

Direct Synthesis of 2,6-Disubstituted Pyridines from Bicyclic Ketals

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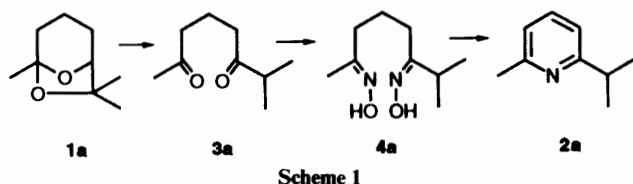
6,8-Dioxabicyclo[3.2.1]octanes **1**, prepared from methyl vinyl ketone dimer, have been readily converted into 2,6-disubstituted pyridine derivatives **2** in one step by treatment with $\text{AlCl}_3\text{-NH}_2\text{OH}\cdot\text{HCl}/\text{AcOH}$. The transformation mechanism of this reaction has been studied by the preparation of a deuterium labelled 1,5-diketone, which was transformed into a pyridine *via* a dioxime, from the bicyclic ketal.

Bicyclic ketals in the 6,8-dioxabicyclo[3.2.1]octane series are very useful intermediates for the synthesis of other important structures. Since the discovery by Mundy in 1985 of the transformation of bicyclic ketals into δ,ϵ -unsaturated ketones,^{1,2} which has been used for the synthesis of solenopsin A,¹ Douglas-Fir tussock moth pheromone¹ and the formal synthesis of sirenin,³ our group has undertaken studies in this area.⁴⁻⁶

We now report the direct transformation of bicyclic ketals into 2,6-disubstituted pyridines and the transformation mechanism. In 1988, Morris and Wishka described the synthesis of a series of 2,6-disubstituted pyridine analogues of leukotriene B_4 (LTB_4) which were found to bind competitively to LTB_4 receptors in human neutrophils.⁷

The bicyclic ketal **1**, which was easily prepared from methyl vinyl ketone (MVK), is a very stable liquid which can be stored for more than a month at room temp. but is unstable under acidic conditions. The 1,5-diketones **3**, which are well known intermediates for pyridines,⁸ were prepared from the bicyclic ketals **1** using aluminium trichloride with sodium iodide at room temp. (Table 1).⁴ We found this a convenient way to prepare pyridines directly from bicyclic ketals and determined the conditions for this transformation.⁹

The pyridines **2** were formed directly in good yield from the bicyclic ketals **1** with $\text{AlCl}_3\text{-NH}_2\text{OH}\cdot\text{HCl}$ in AcOH at reflux for 20 h (Table 2). The 1,5-diketones might be involved as intermediates in this novel rearrangement reaction. In order to establish this mechanism, the 1,5-diketone **3a** was prepared and treated with $\text{NH}_2\text{OH}\cdot\text{HCl}$ to give the 1,5-dioxime **4a**. Finally, the 1,5-dioxime was transformed to the pyridine **2a** by using AlCl_3 in AcOH (Scheme 1).



There are two possible mechanisms for the formation of the 1,5-diketone **3** from the bicyclic ketal **1** using aluminium chloride-sodium iodide in methylene dichloride.⁴ The mechanism 'path a' in Scheme 2 involves O(6)-C(5) bond cleavage followed by 1,2-hydride shift *via* an epoxide intermediate, whereas the alternative mechanism 'path b' involves O(8)-C(5) bond cleavage followed by proton abstraction.

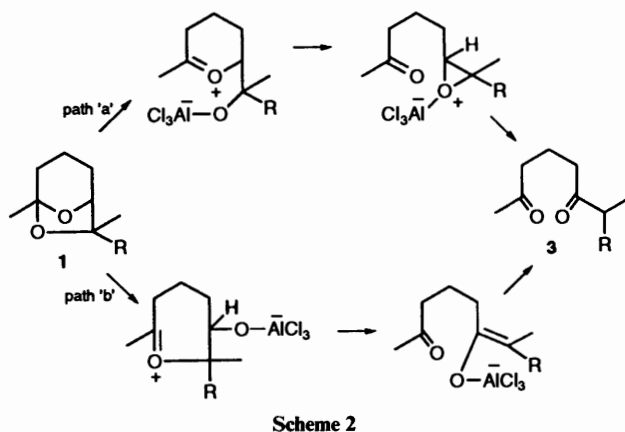
The mechanism for this novel skeletal transformation of the bicyclic ketal **1** into the 1,5-diketone **3** was established *via* a deuterium labelling study. With deuterium labelling at C-1 of the bicyclic ketal, it was possible to differentiate between mechanism 'a' and 'b' as shown in Scheme 3; a deuteriated diketone would result from path 'a', but a protonated diketone would result from path 'b'.

Table 1 Direct transformation of the bicyclic ketals **1** into the 1,5-diketones **3**

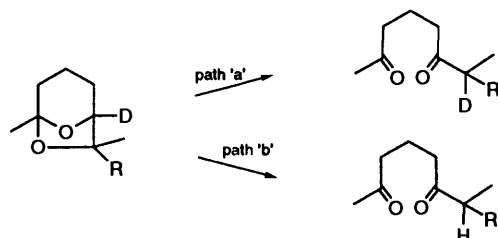
Product	R	Yield (%)
3a	Me	71
3b	Et	75
3c	Pr	91
3d	Pr ⁱ	86
3e	Bu	70
3f	Bu ^t	70
3g	Ph	43

Table 2 Direct transformation of the bicyclic ketals **1** into the pyridines **2**

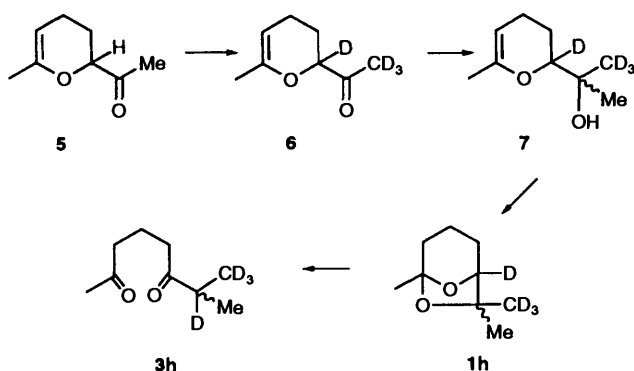
Product	R	Yield (%)
2a	Me	83
2b	Et	99
2c	Pr	84
2d	Pr ⁱ	63
2e	Bu	84
2f	Bu ^t	73
2g	Ph	52



Scheme 2



Scheme 3



Scheme 4

To prepare the bicyclic ketal deuterium labelled at C-1, the MVK dimer **5** was treated with D_2O using NaOD as catalyst (Scheme 4). We found that the less substituted site of the ketone (methyl group) was more reactive towards deuterium exchange even under thermodynamic conditions. Exchange of all α and α' protons gave compound **6** which was treated with MeLi to give the carbinol **7** and cyclized to give the expected deuteriated bicyclic ketal **1h**.

Finally, the bicyclic ketal **1h** was treated with aluminium chloride–sodium iodide in methylene dichloride. The 1H NMR spectrum indicated that the deuteriated diketone **3h** was the only product; the multiplet at δ 2.58 of the methine proton disappeared and methyl signal at δ 1.09 became a singlet. Also, the proton-decoupled ^{13}C NMR spectrum showed that the singlet at δ 40.8 of the methine carbon became a small triplet (J 21 Hz).

In conclusion, we have prepared the 2,6-disubstituted pyridines **2** directly from the bicyclic ketals **1** in high yield. We have also established that the 1,5-diketone is an important intermediate in this transformation. The mechanism for the transformation of the bicyclic ketals into 1,5-diketones was shown to involve O(6)–C(5) bond cleavage followed by a 1,2-hydride shift as shown in path 'a' of Scheme 2. The 1,5-diketones were then transformed into pyridines through 1,5-dioximes.

Experimental

General Experimental Details.—The 1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer at 200 and 50 MHz respectively, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Infrared spectra were recorded on a Shimadzu IR-435 spectrometer with absorption frequencies being reported in cm^{-1} . Mass spectra were obtained using a VG MM16 mass spectrometer and accurate mass data were obtained using a VG 7070 high resolution mass spectrometer. GLC analysis were performed using a Shimadzu GC-7A gas chromatograph equipped with a 7 ft \times $\frac{1}{8}$ in, 10% SE-30 column. The m.p.s were determined using a Fisher-Johns melting point apparatus and are uncorrected. Most of the chemicals used were purchased from Aldrich and used without

further purification unless noted otherwise. Bicyclic ketals **1a–g** were prepared from methyl vinyl ketone (MVK).⁴ Diethyl ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl prior to use. Dry methylene dichloride was obtained by distillation from calcium hydride. Flash chromatography was carried out using silica gel Merck 60 (70–230 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or *p*-anisaldehyde.

General Procedure for the Preparation of the Pyridine **2 from the Bicyclic Ketal **1**.**—A solution of the bicyclic ketal **1** (0.5 mmol) in acetic acid (3 cm^3) was refluxed for 20 h with aluminium trichloride (2 equiv.) and $NH_2OH \cdot HCl$ (3 equiv.). After cooling, 10% aqueous NaOH was added to the reaction product until the solution was neutral and the resulting solution was extracted with several portions of diethyl ether. The organic layer was dried ($MgSO_4$), filtered and evaporated to leave a liquid product which was purified by column chromatography (ether–hexane 3:7).

2-Isopropyl-6-methylpyridine **2a.**¹⁰ (83%) δ_H (200 MHz, $CDCl_3$) 7.52 (1 H, t, J 7.7, 4-H), 6.99 (2 H, dd, J 7.7 and 1.6, 3-H and 5-H), 3.07 (1 H, septet, J 7.1, $CHMe_2$), 2.57 (3 H, s, 6-Me) and 1.32 (6 H, d, J 7.1, Me_2C); $\delta_C(CDCl_3)$ 167.4 (s), 157.9 (s), 137.1 (d), 121.0 (d), 117.3 (d), 37.0 (d), 25.0 (q) and 23.2 (q, 2 \times Me); $\nu_{max}(neat)/cm^{-1}$ 2921, 1589, 1530, 1462, 1427, 1373, 790 and 746; m/z 135 (M^+), 134, 120 (base), 107, 93, 77 and 65 (Found: 135.1045. Calc. for $C_9H_{13}N$: M , 135.1048).

2-(sec-Butyl)-6-methylpyridine **2b.** (99%) δ_H (200 MHz, $CDCl_3$) 7.50 (1 H, t, J 7.7), 6.95 (2 H, dd, J 7.7 and 2.2), 2.80 (1 H, sextet, J 7.1), 2.54 (3 H, s), 1.60 (2 H, m), 1.26 (3 H, d, J 6.9) and 0.85 (3 H, t, J 7.4); $\delta_C(CDCl_3)$ 166.6 (s), 157.9 (s), 136.9 (d), 120.9 (d), 118.2 (d), 44.3 (d), 30.5 (t), 25.2 (q) and 12.5 (q); $\nu_{max}(neat)/cm^{-1}$ 2953, 1588, 1544, 1460, 1440, 1396, 791 and 746; m/z 149 (M^+), 134, 121 (base), 93 and 83 (Found: 149.1203. $C_{10}H_{15}N$ requires M , 149.1205).

6-Methyl-2-(1-methylbutyl)pyridine **2c.** (84%) δ_H (200 MHz, $CDCl_3$) 7.83 (1 H, t, J 7.7), 6.87 (2 H, d, J 7.8), 2.78 (1 H, sextet, J 7.2), 2.47 (3 H, s), 1.80–1.45 (4 H, m), 1.18 (3 H, d, J 7.0) and 0.82 (3 H, t, J 7.1); $\delta_C(CDCl_3)$ 166.6 (s), 157.9 (s), 136.9 (d), 120.9 (d), 119.2 (d), 42.4 (d), 39.9 (t), 25.1 (q), 21.4 (q), 21.3 (t) and 14.7 (q); $\nu_{max}(neat)/cm^{-1}$ 2922, 1591, 1546, 1457, 1376, 1236, 817 and 761; m/z 163 (M^+), 148, 134, 120 (base) and 71 (Found: 163.1360. $C_{11}H_{17}N$ requires M , 163.1361).

2-(1,2-Dimethylpropyl)-6-methylpyridine **2d.** (63%) δ_H (200 MHz, $CDCl_3$) 7.48 (1 H, t, J 7.7), 6.94 (1 H, d, J 7.0), 6.91 (1 H, d, J 7.1), 2.68–2.40 (1 H, m), 2.53 (3 H, s), 1.80–1.46 (1 H, m), 1.24 (3 H, d, J 7.1), 0.93 (3 H, d, J 6.7) and 0.78 (3 H, d, J 6.7); $\delta_C(CDCl_3)$ 166.1 (s), 157.2 (s), 136.1 (d), 120.3 (d), 118.3 (d), 48.3 (d), 33.4 (d), 24.6 (q), 21.5 (q), 19.6 (q) and 17.4 (q); $\nu_{max}(neat)/cm^{-1}$ 2957, 1589, 1546, 1455, 1448, 1341, 1259, 801 and 731; m/z 163 (M^+), 148, 134, 121 (base) and 92 (Found: 163.1359. $C_{11}H_{17}N$ requires M , 163.1361).

6-Methyl-2-(1-methylpentyl)pyridine **2e.** (84%) δ_H (200 MHz, $CDCl_3$) 7.48 (1 H, t, J 7.7), 6.94 (2 H, dd, J 7.7 and 1.6), 2.84 (1 H, sextet, J 7.1), 2.52 (3 H, d, J 6.9), 1.80–1.45 (2 H, m), 1.40–1.10 (4 H, m), 1.25 (3 H, d, J 6.9) and 0.85 (3 H, t, J 7.0); $\delta_C(CDCl_3)$ 166.9 (s), 157.9 (s), 136.9 (d), 120.9 (d), 118.1 (d), 42.6 (d), 37.4 (t), 30.3 (t), 25.1 (q), 23.3 (q), 21.4 (t) and 14.5 (q); $\nu_{max}(neat)/cm^{-1}$ 2952, 1589, 1548, 1488, 1461, 1379, 1154, 790 and 746; m/z 177 (M^+), 162, 120 (base) and 93 (Found: 177.1515. $C_{12}H_{19}N$ requires M , 177.1518).

6-Methyl-2-(1,2,2-trimethylpropyl)pyridine **2f.** (73%) δ_H (200 MHz, $CDCl_3$) 7.43 (1 H, t, J 7.7), 6.88 (2 H, dd, J 7.7 and 1.6), 2.78 (1 H, q, J 7.1), 2.48 (3 H, s), 1.19 (3 H, d, J 7.0), 1.12 (3 H, s), 1.09 (3 H, s) and 0.87 (3 H, s); $\delta_C(CDCl_3)$ 166.9 (s), 157.9 (s), 136.9 (d), 120.9 (d), 118.1 (d), 42.6 (d), 37.9 (s), 25.1 (q),

21.4 (q), 18.4 (q), 18.1 (q) and 14.5 (q); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2951, 1588, 1557, 1452, 1440, 1371, 1227, 1155, 1085, 1027 and 790; m/z 177 (M^+), 162, 121 (base), 93 and 77 (Found: 177.1517. $C_{12}H_{19}N$ requires M , 177.1518).

6-Methyl-2-(α -methylbenzyl)pyridine 2g. (52%) δ_H (200 MHz, $CDCl_3$) 7.80–7.20 (5 H, m), 7.44 (1 H, t, J 7.7), 6.95 (1 H, d, J 7.7), 6.87 (1 H, d, J 7.7), 4.29 (1 H, q, J 7.3), 2.56 (3 H, s) and 1.69 (3 H, d, J 7.3); δ_C ($CDCl_3$) 165.2 (s), 158.0 (s), 145.5 (s), 137.1 (d), 128.9 (d, o -C \times 2), 128.3 (d, m -C \times 2), 126.7 (d, p -C₄), 121.2 (d), 119.2 (d), 47.9 (d), 25.1 (q) and 21.5 (q); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3021, 1685, 1588, 1493, 1451, 1370, 1232, 801 and 695; m/z 197 (M^+), 196 (base), 181, 167, 153, 120, 105, 91 and 77 (Found: 197.1176. $C_{14}H_{15}N$ requires M , 197.1205).

General Procedure for the Preparation of the 1,5-Diketone 3 from the Bicyclic Ketal 1.—A solution of the bicyclic ketal **1** (0.5 mmol) in methylene dichloride was treated for 3 h at ambient temperature with $AlCl_3$ (2 equiv.) and NaI (2 equiv.). 10% Aqueous sodium hydroxide was added to the reaction product and the resulting neutral solution (pH 7–8) was extracted with several portions of diethyl ether. The organic layer was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated to leave a liquid product which was purified by column chromatography (diether ether–hexane 2:8).

7-Methyloctane-2,6-dione 3a. (71%) δ_H (200 MHz, $CDCl_3$) 2.58 (1 H, m, CH), 2.49 (2 H, t, J 7.0, $COCH_2$), 2.46 (2 H, t, J 7.0, $COCH_2$), 2.13 (3 H, s, COMe), 1.83 (2 H, quintet, J 7.0, CH_2) and 1.09 (6 H, d, J 7.2, 2 \times Me); δ_C ($CDCl_3$) 214.2 (s), 208.4 (s), 42.6 (t), 40.8 (d), 39.0 (t), 29.8 (q), 18.2 (q, 2 \times Me) and 17.8 (t); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2963, 1709 (br, C=O), 1465, 1410, 1379, 1174 and 1089; m/z 156 (M^+), 141, 123, 113, 85 (base), 71 and 55 (Found: 156.1148. $C_9H_{16}O_2$ requires M , 156.1150).

7-Methylnonane-2,6-dione 3b. (75%) δ_H (200 MHz, $CDCl_3$) 2.70–2.40 (5 H, m), 2.13 (3 H, s), 1.83 (2 H, m), 1.60–1.45 (2 H, m), 1.12 (3 H, d, J 7.0) and 1.10 (3 H, t, J 7.1); δ_C ($CDCl_3$) 214.5 (s), 208.8 (s), 45.3 (d), 42.8 (t), 39.5 (t), 35.3 (t), 30.1 (q), 17.7 (t), 16.6 (q) and 14.9 (q); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2960, 1707, 1458 and 1431; m/z 170 (M^+), 142, 113, 85 (base) and 57 (Found: 170.1306. $C_{10}H_{18}O_2$ requires M , 170.1307).

7-Methyldecane-2,6-dione 3c. (91%) δ_H (200 MHz, $CDCl_3$) 2.50–2.40 (1 H, m), 2.45 (4 H, br t, J 7.0), 2.12 (3 H, s), 1.81 (2 H, quintet, J 7.0), 1.45–1.15 (4 H, m), 1.03 (3 H, d, J 7.0) and 0.86 (3 H, t, J 7.0); δ_C ($CDCl_3$) 214.9 (s), 209.0 (s), 46.6 (d), 43.1 (t), 40.2 (t), 35.6 (t), 30.3 (q), 21.0 (t), 18.1 (t), 16.7 (q) and 14.6 (q); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2954, 1707, 1456, 1427 and 1374; m/z 184 (M^+), 142, 113, 85 (base), 71 and 55 (Found: 184.1461. $C_{11}H_{20}O_2$ requires M , 184.1463).

7,8-Dimethylnonane-2,6-dione 3d. (86%) δ_H (200 MHz, $CDCl_3$) 2.44 (4 H, t, J 7.0), 2.25 (1 H, quintet, J 7.0), 2.10 (3 H, s), 1.95–1.85 (1 H, m), 1.79 (2 H, p, J 7.0), 0.97 (3 H, d, J 7.0), 0.85 (3 H, d, J 7.0) and 0.82 (3 H, d, J 7.0); δ_C ($CDCl_3$) 214.9 (s), 209.0 (s), 53.3 (d), 43.0 (t), 41.0 (t), 30.6 (d), 30.3 (q), 21.8 (q), 19.3 (q), 18.0 (t) and 13.4 (q); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2958, 1709, 1433, 1369, 1176 and 730; m/z 184 (M^+), 142, 113, 85, 71 (base) and 55 (Found: 184.1460. $C_{11}H_{20}O_2$ requires M , 184.1463).

7-Methylundecane-2,6-dione 3e. (70%) δ_H (200 MHz, $CDCl_3$) 2.50–2.40 (1 H, m), 2.46 (2 H, t, J 7.0), 2.45 (2 H, t, J 7.0), 2.12 (3 H, s), 1.81 (2 H, quintet, J 7.0), 1.45–1.15 (6 H, m), 1.03 (3 H, d, J 7.0) and 0.88 (3 H, t, J 7.0); δ_C ($CDCl_3$) 214.3 (s), 208.5 (s), 46.1 (d), 42.6 (t), 39.8 (t), 35.1 (t), 29.9 (q), 20.5 (t), 17.6 (t), 16.3 (q), 15.3 (t) and 14.1 (q); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2953, 1709, 1458, 1371 and 1174; m/z 198 (M^+), 142, 113, 85, 71 (base) and 55 (Found: 198.1622. $C_{12}H_{22}O_2$ requires M , 198.1620).

7,8,8-Trimethylnonane-2,6-dione 3f. (70%) δ_H (200 MHz, $CDCl_3$) 2.49–2.41 (5 H, m), 2.12 (3 H, s), 1.81 (2 H, quintet, J 7.0), 1.03 (3 H, d, J 7.0) and 0.91 (9 H, s); δ_C ($CDCl_3$) 214.8 (s), 209.0 (s), 55.1 (d), 44.1 (t), 43.0 (t), 34.2 (s), 30.1 (q), 22.1 (q),

18.1 (t) and 13.5 (q \times 3); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2945, 1710, 1458 and 1364; m/z 198 (M^+), 181, 142, 113, 85 (base), 71 and 55 (Found: 198.1608. $C_{12}H_{22}O_2$ requires M , 198.1620).

7-Phenyloctane-2,6-dione 3g. (43%) δ_H (200 MHz, $CDCl_3$) 7.35–7.12 (5 H, m), 3.75 (1 H, q, J 7.0), 2.35 (4 H, t, J 7.0), 2.12 (3 H, s), 1.80–1.70 (2 H, m) and 1.40 (3 H, d, J 7.0); δ_C ($CDCl_3$) 214.5 (s), 208.5 (s), 140.0 (s), 129.1 (d \times 2), 127.9 (d \times 2), 127.3 (d), 52.2 (d), 43.0 (t), 40.2 (t), 30.3 (q), 18.1 (t) and 17.9 (q); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3020, 1710, 1667, 1492, 1450 and 1408; m/z 218 (M^+), 185, 113, 85 (base) and 71 (Found: 218.1305. $C_{14}H_{18}O_2$ requires M , 218.1307).

Preparation of the 1,5-Dioxime 4a from the 1,5-Diketone 3a.—To a solution of the 1,5-diketone **3a** (0.10 g, 0.59 mmol) in absolute ethanol (5 cm^3) was added $NH_2OH \cdot HCl$ (0.10 g, 1.48 mmol), sodium acetate (0.073 g, 0.85 mmol) and toluene-*p*-sulfonic acid (cat.). After being refluxed for 5 h, the reaction mixture was cooled to room temp. and evaporated. Water was added to the reaction mixture which was then extracted with several portions of diethyl ether. The organic layer was dried ($MgSO_4$), filtered and evaporated to leave a solid product, which was recrystallized from hexane to give the dioxime **4a** as a white powder (84%); m.p. 60–62 °C; δ_H (200 MHz, $CDCl_3$) 8.25 (2 H, br s), 2.46 (1 H, m), 2.25 (4 H, m), 1.89 (3 H, s), 1.76 (2 H, m) and 1.09 (6 H, d, J 7.0); δ_C ($CDCl_3$) 165.0 (s), 158.7 (s), 35.3 (t), 33.3 (d), 23.9 (t), 22.0 (t), 20.3 (q \times 2) and 19.7 (q); $\nu_{\max}(KBr)/\text{cm}^{-1}$ 3333, 2961, 1656, 1456, 1377, 1045 and 935; m/z 186 (M^+), 169 (base), 138, 110, 96, 86, 73 and 68 (Found: 186.1369. $C_9H_{18}N_2O_2$ requires M , 186.1368).

Preparation of the Pyridine 2a from the 1,5-Dioxime 4a.—To a solution of the 1,5-dioxime **4a** (0.10 g, 0.54 mmol) in acetic acid (5 cm^3) was added zinc (0.18 g, 2.7 mmol). After refluxing for 18 h, the reaction mixture was cooled to 0 °C and 3 mol dm^{-3} aqueous sodium hydroxide (15 cm^3) added to it. The reaction mixture was extracted with several portions of diethyl ether. The organic layer was dried ($MgSO_4$), filtered and evaporated to leave a liquid product which was purified by column chromatography (diethyl ether–hexane 3:7) to give the title compound (96%). NMR and IR spectra were identical with those for the pyridine **2a** synthesized directly from the bicyclic ketal **1a**.

Preparation of the Deuteriated MVK Dimer 6.—The MVK dimer **5** (1.74 g, 12.4 mmol) in anhydrous tetrahydrofuran (THF) (30 cm^3 , dried over sodium–benzophenone) was treated with D_2O (3 cm^3 , 99.9% deuterium from Aldrich) and 2 drops of a 40% deuteriated sodium hydroxide solution (prepared from sodium hydride and D_2O). The reaction mixture was stirred at 50 °C for 3 h and then cooled to room temp. Pentane (40 cm^3) was added to it and the D_2O layer was discarded. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. This reaction was repeated to give the title compound **6** (1.65 g, 92%); δ_H (200 MHz, $CDCl_3$) 4.50 (1 H, td, J 3 and 1, CH=), 2.05–1.85 (4 H, m, CH_2CH_2) and 1.76 (3 H, d, J 1, $CH_3C=$); δ_C ($CDCl_3$) 210.3 (s, C=O), 150.2 (s, MeC=), 96.7 (d, CH=), 80.3 (small t, J 22, OCD), 26.5 (small m, CD_3), 23.8 (t, CH_2), 20.4 (q, $CH_3C=$) and 19.5 (t, CH_2).

Preparation of the Deuteriated Alcohol 7.—The deuteriated MVK dimer **6** (1.40 g, 9.68 mmol) in anhydrous THF (30 cm^3) was treated with $MeLi \cdot LiBr \cdot Et_2O$ (1.5 mol dm^{-3} solution in Et_2O ; 7.0 cm^3 , 1.08 equiv.) at –76 °C for 20 min. The reaction mixture was quenched with D_2O (2 cm^3) followed by saturated aqueous NH_4Cl . Methylene dichloride extraction and evaporation gave the title compound **7** (1.44 g, 93%). δ_H (200 MHz, $CDCl_3$) 4.44 (1 H, m, CH=), 2.46 (1 H, br s, OH), 2.09–1.75 (4 H, m, CH_2CH_2), 1.73 (3 H, br s, $CH_3C=$), 1.21 (1 H, s, CH_3) and

1.18 (2 H, s, CH₃) indicates 1:2 ratio of diastereoisomers (*threo*:*erythro*); $\delta_{\text{C}}(\text{CDCl}_3)$ 151.2 (MeC=), 96.0 (CH=), 81.9 (small t, *J* 22, OCD), 26.2 and 24.5 (1:2 ratio of diastereoisomer for CH₃, small septet of CD₃ buried in this region), 22.5 (CH₂), 21.4 (CH₃C=) and 20.4 (CH₂).

Preparation of the Deuteriated Bicyclic Ketal 1h.—The deuteriated alcohol **7** (1.30 g, 8.12 mmol) in dry CH₂Cl₂ (10 cm³) was stirred overnight in the presence of a catalytic amount of TsOD·D₂O (prepared from TsOH·H₂O and D₂O) at room temp. The reaction was quenched with NaHCO₃ and the product was purified on a short silica gel column using pentane–Et₂O (4:1) as eluent. Drying and evaporation of the solution gave the desired product **1h** (1.00 g, 88%); $\delta_{\text{H}}(200 \text{ MHz}, \text{CDCl}_3)$ 2.00–1.45 (6 H, m, CH₂CH₂CH₂), 1.40 (3 H, s, CH₃), 1.36 (2 H, s, *endo*-CH₃) and 1.26 (1 H, s, *exo*-CH₃); $\delta_{\text{C}}(\text{CDCl}_3)$ 107.2 (s, OCO), 81.1 (small t, *J* 26, OCD), 80.8 (s, OMe₂), 34.2 (t, CH₂), 29.2 (q, CH₃), 24.2 (t, CH₂), 17.2 (t, CH₂), 25.8 and 20.9 (1:2 ratio of *exo*- and *endo*-CH₃, small septet for CD₃ also buried in this region); *m/z* 160 (M⁺), 118, 99, 72 (base) and 55 (Found: 160.1401. C₉H₁₂D₄O₂ requires *M*, 160.1401).

Preparation of the Deuteriated 1,5-Diketone 3h.—The deuteriated bicyclic ketal **1h** (0.14 g, 1 mmol) in dry CH₂Cl₂ (5 cm³) was treated with AlCl₃ (0.27 g, 2 mmol) and NaI (0.30 g, 2 mmol), dried by azeotropic distillation from the mixture with benzene, followed by heating *in vacuo* for 3 h at room temp. The reaction was quenched by addition of saturated aqueous NaHCO₃. Methylene dichloride (10 cm³) was added and the mixture was filtered through Celite. Purification on a short path silica gel column and evaporation gave the desired product (0.098 g, 70%); $\delta_{\text{H}}(200 \text{ MHz}, \text{CDCl}_3)$ 2.49 (2 H, t, *J* 7, CH₂CO), 2.46 (2 H, t, *J* 7, CH₂CO), 2.13 (3 H, s, CH₃CO), 1.83 (2 H, quintet, *J* 7, CH₂) and 1.09 (3 H, s); $\delta_{\text{C}}(\text{CDCl}_3)$ 214.2 (s, C=O), 208.4 (s,

C=O), 42.6 (t, CH₂CO), 40.8 (small t, *J* 21, CDMe₂), 39.0 (t, CH₂CO), 29.8 (q, CH₃CO), 18.2 (q, CH₃, CD₃ also buried as small multiplet in this region) and 17.8 (t, CH₂); *m/z* 160 (M⁺), 113, 85 (base), 71 and 55 (Found: 160.1400. C₉H₁₂D₄O₂ requires *M*, 160.1401).

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