Selected data. IR ($cm^{-1}$, neat): 1762–1763 (vs), 1174 (vs). $^1H$ NMR ($\delta$, $C_6D_6$; HCCN and $OCH_3$ resonances): (*SS*)/(*SR*)-**4a**, 4.75/4.68 (q, $J_{HH}$ = 7.0 Hz), 3.30/3.20 (q, $J_{HF}$ = 1.2 Hz); (*SS*)/(*SR*)-**4b**, 4.77/4.69 (t, $J_{HH}$ = 6.5 Hz), 3.32/3.22 (q, $J_{HF}$ = 1.2 Hz); (*SS*)/(*SR*)-**4c**, 4.82/4.74 (d, $J_{HH}$ = 5.7 Hz), 3.34/3.24 (q, $J_{HF}$ = 1.2 Hz); (*SS*)/(*SR*)-**4d**, 5.17/5.10 (dd, $J_{HH}$ = 7.3/6.1 Hz), 3.25/3.06 (q, $J_{HF}$ = 1.2 Hz); (*SS*)/(*SR*)-**4e**, 6.04/6.03 (s), 3.31/3.16 (q, $J_{HF}$ = 1.2 Hz).

**Acknowledgment.** We thank the NIH for support of this research and an NSRA postdoctoral Fellowship (C. M.G).

**Supplementary Material Available:** Complete IR, NMR ($^1H$, $^{13}C$), and mass spectroscopic data for (*SS*)-**4a–e** and partial data for (*SR*)-**4a–e** in tabular format (4 pages). Ordering information is given on any current masthead page.

# Total Synthesis of (±)-Clavukerin A: A New Trinorguaiane Sesquiterpene. Biomimetic Synthesis of (±)-Clavularin A from (±)-Clavukerin A

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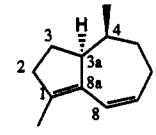
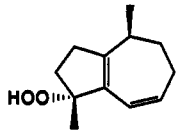
(±)-Clavukerin A, 2,8-dimethylbicyclo[5.3.0]deca-5,7-diene, was first synthesized utilizing thermal [2 + 2] cycloaddition and two carbon ring expansion reactions as key elements. (±)-Clavukerin A was transformed, via photooxidation mimicking the biogenetic reaction, into (±)-clavukerin C, which was further rearranged into (±)-clavularin A by acid catalysis.

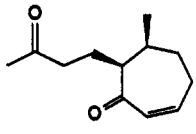
(−)-Clavukerin A, an unstable trinorguaiane sesquiterpene, was first isolated by the Kitagawa[1] group from the Okinawan soft coral, *Clavularia koellikeri*, along with (−)-clavukerin C. Its structure was deduced by spectral and chemical analysis in addition to X-ray crystallography of its diepoxide derivative as (1*S*,2*S*)-2,8-dimethylbicyclo[5.3.0]deca-5,7-diene. From the same coral the Endo group[2] isolated the cytotoxic (−)-clavularins A and B, which were assumed to be derived from (−)-clavukerin C either biogenetically or secondarily during the isolation of the unstable (−)-clavukerin C. Later the Kitagawa group obtained (−)-clavularin A and (−)-clavukerin C from (−)-clavukerin A by chemical oxidation (with $OsO_4/NaIO_4$) and photooxidation[1], respectively. Recently syntheses of (±)-clavularin A and (±)-clavularin B have been reported.[3,4]



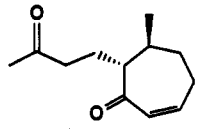

(-)-Clavukerin A




(-)-Clavukerin C



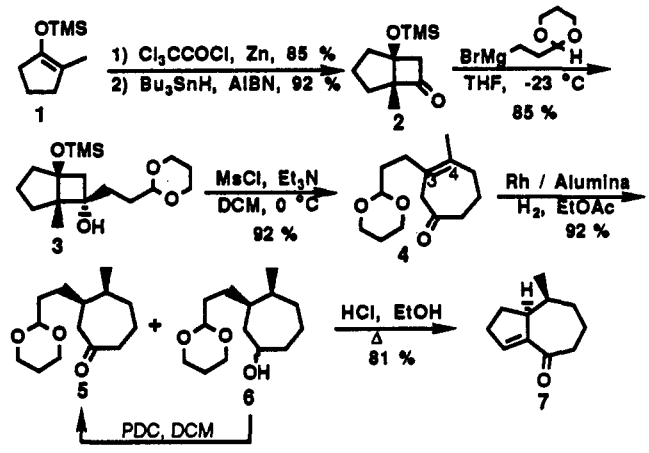

(-)-Clavularin A




(-)-Clavularin B

Here we report our efficient approach to the first total synthesis of (±)-clavukerin A employing our previously reported[5] methodology for the formation of substituted $\beta,\gamma$-unsaturated cycloheptenones. As a preliminary study

**Scheme I**




before the synthesis of (±)-clavukerin A, we undertook the preparation of enone **7**, which has the same trans configuration[6] between the C-3a proton and C-4 methyl as (±)-clavukerin A (Scheme I). A similar synthetic strategy, which involves fusion of the five-membered ring onto a preexisting cycloheptane ring, was first used by Heathcock[7] for the synthesis of the hydroazulene ring system. However, our approach has the distinctive feature that the side chain attachment to the $\beta,\gamma$-unsaturated cycloheptenone was easily accomplished through our method and highly selective stereochemical control of the relative configuration of the C-3 and C-4 substituents was possible via catalytic hydrogenation. Silyl enol ether **1** of 2-methylcyclopentanone was converted to bicyclic ketone **2** according to a known procedure.[5] Addition of the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxane in THF at −23 °C to ketone **2** afforded exclusively endo alcohol **3** in 85% yield.

(1) (a) Kobayashi, M.; Son, B. W.; Kido, M.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 6. (b) Kobayashi, M.; Son, B. W.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 1667. (c) Numbering of the clavukerins and related compounds throughout this paper is based on the hydroazulene ring system.

(2) Endo, M.; Nakagawa, M.; Hamamoto, Y.; Nakanishi, T. *J. Chem. Soc., Chem. Commun.* **1983**, 322.

(3) Still, I. W.; Shi, Y. *Tetrahedron Lett.* **1987**, 2489.

(4) Urech, R. *J. Chem. Soc., Chem. Commun.* **1984**, 989.

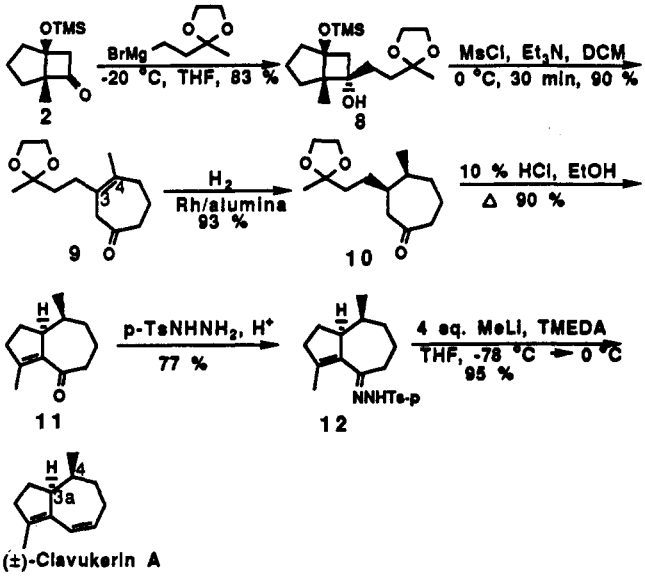
(5) Pak, C. S.; Kim, S. K. *J. Org. Chem.* **1990**, *55*, 1954.

(6) The terms cis and trans in this paper refer to the relationship between the C-3a proton and C-4 methyl of the hydroazulene nucleus.

(7) (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. 5, pp 333–390 and references cited therein. (b) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081. (c) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.

0022-3263/91/1956-6829$02.50/0 

**Scheme II**




Fragmentation of **3** took place by treatment with MsCl and $Et_3N$ in $CH_2Cl_2$ at 0 °C to give $\beta,\gamma$-unsaturated cycloheptenone **4** in 90% yield. This fragmentation reaction might have taken place under the mesylation conditions via chloride ion promoted Si–O bond cleavage.[8] Highly stereoselective catalytic hydrogenation of **4** was achieved in the presence of rhodium on alumina in ethyl acetate, affording a stereoisomeric mixture (cis:trans/15:1) of **5** (74%) in addition to overreduced alcohol **6** (18%), which was readily converted to the corresponding ketone **5** by treatment with PDC. The ratio of stereoisomers of ketone **5** was determined by integration of the distinctively separated C-4 methyl protons ($\delta$ 0.86 ppm for cis, 0.99 ppm for trans). The relative configuration of the major isomer of **5** is opposite to that of Heathcock.[9] Acid-catalyzed cyclization of **5** was carried out according to a known procedure to obtain enone **7** with the same isomeric ratio.

Since our model study proved the possibility of constructing two stereocenters (C-3a and C-4) of (±)-clavukerin A in a stereoselective manner, we employed the same reaction route for the preparation of (±)-clavukerin A simply by using 2-(2-bromoethyl)-2-methyl-1,3-dioxolane as a four-carbon unit (Scheme II). Bicyclic ketone **2** was treated with the corresponding Grignard reagent to give endo alcohol[10] **8** (83%), which was subsequently subjected to fragmentation conditions to afford cycloheptenone **9** (90%).[11] Catalytic hydrogenation in the presence of rhodium on alumina in EtOAc afforded a stereoisomeric mixture (cis:trans/19:1) of **10** (69%) in addition to overreduced alcohol (24%), which was oxidized, without changing the isomeric ratio, to ketone **10** by treatment with PDC. The ratio of the stereoisomers was determined by integration of the C-4 methyl protons ($\delta$ 0.88 ppm for cis, 1.00 ppm for trans). The relative configuration was further confirmed later by analysis of the final product, (±)-clavukerin A. Other trials of hydrogenation for further improvement of stereoselectivity (Pd/C, Wilkinson's catalyst) were not successful.[12]

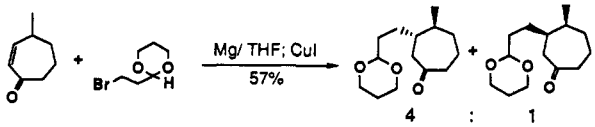
Subsequent reactions were carried out without purification of the stereoisomeric mixture. Acid-catalyzed deketalization of **10** with HCl in aqueous ethanol was accompanied by aldol condensation and dehydration to afford cyclized enone **11** in 90% yield, conserving the same stereoisomeric ratio as for **10** according to the integration of the C-4 methyl protons ($\delta$ 0.75 ppm for cis, 0.95 ppm for trans). Enone **11** was transformed into the corresponding crystalline hydrazone **12** by treatment with $TsNHNH_2$ in the presence of a catalytic amount of concd HCl at −20 °C. Attempts to purify further the stereoisomeric mixture of **12** (cis:trans/19:1) by crystallization were not successful. Hydrazone **12** was treated with $CH_3Li$ (4 equiv) and TMEDA (10 equiv) in THF at −78 °C for 1 h.[13] Then the reaction mixture was warmed to 0 °C, stirred for an additional 1 h, and quenched by the addition of water. After workup, (±)-clavukerin A was obtained as a colorless liquid in 95% yield.[14] Synthetic (±)-clavukerin A containing 5% of its cis isomer was identical with the natural compound in every respect ($^1H$ NMR, $^{13}C$ NMR, UV, HRMS).

With synthetic (±)-clavukerin A in hand, a biomimetic transformation was performed by photooxidation in MeOH–pyridine solution containing methylene blue as a sensitizer to give (±)-clavukerin C in 79% yield.[1b] Even if the more substituted double bond ($C_1$=$C_{8a}$; compared to $C_7$=$C_8$) is attacked preferentially by singlet oxygen,[15] a variety of complications are expected owing to the number of allylic hydrogens present in the $C_1$=$C_{8a}$ ene unit.[16,17] However, singlet oxygen showed a surprising preference for C-3a methine hydrogen abstraction over the other abstractable hydrogens (C-1 methyl, C-2 methylene) so as to generate the hydroperoxy group in the correct stereochemistry as (±)-clavukerin C (Scheme III). No other side products were observed by TLC (single spot, hexane:ether/1:1, $R_f$ = 0.6).

The regiospecificity observed here is very rare[18,19] since methine hydrogens are known to be unreactive compared to methylene or methyl hydrogens.[17] Thus, according to $^1H$ NMR spectra, the isomeric ratio of (±)-clavukerin A has been retained in (±)-clavukerin C exhibiting two methyl doublets ($\delta$ 1.05 major, $\delta$ 1.09 minor isomer) for C-4 methyl, two methyl singlets ($\delta$ 1.28 major, $\delta$ 1.32 minor isomer) for C-1 methyl, and two peroxide, OOH, singlets ($\delta$ 7.20 minor, 7.25 major isomer) which upon treatment with $D_2O$ completely disappeared. Complete disappearance of the C-3a proton peak of (±)-clavukerin A whether it is cis or trans after photooxidation seems to indicate that the ene reaction of singlet oxygen does not seem to have

(8) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(9) According to ref 7b, attachment of a side chain to $\alpha,\beta$-unsaturated cycloheptenone was carried out via 1,4-addition of Grignard reagent to give a 4:1 (trans:cis) mixture.




(10) The stereochemistry of endo alcohol **3** was deduced from our previous results[5] and a single isomer obtained.

(11) During isolation of **9** by column chromatography (silica gel, hexane–ether, 2:1), a small amount of deketalized product was generated. However, further purification was not necessary since deketalized product alone underwent cyclization reaction smoothly.

(12) While 10% Pd/C in ethanol resulted in an inferior isomer ratio (cis:trans/5:1), Wilkinson's catalyst was inert to hydrogenation under atmospheric pressure.

(13) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

(14) (±)-Clavukerin A was extensively decomposed in the refrigerator within a week. However, no trace of (±)-clavukerin C was found in the decomposed product.

(15) Paquette, L. A.; Liotta, D. C. *Tetrahedron Lett.* **1976**, 2681.

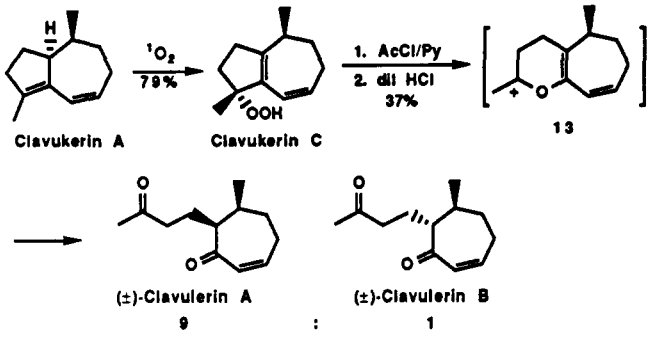
(16) Gollnick, K. *Adv. Photochem.* **1968**, *6*, 1.

(17) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419.

(18) Rousseau, G.; Laperchec, P.; Conia, J. M. *Tetrahedron Lett.* **1977**, 2517.

(19) Lerdal, D.; Foote, C. S. *Tetrahedron Lett.* **1978**, 3227.

**Scheme III**




any dependence on the stereochemical environment of the C-3a proton. The spectral data of (±)-clavukerin C from photooxidation are in complete agreement with those of the natural product ($^1$H NMR, $^{13}$C NMR, UV). Once isolated by column chromatography (silica gel, hexane–ether/2:1), it was slowly decomposed after evaporation of the solvent. However, an ethereal solution was stable enough to be kept for 2 days at room temperature. When an ethereal solution of (±)-clavukerin C was treated with dilute HCl at 0 °C or TFA at 40 °C, it was rapidly transformed into a nonpolar material (TLC, silica gel, single spot, $R_f$ = 0.95, hexane–ether/2:1). Efforts to isolate it were fruitless due to its instability on column chromatography. Presumably after formation of peroxyacetate, acid-catalyzed rearrangement with preferred migration of the vinyl group might have occurred to give unstable nonpolar material from **13**.[20] However, it did not survive during column chromatography (silica gel, hexane:ether-/2:1). Out of several components from the decomposition of (±)-clavukerin C, a mixture of (±)-clavularins A and B (9:1) was obtained in low yield (10–20%). To improve the yield of (±)-clavularins A and B, acetylation (AcCl/Py/ether) of (±)-clavukerin C was performed. Without isolation of the peroxyacetate, the reaction mixture was treated with aqueous TFA or dilute HCl to afford the same nonpolar material at first, which also decomposed spontaneously to give (±)-clavularins A and B in 37% yield.

In summary, a concise total synthesis of (±)-clavukerin A was achieved in an overall 36% yield over eight steps from silyl enol ether 1. A salient feature of this scheme is that two stereocenters (C-3a and (C-4) were constructed in a highly stereoselective manner and the utility of a new methodology for preparing substituted β,γ-cycloheptenone was demonstrated.

## Experimental Section

**General Procedure.** Melting points were determined in a capillary apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ solution. GC analyses were performed on a Shimadzu GC-8A flame ionization detector chromatograph fitted with a 1 m × $^1/_8$ in. column (5% Dexil 300 on Gas Chrom W, 100-120 mesh), working in the range 60–230 °C (5–20 deg min$^{-1}$), with nitrogen as carrier gas (low rate 60 mL min$^{-1}$), the injector and detector temperature being 230 °C. Column chromatography was performed with Merck Kieselgel 60 (70-230 mesh ASTM) silica.

**6-(3,3-(Trimethylenedioxy)propyl)-5-methyl-1-(trimethylsiloxy)bicyclo[3.2.0]heptan-6-ol (3).** To a stirred solution of ketone **2** (1.06 g, 5 mmol) in dry THF (30 mL) was added the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxane[21] (1.5 equiv, 7.5 mmol) in THF dropwise over a period of 10 min at −20 °C under Ar. Stirring was continued for 5 h. The reaction mixture was then allowed to warm 0 °C for 30 min. After the excess Grignard reagent was quenched with water at −20 °C, the resulting mixture was diluted with ether (100 mL) and washed with aqueous $NH_4Cl$ and water; the organic layer was dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was subjected to column chromatography (hexane–ether, 2:1) to give **3** (1.39 g, 85%) as a colorless oil: IR (neat) 3415, 2929, 1244, 1138, 1072, 834 cm$^{-1}$; $^1$H NMR δ 4.57 (t, $J$ = 4.2 Hz, 1 H), 4.11 (dd, $J$ = 5.0, 10.5 Hz, 2 H), 3.78 (dt, 2.1, 12.0 Hz, 2 H), 2.54 (s, 1 H), 2.10 (m, 2 H), 2.09 (d, $J$ = 13.4 Hz, 1 H), 1.87 (d, $J$ = 13.4 Hz, 1 H), 1.76–1.58 (m, 6 H), 1.31 (m, 3 H), 0.95 (s, 3 H), 0.09 (s, 9 H); $^{13}$C NMR δ 102.4, 79.8, 72.0, 66.9, 54.0, 47.5, 40.1, 34.8, 32.6, 29.2, 25.6, 23.8, 17.2, 1.8; MS, $m/z$ (relative intensity) (no M$^+$), 313 (1.5), 312 (6.0), 311 (4.6), 253 (8.7), 235 (11.5), 185 (28.3), 170 (base peaks), 155 (23.1), 143 (14.0), 87 (26.0).

**3-(3,3-(Trimethylenedioxy)propyl)-4-methylcyclohept-3-en-1-one (4).** To a stirred solution of alcohol **3** (677 mg, 2.0 mmol) and triethylamine (485 mg, 4.8 mmol) in $CH_2Cl_2$ (30 mL) was added methanesulfonyl chloride (504 mg, 4.4 mmol) dropwise at 0 °C. After the mixture was stirred for 30 min, the solvent was removed in vacuo at ice-bath temperature. Then the residue was dissolved in ether (100 mL) and washed with water, aqueous $NaHCO_3$, and brine. The organic layer was dried over $Na_2SO_4$ and evaporated below 20 °C. The residue was subjected to column chromatography (silica, hexane–ether, 2:1) to give **4** (438 mg, 92 %) as a colorless liquid: IR 2905, 1697, 1658 (sh), 1137, 1074 cm$^{-1}$; $^1$H NMR δ 4.45 (t, $J$ = 5.1 Hz, 1 H), 4.10 (dd, $J$ = 5.0, 11.0 Hz, 2 H), 3.75 (dt, $J$ = 2.5, 11.0 Hz, 2 H), 3.14 (s, 2 H), 2.51 (t, $J$ = 6.6 Hz, 2 H), 2.27 (t, $J$ = 5.6 Hz, 2 H), 2.18 (t, $J$ = 7.7 Hz, 2 H), 2.07 (m, 1 H), 1.90 (m, 2 H), 1.73 (s, 3 H), 1.66 (m, 1 H), 1.32 (m, 2 H); $^{13}$C NMR δ 209.5, 132.8, 125.9, 101.6, 66.8, 47.8, 43.6, 34.5, 33.1, 29.3, 25.7, 24.4, 20.3; MS $m/e$ (relative intensity) 238 (M$^+$, 5.7), 162 (26.3), 120 (10.5), 113 (48.9), 100 (45.7), 87 (base peak).

**3-(3,3-(Trimethylenedioxy)propyl)-4-methylcycloheptan-1-one (5).** A suspension of β,γ-unsaturated ketone **4** (238 mg, 1.0 mmol) and rhodium on alumina (50 mg) in ethyl acetate (5 mL) was hydrogenated at 0 °C under atmospheric pressure. After 2 h, the catalyst was filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica, ether–hexane, 1:1) to give **5** (178 mg, 74%) as a colorless liquid and overreduced alcohol **6** (43.6 mg, 18%). The overreduced alcohol was converted to ketone **5** quantitatively by treatment with PDC in $CH_2Cl_2$. The combined yield of **5** was 92% (cis:trans = 15:1): IR (neat) 2902, 1687, 1444, 1233, 1136, 1075 cm$^{-1}$; $^1$H NMR δ 4.50 (t, $J$ = 5.0 Hz, 1 H), 4.10 (dd, $J$ = 5.0, 10.5, Hz, 2 H), 3.76 (dt, $J$ = 2.5, 12.2 Hz, 2 H), 2.52 (m, 1 H), 2.43–2.35 (m, 3 H), 2.10–1.98 (m, 2 H), 1.86 (m, 1 H), 1.72–1.26 (m, 9 H), 0.86 (d, $J$ = 7.2 Hz, 3 H), (minor isomer) 0.99 (d, $J$ = 6.7 Hz, for 4-Me); $^{13}$C NMR δ 214.5, 102.1, 66.8, 46.1, 43.7, 38.7, 36.3, 35.5, 33.3, 26.9, 25.7, 20.5, 14.2; MS, $m/e$ (relative intensity) 241 (M$^+$ + 1, 6.7), 240 (M$^+$, 2.2), 223 (14.4), 164 (6.3), 149 (16.9), 113 (13.2), 87 (base peak).

**4-Methyl-2,3,3a,4,5,6-hexahydroazulen-8(7*H*)-one (7).** A stirred solution of ketone **5** (120 mg, 0.5 mmol) in an ethanolic HCl solution (25 mL, EtOH–10% HCl, 5:1) was refluxed for 1 h. The reaction mixture was allowed to warm to rt and poured into water (100 mL) and ether (100 mL). The aqueous layer was washed with ether (100 mL). The combined organic layer was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (hexane–ether, 3:1) to give cyclized product (66 mg, 81%) as a colorless liquid: IR (neat) 2900, 1670, 1602 cm$^{-1}$; $^1$H NMR δ (major isomer) 6.81 (dd, $J$ = 2.5, 4.7 Hz, 1 H), 3.20 (m, 1 H), 2.52–2.40 (m, 4 H), 2.25 (m, 1 H), 1.84–1.62 (m, 5 H), 0.78 (d, $J$ = 7.1 Hz, 3 H), (minor isomer) 0.98 (d, $J$ = 6.1 Hz, for 4-Me); $^{13}$C NMR δ (major isomer) 200.9, 144.7, 143.0, 48.8, 45.1, 37.3, 36.3, 32.1, 29.7, 19.4, 11.8, (minor isomer) 201.4, 148.0, 143.4, 50.7, 44.5, 40.2, 31.1, 30.6, 24.0, 21.4, MS, $m/e$ (relative intensity) 165 (M$^+$ + 1, base peak) 164 (M$^+$, 45.6), 136 (11.1), 135 (10.4), 121 (27.7), 120 (22.1), 108 (13.3), 107 (19.9), 95 (22.8), 94 (33.2), 93 (33.0).

**6-(3,3-(Dimethylenedioxy)butyl)-5-methyl-1-(trimethylsiloxy)bicyclo[3.2.0]heptan-6-ol (8).** The reaction of ketone **2** (2.12 g, 10 mmol) in dry THF (30 mL) with the Grignard reagent

(20) (a) Frimer, A. A. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, 1983; p 222. (b) González, A. G.; Galindo, A.; Afonso, M. del M.; Mansilla, H. *Heterocycles* **1989**, *29*, 1439.

(21) Sato, T.; Kawara, T.; Sakata, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 505.

of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[21] (1.5 equiv, 15 mmol) was carried out as described above for **3**: yield 2.72 g, 83%, as a white solid; mp 44–45 °C; IR (KBr) 3408, 2924, 1245, 1061, 834 $cm^{-1}$; $^1H$ NMR $\delta$ 3.96 (s, 4 H), 2.31 (s, 1 H), 2.12 (m, 1 H), 2.10 (d, $J$ = 13.4 Hz, 1 H), 1.86 (d, $J$ = 13.4 Hz, 1 H), 1.81–1.57 (m, 8 H), 1.35 (s, 3 H), 1.28 (m, 1 H), 0.95 (s, 3 H), 0.09 (s, 9 H); $^{13}C$ NMR $\delta$ 110.2, 79.7, 72.1, 64.6, 54.0, 47.3, 40.0, 34.7, 32.6, 23.84, 23.80, 17.1, 1.8; MS, $m/e$ (relative intensity) (no $M^+$), 226 (10.7), 185 (26.1), 183 (23.6), 170 (base peak), 155 (33.5), 143 (18.0), 141 (11.4), 123 (8.9), 87 (73.2), 73 (82.0). Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.13; H, 9.32. Found: C, 61.95; H, 9.76.

**3-(3,3-(Dimethylenedioxy)butyl)-4-methylcyclohept-3-en-1-one (9).** The fragmentation reaction of **8** was carried out as described above for **4** (960 mg, 2.93 mmol). The residue was subjected to column chromatography (silica gel, hexane–ether, 2:1) to give **9** (627 mg, 90%) (a small amount of ketal **9** was hydrolyzed to the corresponding ketone in the course of column chromatography) as a colorless liquid: IR (neat) 2904, 1697, 1670 (sh), 1245, 1209, 1050 $cm^{-1}$; $^1H$ NMR $\delta$ 3.93 (m, 4 H), 3.15 (s, 2 H), 2.51 (t, $J$ = 6.6 Hz, 2 H), 2.27 (t, $J$ = 6.2 Hz, 2 H), 2.16 (t, $J$ = 8.4 Hz, 2 H), 1.90 (m, 2 H), 1.72 (s, 3 H), 1.68 (t, $J$ = 8.4 Hz, 2 H), 1.35 (s, 3 H); $^{13}C$ NMR $\delta$ 209.4, 132.1, 126.1, 109.6, 64.6, 47.9, 43.7, 36.8, 34.6, 29.7, 24.2, 23.7, 20.2; MS, $m/e$ (relative intensity) 238 ($M^+$, 1.7), 223 (2.5), 194 (4.9), 177 (3.0), 176 (5.0), 161 (3.0), 136 (14.6), 123 (10.3), 107 (10.8), 87 (base peak); HRMS calcd for $C_{14}H_{22}O_3$ 238.1569, obsd 238.1549.

**3-(3,3-(Dimethylenedioxy)butyl)-4-methylcycloheptan-1-one (10).** The hydrogenation reaction of **9** (180 mg, 0.76 mmol) was carried out as described above for **5**: yield 93% (cis:trans = 19:1); IR (neat) 2907, 1689, 1051 $cm^{-1}$; $^1H$ NMR $\delta$ 3.83 (m, 4 H), 2.54–2.38 (m, 4 H), 1.99 (m, 1 H), 1.84 (m, 1 H), 1.74–1.41 (m, 7 H), 1.32 (s, 3 H), 1.28 (m, 1 H), 1.00 (d, $J$ = 6.7 Hz, $CH_3$ for trans isomer), 0.88 (d, $J$ = 7.2 Hz, $CH_3$ for cis isomer); $^{13}C$ NMR $\delta$ 214.5, 109.9, 64.6, 64.5, 46.1, 43.7, 39.0, 37.0, 36.7, 35.5, 26.9, 23.7, 20.5, 14.4; MS, $m/e$ (relative intensity) (no $M^+$), 225 (1.9), 169 (1.9), 99 (6.3), 87 (base peak).

**1,4-Dimethyl-2,3,3a,4,5,6-hexahydroazulen-8(7*H*)-one (11).** The cyclization reaction of **10** was carried out for 5 h as described above for **7**: yield 321 mg, 90%; as a colorless liquid; IR (neat) 2892, 1664, 1605 $cm^{-1}$; $^1H$ NMR $\delta$ 3.24 (m, 1 H), 2.61–2.41 (m, 4 H), 2.09 (dd, $J$ = 1.3, 3.0 Hz, 3 H, long-range coupling), 2.11–1.89 (m, 2 H), 1.79–1.45 (m, 5 H), 0.95 (d, $J$ = 6.2 Hz, minor isomer), 0.75 (d, $J$ = 7.1 Hz, 3 H, major isomer); $^{13}C$ NMR $\delta$ 203.0, 156.4, 136.0, 50.7, 46.0, 39.6, 37.4, 36.4, 27.9, 19.6, 16.7, 12.0; MS, $m/e$ (relative intensity) 178 ($M^+$, 62.9), 163 (11.1), 149 (21.0), 135 (44.4), 123 (16.4), 122 (26.2), 121 (27.4), 109 (base peak); HRMS calcd for $C_{12}H_{18}O$ 178.1358, obsd 178.1354.

**1,4-Dimethyl-2,3,3a,4,5,6-hexahydroazulen-8(7*H*)-one, 8-Tosylhydrazone (12).** To a stirred solution of enone **11** (300 mg, 1.68 mmol) in methanol (15 mL) and two drops of concd HCl was added (*p*-tolylsulfonyl)hydrazine (329 mg, 177 mmol) in methanol (15 mL) dropwise over 15 min at −23 °C. The reaction mixture was stirred for 5 h at −23 °C and poured into ether (200 mL) and water (200 mL). The aqueous layer was washed with ether. The combined organic layer was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was reduced in vacuo to ca. 5% of its original volume. To this solution was added hexane (20 mL) to crystallize the product. The precipitate was filtered to give pure product (350 mg). The mother liquor was further column chromatographed to recover starting material (47.5 mg, 16%) and residual product (95 mg): total yield 445 mg, 77%; mp 130–132 °C dec; IR (neat) 3173, 2892, 1580, 1324, 1180 $cm^{-1}$; $^1H$ NMR $\delta$ 7.86 (d, $J$ = 8.3 Hz, 2 H), 7.69 (br, 1 H), 7.29 (d, $J$ = 8.3 Hz, 2 H), 2.98 (m, 1 H), 2.60 (dd, $J$ = 6.1, 15.8 Hz, 1 H), 2.41 (s, 3 H), 2.27 (t, $J$ = 7.5 Hz, 2 H), 1.92–1.82 (m, 3 H), 1.68 (s, 3 H), 1.71–1.35 (m, 5 H), 0.60 (d, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR $\delta$ 159.1, 143.8, 135.6, 134.0, 129.4, 128.1, 51.7, 38.6, 36.6, 35.2, 28.8, 27.7, 21.6, 20.4, 16.3, 12.3; MS, $m/e$ (relative intensity) 346 (3.6), 191 (base peak), 176 (3.6), 149 (3.5), 135 (4.1), 109 (7.7); HRMS calcd for $C_{19}H_{26}O_2N_2S$ 356.1714, obsd 346.1739.

**(±)-Clavukerin A.** To a solution of hydrazone **12** (346 mg, 1 mmol) and TMEDA (1.16 g, 10 mmol) in THF (10 mL) was added methyllithium (1.4 M solution in hexane, 2.86 mL, 4 mmol) over 5 min at −78 °C. The resulting mixture was stirred for 1 h at −78 °C and then allowed to warm to 0 °C. After additional stirring for 1 h, the reaction mixture was quenched by the addition of water (1 mL) and poured into a mixture of pentane (100 mL) and water (100 mL). The organic layer was washed with dilute HCl and aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed in vacuo (30 Torr) below 10 °C, and the residue was purified by column chromatography (silica gel, pentane) to give (±)-clavukerin A (154 mg, 95%) was a colorless liquid: UV (MeOH) $\lambda_{max}$ 245 nm; IR (neat) 2984, 1660, 1600, 1434, 1350 $cm^{-1}$; $^1H$ NMR $\delta$ 6.21 (d, $J$ = 11.9, Hz, 1 H), 5.55 (td, $J$ = 11.9, 5 Hz, 1 H), 2.89 (m, 1 H), 2.34–2.26 (m, 4 H), 1.95–1.88 (m, 2 H), 1.74 (s, 3 H), 1.80–1.35 (m, 3 H), 0.75 (d, $J$ = 7.0 Hz, 3 H), 0.96 (d, $J$ = 6.3 Hz, minor stereoisomer); $^{13}C$ NMR $\delta$ 138.8, 134.9, 128.8, 123.7, 54.5, 37.8, 34.4, 34.2, 27.2, 26.7, 14.5, 11.4; MS, $m/e$ (relative intensity) 162 ($M^+$, 92), 147 (base peak), 133 (36), 119 (43), 105 (92); HRMS calcd for $C_{12}H_{18}$ 162.1408, obsd 162.1414. $^1H$ NMR and UV spectra are identical with those of reported data.[1a]

**(±)-Clavukerin C.** A UV cell containing (±)-clavukerin A (40 mg, 0.25 mmol), methylene blue (10 mg), and MeOH–pyridine (10:1) was placed 20 cm from the UV lamp (450 W, Ace-Hanovia high-pressure quartz mercury lamp). The mixture was irradiated with a small stream of oxygen while the reaction mixture was monitored by TLC. When the reaction was completed, the reaction mixture was poured into ether (50 mL) and washed with water. The ethereal solution was dried over $MgSO_4$ and concentration in vacuo to ca. 5 mL. The residual solution was subjected to column chromatography (hexane–ether, 2:1) to give (±)-clavukerin C (38 mg, 79%). Since (±)-clavukerin C was not stable, it was immediately subjected to the following reaction: UV (MeOH) $\lambda_{max}$ 254.2, 247.1 (sh) nm; IR (neat) 3356, 2935, $cm^{-1}$; $^1H$ NMR $\delta$ 7.25 (s, 1 H), 5.90 (m, 1 H), 5.81 (d, $J$ = 11.7 Hz, 1 H), 1.28 (s, 3 H), 1.05 (d, $J$ = 7.2 Hz, 3 H); $^{13}C$ NMR $\delta$ 151.3, 134.1, 131.5, 120.8, 97.2, 36.0, 33.6, 33.0, 31.2, 27.1 22.3, 19.5; MS, $m/e$ (relative intensity) 195 ($M^+$ + 1, 3.4), 194 ($M^+$, 3.6), 179 (2.1), 162 (base peak), 161 (94.9), 120 (30.9), 105 (40.6), 81 (18.6); $^1H$ NMR, $^{13}C$ NMR, and UV spectra are identical with those of reported data.[1b]

**(±)-Clavularin A.** To a stirred solution of (±)-clavukerin C (35 mg, 0.18 mmol) and pyridine (28 mg, 0.36 mmol) in ether (10 mL) was added AcCl (28 mg, 0.36 mmol) in ether (5 mL) dropwise at 0 °C. The reaction mixture was refluxed for 2 h, and TFA (3 mL) in water (10 mL) was added. Without isolation of the peroxy ester, the heterogeneous reaction mixture was stirred for additional 30 min at rt. During the reaction, a nonpolar spot appeared on TLC as the peroxy ester spot disappeared (silica gel, $R_f$ = 0.97, hexane–ether, 2:1). When the TLC of the reaction mixture showed only the nonpolar spot, the organic layer was separated and column chromatographed. During column chromatography (silica gel, hexane–ether, 1:1), the nonpolar spot completely disappeared and a new spot (clavularin) was separated as a colorless oil (13 mg, 37%): clavularin A:B = 9:1, UV (*n*-hexane) $\lambda_{max}$ 221.6 nm; IR (neat) 2899, 1706, 1660 $cm^{-1}$; $^1H$ NMR $\delta$ (clavularin A) 6.77 (ddd, $J$ = 3.9, 7.3, 11.7, Hz, 1 H), 6.03 (dd, $J$ = 2.6, 11.7 Hz, 1 H), 2.81 (ddd, $J$ = 3.9, 5.4, 10.0 Hz, 1 H), 2.14 (s, 3 H), 0.83 (d, $J$ = 6.4 Hz, 3 H), (clavularin B) 1.10 (d, $J$ = 6.7 Hz, 3 H); $^{13}C$ NMR $\delta$ (clavularin A) 208.9, 203.8, 148.8, 133.9, 54.0, 41.9, 35.8, 33.9, 30.0, 27.8, 22.3, 16.1; MS, $m/e$ (relative intensity) 194 (36.1), 149 (21.5), 137 (base peak), 109 (32.7); HRMS calcd for $C_{12}H_{18}O_2$ 194.1306, obsd 194.1302. All spectra are identical with the reported data.[2]

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**Registry No.** **1**, 19980-34-8; (±)-**2**, 136490-19-2; (±)-**3**, 136490-20-5; **4**, 136490-21-6; (±)-**5**, 83096-49-5; (±)-*trans*-**5**, 83096-77-9; **6**, 136490-22-7; (±)-**7**, 83096-78-0; (±)-**8**, 136490-23-8; **9**, 136490-24-9; **9** ketone, 136490-26-1; (±)-**10**, 136490-25-0; (±)-*trans*-**10**, 136490-27-2; **10** alcohol, 136490-28-3; (±)-**11**, 136597-90-5; (±)-*cis*-**11**, 75930-91-5; (±)-**12**, 136597-91-6; (±)-*cis*-**12**, 136597-95-0; (±)-clavukerin A, 136597-92-7; (±)-*cis*-clavukerin A, 136597-96-1; (±)-clavukerin C, 136597-93-8; (±)-*cis*-clavukerin C, 136597-97-2; (±)-clavularin A, 136597-94-9; (±)-clavularin B, 94536-97-7; 2-(2-bromoethyl)-1,3-dioxane, 33884-43-4; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6.

**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR spectra of all new compounds (25 pages). Ordering information is given on any current masthead page.