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THE TOTAL SYNTHESIS OF *dl*-CORIOLIN

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Abstract—The total synthesis of *dl*-coriolin has been accomplished via the key intermediate (5RS, 7SR) - 7 - *t* - butyldimethylsilyloxybicyclo[3.3.0]oct - 8 - en - 2 - one, starting from 1,3 - cyclooctadiene.

Coriolin (**1**), a metabolite of *Coriolus consors*, was isolated by Umezawa *et al.* 1969.[1] Its structure was determined in 1971[2a] and was confirmed by X-ray crystallographic analysis in 1974.[2b] The interesting antibacterial and antitumor activities[3] and the fascinating chemical structure possessing the highly functionalized *cis, anti, cis*-tricyclo[6.3.0.$0^{2,6}$]undecane ring system have stirred considerable interest into synthesis of **1**.

Very recently, three independent total syntheses of *dl*-coriolin (**1**) were communicated successively by Tatsuta *et al.*[4a] Danishefsky *et al.*[4b] and our group.[4c] Herein we wish to report a detailed account of the total synthesis of *dl*-coriolin (**1**).

Judging from a synthetic analysis of **1**, it appeared that the key problem in the total synthesis of **1** was the introduction of two hydroxy groups at C-7 and C-11 (coriolin numbering) on the tricyclic ring system with positional and stereochemical control. For the formation of a hydroxy group at C-11, we considered that the enone (**2**) should become a key intermediate. Further, the tricyclic enone (**3**), which could be synthesized from the enone (**2**), seemed to be a promising intermediate from which to form a hydroxy group at C-7. Scheme 1 outlines our synthesis approach.

Synthesis of (5RS,7SR) - 7 - t - butyldimethylsilyloxybicyclo[3.3.0]oct - 8 - en - 2 - one

In this section, the efficient synthesis of the enone (**2**), (5RS,7SR) - 7 - t - butyldimethylsilyloxybicyclo[3.3.0]oct - 8 - en - 2 - one, is described. In regard to the configuration of the silyloxy group at C-7, the stereocontrolled formation of the β-silyloxy group appeared to be unnecessary for the present purpose. However, the anticipation that the enone (**2**) should have broader applicability to the synthesis of other biologically important substances[b] than the isomer (**2'**), and that the conjugate addition of dimethylcopperlithium to the enone (**2**) should proceed more easily than to the isomer (**2'**),[c] prompted us to focus our attention on the stereocontrolled synthesis of the enone (**2**).[5]

For the stereocontrolled construction of the enone (**2**), (1SR,2RS,5RS)-bicyclo[3.3.0]oct - 7 - en - 2 - ol (**4**), obtainable efficiently from 1,3 - cyclooctadiene in two steps,[6] seemed to be a reasonable starting material. As a first attempt, the alcohol (**4**) was stereospecifically converted to the *endo*-epoxide (**5**)[d] by the Sharpless method[7] (catalytic amount of vanadyl acetylacetonate and 1.2 equiv of t-butyl hydroperoxide in benzene, reflux, 3 hr) in 70–75% yield, followed by oxidation with 8 equiv of Collins' reagent or 1.2 equiv of PCC[8] in methylene chloride at 0°C for 1 hr to afford the epoxyketone (**6**) in nearly quantitative yield. Transformation of **6** into the hydroxy-enone (**7**) was found to be the unexpectedly difficult step owing to instability of **7** even under weakly basic conditions. After many attempts, transformation could be best achieved by treatment of **6** with 10 equiv of sodium carbonate in water-t-butyl alco-

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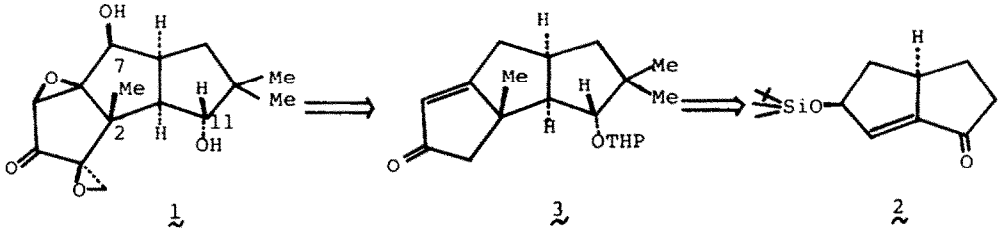
[b]The enone (**2**) was already converted to the biologically interesting prostacyclin analogs, see M. Shibasaki, K. Iseki and S. Ikegami, *Chemistry Letters* 1299 (1979); *Tetrahedron Letters* 169 (1979).

[c]The conjugate addition of dimethylcopperlithium might occur from the α-face of the enone (**2**) owing to the steric environment of the bicyclo[3.3.0]octenone system, therefore, it seemed advantageous for the silyloxy group to be disposed in the β-configuration.

[d]The stereochemistry of the *endo*-epoxide (**5**) was expected from mechanistic ground of the epoxidation, and finally confirmed by PMR spectrometry using the Eu shift reagent Eu(fod)$_3$ in comparison with that of the *exo*-epoxide.



Scheme 1.

hol (3:1, 80 ml/g) at room temperature for 4 hr in 50% yield based on the recovery of the starting epoxy-ketone (**6**; *ca.* 25% recovery). These unsatisfactory results, coupled with the modest yield[e] (60–70% yield) of protection of the hydroxy-enone (**7**) as *t*-butyldimethylsilyl ether,[9] prompted us to exploit another improved synthetic route applicable to practical scale synthesis of the enone (**2**).

The next synthetic strategy is based on the expectation that the bromohydrin from the bicyclo[3.3.0]octene ring system should be obtained in a stereo and regioselective manner.[10] Thus, the alcohol (**4**) underwent benzylation by treatment with sodium hydride and benzyl bromide in DMF to afford the benzyl ether (**8**) in nearly quantitative yield.[f] Then, the benzyl ether (**8**) was reacted with N-bromosuccinimide in DMSO-H_2O (50:1) at room temperature for 0.5 hr, resulting in the stereo and regiocontrolled formation of the expected bromohydrin (**9**), whose structure was established by the fact that the bromohydrin (**9**) could be converted to the enone (**2**) in excellent yield. Hence, this regio- and stereocontrolled formation of **9** is rationalized by considering that the kinetically controlled intermediary bromonium ion was attacked at the less hindered site.[11] The bromohydrin (**9**) was then protected as the t-butyldimethylsilyl ether in nearly quantitative yield, followed by hydrogenolysis over 5% Pd/C in methanol to give **11** in *ca.* 80% yield. Although this route appeared to be attractive for the construction of the enone (**2**), it occasionally suffered from concomitant deprotection of t-butyldimethylsilyl ether, affording the crystalline diol (**12**) as a major product. Therefore, an alternative route was exploited. Without protection of the hydroxy group, the bromohydrin (**9**) was directly hydrogenolyzed over 5% Pd/C in methanol to give the diol (**12**) in *ca.* 80% yield from **8**. Oxidation of bromohydrins such as **13** is sufficiently slow (probably due to the steric effect of the bromine)[g] that the ketone (**14**) should be expected to be obtained by position-controlled oxidation of the diol (**12**). Indeed, oxidation of the diol (**12**) with 3 equiv of PCC[8] in methylene chloride at room temperature for 3.5 hr gave the desired ketone (**14**) in accord with our anticipation. After protection of **14** as t-butyldimethylsilyl ether, the bromo-ketone (**15**) was subjected to dehydrobromination with 2 equiv of DBU in benzene at room temperature for 5 min to provide the enone (**2**) in *ca.* 80% yield from the diol (**12**).

Having established practical scale synthesis of **2**, the enone (**2**) is now available in sufficient quantity to pursue our synthetic studies toward coriolin (**1**).

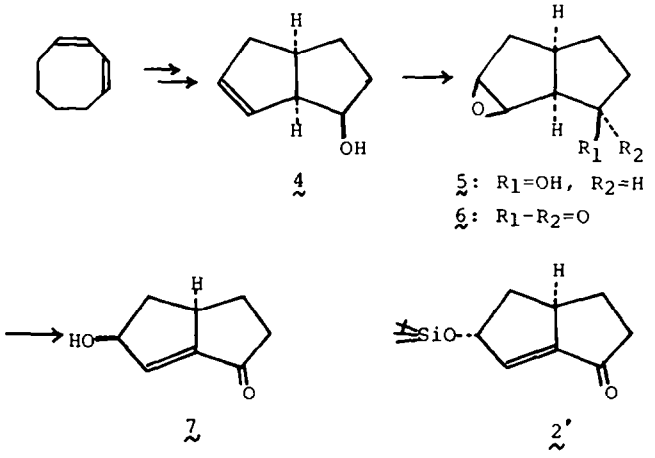
Synthesis of the Tricyclic Key Intermediate

First, in order to introduce suitable substituents into the enone (**2**) for the construction of the BC ring of coriolin (**1**), the enone (**2**) was subjected to dialkylation in THF using 2.2 equiv of potassium t-butoxide and 10 equiv of methyl iodide (−78°–0°). However, probably due to the instability of **2** under the strongly basic conditions, only a trace amount of the desired product (**16**) was obtained. Therefore, it seemed advantageous to introduce a methyl substituent to C-8 by the conjugate addition of dimethylcopperlithium prior to the dialkylation. The methyl-ketone (**17**) was obtained in 95% yield by treatment of **2** with dimethylcopperlithium in ether at −78°. The *exo*-configuration was tentatively assigned to the stereochemistry of the newly formed methyl substituent based upon our previous result.[5] The crucial regiocontrolled formation of the dimethyl substituents at C-3 appeared to be promising, since the enolate anion (**18**) should be thermodynamically unstable. Indeed, treatment of the methyl-ketone (**17**) with 2.2 equiv of potassium t-butoxide and 10 equiv of methyl iodide in THF (−78°–0°) gave the desired dialkylated product (**19**) regiospecifically in 77% yield. Fortunately none of products alkylated at the angular carbon was detected either by the PMR spectrum or by careful tlc analysis. Then, the ketone (**19**) was reduced with lithium in liquid ammonia to furnish a mixture of the *exo*-alcohol (**20**) and the *endo*-alcohol (**21**) in a ratio of *ca.* 5:2 (88% yield). The stereochemistry of **20** was anticipated from a

[e] The hydroxy-enone (**7**) was found to be relatively unstable even under the silylation conditions.[9] Protection of the hydroxy group of **7** as THP ether could be achieved in nearly quantitative yield. However, the conjugate addition of dimethylcopperlithium to the THP ether (**10**) provided the desired product only in modest yield.

[f] Without protection of the hydroxy group, the reaction afforded the desired bromohydrin in modest yield. Further the ketone, (1SR,5SR)-bicyclo[3.3.0]oct-7-en-2-one, as a substrate for the bromohydrin formation was found to be converted to the desired bromohydrin in less satisfactory yield than **4**.

[g] M. Yamazaki, M. Shibasaki and S. Ikegami, unpublished results.



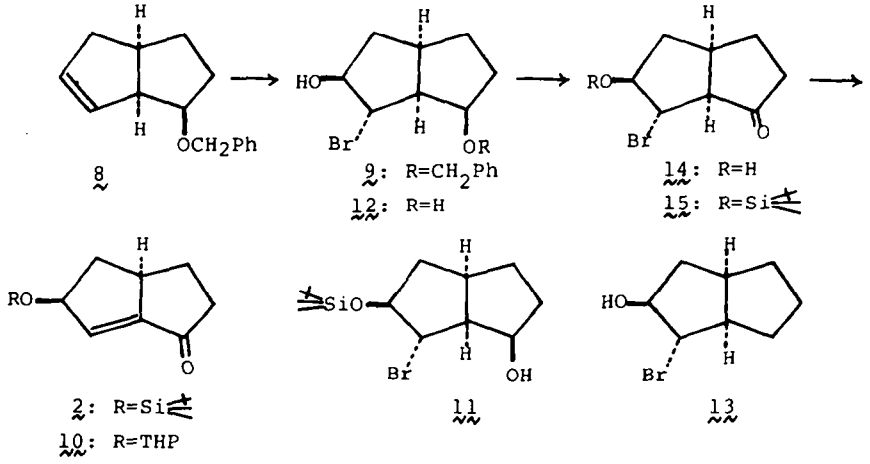
Scheme 2.

mechanistic consideration of the Li-NH_3 reduction and was confirmed by the fact that **20** could be successfully converted to coriolin (**1**). Under other reduction conditions (e.g. sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride), the *endo*-alcohol (**21**) was nearly exclusively formed.

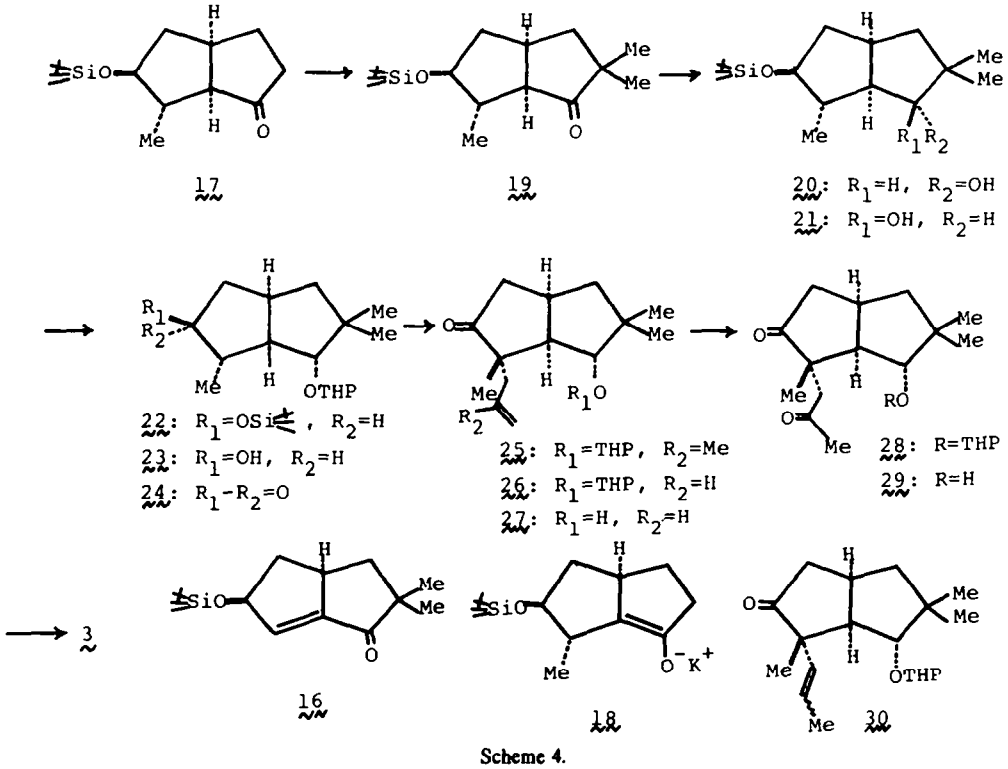
Various attempts to invert the useless alcohol (**21**) into **20** were unsuccessful probably due to steric hindrance around the hydroxy group; however, it was found that the *endo*-alcohol (**21**) could be recycled to the parent ketone (**19**) by oxidation with PDC in DMF[12] at room temperature for 10 hr in 70–75% yield. The *exo*-alcohol (**20**) was protected as tetrahydropyranyl ether to give **22**, which upon selective cleavage of the t-butyldimethylsilyl ether with fluoride ion, provided **23** in nearly quantitative yield. Subsequent oxidation of **23** with PCC[8] in the presence of sodium acetate furnished the ketone (**24**) in 90% yield.

A stereo- and regiocontrolled introduction of an acetonyl fragment at C-2 of the ketone (**24**) was attempted in preparation for the A ring annellation. Thus, the reaction of the ketone (**24**) with methallyl chloride[13] was carried out (NaH, DME, reflux, 2 hr), giving the desired product (**25**) in 45% yield. Although the regio and stereochemistry were well-controlled, the unsatisfactory yield prompted us to seek another way for the introduction of an acetonyl group to **24**.

It is well known that an allyl group can be easily transformed into an acetonyl functionality utilizing palladium chemistry.[14] Further, it is expected that reaction



Scheme 3.



Scheme 4.

with allyl bromide should provide a more satisfactory result than with methallyl chloride because of the higher reactivity of allyl bromide. With these considerations in mind, the ketone (**24**) was treated with 1.2 equiv of sodium hydride in DME at room temperature for 2 hr, followed by the addition of 10 equiv of allyl bromide. After stirring under the same conditions for an additional *ca.* 1.5 hr, we were gratified to find that the desired allyl-ketone (**26**) was exclusively obtained in 76% yield (94% yield based on the recovered starting material). The crucial stereo and regiochemistry of the obtained allyl-ketone (**26**), which could be anticipated from literature precedent,[13,15] was determined by the following facts; (a) **26** could be successfully converted into coriolin (**1**) and none of the isomers were not detected at the final stage of the present total synthesis; (b) the PMR spectrum of the deprotected allyl-ketone (**27**) displayed clean three singlets (δ 0.94, 1.02, 1.16) for the three independent methyl groups. The transformation of the allyl functionality of **26** to the acetonyl group was performed in 77% yield, together with a small amount of the isomerized product (**30**), by treatment with 0.3 equiv of palladium chloride and 1.6 equiv of cuprous chloride in DMF-H_2O (10:1.2) under oxygen atmosphere at room temperature for 24 hr.[14]

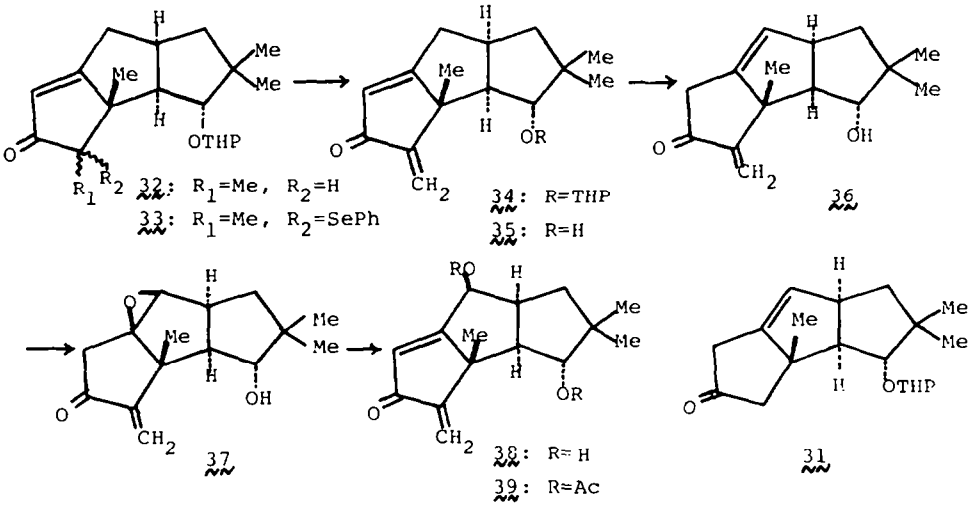
Further confirmation concerning the stereo and regiochemistry of the allyl-ketone (**26**) was obtained at this stage from the PMR spectrum of the deprotected ketone (**29**) which showed four clean singlets (δ 0.94, 1.07, 1.15, 2.11) assignable to the four different methyl groups.

The methyl-ketone (**28**) was then cyclized by treatment with 0.5 equiv of potassium t-butoxide in t-butyl alcohol at 35° for 10 min, providing the tricyclic enone (**3**), the other key synthetic intermediate, in 83% yield.

Synthesis of dl-Coriolin

In this final section, the challenging point is the introduction of a hydroxy group with β-orientation at C-7 (coriolin numbering). Toward this end, conversion of the tricyclic enone (**3**) to the β,γ-unsaturated isomer (**31**) was first attempted. Under the conditions developed by Ringold and Malhotra,[16] it was found that no deconjugation took place. After several attempts, treatment of the tricyclic enone (**3**) with potassium t-butoxide in DMSO at room temperature for *ca.* 10 min was found to afford the β,γ-unsaturated isomer (**31**), which could be isolated by silica gel column chromatography, in 20–30% yield (nearly quantitative yield based on the recovered starting tricyclic enone). Although the β,γ-unsaturated isomer (**31**) could be securely obtained using these deconjugation conditions, the unsatisfactory conversion to **31** prompted us to seek an alternative route. Thus, introduction of the C_3 α-methylene functionality to the cyclopentenone system (**3**), which definitely prevents the formation of the cross-conjugated enolate anion, was first carried out as follows.[17] The tricyclic enone (**3**) was alkylated in THF using 2.2 equiv of LDA and 10 equiv of methyl iodide (−78°–0°) to give the methyl ketone (**32**) as a mixture of stereoisomers in 78% yield. The mixture of stereoisomers of methyl ketone (**32**) was further treated with 2.2 equiv of LDA at −78° for 0.5 hr, followed by addition of 3 equiv of phenylselenenyl bromide (−78°–0°) to provide the selenide (**33**), which was directly oxidized with 30% hydrogen peroxide in THF containing a small amount of acetic acid at 0° for 0.5 hr, furnishing the α-methylene-enone (**34**). Without purification, **34** was deprotected with AcOH-H_2O-THF (3:1:1) to give **35** in *ca.* 50% yield from **32**.

With a sufficient amount of **35** in hand, the deconjugation reaction was again attempted. Thus, **35** was treated with 10 equiv of potassium t-butoxide in DME at room temperature for 1.5 hr, followed by rapid quenching with 10% acetic acid, and we were gratified to find that the deconjugation took place efficiently, affording the β,γ-unsaturated ketone (**36**) as a major product and **35** on the basis of tlc analysis. Without purification, a mixture of **36** and **35** were subjected to epoxidation with MCPBA in methylene chloride at 0° for 0.5 hr. Under these conditions, only the β,γ-unsaturated ketone (**36**) was converted to the β-epoxide (**37**), while **35** remained intact. The stereochemistry of the epoxide (**37**) was assigned as shown based upon the consideration that the undesired α-epoxide would provide an unacceptable *trans*-fusion between the A and B rings.[18] Direct treatment of a mixture of **37** and **35** with 2 equiv of DBU in benzene at 10° for 5 min provided the dihydroxy-α-



Scheme 5.

methylene-enone (**38**) in 29% overall yield from **35** (48% yield based on the 38% recovery of **35**).[h] The enone (**38**) was transformed into the diacetate (**39**), and its structure was confirmed by direct comparison with authentic material[i] prepared from naturally derived coriolin B.[4a]

Since the dihydroxy-α-methylene-enone (**38**) has already been converted into coriolin (**1**) by Tatsuta *et al.*[4a] and Danishefsky *et al.*[4b] this report formally constitutes an efficient stereocontrolled total synthesis of the interesting sesquiterpene, coriolin (**1**), and suggests that 1,3-cyclooctadiene will be a reasonable starting material for the synthesis of other polycyclopentanoids.

For biological studies, the synthesis of structurally related compounds of coriolin (**1**), utilizing the route described herein, is currently under investigation.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were measured on a Hitachi 215 grating infrared spectrophotometer. PMR spectra were recorded with a Varian EM360A NMR spectrometer or a Varian XL-100-12 NMR spectrometer in $CDCl_3$ soln with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained from a JEOL JMS-D300 mass spectrometer and high-resolution mass spectra from a JEOL JMS-01SG-2 mass spectrometer.

In general, reactions were carried out under argon atmosphere unless otherwise mentioned.

(1RS,5RS,8RS)-8-Benzyloxybicyclo[3.3.0]*oct-2-ene* **8**. Sodium hydride (60% dispersed in mineral oil, 4.4 g, 110 mM) was washed with pentane. A soln of (1RS,2SR,5RS)-bicyclo[3.3.0]oct-7-en-2-ol (**4**)[6] (12.4 g, 100 mM) in anhydrous DMF (6 ml) was dropwise added to a suspension of sodium hydride in anhydrous DMF (6 ml) at 0° and the reaction mixture was stirred at room temperature for 45 min, followed by the addition of benzyl bromide (20.5 g, 120 mM) in DMF (13 ml). After stirring at 50–60° for 1 hr, the reaction mixture was poured into ice–water, and extracted with benzene. The combined organic extracts were washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The oily residue was purified by silica gel column chromatography to give **8** (19.4 g, 91% yield) as a colorless oil: ν_{max} (film) 1600, 1500, 1455, 1360, 1110 cm^{-1}; δ (ppm) 1.10–3.03 (7H, m), 3.11–3.61 (1H, m), 3.78–4.25 (1H, m), 4.63 (2H, s), 5.64–6.03 (2H, m), 7.40 (5H, s); (*m/e*) 214 (M^+), 123, 91.79; *m/e* 214.1351 (calc. for $C_{15}H_{18}O_1$, 214.1358 parent peak).

(1SR,2RS,5RS,7SR,8SR)-8-Bromobicyclo[3.3.0]*octane-2,7-diol* **12**. To a stirred soln of **8** (4.60 g, 19.6 mM) in DMSO–H_2O (50:1) (12 ml) was added N-bromosuccinimide (7.20 g, 40.4 mM) at 0°, and then the soln was stirred at 0° for 5 min and for 0.5 hr at room temperature, followed by dilution with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford the crude bromohydrin, which was roughly purified by silica gel column chromatography (ether–petroleum ether 1:1), providing **9** (5.92 g). A suspension of **9** (5.92 g, 19.0 mM) and 10% Pd/C (2.24 g) in 112 ml of MeOH was vigorously stirred at room temperature under hydrogen for *ca.* 2 hr. The mixture was filtered and the filtrate was evaporated *in vacuo* to give a colorless solid, which was purified by silica gel column chromatography (ether–petroleum ether 5:1), affording the crystalline diol (**12**) (3.46 g, 80% yield from **8**): ν_{max} (Nujol) 3300 cm^{-1}; δ (ppm) 1.10–3.20 (10H, m), 4.30 (3H, m); MS (*m/e*) 223, 221 (M^+), 205, 203, 187, 185, 123, 105; m.p. 88–89° (recrystallized from ether).

(5RS,7SR)-7-t-Butyldimethylsilyloxybicyclo[3.3.0]*oct-8-en-2-one* **2**. To a stirred soln of the diol (**12**) (3.46 g, 15.7 mM) in anhydrous CH_2Cl_2 was added PCC (10.18 g, 47.4 mM) at room temperature and the resultant brown black suspension was stirred under the same conditions for 3.5 hr, followed by the addition of *ca.* 2 g of Florisil and 20 ml of ether. After stirring vigorously for *ca.* 15 min, the supernatant was decanted from the black gum. The insoluble residue was washed sedulously 3 times with 20 ml portions of ether. The combined organic soln was passed through a short pad of Florisil, and the solvent was evaporated *in vacuo* to yield the ketone (**14**) (3.11 g) as a pale yellow oil. To a stirred soln of **14** (3.11 g, 14.2 mM) in anhydrous DMF was added t-butyldimethylsilyl chloride (6.40 g, 42.6 mM) at 0°C, followed by the addition of imidazole (2.90 g, 42.6 mM). The reaction mixture was stirred at 0° for 0.5 hr and at room temperature for an additional 1.5 hr. After evaporation of DMF *in vacuo*, ethyl acetate was added to the residual oil. The organic soln was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford **15**, which was further dissolved in 20 mL of benzene. After the addition of DBU (4.3 mL, 28.4 mM) to the benzene soln, the resultant white suspension was stirred at room temperature for 5 min, followed by the addition of saturated NH_4Cl aq. After separation of the benzene layer, the residual aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the crude enone (**2**), which was purified by silica gel column chromatography (ether–petroleum ether 1:4), yielding the enone (**2**) (3.17 g, 80% yield from **12**) as a pale yellow oil: ν_{max} (film) 1720, 1640, 1015 cm^{-1}; δ (ppm) 0.08 (6H, s), 0.90 (9H, s), 1.02–3.30 (7H, m), 5.17 (1H, m), 6.31 (1H, m); MS (*m/e*) 252 (M^+), 195, 75, 73, 57; *m/e* 252.1526 (calc. for $C_{14}H_{24}O_2Si_1$, 252.1546 parent peak).

(1RS,5RS,7SR,8SR)-7-t-Butyldimethylsilyloxy-8-methylbicyclo[3.3.0]*octan-2-one* **17**. An ethereal soln of methyllithium (18.6 mL, 20.8 mM) was added to a magnetically stirred suspension of CuI (2.09 g, 10.39 mM) in anhydrous ether (10 ml) at −78°. The mixture was then stirred at 0° for 20 min, and again cooled to −78°. To the dimethylcopperlithium soln was added the enone (**2**; 1.87 g, 7.42 mM) in anhydrous ether (10 ml), and the reaction mixture was stirred under the same conditions for 15 min and then without a cooling bath for 10 min. After addition of saturated NH_4Cl aq, the aqueous layer was extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the oily residue, which was purified by silica gel column chromatography, providing the methyl ketone (**17**; 1.89 g, 95% yield) as a colorless oil: ν_{max} (film) 1740, 1260, 1115, 835, 780 cm^{-1}; δ (ppm) 0.04 (6H, s), 0.85 (9H, s), 0.99 (3H, d, J = 7Hz), 1.28–2.56 (8H, m), 2.77 (1H, m), 3.77 (1H, m); MS (*m/e*) 269 (M^+), 212, 211, 57; *m/e* 211.1198 (calc. for $C_{11}H_{19}O_2Si_1$, 211.1154 P-t-Bu).

(1RS,5RS,7SR,8SR)-7-t-Butyldimethylsilyloxy-3,3,8-trimethylbicyclo[3.3.0]*octan-2-one* **19**. To a stirred suspension of potassium t-butoxide (90%, 960 mg, 7 mM) in anhydrous THF (10 ml) was added the methyl ketone (**17**) (940 mg, 3.51 mM) in anhydrous THF (20 ml) at −78°. After stirring for 10 min under the same conditions, methyl iodide (2.4 ml, 39 mM) was added, and the whole reaction mixture was gradually warmed to 0°. After additional stirring for 10 min at 0°, the reaction was quenched by the addition of saturated NH_4Cl aq, followed by extraction with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:8) to yield the dimethylated product (**19**) (779 mg, 77% yield) as a colorless oil: ν_{max} (film) 1740, 1115, 840 cm^{-1}; δ (ppm) 0.02 (6H, s), 0.86 (9H, s), 1.02 (3H, d, J = 7Hz), 1.03 (3H, s), 1.06 (3H, s), 1.19–2.49 (6H, m), 2.67 (1H, m), 3.79 (1H, m); MS (*m/e*) 295 ($M^+ - 1$), 281, 253, 240, 239, 221, 171, 159; *m/e* 295.2101 (calc. for $C_{17}H_{31}O_2Si_1$, 295.2094 P-1).

(1RS,2RS,5RS,7SR,8SR)-7-t-Butyldimethylsilyloxy-3,3,8-trimethylbicyclo[3.3.0]*octan-2-ol* **20**. Lithium wire (500 mg) cut into small pieces, was added in one portion to anhydrous liquid ammonia (150 ml), followed by the addition of **19** (1.926 g, 6.51 mM) in anhydrous THF (5 mL). After stirring for *ca.* 4 hr, ammonia was evaporated to give the residue, to which was added

[h]The β,γ-unsaturated ketone (**36**) was found to isomerize gradually to **35** during its work-up. We think that it will be possible to improve the efficiency of the conversion to **38** using careful work-up conditions.

[i]An authentic material was kindly supplied by Prof. K. Tatsuta, Keio University.

saturated NH_4Cl aq. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:8). The *exo*-alcohol (**20**; 1.235 g) was obtained as a colorless oil: ν_{max} (film) 3400, 1465, 1260, 1115, 875, 840, 775 cm^{-1}; δ (ppm) 0.03 (6H, s), 0.86 (3H, s), 0.88 (9H, s), 0.98 (3H, s), 0.99 (3H, d, J = 7Hz), 1.10–2.18 (7H, m), 2.18–2.76 (1H, m), 3.60–3.90 (2H, m); MS (*m/e*) 299 ($M^+ + 1$), 298 (M^+), 297 ($M^+ - 1$), 241, 225, 73; *m/e* 297.2224 (calc. for $C_{17}H_{33}O_2Si$, 297.2251 P-1); R*f* 0.26 (petroleum ether–ether, 4:1, silica gel), and further *endo*-alcohol (**21**) was obtained (468 mg) as a colorless oil: ν_{max} (film) 3460, 1470, 1265, 1120, 885, 840, 780 cm^{-1}; δ (ppm) 0.10 (6H, s), 0.88 (3H, s), 0.92 (9H, s), 0.93 (3H, d, J = 7 Hz), 1.05 (3H, s), 1.20–2.94 (7H, m), 3.30–3.54 (1H, m), 3.73 (1H, broad d, J = 10 Hz), 3.94 (1H, m); MS (*m/e*) 299 ($M^+ + 1$), 241, 223, 81 *m/e* 299.2415 (calc. for $C_{17}H_{35}O_2Si$, 299.2408 P + 1); R_f 0.43 (petroleum ether–ether, 4:1, silica gel).

Oxidation of (1*RS*,2*SR*,5*RS*,7*SR*,8*SR*) - 7 - *t* - *Butyldimethylsilyloxy* - 3,3,8 - *trimethylbicyclo*[3.3.0]*octan* - 2 - *ol* **21** *to* **19**. To a stirred soln of pyridinium dichromate (3.50 g, 9.31 mM) in anhydrous DMF (5 ml) was added the *endo*-alcohol (**21**) (400 mg, 1.34 mM) in anhydrous DMF (2 ml) at 0°. The black brown suspension was stirred under the same conditions for 6 hr and was followed by the addition of water. The resultant aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford the oily residue, which was purified by silica gel column chromatography. The ketone (**19**; 300 mg, 75% yield) was obtained; comparison with an authentic sample showed that the materials were identical in every respect (IR, PMR, MASS, tlc).

(1*RS*,2*RS*,5*RS*,7*SR*,8*SR*) - 7 - *t* - *Butyldimethylsilyloxy* - 2 - (*tetrahydro* - 2 - *pyranyloxy*) - 3,3,8 - *trimethylbicyclo*[3.3.0]*octane* **22**. To a stirred soln of **20** (358 mg, 1.20 mM) in anhydrous CH_2Cl_2 (3 ml) was added freshly distilled dihydropyran (0.55 ml, 6.00 mM) at 0°, followed by the addition of a catalytic amount of p-toluenesulfonic acid. The reaction mixture was stirred under the same conditions for 20 min, and was quenched by the addition of saturated $NaCHO_3$ aq, followed by extraction with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:10) to yield **22** (445 mg, 97% yield) as a colorless oil: ν_{max} (film) 1470, 1260, 1140, 1120, 1080, 1040, 840, 780 cm^{-1}; δ (ppm) 2.26–2.72 (1H, m), 3.30–4.10 (4H, m), 4.54–4.80 (1H, m); MS (*m/e*) 382 (M^+), 325, 297, 159, 149, 107, 85, 75, 73; *m/e* 382.2893 (calc. for $C_{22}H_{42}O_3Si$, 382.2905 parent peak).

(1*RS*,2*SR*,3*SR*,5*RS*,8*RS*) - 8 - (*Tetrahydro* - 2 - *pyranyloxy*) - 2,7,7 - *trimethylbicyclo*[3.3.0]*octan* - 3 - *ol* **23**. A mixture of **22** (412 mg, 1.08 mM) and n-$Bu_4N^+F^-$ (850 mg, 3.26 mM) in anhydrous THF (5 ml) was stirred at room temperature for 20 hr, followed by evaporation of THF *in vacuo*, to which was added saturated NH_4Cl aq. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:1). The alcohol (**23**; 274 mg, 94% yield) was obtained as a colorless oil: ν_{max} (film) 3400, 1020 cm^{-1}; δ (ppm) 3.33–4.27 (5H, m), 4.71 (1H, m); MS (*m/e*) 268 (M^+), 250, 149; *m/e* 268.2039 (calc. for $C_{16}H_{28}O_3$, 268.2039 parent peak).

(1*RS*,2*SR*,5*RS*,8*RS*) - 8 - (*Tetrahydro* - 2 - *pyranyloxy*) - 2,7,7 - *trimethylbicyclo*[3.3.0]*octan* - 3 - *one* **24**. A suspension of the alcohol (**23**) (651 mg, 2.43 mM), sodium acetate (100 mg, 1.21 mM) and pyridinium chlorochromate (1.31 g, 6.08 mM) in anhydrous CH_2Cl_2 (12 ml) was stirred at room temperature for 6 hr, followed by the addition of ether. The supernatant was decanted from the black gum, and the insoluble residue was washed thoroughly with ether. The combined organic layers were washed with saturated $NaHCO_3$ aq and then brine, and dried over $MgSO_4$. Evaporation of the dried solvent *in vacuo* afforded the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:1) to yield the ketone (**24**) (607 mg, 94% yield) as a colorless solid.[†] ν_{max} ($CHCl_3$) 1740, 1035 cm^{-1}; δ (ppm) 3.34–4.04 (3H, m), 4.48–4.74 (1H, m); MS (*m/e*) 266 (M^+), 182, 165, 86; *m/e* 266.1876 (calc. for $C_{16}H_{26}O_3$, 266.1883 parent peak).

(1*RS*,2*SR*,5*RS*,8*RS*) - 2 - *Allyl* - 8 - (*tetrahydro* - 2 - *pyranyloxy*) - 2,7,7 - *trimethylbicyclo*[3.3.0]*octan* - 3 - *one* **26**. To NaH (60% dispersed in mineral oil, 105 mg, 2.63 mM) which was washed with pentane, was added the ketone (**24**) (694 mg, 2.61 mM) in anhydrous DME (5 ml) at 0°. The suspension was stirred at room temperature for 2 hr, followed by the addition of allyl bromide (2.3 ml, 26.6 mM) at 0°. The whole reaction mixture was then stirred at room temperature for an additional 1.5 hr, and was quenched by the addition of saturated NH_4Cl aq. The resultant aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried soln ($MgSO_4$) *in vacuo* gave the oily residue which was purified by silica gel column chromatography (ether–petroleum ether 1:6) to yield the allyl ketone (**26**; 612 mg, 76% yield) as a colorless oil: ν_{max} (film) 1730, 1640, 1030, 915 cm^{-1}; δ (ppm) 3.24–4.18 (3H, m), 4.38–4.78 (1H, m), 4.88–5.20 (2H, m), 5.40–6.00 (1H, m); MS (*m/e*) 306 (M^+), 288, 265, 222, 204, 181, 86; *m/e* 306.2188 (calc. for $C_{19}H_{30}O_3$, 306.2196 parent peak) and further the starting ketone (**24**; 132 mg, 19% recovery). In order to obtain the clean PMR spectrum, **26** was deprotected with AcOH–H_2O–THF (3:1:1) at room temperature for 12 hr. After purification by silica gel column chromatography, the PMR spectrum of **27** was measured: δ (ppm) 0.94 (3H, s), 1.02 (3H, s), 1.16 (3H, s), 1.38–2.92 (9H, m), 3.20–3.54 (1H, m), 4.94–5.20 (2H, m), 5.40–5.98 (1H, m).

(1*RS*,2*SR*,5*RS*,8*RS*) - 8 - (*Tetrahydro* - 2 - *pyranyloxy*) - 2,7,7 - *trimethyl* - 2 - (2 - *oxopropyl*)*bicyclo*[3.3.0]*octan* - 3 - *one* **28**. A suspension of CuCl (325 mg, 3.28 mM) and $PdCl_2$ (117 mg, 0.66 mM) in DMF–H_2O (3.3–0.4 ml) was stirred at room temperature for 2 hr under oxygen, and then the suspension was added in one portion to the allyl ketone (**26**; 612 mg, 2.00 mM). The reaction mixture was stirred at room temperature for 24 hr under oxygen, and was poured into 3N HCl aq, followed by extraction with CH_2Cl_2. The combined organic extracts were successively washed with saturated $NaHCO_3$ aq and brine, dried over $MgSO_4$, and evaporated *in vacuo* to afford the oily residue. Since a portion of the products was hydrolyzed in the reaction medium and/or at the work-up stage, the crude reaction mixture was subjected to protection as THP ether as follows. To a stirred soln of the crude reaction products and dihydropyran (0.90 ml, 9.86 mM) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of p-toluenesulfonic acid at 0°, and the reaction mixture was stirred under the same conditions for 20 min. The reaction was quenched by the addition of saturated $NaHCO_3$ aq, followed by extraction with ether. The combined ether extracts were washed with brine. Concentration of the dried soln ($MgSO_4$) afforded the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:2) to yield the ketone (**28**; 495 mg, 77% yield) as a colorless oil: ν_{max} (film) 1740, 1715, 1370, 1160, 1140, 1080, 1030, 980, 685 cm^{-1}; δ (ppm) 2.10 (3H, s), 3.32–4.12 (3H, m), 4.50–4.76 (1H, m);; MS (*m/e*) 322 (M^+), 279, 254, 238, 220, 84; *m/e* 322.2148 (calc. for $C_{19}H_{30}O_4$, 322.2145 parent peak) and further **30** (81 mg, 13% yield) as a colorless oil: ν_{max} (film) 1740, 1035 cm^{-1}; δ (ppm) 3.25–4.10 (3H, m), 4.38–4.80 (1H, m), 5.24–5.75 (2H, m); MS (*m/e*) 306 (M^+), 238, 222, 204, 69; *m/e* 306.2193 (calc. for $C_{19}H_{30}O_3$, 306.2196 parent peak). In order to obtain the clean PMR spectrum, the ketone (**28**) was deprotected with AcOH–H_2O–THF (3:1:1) at room temperature for 12 hr. After purification by silica gel column chromatography, the PMR spectrum of **29** was measured: δ (ppm) 0.94 (3H, s), 1.07 (3H, s), 1.15 (3H, s), 2.11 (3H, s), 1.62–3.12 (9H, m), 3.71 (1H, m).

(1*SR*,2*RS*,3*RS*,6*SR*) - 3 - (*Tetrahydro* - 2 - *pyranyloxy*) - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undec* - 8 - *en* - 10 - *one* **3**. A soln of the ketone (**28**; 495 mg, 1.54 mM) and potassium t-butoxide (90%, 96 mg, 0.77 mM) in anhydrous t-butyl alcohol (5 ml) was stirred at 35° for 10 min, and was quenched by the addition of saturated NH_4Cl aq. The aqueous layer was extracted with ether, and the

[†]The m.p. was not measured because of the presence of the diastereomeric isomer introduced during the preparation of the THP ether.

combined ether extracts were washed with brine. Concentration of the dried soln ($MgSO_4$) afforded the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:1) to yield the tricyclic enone (**3**) in 83% yield as a colorless oil: ν_{max} (film) 1710, 1640, 1035 cm^{-1}; δ (ppm) 3.34–4.04 (3H, m), 4.60 (1H, m), 5.69 (1H, broad s); MS (*m/e*) 304 (M^+), 276, 220, 192, 163, 111, 85, 78; *m/e* 304.2031 (calc. for $C_{19}H_{28}O_3$, 304.2039 parent peak).

(1*RS*,2*RS*,3*RS*,6*SR*) - 3 - (*Tetrahydro* - 2 - *pyranyloxy*) - 1,4,4,11 - *tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undec* - 8 - *en* - 10 - *one* **32**. To a stirred soln of diisopropylamine (0.14 ml, 1.00 mM) in anhydrous THF (3 ml) was added n-BuLi (1.5 M, 0.67 ml) at −78°C, and the mixture was stirred under the same conditions for 10 min and without a cooling bath for 10 min. The soln was again chilled to −78°, followed by the addition of the tricyclic enone (**3**; 139 mg, 0.46 mM) in anhydrous THF (1 ml). After stirring for 10 min, CH_3I (0.30 ml, 4.82 mM) was added, and the mixture was gradually warmed to 0° over 30 min and was then quenched by the addition of saturated NH_4Cl aq, followed by extraction with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:3) to yield the methyl-enone (**32**; 114 mg, 78% yield) as a colorless oil (a mixture of the stereoisomers): ν_{max} (film) 1705, 1640, 1080, 1030 cm^{-1}; δ (ppm) 3.32–4.10 (3H, m), 4.48–4.76 (1H, m), 5.62 (1H, broad s); MS (*m/e*) 318 (M^+), 234, 206, 177, 111, 85; *m/e* 318.2193 (calc. for $C_{20}H_{30}O_3$, 318.2193 parent peak).

(1*SR*,2*RS*,3*RS*,6*SR*) - 3 - *Hydroxy* - 11 - *methylene* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undec* - 8 - *en* - 10 - *one* **35**. To a stirred soln of LDA in THF (1.3 ml, 0.32 mM) was added the methyl-enone (**32**) (47 mg, 0.15 mM) in anhydrous THF (1 ml) at −78°, and the soln was stirred under the same conditions for 30 min, followed by the addition of phenylselenenyl bromide in THF (0.48 mM, 0.20 ml). Stirring at −78° was continued for 2 hr, and the reaction mixture was then gradually warmed to 0° over 60 min, and was quenched by the addition of saturated NH_4Cl aq. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried soln ($MgSO_4$) afforded the oily residue, which was roughly purified by silica gel column chromatography (ether–petroleum ether 1:2) to yield the selenide (**33**; 53 mg). To a stirred soln of the roughly purified selenide (**33**; 53 mg) in THF (0.60 ml) containing glacial acetic acid (17 μL) was gradually added 30% H_2O_2 aq (80 μL) at 0°. The reaction mixture was stirred under the same conditions for 30 min and then for 1 hr at room temperature, followed by addition of saturated $NaHCO_3$ aq. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried soln ($MgSO_4$) afforded the oily residue, to which was added AcOH–H_2O–THF (3:1:1) (0.5 ml). The soln was stirred at room temperature for 20 hr, followed by evaporation of the solvents *in vacuo* to give the oily residue, which was dissolved in ether. The ether layer was successively washed with saturated $NaHCO_3$ aq and brine. Concentration of the dried soln ($MgSO_4$) afforded the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 3:1) to yield **35** (17 mg, 50% yield from **32**) as a colorless oil; ν_{max} (film) 3440, 1690, 1645, 1620, 680 cm^{-1}; δ (ppm) 0.93 (3H, s), 1.09 (3H, s), 1.28 (3H, s), 1.47–3.02 (7H, m), 3.89 (1H, broad d, J = 8 Hz), 5.37 (1H, s), 5.91 (2H, s); MS (*m/e*) 232 (M^+), 214, 199, 122, 111, 78; *m/e* 232.1467 (calc. for $C_{15}H_{20}O_2$, 232.1464 parent peak).

(1*SR*,2*RS*,3*RS*,6*SR*,7*SR*) - 3,7 - *Dihydroxy* - 11 - *methylene* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undec* - 8 - *en* - 10 - *one* **38**. To a stirred soln of potassium t-butoxide (90%, 100 mg, 0.80 mM) in anhydrous DME (1 ml) was added **35** (16 mg, 0.069 mM) in DME (1 ml) at −78°, and the reaction mixture was stirred at room temperature for 1.5 hr, and was then quenched by the rapid addition of 10% aqueous acetic acid, followed by addition of saturated $NaHCO_3$ aq. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, and dried over $MgSO_4$. Concentration of the dried soln *in vacuo* on an ice-cold bath gave the oily residue, which contained the β,γ-unsaturated ketone (**36**) and **35**. A mixture of the crude oily residue and m-chloroperbenzoic acid (70%, 17 mg, 0.069 mM) in anhydrous CH_2Cl_2 (2.5 ml) was stirred at 0° for 1 hr, followed by dilution with ether. The organic layer was successively washed with saturated Na_2SO_3 aq, saturated $NaHCO_3$ aq and brine. Concentration of the dried soln ($MgSO_4$) afforded the oily residue, which contained the β-epoxide (**37**) and **35**. To a stirred soln of the crude oily residue in benzene (1 ml) was added DBU (30 mg, 0.20 mM) at 0°, and the reaction mixture was stirred under the same conditions for 20 min, and was then quenched by the addition of saturated NH_4Cl aq. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried soln ($MgSO_4$) gave the oily residue, which was purified by silica gel column chromatography (ether) to yield **38** (5 mg, 29% yield, 48% yield based on the recovery of **35**) as an oil: ν_{max} (film) 3400, 1690, 1620 cm^{-1}; δ (ppm) 0.94 (3H, s), 1.13 (3H, s), 1.16 (3H, s), 1.40–2.90 (6H, m), 3.90 (1H, broad d, J = 9 Hz), 4.69 (1H, d, J = 6 Hz), 5.38 (1H, s), 5.96 (1H, s), 6.06 (1H, s); MS (*m/e*) 248 (M^+), 230, 215; *m/e* 248.1416 (calc. for $C_{15}H_{20}O_3$, 248.1413 parent peak) and **35** (6 mg, 38% recovery).

(1*SR*,2*RS*,3*RS*,6*SR*,7*SR*) - 3,7 - *Diacetoxy* - 11 - *methylene* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undec* - 8 - *en* - 10 - *one* **39**. A mixture of **38** (5.0 mg, 0.020 mM), Ac_2O (15 μL, 0.16 mM) and a catalytic amount of 4-dimethylaminopyridine in pyridine (0.1 ml) was stirred at room temperature for 2 hr, followed by dilution with ether. The ether layer was successively washed with saturated $CuSO_4$ aq and water, and dried over $MgSO_4$. Concentration of the dried soln afforded the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether 1:2) to yield the diacetate (**39**) (6.5 mg, 98% yield) as a colorless crystalline solid: ν_{max} ($CHCl_3$) 1740, 1735, 1700, 1627 cm^{-1}; δ (ppm) 1.00 (3H, s), 1.09 (3H, s), 1.47 (3H, s), 1.51–1.73 (2H, m), 2.13 (6H, s), 2.38 (1H, dd, J = 12 Hz, 8 Hz), 2.75–3.28 (1H, m), 5.17 (1H, s), 5.27 (1H, d, J = 8 Hz), 5.63 (1H, d, J = 7 Hz), 5.95 (1H, s), 6.18 (1H, s); MS (*m/e*) 332 (M^+), 290, 230, 212, 202, 187, 136; m.p. 71–74° (recrystallized from benzene–ether). These spectral data were superimposable on those of an authentic material.[f] Further, tlc analysis using four solvent systems showed that the diacetate (**39**) synthesized here is identical with authentic material.[f]

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