A Facile Synthesis of 5-Methyl-6,8-dioxabicyclo[3.2.1]octan-3-ones from 4-(t-Butyldimethylsiloxy)pent-3-en-2-one and Protected α-Ketols. A Synthesis of (±)-Frontalin

Hisahiro Hagiwara * and Hisashi Uda
Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Katahira, Sendai 980, Japan

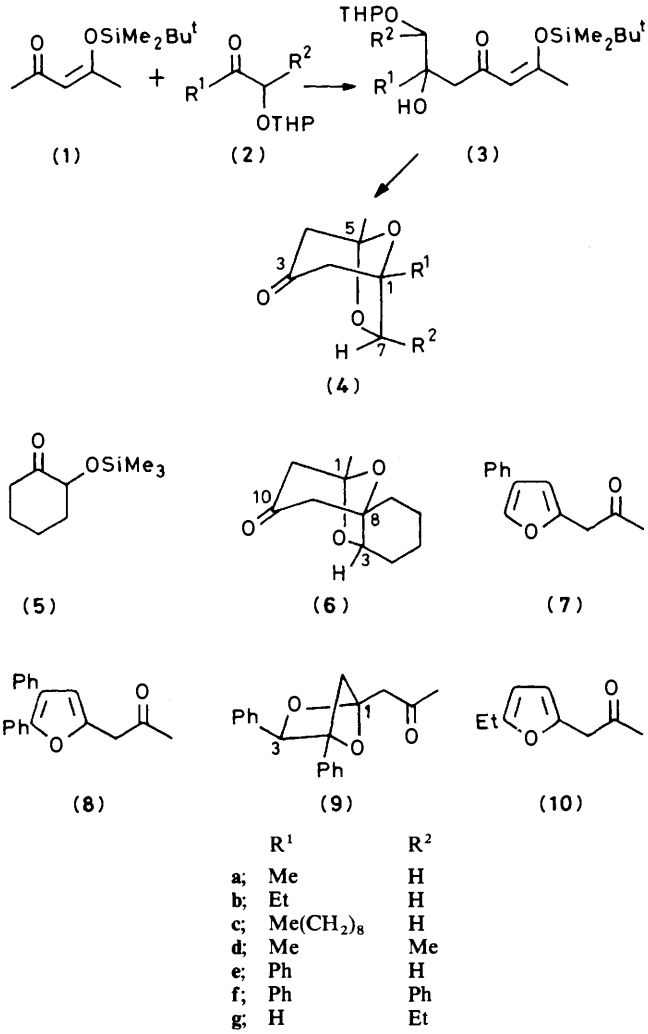
An efficient method for the synthesis of substituted 5-methyl-6,8-dioxabicyclo[3.2.1]octan-3-one derivatives (**4a**—**f**) and (**6**) has been developed. This utilises the cross-aldol condensation of the lithium enolate of 4-(t-butyldimethylsiloxy)pent-3-en-2-one (**1**) with the protected α-ketols (**2a**—**g**) and (**5**) and subsequent acid-catalysed deprotection and intramolecular acetalisation. A short synthesis of (±)-frontalin (**14**) was carried out using this method.

Natural products with a 6,8-dioxabicyclo[3.2.1]octane skeleton, a unique intramolecular acetal structure, have attracted much attention because of their intriguing biological activities; examples of such compounds are aggregation pheromones such as frontalin (**14**),[1] brevicomins,[2] multistriatins,[3] and the marine toxin palytoxin.[4] As part of our work on the synthetic utility of the kinetically controlled enolates of conjugated cyclic enones, we have previously reported that the zinc chloride-assisted cross-aldol condensation reaction with protected α-ketols could be successfully used for the total synthesis of several furanoterpenoids.[5] We have investigated the extension of this methodology for the preparation of other types of compounds and found that the use of 4-(t-butyldimethylsiloxy)pent-3-en-2-one (**1**) as the acyclic kinetic enolate component provides a facile synthesis of the 5-methyl-6,8-dioxabicyclo[3.2.1]octan-3-one derivatives (**4a**—**g**) and (**6**).

Because it is readily available in large quantities, 4-(t-butyldimethylsiloxy)pent-3-en-2-one (**1**)[6] (masked pentane-2,4-dione) rather than 4-methoxypent-3-en-2-one[7] was chosen as the acyclic β-alkoxy-α,β-unsaturated ketonic component. The protected α-ketols (**2a**—**g**) and (**5**) were easily[5b] prepared according to the procedure reported previously.

The siloxyenone (**1**) was treated with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and then with a protected α-ketol (**2a**—**g**) or (**5**) in the presence of zinc chloride. The reaction was quenched at −30 °C with saturated aqueous ammonium chloride. On treatment with toluene-*p*-sulphonic acid monohydrate (PTSA) in hot aqueous dioxane followed by the azeotropic removal of water with benzene, the crude cross-aldol condensation product (**3**) underwent successive deprotection and intramolecular acetal formation to give the thermodynamically more stable 5-methyl-6,8-dioxabicyclo[3.2.1]octan-3-one derivative (**4**) or (**6**) (Scheme 1, Table), rather than the alternative intramolecular acetal, 2,5-dioxabicyclo[2.1.1]hexane skeleton, which was distinguished by the presence of an acetonyl functionality [see structure (**9**)]. The presence of zinc chloride provided somewhat higher yields;[7] in the absence of zinc chloride, the acetal (**4a**) was obtained in 36% yield based on the enone (**1**) (see entry 1, Table). An attempt to employ the dianion of pentane-2,4-dione itself or the kinetically controlled enolate of 4-morpholinopent-3-en-2-one gave none of the desired product.

Of the protected α-ketols examined, the alkyl substituted derivatives (**2a**—**d**) gave the dioxabicyclo-octanones (**4a**—**d**) as the sole isolable products in better yields (entries 1—4) than the phenyl-substituted derivatives (**2e**) and (**2f**). In the last-named cases, the furan derivatives (**7**) and (**8**) were also produced as the minor products (entries 5 and 6). The formation of the furans (**7**) and (**8**) would be due to the easy dehydration of compound (**3**) leading to the 1,4-dicarbonyl compounds. In the case of the protected benzoin (**2f**), a compound with the 2,5-dioxabicyclo[2.1.1]hexane skeleton, an alternative acetal derivative (**9**) was obtained. 2-Hydroxycyclohexanone trimethylsilyl ether (**5**), a cyclic protected α-ketol, also gave, albeit in low yield, the corresponding dioxatricyclododecanone derivative (**6**) (entry



	R^1	R^2
a;	Me	H
b;	Et	H
c;	$Me(CH_2)_8$	H
d;	Me	Me
e;	Ph	H
f;	Ph	Ph
g;	H	Et

Scheme 1.

Table. 5-Methyl-6,8-dioxabicyclo[3.2.1]octan-3-ones from 4-(t-butyldimethylsiloxy)pent-3-en-2-one (**1**) and protected α-ketols

Entry	Protected α-ketols	Product	Yield (%)
1	(**2a**)	(**4a**)	59[a]
2	(**2b**)	(**4b**)	69[b]
3	(**2c**)	(**4c**)	40[b]
4	(**2d**)	(**4d**)	46[b,c]
5	(**2e**)	(**4e**), (**7**)	*ca.* 75 (68:32 mixture)[b]
6	(**2f**)	(**4f**), (**8**), (**9**)	27[b], 7[b], 12[b]
7	(**5**)	(**6**)	20[b]
8	(**2g**)	(**10**)	55[a]

[a] Yields are for the isolated pure products based on the amount of enone (**1**) consumed, and were not optimised. [b] Yields are for the isolated pure products based on the amount of α-ketol (**2**) consumed, and were not optimised. [c] A mixture of the C-7 epimers.

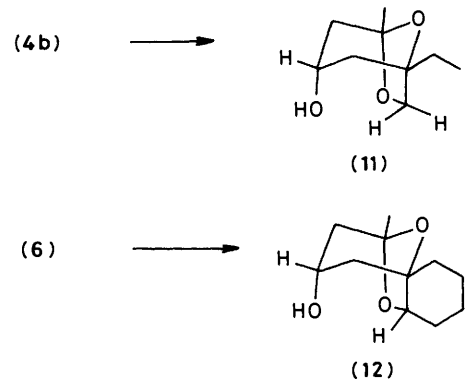
7). The reaction of the protected α-hydroxyaldehyde (**2g**) was also investigated (entry 8). However, the product obtained was the furan derivative (**10**), not the dioxabicyclo-octanone derivative. The products (**4f**) and (**6**), with a substituent at C-7, were obtained as single stereoisomers. However, two epimeric (at C-7) isomers of (**4d**) were produced in a ratio of 72:28 as determined by gas liquid partition chromatography (g.l.p.c.).

The above examples show this procedure to be a convenient method for the synthesis of 6,8-dioxabicyclo[3.2.1]octane derivatives because of the ready availability of both the starting 4-(t-butyldimethylsiloxy)pent-3-en-2-one (**1**) and the protected α-ketols (**2a**—**g**) and (**5**), and the straightforward nature of the practical operations. It can also be used in the synthesis of analogues of the biologically important compound frontalin and other pheromones.

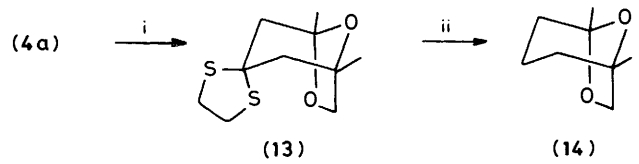
Stereochemistry.—The stereochemistry shown in structures (**4f**), (**6**), and (**9**) (Scheme 1) was established on the basis of ^{1}H n.m.r. spectroscopic properties. In the 6,8-dioxabicyclo-[3.2.1]octane derivatives (**4a**—**c**), and (**4e**), the signal of the methylene protons at C-7 appears as an AB-type quartet. The B part is split further, with a small coupling constant (*ca.* 1 Hz), indicating the presence of W-type long-range coupling with the axial proton at C-2; this was confirmed by decoupling experiments. Thus, the B part of the signal is assignable to the *exo*-proton (R^2 = H). On the other hand, the methine proton at C-7 in compounds (**4f**) and (**6**) appears as a clear singlet in the former and a doublet of doublets in the latter; the spectral pattern was unchanged on irradiation at the C-2 proton. These results strongly suggest that the proton at C-7 in compounds (**4f**) and (**6**) has the *endo*-configuration as shown.

Further confirmation was obtained from the reduction of compound (**4b**) with L-Selectride at −78 °C which gave exclusively the *endo* axial alcohol (**11**) by *exo* attack of hydride (Scheme 2); the configuration of the alcohol (**11**) was apparent from the half-height width of the proton signal at C-3 ($w_{\frac{1}{2}}$ *ca.* 9 Hz). In this axial alcohol the signal of the *endo* proton at C-7 was shifted 0.52 p.p.m. to lower field than in the original ketone (**4b**). In a similar fashion, compound (**6**) was also reduced with L-Selectride to give the *endo* axial alcohol ($w_{\frac{1}{2}}$ of 3-H, *ca.* 9 Hz); in this alcohol the methine proton signal was shifted 0.32 p.p.m. to lower field, clearly establishing the stereochemistry at the C-7 position in the stereoisomers (**4f**) and (**6**) as that shown (Scheme 2).

On irradiation of the C-6 protons of the dioxabicyclo[2.1.1]hexane derivative (**9**), a 12% increase in height was observed without a change in the integrated area. This W-type coupling suggests that the phenyl group at C-3 is *cis* to the C-6



Scheme 2.



Scheme 3. *Reagents:* i, ethane-1,2-dithiol–$Zn(OSO_2CF_3)_2$–CH_2Cl_2; ii, Raney-Ni (W-2)–acetone

methylene bridge as indicated in the structure (**9**). The formation of the single stereoisomer of (**6**) is accounted for by the well-precedented preferential equatorial attack of a nucleophile on an α-substituted cyclohexanone.[8] The acetal (**4f**) clearly arose from the *erythro*-isomer (**3f**). In the case of the *threo*-isomer, the bulky phenyl substituent prevents cyclisation to give the dioxabicyclo[3.2.1]octane framework (*endo* Ph at C-7), and another type of cyclisation leading to compound (**9**) takes place instead.

Synthesis of (±)-*Frontalin.*—Frontalin (**14**) has been isolated as the principal component of the aggregation pheromone of the southern pine beetle (*Dendroctonus frontalis*), which is an insect pest responsible for timber losses in coniferous forests; it contains an intramolecular acetal linkage, the 6,8-dioxabicyclo[3.2.1]octane framework. There are a number of reports of the total synthesis of frontalin in both the racemic[9] and optically active forms;[10] our approach is short and straightforward, giving the frontalin framework in the first stage of the synthesis, and providing easy access to frontalin analogues, unlike previous routes.

Our synthetic pathway is illustrated in Scheme 3. A number of methods of converting the carbonyl group at C-3 of compound (**4a**) into the labile acetal moiety were examined. Thioacetalisation with ethane-1,2-dithiol was found to be successful, but only with zinc trifluoromethanesulphonate as a Lewis acid catalyst;[11] the thioacetal (**13**) was obtained in 66% yield. With boron trifluoride–ether the thioacetal was formed in only 20% yield. The reductive removal of the thioacetal group of compound (**13**) with Raney–Ni (W-2) in refluxing ethanol and acetone gave, after extractive work-up with n-pentane, (±)-frontalin (**14**) in 67% yield, identical with the authentic sample.

Experimental

All m.p.s were uncorrected. Liquids were normally purified, after chromatographic separation, by evaporative short-path distillation; oil-bath temperatures are recorded. I.r. spectra were recorded for solutions in carbon tetrachloride, unless otherwise indicated, on a Jasco A-3 spectrophotometer. ^{1}H N.m.r. spectra

were obtained for solutions in deuteriochloroform with a Jeol PMX-60 (60 MHz), an FX-90 (90 MHz), or a PS-100 (100 MHz) instrument with tetramethylsilane as internal standard. Mass spectra were obtained on a Jeol JMS-DX 300 (70 eV) spectrometer. G.l.p.c. was carried out on a Jeol JGC-20K gas chromatograph or a JMS DX-300 spectrometer. High pressure liquid chromatography (h.p.l.c.) was carried out on a Jasco PRC-50 instrument. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether refers to diethyl ether.

Preparation of the Protected α-Ketols (**2b—f**).—The procedure is the same as previously reported for the preparation of acetonyl tetrahydropyranyl ether (**2a**). The α-ketols which were used for the preparation of compounds (**2b**), (**2d**), and (**2f**) are commercially available, and those for compounds (**2c**) and (**2e**) were prepared according to the procedure of Rubottom.[12]

1-*Tetrahydropyranyloxybutan-2-one* (**2b**). From 1-hydroxybutan-2-one (1.32 g, 15 mmol), compound (**2b**) was prepared in 88% yield (2.25 g); b.p. 90—100 °C at 0.6 mmHg; $\nu_{max.}$ 1 740 (shoulder), 1 725, 1 200, 1 140, 1 080, 1 045, and 980 cm^{-1}; δ (60 MHz) 1.08 (3 H, t, *J* 7 Hz, CH_2Me), 1.3—2.2 (6 H, m, CH_2), 2.55 (2 H, q, *J* 7 Hz, CH_2Me), 3.2—4.2 [2 H, m, $OCHOCH_2(CH_2)_3$], 4.18 (2 H, d, *J* 2 Hz, OCH_2COEt), and 4.65 [1 H, br s, $w_{\frac{1}{2}}$ 4 Hz, $OCHO(CH_2)_4$]; *m/z* (no M^+), 85 (100).

1-*Tetrahydropyranyloxyundecan-2-one* (**2c**). From 1-hydroxyundecan-2-one (713 mg, 3.8 mmol), compound (**2c**) was prepared in 93% yield (958 mg); b.p. 145—155 °C at 0.3 mmHg; $\nu_{max.}$ 1 730 (shoulder), 1 715, 1 200, 1 130, 1 075, 1 040, 1 020, and 970 cm^{-1}; δ (60 MHz) 0.88 (3 H, t, *J* 4 Hz, Me), 1.28 (14 H, br s, CH_2), 1.2—2.1 (6 H, m, CH_2), 2.48 (2 H, t, *J* 7 Hz, CH_2COCH_2O), 3.2—4.2 [2 H, m, $OCHOCH_2(CH_2)_3$], 4.15 (2 H, d, *J* 2 Hz, OCH_2COCH_2), and 4.63 [1 H, br s, $OCHO(CH_2)_4$]; *m/z* (no M^+), 181 (100), 139 (39), 121 (56), and 43 (54).

2-*Tetrahydropyranyloxybutan-3-one* (**2d**). From 2-hydroxybutan-3-one (1.34 g, 15 mmol), compound (**2d**) was prepared in 71% yield (1.84 g); b.p. 70—80 °C at 0.5 mmHg; $\nu_{max.}$ 1 720, 1 355, 1 200, 1 140, 1 085, and 1 040 cm^{-1}; δ (60 MHz) 1.28 and 1.37 (total 3 H, each d, *J* 7 Hz, Me), 1.4—2.1 (6 H, m, CH_2), 2.17 and 2.23 (total 3 H, each s, MeCO), 3.2—4.5 [3 H, m, 2-H and $OCHOCH_2(CH_2)_3$], and 4.58 [1 H, br s, $w_{\frac{1}{2}}$ 6 Hz, $CHO(CH_2)_4$]; *m/z* (no M^+), 129 (15), 85 (100), and 43 (85).

Phenacyl tetrahydropyranyl ether (**2e**). From phenacyl alcohol (955 mg, 7 mmol), compound (**2e**) was prepared in quantitative yield (1.62 g); m.p. 52—53 °C (crystallised on standing in a freezer); $\nu_{max.}$ 1 710, 1 690, 1 200, 1 140, 1 040, and 980 cm^{-1}; δ (60 MHz) 1.3—2.3 (6 H, m, CH_2), 3.3—4.2 [2 H, m, $OCHOCH_2(CH_2)_3$], 4.78 [1 H, br s, $OCHO(CH_2)_4$], 4.89 (2 H, s, $COCH_2O$), and 7.3—8.2 (5 H, m, aromatic H); *m/z* (no M^+), 162 (9), 120 (21), 105 (46), and 85 (100).

Benzoin tetrahydropyranyl ether (**2f**). From benzoin (3.18 g, 15 mmol), compound (**2f**) was prepared in 78% yield (3.47 g); b.p. 175—185 °C at 0.1 mmHg; $\nu_{max.}$ 1 700, 1 680, 1 600, 1 450, 1 200, 1 130, 1 085, 1 045, and 990 cm^{-1}; δ (60 MHz) 1.2—2.3 (6 H, m, CH_2), 3.23—4.10 [2 H, m, $OCHOCH_2(CH_2)_3$], 4.63—4.90 [1 H, m, $OCHO(CH_2)_4$], 6.00 and 6.07 (total 1 H, each s, 1-H), and 7.2—7.8 and 7.8—8.2 (total 10 H, each m, aromatic H); *m/z* (no M^+), 191 (8) and 85 (100).

2-*Tetrahydropyranyloxybutyraldehyde* (**2g**). Protection of methyl 2-hydroxybutyrate (1.78 g, 15 mmol) was achieved in the same manner as described in the general procedure to give methyl 2-tetrahydropyranyloxybutyrate (3.24 g, 100%), which was reduced with lithium aluminium hydride (555 mg, 15 mmol) in anhydrous ether (40 ml) at 0 °C for 1.5 h. The alcohol obtained (2.27 g, 13 mmol, 87%) was oxidised with pyridinium chlorochromate (4.23 g, 19.5 mmol) and sodium acetate (216 mg, 2.6 mmol) in anhydrous methylene dichloride (50 ml) at room temperature for 2 h. Ordinary work-up followed by silica-gel column chromatography [eluant hexane–ethyl acetate (3:1)] gave the aldehyde (**2g**) (831 mg, 37%), which was used immediately without further purification; δ (60 MHz) 1.07 (3 H, t, *J* 6 Hz, Me), 1.2—2.3 (8 H, m, CH_2Me and CH_2), 3.3—4.5 [3 H, m, $OCHOCH_2(CH_2)_3$ and 2-H], 4.87 [1 H, br s, $OCHO(CH_2)_4$], and 9.88 (1 H, br s, aldehydic H).

General Procedure for the Cross-aldol Reaction.—The procedure is the same as that previously reported for the synthesis of furans.[5b]

General Procedure for the Synthesis of 5-Methyl-6,8-dioxabicyclo[3.2.1]*octan-3-one.*—The crude cross-aldol product (*ca.* 1 mmol) and PTSA (50 mg) were dissolved in aqueous dioxane (75%, 4 ml), and the resulting solution was heated at 70—80 °C for 1 h. Benzene (30 ml) was added and the resulting solution was refluxed for 1 h using a Dean–Stark water separator. After the mixture had cooled to room temperature, the product was extracted with ether (2 × 30 ml). The combined extracts were washed with water and then brine. After evaporation of the solvent, the residue was purified by column chromatography or silica-gel t.l.c. to give the dioxabicyclo-octanone (**4a—f**) or (**6**).

1,5-*Dimethyl-6,8-dioxabicyclo*[3.2.1]*octan-3-one* (**4a**). The reaction of 4-(t-butyldimethylsiloxy)pent-3-en-2-one (**1**) (324 mg, 1.5 mmol) and acetonyl tetrahydropyranyl ether (**2a**) (355 mg, 2.3 mmol) was carried out in the same manner as described in the general procedure and gave the *dioxabicyclo-octanone* (**4a**) [139 mg, 59% based on (**1**) consumed]; $\nu_{max.}$ 1 740, 1 390, 1 250, 1 135, and 1 040 cm^{-1}; δ (90 MHz) 1.32 (3 H, s, 1-Me), 1.40 (3 H, s, 5-Me), 2.22 (2 H, s, $w_{\frac{1}{2}}$ 3 Hz), 2.28 (2 H, s, $w_{\frac{1}{2}}$ 2 Hz) (2- and 4-CH_2), 3.16 (1 H, d, B part of AB type q, *J* 7.2 Hz, 7-*H*H), and 3.41 (1 H, d, A part of AB type q, *J* 7.2 Hz, 7-H*H*); *m/z* 136 (100), 111 (69), 107 (77), 94 (64), and 79 (100) (Found: *m/z* 156.0778. $C_8H_{12}O_3$ requires *M*, 156.0786).

1-*Ethyl-5-methyl-6,8-dioxabicyclo*[3.2.1]*octan-3-one* (**4b**). The reaction of compound (**2b**) (171 mg, 1 mmol) was carried out in the same manner as described in the general procedure and gave the *dioxabicyclo-octanone* (**4b**) (117 mg, 69%); b.p. 60—80 °C at 15 mmHg; $\nu_{max.}$ 1 735, 1 390, 1 330, 1 255, 1 040, and 920 cm^{-1}; δ (100 MHz) 0.98 (3 H, t, *J* 7 Hz, 1-CH_2Me), 1.51 (3 H, s, 5-Me), 1.77 (2 H, q, *J* 7 Hz, 1-CH_2Me), 2.43 (2 H, s, $w_{\frac{1}{2}}$ 4 Hz), 2.50 (2 H, s, $w_{\frac{1}{2}}$ 2 Hz) (2- and 4-CH_2) (these two peaks became the same height on irradiation at 3.6 p.p.m.), 3.51 (1 H, d, B part of AB type q, *J* 8 and $w_{\frac{1}{2}}$ 4 Hz, 7-*H*H), and 3.70 (1 H, d, A part of AB type q, *J* 8 and $w_{\frac{1}{2}}$ 2 Hz, 7-H*H*) (this AB type q became symmetrical on irradiation at 2.4 p.p.m.); *m/z* 170 (M^+, 0.5), 110 (100), and 43 (100) (Found: *m/z* 170.0960. $C_9H_{14}O_3$ requires *M*, 170.0943) (Found: C, 63.2; H, 8.2. $C_9H_{14}O_3$ requires C, 63.5; H, 8.3%).

5-*Methyl*-1-*nonyl-6,8-dioxabicyclo*[3.2.1]*octan-3-one* (**4c**). The reaction of compound (**2c**) (255 mg, 0.95 mmol) was carried out in the same manner as described in the general procedure and gave the *dioxabicyclo-octanone* (**4c**) (102 mg, 40%); m.p. 47—48 °C (from n-hexane); $\nu_{max.}$ 1 730, 1 390, 1 245, and 1 040 cm^{-1}; δ (60 MHz) 0.90 (3 H, t, *J* 8 Hz, Me), 1.0—1.7 (16 H, br s, CH_2), 1.55 (3 H, s, 5-Me), 2.50 (2 H, s, $w_{\frac{1}{2}}$ 3 Hz), and 2.57 (2 H, s, $w_{\frac{1}{2}}$ 2 Hz) (2- and 4-CH_2), 3.60 (1 H, d, B part of AB type q, *J* 7 and $w_{\frac{1}{2}}$ 3 Hz, 7-*H*H), and 3.81 (1 H, d, A part of AB type q, *J* 7 and $w_{\frac{1}{2}}$ 2 Hz, 7-H*H*); *m/z* 268 (M^+, 0.3), 208 (6), 109 (39), 96 (90), and 43 (100) (Found: C, 71.9; H, 10.4. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.5%).

1,5,7-*Trimethyl-6,8-dioxabicyclo*[3.2.1]*octan-3-one* (**4d**). The reaction of compound (**2d**) (176 mg, 1 mmol) was carried out in the same manner as described in the general procedure and gave the *dioxabicyclo-octanone* (**4d**) (81 mg, 46%) as an inseparable

mixture of two isomers epimeric at C-7 (72:28), whose ratio was determined by g.l.p.c. on 1% OV-1 column (JMS-DX 300, 1-m, 70 °C); b.p. 60—80 °C at 13 mmHg; $\nu_{max.}$ 1 730, 1 390, 1 295, 1 250, 1 205, and 1 095 cm^{-1} δ (60 MHz) 1.14 (3 H, d, *J* 7 Hz, 7-Me), 1.38 (3 H, s, 1-Me), 1.54 (3 H, s, 5-Me), 2.5 (4 H, m, 2- and 4-CH_2), and 3.83 (1 H, m, 7-H); *m/z* 170 (M^+, 0.7), 126 (26), 110 (100), and 43 (100). (The major and minor isomers have identical spectral patterns.) (Found for major isomer: *m/z* 170.0938. $C_9H_{14}O_3$ requires *M*, 170.0942) (Found for mixtures: C, 63.4; H, 8.0. $C_9H_{14}O_3$ requires C, 63.5; H, 8.3%).

5-*Methyl*-1-*phenyl*-6,8-*dioxabicyclo*[3.2.1]*octan*-3-*one* (**4e**) *and* 3-*phenyl*-5-(2-*oxopropyl*)*furan* (**7**). The reaction of compound (**2e**) (163 mg, 0.74 mmol) was carried out in the same manner as described in the general procedure and gave inseparable mixture of the *dioxabicyclo-octanone* (**4e**) and the *furan* (**7**) [total 111 mg, (**4e**):(**7**) = 68:32, the ratio was determined by g.l.p.c. on a 1% OV-1 column (JMS-DX 300, 1 m, 140 °C)]; $\nu_{max.}$ 1 735, 1 620, 1 460, 1 395, 1 310, 1 255, and 1 330 cm^{-1}; δ (60 MHz) 1.67 [s, 1-Me of (**4e**)], 2.20 [s, COMe of (**7**)], 2.70 (s) and 2.8 (m) [2- and 4-CH_2 of (**4e**)], 3.77 [s, CH_2COMe of (**7**)], 3.82 [qd, B part of AB type q, *J* 7 and 2 Hz, 7-*H*H of (**4e**)], 4.20 [d, A part of AB type q, *J* 7 Hz, 7-H*H* of (**4e**)], 6.42 [s, 4-H of (**7**)], 7.70 [s, 2-H of (**7**)], and 7.1—7.6 (5 H, m, aromatic H). Dioxabicyclo-octanone (**4e**) had, by g.l.p.c. mass, *m/z* 218 (M^+, 8), 188 (10), 158 (52), 134 (45), 105 (80), and 43 (100) (Found: *m/z* 218.0943. $C_{13}H_{14}O_3$ requires M^+, 218.0943). The furan (**7**) had, by g.l.p.c. mass, *m/z* 200 (M^+, 52), 157 (100), 129 (76), and 128 (83) (Found: *m/z* 200.0861. $C_{13}H_{12}O_2$ requires *m*, 200.0837).

1,7-*Diphenyl*-5-*methyl*-6,8-*dioxabicyclo*[3.2.1]*octan*-3-*one* (**4f**), 2,3-*diphenyl*-5-(2-*oxopropyl*)*furan* (**8**), *and* 1-(2-*oxopropyl*)-3,4-*diphenyl*-2,5-*dioxabicyclo*[2.1.1]*hexane* (**9**). The reaction of compound (**2f**) (300 mg, 1 mmol) was carried out in the same manner as described in the general procedure and gave, after separation by high pressure liquid chromatography, the *dioxabicyclo-octanone* (**4f**) (78 mg, 27%), the *furan* (**8**) (19 mg, 7%), and the *dioxabicyclohexane* (**9**) (35 mg, 12%). The dioxabicyclo-octanone (**4f**) had m.p. 115—116 °C (from ether and n-hexane); $\nu_{max.}$ 1 725, 1 600, 1 450, 1 385, 1 255, 1 045, and 1 035 cm^{-1}; δ (60 MHz) 1.80 (3 H, s, 5-Me), 2.46 (1 H, d, B part of AB type q, *J* 18 Hz), 2.62 (1 H, br s), 2.76 (1 H, br s), and 2.97 (1 H, d, A part of AB type q, *J* 18 Hz) (2- and 4-CH_2), 5.00 (1 H, s, 7-H) (peak height unchanged on irradiation at 2.7 p.p.m.), and 6.9—7.7 (10 H, m, aromatic H); *m/z* (no M^+), 188 (42), 160 (22), and 105 (38) (Found: C, 77.8; H, 6.4. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%). The furan (**8**) had $\nu_{max.}$ 1 740, 1 680, 1 600, 1 450, 1 360, and 1 220 cm^{-1}; δ (60 MHz) 2.25 (3 H, s, COMe), 3.78 (2 H, s, CH_2COMe), 6.37 (1 H, s, 4-H), and 7.0—7.7 (10 H, m, aromatic H); *m/z* (no M^+), 234 (86), 105 (100), and 77 (84). This furan decomposed on standing at room temperature overnight. The dioxabicyclohexane (**9**) was crystalline (block) but did not have a clear m.p. even after several recrystallisations from ether and n-hexane; $\nu_{max.}$ ($CHCl_3$) 1 735, 1 395, 1 320, and 1 260 cm^{-1}; δ (100 MHz) 1.88 (3 H, s, COMe), 2.70 (1 H, d, B part of AB type q, *J* 17 Hz, C*H*HCOMe), 2.77 (1 H, d, B part of AB type q, *J* 16 Hz, 6-*H*H), 2.83 (1 H, d, A part of AB type q, *J* 17 Hz, CH*H*COMe), 3.18 (1 H, d, A part of AB type q, *J* 16 Hz, 6-H*H*), 5.10 (1 H, s, 3-H) (irradiation at 2.9 p.p.m. caused 12% height increment without increment of the integrated area), and 6.9—7.4 (10 H, m, aromatic H); *m/z* (no M^+), 188 (52), 160 (44), 105 (78), 103 (60), and 43 (100) (Found: C, 77.2; H, 6.0. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%).

2-*Ethyl*-5-(2-*oxopropyl*)*furan* (**10**). The reaction of the ketone (**1**) (216 mg, 1 mmol) and the aldehyde (**2g**) (222 mg, 1.29 mmol) was carried out in the same manner as described in the general procedure and gave the *furan* (**10**) (83 mg, 55%); $\nu_{max.}$ 1 720, 1 680, 1 610, 1 570, and 1 360 cm^{-1}; δ (60 MHz) 1.12 (3 H, t, *J* 8 Hz, Me), 2.17 (3 H, s, COMe), 2.63 (2 H, q, *J* 8 Hz, CH_2Me), 3.65 (2 H, s, CH_2COMe), 5.91 (1 H, d, B part of AB type q, *J* 3 Hz, 3-H), and 6.05 (1 H, d, A part of AB type q, *J* 3 Hz, 4-H); *m/z* (no M^+), 109 (41), and 43 (100). This furan decomposed on standing at room temperature overnight.

1-*Methyl*-2,12-*dioxatricyclo*[6.3.1.$0^{3,8}$]*dodecan*-10-*one* (**6**). The reaction of the α-ketol (**5**) (184 mg, 1 mmol) was carried out in the same manner as described in the general procedure and gave the *tricyclododecanone* (**6**) (39 mg, 20%); b.p. 55—65 °C at 0.4 mmHg; $\nu_{max.}$ 1 725, 1 385, 1 250, and 1 020 cm^{-1}; δ (100 MHz) 1.4—1.8 (8 H, m, CH_2), 1.56 (3 H, s, 1-Me), 2.35 and 2.52 (each 2 H, each s, 9- and 11-CH_2), and 3.84 (1 H, dd, *J* 9 and 7 Hz, 3-H) (peak heights unchanged upon irradiation at 2.5 p.p.m.); *m/z* 196 (M^+, 0.6), 136 (59), and 43 (100) (Found: *m/z* 196.1117. $C_{11}H_{16}O_3$ requires *M*, 196.1100) (Found: C, 67.6; H, 8.4. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%).

1-*Ethyl*-5-*methyl*-6,8-*dioxabicyclo*[3.2.1]*octan*-3-ol (**11**).—To a stirred solution of L-Selectride (0.5 ml, 1M in THF, 0.5 mmol) was added a solution of the ketone (**4b**) (38 mg, 0.22 mmol) in THF (1 ml) at −100 °C under nitrogen. After the mixture had been stirred at −100 to −50 °C for 2 h, aqueous sodium hydroxide (0.3 ml, 10%) and hydrogen peroxide (0.5 ml, 30%) were added at −50 °C. Stirring was continued for 30 min at room temperature, and the product was extracted with ether (2 × 20 ml). The combined extracts were washed with water and brine. Evaporation of the solvent followed by h.p.l.c. separation gave the *alcohol* (**11**) (10 mg, 26%); $\nu_{max.}$ 3 560, 3 450, 1 390, 1 210, 1 125, and 1 030 cm^{-1}; δ (90 MHz) 0.96 (3 H, t, *J* 7 Hz, 5-CH_2*Me*), 1.90 (3 H, s, 1-Me), 1.70 (2 H, q, *J* 7 Hz, 5-C*H*$_2$Me), 1.92 (4 H, m, 2- and 4-CH_2), 3.12 (1 H, br, OH), 3.50 (1 H, dd, B part of AB type q, *J* 7 and 2 Hz, 7-*H*H), 4.10 (1 H, br s, $w_{\frac{1}{2}}$ 9 Hz, 3-H), and 4.22 (1 H, d, A part of AB type q, *J* 7 Hz, 7-H*H*); *m/z* 172 (M^+, 0.6), 96 (27), 85 (38), and 43 (100).

1-*Methyl*-2,12-*dioxabicyclo*[6.3.1.$0^{3,8}$]*dodecan*-10-*ol* (**12**).—To a stirred solution of L-Selectride (0.34 ml, 1M in THF, 0.34 mmol) was added a solution of the ketone (**6**) (33 mg, 0.17 mmol) in THF (1.5 ml) at −100 °C under nitrogen. After the mixture had been stirred at −100 to −70 °C for 1.5 h, aqueous sodium hydroxide (0.3 ml, 10%) and hydrogen peroxide (0.5 ml, 30%) were added at −70 °C. Stirring was continued for 1 h at an ice-bath temperature and the product was extracted with ether (2 × 20 ml). The combined extracts were washed with brine, and the solvent was evaporated. H.p.l.c. separation of the residue gave the *alcohol* (**12**) (19 mg, 58%); $\nu_{max.}$ 3 550, 1 390, 1 220, 1 120, 1 045, and 1 010 cm^{-1}; δ (90 MHz) 1.1—1.7 (8 H, m, CH_2), 1.50 (3 H, s, Me), 1.84 (2 H, d, *J* 3.6 Hz) and 1.90 (2 H, d, *J* 3.6 Hz) (2- and 4-CH_2), 3.7 (1 H, br, OH), 4.00 (1 H, br s, $w_{\frac{1}{2}}$ 9 Hz, 10-H), and 4.16 (1 H, dd, *J* 9 and 7.5 Hz, 3-H); *m/z* 198 (M^+, 1.5), 156 (19), 138 (78), 94 (100), and 79 (82).

1,5-*Dimethyl*-6,8-*dioxabicyclo*[3.2.1.]*octan*-3-*one* *Ethylene Dithioacetal* (**13**).—A stirred mixture of the ketone (**4a**) (115 mg, 0.74 mmol), zinc triflate (trifluoromethanesulphonate) (411 mg, 1.1 mmol), and ethane-1,2-dithiol (186 μl, 2.2 mmol) in methylene dichloride (10 ml) was heated under reflux for 2 h. The resulting mixture was poured into water. The product was extracted with ether (2 × 2 ml), and the combined extracts were washed with water and brine. After evaporation of the solvents, the residue was purified by silica-gel column chromatography [hexane–ethyl acetate (1:3) as eluant] to give the *thioacetal* (**13**) [94 mg, 66% based on recovered (**4a**)] and the ketone (**4a**) (32 mg); $\nu_{max.}$ 1 395, 1 385, 1 230, 1 210, 1 190, and 1 040 cm^{-1}; δ (60 MHz) 1.32 (3 H, s, 1-Me), 1.48 (3 H, s, 5-Me), 2.32 and 2.43 (each 2 H, each s, 2- and 4-CH_2), 3.28 (4 H, s, SCH_2CH_2S), 3.43 (1 H, d, B part of AB type q, *J* 7 Hz, 7-*H*H), and 4.57 (1 H, d, A part of AB type q, *J* 7 Hz, 7-H*H*);

m/z 232 (M^+, 2.8), 231 (20), 171 (42), 143 (100), and 111 (73) (Found: *m/z* 232.0564. $C_{10}H_{16}O_2S_2$ requires *M*, 232.0591).

(±)-*Frontalin* (**14**).—A slurry of the thioacetal (**13**) (77 mg, 0.29 mmol) and Raney-Ni (W-2 in ethanol; 1 ml) in acetone (4 ml) was heated under reflux for 1 h. After the mixture had been cooled to room temperature, the Raney-Ni was removed by filtration with the aid of n-pentane (30 ml). The organic layer was washed with brine, and the solvent was distilled off through a Vigreux column, leaving (±)-frontalin (**14**) [31 mg, 75%, 88% purity analysed by g.l.p.c. on a 10% Carbowax 20 M column (JGC-20K, 2-m, 115 °C)]; $\nu_{max.}$(neat) 1 450, 1 380, 1 260, 1 130, and 1 040 cm^{-1}; δ (90 MHz) 1.33 (3 H, s, 1-Me), 1.43 (3 H, s, 5-Me), 1.57 (6 H, s, CH_2), 3.43 (1 H, d, B part of AB type q, *J* 7.2 Hz, 7-*H*H), and 3.90 (1 H, d, A part of AB type q, *J* 7.2 Hz, 7-H*H*); *m/z* 142 (M^+, 37), 112 (48), 100 (100), and 72 (100).

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