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SYNTHESIS AND REACTIONS OF 2-ARYL-8-OXABICYCLO[3.2.1]OCT-6-EN-3-ONES

JOHN MANN,*[a] PHILIP D. WILDE,[a] and MARK W. FINCH[b]

a. Department of Chemistry, Reading University, P.O.Box 224, Whiteknights, Reading, Berkshire, RG6 2AD, UK.

b. Lilly Research Centre Ltd., Eli Lilly and Company, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK.

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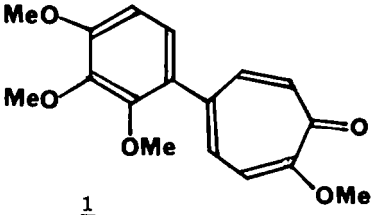
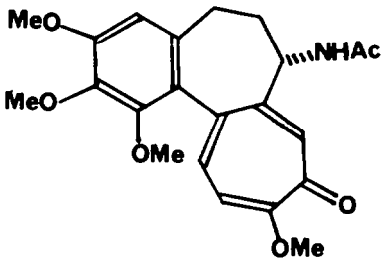
Abstract: A number of 1-aryl-1-bromopropanones have been prepared and converted into the corresponding oxyallyl carbocations. These were reacted with furan to produce the expected 2-aryl-8-oxabicyclo[3.2.1]oct-6-en-3-ones, as well as a number of interesting side-products. These included 3-aryl-propanoic acid esters produced via Favorskii rearrangements. Attempts to cleave the ether linkage in the cycloadducts using bromotrimethylsilane produced instead 1-aryl-3-furylpropanones in excellent yield.

In 1976 Fitzgerald published results which showed[1] that the 5-aryltropolone 1 had similar biological potency to colchicine 2 as a mitotic inhibitor. Neither 2-methoxytropone nor 1,2,3-trimethoxybenzene had any activity by themselves, and we were interested in preparing similar structures using oxyallyl methodology. [The cycloaddition reactions and consequent synthetic utility of oxyallyl carbocations 3 have been extensively reviewed.[2]] Our plan involved cycloaddition reactions of carbocations (3,R=aryl), derived from 1-aryl-1-bromopropanones 4, with furan, and subsequent manipulation of the functionality in the cycloadducts 5 to provide species like 1 for biological evaluation.



1



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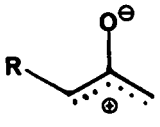

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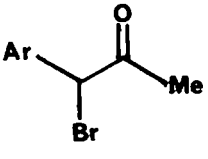

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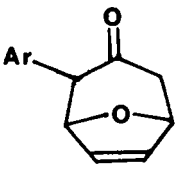


5

The required 1-aryl-1-bromopropanones 4 were prepared from the corresponding ketones by bromination with N-bromosuccinimide, though variable amounts of ring brominated products were always obtained. The ketone (2,3,4-trimethoxyphenyl)-propanone was not commercially available, and the best route to this compound is shown in FIGURE ONE.

The cycloaddition reactions were carried out according to the method first introduced by Föhlisch,[3] and the bromopropanones were treated with 1.5 equivalents of triethylamine in the presence of 15 equivalents of furan and either methanol or 2,2,2-trifluoroethanol as solvents. The results of these reactions are assembled in TABLE ONE, and a number of generalisations may be made.

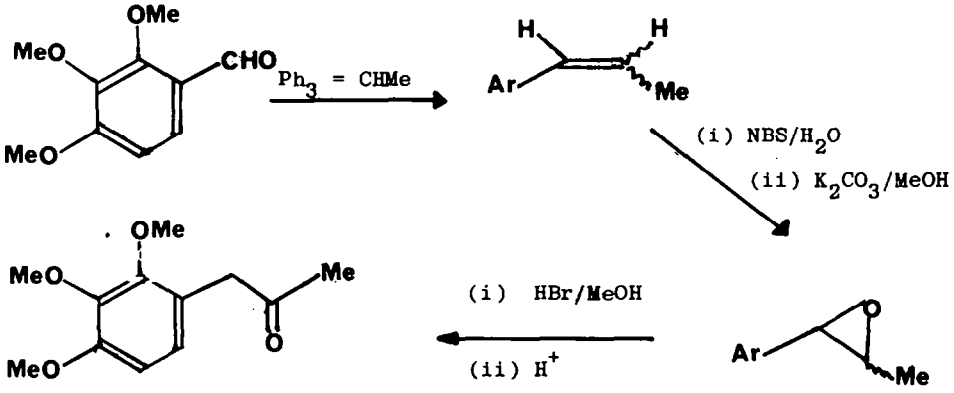


FIGURE ONE

Firstly, as the aryl ring becomes more electron-rich, so the yield of cycloadduct falls, and the major side-product 6 is one derived from decomposition of an initially formed Friedel-Crafts product 7 (FIGURE TWO). When the aryl ring is only moderately electron-rich, good yields of cycloadducts are obtained, and the major side-product 8 is now formed by means of a Favorskii rearrangement (FIGURE THREE). To our knowledge, only one other instance of this kind of reaction, occurring during an oxyallyl process, has been reported.[2]

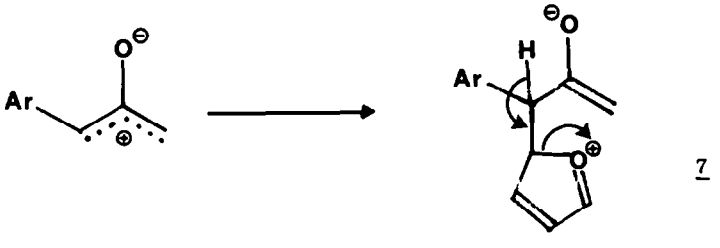
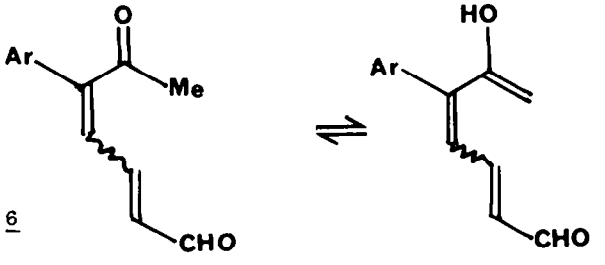


FIGURE TWO



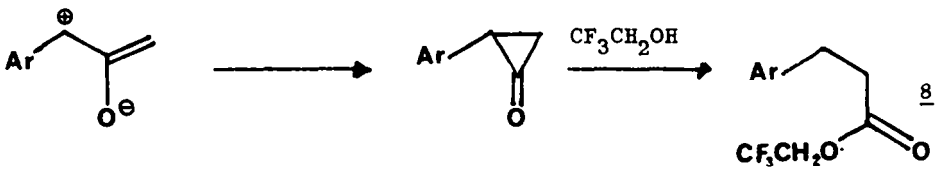
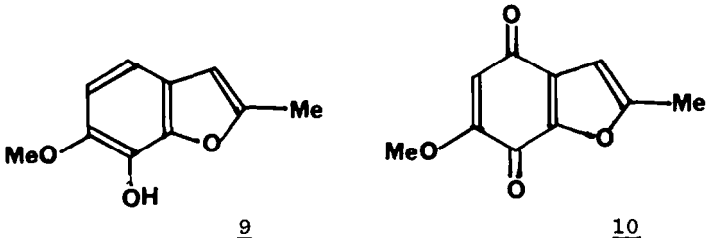


FIGURE THREE

The corresponding ethyl ester was produced if ethanol was employed in place of trifluoroethanol.

The disappointing yield of cycloadduct from 1-bromo-1-(2,3,4-trimethoxyphenyl)-propanone 4d, prompted us to try to prepare the corresponding 1-bromo-1-arylpropanone with one or more of the methoxyls replaced by acetoxyls. This would be less electron-rich and might give better yields of cycloadducts. To this end treatment of (2,3,4-trimethoxyphenyl)-propanone with boron tribromide, with the aim of cleaving one or more of the methyl ethers, led instead to the benzofuran 9. This compound has been prepared previously by Stevenson as the penultimate intermediate of an eight-stepsynthesis of the natural product acamelin 10, and the spectral data for our compound (and the corresponding acetate) were identical to those reported by Stevenson[4].



9 10

A synthesis of 1-bromo-1-(3-methoxy,4-acetoxyphenyl)propanone 4f was accomplished starting from isoeugenol (FIG. FOUR), but attempted cycloaddition under the usual conditions led to acetate cleavage and a small yield of the Favorskii product.

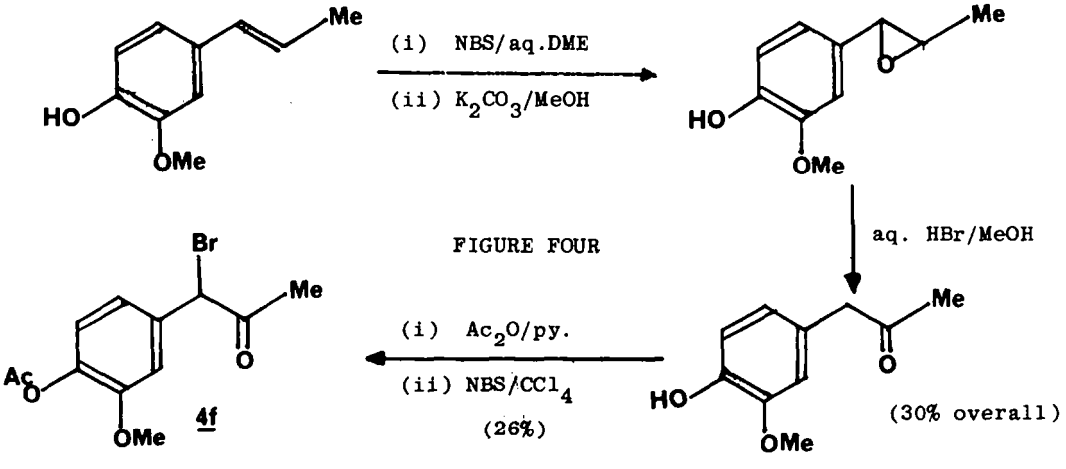


FIGURE FOUR

TABLE ONE

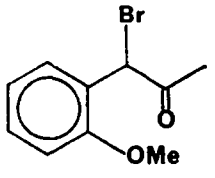
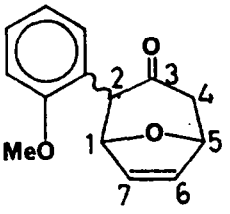
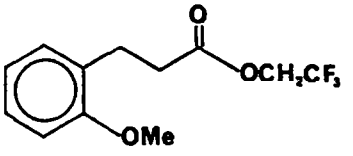
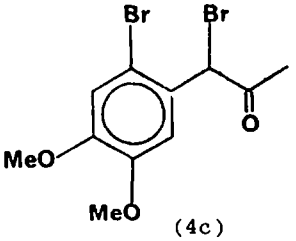
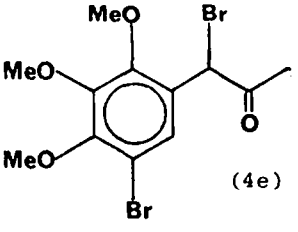
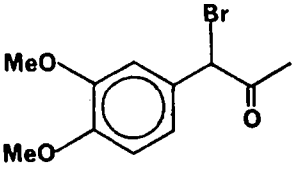
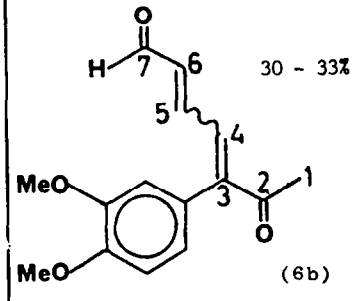
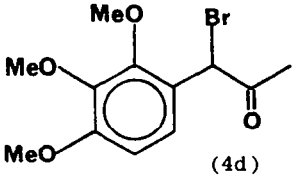
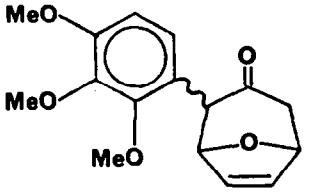
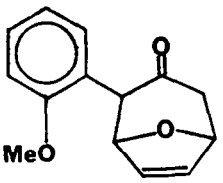
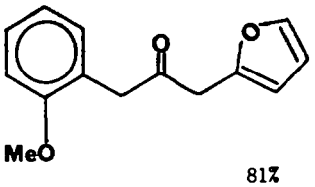
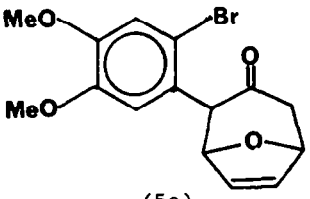
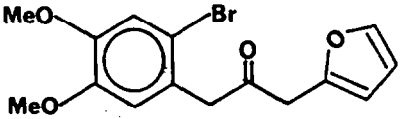
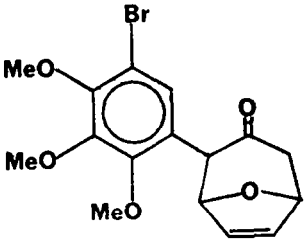
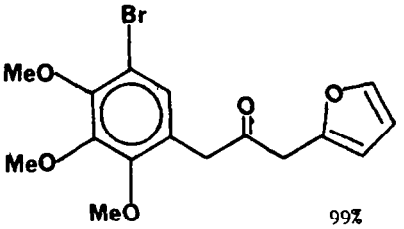
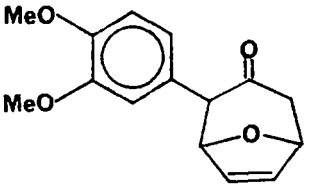
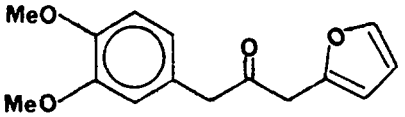
Starting α-Bromoketone	Cycloadduct	Favorskii (or other) product
 (4a)	 73% (5a)	 20%
 (4c)	54% (5c)	27%
 (4e)	31 - 38% (5e)	25%
 (4b)	23 - 28% (5b)	 30 - 33% (6b) Ratio of 3E, 5E to 3Z,5Z 6:1
 (4d)	 10% combined yield of (5d) and dienal (6d)	

TABLE TWO

Starting cycloadduct	Rearrangement product
 (5a)	 81% (11a)
 (5c)	 84% (11c)
 (5e)	 99% (11e)
 (5b)	 70% (11b)

The synthesis of compound (11a) is described in full in the Experimental section; and key n.m.r. data (60MHz, $CDCl_3$) for the other compounds is given below:

(11b) 3.65 and 3.75 (1-H and 3-H), 3.85 (2xOMe), 6.10 (3"-H), 6.30 (4"-H), 6.65 (aryl-H), 7.30 (5"-H).

(11c) 3.85 (1-H,3-H,2xOMe), 6.20 (3"-H), 6.30 (4"-H), 6.60 and 6.95 (aryl-H), 7.30 (5"-H).

(11e) 3.60 (1-H and 3-H), 3.75 (OMe), 3.96 (2xOMe, 1-H and 3-H), 6.15 (3"-H), 6.30 (4"-H), 6.90 (aryl-H), 7.30 (5"-H).

Further attempts to prepare appropriately functionalised 1-bromo-1-arylpropanones were halted when it was discovered that the cycloadducts 5 could not be converted into the desired tropones (and thence into the tropolones 1). Attempted cleavage of the ether bridge in compounds 5 with HBr and BF_3 led to extensive decomposition, but reaction with bromotrimethylsilane provided excellent yields of the 1-aryl-3-furylpropanones 11 (TABLE TWO), and none of the desired tropones. A possible mechanism is shown in FIG. FIVE.

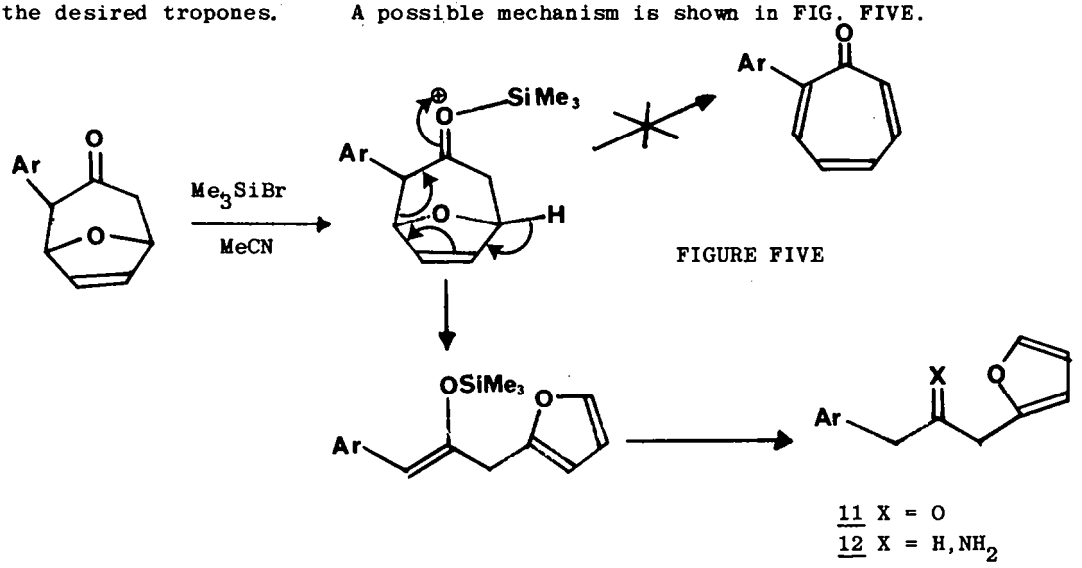


FIGURE FIVE

11 X = O
12 X = H,NH_2

These readily available compounds are ideally suited for conversion into novel 1-aryl-3-furyl-2-aminopropanes 12, which have obvious structural analogy with the amphetamines, etc.; and progress in this area will be reported in a separate publication.

Experimental

I.r. spectra were recorded with a Perkin-Elmer 157 double beam grating spectrophotometer (all samples were dissolved in CH_2Cl_2); n.m.r. spectra were recorded with a Perkin-Elmer R34 (220MHz) instrument, or with a Bruker WM400 (400MHz) instrument (University of Warwick) using tetramethylsilane as internal standard; flash chromatography was performed using Merck silica gel (250-400 mesh); solvents were distilled from calcium hydride when required anhydrous; and pet. ether means the fraction boiling between 40 and 60°C. T.l.c. - 0.25 mm SiO_2.

1-Bromo-1-(2'-methoxyphenyl)propan-2-one (4a)

To a stirred solution of 2-methoxyphenylacetone (5.71 g, 34.8 mmol) in dry CCl_4 (170 ml) were added N-bromosuccinimide (NBS) (6.19 g, 34.8 mmol) and benzoyl peroxide (catalytic amount). The reaction mixture was illuminated (150 W tungsten lamp) for 4 hours, filtered and concentrated to an orange oil. Trituration with ether and petrol gave 6.22 g of white crystals. A repeat trituration gave a further 0.32 g of crystals, (total yield 6.54 g, 77%).

t.l.c.: Rf = 0.24 (3:1 petrol:ether).

m.p.: 57 - 58°C (n-hexane).

i.r. (nujol mull) ν_{max}: 1725, 1600, 1590, 1490, 1440, 1260, 750 and 690 cm^{-1}.

n.m.r. (60 MHz) δ: 2.20 (3H, s, 3-Me), 3.80 (3H, s, OMe), 5.85 (1H, s, 1-H), 6.70 → 7.45 (4H, m, phenyl ring).

C,H,Br analysis: Found: C, 49.17; H, 4.49; Br, 32.65.

$C_{10}H_{11}BrO_2$ requires: C, 49.39; H, 4.56; Br, 32.89.

1-Bromo-1-(3',4'-dimethoxyphenyl)propan-2-one (4b)

Using the same procedure, from 3,4-dimethoxyphenyl acetone (4.95 g, 25.5 mmol) were obtained (4b) (4.54 g, 64%) and 1-(2'-bromo-4',5'-dimethoxyphenyl) propan-2-one (1.34 g, 19%).

Data for (4b) are:

t.l.c.: R_f = 0.35 (2:1 ether:petrol).

m.p.: 81-83°C (ether/petrol).

i.r. (CH_2Cl_2 soln.)ν_{max}: 2940, 1735, 1605, 1595 and 1145 cm^{-1}.

n.m.r. (60 MHz) δ: 2.30 (3H, s, 3-Me), 3.85 (6H, s, 2 x OMe), 5.40 (1H, s, 1-H), 6.70 → 7.10 (3H, m, phenyl ring).

1-Bromo-1-(2'-bromo-4',5'-dimethoxyphenyl)propan-2-one (4c)

To 1-(2'-bromo-4',5'-dimethoxyphenyl)propan-2-one (1.34 g, 4.9 mmol, from preceding experiment) in dry CCl_4 (40 ml) was added NBS (0.89 g, 5.0 mmol) and a few crystals of benzoyl peroxide. The reaction mixture was irradiated (150 W tungsten lamp) until the NBS had been consumed. Filtration and concentration gave an oil which was purified by f.c.c. to give (4c) as an oil. This was triturated with ether and petrol to give a white crystalline solid (1.38 g, 80%).

t.l.c. : R_f = 0.48 (2:1 ether:petrol).

m.p.: 60 - 63°C.

i.r. (thin film)ν_{max}: 2940. 1735, 1600, 1570 (w), 1510, 1265, 1170, and 805 (w) cm^{-1}.

n.m.r. (60 MHz)δ: 2.30 (3H, s, 3-Me), 3.85 (6H, s, 2 x OMe), 5.95 (1H, s, 1-H), 7.00 (2H, s, phenyl ring).

1-(2',3',4'-Trimethoxyphenyl)-prop-1-ene (cis and trans isomers)

To a stirred suspension of ethyl triphenylphosphonium iodide (24.82 g, 59.4 mmol) in dry THF (80 ml), at -78°C under N_2, was added n-BuLi (1.6 M in hexane, 35 ml, 56 mmol). After 10 minutes the cold-bath was removed, and after a further hour 2,3,4-trimethoxybenzaldehyde (8.84 g, 45.1 mmol) in dry THF (100 ml) was added. Overnight stirring was followed by the addition of H_2O (60 ml), the phases separated and the aqueous layer extracted with petrol (2 x 60 ml). The combined extracts were concentrated, and then more H_2O (60 ml) + petrol (60 ml) added. Phase separation, aqueous extraction (2 x 50 ml petrol), followed by drying and concentration of the combined petrol extracts gave a pale orange oil (9.44 g). This was used in the next reaction without further purification. A purified sample gave:

t.l.c.: R_f = 0.50 (1:1 ether:petrol).

i.r.(thin film)ν_{max}: 2940, 1600, 1495, 1295, 1100, 815, 795, 725 and 695 cm^{-1}.

n.m.r. (60 MHz)δ: 1.85 (3H, m, 3-Me), 3.90 (9H, s, 3 x OMe), 5.50 → 7.20 (4H, m, olefinics + phenyl ring).

1-(2',3',4'-Trimethoxyphenyl)-1,2-epoxypropane

To a stirred solution of the above alkene (9.44 g crude product) in DME (200 ml) and H_2O (80 ml) at 0°C was added NBS (8.08 g, 45.4 mmol) in DME (150 ml) over 40 minutes. After a further 75 minutes H_2O (100 ml) was added, and the solution extracted with CH_2Cl_2 (4 x 100 ml). The combined CH_2Cl_2 extracts were dried and concentrated to an orange oil. This was dissolved in

AR MeOH (200 ml), and added to a stirred suspension of anhydrous potassium carbonate (18.66 g, 135 mmol) in MeOH (200 ml). After 30 minutes ether (300 ml) was added, and enough H_2O such that the initially formed emulsion broke up (∿ 300 ml). The layers were separated and the aqueous extracted with ether (3 x 100 ml). The combined ethereal extracts were dried and concentrated to give an oil. Analysis by t.l.c. and n.m.r. showed it to be reasonably pure, and so it was used crude in the next reaction. The crude sample gave:

t.l.c.: R_f = 0.49 (2:1:1 ether:petrol:CCl_4).

n.m.r. (60 MHz)δ: 1.45 (3H, d, J = 5 Hz, 3-Me), 2.95 (1H, qd, J = 5 Hz and 2 Hz, 2-H), 3.85 (10H, s, 3 x OMe + 1-H), 6.55 (1H, d, J = 8 Hz, aromatic), 6.75 (1H, d, J = 8 Hz, aromatic).

1-(2',3',4'-Trimethoxyphenyl)propan-2-one

The crude epoxide, from above, was dissolved in AR MeOH (300 ml) and 48% aq. HBr (6.2 ml, 55 mmol) added dropwise. After 15 minutes a new spot on t.l.c. had formed at R_f = 0.21 (3:2:2 ether:petrol:CCl_4). (A purified sample indicated that it was probably the α-methoxy-β-hydroxy compound). The solvent was removed *in vacuo* to give a deep red oil which now contained a new spot on t.l.c. Purification by f.c.c., using 2:1:1 ether:petrol:CCl_4 as eluant, gave the desired ketone (4.24 g, 42% from 2,3,4-trimethoxybenzaldehyde), as a pale red oil.

t.l.c.: R_f = 0.21 (1:1 ether:petrol).

i.r. (thin film)ν_{max}: 2940, 1720, 1600, 1495, 1470, 1100 and 795 cm^{-1}.

n.m.r. (60 MHz)δ: 2.15 (3H, s, 3-Me), 3.60 (2H, s, 1-CH_2), 3.90 (9H, s,3 x OMe), 6.60 (1H, d, J = 8 Hz, aromatic), 6.80 (1H, d, J = 8 Hz, aromatic).

m.s. m/z (%): 224.1045 (27) (M^+; $C_{12}H_{16}O_4$ requires 224.1047), 181.0866 (100), 166.0630 (40), 136.0516 (14).

1-Bromo-1-(2',3',4'-trimethoxyphenyl)propan-2-one (4d)

To NBS (recrystallized from H_2O, 1 mole equivalent) under N_2 was added a 0.2 M solution of the above ketone in dry CCl_4. Benzoyl peroxide (catalytic amount) was added, and the reaction mixture illuminated (150 W tungsten lamp) until the NBS had been consumed. Filtration and concentration gave an orange oil. This was flash chromatographed (1:1 ether:petrol) to give (4d) and (5'-bromo-2',3',4'-trimethoxy)propan-2-one as co-chromatographing compounds. N.m.r. integration was used to determine the ratio of them in the mixture. The yield of (4d) was non-reproducible and varied from 0 - 57%.

t.l.c.: R_f = 0.33 (1:1 ether:petrol).

1-Bromo-1-(5'-bromo-2',3',4'-trimethoxyphenyl)propan-2-one (4e)

To the inseparable mixture of (4d) and(5'-bromo-2',3',4'-trimethoxyphenyl) propan-2-one (1.23 g, 4.1 mmol) in dry CCl_4 (25 ml) was added recrystallized NBS (0.72 g, 4.1 mmol) and a few crystals of benzoyl peroxide. The reaction mixture was irradiated (150 W tungsten lamp) for 3 hours, filtered and concentrated to a red oil (1.59 g). This was essentially pure by t.l.c. and n.m.r. analysis, and this was used in cycloaddition experiments.

t.l.c.: R_f = 0.43 (1:1 ether:petrol).

i.r. (thin film)ν_{max}: 2940, 1735, 1585, 1460, 1405, 1000, 810 and 730 cm^{-1}.

n.m.r. (60 MHz)δ: 2.30 (3H, s, 3-Me), 3.95 (9H, s, 3 x OMe), 5.70 (1H, s, 1-H), 7.35 (1H, s, aromatic).

Cycloadditions

Two representative examples are given below.

2-(2'-Methoxyphenyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (5a)

To a stirred solution of furan (13 ml, 179 mmol) in CF_3CH_2OH (15 ml), under N_2, was added Et_3N (2.6 ml, 19 mmol), followed by the α-bromo-ketone (4a) (2.97 g, 12. mmol) via a solid addition tube. After 24 hours at RT, the mixture was poured into H_2O (30 ml) and extracted with petrol (7 x 30 ml). The combined petrol extracts were dried, concentrated and purified by flash column chromatography (f.c.c.) using 2:1 ether:petrol as eluant, to give the required cycloadduct (5a), as a yellow solid, as a 15:1 mixture of equatorial:axial isomers (2.06 g, 73%), plus the Favorskii rearrangement product (8a) (0.64 g, 20%), as a clear oil. Recrystallization of the cycloadduct mixture gave a pure sample of the equatorial isomer.

Data for (5a); equatorial isomer:

t.l.c.: Rf = 0.39 (2:1 ether:petrol).

m.p.: 92 - 94°C (ether).

i.r. (thin film)ν_{max}: 2960, 1715, 1605, 1590, 1495, 1245, 755 and 720 cm^{-1}.

n.m.r. (220 MHz)δ: 2.46 (1H, dd, J_{gem} = 16.5 Hz and $J_{4\text{-}endo,5}$ = 0.5 Hz, 4-H_{endo}), 2.91 (1H, dd, J_{gem} = 16.5 Hz and $J_{4\text{-}exo,5}$ = 5 Hz, 4-H_{exo}), 3.87 (3H, s, OMe), 4.65 (1H, d, $J_{2,1}$ = 4.5 Hz, 2-H), 5.05 (1H, dd, $J_{1,2}$ = 4.5 Hz and $J_{1,7}$ = 1.5 Hz, 1-H), 5.18 (1H, ddd, $J_{5,4\text{-}exo}$ = 5 Hz, $J_{5,6}$ = 1.5 Hz and $J_{5,4\text{-}endo}$ = 0.5 Hz, 5-H), 6.32 (1H, dd, $J_{7,6}$ = 6 Hz and $J_{7,1}$ = 1.5 Hz, 7-H), 6.48 (1H, dd, $J_{6,7}$ = 6 Hz and $J_{6,5}$ = 1.5 Hz, 6-H), 6.90 → 7.40 (4H, m, phenyl ring).

C, H analysis: Found: C, 71.88; H, 6.48. $C_{14}H_{14}O_3$ requires: C, 72.01; H, 6.13.

Data for (8a):

t.l.c.: Rf = 0.69 (2:1 ether:petrol).

i.r. (thin film)ν_{max}: 2940, 1765, 1605, 1590, 1500, 1285, 1245, 1170, 1140 and 750 cm^{-1}.

n.m.r. (^1H, 60 MHz)δ: 2.50 → 3.10 (4H, m, both 2-H + both 3-H), 3.80 (3H, s, OMe), 4.40 (2H, q, $J_{H,F}$ = 8.5 Hz, OCH_2), 6.70 → 7.25 (4H, m, phenyl ring).

n.m.r. (^{13}C, 22.5 MHz)δ: 25.98 (3-C), 33.52 (2-C), 55.18 (OMe), 60.24 (OCH_2), 110.23 (3'-C), 120.47 (5'-C), 123.01 (CF_3), 127.85 (4'-C), 128.11 (1'-C), 129.96 (6'-C), 157.47 (2'-C), 171.71 (1-C).

m.s. m/z (%): 262.0818 (31) (M^+; $C_{12}H_{13}F_3O_3$ requires 262.0815).

2-(3',4'-dimethoxyphenyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one, (5b) and side-products (6b)

This reaction was performed as in the previous experiment but using (4b) (4.44 g, 16.3 mmol), furan (16.5 ml, 230 mmol), CF_3CH_2OH (16.5 ml) and Et_3N (3.4 ml, 24 mmol). Addition of H_2O (25 ml) was followed by extraction into ether (6 x 25 ml). The ethereal extracts were combined, dried and concentrated to a black oil, which was purified by f.c.c., using 5:1 ether:petrol as eluant, to give a quantity of red oil, (6) as a bright yellow solid (1.37 g, 33%), and an off-white crystalline compound which was exclusively the equatorial isomer of the desired cycloadduct (5b) (1.7 g, 28%).

Data for (6b)

t.l.c.: Rf = 0.32 (5:1 ether:petrol).

m.p.: 90 - 93°C (ether).

i.r. ($CDCl_3$ soln)ν_{max}: 2840 (w), 1680, 1605 (w), 1520, 1260, 1140, 1030 and 815 cm^{-1}.

n.m.r. (^1H, 400 MHz)δ. Data for 3E, 5E isomer: 2.36 (3H, s, COMe), 3.87 (3H, s, OMe), 3.93 (3H, s, OMe), 6.46 (1H, ddd, $J_{6,5}$ = 15.4 Hz, $J_{6,7}$ = 7.8 Hz and $J_{6,4}$ = 0.6 Hz, 6-H), 6.68 (1H, d, $J_{2',6'}$ = 2.0 Hz, 2'-H), 6.74 (1H, dd, $J_{6',5'}$ = 8.1 Hz and $J_{6',2'}$ = 2.0 Hz, 6'-H), 6.93 (1H, d, $J_{5',6'}$ = 8.1 Hz, 5'-H), 7.11 (1H, dd, $J_{5,6}$ = 15.4 Hz and $J_{5,4}$ = 11.4 Hz, 5-H), 7.31 (1H, d, $J_{4,5}$ = 11.4 Hz, 4-H), 9.52 (1H, d, $J_{7,6}$ = 7.8 Hz, CHO). 3Z,5E isomer shows signals at: 2.36 (3H, s, COMe), 3.90 (3H, s, OMe), 3.91 (3H, s, OMe), 6.30 (1H, dd, J = 15 Hz and J = 8 Hz), 6.59 (1H, dd, J = 11.8 Hz and J = 0.7 Hz), 6.83 (1H, d, J = 1.8Hz), 6.89 (2H, m), 7.34 (1H, d, J = 12 Hz), 9.60 (1H, d, J = 8.0 Hz, CHO).

n.m.r. (^{13}C, 22.5 MHz)δ. Data for 3E,5E isomer: 27.95 (1-C), 55.91 (OMe), 55.99 (OMe), 111.11 (2'-C), 112.79 (5'-C), 122.76 (6'-C), 126.69 (1'-C), 134.08 (4-C or 5-C), 136.93 (4-C or 5-C), 146.76 (6-C), 148.25 (3-C), 148.93 (4'-C), 149.58 (3'-C), 193.10 (7-C), 198.71 (2-C).

m.s. m/z (%): 260.1036 (16) (M^+; $C_{15}H_{16}O_4$ requires 260.1048), 231.1023 (53) (M^+ - CHO; $C_{14}H_{15}O_3$ requires 231.1021).

Data for cycloadduct (5b) (equatorial isomer):

t.l.c.: Rf = 0.25 (5:1 ether:petrol).

m.p.: 114 - 116°C (ether).

i.r. ($CDCl_3$ soln.)ν_{max}: 2970, 1720, 1610, 1595, 1520, 1145, 1030, and 850 cm^{-1}.

n.m.r. (60 MHz)δ: 2.40 (1H, d, J_{gem} = 15 Hz, 4-H_{endo}), 2.90 (1H, dd, J_{gem} = 15 Hz and $J_{4\text{-exo},5}$ = 4 Hz, 4-H_{exo}), 3.85 (6H, s, 2 x OMe), 3.95 (1H, d, $J_{2,1}$ = 4 Hz, 2-H), 5.00 (2H, m, 1-H + 5-H), 6.35 (2H, m, 6-H + 7-H), 6.50 - 6.90 (3H, m, phenyl ring).

C, H analysis: Found: C, 68.03; H, 6.07. $C_{15}H_{16}O_4$ requires: C, 69.20; H, 6.20.

7-Hydroxy-6-methoxy-2-methylbenzofuran (9)

The ketone, 1-(2',3',4'-trimethoxyphenyl)propan-2-one (1.02 g, 4.5 mmol) was dissolved in dry CH_2Cl_2 (15 ml) in a 2-neck flask, fitted with an air condenser with silica guard tube, and a rubber septum. This was taken to -78°C and a solution of BBr_3 in CH_2Cl_2 (25 g/100 ml, 4.6 ml, 4.6 mmol) added dropwise. After 45 minutes at -78°C, the cold bath was removed and it was left stirring for a further 3½ hours. The reaction was quenched by the careful addition of H_2O (15 ml). Ether (25 ml) was added and the mixture extracted with aq. NaOH (2M, 3 x 15 ml). Acidification of the basic extracts with aq. HCl (2M) led to the precipitation of a brown solid which was extracted into ether. Drying, concentration and purification by f.c.c., using 1:1 ether:petrol as eluant, gave (9) (0.29 g) as a very pale yellow oil, in 36% yield (non-optimized).

t.l.c.: Rf = 0.33 (1:1 ether:petrol).

i.r. (thin film)ν_{max}: 3500 (br), 2920, 1615, 1600, 1405, 1285, 1090, 945, 805, and 750 cm^{-1}.

n.m.r. (100 MHz)δ: 2.40 (3H, d, J = 1 Hz, Me), 3.86 (3H, s, OMe), 5.69 (1H, br s, OH), 6.25 (1H, q, J = 1 Hz, 3-H), 6.79 (1H, d, J = 8 Hz, aromatic), 6.91 (1H, d, J = 8 Hz, aromatic).

m.s. m/z: 178.0632 (M^+; $C_{10}H_{10}O_3$ requires 178.0630).

1-(2'-Methoxyphenyl)-3-(2' -furyl)propan-2-one (11a)

To LiBr (1.36 g, 15.7 mmol) in dry CH_3CN (30 ml) under N_2 was added dry trimethylsilyl chloride (TMSCl) (2.0 ml, 15.7 mmol). After stirring at RT for 1 hour, (5a) (1.60 g, 7.8 mmol) was added as a solution in dry CH_3CN (20 ml). This was stirred overnight, and then the reaction quenched by the addition of saturated aq. $NaHCO_3$ (30 ml). Extraction with ether (3 x 50 ml), combination of the organic extracts, drying and concentration gave a brown oil which was purified by f.c.c. using 1:1 ether:petrol as eluant, to give the title product (1.29 g, 81%) as a pale yellow oil.

t.l.c.: R_f = 0.43 (1:1 ether:petrol).

i.r. (thin film)ν_{max}: 2940, 1725, 1605, 1590, 1395, 1250, 1015, and 750 cm^{-1}.

n.m.r. (^1H, 100 MHz, CCl_4)δ: 3.60 (2H, s, 1-CH_2 or 3-CH_2), 3.62 (2H, s, 1-CH_2 or 3-CH_2), 3.72 (3H, s, OMe), 6.09 (1H, m, 3''-H), 6.24 (1H, m, 4''-H), 6.74 → 7.20 (4H, m, phenyl ring), 7.26 (1H, m, 5''-H).

n.m.r. (^{13}C, 22.5 MHz)δ: 41.44 (1-C or 3-C), 43.94 (1-C or 3-C), 55.31 (OMe), 108.19 (3''-C), 110.46 (3'-C), 110.57 (4''-C), 120.65 (5'-C), 123.19 (1'-C), 128.61 (4'-C), 131.21 (6'-C), 141.94 (5''-C), 148.38 (2''-C), 157.32 (2'-C), 203.75 (2-C).

m.s. m/z: 230.0941 (33) (M^+; $C_{14}H_{14}O_3$ requires 230.0943), 149.0572 (45), 122.0705 (35), 121.0627 (100).

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