Rearrangement Approaches to Cyclic Skeletons. Part 8.[1] Total Synthesis of (±)-Nakafuran-8, a Marine Metabolite with Antifeedant Properties, on the Basis of Bridgehead Substitution of a Bicyclo[2.2.2]oct-5-en-2-one System[2]

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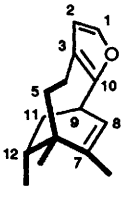
The first total synthesis of (±)-nakafuran-8, a furanosesquiterpene containing a bicyclo[4.2.2]-decane skeleton, has been accomplished by a rearrangement strategy starting from 8-*endo*-1-methoxy-4,5,8-trimethylbicyclo[2.2.2]oct-5-en-2-one. The methoxy group was replaced by hydrogen *via* (1) the pinacol-type rearrangement into the 1-methoxybicyclo[3.2.1]oct-3-en-2-one, (2) DIBAL-H reduction, and (3) the pinacol-type rearrangement to give 8-*endo*-4,5,8-trimethylbicyclo[2.2.2]oct-5-en-2-one. The ring enlargement of this product gave 10-*exo*-6,7,10-trimethylbicyclo[4.2.2]dec-7-en-2-one, the key precursor of (±)-nakafuran-8, *via* the corresponding bicyclo[3.2.2]non-6-en-2-one.

Nakafuran-8 **1** and -9 **2** are novel sesquiterpenoids first isolated from the marine sponge *Dysidea fragilis*.[3] These compounds are interesting not only as the principal metabolite common to nudibranchs, *Hypselodoris godeffroyana* and *Chromodoris maridadilus*, grazing on that sponge, but also as the repellent substance against reef fishes.[3] Nakafuran-8 and its analogues are of particular interest in total syntheses because of the unique bicyclo[4.2.2]decadiene skeleton with a furan ring and three adjacent methyl groups, including the 12-*exo*-methyl, in addition to its biological properties. We report the first total synthesis of (±)-**1**.



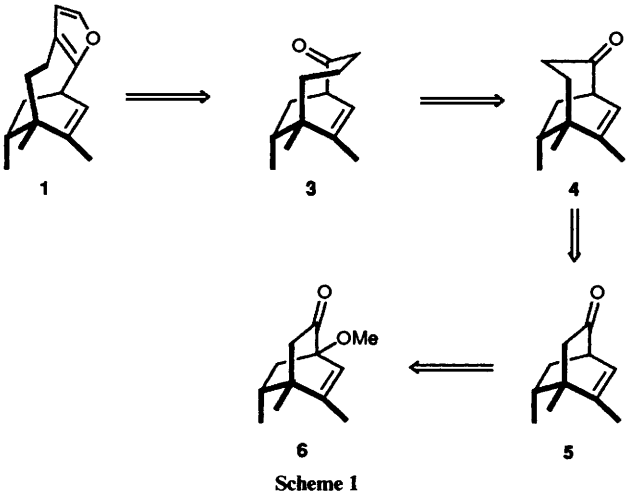
1

2

Results and Discussion

Scheme 1 shows our retrosynthetic consideration based on a rearrangement strategy. The bicyclo[4.2.2]dec-7-en-2-one **3** seemed to be a reasonable synthetic intermediate, which would be derived from ketone **7** by sequential ring enlargements through ketone **4**. We are inclined to rely on a Diels–Alder sequence for preparation of a bicyclo[2.2.0]oct-5-en-2-one. However, the mode of substitution of **5** suggests that this ketone cannot be obtained selectively from 1,2,6-trimethylcyclohexa-1,3-diene and a dienophile which is synthetically equal to a ketene, such as α-chloroacrylonitrile. Our recent development of a method to replace the C-1 bridgehead methoxy group of a bicyclo[2.2.2]oct-5-en-2-one by hydrogen[1] prompted us to select ketone **6** as the precursor of **5**. Ketone **6** has already been prepared stereoselectively starting from α-chloroacrylonitrile and 1-methoxy-3,4,5-trimethylcyclohexa-1,4-diene which isomerizes to the corresponding 1,3-diene under the reaction conditions.[4]

The rearrangement approach to the replacement of the methoxy group of **6** by hydrogen was carried out as shown in Scheme 2. Treatment of **6** with BF_3–2MeOH complex in dry CH_2Cl_2 at room temperature gave α,β-unsaturated ketone **7** and a small amount of the bridgehead hydroxy derivative of **7**. Without purification, the mixture of the unsaturated ketones was reduced by DIBAL-H (diisobutylaluminium hydride) in hexane. Treatment of the resulting alcohols **8** with toluene-*p*-sulfonic acid (TsOH; 0.1 equiv.) in boiling benzene for 1 h gave the desired ketone **5** in 74% overall yield from **6**. The first stage of this transformation should be a pinacol-type skeletal migration through the corresponding dimethyl acetal to produce α,β-unsaturated ketone **7**. The second rearrangement must proceed through the allylic cation intermediate **9**.



Scheme 1

Table 1 Ring enlargement of bridged bicyclic ketones

Substrate	Method[a]	Products (ratio)	Yield (%)
5	A	**4**, **10** (7:3)	70
5	B	**4**, **10** (12:1)	61
4	A	**3**, **11** (2:1)	67
4	B	**3**, **11** (1:3)	57

[a] Described in the text.

The following two steps were ring enlargements of the bicyclic systems. Table 1 and Scheme 3 show the results from Shioiri's ring enlargement[5] (method A) by a combination of trimethylsilyldiazomethane and BF_3–diethyl ether complex and Tieffeneau–Demjanov ring expansion[6] (method B) by sequential treatment with (1) trimethylsilyl cyanide in the presence of

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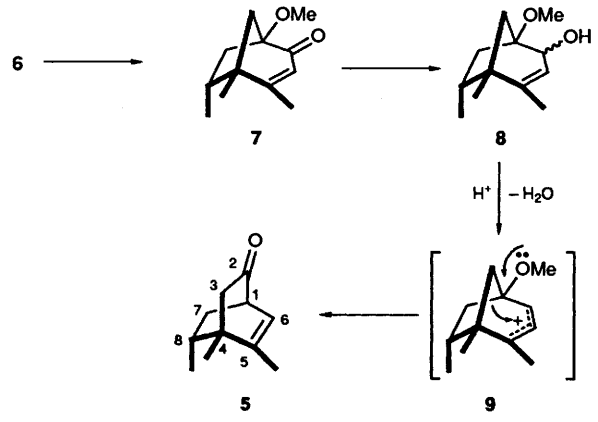
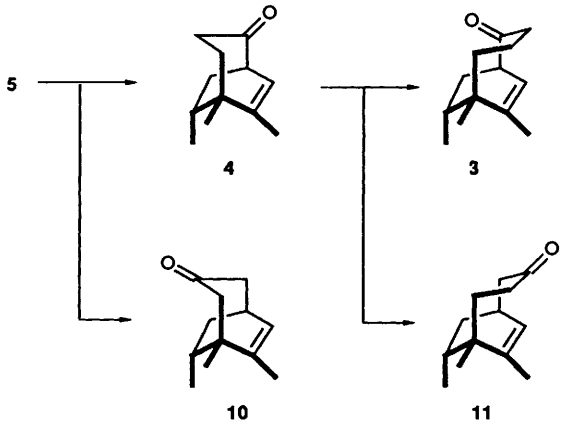


Scheme 2

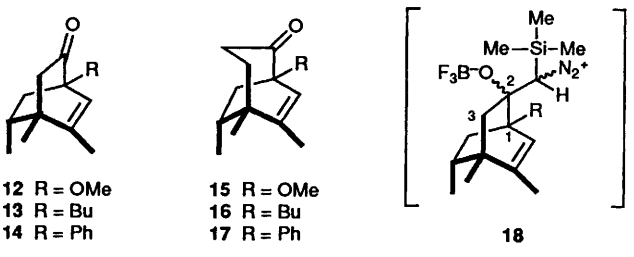
a catalytic amount of zinc iodide,[7] (2) lithium aluminium hydride, and (3) sodium nitrite in aqueous acetic acid. Ring enlargement of **5** by both methods gave mainly the desired 2-oxo analogue **4**.[9]* In the case of **4**, only method A resulted in 2-oxo analogue **3** as the major product. Although the exact explanation of the selectivity is not clear, the presence or the absence of the bulky substituent, *e.g.* a trimethylsilyl group, may control the product composition.[5]



Scheme 3

It has already been reported that the ring enlargement of bicyclo[2.2.2]oct-5-en-2-one **12** by Shioiri's method gives only the 2-oxo homologue **15**.[9] In order to clarify the relationship between the bridgehead substituent and the product composition, we have investigated the ring enlargement of the bridgehead alkyl and aryl ketones (**13** and **14**, respectively).

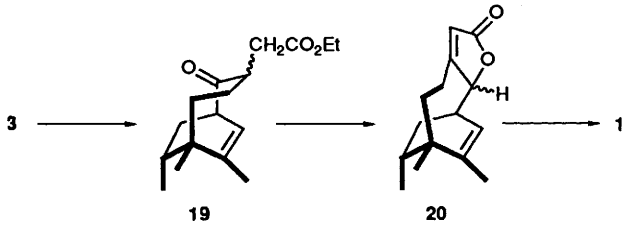
Treatment of ketone **13** with trimethylsilyldiazomethane and BF_3–diethyl ether complex followed by desilylation gave only the 2-oxo homologue **16** in 85% yield. A similar treatment of ketone **14** formed ketone **17** in 62% yield. Exclusive formation of



* For a conformational study of this bicyclic system see ref. 8.

the 2-oxo derivatives means that the secondary C-3 atom of the diazonium betaine intermediates (such as **18**) migrates in preference to the quaternary C-1 atom. In the case of **5**, the C-1 atom is tertiary. The difference between secondary and tertiary carbons should be insufficient to give the 2-oxo homologue **4** exclusively.

The final stage of this work is construction of the furan ring (Scheme 4). Treatment of the lithium enolate of **3** with ethyl iodoacetate in the presence of HMPA (hexamethylphosphoramide) gave a stereoisomeric mixture of keto esters **19** in quantitative yield. Hydrolysis of **19** with K_2CO_3 in aqueous methanol followed by treatment with TsOH[11] in boiling benzene for 4.5 h gave a mixture of conjugated lactones **20**. DIBAL-H reduction of **20** followed by acidic work-up gave the furan, (±)-**1**, in 37% yield from **3**. This furan has spectral characteristics identical with those of natural nakafuran-8. Thus, the first total synthesis of (±)-nakafuran-8 has been accomplished.



Scheme 4

In conclusion, we have developed a method to prepare a bicyclo[4.2.2]oct-7-en-2-one from a bicyclo[2.2.2]oct-5-en-2-one by consecutive ring enlargements and applied this method to the first total synthesis of nakafuran-8 in combination with the previously developed method for formal substitution at the C-1 bridgehead of the bicyclo[2.2.2]oct-5-en-2-one system.

Experimental

General.—^{1}H NMR spectra were measured at 90 and 270 MHz in $CDCl_3$ using TMS [$(CH_3)_4Si$] as the internal standard, *J* values are given in Hz. THF (tetrahydrofuran) and diethyl ether were distilled from benzophenone ketyl under argon immediately prior to use. Dichloromethane and hexane were distilled from CaH_2 immediately prior to use. $TMSCHN_2$ (trimethylsilyldiazomethane) solution (10% in hexane) was obtained from the Tokyo Kasei Co. All reactions were monitored by analytical TLC using Merck pre-coated silica gel $60F_{254}$ plates. Column chromatography was carried out with Merck silica gel 60 (70–230 mesh ASTM). Semi-preparative HPLC was performed on a Hitachi L-6000 model using an Merck Hiber® prepacked column RT (250 × 10 mm). Removal of solvent under reduced pressure refers to the use of a rotary evaporator operating at aspirator pressure and then rotary pump pressure.

Preparation of 8-endo-4,5,8-*trimethylbicyclo*[2.2.2]*oct-5-en-2-one* **5** *by Formal Bridgehead Substitution.*—To a solution of ketone **6** (1.61 g, 8.3 mmol) in CH_2Cl_2 (34 cm^3) was added BF_3–methanol complex (1.80 cm^3, 16.4 mmol) at 0 °C under argon. After 15 min stirring, the mixture was allowed to warm to room temperature and stirred for 1.5 h. The resulting mixture was poured into saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with two portions of CH_2Cl_2. The organic layers were combined, washed with saturated $NaHCO_3$ solution and saturated brine, and dried ($MgSO_4$). Evaporation of the solvent gave a mixture of enone **7** and a small amount of the 1-hydroxy analogue as a pale yellow liquid (1.53 g). To a solution of the liquid in hexane (34

cm^3) was added a solution of DIBAL-H (1 mol dm^{-3} in hexane; 12 cm^3) under argon at 0 °C. After 2 h stirring, the mixture was treated with saturated aqueous NH_4Cl. The resulting mixture was filtered through Celite and the filtrate was extracted with two portions of diethyl ether. The extracts were combined, washed with saturated aqueous NH_4Cl and saturated brine, and dried ($MgSO_4$). Evaporation of the solvent gave a mixture of enol **8** and the 1-hydroxy analogues as a pale yellow liquid (1.55 g). A solution of the oil and TsOH (160 mg) in benzene (34 cm^3) was heated under reflux for 1 h. After cooling to room temperature, the solution was stirred with saturated aqueous $NaHCO_3$ and allowed to separate. The aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with saturated aqueous NH_4Cl and saturated brine, and dried ($MgSO_4$). Evaporation of the solvent gave a yellow liquid (1.57 g). Chromatography of the oil on silica gel (50 g; 5:1, hexane–ethyl acetate) followed by HPLC (15:1, hexane–ethyl acetate) gave the title compound **5** (1.01 g, 74%) as a colourless oil (Found: M^+, 164.1210. $C_{11}H_{16}O$ requires *M*, 164.1201); $\nu_{max}(CCl_4)/cm^{-1}$ 1720s (CO); $\delta_H(CDCl_3)$ 5.86 (1 H, br d, *J* 6.5, $W_{\frac{1}{2}}$ 5, 6-H), 2.94 (1 H, ddd, *J* 6.5, 3.2 and 2.2, 1-H), 2.13 (1 H, ddd, *J* 13.0, 9.5 and 2.2, 7-H_{exo}), 1.92 (1 H, d, *J* 18.0, 3-H), 1.85 (1 H, d, *J* 18.0, 3-H), 1.80 (3 H, d, *J* 1.3, 5-Me), 1.74 (1 H, dqd, *J* 9.5, 6.5 and 4.8, 8-H), 1.18 (3 H, s, 4-Me), 1.08 (1 H, ddd, *J* 13.0, 4.8 and 3.2, 7-H_{endo}) and 0.83 (3 H, d, *J* 6.5, 4-Me); $\delta_C(CDCl_3)$ 213.42 (s), 145.47 (s), 121.23 (d), 49.07 (d), 47.84 (t), 43.01 (s), 37.44 (3), 33.29 (t), 1989 (q), 19.34 (q) and 19.25 (q). The DNP (2,4-dinitrophenyl) derivative of **5**: m.p. 149.5–151 °C (Found: C, 59.0; H, 5.6; N, 16.2. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.85; N, 16.3%).

Ring Enlargement of Compound **5**.—(*a*) *General procedure for method A*. To a solution of ketone **5** (214 mg, 1.3 mmol) in CH_2Cl_2 (5.5 cm^3) was added BF_3–diethyl ether complex (0.25 cm^3, 2.0 mmol) under argon at −78 °C. To this mixture was added a solution of $TMSCHN_2$ hexane (0.58 mol dm^{-3}; 4.5 cm^3, 2.6 mmol) at −78 °C. After 1 h stirring, the mixture was allowed to warm to room temperature and then treated with saturated aqueous $NaHCO_3$. The mixture was extracted with three portions of CH_2Cl_2. The organic layers were combined, washed with brine, dried ($MgSO_4$), and then filtered. Evaporation of the solvent gave an oil (288 mg). In order to cleave the C–Si bond, the oil was dissolved in a mixture of methanol (18 cm^3) and water (2 cm^3) and treated with K_2CO_3 (334 mg) at room temperature for 1.3 h. The resulting mixture was extracted with three portions of CH_2Cl_2. The organic layers were combined, washed with water and brine, and filtered. Concentration of the filtrate gave a colourless oil. Chromatography of the oil on silica gel (8.7 g; 10:1, hexane–ethyl acetate) gave a 7:3 mixture of 9-*exo*-5,6,9-trimethylbicyclo[3.2.2]non-6-en-2-one **4** and 8-*exo*-1,7,8-trimethylbicyclo[3.2.2]non-6-en-3-one **10** as a colourless oil (162 mg, 70%).

(*b*) *General procedure for method B*. A two-necked flask equipped with a rubber septum, a Teflon stirring bar, and a three way stopcock connected with a balloon filled with argon was charged with ketone **5** (1.63 g, 9.92 mmol) and zinc iodide (15 mg). To this mixture was added trimethylsilyl cyanide (1.4 cm^3, 11.1 mmol) at 0 °C. After 30 min stirring, the mixture was allowed to warm to room temperature, stirred for 8.5 h, and dissolved in diethyl ether (10 cm^3). Another two-necked flask equipped with a rubber septum, a Teflon stirring bar, and a reflux condenser connected with an argon inlet was charged with $LiAlH_4$ (550 mg, 14.5 mmol) and diethyl ether (20 cm^3). To the suspension was added the diethyl ether solution of the trimethylsiloxy nitrile through a double ended needle. The reaction mixture was stirred at room temperature overnight and then heated under reflux for 30 min. After being cooled to 0 °C, the resulting mixture was successively treated with water (0.55 cm^3), 15% NaOH solution (0.55 cm^3) and water (1.65 cm^3). Granule precipitates were filtered off and then the filtrate was concentrated to give a colourless oil. A solution of this oil was dissolved in acetic acid (3 cm^3) and diluted with water (15 cm^3). To this mixture was added a solution of sodium nitrite (1.03 g, 15 mmol) in water (5 cm^3) over a period of 3 h using a microtube pump. After stirring overnight, the resulting mixture was extracted with diethyl ether. The extracts were combined, washed with 5% sodium carbonate and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow oil (1.66 g). Chromatography of the oil on silica gel (50 g; 10:1, hexane–ethyl acetate) gave a 12:1 mixture of **4** and **10** (1.07 g, 61%) as a colourless oil. Ketones **4** and **10** were isolated by HPLC (15:1, hexane–ethyl acetate).

4: (Found: M^+, 178.1373. $C_{12}H_{18}O$ requires *M*, 178.1358); $\nu_{max}(CCl_4)/cm^{-1}$ 1705s (CO); $\delta_H(CDCl_3)$ 5.74 (1 H, br d, *J* 7, $W_{\frac{1}{2}}$ 5, 7-H), 2.89 (1 H, br t, *J* 7, $W_{\frac{1}{2}}$ 3, 1-H), 2.7–2.3 (3 H, m), 2.04 (1 H, m), 1.84 (1 H, ddd, *J* 14.0, 8.5 and 7.0, 4-H), 1.75 (3 H, d, *J* 1.2, 6-Me), 1.62 (1 H, ddd, *J* 14.0, 7.0 and 5.0, 4-H), 1.39 (1 H, ddd, *J* 14.5, 6.5 and 4.0, 8-H)$_{exo}$), 1.08 (3 H, s, 5-Me) and 0.89 (3 H, d, *J* 6.5, 9-Me); $\delta_C(CDCl_3)$ 209.88 (s), 144.98 (s), 120.85 (d), 48.89 (d), 40.55 (s), 39.89 (t), 39.20 (t), 37.04 (d), 33.75 (t), 24.71 (q), 21.54 (q) and 20.23 (q). The derivative of **4**: m.p. 160–162 °C (Found: C, 60.3; H, 6.2; N, 15.55. $C_{18}H_{22}N_4O_4$ requires C, 60.35; H, 6.2; N, 15.6%).

10: (Found: M^+, 178.1366. $C_{12}H_{18}O$ requires *M*, 178.1358); $\nu_{max}(CCl_4)/cm^{-1}$ 1695s (CO); $\delta_H(CDCl_3)$ 5.97 (1 H, br d, *J* 7, $W_{\frac{1}{2}}$ 5, 6-H), 2.54 (2 H, m, 5-H and 9-H_{endo}), 2.45 (1 H, m), 2.38–2.33 (2 H, m), 2.04 (1 H, dd, *J* 12.0 and 9.5), 1.92 (1 H, ddd, *J* 9.5, 6.5 and 3.8), 1.76 (3 H, d, *J* 1.2, 7-Me), 1.28 (1 H, m, 9-H_{exo}), 1.05 (3 H, s, 1-Me) and 0.81 (3 H, d, *J* 6.5, 8-Me); $\delta_C(CDCl_3)$ 212.64 (s), 142.09 (s), 127.86 (d), 58.78 (t), 48.61 (t), 39.22 (s), 38.24 (3), 36.04 (t), 28.51 (d), 24.31 (q), 21.20 (q) and 20.14 (q). The Dnp derivative of **10**: m.p. 138–140 °C (Found: C, 60.2; H, 6.0; N, 15.55. $C_{18}H_{22}N_4O_4$ requires C, 60.35; H, 6.2; N, 15.6%).

Ring Enlargement of Compound **4**.—(*a*) *Method A*. Ketone **4** (120 mg, 0.67 mmol) was treated with $TMSCHN_2$ (10% hexane solution; 1 cm^3) and BF_3–diethyl ether complex (0.125 cm^3, 1.0 mmol) in CH_2Cl_2 (7.5 cm^3) under argon at −78 °C. After 1 h stirring, the resulting mixture was treated with saturated aqueous $NaHCO_3$ and then allowed to warm to room temperature. Usual work-up gave a crude mixture of the products as an oil (156 mg). The oil was treated with K_2CO_3 (334 mg) in methanol (6 cm^3)–water (1.2 cm^3) at room temperature overnight. A 2:1 mixture of 10-*exo*-6,7,10-trimethylbicyclo[4.2.2]dec-7-en-2-one and -3-one **3** and **11**, respectively (101 mg, 79%) was obtained as a colourless oil after chromatography on silica gel (5 g, 10:1, hexane–ethyl acetate).

(*b*) *Method B, Tieffeneau–Demjanov ring enlargement*. Ketone **4** (315 mg, 1.77 mmol) was treated by a method similar to that of **5**. After treatment with trimethylsilyl cyanide (0.25 cm^3, 2 mmol) and zinc iodide (10 mg) at 0 °C, the resulting mixture was reduced with $LiAlH_4$ (87 mg, 2.3 mmol) in diethyl ether (5 cm^3). The resulting mixture of amino alcohols was dissolved in acetic acid (0.5 cm^3), diluted with water (3 cm^3), and then treated with a solution of sodium nitrite (180 mg, mmol) in water (0.87 cm^3) over a period of 1 h. After stirring for 3 h, the resulting mixture was extracted with diethyl ether. The extracts were combined, washed with 5% sodium carbonate and with brine, and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow oil (339 mg). Chromatography of the oil on silica gel (10 g; 10:1, hexane–ethyl acetate) gave a 1:3 mixture of compounds **3** and **11** (192 g, 57%) as a colourless oil. Ketones **3** and **11** were isolated by HPLC (20:1, hexane–ethyl acetate).

3: (Found: M^+, 192.1510. $C_{13}H_{20}O$ requires *M*, 192.1514); $\nu_{max}(CCl_4)/cm^{-1}$ 1700s (CO); $\delta_H(CDCl_3)$ 5.45 (1 H, dq, *J* 6.5 and 1.3, 8 H), 3.15 (1 H, m, 1-H), 2.6–2.4 (2 H, m), 2.22 (1 H, ddd, *J*

15.0, 8.0 and 2.6), 1.9–1.45 (6 H, m), 1.72 (3 H, d, *J* 1.3, 7-Me), 1.08 (3 H, s, 6-Me) and 0.88 (3 H, d, *J* 6.8, 10-Me); $\delta_C(CDCl_3)$ 213.47 (s), 142.63 (s), 119.74 (d), 48.34 (d), 43.89 (t), 41.63 (t), 40.96 (s), 37.85 (d), 30.74 (t), 27.15 (q), 23.88 (t), 20.96 (q) and 20.78 (q). The Dnp derivative of **3**: m.p. 143–145 °C (Found: C, 61.2; H, 6.4; N, 15.0. $C_{19}H_{24}N_4O_4$ requires C, 61.3; H, 6.5; N, 15.0%).

11: (Found: M^+, 192.1534. $C_{13}H_{20}O$ requires *M*, 192.1514); $\nu_{max}(CCl_4)/cm^{-1}$ 1695s (CO); $\delta_H(CDCl_3)$ 5.81 (1 H, br d, *J* 6.0, $W_{\frac{1}{2}}$ 4.5, 8-H), 2.53 (1 H, m, 1-H), 2.5–2.3 (3 H, m), 1.88 (1 H, ddd, *J* 14.0, 7.5 and 2.2), 1.8–1.4 (5 H, m), 1.65 (3 H, br s, $W_{\frac{1}{2}}$ 3.5, 7-Me), 1.03 (3 H, s, 6-Me) and 0.88 (3 H, d, *J* 6.8, 10-Me); $\delta_C(CDCl_3)$ 215.28 (s), 138.42 (s), 126.78 (d), 53.14 (t), 40.46 (s), 40.21 (t), 39.32 (t), 37.60 (d), 35.91 (t), 29.42 (d), 25.72 (q), 20.99 (q) and 20.29 (q). The Dnp derivative of **11**: m.p. 148–150 °C (Found: C, 61.2; H, 6.5; N, 14.9. $C_{19}H_{24}N_4O_4$ requires C, 61.3; H, 6.5; N, 15.0%).

Ring Enlargement of 1-*Butyl*-4-*methylbicyclo*[2.2.2]*oct*-5-*en*-2-*one* **13**.—Following the general procedure of method A, ketone **13** (162 mg, 0.84 mmol) was treated with $TMSCHN_2$ (2.81 mol dm^{-3} hexane solution; 1 cm^3) and BF_3–diethyl ether complex (0.16 cm^3, 1.3 mmol) in CH_2Cl_2 (4 cm^3) under argon at 78 °C. After 2 h stirring, the mixture was treated with saturated aqueous $NaHCO_3$ and then allowed to warm to room temperature. Usual work-up gave a crude mixture of the products as an oil (257 mg). The oil was treated with K_2CO_3 (248 mg) in methanol (12 cm^3)–water (2 cm^3) at room temperature overnight. 1-Butyl-5-methylbicyclo[3.2.2]non-6-en-2-one[10] **16** (148 mg, 85%) was obtained as colourless oil after chromatography on silica gel (10 g; 30:1, hexane–ethyl acetate).

Ring Enlargement of 4-*Methyl*-1-*phenylbicyclo*[2.2.2]*oct*-5-*en*-2-*one* **14**.—Following the general procedure of method A, ring enlargement of ketone **14** (210 mg, 0.99 mmol) was carried out by treating it with $TMSCHN_2$ (2.81 mol dm^{-3} hexane solution; 1 cm^3) and BF_3–diethyl ether complex (0.19 cm^3, 1.5 mmol) in CH_2Cl_2 (4 cm^3) under argon at 78 °C. Usual work-up gave a crude mixture of the products as an oil (322 mg). Treatment of the oil with K_2CO_3 (212 mg) in methanol (12 cm^3)–water (2 cm^3) at room temperature for 3 h followed by chromatography on silica gel (10 g; 20:1, hexane–ethyl acetate) gave 5-methyl-1-phenylbicyclo[3.2.2]non-6-en-2-one[10] **17** (139 mg, 62%).

(±)-*Nakafuran*-8 **1**.—A two-necked flask (30 cm^3) equipped with a rubber septum, a Teflon stirring bar, and a three way stopcock connected to a balloon filled with argon was charged with a solution of LDA (lithium diisopropylamide (1.99 mol dm^{-3}; 0.2 cm^3) and THF (tetrahydrofuran) (2 cm^3) at −78 °C. To this solution was added a solution of ketone **3** (51 mg, 0.27 mmol) in THF (2 cm^3). The mixture was stirred for 30 min. After addition of HMPA (0.5 cm^3) followed by stirring for 15 min, a solution of ethyl iodoacetate (0.06 cm^3, 0.51 mmol) in THF (1.5 cm^3) was added to this mixture. The resulting mixture was stirred for 30 min, allowed to warm to room temperature over 1 h, and then treated with saturated aqueous NH_4Cl. The resulting mixture was extracted with three portions of diethyl ether. The organic layers were combined, washed with water and saturated brine, dried ($MgSO_4$), and then filtered. Evaporation of the solvent gave an oil. Chromatography of the oil on silica gel (14 g; 10:1, hexane–ethyl acetate) gave keto ester **19** (76 mg, 0.27 mmol) as colourless oil.

To a solution of keto ester **19** (76 mg, 0.27 mmol) in methanol (6 cm^3) and water (2 cm^3) was added K_2CO_3 (429 mg). This mixture was stirred at 30 °C for 23 h and then diluted with water. After extraction with three portions of diethyl ether, the aqueous layer was acidified with 2 mol dm^{-3} hydrochloric acid. The resulting aqueous solution was extracted with three portions of diethyl ether. The organic layers were combined, washed with saturated brine, dried ($MgSO_4$), and then filtered. Evaporation of the solvent gave an oil (46 mg). A solution of the oil (46 mg) and TsOH (9 mg) in benzene (8 cm^3) was heated under reflux for 4 h. After cooling, the solution was diluted with diethyl ether, washed with saturated aqueous $NaHCO_3$ and with brine, dried ($MgSO_4$), and then filtered. Removal of the solvent under reduced pressure gave lactones **20** as a pale yellow oil (38 mg).

To a solution of lactones **20** (38 mg, 0.16 mmol) in THF (2.5 cm^3) was added a solution of DIBAL-H (1 mol dm^{-3} in hexane; 0.7 cm^3) at −10 °C. After 40 min stirring, 0.5 mol dm^{-3} sulfuric acid (2 cm^3) was added to the solution. The mixture was allowed to warm to 0 °C and then stirred for 90 min. The resulting mixture was extracted with three portions of diethyl ether. The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and saturated brine, and then dried ($MgSO_4$). Evaporation of the solvent gave an oil (38 mg). Chromatography of the oil on silica gel (13 g; 10:1, hexane–ethyl acetate) followed by HPLC (15:1, hexane–ethyl acetate) gave the title compound **1** (21 mg, 37% from **3**) as colourless oil (Found: M^+, 216.1516. $C_{15}H_{20}O$ requires *M*, 216.1514); $\nu_{max}(CCl_4)/cm^{-1}$ 3030w, 2925s, 1505m, 1455m, 898m, 880m, 733m and 700m; $\delta_H(CDCl_3)$ 7.13 (1 H, d, *J* 1.5), 6.07 (1 H, d, *J* 1.5), 5.98 (1 H, br d, *J* 7.0, $W_{\frac{1}{2}}$ 4), 3.46 (1 H, ddd, *J* 7.0, 3.5 and 3.5), 2.43 (1 H, dddd *J* 15.0, 10.8 and 6.8), 2.27 (1 H, ddd, *J* 15.0, 3.6 and 3.6), 1.90–1.65 (4 H, m), 1.70 (3 H, d, *J* 1.2), 1.26 (1 H, ddd, *J* 11.8, 11.8 and 4.0), 1.06 (3 H, s) and 0.89 (3 H, d, *J* 7); $\delta_C(CDCl_3)$ 150.95 (s), 141.04 (s), 138.27 (d), 124.43 (d), 118.40 (s), 113.64 (d), 47.94 (t), 40.80 (s), 38.98 (t), 36.50 (d), 34.67 (d), 24.25 (q), 23.09 (t), 20.23 (q) and 18.67 (q).

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