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Construction of AB-Ring System of Taxane Framework by A-Ring Annulation Strategy: Synthesis of 1-Hydroxy-8,11,11-trimethylbicyclo-[5.3.1]undec-7-en-9-one by Way of Intramolecular Aldol Cyclization to Form the C1–C10 Bond

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Construction of the AB-ring system of the taxane framework *via* an A-ring annulation strategy was demonstrated by base-mediated intramolecular aldol reaction of (*Z*)-2,2-dimethyl-3-(1-methyl-2-oxopropylidene)cyclooctanone, affording the title compound, 1-hydroxy-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-9-one. A cyclization precursor, the tetra-substituted (*Z*)-alkene, was prepared from the corresponding cyclooctanone derivative, 3-[(α,α-dimethylbenzyl)dimethylsiloxy]-2,2-dimethylcyclooctanone *via* a bicyclic α,β-unsaturated lactone intermediate.

Key words taxane AB-ring system; A-ring annulation strategy; intramolecular aldol reaction; 1-hydroxy-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-9-one; tetra-substituted alkene; bicyclic lactone

Taxol is one of the most promising antineoplastic agents currently available.[1,2] Several other natural taxanes were recently found to be inhibitors of P-glycoprotein, which is involved in multidrug resistance in tumor cells.[3] Even before these important biological activities of taxanes were known, taxane diterpenes had been popular targets of synthetic studies in natural products chemistry, since they have a complex core structure consisting of an eight-membered ring carbocycle and peripheral rings.[4]

As shown in Fig. 1, our strategy for the synthesis of taxol and related compounds is based on the initial preparation of an eight-membered carbocyclic compound corresponding to the B-ring of taxanes, followed by construction of the C-ring and the A-ring on this framework.[5] Preparation of a cyclooctane derivative and its conversion to a bicyclic intermediate corresponding to the BC-ring system of taxol were reported from our laboratory.[6] However, the subsequent step of constructing the A-ring on these precursors involves some difficult problems and only a reductive coupling of diketone using lower-valent titanium gave a successful result.[7,8] Since the above method has limitations as regards scale-up and so on, development of a general method for A-ring annulation utilizing the aldol reaction was selected as a target in our synthetic program on taxanes.

A few examples of A-ring annulation of cyclooctanone derivatives have been reported, but none of the resulting systems has an oxygenated function at the C-1 position, which corresponds to the basic skeleton of taxol, except Magnus' cyclized compound and our previously reported bicyclic and tricyclic compounds.[7–9]

We considered that aldol reaction is an effective tool in A-ring annulation, as shown in Fig. 2. Conversion of a 1,5-dicarbonyl compound to the *tert*-butyldimethylsilyl

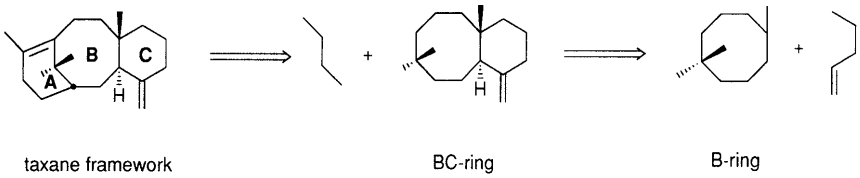

Fig. 1. Synthetic Strategy for the Taxane Framework

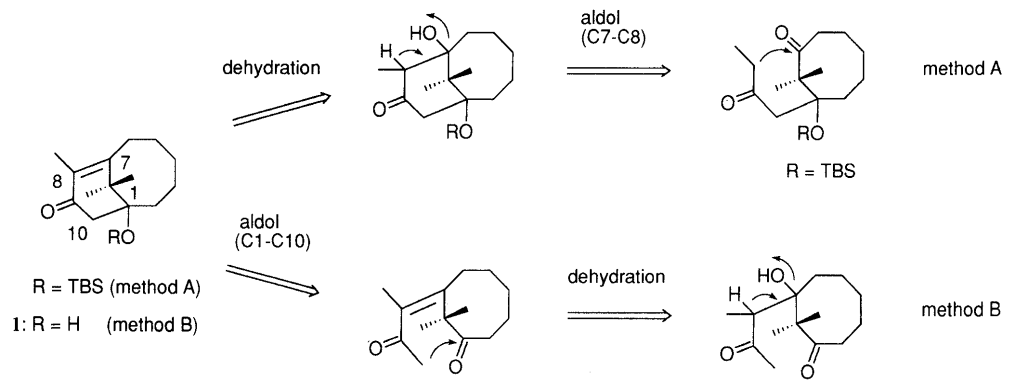

Fig. 2. A-Ring Annulations by Aldol Reaction

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(TBS) ether of the title compound **1** was tried first *via* ring closure and successive dehydration to form the C7–C8 double bond (method A). The resulting bicyclic compound has a similar enone structure to that of the A-ring of some naturally occurring taxanes and a synthetic intermediate of taxol reported independently by Nicolaou *et al.* and by Danishefsky *et al.*[10]

Since the precursor employed in method A for cyclization contains three active methylene sites which exhibit similar acidities, the following side reactions readily took place; that is, undesirable C6–C9 aldol cyclization affording a bicyclo[4.2.2]decane system and β-elimination of the C1 oxygenated function competing with cyclization and also with dehydration. Consequently, the desired product **1** was not obtained in a reasonable yield.[7]

Thus, an alternative A-ring annulation strategy (Fig. 2, method B) was planned by choosing the cyclooctanone derivative **2** having a C7–C8 double bond as a starting material to achieve the formation of the C1–C10 single bond of **1** by aldol reaction. As a precursor of cyclization, **2** is entropically advantageous compared to that of method A because the nucleophilic center of the acetyl methyl (C10) comes close to the cyclooctanone carbonyl (C1) owing to the influence of the tetra-substituted alkene structure (C7–C8) which is introduced prior to cyclization. Therefore, the intramolecular cyclization of **2** should occur *via* the favored aldol reaction without any of the side reactions mentioned above.

In this paper, we would like to describe the preparation of the dicarbonyl compound **2** and its aldol cyclization leading to the bicyclic AB-ring system of the taxane model compound 1.

Synthetic Plan (Chart 1) The synthetic plan for the 1,5-diketone **2**, a precursor of the cyclization, is outlined in Chart 1. The methyl ketone part of **2** was formed *via* addition of one carbon to the ester carbonyl of the α,β-unsaturated lactone **3**. The fully substituted alkene part of **3** with the desired geometry was constructed by dehydration of the bicyclic β-hydroxylactone **4**. The lactone **4** was obtained from the eight-membered carbocycle **6** by introducing a three-carbon unit, followed by lactone formation.

Introduction of the A-Ring Segment onto the Cyclooctanone 6 (Chart 2)[11] The introduction of a three-carbon unit onto the cyclooctanone **6** was achieved by using vinyl metal in the presence of cerium(III) chloride, while no adduct was obtained with the lithium enolate prepared from methyl propionate.[7,12] Addition of isopropenylmagnesium bromide to the cyclooctanone **6** proceeded smoothly to afford an isomeric mixture of allyl alcohols **5a** and **5b** in high yield (94%) with a ratio of 5/2.[13] The relative stereochemistry of **5a** was confirmed to be *cis* by the following transformations; 1) removal of the silyl protecting group with tetrabutylammonium fluoride (TBAF) and 2) silylene acetalization of the resulting 1,3-diol using dichlorodimethylsilane and imidazole. On the other hand, the desilylation product of the other isomer **5b** did not form such a silylene bridge, indicating that **5b** has a *trans* configuration. Subsequent hydroboration of a mixture of **5a** and **5b** proceeded stereoselectively and after chromatographic separation, the corresponding diols **7a** and **7b** were obtained as major products, together with small amounts of their epimers at the newly formed chiral center of the side chain. Relative stereochemistry was

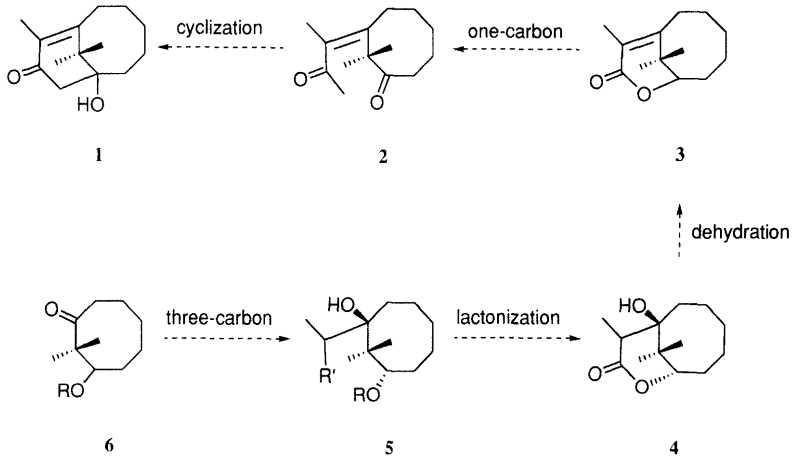
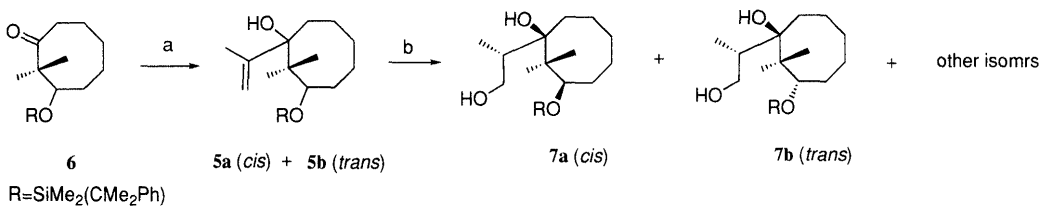
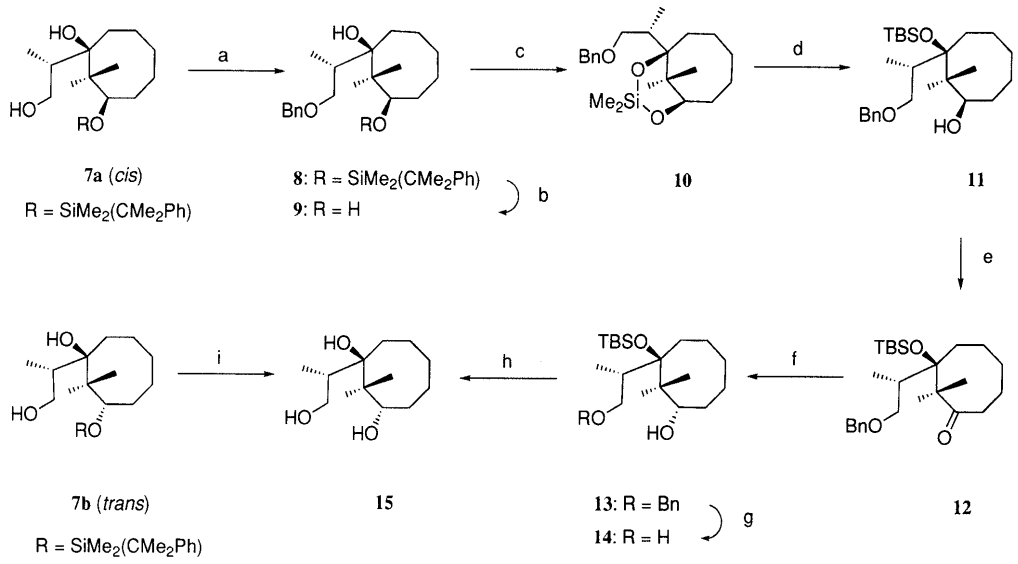


Chart 1



a) CH_2=C(CH_3)MgBr (3.0 eq), $CeCl_3$ (1.2 eq), THF, −45°C, 94% b) BH_3•THF (3.0 eq), THF, 0°C to r.t.; 2 N NaOH, 30% H_2O_2, 0°C to r.t.; separation on SiO_2, **7a** 54%, **7b** 19%, other isomers 12%.

Chart 2



a) BnBr (2.0 eq), NaH (1.5 eq), THF, 0°C to r.t., 81% b) TBAF (1.5 eq), THF, r.t., 99% c) Me_2SiCl_2 (1.2 eq), imidazole (4.0 eq), DMF, 0°C, 91% d) *tert*-BuLi (2.0 eq), Et_2O, −78°C, 81% e) TPAP (0.1 eq), NMO (1.5 eq), CH_2Cl_2, r.t., 100% f) DIBAL (2.0 eq), CH_2Cl_2, −78°C, **13** 65%,**11** 16% g) H_2, 10% Pd-C, EtOH, r.t., 94% h) TBAF (2.0 eq), THF, 60°C, 91% i) TBAF (2.0 eq), THF, r.t., 92%.

Chart 3

confirmed by nuclear Overhauser effect (NOE) experiments on the bicyclic lactone intermediate **4**, as described later. The major hydroboration products, **7a** and **7b**, were employed for further transformations.

Inversion of Secondary Hydroxyl Group (Chart 3) Since one of the major hydroboration products **7a**, derived from **5a**, has a *cis*-cyclooctane-1,3-diol structure, inversion of the secondary hydroxyl group attached to the cyclooctane ring was necessary to prepare the bicyclic lactone intermediate **4**. On the other hand, **7b**, which has a *trans*-cyclooctane-1,3-diol system, could be employed without such tedious procedures.

Inversion of the secondary hydroxyl group was examined using **5a**, having *cis* configuration. As shown in Fig. 3, conventional methods such as oxidation–reduction or Mitsunobu reaction resulted in cleavage of the cyclooctane ring.[14] These undesirable reactions could be prevented by protecting the free tertiary alcohol. Concerning this protection, it was shown in our previous communications that silyl protection of the highly hindered tertiary hydroxyl group could be achieved by regioselective bond cleavage of the silylene bridge formed from the 1,3-diol and dichlorodimethylsilane as described below.[7,8]

Successive benzylation and desilylation of **7a** afforded the cyclooctane-1,3-diol **9**, which then gave the cyclic silylene acetal **10** on treatment with dichlorodimethylsilane and imidazole. The desired silyl protection of the tertiary alcohol was achieved by treatment of **10** with *tert*-BuLi at −78 °C, affording **11** in good yield (81%).

Inversion of the secondary hydroxyl group of the TBS ether **11** was examined using the cyclooctanone **12** which was obtained by oxidation of **11** with the tetra-*n*-propylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) system.[15] Reduction of **12** using sodium borohydride did not proceed smoothly and

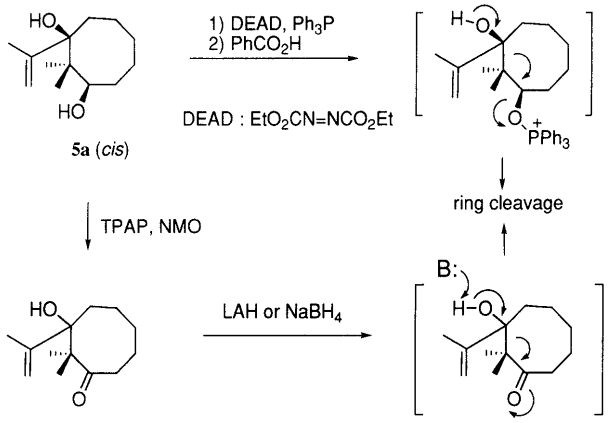


Fig. 3. Inversion of Secondary Alcohol

gave a trace amount of an isomerized product **13** at room temperature. The desired product **13** was generated by diisobutylaluminum hydride (DIBAL) reduction at −78 °C with acceptable selectivity (**13**/**11** = 4/1 to 5/1), while reduction with AlH_3 proceeded with moderate selectivity (**13**/**11** = 2/1). Separation of **13** and **11** was performed by chromatography on silica gel. Successive removal of protecting groups of **13**, debenzylation and desilylation, gave the naked triol **15** which was identical to that obtained by desilylation of **7b**, one of the major hydroboration products.

Construction of the Tetra-Substituted Alkene Part (Chart 4) Although oxidation of the resulting triol **15** with pyridinium chlorochromate gave the α,β-unsaturated lactone **3** in poor yield, oxidation with TPAP/NMO proceeded smoothly at room temperature and the bicyclic β-hydroxylactone **4** was obtained in good yield. When the above oxidation was carried out at lower temperature (0 °C), the major product was the corresponding lactol **16** instead of the lactone **4**. The stereochemistry of the chiral

center of the side chain was confirmed by an NOE experiment on **4**, as shown in Fig. 4. The bridgehead hydroxyl group of the bicyclic lactone **4** was eliminated smoothly by treatment with thionyl chloride in the presence of pyridine at 0 °C to afford the key intermediate, the α,β-unsaturated lactone **3**, with the (*Z*)-alkene structure at the desired position.

Preparation of Cyclization Precursor and Its Aldol Reaction (Chart 5) Next, the preparation of the dicarbonyl compound **2** from the unsaturated lactone **3** was examined. Alkylation of **3** with methyllithium or methylmagnesium bromide proceeded in tetrahydrofuran (THF) and hexamethylphosphoramide, but the resulting adducts were not stable enough for further manipulation. Similarly, DIBAL reduction of **3** in dichloromethane afforded an unstable lactol **17a** and facile cleavage of the eight-membered ring of the lactol took place, probably through vinylogous retro-aldol reaction of the δ-hydroxy-α,β-unsaturated carbonyl system (**17b**). Further, treatment of **3** with lithium aluminum hydride (LAH) resulted in the saturation of the double bond *via* 1,4-reduction.

Finally, it was found that DIBAL reduction of **3** in THF produced the allylic alcohol **18** as a major product, along with a small amount of the lactol **17a**, and successive reduction with LAH afforded **18** as a sole product. The oxidation of **18** gave its precursor, the lactol **17a**, and this result indicated that the secondary alcohol of **18** should be oxidized before modification of the allylic alcohol part. Thus the primary hydroxyl group of **18** was protected as its TBS ether and then oxidation of the secondary alcohol gave a cyclootanone **19**. Removal of the TBS protection of **19** gave a mixture of a ketoalcohol and its cyclic hemiacetal, which were subsequently oxidized to afford the aldehyde **20**. Monomethylation of **20** with methylmagnesium bromide proceeded at −45 °C and an isomeric mixture of secondary alcohols was obtained, which were in turn oxidized to the ketoenone **2**.

After screening several bases for the intramolecular aldol-type cyclization of **2**, the desired bicyclic compound **1** was finally obtained in good conversion yield by using sodium methoxide at room temperature. At an elevated temperature (50 °C), the yield of **1** decreased because of the formation of an unidentified by-product, probably by the vinylogous retro-aldol reaction of **1**. The isolated **1** was also converted to the same product under the cyclization conditions. Sodium hydride also gave **1** in moderate yield, whereas no reaction took place when

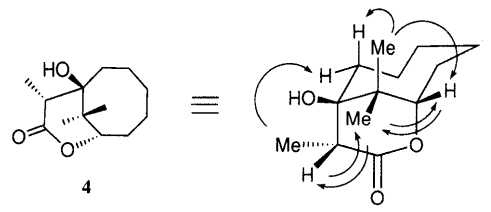
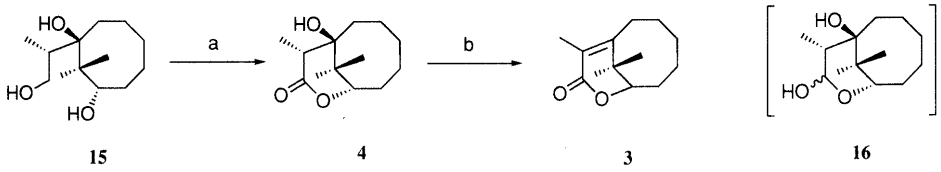
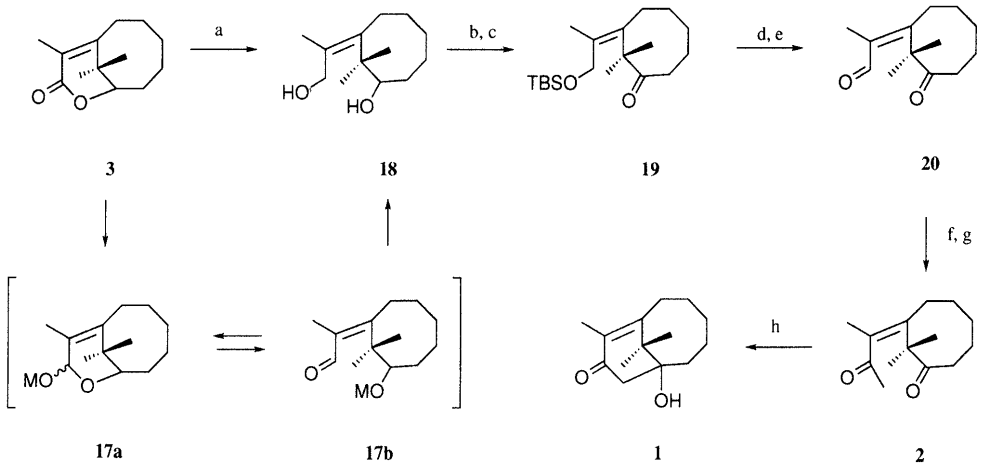


Fig. 4. NOE Experiments on the Bicyclic Lactone **4**



a) TPAP (0.1 eq), NMO (3.0 eq), CH_2Cl_2, r.t., 65%. b) $SOCl_2$ (1.5 eq), pyridine (4.0 eq), CH_2Cl_2, 0°C, 81%.

Chart 4



a) DIBAL (3.0 eq), THF, −78°C to 0°C; LAH (3.0 eq), −78°C to 0°C, 75%. b) TBSCl (1.5 eq), imidazole (2.0 eq), DMF, 0°C, 76%. c) TPAP (0.05 eq), NMO (1.8 eq), CH_2Cl_2, r.t., 92%. d) TBAF (2.2 eq), THF, r.t., 91%. e) TPAP (0.05 eq), NMO (2.5 eq), CH_2Cl_2, r.t., 99%. f) MeMgBr (2.8 eq), THF, −78°C to −45°C, 81%. g) TPAP (0.08 eq), NMO (1.7 eq), CH_2Cl_2, r.t., 97%. h) 3 M NaOMe, MeOH (10 eq), THF, r.t., 66% (93% based on 72% conversion).

Chart 5

1,8-diazabicyclo-[5.4.0]undec-7-ene was used, and potassium *tert*-butoxide induced rapid decomposition of **2**.

In conclusion, a novel annulation method for construction of the AB-ring system of the taxane framework was successfully demonstrated; that is, synthesis of the title compound, 1-hydroxy-8,11,11-trimethylbicyclo[5.3.1]-undec-7-en-9-one, was achieved *via* C1–C10 bond formation by base-mediated intramolecular aldol reaction. This synthetic procedure represents a new approach for the synthesis of taxane diterpenes, including taxol.

Experimental

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX 270 (270 MHz) instrument or a Bruker AVANCE DPX 300 (300 MHz) instrument. Chemical shifts were reported in δ units relative to internal tetramethylsilane (Me_4Si). ^{13}C-NMR spectra were recorded on a JEOL JNM-EX 270 (67.8 MHz) instrument or a Bruker AVANCE DPX 300 (75.5 MHz) instrument using the 77.0 ppm resonance of $CDCl_3$ as the internal standard. IR spectra were recorded on a Horiba FT-300 IR spectrometer. High-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-SX102A instrument using 4-nitrobenzyl alcohol as a matrix. Reactions were conducted under a dry argon atmosphere unless otherwise noted. CH_2Cl_2 and *N*,*N*-dimethylformamide (DMF) were distilled successively from P_2O_5 and CaH_2. THF and diethyl ether (Et_2O), were distilled from sodium benzophenone ketyl. Analytical TLC was done on precoated (0.25 mm) Silica gel 60 F_{254} plates (E. Merck). Preparative TLC was performed on silica gel-coated plates (Wakogel, B-5F). "Column chromatography" refers to flash chromatography using 200—300 mesh silica-gel (Wakogel, C-300). The following abbreviations are used for solvents and reagents: ethyl acetate (EtOAc), hexane (Hex), methyl alcohol (MeOH), ethyl alcohol (EtOH), 4-dimethylaminopyridine (DMAP), acetic acid (AcOH), potassium sodium tartrate (NaK tartrate), and sodium methoxide (NaOMe).

3-[(α,α-Dimethylbenzyl)dimethylsiloxy]-2,2-dimethylcyclooctanone (6) Cyclooctane-1,3-dione[11] was converted to **6** in three steps as follows; 1) A solution of cyclooctane-1,3-dione (4.2 g, 30 mmol) in DMF (15 ml) and iodomethane (10 ml, 0.16 mol) were added to a suspension of potassium carbonate (10.4 g, 75 mmol) and acetone (35 ml). After having been stirred at reflux temperature for 30 h, the reaction mixture was cooled to room temperature, and filtered through a pad of Celite, then the acetone was removed *in vacuo*. The residue was poured into H_2O and extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to column chromatography (eluent: EtOAc/Hex = 1/10) to afford 2,2-dimethylcyclooctane-1,3-dione (4.9 g, 97%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.44—2.36 (4H, m), 1.73—1.48 (6H, m), 1.22 (6H, s); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 211.6, 61.3, 40.8, 27.2, 24.8, 21.2; IR (thin film) ν_{max} 1691 cm^{-1}. 2) A solution of 2,2-dimethylcyclooctane-1,3-dione (4.2 g, 25 mmol) in EtOH (30 ml) was treated with $NaBH_4$ (0.28 g, 7.5 mmol) at room temperature for 2 h. After addition of 1 N HCl to pH 2, the reaction mixture was extracted with Et_2O and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (eluent: EtOAc/Hex = 1/8) to afford 3-hydroxy-2,2-dimethylcyclooctanone (3.6 g, 84%) as a white solid. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.31 (1H, dd, J = 10.9, 4.3 Hz), 2.75 (1H, dt, J = 11.8, 3.3 Hz), 2.27—2.16 (1H, m), 1.94—1.52 (7H, m), 1.35—1.22 (1H, m), 1.14 (3H, s), 1.03 (3H, s); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 217.8, 72.6, 52.1, 37.0, 35.4, 29.9, 26.2, 23.8, 22.9, 14.0; IR (KBr disk) ν_{max} 3403, 1691 cm^{-1}. 3) A solution of 3-hydroxy-2,2-dimethylcyclooctanone (2.6 g, 15 mmol) in DMF (20 ml) was treated with chloro(α,α-dimethylbenzyl)-dimethylsilane (9.6 g, 45 mmol), imidazole (6.8 g, 0.1 mol) and DMAP (0.18 g, 1.5 mmol) at room temperature for 1 h. After addition of phosphate buffer (pH 7.0) under ice-water cooling, the reaction mixture was extracted with Et_2O and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (eluent: EtOAc/Hex = 1/50) to afford **6** (5.3 g, 100%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25 (4H, m), 7.07 (1H, m), 4.14 (1H, dd, J = 10.3, 4.9 Hz), 2.62 (1H, dt, J = 12.0, 3.3 Hz), 2.18 (1H, m), 1.90—1.35 (6H, m), 1.36 (3H, s), 1.36 (3H, s), 1.12 (1H, m), 0.98 (3H, s), 0.91 (3H, s), 0.72 (1H, m), 0.00 (6H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 218.5, 148.4, 128.1, 127.0, 126.3, 124.8, 73.9, 53.2, 37.5, 36.0, 30.3, 28.9, 26.8, 24.8, 24.1, 24.1, 23.3, 15.1, −3.3, −3.7; IR (thin film) ν_{max} 2937, 1699, 1466, 1253, 1068, 829, 779, 698 cm^{-1}; FAB HR-MS *m*/*z*: Calcd for $C_{21}H_{35}O_2Si$ $[M+H]^+$: 347.2406. Found: 347.2424.

3-[(α,α-Dimethylbenzyl)dimethylsiloxy]-1-isopropenyl-2,2-dimethylcyclooctanol (5a, 5b) A solution of **6** (695 mg, 2.01 mmol) in THF (7.0 ml) was added to a stirred suspension of $CeCl_3$ (584 mg, 2.37 mmol) in THF (9.5 ml) at room temperature and after an interval of 1 h isopropenylmagnesium bromide (*ca.* 1.0 M in THF, 6.0 ml, 6.0 mmol; prepared from isopropenyl bromide and magnesium turnings in THF at 50 °C in the presence of a small amount of dibromoethane) was added to the resulting mixture at −45 °C. After having been stirred at −45 °C for 1 h, the reaction mixture was treated with a solution of AcOH (0.36 ml) in H_2O (20 ml) at room temperature and poured into saturated $NaHCO_3$. The whole was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: EtOAc/Hex = 1/20) to afford **5** (754 mg, 94%, **5a**/**5b** = *ca.* 52). Analytical sample of **5a** and **5b** were obtained by preparative TLC (EtOAc/Hex = 1/8). **5a** (*cis*): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26 (4H, m), 7.07 (1H, m), 4.99 (1H, br s), 4.96 (1H, br s), 4.78 (1H, br s), 3.58 (1H, dd, J = 7.9, 2.3 Hz), 2.00—1.50 (7H, m), 1.75 (3H, s), 1.44 (3H, s), 1.42 (3H, s), 1.38 (2H, m), 0.94 (3H, s), 0.89 (3H, s), 0.86 (1H, m), 0.02 (3H, s), −0.02 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 153.9, 147.8, 128.4, 126.9, 125.0, 112.0, 83.7, 80.5, 53.9, 43.6, 37.6, 32.0, 31.1, 30.5, 28.9, 28.2, 24.7, 24.2, 23.1, 22.4, 22.3, 22.2, −3.2, −4.4; IR (thin film) ν_{max} 3465, 2908, 1599, 1458, 1253, 1091, 1014, 823, 779, 700 cm^{-1}; FAB HR-MS *m*/*z*: Calcd for $C_{24}H_{41}O_2Si$ $[M+H]^+$: 389.2876. Found: 389.2895. **5b** (*trans*): Colorless prisms (EtOAc/Hex), mp 72.5—73.5 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26 (4H, m), 7.07 (1H, m), 4.92 (1H, m), 4.86 (1H, m), 3.95 (1H, dd, J = 6.0, 2.1 Hz), 2.12 (1H, m), 1.92 (1H, m), 1.79 (3H, d, J = 0.8 Hz), 1.75 (4H, m), 1.43 (4H, m), 1.36 (6H, s), 0.93 (3H, s), 0.81 (3H, s), −0.01 (3H, s), −0.03 (3H, s); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 153.2, 148.5, 127.5, 126.6, 124.1, 111.4, 79.9, 76.3, 46.2, 35.1, 34.7, 28.9, 28.6, 26.8, 23.8, 23.7, 22.3, 21.7, 21.3, 19.4, −3.8, −4.4; IR (thin film) ν_{max} 3610, 3500, 2950, 1470, 1252, 1057, 1012, 865, 825, 779, 698 cm^{-1}; FAB HR-MS *m*/*z*: Calcd for $C_{24}H_{41}O_2Si$ $[M+H]^+$: 389.2876. Found: 389.2846.

3-[(α,α-Dimethylbenzyl)dimethylsiloxy]-2,2-dimethyl-1-(2-hydroxy-1-methylethyl)cyclooctanol (7a, 7b) A solution of **5a** and **5b** (*ca.* 5:2 mixture, 627 mg, 1.6 mmol) in THF (3.0 ml) was added to a stirred solution of borane–THF complex (1.0 M in THF, 4.8 ml, 4.8 mmol) in THF (12.0 ml) at 0 °C. The reaction mixture was stirred at room temperature for 12 h, treated successively with H_2O (5.0 ml), 2 N NaOH (5.0 ml) and 30% H_2O_2 (2.5 ml) under ice-water cooling, and then stirred at room temperature for 1 h. THF was removed under reduced pressure and the residue was taken up in EtOAc. The solution was washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and subjected to column chromatography (eluent: EtOAc/Hex = 1/10) to afford **7a** (356 mg, 54%), **7b** (125 mg, 19%) and other isomers (79 mg, 12%). **7a**: Colorless oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.28 (4H, m), 7.14 (1H, m), 3.70 (2H, m), 3.50 (2H, m), 2.75 (1H, br s), 1.88 (1H, m), 1.8—1.2 (10H, m), 1.44 (6H, s), 1.15 (3H, d, J = 6.9 Hz), 1.10 (3H, s), 0.97 (3H, s), 0.08 (3H, s), 0.05 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 147.5, 127.9, 126.4, 124.5, 79.6, 67.1, 60.3, 46.1, 43.1, 31.9, 29.7, 28.4, 28.3, 23.9, 23.9, 21.0, 20.3, 20.1, 14.1, 14.0, −3.7, −4.6; IR (thin film) ν_{max} 3455, 2956, 1469, 1253, 1080, 1010, 825, 779, 700 cm^{-1}; FAB HR-MS *m*/*z*: Calcd for $C_{24}H_{43}O_3Si$ $[M+H]^+$: 407.2981. Found: 407.2959. **7b**: Colorless oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.27 (4H, m), 7.11 (1H, m), 3.85 (2H, m), 3.33 (1H, dd, J = 10.2, 7.9 Hz), 2.08 (1H, m), 1.93 (1H, m), 1.85—1.20 (9H, m), 1.38 (6H, s), 1.02 (3H, d, J = 6.9 Hz), 0.99 (3H, s), 0.88 (3H, s), 0.00 (3H, s), −0.02 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 148.9, 128.0, 127.1, 126.3, 124.6, 78.5, 66.8, 48.8, 44.9, 35.0, 29.8, 29.7, 29.1, 26.9, 24.3, 24.2, 22.9, 21.2, 19.2, 13.6, −3.2, −4.0; IR (thin film) ν_{max} 3367, 2960, 1469, 1252, 1010, 825, 779, 698 cm^{-1}; FAB HR-MS *m*/*z*: Calcd for $C_{24}H_{41}O_3Si$ $[M-H]^+$: 405.2825. Found: 405.2863.

***cis*-1-(2-Benzyloxy-1-methylethyl)-3-[(α,α-dimethylbenzyl)dimethylsiloxy]-2,2-dimethylcyclooctanol (8)** A stirred solution of **7a** (390 mg, 0.96 mmol) in THF (12 ml) was treated with sodium hydride (55% dispersion in mineral oil, 63.0 mg, 1.44 mmol) at 0 °C for 15 min and then with benzyl bromide (0.23 ml, 1.90 mmol) at room temperature for 18 h. The reaction mixture was poured into saturated NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with

brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was then purified by column chromatography (eluent: EtOAc/Hex = 1/10) to afford **8** (386 mg, 81%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.4—7.1 (9H, m), 7.06 (1H, m), 4.42 (2H, s), 4.14 (1H, br s), 3.58 (1H, dd, J = 9.1, 3.2 Hz), 3.49 (1H, m), 3.12 (1H, br t, J = 7.9 Hz), 2.12 (1H, m), 2.0—1.0 (10H, m), 1.41 (3H, s), 1.40 (3H, s), 1.05 (3H, s), 1.03 (3H, d, J = 8.4 Hz), 0.85 (3H, s), 0.00 (3H, s), −0.04 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 147.6, 138.5, 128.7, 128.3, 127.8, 127.7, 127.6, 127.5, 127.4, 126.5, 124.4, 83.0, 77.8, 74.0, 73.0, 60.3, 45.8, 43.5, 30.0, 29.6. 28.5, 23.8, 23.6, 21.1, 21.0, 14.1, 13.9, −3.9, −4.7; IR (thin film) ν_{max} 3473, 2935, 1469, 1253, 1078, 1009, 825, 779, 698 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{31}H_{49}O_3Si$ $[M+H]^+$: 497.3451. Found: 497.3466.

***cis*-1-(2-Benzyloxy1-l-methylethyl)-2,2-dimethyl-1,3-cyclooctanediol (9)** A solution of **8** (570 mg, 1.1 mmol) in THF (11 ml) was treated with TBAF (1 M in THF solution, 1.7 ml, 1.7 mmol) at room temperature for 5 h. The reaction mixture was poured into brine and the whole was extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (eluent: EtOAc/Hex = 1/2) to afford **9** (363 mg, 99%) as a white solid. Crystallization from EtOAc/Hex gave colorless prisms (mp 120.5—121.5 °C). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.23 (5H, m), 4.37 (2H, s), 3.52 (1H, dd, J = 9.2, 3.6 Hz), 3.45 (1H, dd, J = 7.6, 1.6 Hz), 3.27 (1H, dd, J = 8.9, 7.6 Hz), 2.00 (2H, m), 1.80—1.30 (8H, m), 1.20 (1H, m), 1.12 (3H, s), 0.99 (3H, d, J = 6.9 Hz), 0.87 (3H, s); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 138.7, 129.0, 128.7, 128.3, 81.9, 80.0, 75.1, 74.0, 46.1, 43.8, 31.9, 31.2, 29.9, 24.0, 22.0, 21.7, 14.9; IR (KBr disk) ν_{max} 3355, 2929, 1452, 1095, 1001, 739, 698 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{20}H_{33}O_3$ $[M+H]^+$: 321.2430. Found: 321.2448.

1-(2-Benzyloxy-1-methylethyl)-9,9,11,11-tetramethyl-8,10-dioxa-9-silabicyclo[5.3.1]undecane (10) Dichlorodimethylsilane (95 μl, 0.78 mmol) was added to a solution of **9** (202 mg, 0.63 mmol) and imidazole (177 mg, 2.60 mmol) in DMF (6.0 ml). After having being stirred at 0 °C for 1 h, the reaction mixture was poured into saturated $NaHCO_3$ and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (eluent: EtOAc/Hex = 1/4) to afford **10** (215 mg, 91%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25 (5H, m), 4.40 (2H, s), 3.69 (1H, dd, J = 6.6, 2.4 Hz), 3.53 (1H, dd, J = 9.0, 2.9 Hz), 2.97 (1H, t, J = 9.0 Hz), 2.32 (1H, m), 2.0—1.3 (9H, m), 1.29 (3H, s), 1.14 (1H, m), 0.96 (3H, d, J = 6.6 Hz), 0.95 (3H, s), 0.21 (3H, s), 0.20 (3H, s); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 138.5, 128.3, 127.8, 127.6, 127.5, 86.5, 81.1, 73.1, 72.6, 45.2, 43.9, 33.6, 31.3, 29.9, 29.6, 26.9, 24.5, 22.6, 13.4, 2.2, 2.0; IR (thin film) ν_{max} 2914, 1454, 1257, 1101, 1055, 1016, 962, 906, 848, 791 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{22}H_{37}O_3Si$ $[M+H]^+$: 377.2481. Found: 377.2466.

***cis*-3-(2-Benzyloxy-1-methylethyl)-3-(*tert*-butyldimethylsiloxy)-2,2-dimethylcyclooctanol (11)** A stirred solution of **10** (254 mg, 0.67 mmol) in Et_2O (7.6 ml) was treated with *tert*-BuLi (1.76 M in pentane, 0.80 ml, 1.4 mmol) at −78 °C for 30 min. Then saturated NH_4Cl was added to the reaction mixture and the whole was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and purified by column chromatography (eluent: EtOAc/Hex = 1/6) to afford **11** (239 mg, 81%). Crystallization from EtOAc/Hex afforded colorless prisms (mp 87.0—88.5 °C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26 (5H, m), 4.44 (1H, d, J = 11.8 Hz), 4.39 (1H, d, J = 11.8 Hz), 3.74 (1H, dd, J = 8.3, 2.4 Hz), 3.56 (1H, m), 3.25 (1H, dd, J = 9.5, 8.3 Hz), 2.00 (2H, m), 1.80 (4H, m), 1.30 (5H, m), 1.12 (3H, d, J = 6.8 Hz), 1.00 (3H, s), 0.95 (3H, s), 0.82 (9H, s), 0.05 (6H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 138.9, 128.8, 128.3, 128.0, 126.3, 85.6, 73.9, 73.6, 48.9, 36.1, 28.9, 26.9, 24.4, 22.1, 19.7, 15.9, −0.6, −0.8; IR (KBr disk) ν_{max} 3456, 2929, 1464, 1255, 1060, 835, 771 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{26}H_{45}O_3Si$ $[M-H]^+$: 433.3138. Found: 433.3134.

3-(2-Benzyloxy-1-methylethyl)-3-(*tert*-butyldimethylsiloxy)-2,2-dimethylcyclooctanone (12) A stirred solution of **11** (228 mg, 0.53 mmol) in CH_2Cl_2 (6.8 ml) was treated with NMO (94.5 mg, 0.81 mmol) and TPAP (19 mg, 0.054 mmol) at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (eluent: EtOAc/Hex = 1/6) to afford **12** (227 mg, 100%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26 (4H, m), 7.20 (1H, m), 4.47 (1H, d, J = 11.8 Hz), 4.34 (1H, d, J = 11.8 Hz), 3.65 (1H, dd, J = 8.5, 2.3 Hz), 3.12 (1H, dd, J = 9.6, 8.5 Hz), 2.60 (1H, m), 2.20 (2H, m), 1.81 (4H, m), 1.48 (2H, m), 1.25 (1H, m), 1.18 (3H, s), 1.16 (3H, s), 1.13 (3H, d, J = 6.6 Hz), 0.88 (1H, m), 0.84 (9H, s), 0.06 (3H, s), 0.03 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 218.8, 139.1, 128.7, 128.2, 127.8, 84.4, 73.5, 73.3, 57.3, 39.1, 36.7, 30.3, 27.7, 26.9, 24.4, 24.1, 22.4, 19.8, 16.3, −0.6, −0.7; IR (KBr) ν_{max} 2931, 1693, 1466, 1255, 1099, 835, 771 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{26}H_{45}O_3Si$ $[M+H]^+$: 433.3138. Found: 433.3123.

***trans*-3-(2-Benzyloxy-1-methylethyl)-3-(*tert*-butyldimethylsiloxy)-2,2-dimethylcyclooctanol (13)** A stirred solution of **12** (178 mg, 0.41 mmol) in CH_2Cl_2 (5.4 ml) was treated with DIBAL (1.0 M in hexane, 0.84 ml, 0.84 mmol) at −78 °C. After 1 h, the reaction was quenched by adding MeOH and saturated NaK tartrate, and the mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified by preparative TLC (EtOAc/Hex = 1/3) to afford **13** (117 mg, 65%) and **11** (29 mg, 16%). Colorless oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.25—7.15 (5H, m), 4.40 (1H, d, J = 11.5 Hz), 4.32 (1H, d, J = 11.5 Hz), 3.80 (1H, dd, 4.9, 2.6 Hz), 3.70 (1H, dd, J = 8.0, 2.3 Hz), 3.14 (1H, dd, J = 9.6, 8.0 Hz), 2.0—1.1 (11H, m), 1.06 (3H, d, J = 6.9 Hz), 0.89 (6H, s), 0.79 (9H, s), 0.00 (6H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 139.0, 128.8, 128.2, 127.9, 84.5, 77.4, 74.1, 73.6, 60.8, 49.4, 34.3, 29.8, 27.4, 27.0, 24.0, 21.5, 21.0, 20.2, 16.1, 14.6, −1.0, −1.1; IR (KBr) ν_{max} 3454, 2929, 1466, 1254, 1078, 833, 771 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{26}H_{45}O_3Si$ $[M-H]^+$: 433.3138. Found: 433.3148.

***trans*-3-(*tert*-Butyldimethylsiloxy)-2,2-dimethyl-3-(2-hydroxy-1-methylethyl)cyclooctanol (14)** A mixture of **13** (154 mg, 0.35 mmol), 10% palladium on charcoal and EtOH (4.5 ml) was vigorously stirred under a hydrogen atmosphere at room temperature for 1 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (eluent: EtOAc/Hex = 1/4) to afford **14** (115 mg, 94%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.01 (1H, dd, J = 9.7, 2.7 Hz), 3.91 (1H, dd, J = 5.5, 2.7 Hz), 3.47 (1H, t, J = 9.7 Hz), 2.0—1.1 (11H, m), 1.18 (3H, d, J = 6.9 Hz), 1.03 (3H, s), 1.02 (3H, s), 0.93 (9H, s), 0.15 (3H, s), 0.14 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 84.8, 77.5, 66.1, 49.4, 36.0, 34.1, 29.5, 27.3, 26.7, 24.2, 21.4, 21.1, 20.1, 15.2, −0.6, −1.0; IR (KBr) ν_{max} 3370, 2933, 1468, 1255, 1022, 831, 771 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{19}H_{40}O_3SiNa$ $[M+Na]^+$: 367.2644. Found: 367.2625.

***trans*-1-(2-Hydroxy-1-methylethyl)-2,2-dimethyl-1,3-cyclooctanediol (15)** a) Step h (Chart 3): A solution of **14** (51.1 mg, 0.15 mmol) in THF (2.5 ml) was treated with TBAF (1 M in THF, 0.30 ml, 0.30 mmol) at 60 °C for 30 min. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative TLC (EtOAc) to afford **15** (31.1 mg, 91%).

b) Step i (Chart 3): A solution of **7b** (485 mg, 1.2 mmol) in THF (10 ml) was treated with TBAF (1 M in THF, 2.3 ml, 2.3 mmol) at room temperature for 3 h. The reaction mixture was concentrated and purified by column chromatography (eluent: EtOAc/Hex = 2/1) to afford **15** (257 mg, 92%). Colorless oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.05 (1H, dd, J = 5.6, 3.0 Hz), 3.87 (1H, dd, J = 10.2, 3.3 Hz), 3.33 (1H, dd, J = 10.2, 8.2 Hz), 2.15 (1H, m), 2.0—1.2 (10H, m), 1.08 (3H, s), 1.05 (3H, d, J = 6.9 Hz), 1.02 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 76.8, 68.4, 66.6, 48.1, 44.8, 34.8, 30.1, 27.4, 26.0, 21.9, 20.4, 18.7, 13.6; IR (thin film) ν_{max} 3424, 2952, 1469, 1375, 1265, 1022, 989, 963, 737 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{13}H_{25}O_2$ $[M-17]^+$: 213.1855. Found: 213.1846.

1-Hydroxy-10,11,11-trimethyl-8-oxabicyclo[5.3.1]undecan-9-one (4) Oxidation of **15** (83.4 mg, 0.36 mmol) using NMO (127 mg, 1.1 mmol) and TPAP (18.9 mg, 0.054 mmol) as described for the preparation of **12** afforded **4** (53.0 mg, 65%) as a white solid. Crystallization from EtOAc/Hex gave colorless prisms (mp 140.5—142.5 °C); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.59 (1H, d, J = 8.9 Hz), 2.87 (1H, q, J = 6.9 Hz), 2.15 (1H, m), 1.85 (5H, m), 1.57 (3H, m), 1.32 (3H, s), 1.30 (3H, d, J = 6.9 Hz), 1.16 (3H, s), 0.95 (1H, m); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 174.5, 87.6, 76.1, 42.5, 39.6, 37.2, 31.4, 29.9, 29.4, 25.3, 25.1, 22.1, 9.8; IR (KBr disk) ν_{max} 3425, 2931, 1701, 1454, 1382, 1199, 1149, 1082, 1049, 1005, 962 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{13}H_{23}O_3$ $[M+H]^+$: 227.1647. Found: 227.1642.

8,11,11-Trimethyl-10-oxabicyclo[5.3.1]undec-7-en-9-one (3) Pyridine (60 μl, 0.74 mmol) and thionyl chloride (18 μl, 0.25 mmol) were added to a solution of **4** (39.0 mg, 0.17 mmol) in CH_2Cl_2 (2.0 ml) at 0 °C. After having been stirred for 30 min, the reaction mixture was poured into saturated $NaHCO_3$ and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc/Hex = 1/2) to afford **3** (29.0 mg, 81%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$)

δ 4.26 (1H, t, J=3.3 Hz), 2.58 (1H, m), 2.36 (1H, m), 2.09 (1H, m), 1.97 (3 H, d, J=0.7 Hz), 1.90 (1 H, m), 1.70—1.40 (5 H, m), 1.33 (1 H, m), 1.30 (3 H, s), 1.21 (3 H, s); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 166.1, 157.9, 123.2, 84.9, 36.5, 32.4, 31.8, 28.6, 27.8, 26.4, 24.1, 23.0, 14.2; IR (thin film) ν_{max} 2937, 1709, 1513, 1462, 1377, 1249, 1088, 837 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{13}H_{21}O_2$ $[M+H]^+$: 209.1542. Found: 209.1529.

(*Z*)-3-(2-Hydroxy-1-methylethylidene)-2,2-dimethylcyclooctanol (18) A solution of **3** (30.7 mg, 0.15 mmol) in THF (1.5 ml) was treated with DIBAL (1.0 M in hexane, 0.45 ml, 0.45 mmol) at -78 °C and the reaction mixture was stirred at 0 °C for 30 min. Then LAH (1.0 M in THF, 0.45 ml, 0.45 mmol) was added to the reaction mixture at -78 °C and stirring was continued at 0 °C for 30 min. After treatment with MeOH (0.2 ml) and then with saturated NaK tartrate (3.0 ml) at room temperature for 1 h, the whole was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc/Hex=2/1) to afford **18** (23.6 mg, 75%) as a colorless foam. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.40 (1H, d, J=11.5 Hz), 4.17 (1H, d, J=11.5 Hz), 4.09 (1H, dd, J=8.9, 4.9 Hz), 2.35 (1H, m), 2.14 (1H, m), 1.84 (3H, s), 1.9—1.2 (8H, m), 1.35 (3H, s), 1.15 (3H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 145.2, 129.4, 75.4, 64.9, 44.4, 36.0, 29.7, 9.4, 28.7, 24.1, 21.9, 21.0; IR (thin film) ν_{max} 3350, 2922, 1450, 1002 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{13}H_{23}O_2$ $[M-H]^+$: 211.1698. Found: 211.1684.

(*Z*)-3-(2-*tert*-Butyldimethylsiloxy-1-methylethylidene)-2,2-dimethylcyclooctanone (19) A solution of **18** (31.8 mg, 0.15 mmol) in DMF (0.95 ml) was treated with TBSCl (37.4 mg, 0.25 mmol) and imidazole (19.5 mg, 0.29 mmol) at room temperature for 2 h. The reaction mixture was poured into saturated $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc/Hex=1/3) to afford (*Z*)-3-(2-*tert*-butyldimethylsiloxy-1-methylethylidene)-2,2-dimethylcyclooctanol (37.2 mg, 76%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.24 (1H, d, J=11.2 Hz), 4.16 (1H, d, J=11.2 Hz), 3.99 (1H, dd, J=9.5, 4.6 Hz), 2.27 (1H, m), 2.05 (1H, m), 1.1—2.0 (8H, m), 1.70 (3H, s), 1.24 (3H, s), 1.07 (3H, s), 0.84 (9H, s), 0.00 (6H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 142.7, 129.7, 75.6, 64.9, 44.4, 36.0, 29.6, 29.4, 28.3, 27.8, 26.4, 24.0, 21.4, 20.5, 18.7, -4.8; IR (thin film) ν_{max} 3400, 2930, 1466, 1253, 1057, 841, 775 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{19}H_{37}O_2Si$ $[M-H]^+$: 325.2563. Found: 325.2568. Then, treatment of the silylated product (43.1 mg, 0.13 mmol) with TPAP (1.9 mg, 5.4 μmol) and NMO (26.4 mg, 0.23 mmol) as described for **12** afforded **19** (39.4 mg, 92%) as a colorless oil after purification by preparative TLC (EtOAc/Hex=1/3). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.26 (2H, s), 2.47 (2H, m), 1.95 (2H, m), 1.75 (3H, s), 1.68 (2H, m), 1.53 (4H, m), 1.32 (6H, s), 0.90 (9H, s), 0.07(6H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 217.1, 137.5, 133.1, 64.0, 56.7, 39.2, 31.8, 27.5, 26.9, 26.3, 25.2, 25.1, 20.5, 18.7, -4.8; IR (thin film) ν_{max} 2931, 1707, 1253, 1059, 841, 777 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{19}H_{37}O_2Si$ $[M+H]^+$: 325.2563. Found: 325.2536.

(*Z*)-2-(2,2-Dimethyl-3-oxocyclooctylidene)propanal (20) Treatment of **18** (39.4 mg, 0.12 mmol) with TBAF (1 M in THF, 0.28 ml, 0.28 mmol) as described for **15** (method b) gave (*Z*)-3-(2-hydroxy-1-methylethylidene)-2,2-dimethylcyclooctanone (23.1 mg, 91%) as a mixture with its acetal form (*ca.* 3/1 ratio; ^{1}H-NMR analysis) after preparative TLC (EtOAc/Hex=2/1). Then oxidative treatment of a mixture of the desilylated products (23.1 mg, 0.11 mmol) with TPAP (1.4 mg, 4.0 μmol) and NMO (34.0 mg, 0.29 mmol) as described for **12** gave **20** (22.6 mg, 99%) as a colorless oil after purification by preparative TLC (EtOAc/Hex=1/2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.49 (1H, s), 2.51 (2H, m), 2.21 (2H, m), 1.86 (3H, s), 1.71 (2H, m), 1.61 (4H, m), 1.49 (6H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 213.6, 193.0, 161.2, 136.6, 57.6, 39.6, 33.7, 27.5, 27.3, 26.6, 24.6, 13.9; IR (thin film) ν_{max} 2931, 2864, 1705, 1662, 1599, 1448, 1379, 1261, 1101, 1030 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{13}H_{21}O_2$ $[M+H]^+$: 209.1542. Found: 209.1548.

(*Z*)-2,2-Dimethyl-3-(1-methyl-2-oxopropylidene)cyclooctanone (2) Methylmagnesium bromide (3.0 M in Et_2O, 0.10 ml, 0.30 mmol) was added to a solution of **20** (22.2 mg, 0.11 mmol) in Et_2O (1.6 ml) at -78 °C. The mixture was stirred at -45 °C for 30 min, then the reaction was quenched by the addition of saturated NH_4Cl. The whole was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to preparative TLC (EtOAc/Hex=1/2) to afford (*Z*)-2,2-dimethyl-3-(2-hydroxy-1-methylpropylidene)cyclooctanone (19.3 mg, 81%) as a mixture with its ketal form (*ca.* 5/1 ratio; ^{1}H-NMR analysis). Then, similar oxidative treatment of a mixture of the methylated products (19.3 mg, 0.086 mmol) with TPAP (2.3 mg, 6.5 μmol) and NMO (17.9 mg, 0.15 mmol) as described for **12** afforded **2** (18.5 mg, 97%) as a colorless oil after purification by preparative TLC (EtOAc/Hex=1/2). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.50 (2H, m), 2.39 (3H, s), 2.05 (2H, m), 1.83 (3H, s), 1.71 (2H, m), 1.58 (4H, m), 1.20 (6H, s); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 216.4, 209.6, 137.5, 135.9, 55.9, 38.8, 30.7, 30.6, 27.4, 26.3, 25.9, 24.5, 17.9; IR (thin film) ν_{max} 2929, 1697, 1462, 1356, 1095 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1698. Found: 223.1675.

1-Hydroxy-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-9-one (1) A solution of **2** (2.1 mg, 9.5 μmol) in THF (0.10 ml) was treated with NaOMe (3 M in MeOH, 30 μl, 90 μmol) at 0 °C. After having been stirred at room temperature for 6 h, the reaction mixture was subjected to preparative TLC (EtOAc/Hex=1/1) to afford **1** (1.4 mg, 67%) as a white amorphous solid, together with unreacted **2** (0.6 mg, 28%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.88 (1H, dd, J=19.1, 1.3 Hz), 2.69 (1H, m), 2.50 (1H, m), 2.50 (1 H, d, J=19.1 Hz), 1.85 (3 H, s), 2.00-1.40 (5H, m), 1.31 (3 H, s), 1.16 (3 H, s), 1.40—1.00 (2H, m), 0.88 (1H, m); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 199.2, 166.9, 132.5, 49.9, 45.4, 43.7, 30.8, 30.1, 29.4, 29.2, 28.5, 26.4, 22.2, 13.2; IR (thin film) ν_{max} 3433, 2923, 1673, 1647, 1448, 1082, 1035 cm^{-1}; FAB HR-MS m/z: Calcd for $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1698. Found: 223.1673.

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