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Synthesis of Chiloscyphones and the Biological Activities of Their Synthetic Intermediates Against Methicillin-Resistant S*taphylococcus aureus* (MRSA)

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The total syntheses of chiloscyphone (**1**) and isochiloscyphone (**2**) have been achieved. Furthermore, the synthetic intermediate **5** shows biological activity against methicillin-resistant *Staphyrococcus aureus*, and compounds **5**, **17**, and **18**, display imipenem-type activity. The tricyclic lactone framework, which includes an α,β-unsaturated ketone moiety, might play a crucial role in the anti-MRSA activity.

Introduction

It has been known for a long time that liverwort extracts show a variety of antimicrobial activities,[1] and many natural products with attractive biological activities, such as anticancer, fish-killing, and antifeedant properties, have been isolated from the liverwort.[2] In addition, a bicyclo[4.3.0]-nonane framework is shared by such members as chiloscyphone (**1**),[3] isochiloscyphone (**2**),[4] acutifolone A (**3**),[5] and pinguisenol (**4**; Figure 1).[6] These natural products have attractive and important dispositions from the viewpoint of biological evaluation and organic synthesis.[7] However, the structure–activity relationship studies of these natural products and their derivatives have been limited owing to the difficulty of functional-group arrangement, even though their congeners would provide a considerable amount of information. Against such a background, we have constructed potent intermediates possessing the bicyclo[4.3.0]nonane framework towards the total synthesis of **1** and **2**, and submitted them to assessment for a variety of antimicrobial activities (Gram-positive and Gram-negative bacteria). We describe herein a practical synthesis, as well as the biological activities, of these synthetic intermediates.

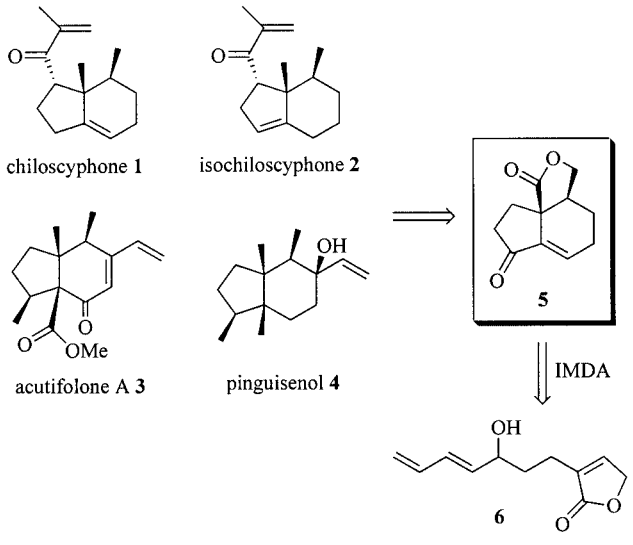

Figure 1. Sesquiterpenoids isolated from the liverwort.

Results and Discussion

Synthesis

We have recently reported the construction of a bicyclo[4.3.0]nonane structure carrying *cis*-oriented continuous substitution by the intramolecular Diels–Alder reaction.[8] In this previous paper, we revealed that our synthetic route towards natural products from the liverwort is more effective than the conventional methodologies[9] from the viewpoints of not only being able to construct the bicyclo[4.3.0]-nonane framework but also to introduce a variety of functional groups into desired positions. In a retrosynthetic analysis, **1** and **2** would be obtained from the synthetic intermediate **5**, which proved to be a practical common intermediate and could be readily obtained from the triene **6**.

Synthesis of the Diels–Alder precursors **6** and **14** commenced by treatment of **7**[10] with butadienyllithium[11] to give **8**, which, upon protection with a TBDPS group, furnished **9** (Scheme 1). Selective removal of the TBS group produced **10**, which was sequentially oxidized with SO_3·py, DMSO, and Et_3N, and then PDC to provide the carboxylic

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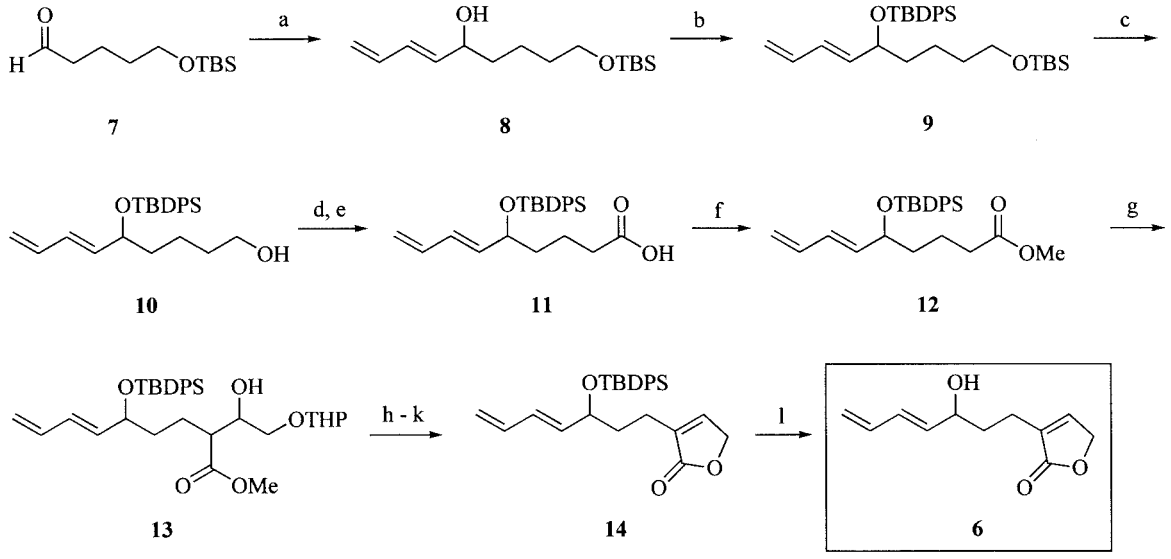
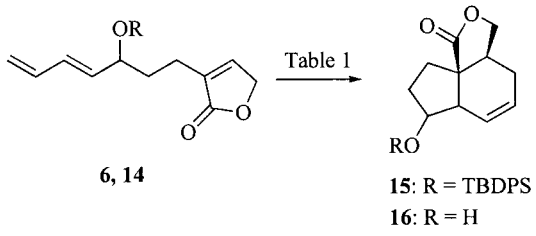


Scheme 1. Reagents and conditions: (a) (*E*)-*n*Bu_3SnCH=CHCH=CH_2, *n*BuLi, THF, –78 °C, 93%; (b) TBDPSCl, Imid, DMF, room temp., 100%; (c) PPTS, EtOH, room temp., 95%; (d) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C; (e) PDC, DMF, room temp., 82% in two steps; (f) K_2CO_3, MeI, DMF, 0 °C, 99%; (g) LDA, THPOCH_2CHO, THF, –78 °C, 95%; (h) PPTS, MeOH, room temp.; (i) Et_3N, MeOH, room temp.; (j) Ac_2O, py, room temp.; (k) DBU, PhMe, 0 °C, 87% in four steps; (l) TBAF, AcOH, THF, room temp., 92%.

acid **11**. After esterification, ester **12** was submitted to an aldol reaction with THPOCH_2CHO to give **13**. Removal of the THP group, followed by cyclization under the basic conditions, afforded the corresponding five-membered lactone, a secondary alcohol of which was acetylated, followed by elimination to give the triene **14**. Subsequent removal of the TBDPS group furnished the triene **6**.

The trienes **6** and **14** were subjected to an intramolecular Diels–Alder reaction (Scheme 2, Table 1), and triene **14** was studied first under a variety of Lewis acidic conditions. With Et_2AlCl, $ZnCl_2$, or $LiClO_4$ as Lewis acid the desired tricyclic **15** was not obtained (entries 1, 3, and 4). Reaction with a stronger Lewis acid such as $EtAlCl_2$ was also unsuccessful due to removal of the TBDPS group and concomitant undesired rearrangement (entry 2). Heating **14** at 180 °C in toluene in a sealed tube in the presence of BHT, however, provided the expected product **15** (entry 5). The reason for the low yield in this reaction might be due to its slow reaction rate, which causes considerable amounts of unreacted **14** to remain. Ultimately, use of the triene **6**, which contains a free hydroxy group, gave the desired tricyclic compound **16** in high yield as a diastereomeric mixture (1:1.1:0.6, entry 6). Other solvents and radical inhibitors had no effect on the high yield of this procedure (entries 7 and 8).



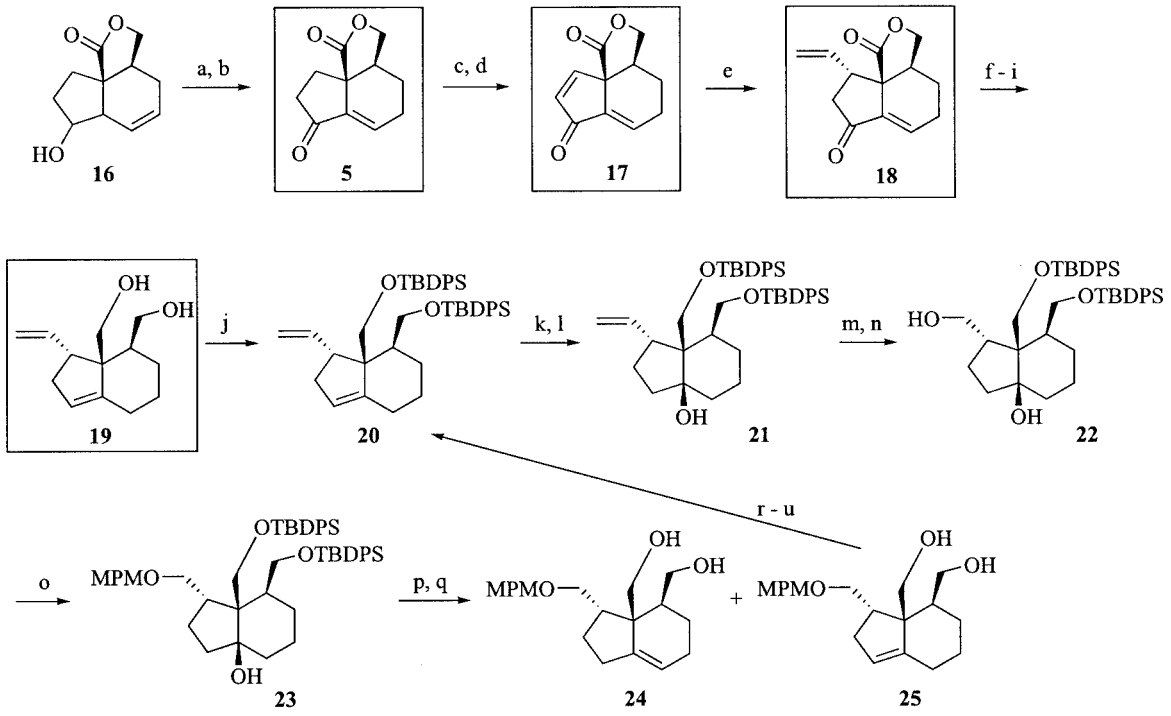
Scheme 2. Intramolecular Diels–Alder reaction.

Table 1. Intramolecular Diels–Alder reaction.

Entry	Substrate	Reagents and conditions	Results
1	**14**	Et_2AlCl, CH_2Cl_2, r.t.	no reaction
2		$EtAlCl_2$, CH_2Cl_2, –78 °C	dec.
3		$ZnCl_2$, PhMe, 70 °C	no reaction
4		$LiClO_4$, CH_3NO_2, 80 °C	no reaction
5[a]		BHT, PhMe, 180 °C	**15** (13%)[b]
6[a]	**6**	BHT, PhMe, 180 °C	**16** (83%)[b]
7[a]		BHT, PhH, 180 °C	**16** (72%)[b]
8[a]		methylene blue, PhMe, 180 °C	**16** (24%)[b]

[a] Reactions were carried out in a sealed tube. [b] A diastereomeric mixture was obtained (1:1.1:0.6).

The tricyclic compound **16** was then oxidized, followed by isomerization with DBU to afford the important intermediate **5**, which was converted under the Ito–Saegusa conditions[12] into the dienone **17**. Modification of the adjacent β-face lactone moiety by selective Michael addition of a vinyl group furnished **18** as a single product. Selective reduction of the unsaturated ketone, mesylation, and elimination provided a tri-substituted olefin, which was further reduced with DIBAL-H to give the diol **19**. After protection of **19** with a TBDPS group, selective epoxidation of the tri-substituted olefin and reductive opening by $LiEt_3BH$ gave **21**. In this process, the β-epoxide is obtained by attack of the reagent at the convex face. Oxidative cleavage of the terminal olefin furnished an aldehyde, which, upon reduction, afforded the diol **22**. Compound **22** was protected as an MPM ether to give **23**, which was treated with $SOCl_2$ at –30 °C, followed by removal of the TBDPS group, to afford a mixture of chromatographically separable **24** and



Scheme 3. Reagents and conditions: (a) TFAA, DMSO, Et_3N, CH_2Cl_2, –60 °C; (b) DBU, PhMe, 0 °C, 87% in two steps; (c) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (d) $Pd(OAc)_2$, CH_3CN, room temp., 98% in two steps; (e) CH_2=CHMgBr, CuI, THF, –78 °C, 75%; (f) $NaBH_4$, MeOH, 0 °C; (g) MsCl, py, room temp.; (h) AcOK, DMF, H_2O, 80 °C; (i) DIBAL-H, CH_2Cl_2, 0 °C, 75% in four steps; (j) TBDPSCl, Imid, DMF, 0 °C, 97%; (k) *m*CPBA, NaH_2PO_4, CH_2Cl_2, –20 °C; (l) $LiEt_3BH$, THF, room temp., 74% in two steps; (m) OsO_4, Me_3NO, acetone, H_2O, room temp., then $NaIO_4$, NaH_2PO_4, room temp.; (n) $NaBH_4$, MeOH, 0 °C, 58% in two steps; (o) MPMCl, NaH, nBu_4NI, DMF, 0 °C, 70%; (p) $SOCl_2$, py, –30 °C; (q) TBAF, THF, 50 °C, 94% (**24**: 18%, **25**: 76%) in two steps; (r) TBDPSCl, Imid, DMF, 0 °C; (s) DDQ, CH_2Cl_2, H_2O, 0 °C; (t) IBX, DMSO, THF, room temp.; (u) Ph_3PCH_3Br, NaHMDS, THF, –40 °C, 65% in four steps.

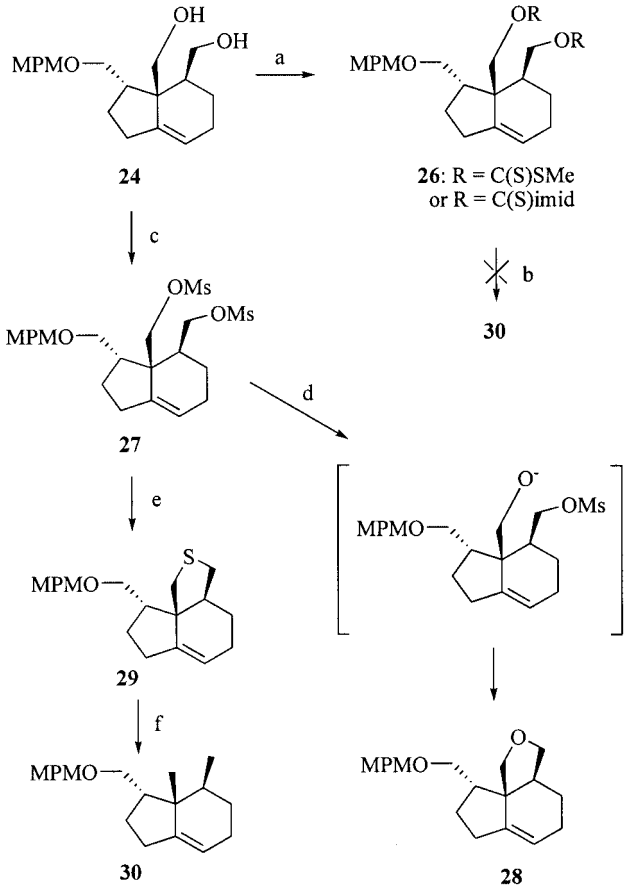
25. The regioisomer of the olefin was confirmed by transformation of **25** into the precursor **20**. Compounds **24** and **25** were then used for synthesis of **1** and **2** (Scheme 3).

Deoxygenation of the diol moiety of **24** was examined first (Scheme 4). Compound **24** was converted into the thioester **26**, which was treated with nBu_3SnH to afford an unknown compound that is probably produced by intramolecular radical coupling. Alternatively, **24** was mesylated to give **27**, which was deoxygenated under hydride reduction conditions with $LiAlH_4$ in Et_2O, $LiEt_3BH$ in THF, or $NaBH_4$ in DMSO to furnish the undesired cyclic compound **28** by cleavage of the S–O bond and successive cyclization. The dimesylated derivative **27** was converted into the cyclic sulfide **29**, which was desulfurized with Raney Ni W-4[13] to afford the desired deoxygenated product **30**.

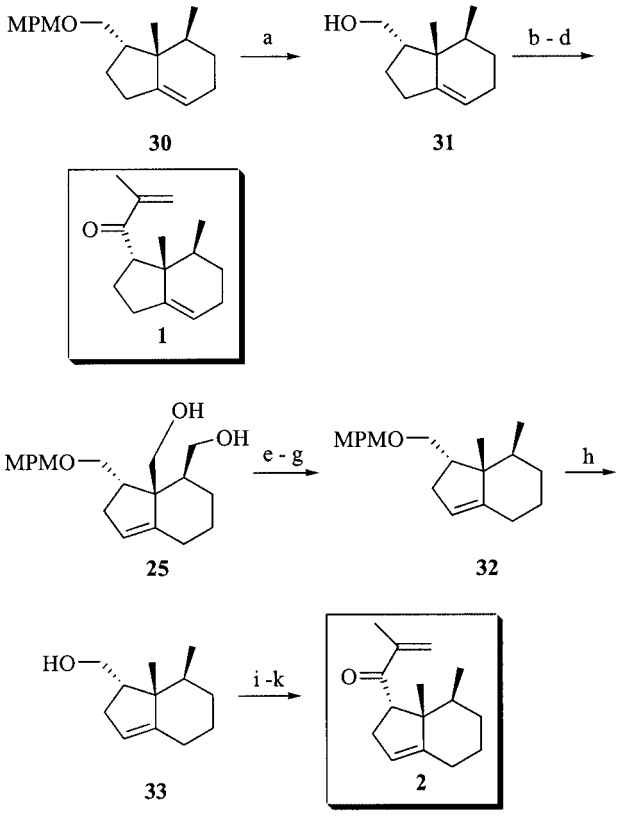
To complete the total synthesis of chiloscyphone **1** and isochiloscyphone **2**, removal of the MPM group of **30** gave the alcohol **31**, which was oxidized, followed by alkylation and further oxidation, to afford **1** (Scheme 5). The yields of the desired product were improved by using the mild oxidation conditions with IBX. Compound **25** was converted into **2** in a similar way. The spectroscopic data of the synthetic **1** and **2** were superimposable with those of the natural products.[4,5]

Evaluation of the Antimicrobial Activity

The obtained synthetic intermediates **5**, **6**, and **17**–**19**, were assessed for various antimicrobial activities against *Bacillus subtilis* PCI 219, *Staphylococcus aureus* FDA 209P, methicillin-resistant *Staphyrococcus aureus*K-24 (a clinical isolate, MRSA), *Micrococcus luteus* PCI 1001, *Mycobacterium smegmatis* ATCC 607, *Escherichia coli* NIHJ, *Escherichia coli* NIHJJ-2 IFO 12734, *Pseudomonas aeruginosa* P-3, *Xanthomonas campestris* pv. *oryzae* KB 88, *Bacteroides fragilis* ATCC 23745, *Acholeplasma laidlawii* PG 8, *Pyricularia oryzae* KF 180, *Aspergillus niger* ATCC 6275, *Mucor racemosus* IFO 4581, *Candida albicans* ATCC 64548, and *Saccharomyces cerevisiae*.[14] Among these, methicillin-resistant *Staphyrococcus aureus* (MRSA) is a drug-resistant bacteria that cause serious infections, therefore chemicals with significant potential as leads for the development of anti-bacterial drugs are urgently required. As shown in Table 2, compound **17** shows antimicrobial activity against *B. subtilis*, *S. aureus*, *M. luteus*, *E. coli* NIHJ, *X. oryzae*, and *A. liadlawii*, as well as anti-MRSA activity. It is thought that the two unsaturated ketone groups of **17** strongly affect these bacterial pathogens. Furthermore, **17** potentiates the imipenem activity, and **5** and **18** also showed selective po-



Scheme 4. Reagents and conditions: (a) DBU, CS_2, MeI, DMF, room temp.; or $(Imid)_2CS$, pyr, room temp.; (b) nBu_3SnH, AIBN, benzene, reflux; (c) MsCl, py, room temp.; (d) $LiAlH_4$, Et_2O, reflux; or $LiEt_3BH$, THF, reflux; or $NaBH_4$, DMSO, 100 °C; (e) $Na_2S{\cdot}9H_2O$, DMF, 50 °C; (f) Raney Ni W-4, THF, room temp., 66% in three steps.



Scheme 5. Reagents and conditions: (a) DDQ, CH_2Cl_2, H_2O, 0 °C, 92%; (b) IBX, DMSO, THF, room temp.; (c) CH_2=C(Me)MgBr, THF, 0 °C; (d) IBX, DMSO, THF, room temp., 75% in three steps; (e) MsCl, py, room temp.; (f) $Na_2S{\cdot}9H_2O$, DMF, 50 °C; (g) Raney Ni W-4, THF, room temp., 60% in three steps; (h) DDQ, CH_2Cl_2, H_2O, 0 °C, 85%; (i) IBX, DMSO, THF, room temp.; (j) CH_2=C(Me)MgBr, THF, 0 °C; (k) IBX, DMSO, THF, room temp., 73% in three steps.

Table 2. Antimicrobial activity.[a]

	6	5	17	18	19
Bacillus subtilis	–	11	44	–	–
Staphylococcus aureus	–	–	19	–	–
Micrococcus luteus	–	–	23	–	–
Esherichia coli[b]	–	–	15	–	–
Esherichia coli[c]	–	14	–	12	–
Pseudomonas aeruginosa	–	–	–	–	–
Xanthomonas campestris pv. *oryzae*	–	25	22	–	–
Bacteroides fragilis	–	–	–	–	–
Acholeplasma laidlawii	10	–	21	–	–
Pyricularia oryzae	–	–	–	–	–
Aspergillus niger	–	–	–	–	–
Mucor racemosus	–	–	–	–	–
Candida albicans	–	–	–	–	–
Saccharomyces cerevisiae	–	–	–	–	–
Mycobacterium smegmatis	–	–	–	–	–
Methicillin-resistant *Staphylococcus aureus*	–	–	16	–	–
Potentiation of imipenem	–	15	30	20	–

[a] The values indicate the diameter of the inhibitory zone on the plates in mm. [b] *Escherichia coli* NIHJ. [c] *Escherichia coli* NIHJJ-2 IFO 12734.

tentiation of imipenem activity. A tricyclic lactone structure including an α,β-unsaturated ketone might therefore be effective in potentiating imipenem activity against MRSA.

Conclusions

We have achieved the total synthesis of chiloscyphone (**1**) and isochiloscyphone (**2**) from the key intermediate **5**, which was synthesized effectively by an intramolecular Diels–Alder reaction. The synthetic intermediates **5**, **17**, and **18** exhibit biological activity against MRSA and/or potentiation of imipenem activity. The tricyclic derivatives might be essential for anti-MRSA activity. It is expected that these results will contribute to the development of new anti-MRSA drugs. A detailed structure–activity relationship study is now in progress.

Experimental Section

General: IR spectra were recorded with a JASCO Model A-202 spectrophotometer. ^1H NMR spectra were recorded at 400 MHz,

and ^{13}C NMR spectra were recorded at 100 MHz with JEOL JNM GX-400 spectrometers with $CDCl_3$ as solvent and tetramethylsilane as internal standard. High-resolution mass spectra were obtained with a Hitachi M-80 B GC-MS spectrometer operating at an ionization energy of 70 eV. Silica gel column chromatography was carried out using Kanto Chemical silica 60 N (spherical, neutral, 63–210 μm). Thin-layer chromatography (TLC) was carried out on 0.25-mm precoated silica gel plates of silica gel 60 F254 (E. Merck, Darmstadt) and visualized with either UV (254 nm) or 5% phosphomolybdic acid in ethanol.

(3*E*)-9-(*tert*-Butyldimethylsiloxy)nona-1,3-dien-5-ol (8): *n*BuLi (1.58 M solution in hexane; 21 mL, 33 mmol) was added dropwise to a solution of (*E*)-*n*$Bu_3SnCH{=}CHCH{=}CH_2$ (11.7 g, 34 mmol) in THF (40 mL) at –78 °C; the resulting solution was stirred at the same temperature for 20 min. A solution of **7** (8.09 g, 37 mmol) in THF (10 mL) was then added dropwise at the same temperature and the mixture stirred for another 10 min. After the addition of saturated aq. NH_4Cl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 20:1→10:1) gave **8** (8.33 g, 93%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3359, 2931, 2858 cm^{-1}. ^1H NMR: δ = 6.40–6.17 (complex, 2 H), 5.71 (dd, J = 6.8, 14.6 Hz, 1 H), 5.20 (d, J = 15.7 Hz, 1 H), 5.09 (d, J = 9.2 Hz, 1 H), 4.15 (m, 1 H), 3.61 (t, J = 6.1 Hz, 2 H), 1.61–1.36 (complex, 6 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR: δ = 136.4, 136.2, 130.9, 117.4, 72.5, 63.1, 48.7, 37.0, 32.7, 26.1, 21.8, –5.1 ppm. HRMS: calcd. for $C_{15}H_{30}O_2Si$ [M^+] 270.2015; found 270.2033.

(3*E*)-5-(*tert*-Butyldimethylsiloxy)-9-(*tert*-butyldiphenylsiloxy)nona-1,3-diene (9): A mixture of **8** (7.89 g, 29 mmol), imidazole (5.20 g, 76 mmol), and TBDPSCl (10 mL, 38 mmol) in DMF (50 mL) was stirred at room temperature for 12 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc/hexane and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 30:1) gave **9** (14.8 g, 100%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2931, 2864 cm^{-1}. ^1H NMR: δ = 7.68–7.63 (complex, 4 H), 7.41–7.32 (complex, 6 H), 6.21 (m, 1 H), 5.87 (dd, J = 10.0, 15.4 Hz, 1 H), 5.61 (dd, J = 7.0, 15.4 Hz, 1 H), 5.03 (d, J = 16.8 Hz, 1 H), 4.99 (d, J = 10.0 Hz, 1 H), 4.17 (m, 1 H), 3.50 (t, J = 6.6 Hz, 2 H), 1.55–1.27 (complex, 6 H), 1.06 (s, 9 H), 0.88 (s, 9 H), 0.02 (s, 6 H) ppm. ^{13}C NMR: δ = 136.5, 135.9, 135.8, 134.4, 134.2, 130.6, 129.4, 127.4, 127.3, 116.4, 73.9, 63.1, 37.7, 32.8, 27.1, 26.0, 21.0, 19.4, 18.4, –5.2 ppm. HRMS: calcd. for $C_{31}H_{48}O_2Si_2$ [M^+] 508.3193; found 508.3186.

(6*E*)-5-(*tert*-Butyldiphenylsiloxy)nona-6,8-dien-1-ol (10): A mixture of **9** (28.6 g, 56 mmol) and PPTS (697 mg, 2.8 mmol) in EtOH (100 mL) was stirred at room temperature for 18 h. After the addition of pyridine (1 mL) at 0 °C, the resulting mixture was concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 5:1) gave **10** (21.1 g, 95%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3340, 2933, 2858 cm^{-1}. ^1H NMR: δ = 7.69–7.62 (complex, 4 H), 7.44–7.33 (complex, 6 H), 6.23 (m, 1 H), 5.90 (dd, J = 10.6, 15.2 Hz, 1 H), 5.63 (dd, J = 6.8, 15.2 Hz, 1 H), 5.05 (d, J = 16.8 Hz, 1 H), 5.00 (d, J = 10.0 Hz, 1 H), 4.18 (m, 1 H), 3.51 (t, J = 6.4 Hz, 2 H), 1.55–1.37 (complex, 6 H), 1.07 (s, 9 H) ppm. ^{13}C NMR: δ = 136.5, 136.3, 135.9, 135.8, 134.4, 134.0, 130.7, 129.5, 129.4, 127.4, 127.3, 116.6, 73.8, 62.8, 37.6, 32.7, 27.1, 20.8, 19.4 ppm. HRMS: calcd. for $C_{21}H_{25}O_2Si$ [$M - C_4H_9^+$] 337.1624; found 337.1654.

(6*E*)-5-(*tert*-Butyldiphenylsiloxy)nona-6,8-dienoic Acid (11): SO_3·py (25.0 g, 157 mmol) was added to a solution of **10** (20.7 g, 53 mmol) in DMSO (50 mL), CH_2Cl_2 (50 mL), and Et_3N (50 mL) at 0 °C; the resulting solution was stirred at the same temperature for 30 min. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. A mixture of the crude residue and PDC (40.0 g, 106 mmol) in DMF (110 mL) was stirred at room temperature for 8 h. After the addition of H_2O at 0 °C, the resulting slurry was partitioned between EtOAc/hexane and H_2O, the combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 20:1→1:1) gave **11** (17.6 g, 82% in two steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2931, 2858, 1709 cm^{-1} ^1H NMR: δ = 7.68–7.62 (complex, 4 H), 7.42–7.33 (complex, 6 H), 6.21 (m, 1 H), 5.89 (m, 1 H), 5.61 (dd, J = 6.6, 15.3 Hz, 1 H), 5.05 (d, J = 16.2 Hz, 1 H), 5.02 (d, J = 9.7 Hz, 1 H), 4.19 (m, 1 H), 2.21 (t, J = 6.6 Hz, 2 H), 1.63–1.49 (complex, 4 H), 1.06 (s, 9 H) ppm. ^{13}C NMR: δ = 180.8, 136.3, 135.8, 134.1, 133.9, 130.9, 129.5, 129.4, 127.4, 127.3, 116.8, 73.4, 37.0, 33.7, 27.1, 19.8, 19.4 ppm. HRMS: calcd. for $C_{25}H_{32}O_3Si$ [M^+] 408.2121; found 408.2110.

Methyl (6*E*)-5-(*tert*-Butyldiphenylsiloxy)nona-6,8-dienoate (12): A mixture of **11** (11.5 g, 28 mmol) and K_2CO_3 (15.6 g, 113 mmol) in DMF (100 mL) was stirred at 0 °C for 5 min. MeI (5.3 mL, 85 mmol) was added dropwise to this mixture at the same temperature and stirred for another 2 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc/hexane and H_2O. The combined organic layers were washed with saturated aq. $Na_2S_2O_3$, saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 15:1) gave **12** (11.8 g, 99%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2952, 2858, 1741 cm^{-1}. ^1H NMR: δ = 7.67–7.62 (complex, 4 H), 7.44–7.33 (complex, 6 H), 6.21 (m, 1 H), 5.88 (dd, J = 10.6, 15.2 Hz, 1 H), 5.61 (dd, J = 6.8, 15.2 Hz, 1 H), 5.05 (d, J = 16.8 Hz, 1 H), 5.00 (d, J = 10.0 Hz, 1 H), 4.19 (m, 1 H), 3.63 (s, 3 H), 2.17 (t, J = 7.0 Hz, 2 H), 1.62–1.46 (complex, 4 H), 1.05 (s, 9 H) ppm. ^{13}C NMR: δ = 173.8, 136.4, 135.9, 135.8, 134.2, 134.0, 130.9, 129.5, 129.4, 127.4, 127.3, 116.8, 73.5, 51.4, 37.2, 34.0, 27.1, 20.1, 19.4 ppm. HRMS: calcd. for $C_{26}H_{34}O_3Si$ [M^+] 422.2277; found 422.2297.

Methyl (6*E*)-5-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-[1-hydroxyethyl-2-(2*H*-3,4,5,6-tetrahydropyran-2-yloxy)]nona-6,8-dienoate (13): *n*BuLi (1.58 M solution in hexane; 24 mL, 38 mmol) was added dropwise to a solution of diisopropylamine (6.0 mL, 43 mmol) in THF (50 mL) at –10 °C and the resulting solution was stirred at the same temperature for 30 min. A solution of **12** (14.6 g, 35 mmol) in THF (20 mL) was then added dropwise to this solution at –78 °C and the resulting solution was stirred at the same temperature for another 30 min. A solution of $THPOCH_2CHO$ (5.70 g, 40 mmol) in THF (3 mL) was added dropwise at –78 °C and the resulting solution was stirred at the same temperature for another 3 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 15:1→1:1) gave **12** (5.11 g, 35% recovery) and **13** (12.0 g, 95% conv.) as a diastereomeric mixture.

2-[(4*E*)-3-(*tert*-Butyldiphenylsiloxy)-4,6-heptadienyl]-2-buten-4-olide (14): A mixture of **13** (12.0 g, 21 mmol) and PPTS (504 mg, 2.0 mmol) in MeOH (60 mL) was stirred at room temperature for

12 h. After the addition of saturated aq. $NaHCO_3$ at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. A mixture of the crude residue and Et_3N (40 mL) in MeOH (400 mL) was stirred at room temperature for 24 h, then the mixture was concentrated in vacuo. A mixture of this crude residue and Ac_2O (10 mL) in pyridine (20 mL) was stirred at room temperature for 12 h, then the mixture was concentrated in vacuo. The crude residue and DBU (6.4 mL, 43 mmol) in PhMe (200 mL) was stirred at 0 °C for 2 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 5:1) gave **14** (7.98 g, 87% in four steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2931, 2858, 1759 cm^{-1}. ^1H NMR: δ = 7.69–7.62 (complex, 4 H), 7.44–7.33 (complex, 6 H), 6.79 (t, J = 1.6 Hz, 1 H), 6.23 (m, 1 H), 5.93 (dd, J = 10.4, 15.2 Hz, 1 H), 5.63 (dd, J = 6.8, 15.2 Hz, 1 H), 5.08 (d, J = 17.2 Hz, 1 H), 5.03 (d, J = 10.4 Hz, 1 H), 4.65 (d, J = 1.6 Hz, 2 H), 4.23 (m, 1 H), 2.28–2.20 (complex, 2 H), 1.77–1.70 (complex, 2 H), 1.07 (s, 9 H) ppm. ^{13}C NMR: δ = 173.9, 143.7, 136.1, 135.9, 135.8, 135.3, 134.1, 134.0, 133.7, 131.3, 129.6, 129.5, 127.5, 127.3, 117.2, 73.0, 70.0, 35.2, 27.1, 20.6, 19.4 ppm. HRMS: calcd. for $C_{23}H_{23}O_3Si$ [M – $C_4H_9^+$] 375.1416; found 375.1391.

2-(3-Hydroxy-4,6-heptadienyl)-2-buten-4-olide (6): A solution of AcOH (0.80 mL, 14 mmol) and TBAF (1 M solution in THF; 16 mL, 16 mmol) was added dropwise to a solution of **14** (2.34 g, 5.4 mmol) in THF (15 mL) at 0 °C and the resulting solution was stirred at room temperature for 15 h. After the addition of saturated aq. $NaHCO_3$ at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 3:1→1:1) gave **6** (966 mg, 92%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3421, 2931, 1747 cm^{-1}. ^1H NMR: δ = 7.15 (t, J = 1.6 Hz, 1 H), 6.39–6.19 (complex, 3 H), 5.71 (dd, J = 6.5, 14.3 Hz, 1 H), 5.21 (d, J = 15.7 Hz, 1 H), 5.11 (d, J = 10.0 Hz, 1 H), 4.78 (d, J = 1.6 Hz, 2 H), 4.19 (m, 1 H), 2.46–2.38 (complex, 2 H), 1.85–1.77 (complex, 2 H) ppm. ^{13}C NMR: δ = 174.3, 144.6, 136.0, 135.5, 133.8, 131.4, 117.9, 71.4, 70.2, 34.9, 21.5 ppm. HRMS: calcd. for $C_{11}H_{14}O_3$ [M^+] 194.0943; found 194.0915.

(1*S*,5*S*)-10-Hydroxy-3-oxatricyclo[7.3.0.0^{1,5}]dodec-7-en-2-one (16): A solution of **6** (874 mg, 4.5 mmol) and BHT (99 mg, 0.45 mmol) in dry PhMe (45 mL) was heated at 180 °C for 48 h in a sealed tube. After being cooled to room temperature, the tube was opened and the mixture was concentrated in vacuo. The crude products were purified by silica gel column chromatography (hexane/EtOAc, 1:1) to give **16** (725 mg, 83%) as a diastereomeric mixture. IR (film): $\tilde{\nu}$ = 3419, 2939, 1747 cm^{-1}. HRMS: calcd. for $C_{11}H_{14}O_3$ [M^+] 194.0943; found 194.0917.

(1*S*,5*S*)-3-Oxatricyclo[7.3.0.0^{1,5}]dodec-8-ene-2,10-dione (5): A solution of DMSO (2.0 mL, 28 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of TFAA (2.0 mL, 14 mmol) in CH_2Cl_2 (35 mL) at –60 °C and the resulting solution was stirred at the same temperature for 15 min. A solution of **16** (917 mg, 4.7 mmol) in CH_2Cl_2 (8 mL) was then added dropwise to this mixture at the same temperature and stirred for another hour. Et_3N (8.0 mL, 58 mmol) was added to this reaction mixture and stirred at 0 °C for another 15 min. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and DBU (1.2 mL, 8.0 mmol) in PhMe (90 mL) was stirred at 0 °C for 2 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 1:1) gave **5** (790 mg, 87% in two steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2912, 1761, 1722, 1651 cm^{-1}. ^1H NMR: δ = 6.84 (t, J = 3.8 Hz, 1 H), 4.56 (dd, J = 5.0, 9.2 Hz, 1 H), 4.09 (d, J = 9.2 Hz, 1 H), 2.80–2.71 (m, 1 H), 2.49 (dd, J = 8.8, 12.4 Hz, 1 H), 2.39–2.22 (complex, 4 H), 1.96–1.90 (m, 1 H), 1.84–1.78 (m, 1 H), 1.66–1.56 (m, 1 H) ppm. ^{13}C NMR: δ = 203.1, 177.6, 136.1, 134.4, 70.9, 49.2, 39.1, 35.2, 31.1, 24.4, 24.0 ppm. HRMS: calcd. for $C_{11}H_{12}O_3$ [M^+] 192.0786; found 192.0766.

(1*S*,5*S*)-3-Oxatricyclo[7.3.0.0^{1,5}]dodec-8,11-diene-2,10-dione (17): Et_3N (2.5 mL, 18 mmol) was added dropwise to a solution of **5** (523 mg, 2.7 mmol) in CH_2Cl_2 (25 mL) at 0 °C and the resulting solution was stirred at the same temperature for 5 min. A solution of TMSOTf (1.5 mL, 8.3 mmol) in CH_2Cl_2 (1 mL) was then added dropwise to this solution at the same temperature and the mixture was stirred at the same temperature for another 30 min. After the addition of saturated aq. $NaHCO_3$ at 0 °C, the resulting slurry was partitioned between $CHCl_3$ and H_2O. The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. The crude residue and $Pd(OAc)_2$ (702 mg, 3.1 mmol) in CH_3CN (50 mL) was stirred at room temperature for 1 h. The reaction mixture was then filtered through a Celite pad and washed with EtOAc. The filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 1:1) gave **17** (508 mg, 98% in two steps) as a colorless powder. IR (KBr): $\tilde{\nu}$ = 2916, 1761, 1703, 1658 cm^{-1}. ^1H NMR: δ = 7.41 (d, J = 5.8 Hz, 1 H), 6.83 (t, J = 4.2 Hz, 1 H), 6.56 (d, J = 5.8 Hz, 1 H), 4.69 (dd, J = 5.2, 9.6 Hz, 1 H), 4.22 (d, J = 9.6 Hz, 1 H), 2.60–2.55 (m, 1 H), 2.40–2.28 (complex, 2 H), 2.04–1.96 (m, 1 H), 1.84–1.74 (m, 1 H) ppm. ^{13}C NMR: δ = 193.4, 174.2, 151.7, 138.1, 135.9, 133.4, 71.4, 55.1, 36.4, 26.2, 23.8 ppm. HRMS: calcd. for $C_{11}H_{10}O_3$ [M^+] 190.0630; found 190.0656.

(1*S*,5*S*,12*R*)-12-Vinyl-3-oxatricyclo[7.3.0.0^{1,5}]dodec-8-ene-2,10-dione (18): CH_2=CHMgBr (1.32 M solution in THF; 4.3 mL, 5.7 mmol) was added dropwise to a mixture of CuI (216 mg, 1.1 mmol) in THF (6 mL) at –25 °C and the resulting mixture was stirred at –20 °C for 30 min. A solution of **17** (359 mg, 1.9 mmol) in THF (7 mL) was then added dropwise to this mixture at –78 °C and the mixture was stirred at the same temperature for another 30 min. After the addition of saturated aq. NH_4Cl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 2:1) gave **18** (309 mg, 75%) as a colorless powder. IR (KBr): $\tilde{\nu}$ = 2939, 1759, 1724, 1651 cm^{-1}. ^1H NMR: δ = 6.94 (t, J = 3.8 Hz, 1 H), 5.47 (m, 1 H), 5.19–5.14 (complex, 2 H), 4.45 (dd, J = 5.2, 9.2 Hz, 1 H), 4.04 (dd, J = 0.8, 5.2 Hz, 1 H), 3.16–3.09 (complex, 2 H), 2.46–2.18 (complex, 3 H), 1.91–1.65 (complex, 3 H) ppm. ^{13}C NMR: δ = 202.3, 177.3, 135.9, 134.3, 118.0, 114.5, 70.3, 44.6, 41.9, 40.6, 35.2, 24.1, 23.9 ppm. HRMS: calcd. for $C_{13}H_{14}O_3$ [M^+] 218.0943; found 218.0928.

{(1*S*,2*S*,9*R*)-1-Hydroxymethyl-9-vinylbicyclo[4.3.0]non-6-en-2-yl}methan-1-ol (19): A mixture of **18** (259 mg, 1.2 mmol) and $NaBH_4$ (151 mg, 4.0 mmol) in MeOH (10 mL) was stirred at 0 °C for 10 min. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and MsCl (0.50 mL, 6.5 mmol) in pyridine (3 mL) was stirred at room

temperature for 4 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and AcOK (1.17 g, 12 mmol) in DMF (14 mL) and H_2O (7 mL) was stirred at 80 °C for 24 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc/hexane and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. DIBAL-H (1.0 M solution in PhMe; 12 mL, 12 mmol) was added to the crude residue in CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred at the same temperature for 1 h. After the addition of 3 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography ($CHCl_3$/MeOH, 40:1) gave **19** (185 mg, 75% in four steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 3296, 2927, 2856 cm^{-1}. ^1H NMR: δ = 5.78 (m, 1 H), 5.34 (br. s, 1 H), 5.05–4.93 (complex, 2 H), 3.74 (d, J = 11.6 Hz, 1 H), 3.69 (dd, J = 4.4, 11.2 Hz, 1 H), 3.60 (dd, J = 4.8, 11.2 Hz, 1 H), 3.33 (d, J = 11.6 Hz, 1 H), 3.10 (m, 1 H), 2.67 (m, 1 H), 2.38 (m, 1 H), 1.93 –1.76 (complex, 3 H), 1.62–1.55 (complex, 3 H), 1.27 (m, 1 H) ppm. ^{13}C NMR: δ = 144.4, 141.4, 121.7, 113.6, 64.2, 63.3, 56.4, 48.1, 42.6, 37.2, 27.1, 26.3, 25.5 ppm. HRMS: calcd. for $C_{13}H_{20}O_2$ [M^+] 208.1463; found 208.1452.

(1*S*,5*S*,6*R*,7*R*)-5,6-Bis[(*tert*-butyldiphenyl)siloxymethyl]-7-vinylbicyclo[4.3.0]nonan-1-ol (20): A mixture of **19** (162 mg, 0.78 mmol), imidazole (0.52 g, 7.6 mmol), and TBDPSCl (1.0 mL, 3.9 mmol) in DMF (4 mL) was stirred at 0 °C for 3 h. After the addition of 1 M HCl at 0 °C, the resulting slurry was partitioned between EtOAc/hexane and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 50:1) gave **20** (516 mg, 97%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2929, 2856 cm^{-1}. ^1H NMR: δ = 7.72–7.24 (complex, 20 H), 5.78 (m, 1 H), 5.22 (br. s, 1 H), 4.85–4.79 (complex, 2 H), 3.87 (dd, J = 3.0, 9.8 Hz, 1 H), 3.72–3.55 (complex, 2 H), 3.24 (dd, J = 3.0, 9.8 Hz, 1 H), 2.82 (m, 1 H), 2.36–2.32 (complex, 2 H), 2.21 (m, 1 H), 1.90–1.78 (complex, 5 H), 1.38 (m, 1 H), 1.00 (s, 9 H), 0.88 (s, 9 H) ppm. ^{13}C NMR: δ = 145.2, 140.8, 135.7, 135.6, 135.5, 134.0, 133.4, 133.3, 129.4, 129.3, 129.2, 127.5, 127.4, 127.3, 120.7, 113.3, 65.3, 65.1, 55.8, 55.2, 48.3, 44.4, 37.1, 27.8, 26.9, 26.8, 26.4, 26.1, 19.3, 19.1 ppm. HRMS: calcd. for $C_{45}H_{56}O_2Si_2$ [M^+] 684.3819; found 684.3811.

(1*S*,5*S*,6*R*,7*R*)-5,6-Bis[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-7-vinylbicyclo[4.3.0]nonan-1-ol (21): A mixture of **20** (474 mg, 0.69 mmol), NaH_2PO_4 (610 mg), and *m*CPBA (601 mg, 2.3 mmol) in CH_2Cl_2 (7 mL) was stirred at –20 °C for 2 h. After the addition of saturated aq. $Na_2S_2O_3$, the resulting slurry was partitioned between $CHCl_3$ and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. $LiEt_3BH$ (1.0 M solution in THF; 3.5 mL, 3.5 mmol) was added dropwise to the crude residue in THF (3.5 mL) at 0 °C and the mixture was stirred at room temperature for 3 h. After the addition of 1 M HCl, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 40:1) gave **21** (361 mg, 74% in two steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 3585, 2931, 2856 cm^{-1}. ^1H NMR: δ = 7.68–7.25 (complex, 20 H), 6.18 (m, 1 H), 4.87–4.83 (complex, 2 H), 4.06 (dd, J = 2.4, 10.4 Hz, 1 H), 3.78 (d, J = 10.4 Hz, 1 H), 3.73 (d, J = 10.4 Hz, 1 H), 3.71 (d, J = 10.4 Hz, 1 H), 2.96 (m, 1 H), 2.83 (m, 1 H), 2.31–2.27 (complex, 2 H), 1.71–1.43 (complex, 5 H), 1.31–1.17 (complex, 3 H), 1.03 (s, 9 H), 0.80 (s, 9 H) ppm. ^{13}C NMR: δ = 143.7, 136.0, 135.7, 135.6, 135.5, 134.2, 133.1, 132.7, 129.6, 129.5, 129.2, 127.7, 127.5, 127.4, 127.3, 113.9, 82.7, 66.5, 63.2, 54.6, 53.2, 44.6, 40.0, 37.0, 30.9, 27.0, 26.9, 26.6, 24.9, 20.5, 19.3, 19.0 ppm. HRMS: calcd. for $C_{45}H_{58}O_3Si_2$ [M^+] 702.3924; found 702.3919.

(1*S*,5*S*,6*R*,7*S*)-5,6-Bis[(*tert*-butyldiphenylsiloxy)methyl]-7-(hydroxymethyl)bicyclo[4.3.0]nonan-1-ol (22): To a solution of **21** (361 mg, 0.51 mmol) and Me_3NO (170 mg, 1.5 mmol) in acetone (5.0 mL) and H_2O (1.5 mL) was added OsO_4 0.04 M solution in *t*BuOH (0.65 mL, 0.026 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h. To this mixture were added NaH_2PO_4 (310 mg, 2.6 mmol) and $NaIO_4$ (551 mg, 2.6 mmol) at 0 °C. The mixture was stirred at room temperature for another hour. After the addition of saturated aq. Na_2SO_3, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $Na_2S_2O_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and $NaBH_4$ (101 mg, 2.6 mmol) in MeOH (5.0 mL) was stirred at 0 °C for 20 min. After the addition of 1 M HCl, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 3:1) gave **22** (212 mg, 58% in two steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 3221, 2931, 2858 cm^{-1}. ^1H NMR: δ = 7.72–7.24 (complex, 20 H), 3.95 (d, J = 9.2 Hz, 1 H), 3.83–3.77 (complex, 2 H), 3.54 (dd, J = 2.0, 11.2 Hz, 1 H), 3.39 (dd, J = 4.4, 11.2 Hz, 2 H), 2.81 (d, J = 10.8 Hz, 1 H), 2.51 (m, 1 H), 2.31–2.23 (complex, 2 H), 1.80–1.68 (complex, 3 H), 1.55–1.34 (complex, 3 H), 1.22–1.16 (complex, 2 H), 1.05 (s, 9 H), 0.83 (s, 9 H) ppm. ^{13}C NMR: δ = 135.7, 135.6, 135.5, 134.2, 133.9, 133.0, 132.7, 129.6, 129.4, 129.3, 127.7, 127.6, 127.5, 80.3, 67.8, 63.7, 62.2, 60.4, 54.4, 41.2, 40.0, 37.2, 30.2, 27.0, 26.9, 25.6, 21.8, 20.4, 19.3, 19.0, 14.3 ppm. HRMS: calcd. for $C_{44}H_{58}O_4Si_2$ [M^+] 706.3874; found 706.3871.

(1*S*,5*S*,6*R*,7*S*)-5,6-Bis[(*tert*-butyldiphenylsiloxy)methyl]-7-[(4-methoxyphenyl)methoxy]bicyclo[4.3.0]nonan-1-ol (23): To a solution of **22** (212 mg, 0.30 mmol) in DMF (5 mL) was added NaH 60% dispersion in oil (250 mg, 6.3 mmol) at 0 °C. The mixture was stirred at the same temperature for 10 min. To this mixture were added MPMCl (0.40 mL, 3.0 mmol) and TBAI (11 mg, 0.03 mmol) at 0 °C. The mixture was stirred at the same temperature for another 20 min. After the addition of MeOH, the resulting slurry was partitioned between EtOAc/hexane and H_2O. The combined organic layers were washed with 1 M HCl, saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 20:1→5:1) gave **23** (174 mg, 70%) as a colorless powder. IR (KBr): $\tilde{\nu}$ = 3396, 2931, 2858 cm^{-1}. ^1H NMR: δ = 7.71–7.24 (complex, 22 H), 6.89–6.86 (complex, 2 H), 4.79 (br. s, 1 H), 4.51 (d, J = 11.6 Hz, 1 H), 4.36 (d, J = 11.6 Hz, 1 H), 3.98 (d, J = 9.7 Hz, 1 H), 3.88–3.73 (complex, 2 H), 3.78 (s, 3 H), 3.53 (dd, J = 2.2, 9.7 Hz, 1 H), 3.37 (dd, J = 4.5, 9.7 Hz, 1 H), 2.82 (d, J = 9.7 Hz, 1 H), 2.61 (m, 1 H), 2.43 (m, 1 H), 2.23 (m, 1 H), 1.92–1.38 (complex, 9 H), 1.09 (s, 9 H), 0.78 (s, 9 H) ppm. ^{13}C NMR: δ = 159.1, 135.6, 135.5, 135.4, 134.2, 133.9, 133.0, 132.7, 129.5, 129.4, 129.3, 129.2, 127.6, 127.5, 127.4, 113.8, 79.5, 73.1, 70.3, 68.0, 63.9, 60.4, 55.2, 54.5, 40.2, 39.8, 37.2, 29.9, 27.1, 26.9, 26.1, 22.7, 20.5, 19.4, 19.0, 14.3 ppm. HRMS: calcd. for $C_{52}H_{66}O_5Si_2$ [M^+] 826.4449; found 826.4440.

[(3*S*,4*S*,3a*R*)-3a-(Hydroxymethyl)-3-{[(4-methoxyphenyl)methoxy]-methyl}-2,3,4,5,6,3a-hexahydroinden-4-yl]methan-1-ol (24). [(2*S*,9*S*,1*R*)-1-(Hydroxymethyl)-9-{[(4-methoxyphenyl)methoxy]-

methyl}bicyclo[4.3.0]non-6-en-2-yl]methan-1-ol (25): A mixture of **23** (108 mg, 0.13 mmol) and $SOCl_2$ (0.20 mL, 2.7 mmol) in pyridine (1.2 mL) was stirred at –30 °C for 20 min. After the addition of MeOH, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with 1 M HCl, saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue in THF (1.5 mL) was added TBAF 1 M solution in THF (1.5 mL, 1.5 mmol) at 0 °C. The mixture was stirred at 50 °C for 3 h. After the addition of H_2O, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 1:1) gave **24** (8.0 mg, 18% in two steps) and **25** (33.0 mg, 76% in two steps) as a colorless oil.

24: IR (film): $\tilde{\nu}$ = 3330, 2929, 2856 cm^{-1}. ^1H NMR: δ = 7.22 (d, J = 8.8 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 5.57 (m, 1 H), 4.40 (complex, 2 H), 3.80 (s, 3 H), 3.72 (dd, J = 5.4, 11.8 Hz, 2 H), 3.40 (m, 1 H), 3.34 (m, 1 H), 3.24 (complex, 2 H), 2.91 (m, 1 H), 2.33 (m, 1 H), 2.12–1.99 (complex, 4 H), 1.83 (m, 1 H), 1.40–1.35 (complex, 3 H) ppm. ^{13}C NMR: δ = 159.4, 141.9, 129.5, 129.1, 122.5, 122.4, 113.8, 72.9, 72.3, 66.0, 61.8, 55.3, 51.7, 42.1, 38.9, 27.3, 25.2, 25.1, 21.6 ppm. HRMS: calcd. for $C_{20}H_{28}O_4$ [M^+] 332.1988; found 332.1984.

25: IR (film): $\tilde{\nu}$ = 3348, 2929, 2856 cm^{-1}. ^1H NMR: δ = 7.25–7.23 (complex, 2 H), 6.89–6.87 (complex, 2 H), 5.31 (m, 1 H), 4.43 (s, 2 H), 3.93 (d, J = 10.8 Hz, 1 H), 3.80 (s, 3 H), 3.67 (dd, J = 5.2, 10.8 Hz, 1 H), 3.61 (m, 1 H), 3.43 (m, 1 H), 3.33 (dd, J = 4.0, 10.8 Hz, 1 H), 3.22 (d, J = 10.8 Hz, 1 H), 2.87 (m, 1 H), 2.56 (m, 1 H), 2.32 (m, 1 H), 1.84–1.80 (complex, 3 H), 1.49–1.11 (complex, 4 H) ppm. ^{13}C NMR: δ = 159.4, 145.2, 129.6, 129.0, 121.9, 121.8, 113.9, 73.0, 71.9, 65.4, 64.0, 55.7, 55.3, 44.0, 41.1, 34.5, 27.6, 26.1, 25.9 ppm. HRMS: calcd. for $C_{20}H_{28}O_4$ [M^+] 332.1988; found 332.1986.

{[(1*S*,7*S*,7a*S*)-7,7a-Dimethyl-2,3,5,6,7,7a-hexahydroindenyl]methoxy}(4-methoxyphenyl)methane (30): A mixture of **24** (10.0 mg, 0.030 mmol) and MsCl (0.1 mL) in pyridine (0.5 mL) was stirred at room temperature for 1 h. After the addition of 1 M HCl, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and $Na_2S{\cdot}9H_2O$ (71 mg, 0.50 mmol) in DMF (3.0 mL) was stirred at 50 °C for 12 h. After the addition of H_2O, the resulting slurry was partitioned between EtOAc/hexane and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and Raney Ni W-4 (ca.100 mg) in THF (3.0 mL) was stirred at room temperature for 3 h. The reaction mixture was filtered through a Celite pad, and washed with EtOAc. The filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 10:1) gave **30** (6.0 mg, 66% in three steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2954, 2922, 2852 cm^{-1}. ^1H NMR: δ = 7.25 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 5.31 (m, 1 H), 4.39 (complex, 2 H), 3.80 (s, 3 H), 3.43 (dd, J = 5.2, 9.2 Hz, 1 H), 2.96 (t, J = 9.2 Hz, 1 H), 2.41 (m, 1 H), 2.22–1.42 (complex, 9 H), 0.90 (d, J = 7.6 Hz, 3 H), 0.89 (s, 3 H) ppm. ^{13}C NMR: δ = 159.0, 147.2, 130.9, 129.1, 129.0, 117.4, 116.3, 113.7, 72.6, 70.8, 55.3, 47.0, 46.2, 32.4, 27.4, 26.6, 25.7, 23.4, 20.2, 17.0 ppm. HRMS: calcd. for $C_{20}H_{28}O_2$ [M^+] 300.2089; found 300.2081.

[(1*S*,7*S*,7a*S*)-7,7a-Dimethyl-2,3,5,6,7,7a-hexahydroindenyl]-methan-1-ol (31): A mixture of **30** (6.0 mg, 0.020 mmol) and DDQ (21 mg, 0.090 mmol) in CH_2Cl_2 (0.5 mL) and H_2O (0.025 mL) was stirred at 0 °C for 10 min. After the addition of saturated aq. $NaHCO_3$, the resulting slurry was partitioned between $CHCl_3$ and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (PhMe/EtOAc, 10:1) gave **31** (3.3 mg, 92%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3334, 2954, 2922, 2852 cm^{-1}. ^1H NMR: δ = 5.34 (m, 1 H), 3.63 (dd, J = 4.8, 10.0 Hz, 1 H), 3.32 (dd, J = 7.2, 10.0 Hz, 1 H), 2.47 (m, 1 H), 2.30 (m, 1 H), 2.04–1.42 (complex, 8 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.91 (s, 3 H) ppm. ^{13}C NMR: δ = 147.5, 117.3, 63.8, 49.3, 46.0, 32.6, 27.8, 26.6, 25.7, 23.1, 20.2, 16.9 ppm. HRMS: calcd. for $C_{12}H_{20}O$ [M^+] 180.1514; found 180.1518.

Chiloscyphone (1): A mixture of **31** (3.3 mg, 0.018 mmol) and IBX (20 mg, 0.073 mmol) in DMSO (0.3 mL) and THF (0.6 mL) was stirred at room temperature for 1 h. The mixture was concentrated and through a silica gel short column, and washed with EtOAc/hexane. The filtrate was concentrated in vacuo The crude residue in THF (0.5 mL) was added isopropenylmagnesium bromide 0.5 M solution in THF (0.5 mL, 0.25 mmol) at 0 °C. The mixture was stirred at the same temperature for 30 min. After the addition of 1 M HCl, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and IBX (21 mg, 0.073 mmol) in THF (0.6 mL) and DMSO (0.3 mL) was stirred at room temperature for 12 h. The mixture was concentrated and purified by silica gel column chromatography (hexane/EtOAc, 20:1) to give **1** (3.0 mg, 75% in three steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2952, 2856, 1665 cm^{-1}. ^1H NMR: δ = 5.94 (br. s, 1 H), 5.73 (br. s, 1 H), 5.42 (m, 1 H), 3.58 (dd, J = 7.6, 1.6 Hz, 1 H), 2.53 (m, 2 H), 2.10–1.84 (complex, 6 H), 1.70–1.25 (complex, 4 H), 0.98 (s, 3 H), 0.85 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 206.5, 146.5, 146.0, 123.7, 117.1, 52.6, 49.8, 33.1, 29.1, 27.1, 26.1, 25.5, 20.6, 17.8, 17.5 ppm. HRMS: calcd. for $C_{15}H_{22}O$ [M^+] 218.1671; found 218.1666.

{[(1*S*,7*S*,7a*S*)-7,7a-Dimethyl(2,4,5,6,7,7a-hexahydroindenyl)]methoxy}(4-methoxyphenyl)methane (32): A mixture of **25** (12.0 mg, 0.036 mmol) and MsCl (0.1 mL) in pyridine (0.5 mL) was stirred at room temperature for 1 h. After the addition of 1 M HCl, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and $Na_2S{\cdot}9H_2O$ (120 mg, 0.50 mmol) in DMF (3.6 mL) was stirred at 50 °C for 12 h. After the addition of H_2O, the resulting slurry was partitioned between EtOAc/hexane and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and Raney Ni W-4 (ca.100 mg) in THF (3.6 mL) was stirred at room temperature for 3 h. The reaction mixture was filtered through a Celite pad, and washed with EtOAc. The filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 10:1) gave **32** (6.5 mg, 60% in three steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2924, 2852 cm^{-1}. ^1H NMR: δ = 7.26 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.09 (m, 1 H), 4.45 (d, J = 11.2 Hz, 1 H), 4.39 (d, J = 11.2 Hz, 1 H), 3.81 (s, 3 H), 3.51 (dd, J = 4.4, 8.8 Hz, 1 H), 3.20 (dd, J = 8.8, 10.2 Hz, 1 H), 2.43 (m, 1 H), 2.30–2.17 (complex, 2 H), 1.93 (m, 1 H), 1.68 (m, 1 H), 1.45–1.12 (complex, 5 H), 0.91 (s, 3 H), 0.85 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 158.9, 149.0, 130.8, 129.1, 128.9, 118.2, 118.1, 113.6, 72.7, 71.1, 55.3, 50.2, 47.3, 35.1, 33.0, 30.8, 26.4, 26.2, 18.0, 17.9 ppm. HRMS: calcd. for $C_{20}H_{28}O_2$ [M^+] 300.2089; found 300.2085.

[(1*S*,7*S*,7a*S*)-7,7a-Dimethyl-2,4,5,6,7,7a-hexahydroindenyl]-methan-1-ol (33): A mixture of **32** (15.0 mg, 0.050 mmol) and DDQ (28 mg, 0.12 mmol) in CH_2Cl_2 (1.0 mL) and H_2O (0.05 mL) was

stirred at 0 °C for 10 min. After the addition of saturated aqueous $NaHCO_3$, the resulting slurry was partitioned between $CHCl_3$ and H_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel column chromatography (PhMe/EtOAc, 10:1) gave **33** (7.7 mg, 85%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3334, 2956, 2925, 2852 cm^{-1}. ^1H NMR: δ = 5.15 (m, 1 H), 3.70 (dd, J = 4.0, 10.0 Hz, 1 H), 3.49 (dd, J = 8.0, 10.0 Hz, 1 H), 2.50 (m, 1 H), 2.30 (m, 1 H), 2.18 (m, 1 H), 2.05–1.91 (complex, 2 H), 1.73–1.15 (complex, 5 H), 0.92 (s, 3 H), 0.89 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR: δ = 150.2, 118.2, 64.1, 50.1, 49.6, 34.9, 32.5, 30.7, 26.4, 26.2, 18.0, 17.8 ppm. HRMS: calcd. for $C_{12}H_{20}O$ [M^+] 180.1514; found 180.1514.

Isochiloscyphone (2): A mixture of **33** (3.6 mg, 0.020 mmol) and IBX (21 mg, 0.073 mmol) in DMSO (0.3 mL) and THF (0.6 mL) was stirred at room temperature for 1 h. The mixture was concentrated and through a silica gel short column, and washed with EtOAc/hexane. The filtrate was concentrated in vacuo. The crude residue in THF (0.5 mL) was added isopropenylmagnesium bromide 0.5 M solution in THF (0.5 mL, 0.25 mmol) at 0 °C. The mixture was stirred at the same temperature for 30 min. After the addition of 1 M HCl, the resulting slurry was partitioned between EtOAc and H_2O. The combined organic layers were washed with saturated aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue and IBX (20 mg, 0.073 mmol) in THF (0.6 mL) and DMSO (0.3 mL) was stirred at room temperature for 12 h. The mixture was concentrated and purified by silica gel column chromatography (hexane/EtOAc, 20:1) to give **2** (3.2 mg, 73% in three steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2925, 2854, 1662 cm^{-1} ^1H NMR: δ = 6.02 (br. s, 1 H), 5.77 (br. s, 1 H), 5.19 (m, 1 H), 3.71 (m, 1 H), 2.45 (complex, 2 H), 2.31 (m, 1 H), 1.90 (br. s, 3 H), 1.68–1.25 (complex, 6 H), 1.10 (s, 3 H), 0.60 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR: δ = 205.1, 149.1, 140.5, 124.0, 118.0, 52.3, 35.4, 35.3, 31.3, 29.7, 27.1, 26.2, 19.9, 18.2, 17.9 ppm. HRMS: calcd. for $C_{15}H_{22}O$ [M^+] 218.1671; found 218.1677.

Antimicrobial Activity against 15 Species of Microorganisms: Antimicrobial activity against 15 species of microorganisms was measured by the agar diffusion method using paper disks (i.d 6 mm, ADVANTEC). The microorganisms were as follows; *Bacillus subtilis* PCI 219, *Staphylococcus aureus* FDA 209P, methicillin-resistant *Staphyrococcus aureus* K-24 (a clinica isolate, MRSA), *Micrococcus luteus* PCI 1001, *Mycobacterium smegmatis* ATCC 607, *Escherichia coli* NIHJ, *Escherichia coli* NIHJJ-2 IFO 12734, *Pseudomonas aeruginosa* P-3, *Xanthomonas campestris* pv. *oryzae* KB 88, *Bacteroides fragilis* ATCC 23745, *Acholeplasma laidlawii* PG 8, *Pyricularia oryzae* KF 180, *Aspergillus niger* ATCC 6275, *Mucor racemosus* IFO 4581, *Candida albicans* ATCC 64548 and *Saccharomyces cerevisiae*. Media for microorganisms were as follows: GAM agar (Nissui Seiyaku Co.) for *B. fragilis*; Bacto PPLO agar (Difco) supplemented with 15% horse serum, 0.1% glucose, 0.25% phenol red (5 mg/mL) and 1.5% agar for *A. laidlawii*; Mueller–Hinton broth (Difico) and 1.5% agar (Shimizu Shokuhin Co.) for MRSA; Taiyo agar (Shimizu Syokuhin Kaisya Ltd.) for the other bacteria; a medium composed of 1.0% yeast extract, and 0.8% agar for fungi and yeasts. A paper disk containing 10 μg of a sample was placed on an agar plate. Bacteria except for *X. oryzae* were incubated at 37 °C for 24 h. Yeasts and *X. oryzae* were incubated at 27 °C for 24 h. Fungi were incubated at 27 °C for 48 h. Antimicrobial activity was expressed as diameter [mm] of the inhibitory zone.

In vitro Assay for Potential of Imipenem Activity Against Methicillin-Resistant *Staphylococcus Aureus*: MRSA (2.0×10^7 CFU) was spread on the HMA medium in a plastic plate (10 × 14 cm, Eikiken Kizai Co) containing Mueller–Hinton broth and 1.5% agar plate with or without imipenem at 10 μg/mL (HMA+IMP plate or HMA plate, respectively), which concentration has no effect on MRSA growth. Paper disks (Advantec) containing a sample (10 μg) were placed on the HMA+IMP and HMA plate, and incubated at 37 °C for 20 h. Anti-MRSA activity was expressed as diameter [mm] of the inhibitory zone on the plates. If the sample potentiates the imipenem activity, larger inhibitory zone is observed on the HMA+IMP plate than on the HMA plate.

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