Chiral Synthesis of a Trinorguaiane Sesquiterpene, Clavukerin A

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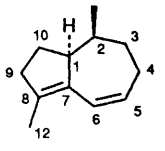
An enantiospecific synthesis of clavukerin A, a novel trinorguaiane sesquiterpene, was accomplished starting from (−)-carvone.

Clavukerin A **1**, a new trinorguaiane sesquiterpene, was isolated from the Okinawan soft coral *Clavularia koellikeri* (stolonifer), together with clavukerin C **2**, by Kitagawa and his co-workers.[1] The structure of clavukerin A was elucidated based on both chemical and spectral evidence in addition to an X-ray crystallographic analysis, and its absolute configuration was also proposed following a CD study, as shown below. They established that the oxidative treatment of clavukerin A provided clavukerin C **2** and clavularin A **3**, the latter of which was also isolated from the same coral as a cytotoxic compound along with clavularin B **4** by Endo's group.[2] With regards to the



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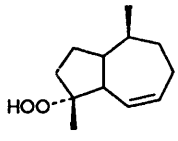

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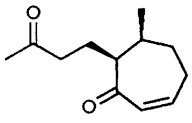

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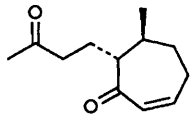

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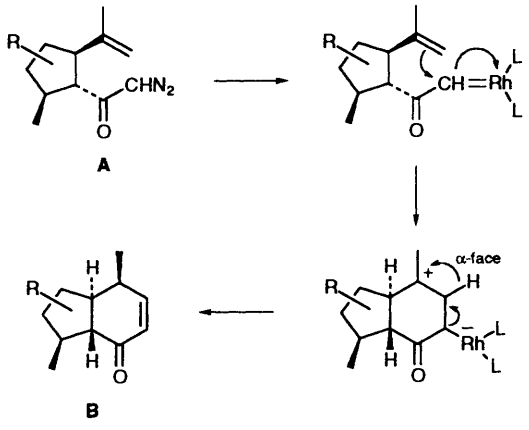
synthesis of clavukerin A, three total syntheses, including one enantiocontrolled route[3] and another two for the racemate,[4,5] have been reported recently, and these syntheses involved an aldol-type condensation as a key reaction to construct the bicyclic ring system. Our own interest in the synthesis of clavukerin A **1** gew out of a desire to find a new route for the total synthesis of clavukerin A and its congeners.

Our synthesis of clavukerin A **1** began with the preparation of the cyclohexenone derivative **5** in an optically active form by employing an intramolecular addition reaction of the γ,δ-unsaturated diazoketone, readily accessible from (−)-carvone.

In 1984, Doyle published[6] their findings that the intramolecular cyclization of γ,δ-unsaturated diazoketones in the presence of catalysts such as $Cu(OTf)_2$ and $Rh_2(OAc)_4$ brought about cyclopropanation to give corresponding adducts; however, when we applied this procedure to the γ,δ-unsaturated diazoketone **A**, the isolated product was the cyclohexenone derivative **B**, and we proposed the reaction mechanism for this novel cyclohexenone formation as shown in Scheme 1.[7]

As part of our ongoing effort directed toward the exploitation of cyclohexenone derivatives as starting materials for the synthesis of natural products,[8] we intend to develop a new chiral synthetic route to clavukerin A and report herein its enantiospecific synthesis.



Scheme 1

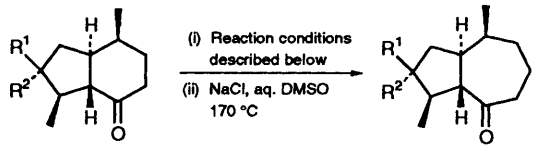
Results and Discussion

Deprotection of the ketal group of the enone **5**[8] with 70% perchloric acid in acetone afforded the ketone **6**, which on reduction with sodium borohydride (sodium boranuide) gave the alcohols **7** and **8** in 44 and 43% yield, respectively. Further catalytic reduction of the alcohols **7** and **8** over 10% palladium on carbon furnished the 6-membered ketones **9** and **10** in 95 and 92% yield, respectively. Although the stereochemistry of the hydroxy group of the ketones **9** and **10** could not be determined at this stage, we tentatively assigned its stereochemistry as shown in Scheme 2 based on NMR data. These alcohols **9** and **10** are mutually interconvertible by the Mitsunobu reaction[9] using diethyl azodicarboxylate (DEAD), triphenylphosphine and benzoic acid, followed by hydrolyses of the resulting benzoates **11** and **12**.

In order to construct a trinorguaiane ring system, the cyclohexanones **9**, **10** and **13**–**15** were subjected to ring-expansion reactions with ethyl diazoacetate under a variety of reaction conditions to give the β-keto esters, which on treatment with sodium chloride in aq. dimethyl sulfoxide (DMSO)[10] provided the 7-membered ketones **16**–**20**, respectively, and the results are summarized in Table 1. The reaction of compounds **13**–**15** with ethyl α-lithiodiazoacetate, followed by treatment of the adducts with rhodium acetate[11] gave the desired 7-membered ketones **18**–**20** in 73–93% yield after deethoxycarbonylation with sodium chloride in aq. DMSO.[10] The 7-membered ketones **16** and **17** were also prepared, with ease of handling, by reaction of the alcohols **9** and **10** with ethyl diazoacetate in the presence of boron trifluoride–diethyl ether in dichloromethane[12] in good yields. Since the desired carbon framework for clavukerin A was thus constructed stereoselectively, we focused our attention on introduction of the conjugate diene system.

Although dehydration of both alcohols **16** and **17** with

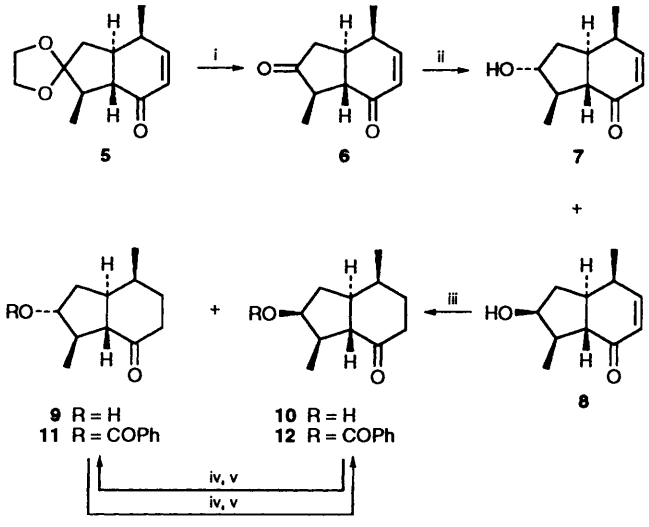
Table 1 Ring-expansion reactions for the cyclohexanone derivatives by employing ethyl diazoacetate



9, 10, 13–15 **16–20**

Starting material			Reaction conditions		
	R^1	R^2	Reagent	Temp. (T/°C)[a]/Time (t/h)	Product yield (%)[b]
9	H	OH	BF_3·OEt_2, Et_2O	r.t./12	**16**/89
10	OH	H	BF_3·OEt_2, Et_2O	r.t./12	**17**/93
13	H	TBDMSO[c]	LDA, THF, then	−40/12	**18**/86
			$Rh_2(OAc)_4$, CH_2Cl_2	r.t./1	
14	TBDMSO	H	LDA. THF; then	−40/12	**19**/73
			$Rh_2(OAc)_4$, CH_2Cl_2	r.t./1	
			BF_3·OEt_2, Et_2O	r.t./1	[d]
15	$O[CH_2]_2O$		LDA, THF; then	−40/12	
			$Rh_2(OAc)_4$, CH_2Cl_2	r.t./1	**20**/93

[a] r.t. = room temp. [b] Overall yield of the two-step process. [c] TBDMSO = Me_2Bu^tSiO. [d] No isolable product was obtained.



Scheme 2 *Reagent and conditions:* i, 70% $HClO_4$, acetone; ii, $NaBH_4$, MeOH–CH_2Cl_2 (1:1), 0 °C; iii, H_2, 10% Pd–C, AcOEt; iv, DEAD, Ph_3P, $PhCO_2H$, THF; v, NaOH, MeOH

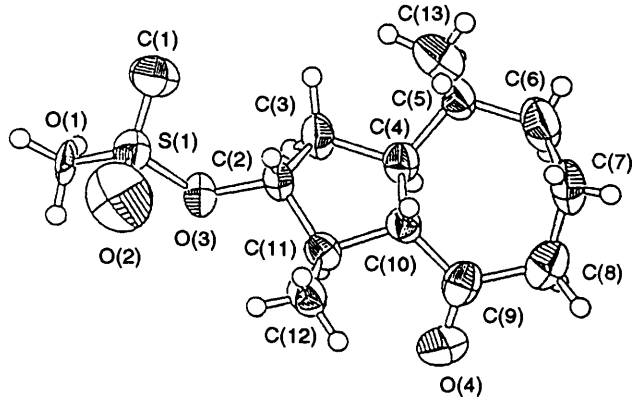


Fig. 1 ORTEP drawing of the methanesulfonate **22**

thionyl dichloride or phosphoryl trichloride afforded a complex mixture, elimination of the corresponding methanesulfonates **21** and **22** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene gave a mixture of the two olefins **23** and **25** in the ratio 1:1. Attempted isomerization of the former olefin **23** to the latter **25** on treatment with DBU, however, failed. Direct dehydration of the β-alcohol **17** under the Mitsunobu reaction conditions[13] provided the enones **24** and **25** in 20% yield in the ratio 1:1 as an inseparable mixture, which on exposure to DBU afforded the enone **25** as the sole product. The best result for the synthesis of compound **25** was obtained by adsorption of the β-methanesulfonate on silica gel to give the olefins **24** and **25**, in 80% yield, in the ratio 1:1 which, without separation, was treated with DBU to give the olefin **25** in 75% overall yield. The results for the elimination of the alcohols or the corresponding methanesulfonates are summarized in Table 2.

The stereochemistry of the hydroxy group of the α-alcohol was unambiguously determined by an X-ray crystallographic analysis of the methanesulfonate **22** at this stage as shown in Fig. 1. Finally, the conjugate diene system was introduced by employing the Shapiro reaction according to the literature[4] with a slight modification as follows. The α,β-conjugated enone **25** was converted into the tosylhydrazone **26**, which on treatment with methyllithium furnished clavukerin A **1**, $[\alpha]_D$ −50* (*c* 0.1, $CHCl_3$) {lit.,[1] $[\alpha]_D$ −53 ($CHCl_3$)} (see Scheme 3).

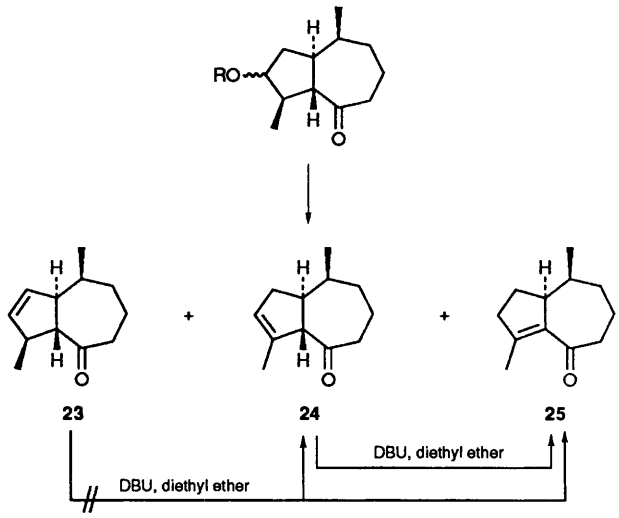
Since the spectral data, including its specific optical rotation of the synthetic clavukerin A were identical with those of the natural product, the absolute configuration of clavukerin A was confirmed to be (1*S*,2*S*). Furthermore, since clavukerin A has already been transformed into clavularin A and clavularin B *via* clavukerin C, this synthesis, therefore, constitutes their chiral synthesis.

Experimental

General Methods.—M.p.s were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX 270 instrument (270 MHz), chemical shifts are reported in ppm on the δ-scale from internal Me_4Si, and *J*-values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter. All new compounds described in this Experimental section were homogeneous on TLC.

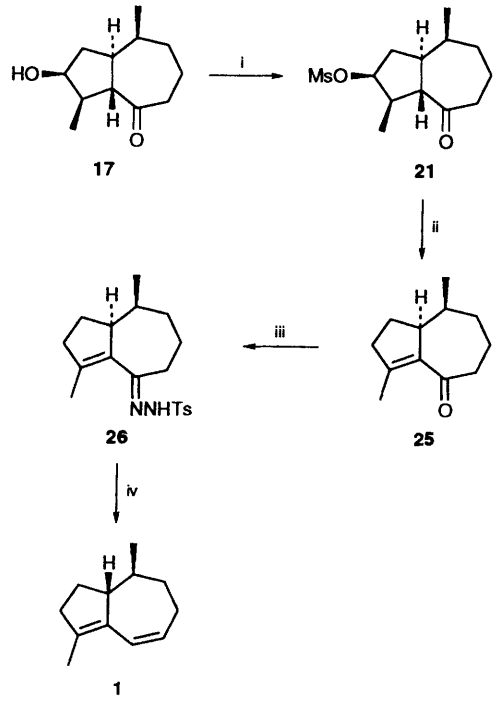
* Throughout this paper, $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}.

Table 2 Elimination reaction of the 7-membered ketones



Starting material R	Reaction conditions		Yield (%)	Products proportions
	Reagent	Temp. (T/°C)[a]/Time (t/h)		**23**:**24**:**25**
21 Ms (β)	DBU, benzene	reflux/1	72	1:0:1
	silica gel	r.t./12	80	0:1:1
17 H(β)	DEAD, Ph_3P, THF	50/1	20	0:1:1
22 Ms (α)	DBU, benzene	reflux/1	75	1:0:1

[a] r.t. = room temp.



Scheme 3 *Reagents and conditions:* i, Ms_2O, pyridine, CH_2Cl_2; ii, silica gel, then DBU, diethyl ether; iii, *p*-$TsNHNH_2$, ethereal HCl, MeOH; iv, MeLi, THF, −78 °C

(1S,5S,6S,9R)-5,9-*Dimethylbicyclo*[4.3.0]*non*-3-*ene*-2,8-*dione* **6**.—A solution of the ketal **5**[8] (0.7 g, 3.15 mmol) and 70% perchloric acid (0.14 cm^3) in acetone (7 cm^3) was stirred at ambient temperature for 5 h. After being basified with saturated aq. sodium hydrogen carbonate, the mixture was extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (4:1, v/v) afforded the *ketone* **6** (0.47 g, 84%) as a solid, m.p. 58 °C (Found: C, 74.25; H, 8.05. $C_{11}H_{14}O_2$ requires C, 74.15; H, 7.90%); $[\alpha]_D$ +58.41 (*c* 1.1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 and 1690; δ 1.15 (3 H, d, *J* 7.3, Me), 1.28 (3 H, d, *J* 6.7, Me), 2.05–2.84 (6 H, m, 1-, 5-, 6-H, 7-H_2 and 9-H), 6.00 (1 H, dd, *J* 1.3 and 10.4, 3-H) and 6.93 (1 H, dd, *J* 5.5 and 10.4, 4-H).

(1S,5S,6S,8R,9R)- *and* (1S,5S,6S,8S,9R)-8-*Hydroxy*-5,9-*dimethylbicyclo*[4.3.0]*non*-3-*en*-2-*one* **7** *and* **8**.—To a stirred solution of the ketone **6** (1.1 g, 6.18 mmol) in methanol (20 cm^3) was added sodium boranuide (0.24 g, 6.34 mmol) portionwise at 0 °C and the resulting mixture was further stirred at the same temperature for 2 h before being treated with saturated aq. ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:1, v/v) afforded the β-*alcohol* **8** (0.47 g, 44%) as an oil; $[\alpha]_D$ +259.93 (*c* 0.6, $CHCl_3$) (Found: C, 73.3; H, 9.05. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1695; δ 1.11 (3 H, d, *J* 6.7, Me), 1.22 (3 H, d, *J* 6.7, Me), 1.46–2.65 (7 H, m, 1-, 5-, 6-H, 7-H_2, 9-H and OH), 4.19–4.25 (1 H, m, 8-H), 5.88 (1 H, dd, *J* 1.2 and 9.8, 3-H) and 6.85 (1 H, dd, *J* 4.9 and 9.8, 4-H). Further elution with the same solvent system gave the α-*alcohol* **7** (0.46 g, 43%) as an oil; $[\alpha]_D$ +94.85 (*c* 0.6, $CHCl_3$) (Found: C, 73.25; H, 9.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1695; δ 1.06 (3 H, d, *J* 6.7, Me), 1.24 (3 H, d, *J* 6.7, Me), 1.63–2.71 (7 H, m, 1-, 5-, 6-H, 7-H_2, 9-H and OH), 3.90–3.94 (1 H, m, 8-H), 5.89 (1 H, dd, *J* 1.2 and 9.8, 3-H) and 6.86 (1 H, dd, *J* 4.9 and 9.8, 4-H).

(1S,5S,6S,8R,9R)-8-*Hydroxy*-5,9-*dimethylbicyclo*[4.3.0]*nonan*-2-*one* **9**.—The catalytic hydrogenation of enone **7** (1.14 g, 6.33 mmol) in ethyl acetate (22 cm^3) was carried out as the same

procedure as for the preparation of compound **10** (see below) to afford the *ketone* **9** (1.1 g, 95%) as an oil; $[\alpha]_D$ +110.14 (*c* 0.5, $CHCl_3$) (Found: C, 72.6; H, 10.15. $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1715; δ 1.08 (3 H, d, *J* 6.7, Me), 1.12 (3 H, d, *J* 7.3, Me), 1.46 (1 H, ddd, *J* 4.3, 11.6 and 13.4, 7-H), 1.66–2.50 (10 H, m, 1-H, 3- and 4-H_2, 5-, 6-, 7- and 9-H and OH) and 4.17 (1 H, dt, *J* 4.3 and 6.7, 8-H).

(1S,5S,6S,8S,9R)-8-*Hydroxy*-5,9-*dimethylbicyclo*[4.3.0]*nonan*-2-*one* **10**.—A solution of the enone **8** (0.53 g, 2.94 mmol) in ethyl acetate (10 cm^3) containing 10% palladium on carbon (0.2 g) was stirred at ambient temperature under hydrogen for 5 h. After the insoluble material had been filtered off, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (4:1, v/v) afforded the *ketone* **10** (0.49 g, 92%) as an oil; $[\alpha]_D$ +59.53 (*c* 0.4, $CHCl_3$) (Found: C, 72.5; H, 10.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1710; δ 1.07 (3 H, d, *J* 6.7, Me), 1.12 (3 H, d, *J* 6.7, Me), 1.63 (1 H, ddd, *J* 1.8, 4.9 and 12.2, 7-H), 1.79 (1 H, dd, *J* 7.3 and 12.2, 7-H), 1.84–2.49 (9 H, m, 1-H, 3-H_2, 5- and 6-H, 7-H_2, 9-H and OH) and 3.82–3.86 (1 H, m, 8-H).

(1S,5S,6S,8R,9R)-5,9-*Dimethyl*-2-*oxobicyclo*[4.3.0]*nonan*-8-*yl Benzoate* **11**.—To a stirred solution of the alcohol **10** (0.2 g, 1.10 mmol) and triphenylphosphine (0.67 g, 2.55 mmol) in dry tetrahydrofuran (THF) (4 cm^3) was added a solution of DEAD (0.36 cm^3, 2.24 mmol) and benzoic acid (0.3 g, 2.46 mmol) in dry THF (4 cm^3) at ambient temperature and the resulting solution was further stirred for 2 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (93:7, v/v) afforded the *benzoate* **11** (0.24 g, 97%) as an oil; $[\alpha]_D$ +1.68 (*c* 0.5, $CHCl_3$) (Found: C, 74.95; H, 7.85. $C_{18}H_{22}O_3$ requires C, 75.50; H, 7.75%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710; δ 1.11 (3 H, d, *J* 7.2, Me), 1.20 (3 H, d, *J* 6.7, Me), 1.79–2.49 (10 H, m, 1-H, 3- and 4-H_2, 5- and 6-H, 7-H_2 and 9-H), 4.95 (1 H, ddd, *J* 1.8, 4.3 and 7.3, 8-H), 7.39–7.58 (3 H, m, ArH) and 8.01–8.04 (2 H, m, ArH).

To a stirred solution of the benzoate **11** (0.2 g, 0.89 mmol) in methanol (4 cm^3) was added 10% aq. sodium hydroxide (0.35 cm^3) and the solution was further stirred at room temperature for 5 h before being treated with brine and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:1, v/v) afforded the alcohol **9** (0.15 g, 93%), which was identical with an authentic sample prepared as above.

(1S,5S,6S,8S,9R)-5,9-*Dimethyl*-2-*oxobicyclo*[4.3.0]*nonan*-8-*yl Benzoate* **12**.—The benzoate **12** (0.61 g, 98%) was obtained from the alcohol **9** (0.5 g, 2.75 mmol) by using the same procedure as for the preparation of the benzoate **11**. *Compound* **12**; $[\alpha]_D$ +126.74 (*c* 1.1, $CHCl_3$) (Found: C, 75.5; H, 7.85%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 and 1720; δ 1.13 (6 H, d, *J* 6.7, 5-and 9-Me), 1.57–2.63 (10 H, m, 1-H, 3- and 4-H_2, 5- and 6-H, 7-H_2 and 9-H), 5.38 (1 H, dt, *J* 4.3 and 7.3, 8-H), 7.42–7.80 (3 H, m, ArH) and 8.00–8.06 (2 H, m, ArH).

Hydrolysis of the benzoate **12** with 10% aq. sodium hydroxide solution afforded the alcohol **10**, which was identical with an authentic specimen.

(1S,5S,6S,8R,9R)-8-(tert-*Butyldimethylsiloxy*)-5,9-*dimethylbicyclo*[4.3.0]*nonan*-2-*one* **13**.—A solution of the alcohol **9** (0.57 g, 3.13 mmol), *tert*-butyldimethylsilyl chloride (0.58 g, 3.85 mmol) and imidazole (0.24 g, 3.53 mmol) in dimethylformamide (DMF) (12 cm^3) was stirred at ambient temperature for 2 h. The solution was treated with saturated aq. ammonium chloride and then extracted with diethyl ether. The ethereal layer was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) afforded the *silyl ether* **13** (0.88 g, 95%) as an oil; $[\alpha]_D$ +47.56 (*c* 0.8, $CHCl_3$) (Found: C, 69.0; H, 11.1. $C_{17}H_{32}O_2Si$ requires C, 68.85; H, 10.90%); $\nu_{max}(CHCl_3)$ 1710; δ 0.03 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.87 (9 H, s, Bu^t), 1.05 (3 H, d, *J* 7.3, Me), 1.06 (3 H, d, *J* 6.7, Me), 1.50–1.80 (2 H, m, 7-H_2), 1.85–2.37 (8 H, m, 1-H, 3- and 4-H_2, 5-, 6- and 7-H) and 3.25 (1 H, ddd, *J* 1.8, 2.4 and 7.3, 8-H).

(1S,5S,6S,8S,9R)-8-(tert-*Butyldimethylsiloxy*)-5,9-*dimethylbicyclo*[4.3.0]*nonan*-2-*one* **14**.—The silyl ether **14** (0.83 g, 85%) was obtained as an oil from the alcohol **10** (0.6 g, 3.30 mmol) by using the same procedure as for the preparation of the silyl ether **13**. Compound **14**; $[\alpha]_D$ +87.93 (*c* 0.9, $CHCl_3$) (Found: C, 69.15; H, 10.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1705; δ 0.03 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.89 (9 H, s, Bu^t), 1.00 (3 H, d, *J* 6.7, Me), 1.10 (3 H, d, *J* 6.7, Me), 1.44 (1 H, ddd, *J* 4.3, 11.0 and 12.8, 7-H), 1.77–2.26 (9 H, m, 1-H, 3- and 4-H_2, 5-, 6-, 7- and 9-H) and 4.08 (1 H, dt, *J* 4.3 and 6.7, 8-H).

(1S,5S,6S,9R)-8,8-*Ethylenedioxy*-5,9-*dimethylbicyclo*[4.3.0]-*nonan*-2-*one* **15**.—A solution of the enone **5** (0.5 g, 2.25 mmol) in ethyl acetate (5 cm^3) containing 10% palladium on carbon (0.25 g) was stirred at ambient temperature under hydrogen for 12 h. After the insoluble material had been filtered off, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (17:3, v/v) afforded the *ketone* **15** (0.47 g, 93%) as an oil; $[\alpha]_D$ +77.53 (*c* 0.4, $CHCl_3$) (Found: C, 69.35; H, 9.2. $C_{13}H_{20}O_3$ requires C, 69.60; H, 9.00%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720; δ 0.99 (3 H, d, *J* 6.1, Me), 1.08 (3 H, d, *J* 7.3, Me), 1.24–2.48 (10 H, m, 1-H, 3- and 4-H_2, 5- and 6-H, 7-H_2 and 9-H) and 3.74–3.97 (4 H, m, OCH_2CH_2O).

(1S,6S,7S,9R,10R)-9-*Hydroxy*-6,10-*dimethylbicyclo*[5.3.0]-*decan*-2-*one* **16**.—A solution of the ketone **9** (0.5 g, 2.75 mmol) and boron trifluoride–diethyl ether (1.70 cm^3, 13.82 mmol) in diethyl ether (25 cm^3) was stirred at ambient temperature for 5 min under argon. To this solution was added ethyl α-diazoacetate (1.49 cm^3, 13.78 mmol) and the resulting solution was further stirred for 12 h at the same temperature. The mixture was diluted with diethyl ether and the ethereal layer was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was dissolved in DMSO (25 cm^3). Sodium chloride (0.64 g, 10.95 mmol) and water (0.25 cm^3) were added to the solution and the resulting mixture was heated at 170 °C for 4 h. After being cooled to room temperature, the mixture was extracted with ethyl acetate and the extract was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:1, v/v) afforded the 7-*membered ketone* **16** (0.48 g, 89%) as an oil; $[\alpha]_D$ −2.29 (*c* 0.6, $CHCl_3$) (Found: C, 72.3; H, 10.35. $C_{12}H_{20}O_2 \cdot \frac{1}{5}H_2O$ requires C, 72.10; H, 10.30%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1700; δ 0.982 (3 H, d, *J* 7.9, Me), 0.984 (3 H, d, *J* 6.7, Me), 1.54–1.95 (7 H, m, 4-, 5- and 8-H_2 and OH), 2.05–2.15 (1 H, m, 6-H), 2.25–2.38 (2 H, m, 7- and 10-H), 2.42 (1 H, dd, *J* 3.7 and 10.4, 3-H), 2.46 (1 H, t, *J* 4.9, 1-H), 2.56 (1 H, dd, *J* 7.3 and 10.4, 3-H) and 3.73 (1 H, q, *J* 5.5, 9-H).

(1S,6S,7S,9S,10R)-9-*Hydroxy*-6,10-*dimethylbicyclo*[5.3.0]-*decan*-2-*one* **17**.—The 7-membered ketone **17** (0.30 g, 93%) was prepared from the ketone **10** (0.30 g, 1.65 mmol) by using ethyl α-diazoacetate (0.90 cm^3, 8.32 mmol) and boron trifluoride-diethyl ether (1.02 cm^3), followed by deethoxycarbonylation

with sodium chloride (0.38 g) and water (0.15 cm^3) in refluxing DMSO (15 cm^3), and adopting the same procedure as for the preparation of isomer **16**. *Compound* **17**; $[\alpha]_D$ +34.09 (*c* 0.2, $CHCl_3$) (Found: C, 72.25; H, 10.25. $C_{12}H_{20}O_2 \cdot \frac{1}{5}H_2O$ requires C, 72.10; H, 10.30); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1695; δ 0.99 (3 H, d, *J* 6.7, Me), 1.07 (3 H, d, *J* 7.3, Me), 1.46–2.55 (12 H, m, 3-, 4- and 5-H_2, 6- and 7-H, 8-H_2, 10-H and OH), 2.86 (1 H, t, *J* 10.4, 1-H) and 4.65 (1 H, dt, *J* 1.8 and 4.9, 9-H) (Found: M^+, 196.1456. $C_{12}H_{20}O_2$ requires M, 196.1462).

(1S,6S,7S,9R,10R)-9-(tert-*Butyldimethylsiloxy*)-6,10-*dimethylbicyclo*[5.3.0]*decan*-2-*one* **18**.—To a stirred solution of the cyclohexanone **13** (0.3 g, 1.01 mmol) and ethyl α-diazoacetate (0.55 cm^3) in THF (15 cm^3) was added lithium diisopropylamide (LDA) (1.5 mol dm^{-3} solution in cyclohexane) (1.68 cm^3, 2.52 mmol) at −40 °C under argon over a period of 1 h and the resulting solution was further stirred for 12 h at the same temperature before being treated with saturated aq. ammonium chloride and extracted with diethyl ether. The ethereal layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was taken up with dichloromethane (15 cm^3). To this solution was added rhodium acetate (22 mg, 0.95 mmol), and the mixture was stirred for 1 h at ambient temperature. The solvent was evaporated off, and the residue was dissolved in DMSO (15 cm^3). Sodium chloride (0.24 g, 4.0 mmol) and water (0.15 cm^3) were added to the solution and the mixture was heated at reflux for 2 h. The solution was diluted with ethyl acetate and the organic layer was washed with water, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) afforded the *7-membered ketone* **18** (0.27 g, 86%) as an oil; $[\alpha]_D$ −26.05 (*c* 0.6, $CHCl_3$) (Found: C, 69.35; H, 11.15. $C_{18}H_{34}O_2Si$ requires C, 69.60; H, 11.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1695; δ 0.03 (3 H, s, SiMe), 0.05 (3 H, s, SiMe), 0.88 (9 H, s, Bu^t), 0.95 (3 H, d, *J* 6.7, Me), 0.96 (3 H, d, *J* 6.7, Me), 1.58–2.45 (12 H, m, 1-H, 3-, 4- and 5-H_2, 6- and 7-H, 8-H_2 and 10-H) and 3.57 (1 H, q, *J* 7.3, 9-H).

(1S,6S,7S,9S,10R)-9-(tert-*Butyldimethylsiloxy*)-6,10-*dimethylbicyclo*[5.3.0]*decan*-2-*one* **19**.—The 7-membered ketone **19** (0.27 g, 93%) was prepared from the cyclohexanone **14** (0.28 g, 0.95 mmol), ethyl α-diazoacetate (0.51 cm^3, 4.72 mmol) and LDA (1.5 mol dm^{-3} solution in cyclohexane) (1.58 cm^3, 2.37 mmol) according to the same procedure as described for the preparation of isomer **18**. *Compound* **19**; $[\alpha]_D$ +56.70 (*c* 0.2, $CHCl_3$) (Found: C, 69.3; H, 11.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1690; δ 0.04 (3 H, s, SiMe), 0.05 (3 H, s, SiMe), 0.90 (9 H, s, Bu^t), 0.91, (3 H, d, *J* 7.9, Me), 1.05 (3 H, d, *J* 7.3, Me), 1.42–2.52 (11 H, m, 3-, 4- and 5-H_2, 6- and 7-H, 8-H_2 and 10-H), 2.87 (1 H, t, *J* 9.8, 1-H) and 3.98–4.02 (1 H, m, 9-H).

Desilylation of Compound **18**.—To a stirred solution of the silyl ether **18** (0.27 g, 0.87 mmol) in THF (6 cm^3) was added a solution of tetrabutylammonium fluoride (TBAF) (1.7 cm^3; 1 mol dm^{-3} solution in THF) at room temperature and the resulting solution was further stirred for 2 h. The mixture was treated with saturated aq. ammonium chloride and then extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (3:1, v/v) afforded the alcohol **16** (0.17 g, 100%), identical with an authentic specimen.

Desilylation of Compound **19**.—Desilylation of the silyl ether **19** (0.27 g, 0.87 mmol) with TBAF (1.7 cm^3) was carried out by using the same procedure as above for the preparation of the alcohol **16**, and gave the alcohol **17** (0.17 g, 100%), identical with an authentic specimen.

(1S,6S,7S,10R)-9,9-*Ethylenedioxy*-6,10-*dimethylbicyclo*-[5.3.0]*decan*-2-*one* **20**.—The 7-membered ketone **20** (0.18 g, 94%) was obtained from reaction of the 6-membered ketone **15** (0.18 g, 0.80 mmol) with ethyl α-diazoacetate (0.44 cm^3, 4.07 mmol) in the presence of LDA (1.5 mol dm^{-3} solution in cyclohexane) (1.34 cm^3, 2.01 mmol) in THF (3.6 cm^3) by using the same procedure as for the preparation of compound **18**. The *title compound* **20**; $[\alpha]_D$ +13.45 (*c* 0.6, $CHCl_3$) (Found: C, 69.65; H, 9.25. $C_{14}H_{22}O_3 \cdot \frac{1}{6}H_2O$ requires C, 69.70; H, 9.35%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1695; δ 0.90 (3 H, d, *J* 6.7, Me), 1.01 (3 H, d, *J* 7.3, Me), 1.48–2.55 (11 H, m, 3-, 4- and 5-H_2, 6- and 7-H, 8-H_2 and 10-H), 2.70 (1 H, t, *J* 9.8, 1-H), 3.84–3.95 (4 H, m, OCH_2CH_2O) (Found: M^+, 238.1574. $C_{14}H_{22}O_3$ requires M, 238.1569).

(1S,6S,7S,9S,10R)-6,10-*Dimethyl*-2-*oxobicyclo*[5.3.0]*decan*-9-*yl Methanesulfonate* **21**.—A solution of the alcohol **17** (0.2 g, 1.02 mmol), methanesulfonic anhydride (0.26 g, 1.49 mmol) and pyridine (0.4 cm^3, 4.94 mmol) in dichloromethane (4 cm^3) was stirred at ambient temperature for 5 h and the mixture was then diluted with a large excess of diethyl ether. The organic layer was washed with water, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:1, v/v) afforded the methanesulfonate **21** (0.25 g, 89%) as an oil; $[\alpha]_D$ +65.06 (*c* 0.2, $CHCl_3$) (Found: C, 56.95; H, 8.3. $C_{13}H_{22}O_4S$ requires C, 56.90; H, 8.10); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700; δ 1.04 (3 H, d, *J* 6.7, Me), 1.09 (3 H, d, *J* 6.7, Me), 1.51–2.56 (11 H, m, 3-, 4- and 5-H_2, 6- and 7-H, 8-H_2 and 10-H), 2.91 (1 H, t, *J* 10.4, 1-H), 3.00 (3 H, s, Me) and 4.93–4.98 (1 H, m, 9-H).

(1S,6S,7S,9R,10R)-6,10-*Dimethyl*-2-*oxobicyclo*[5.3.0]*decan*-9-*yl Methanesulfonate* **22**.—Methanesulfonylation of the alcohol **16** (0.1 g, 0.51 mmol) with methanesulfonic anhydride (0.13 g, 0.75 mmol) was carried out by using the same procedure as for the preparation of isomer **21** to provide title compound **22** (0.13 g, 93%) as needles, m.p. 124 °C; $[\alpha]_D$ −28.91 (*c* 0.3, $CHCl_3$) (Found: C, 56.8; H, 8.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700; δ 1.00 (3 H, d, *J* 6.7, Me), 1.05 (3 H, d, *J* 6.7, Me), 1.50–2.20 (7 H, m, 4- and 5-H_2, 6-H and 8-H_2), 2.25–2.60 (4 H, m, 1-H, 3-H_2 and 7-H), 2.65–2.90 (1 H, m, 10-H), 3.03 (3 H, s, SMe) and 4.61 (1 H, dt, *J* 4.9 and 10.4, 9-H).

X-Ray Analysis of the Methanesulfonate **22**.—All the measurements were performed on a Rigaku AFC-7R diffractometer using Cu-Kα radiation. The unit-cell dimensions were determined by least-squares calculation from 20 high-angle reflections. Intensity data were collected by using the $2\theta/\omega$ scan technique for $8° < 2\theta < 120°$ with an average scan rate of 16°/min. In total 2280 independent reflections were collected, and 1144 satisfying the condition $F_o < 3\sigma(F)$ were used for calculation.

Crystal data for compound **22**: $C_{13}H_{22}O_4S$, $M = 274.38$. Monoclinic $a = 8.211(3)$, $b = 8.356(5)$, $c = 10.821(4)$ Å, $V = 710.1(5)$ Å^3, $D_c = 1.28$ g cm^{-3}; $Z = 2$. Space group $P2_1$. The structure was solved by the direct method using SAPI 91 [14] and the Rigaku crystallographic package TEXSAN.[15] The structure was refined by the block-diagonal least-squares method using anisotropic thermal parameters for all non-hydrogen atoms. The final *R*-factor was finally reduced to 0.073.*

Elimination of the Methanesulfonate **21** *with DBU*.—To a stirred solution of compound **21** (0.1 g, 0.37 mmol) in benzene (2 cm^3) was added DBU (0.1 cm^3, 0.73 mmol) at room temperature

* *Supplementary publication* (see 'Instructions for Authors', in the January issue): Tables of atomic coordinates, bond lengths and angles *etc.* have been deposited at the CCDC.

and the mixture was heated at reflux for 1 h. The solution was treated with saturated aq. ammonium chloride and extracted with diethyl ether. The ethereal layer was washed with water, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (19:1, v/v) afforded the olefins **23** and **25** (46.8 mg, 72%) as an inseparable mixture; δ 0.77 (1.5 H, d, *J* 6.7, Me), 0.92 (1.5 H, d, *J* 7.3, Me), 1.03 (1.5 H, d, *J* 6.7, Me), 1.43–2.91 (10 H, m, 1-H, 3-, 4- and 5-H_2, 6-H and 10-H of **23** and 3-, 4- and 5-H_2, 6-H and 8- and 9-H_2 of **25**), 2.08–2.10 (1.5 H, m, 10-Me of **25**), 3.10–3.38 (1 H, m, 7-H of **23** and **25**), 5.27–5.30 (0.5 H, m, 9-H of **23**) and 5.51–5.55 (0.5 H, m, 8-H of **23**).

Elimination of the Methanesulfonate **21** *with Silica Gel.*—To a solution of the methanesulfonate **21** (0.1 g, 0.37 mmol) in diethyl ether (2 cm^3) was added silica gel (0.1 g). After the solvent was evaporated off, the residue was kept at room temperature for 12 h. Silica gel was washed with diethyl ether several times and the ethereal layer was concentrated to give the olefins **24** and **25** as an inseparable mixture; δ 0.76 (1.5 H, d, *J* 7.3, Me), 1.01 (1.5 H, d, *J* 6.7, Me), 1.18–2.60 (10.5 H, m, 3-, 4- and 5-H_2, 6-H and 7-H and 8-H_2 of **24** and 3-, 4- and 5-H_2, 6-H and 8- and 9-H_2 of **25**), 1.77 (1.5 H, t, *J* 1.8, Me), 2.09 (1.5 H, t, *J* 1.2, Me), 3.20–3.27 (0.5 H, m, 7-H of **25**), 3.44–3.75 (0.5 H, m, 1-H of **24**), 5.43 (0.5 H, t, *J* 1.8, 9-H of **24**), which without further purification was subjected to isomerization.

The olefins obtained above was dissolved in diethyl ether (2 cm^3) and DBU (0.1 cm^3, 0.73 mmol) was added to the solution. The resulting mixture was further stirred for 5 h at ambient temperature and was then treated with saturated aq. ammonium chloride and extracted with diethyl ether. The extract was washed with water, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) afforded the *olefin* **25** (48.7 mg, 75%) as an oil; $[\alpha]_D$ +95.49 (*c* 0.1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1670; δ 0.77 (3 H, d, *J* 6.7, 6-Me), 1.49–2.52 (11 H, m, 3-, 4- and 5-H_2, 6-H and 8- and 9-H_2), 2.08 (3 H, d, *J* 1.8, 10-Me) and 3.19–3.27 (1 H, m, 7-H) (Found: M^+, 178.1350. $C_{12}H_{18}O$ requires M, 178.1356).

Elimination of the Methanesulfonate **22** *with DBU.*—The elimination of the α-methanesulfonate **22** with DBU was carried out by using the same procedure as described above for **21**, to give a mixture of the olefins **23** and **25** in the ratio 1:1, which was identical with an authentic specimen obtained from the reaction of β-methanesulfonate **21** with DBU.

Dehydration of the Alcohol **17**.—A solution of the alcohol **17** (0.1 g, 0.51 mmol), triphenylphosphine (0.27 g, 1.03 mmol) and DEAD (0.16 cm^3, 1.02 mmol) in THF (5 cm^3) was heated at 50 °C for 1 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (19:1, v/v) afforded the olefins **24** and **25** (18.2 mg, 20%) as an inseparable mixture, identical with the authentic sample obtained from the reaction of the β-methanesulfonate **21** with silica gel.

(6S,7S)-6,10-*Dimethylbicyclo*[5.3.0]*dec*-1(10)-*en*-2-*one Toluene*-p-*sulfonylhydrazone* **26**.—To a stirred solution of ketone **25** (0.15 g, 0.84 mmol) and toluene-*p*-sulfonylhydrazine (0.24 g, 1.29 mmol) in dry methanol (4.5 cm^3) were added a few drops of diethyl ether saturated with hydrogen chloride and the mixture was further stirred at ambient temperature for 4 h. The solution was diluted with diethyl ether and the ethereal layer was washed successively with water, saturated aq. sodium hydrogen carbonate and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (17:3, v/v) afforded the hydrazone **26** (0.26 g, 97%) as an unstable solid; δ 0.60 (3 H, d, *J* 7.3, 6-Me), 1.23–2.36 (10 H, m, 4- and 5-H_2, 6- and 7-H and 8- and 9-H_2), 1.70 (3 H, d, *J* 1.2, 10-Me), 2.41 (3 H, s, Me), 2.59 (1 H, dd, *J* 6.1 and 14.6, 3-H), 2.99 (1 H, m, 3-H), 3.49 (1 H, s, NH), 7.28 (2 H, d, *J* 8.5, ArH) and 7.58 (2 H, d, *J* 8.5, ArH), which without further purification was used in the next reaction.

(−)-*Clavukerin A* **1**.—To a stirred solution of the hydrazone **26** (45 mg, 0.13 mmol) in dry THF (1.3 cm^3) was added methyllithium (1.16 mol dm^{-3} solution in diethyl ether) (0.45 cm^3, 0.52 mmol) dropwise at −78 °C and the resulting mixture was further stirred at the same temperature for 2 h before being allowed to warm to room temperature and treated with water (10 cm^3) and pentane (10 cm^3). The organic layer was separated and washed successively with 10% aq. potassium hydrogen sulfate, saturated aq. sodium hydrogen carbonate, and brine, and dried over Na_2SO_4. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with pentane afforded (−)-clavukerin A **1** (17 mg, 81%) as an oil; $[\alpha]_D$ −50.28 (*c* 0.1, $CHCl_3$) {lit.,[1] $[\alpha]_D$ −53 (*c* 0.3, $CHCl_3$)}; δ 0.75 (3 H, d, *J* 6.7, 6-Me), 1.22–2.36 (9 H, m, 4- and 5-H_2, 6-H and 8- and 9-H_2), 2.80–2.95 (1 H, m, 7-H), 5.54 (1 H, dt, *J* 4.9 and 12.2, 3-H) and 6.21 (1 H, d, *J* 12.2, 2-H), whose spectroscopic data were identical with those reported.[1]

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