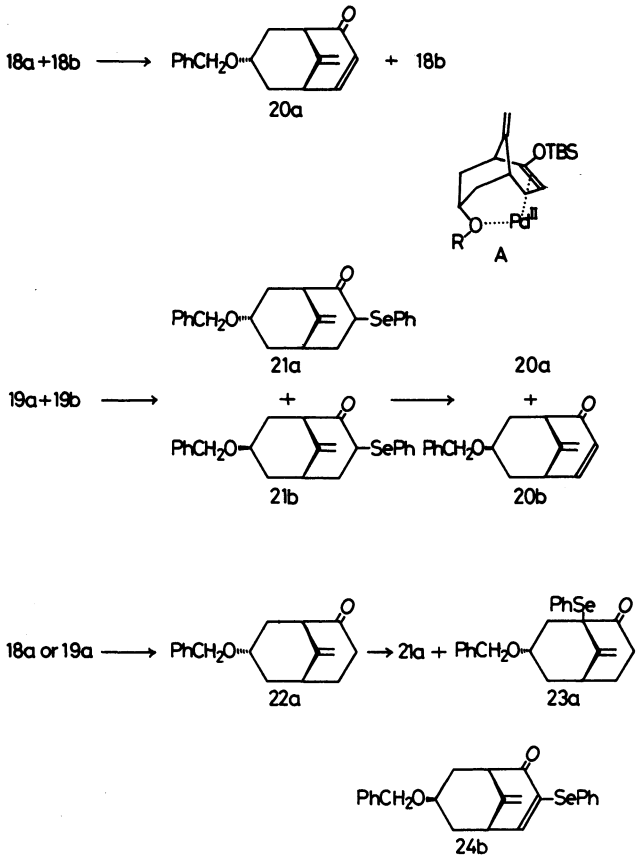
($R'=SiMe_3$; TMS), respectively. These silyl enol ethers were then converted into 9-methylene derivatives **18** (R'=TBS) or **19** (R'=TMS), respectively, by treating with methylenetriphenylphosphorane. The ratio of **18a** to **18b** (or **19a** to **19b**) remained unchanged during these transformations.

The conversion of the silyl enol ether into an α,β-unsaturated carbonyl compound **20** was achieved either oxidation with palladium acetate or benzeneselenenylation followed by oxidation-elimination of the phenylseleno group. The stable TBS enolates (**18a**+**18b**) were treated with palladium acetate in acetonitrile.[21] Of interest, only **18a** was converted into an anticipated **20a** (99% based on the amount of **18a** in the mixture) but **18b** recovered almost quantitatively. The coordination of Pd(II) with both the oxygen of the benzyloxyl group and the olefin as shown in **A** may accelerate the reaction.

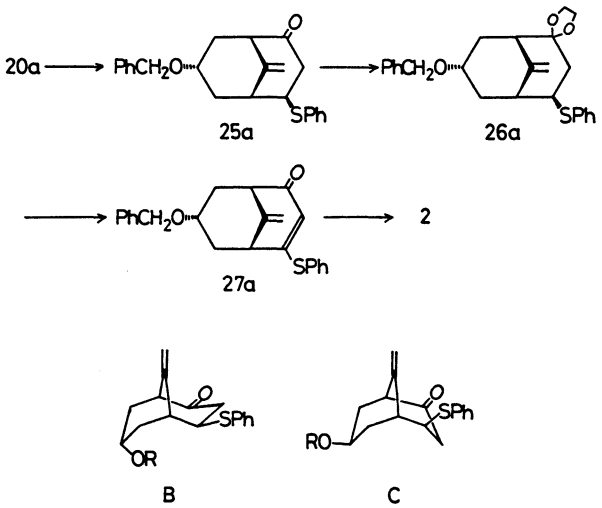
On the other hand, benzeneselenenylation[22,23] was successfully carried out with unstable TMS enolates (**19a**+**19b**). The reaction with one equivalent of benzeneselenenyl chloride in THF gave a mixture of phenylseleno ketones **21a** and **21b**, which without a further purification was oxidized with H_2O_2 in dichloromethane-pyridine[23] to give a mixture of **20a** and **20b** in 46% yield. In the large scale preparation of **20**, the TMS enolates (**17a** and **17b**) were successively treated with methylenetriphenylphosphorane, benzeneselenenyl chloride, and H_2O_2 to give **20** (**20a**/**20b**=9.6/1.0)[24] in 50% overall yield.

The benzeneselenenylation of 7-benzyloxy-9-methylenebicyclo[3.3.1]nonan-2-one (**22a**), obtained by the hydrolysis of **18a** or **19a**, gave a 2-phenylseleno ketone **21a** in 43% yield accompanied with 11% of a bridgehead seleno ketone **23a**; while the reaction of TMS enol ethers (**19a** and **19b**) with two equivalent benzeneselenenyl chloride afforded, besides **21a** (24%), an α-phenylseleno α,β-unsaturated ketone **24b** in 18% yield.

Conversion from the α,β-unsaturated ketone **20a** into β-dicarbonyl compound **2** was achieved under a similar process to that used in the preparation of **1**, except for a slight modification of the reaction conditions. A direct conversion of **20a** to an acetal **26a** was unsuccessful. The addition of thiophenol to **20a** in the presence of a catalytic amount of triethylamine



Scheme 6.



Scheme 7.

afforded a 4-phenylthio ketone **25a** in quantitative yield. On the other hand, **20b** did not react at all. Thus, when the mixture of **20a** and **20b** was subjected to the thiophenol addition, **25a** and unreacted **20b** were obtained; they were separable by chromatography. The difference in the reactivity of **20a** and **20b** toward thiophenol can be rationalized by comparing their conformations: In **20a** the axial benzyloxyl group distorts the other ring to the boat form resulting the phenylthio group being equatorial (**B**), while in **20b**,

the axial phenylthio group (**C**), if produced, is eliminated easily to revert to the starting **20b**.[25]

The acetalization of **25a** was employed by 1,2-bis(trimethylsiloxy)ethane to give **26a** in high yield.[26] The oxidation of **26a** with NCS in the presence of water gave a vinyl sulfide **27a**, which was hydrolyzed to the target β-diketone **2** in good yield. The diketone **2** exists almost in a ketonic form, even in solution (cf. **1**).

A successful preparation of **1** and **2** proved that the present method has wide applications to the preparation of a bicyclic β-diketone.

Experimental

Melting points are uncorrected. Column chromatography was performed with Wako C-300 silica gel unless otherwise stated. IR and UV spectra were recorded on a Hitachi 215 grating and a Hitachi 340 spectrophotometers, respectively. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ on a JEOL LMN-FX90Q spectrometer using TMS as the internal standard unless otherwise stated. High-resolution mass spectra were performed at Nippon Roche Research Center, Kamakura.

Bicyclo[3.3.1]non-2-ene (4). A solution of 825 mg of MCPBA (100% activity: washed three times with KH_2PO_4-NaH_2PO_4 buffer, pH=7.50, and dried under reduced pressure) in 40 ml of $CHCl_3$ was added gradually to an ice-cooled and stirred solution of 1.00 g of 2-morpholinobicyclo[3.3.1]-nonane (**3**)[5] in 20 ml of $CHCl_3$. Stirring was continued for 3 h, during which the mixture was allowed to come to room temperature. Removing of the solvent under reduced pressure and chromatography (alumina, $CHCl_3$) of the residue gave 1.02 g (95%) of an *N*-oxide. The flask containing 1.02 g of the *N*-oxide equipped with a distillation set and tandem Dry Ice traps, was heated slowly to 110 °C under reduced pressure. After 1 h, the temperature was raised to 145 °C and kept for 5 h. In the first trap, 370 mg (65%) of **4** was collected. Mp, 96—98 °C (purified by sublimation, lit,[5] 96.5—98.5 °C).

Bicyclo[3.3.1]non-3-en-2-one (5). A) From **4**. According to the known procedure,[5] **5** was obtained from **4** in a comparable yield. Mp 97—98 °C (from pentane) (lit,[5] 97.5—98.5 °C).

B) From **6**. To a solution of 22.8 g of phenyltrimethylammonium tribromide[27] in 400 ml of THF, was added a solution of 8.38 g of **6** in 40 ml of THF at a once at 0 °C. The mixture was stirred for 30 min at that temperature and then was poured into a solution of saturated aqueous NaCl and 0.1 M (1 M=1 mol dm^{-3}) aqueous $Na_2S_2O_3$ (1 : 1) through a filter paper. The solids were washed with ether, and the filtrate was extracted with CH_2Cl_2. The combined organic solution was washed with water, brine, and dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the crude product from pentane gave 10.4 g of 3-bromobicyclo[3.3.1]nonan-2-one. Chromatography of the mother liquid with CH_2Cl_2 gave further 1.86 g of the product. The total yield was 12.3 g (93%). Mp 115—116 °C (from benzene); IR ($CHCl_3$) 2940, 2860, and 1715 cm^{-1}; ^1H NMR δ=1.00—3.32 (12H, m), and 4.87 (1H, dd, *J*=12 and 9 Hz).

Found: C, 49.76; H, 6.02%. Calcd for $C_9H_{13}OBr$: C, 49.79: H, 6.03%.

A mixture of 4.71 g of the bromo ketone, 14.2 g of freshly dried LiBr (heated at 120 °C for 20 h under reduced pressure), 8.70 g of anhyd Li_2CO_3 (dried under reduced pressure prior to use) and 80 ml of DMF was heated at 110 °C for 5 h. The cooled mixture was poured into 500 ml of ice-cooled 10% AcOH-H_2O by filtration and the solids were washed with CH_2Cl_2. The combined organic solution was shaken with saturated $NaHCO_3$, water, brine, and dried over $MgSO_4$. Distillation of the solvent at the ordinary pressure and chromatography of the residue with CH_2Cl_2-pentane (10 : 2) gave 2.82 g (95%) of **5**.

Bicyclo[3.3.1]nonan-2-one (6). A mixture of 10.0 g of **3** and 15.3 g of $Hg(OAc)_2$ in 100 ml of 5% AcOH-H_2O was heated at 90 °C for 2 h. After cooling to room temperature, 250 ml of brine was added to the mixture. The precipitates were filtered off and washed with ether. The filtrate was extracted with ether and the combined organic solution was washed with 1 M HCl, water, and dried over anhyd Na_2SO_4. Evaporation of the solvent at the ordinary pressure and sublimation of the residue gave 4.0 g (61%) of **6** as crystals; mp 131—134 °C (lit,[5] mp 134—137 °C); IR ($CHCl_3$) 2930, 2860, 1690, and 1450 cm^{-1}.

3,4-*exo*-Epoxybicyclo[3.3.1]nonan-2-one (7). To a solution of 243 mg of **5** in 50 ml of MeOH, was added 0.56 ml of 30% H_2O_2 and then was added drop by drop 0.88 ml of 6 M NaOH solution over a period of 2 h at 0 °C. The whole was allowed to warm and kept in the range of 15—20 °C for 4 h. The products were extracted with ether and the extract was washed with water, brine, and dried over $MgSO_4$. Careful concentration of the solution under 30 mmHg (1 mmHg= 133.32Pa) and filtration of the residue through a silica-gel layer with CH_2Cl_2-pentane (1 : 1) gave 248 mg (91%) of **7**; mp 94—96 °C (from pentane); IR ($CHCl_3$) 2950, 1700, 1080, and 1000 cm^{-1}; ^1H NMR δ=2.37—2.67 (2H, m), 3.26 (1H, d, *J*=3.5 Hz), and 3.37 (1H, t, *J*=3.5 Hz).

Found: C, 70.91; H, 7.96%. Calcd for $C_9H_{10}O_2$: C, 71.02; H, 7.94%.

Bicyclo[3.3.1]nonane-2-*endo*, 4-*exo*-diol (8). A mixture of 614 mg of **7**, 240 mg of $LiAlH_4$, and 100 ml of dry ether was refluxed for 5 h. Work up as usual and chromatography with ether gave 603 mg (97%) of **8** accompanied with 13 mg (2.1%) of a 1,2-diol.

8; Mp 205—206 °C (from hexane); IR ($CHCl_3$) 3600, 3400br, 2950, and 2905 cm^{-1}; ^1H NMR δ=1.20—2.30 (12H, m), 3.88 (1H, m, $W_{1/2}$=7 Hz), 4.00 (1H, m, $W_{1/2}$=12 Hz), and 4.66 (2H, s).

Found: C, 68.87; H, 10.28%. Calcd for $C_9H_{16}O_2$: C, 69.19; H,10.33%.

Bycyclo[3.3.1]nonane-2,4-dione (1). A) From **11**. Procedure (i). A mixture of 176 mg of **11**, 25 ml of 25% KOH solution and 25 ml of water was refluxed for 2 h. To the resulted solution, 90 ml of CH_2Cl_2 and 90 ml of 2M HCl solution were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with water, brine, and dried over anhyd Na_2SO_4. Evaporation of the solvent and recrystallization of the residue gave 109 mg (99%) of **1**.

1; Mp 136—138 °C (from benzene); UV (EtOH) 255 nm (log ε=4.13); UV (EtOH-OH^-) 281 nm (4.31); IR (KBr) 3400br, 1625, 1590, 1185, and 1145 cm^{-1}; IR ($CHCl_3$) 3200br, 1730sh, 1705, 1630sh, 1600br, 1185, and 1145 cm^{-1}; ^1H NMR δ=1.20—2.83 (10H, m), 3.37 (2H×1/3, br. AB, *J*=12 Hz), 5.62 (1H×2/3, s), and 6.82 (1H×2/3, br. s.).

Found: C, 70.74; H, 7.89%. Calcd for $C_9H_{12}O_2$: C, 71.02; H,

7.94%.

Procedure (ii). A mixture of 120 mg of **11**, 15 ml of concd HCl and 11 ml of dioxane was refluxed for 6 h. The resulting mixture was poured into 50 ml of water and was extracted with CH_2Cl_2. The extract was washed with 5% $NaHCO_3$ solution, water, brine, and dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the residue gave 74 mg (99%) of **1**.

B) From **7**. A mixture of 249 mg of the epoxy ketone **7**, 7.7 mg of 1,2-bis(diphenylphosphino)ethane, and 24.8 mg of tetrakis(triphenylphosphine)palladium (prepared[28] prior to use) in 1 ml of degassed toluene was placed in a sealed tube under argon and heated at 80 °C for 24 h. Chromatography of the residue with CH_2Cl_2-ether (1 : 1) afforded 48 mg (20%) of **1** and 20 mg (10%) of the starting **7**.

C) From **8**. To a solution of 408 mg of **8** in CH_2Cl_2 (12.3 ml) and ether (4.1 ml), were added 523 mg of celite and 523 mg of CrO_3 successively at −60 °C. The temperature was kept in the range of −60—−40 °C for 6 h. To the mixture were added 82 ml of ether and 500 mg of Celite, and after 15 min, the suspension was filtered through a Celite pad. Removal of the solvent and chromatography on silica gel gave 118 mg (30%) of **1**, 139 mg (34%) of 4-*endo*-hydroxybicyclo-[3.3.1]nonan-2-one (**9**) and 81 mg (20%) of the starting diol **8**.

9; Oil; IR (CCl_4) 3600, 3460, 2940, 2855, and 1700 cm^{-1}; ^1H NMR δ=1.36—2.90 (12H, m), 3.25 (1H, br. s), and 4.17 (1H, br. t, J=4.5 Hz).

2,2-Ethylenedioxy-4-*exo*-phenylthiobicyclo[3.3.1]nonane (10). A mixture of 3.40 g of **5**, 3.30 g of thiophenol, 3.10 g of ethylene glycol, 70 mg of *p*-TsOH, and 300 ml of benzene was refluxed through a water separator for 10 h. After the solvent had been removed, the residue was dissolved in 100 ml of CH_2Cl_2. The solution was washed with a 1M NaOH solution, water, brine, and dried over anhyd Na_2SO_4. Evaporation of the solvent afforded 5.86 g (81%) of **10** as crystals; mp 107.5—108.5 °C (from hexane); IR (KBr) 1585, 1115, 1080, 1050, 1035, 745, and 690 cm^{-1}; ^1H NMR δ=1.25—2.04 (10H, m), 2.06 (1H, br. d, J=16.3 Hz), 2.39 (1H, dd, J=16.3 and 7.3 Hz), 3.62 (1H, br. d, J=7.3 Hz), 3.98 (4H, m), and 7.18—7.50 (5H, m).

Found: C, 70.32; H, 7.60%. Calcd for $C_{17}H_{22}O_2S$: C, 70.30; H, 7.63%.

4-Phenylthiobicyclo[3.3.1]non-3-en-2-one (11). To a solution of 4.56 g of **10** in 1 L of CCl_4, was added successively 2.36 g of NCS (98% activity) and 1 ml of water. After vigorous stirring for 5 h, the resulted white crystals were removed by filtration. Evaporation of the solvent and chromatography of the residue with benzene-AcOEt (92 : 8) gave 3.42 g (89%) of **11** as an oil; IR ($CHCl_3$) 1635, 1560, 1345, 1290, 1150, 1085, 1055, 980, and 875 cm^{-1}; ^1H NMR δ=1.40—2.00 (7H, m), 2.12—2.78 (3H, m), 5.61 (1H, s), and 7.43 (5H, br. s.)

Found: m/z 244.0920. Calcd for $C_{15}H_{16}OS$: M, 244.0921.

7-*endo*-Benzyloxybicyclo[3.3.1]nonane-2,9-dione(15a) and 7-*exo*-Benzyloxybicyclo[3.3.1]nonane-2,9-dione(15b). A mixture of 4-benzyloxycyclohexanone[17] (40 g), 17 g of morpholine, 400 mg of TsOH in 400 ml of benzene-toluene (1 : 1) was refluxed through a Dean-Stark trap until no more water separated (ca. 36 h). Evaporation of the solvent and excess morpholine gave a crystalline enamine (52 g). To a boiling mixture of 20 g of the crude enamine, 500 mg of hydroquinone, and 1 L of dry benzene, a solution of acryloyl chloride (16.7 g) in 250 ml of dry benzene was added drop by drop over a period of 2 h. The whole was vigorously stirred at that temperature for an additional 18 h. The precipitates were collected by filtration, washed with dry hexane and then dissolved in 500 ml of ice-cooled water. The solution was kept at 0 °C for 4 h and then was extracted with CH_2Cl_2 (100 ml×5). The combined extracts were dried over $MgSO_4$ and were evaporated. The residue was distilled (bath temp 180 °C/0.03 mmHg) to give 15.1 g (80%) of a bicyclic dione **15** as an epimeric mixture of the 7-benzyloxyl group (**15a**/**15b**=2.2/1.0). The each epimer could be separable by preparative TLC.

15a: Oil; IR (CCl_4) 1730, 1705, 1140, 1090, 1070, and 695 cm^{-1}; ^1H NMR δ=1.50—3.20 (10H, m), 3.72 (1H, br. s, $W_{1/2}$=8 Hz), 4.20 and 4.50 (2H, AB, J=11.6 Hz), and 7.30 (5H, s); ^{13}C NMR δ=22.7(t), 37.5(t), 38.2(t), 40.8(t), 43.2(d), 60.0(d), 70.0(t), 72.0(d), 127.6(d), 128.4(d), 137.7(s), 209.0(s), and 212.0(s).

Found: C, 73.82; H, 7.03%. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02%.

15b: Oil; IR (CCl_4) 1735, 1705, 1090br and 695 cm^{-1}; ^1H NMR δ=1.50—2.95 (9H, m), 3.18 (1H, m), 3.89 (1H, tt, J=10.4 and 5.8 Hz), 4.50 (2H, s), and 7.30 (5H, s); ^{13}C NMR δ=23.0(t), 38.1(t), 38.6(t), 40.0(t), 42.7(d), 62.3(d), 69.9(d), 71.0(t), 127.5(d), 127.8(d), 129.6(d), 137.9(s), 208.4(s), and 209.3(s).

7-Benzyloxy-1-(*t*-butyldimethylsiloxy)-9-methylenebicyclo-[3.3.1]non-2-ene (18). To an ice-cooled mixture of 30 g of **15** (**15a**/**15b**=2.2/1.0), 32.4 ml of triethylamine, and 1 L of carbon tetrachloride, was added 46 g of TBSOTf drop by drop, and the solution was stirred at room temperature for 6 h. The triethylammonium trifluoromethanesulfonate produced was removed through a short alumina column. Concentrating the filtrate gave a crude oily **16** (43 g, 100%), IR (CCl_4): 1720, 1660, 1190, 1175, and 1090 cm^{-1}, which was employed for the next reaction without a further purification.

To a suspension of 48.5 g of methyltriphenylphosphonium bromide in 300 ml of dry tetrahydrofuran at 0 °C under argon was added drop by drop 97.5 ml (1.50 mol) of butyllithium-hexane solution. The mixture was stirred for 1.5 h at room temperature. To the resulting Wittig reagent, a solution of 43 g of the TBS enol ethers **16** in 500 ml of THF was added at a once and the whole was stirred for 1.5 h. After most of the solvent had been evaporated below 40 °C, 30 ml of benzene was added and the solution was filtered through a short alumina column. Evaporating the solvent gave 43.7 g (100%) of a mixture of **18a** and **18b** (**18a**/**18b**=2.2/1.0); IR (CCl_4) 1660, 1190sh, 1175, 1095, and 890 cm^{-1}.

7-*endo*-Benzyloxy-9-methylenebicyclo[3.3.1]non-3-en-2-one (20a) and 7-*exo*-Benzyloxy-9-methylenebicyclo[3.3.1]non-3-en-2-one(20b). A) From **18**. To a vigorously stirred solution of **18** (512 mg) in 10 ml of dry acetonitrile, was added 273 mg of $Pd(OAc)_2$ under argon at 0 °C, and the whole was stirred at room temperature for 8 h. Chromatography of the mixture with benzene and $CHCl_3$ gave 271 mg (99% based on **18a**) of **20a** and 110 mg of the recovered **18b**.

20a: Mp 88.5—89.5 °C (from hexane); IR (KBr) 1670, 1650, 900, and 695 cm^{-1}; ^1H NMR δ=1.5—3.2 (6H, m), 3.77 (1H, br. s), 4.23 and 4.30 (2H, AB, J=11.6 Hz) 4.73 (1H, s) 4.77 (1H, s), 5.98 (1H, d, J=9.7 Hz), 7.14 (1H, dd, J=9.7 and 6.5 Hz), and 7.30 (5H, br. s); ^{13}C NMR δ=34.7(t), 36.7(t), 39.8(d), 52.2(d), 70.3(t), 72.9(d), 104.8(t), 127.3(d), 128.3(d), 130.0(d), 138.5(s), 150.2(s), 152.0(d), 153.1(d), and 202.1(s).

Found: C, 80.42; H, 7.23%. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13%.

B) From **19** via **21**. To an ice-cooled solution of 9.23 g of **15** (**15a**/**15b**=2.2/1.0) and 5.97 ml of triethylamine in 90 ml of CCl_4, 6.91 ml of TMSOTf was added drop by drop and the mixture was stirred at room temperature for 6 h. The whole was filtered through an anhyd K_2CO_3 column with CCl_4 and concentration of the solvent gave 11.8 g (100%) of **17**; ^{1}H NMR δ=0.1 (9H, s), 1.7—2.5 (8H, m), 3.4 (1H, m), 4.2 and 4.4 (2H, AB, J=13 Hz), 4.7 (1H, m), and 7.2 (5H, s).

To a suspension of 1.26 g of methyltriphenylphosphonium bromide in 20 ml of THF, 2.99 ml of 1.3 M butyllithium-hexane solution was added at 0 °C and the whole was stirred at room temperature for 30 min. A solution of 1.06 g of **17** in 20 ml of THF was added and the stirring was continued for 1 h. The TMS enol ethers **19** were unstable and were used immediately to a subsequent reaction without a further purification.

A solution of 615 mg (1 molar equivalent) of benzeneselenenyl chloride in 10 ml of THF was added to the mixture and the whole was stirred for 1 h when **19** disappeared (TLC check). After evaporating the solvent, the oily residue (1.28 g) containing a crude **21** was dissolved in 10 ml of CH_2Cl_2, 0.5 ml of pyridine was added and 1.9 ml of 15% aqueous H_2O_2 was added drop by drop under vigorous stirring at room temperature. After 25 min, 5 ml of CH_2Cl_2 and 6.2 ml of saturated $NaHCO_3$ were added and the mixture was stirred for 30 min. An organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was washed with 3M HCl, water, saline, and dried over anhyd Na_2SO_4. After the solvent had been evaporated, the residue was chromatographed with hexane-AcOEt (5 : 1) to give 404 mg of **20a** and **20b** (**20a**/**20b**=9.6/1.0). **20b**: ^{1}H NMR δ=4.38 (2H, s) and 6.00 (1H, d, J=9.6 Hz).

When 2 molar equivalents of benzeneselenenyl chloride were used, 18% of **24b** was obtained accompanied with 24% of a mixture of **21a** and **21b**, and 30% of unknown materials.

24b; Oil; ^{1}H NMR δ=1.2—2.7 (4H, m), 3.0—3.35 (1H, m), 3.35—3.55 (1H, m), 3.67 (1H, tt, J=11.0 and 5.0 Hz), 4.48 (2H, br. s), 4.76 (2H, s), 6.50 (1H, d, J=6.6 Hz), and 7.2—7.8 (10H, m); ^{13}C NMR δ=34.4(t), 37.0(t), 42.4(d), 53.9(d), 70.7(t), 71.1(d), 106.6(t), 126.5(s), 127.5(d), 128.3(d), 128.8(d), 129.6(d), 136.6(d), 136.9(s), 138.4(s), 146.1(d), 147.5(s), and 196.8(s).

Found: m/z 410.0787. Calcd for $C_{23}H_{22}O_2Se$: M, 410.0783.

7-*endo*-Benzyloxy-9-methylenebicyclo[3.3.1]nonan-2-one (22a). The TMS (**18**) or TBS (**19**) enolates were hydrolyzed by a usual method to give a mixture of saturated ketones **22a** and **22b**. From those 7-*endo*-benzyloxy-9-methylenebicyclo-[3.3.1]nonan-2-one (**22a**) was obtained by chromatography with benzene.

22a; Oil; ^{1}H NMR δ=2.5—3.1 (10H, m), 3.65 (1H, quint, J=3.0 Hz), 4.13 and 4.41 (2H, AB, J=11.4), 4.70 and 4.78 (2H, AB, J=2.0 Hz), and 7.25 (5H, s).

Found: m/z 256.1458. Calcd for $C_{17}H_{20}O_2$: M, 256.1462.

Benzeneselenenylation of 22a. To a solution of 0.25 mmol of LDA in 4 ml of THF, was added a solution of 64 mg of **22a** in 5 ml of THF at −78 °C and the mixture was stirred at room temperature for 30 min. Benzeneselenenyl chloride (54 mg) was added to the cooled (−78 °C) solution and the mixture was stirred at that temperature for 5 h. After had been warmed to 0 °C, a piece of ice was added and the solution was acidified, extracted with ether. The ether layer was washed with water, saline, and dried over anhyd Na_2SO_4. Evaporating the solvent and the chromatography of the residue with benzene-AcOEt (7 : 1) gave 44 mg (43%) of **21a** and 11 mg (11%) of **23a**.

21a; Oil; IR ($CHCl_3$) 1685, 1650, 1080br, and 895 cm^{-1}; ^{1}H NMR δ=1.5—3.0 (7H, m), 3.25 (1H, m), 3.65 (1H, m), 3.79 (1H, dd, J=7.6 and 2.0 Hz), 4.05 and 4.39 (2H, AB, J=12.0 Hz), 4.79 and 4.90 (2H, AB, J=1.8 Hz), and 7.1—7.6 (10 H, m).

23a; Mp 85—86 °C (from hexane); IR ($CHCl_3$) 1715 and 900 cm^{-1}; ^{1}H NMR δ=1.5—3.2 (9H, m), 3.72 (1H, m), 4.05 and 4.45 (2H, AB, J=12.0 Hz), 5.15 and 5.61 (2H, AB, J=1.8 Hz), and 7.1—7.8 (10H, m); ^{13}C NMR δ=25.1(t), 37.9(d), 39.1(t), 40.4(t), 42.5(t), 61.4(s), 69.7(t), 74.7(d), 112.0(t), 127.3—138.5 (Ph-X2), 150.1(s), and 210.2(s).

Found: C, 67.33; H, 5.94%. Calcd for $C_{17}H_{24}O_2Se$: C, 67.14; H, 5.88%.

7-*endo*-Benzyloxy-9-methylene-4-*exo*-phenylthiobicyclo-[3.3.1]nonan-2-one (25a). A) From **20a**. To a solution of 825 mg of the enone **20a** and 358 mg of thiophenol in 5 ml of chloroform at 0 °C was added 0.02 µl of triethylamine. The solution was stirred at room temperature for 6 h and was filtered through a short silica-gel column. The solvent was removed and the residue was recrystallized from hexane to give 1.11 g (94%) of a sulfide **25a**, mp 82.5—83 °C; IR (KBr) 1710, 1075, 1040, 915, 750, 735, 730, 695, and 685 cm^{-1}; ^{1}H NMR δ=1.54—1.98 (2H, m), 2.20 (1H, dd, J=16 and 8 Hz), 2.50—3.00 (4H, m), 2.73 (1H, dd, J=16 and 6 Hz). 3.69 (1H, br. s), 4.06 (1H, ddd, J=8, 6, and 1 Hz), 4.13 and 4.45 (2H, AB, J=11.6 Hz), 4.84 and 4.89 (2H, AB J=1.8 Hz), and 7.30 (5H, br. s).

Found: C, 75.85; H, 6.63%. Calcd for $C_{23}H_{24}O_2S$: C, 75.78; H, 6.63%.

B) From the mixture of **20a** and **20b**. Triethylamine (0.0035 µl) was added to the solution of 144 mg of **20** (**20a**/**20b**=3.5/1.0) and 0.064 ml of thiophenol in 1 ml of $CHCl_3$ and the mixture was stirred at room temperature for 6 h. The solvent was removed and the residue was chromatographed with hexane-AcOEt (5 : 1) and recrystallized from hexane to give 200 mg (97%) of **25a**. **20b** was recovered from the mother liquid.

7-*endo*-Benzyloxy-2,2-ethylenedioxy-9-methylene-4-*exo*-phenylthiobicyclo[3.3.1]nonane(26a). To a solution of 80 mg of TBSOTf in 40 ml of dichloromethane was added at −78 °C 934 mg of 1,2-bis(trimethylsiloxy)ethane[26] and 1.04 g of the sulfide **25a** successively. The solution was stirred for 4 h at −10 °C, and filtered through a short silica-gel column. The solvent was removed and chromatography of the residue with hexane-AcOEt (6 : 1) gave 1.07 g (93%) of an acetal **26a** as an oil: IR ($CHCl_3$) 1655, 1580, 1355, and 900 cm^{-1}; ^{1}H NMR δ=1.4—2.7 (5H, m), 3.05 (1H, dd, J=14.8 and 6.8 Hz), 3.4—3.7 (2H, m), 3.53 (1H, d, J=6.8 Hz), 3.6 (1H, m), 3.94 (4H, m), 4.31 and 4.58 (2H, AB, J=11.6 Hz), 4.84 and 4.97 (2H, AB, J=2.2 Hz), and 7.32 (10H, br. s.)

Found: m/z 408.1763. Calcd for $C_{25}H_{28}O_3S$: M, 408.1758.

7-*endo*-Benzyloxy-9-methylene-4-phenylthiobicyclo[3.3.1]-non-3-en-2-one(27a). To a solution of 680 mg of **26a** in 30 ml of CCl_4 was added 234 mg of NCS and 0.5 ml of water at a once and the suspension was stirred for 3 h. Filtration of the precipitates at room tempertature, evaporation of the solvent and chromatography of the residue with hexane-AcOEt (7 : 1) gave 537 mg (89%) of a vinyl sulfide **27a** as an oil; IR (CCl_4) 1660sh, 1650, 1580, 1080, and 900 cm^{-1}; ^{1}H NMR δ=1.8—2.2 (2H, m), 2.4—2.8 (2H, m), 3.17 (2H, br. s), 3.89 (1H, br. s), 4.37 and 4.47 (2H, AB, J=10.8 Hz), 4.84 (1H, s), 5.45 (1H, s), and 7.3 (10H, br. s).

Found: *m/z* 362.1346. Calcd for $C_{23}H_{22}O_2S$: M, 362.1339.

7-*endo*-Benzyloxy-9-methylenebicyclo[3.3.1]nonane-2,4-dione(2). To a solution of 500 mg of **27a** in 15 ml of ethanol, was added 15 ml of 25% aqueous KOH solution under argon and the solution was heated to reflux for 12 h. After had been cooled to room temperature, the whole was poured into ice-water. The solution was acidified, extracted with ether (100 ml×3). The extracts were dried over anhyd Na_2SO_4 and was concentrated to give a crude diketone **2** as crystals. Recrystallization from hexane-benzene (10 : 1) gave 343 mg (92%) of pure **2**; mp 91—91.5 °C; IR (CCl_4) 1720sh, 1710, 1235, 1080, 905, and 690 cm^{-1}; ^1H NMR δ=1.94 (2H, br. d, J=16.1 Hz), 2.65 (2H, br. d, J=15.2 Hz), 3.12 and 3.28 (2H, AB, J=17.9 Hz), 3.69 (1H, quint, J=5.4 Hz), 4.27 (2H, s), 5.02 (2H, s), and 7.25 (5H, br. s); ^{13}C NMR δ=38.8(t), 51.7(d), 55.3(t), 69.8(t), 72.2(d), 111.3(t), 127.4(d), 127.6(d), 128.5(d), 137.5(s), 145.2(s), and 205.1(s).

Found: C, 75.48; H, 6.68%. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

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