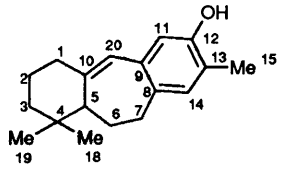
Synthetic Studies Towards Complex Diterpenoids. Part 19.[1] Total Synthesis of (±)-Deoxofaveline, (±)-Faveline Methyl Ether and (±)-Faveline

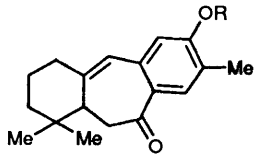
Ajit K. Ghosh, Chhanda Mukhopadhyay (née Ray) and Usha Ranjan Ghatak*
Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta – 700 032, India

Simple and efficient syntheses have been developed for the cytotoxic dinorditerpenoids, (±)-deoxofaveline **1**, (±)-faveline methyl ether **2** and (±)-faveline **3**, having a hexahydrodibenzo[*a,d*]cycloheptene ring system, through the enolizable tricyclic ketone mixture **12** and **13**, prepared from the easily accessible 2-arylethyl-3,3-dimethylcyclohexanone **7**.

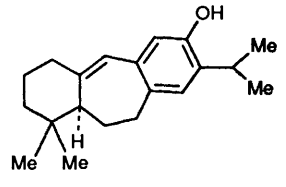
Recently, Endo *et al.*[2] reported the isolation and elucidation of the gross structures of deoxofaveline **1**, faveline methyl ether **2** and faveline **3** from the bark of *Cnidoscolus phyllocanthus* (MART). PAX et K. Hoffm (Euphorbiaceae), representing a group of rearranged 9(10 ⟶ 20)-*abeo*-16,17-dinorabieta-8,11,13-triene diterpenoids. Shortly thereafter, several structurally related ring-A oxygenated dinorditerpenoids were isolated[3,4] from the Euphorbiaceae family, two of which were reported[4] to exhibit activity against *Escherichia coli* and *Staphylococcus aureus*. The dinorditerpenoids **1**, **2** and **3** display[2] significant activity against P-388 murine leukaemia cells. A number of total syntheses of the rearranged 9(10 ⟶ 20)-*abeo*-abieta-8,11,13-triene diterpenoids (±)-isopisiferin **4**,[1,5] (±)-pisiferin **5a**[6] and (±)-barbatusol **5b**[7,8] have been recorded. We present in this paper the first total synthesis of the diterpenoids, (±)-deoxofaveline **1**,[9] (±)-faveline methyl ether **2**[9] and (±)-faveline **3**[9] following a converging general route[1] developed for the tricyclic benzocycloheptene derivatives.



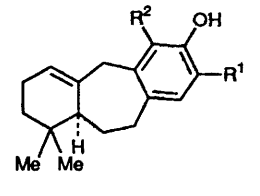
1



2 R = Me
3 R = H



4



5a R^1 = Pr^i, R^2 = H
5b R^1 = H, R^2 = OH

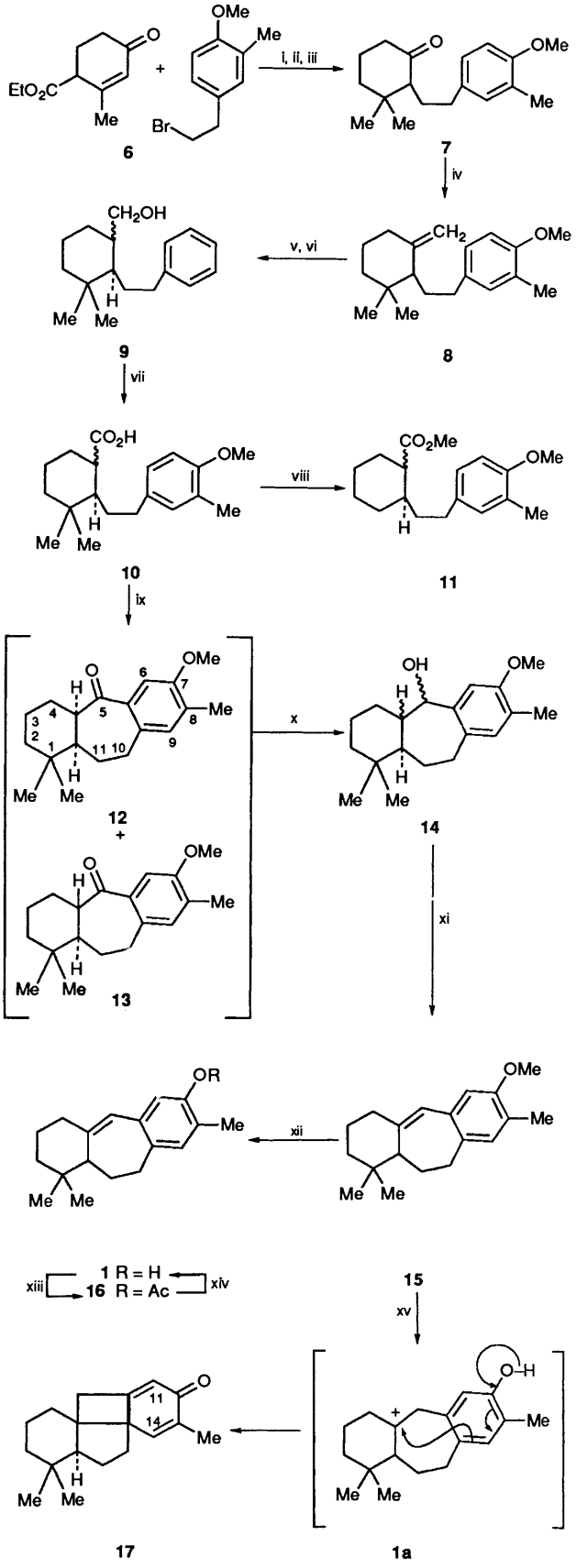
Results and Discussion

The known *gem*-dimethylcyclohexanone **7**,[10] prepared from Hagemann's ester **6** in three steps (Scheme 1), was smoothly converted into the alkene **8** by a Wittig reaction.[1,11] Hydroboration of the alkene **8** followed by oxidation[12] with alkaline hydrogen peroxide gave an epimeric mixture of the alcohols **9**, which on oxidation with Jones reagent[13] afforded an epimeric mixture of the acids **10**. Cyclization of the acids **10** with polyphosphoric acid gave a mixture of the epimeric ketones **12** and **13** in a ratio of *ca.* 90:10, as revealed by their ^{1}H NMR spectrum. Recrystallization of this mixture afforded the major epimer **12**, m.p. 116–117 °C, assigned as *cis* stereochemistry by analogy.[1,6] Reduction of the epimeric mixture of the ketones **12** and **13** (*ca.* 9:1) followed by dehydration of the crude alcohol **14** with potassium hydrogen sulphate[14] gave the styrene **15** m.p. 85–86 °C.

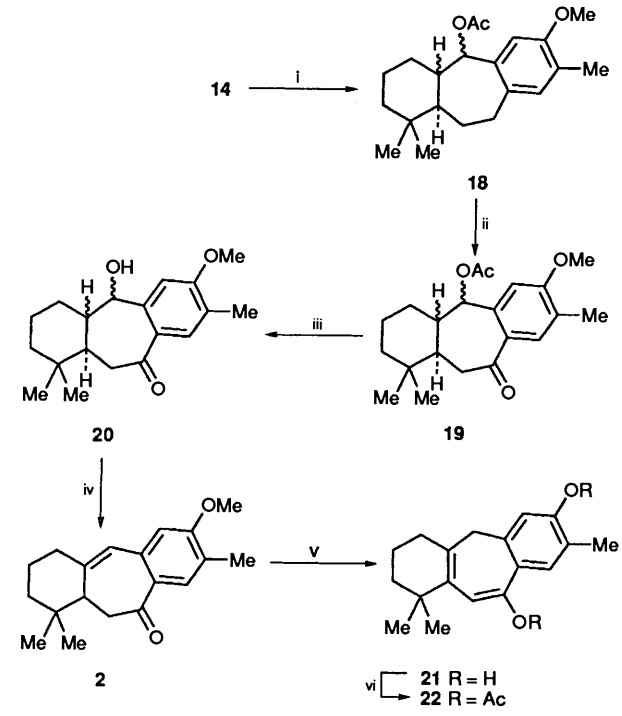
Deprotection of the *O*-methyl ether **15** proceeded smoothly with NaH–EtSH in boiling dimethylformamide (DMF)[15] to afford the crude phenol **1**, in excellent overall yield, which was directly converted into the acetate **16**, m.p. 159–160 °C. Finally, deacetylation of the acetate **16** with $LiAlH_4$ regenerated (±)-deoxofaveline **1**, m.p. 148–149 °C, having IR and ^{1}H NMR spectra identical with those of the natural deoxofaveline[2] (see Experimental section). When the methyl ether **15** was subjected to demethylation with $AlCl_3$–EtSH[16] at room temperature, the tetracyclic dienone **17** was isolated in excellent yield, arising from an Ar_1-5 cyclization of the intermediate phenol **1** through the carbocation **1a**. This result is similar to that of the earlier observations in the demethylation of isopisiferin methyl ether[1] and related compounds.[1,6] The assigned structure of the dienone **17** was supported by its IR and UV spectra (see Experimental section). The ^{1}H NMR spectrum of **17** showed the olefinic Me doublet at δ 1.79 (J 2 Hz) coupled with the C-14 allylic hydrogen at δ 6.42 (d, J 2 Hz); the C-11 olefinic proton singlet appeared at δ 6.10. The synthesis of (±)-faveline methyl ether **2** was readily accomplished through the diastereoisomeric mixture of the alcohols **14** (Scheme 2). The diastereoisomeric mixture of the acetates **18** was oxidized with pyridinium chlorochromate (PCC)–Celite[17] in refluxing dichloromethane[17] to afford the benzylic ketone **19**, which was hydrolysed and dehydrated to give (±)-faveline methyl ether **2**, in excellent overall yield, identical (IR and ^{1}H NMR) with the natural compound.[2]

The remaining problem of the *O*-demethylation in the conversion of the methyl ether **2** into (±)-faveline **3** turned out to be more difficult than initially anticipated. Thus, attempted demethylation of **2** with NaH–EtSH in refluxing DMF[15] led to the poorly soluble phenolic dienol **21** in 90% yield, involving migration of the exocyclic styrenoid bond, which was characterized through the diacetate **22** (Scheme 2). Likewise, *O*-demethylation of **2** with other reagents such as, $AlCl_3$–EtSH,[16], BBr_3 in CH_2Cl_2[18] or Me_3SiCl–NaI in acetonitrile[19] gave intractable products, in each case. To overcome this problem, the deprotection of the phenolic methoxy group was carried out at early stage in the sequence leading to the synthesis of (±)-**3** (Scheme 3).

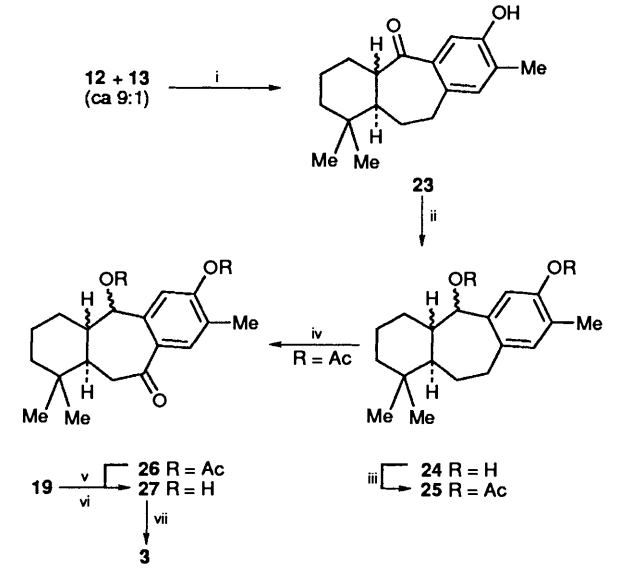
Accordingly, the epimeric mixture of ketones **12** and **13** (*ca.* 9:1) was smoothly demethylated with NaH–EtSH–DMF to



Scheme 1 *Reagents and conditions:* i, Bu^t-OK–Bu^t-OH, H^+; ii, KOH–EtOH–H_2O, H^+; iii, $LiMe_2Cu$–BF_3·Et_2O; iv, Sodium *tert*-pentoxide–$Ph_3P^+MeI^-$–toluene; v, B_2H_6–THF; vi, NaOH–H_2O_2; vii, Jones reagent; viii, CH_2N_2–Et_2O; ix, PPA; x, $NaBH_4$–EtOH; xi, $KHSO_4$, heat; xii, NaH–EtSH–DMF, heat; xiii, Ac_2O-pyridine; xiv, $LiAlH_4$–Et_2O; xv, EtSH–$AlCl_3$–CH_2Cl_2



Scheme 2 *Reagents and conditions:* i, Ac_2O–pyridine; ii, PCC–CH_2Cl_2, heat, 15 h; iii, 2% methanolic KOH, H^+; iv, $KHSO_4$, heat; v, NaH–EtSH–DMF, heat; vi, Ac_2O–pyridine



Scheme 3 *Reagents and conditions:* i, NaH–EtSH–DMF, heat; ii, $NaBH_4$–EtOH; iii, Ac_2O–pyridine; iv, PCC–benzene, heat, 18 h; v, 2% methanolic KOH, H^+; vi, BBr_3–CH_2Cl_2; vii, $KHSO_4$, heat

give the keto-phenols **23** which was reduced to the alcohols **24** and directly converted into the diacetates **25**, in excellent overall yield. The PCC–Celite oxidation[17] of **25** in boiling benzene for 18 h furnished the desired ketone **26** in 42% yield. Attempted benzylic oxidation of the diacetates **25** with PCC–Celite in boiling methylene dichloride or CrO_3 in acetic acid[20] gave mostly the recovered diacetates, possibly due to the inactivation by the electron-withdrawing *para* *O*-acetate moiety. Alkaline hydrolysis of the keto diacetates **26** or direct treatment of *O*-methyl ketoacetates **19** with BBr_3 in methylene dichloride gave the deprotected keto phenolic alcohols **27**, which on dehydration with potassium hydrogen sulphate gave (±)-faveline **3**, m.p. 194–196 °C in excellent yield, identical (IR and ^1H NMR) with the natural product.[2]

In conclusion, in the present work, a simple convergent route has been developed for three newly discovered cytotoxic rearranged dinorditerpenoids incorporating a hexahydro-1*H*-dibenzo[*a*,*d*]cycloheptene skeleton.

Experimental

The compounds described are all racemates. Unless otherwise stated, IR spectra of solids (KBr), and liquids (film) were recorded on a Perkin-Elmer model PE 298 instrument. UV Spectra were recorded on a Beckman DU spectrometer for solution in ethanol (95%). Unless otherwise stated, ^{1}H NMR spectra were recorded at 200 MHz on an XL-200 and at 100 MHz on an FX-100 spectrometer for solution in $CDCl_3$ with $SiMe_4$ as internal standard, with *J* values given in Hz. Column chromatography was performed on neutral alumina (Brockmann Grade 1, of BDH, India) or silica-gel [Glaxo Laboratories (India) Ltd.]. Light petroleum refers to the fraction of b.p. 60–80 °C. Ether refers to diethyl ether. Elemental analyses were performed by S. K. Sarkar of this laboratory.

2-(4-*Methoxy*-3-*methylphenethyl*)-3,3-*dimethyl*-1-*methylenecyclohexane* **8**.—A suspension of methyl(triphenyl)phosphonium iodide (22.06 g, 54.74 mmol) in toluene (5 cm^3) and a toluene solution of freshly prepared sodium *tert*-pentoxide (20.27 cm^3 of 2.7 mol dm^{-3}) was stirred at room temperature (25 °C) for 20 min. The ketone **7** (5 g, 18.24 mmol) in toluene (5 cm^3) was added dropwise and the mixture refluxed for 2 h. The cooled reaction mixture quenched with saturated aqueous NH_4Cl and the mixture extracted with ether. Evaporation of the extract yielded an oil which was immediately filtered through silica gel with light petroleum as eluent. The filtrate was evaporated to give an oil, which was dissolved in light petroleum (10 cm^3) and to which methyl iodide (3 cm^3) was added. The mixture was set aside at room temperature for 1 h after which the precipitated methyl(triphenyl)phosphonium iodide was filtered off and the filtrate concentrated under reduced pressure to give the pure alkene **8** (4.6 g, 93%) as an oil, b.p. 140 °C (0.1 mm Hg) (Found: C, 84.0; H, 10.25. $C_{19}H_{28}O$ requires C, 83.77; H, 10.36); ν_{max}(film)/cm^{-1} 1640 (C=C); δ_H 0.83 (3 H, s, CMe), 0.91 (3 H, s, CMe), 2.21 (3 H, s, ArMe), 1.10–2.60 (11 H, m), 3.80 (3 H, s, ArOMe), 4.63 and 4.83 (2 H, m, C=CH$_2$), 6.76 (1H, d, *J* 8, 5-ArH) and 6.96–7.06 (2 H, m, 2 and 6-ArH).

trans- *and* cis-[2-(4-*Methoxy*-3-*methylphenethyl*)3,3-*dimethylcyclohexyl*]*methanol* **9**.—Diborane gas [prepared from $NaBH_4$ (4.60 g, 119 mmol) and BF_3·Et_2O (18.4 cm^3, 146.7 mmol) in diglyme (16.9 cm^3)] was passed through a cold (0 °C) solution of the alkene **8** (4 g, 14.8 mmol) in dry tetrahydrofuran (THF) (15 cm^3) for 2 h under a continuous slow stream of N_2. The cooled mixture was then carefully decomposed with water (*ca.* 0–10 °C) and added to aqueous NaOH (3 mol dm^{-3}; 51 cm^3). To the well-stirred cooled mixture (*ca.* 0–10 °C), H_2O_2 (30% v/v; 20 cm^3) was added dropwise. Stirring was continued for an additional 30 min after which further H_2O_2 (10 cm^3) was added to the mixture which was then set aside overnight. It was then extracted with ether and the extract washed with water, dried (Na_2SO_4), and evaporated to afford the alcohol **9** (4.2 g, 98.4%) as an oil, in a *ca.* 1:2 epimeric mixture (^{1}H NMR), b.p. 180 °C (0.05 mmHg) (Found: C, 78.4; H, 10.5. $C_{19}H_{30}O_2$ requires C, 78.57; H, 10.41%); ν_{max}/cm^{-1} 3340 (br, OH); δ_H 0.78 and 0.90 (each s, CMe$_2$, minor epimer), 0.96 and 1.0 (each s, CMe$_2$, major epimer), 1.04–2.10 (10 H, m), 2.22 (3 H, s, ArMe), 2.30–2.68 (2 H, m, ArCH$_2$), 3.46 and 3.58 (2 H, each m, OCH$_2$, for the minor and the major epimers respectively), 3.80 (3 H, s, ArOMe), 6.77 (1 H, d, *J* 8, 5-ArH) and 7.00–7.06 (2 H, m, 2 and 6-ArH).

trans- *and* cis-*Methyl* 2-(4-*Methoxy*-3-*methylphenethyl*)-3,3-*dimethylcyclohexanecarboxylate* **11**.—The cooled alcohol **9** (4 g, 13.79 mmol) in acetone (50 cm^3) was stirred with an excess of Jones reagent (5.28 cm^3, 14 mmol) for 45 min. After dilution with water, the mixture was extracted with ether. The ether extract was washed with aqueous KOH (0.36 mol dm^{-3}; 60 cm^3). The aqueous portion was acidified with HCl (6 mol dm^{-3}) and work-up afforded the acid **10** (2.64 g, 62%) as a thick glass [ν_{max}(film)/cm^{-1} 1700 (CO$_2$H)] which was used directly in the next step. A small portion of the acid **10** was esterified (CH_2N_2 in ether) to afford the esters **11** as a *ca.* 1:3 epimeric mixture (^{1}H NMR), b.p. 160 °C (0.01 mmHg) (Found: C, 75.6; H, 9.5. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%); ν_{max}(film)/cm^{-1} 1735 (ester); δ_H 0.80 and 0.93 (each s, CMe$_2$, minor epimer), 0.98 and 1.03 (each s, CMe$_2$, major epimer), 1.06–2.00 (9 H, m), 2.20–2.86 (3 H, m), 3.67 and 3.73 (3 H, each s, CO$_2$Me, for the major and the minor epimers, respectively), 3.80 (3 H, s, ArOMe), 6.78 (1 H, d, *J* 8, 5-ArH) and 6.96–7.04 (2 H, m, 2 and 6-ArH).

cis-7-*Methoxy*-1,1,8-*trimethyl*-1,2,3,4,4a,10,11,11a-*octahydrodibenzo*[a,d]*cyclohepten*-5-*one* **12** *and its* C-4a-*Epimer* **13**.—To a well stirred homogeneous solution of polyphosphoric acid (PPA), prepared from P_2O_5 (24 g) and H_3PO_4 (12 cm^3) was added the acid **10** (2 g, 6.6 mmol) and the mixture was heated at 80–85 °C for 2 h. The red mixture was cooled, decomposed with ice and extracted with ether. The ether extract was washed with aqueous NaOH (0.5 mol dm^{-3}; 20 cm^3) and then evaporated to afford a solid stereoisomeric mixture of ketones **12** and **13** in a ratio of *ca.* 9:1 (^{1}H NMR) in 89% yield; δ_H 0.74 and 0.90 (each s, CMe$_2$ for the minor isomer), 0.97 and 0.98 (each s, CMe$_2$ for the major isomer), 1.16–2.26 (9 H, m), 2.20 (3 H, s, ArMe), 2.60–3.22 (3 H, m, ArCH$_2$ and ArCOCH), 3.85 (3 H, s, ArOMe), 6.96–7.07 (1 H, m, 9-ArH) and 7.20–7.27 (1 H, m, 6-ArH). Recrystallization afforded the pure major isomer **12** (1.34 g, 80%) m.p. 116–117 °C (ether–light petroleum) (Found: C, 79.8; H, 9.1. $C_{19}H_{26}O_2$ requires C, 79.68; H, 9.15%); ν_{max}($CHCl_3$)/cm^{-1} 1670 (CO); λ_{max}/nm 312 (log ε 3.41) and 262 (log ε 3.81); δ_H 0.98 (3 H, s, CMe), 0.99 (3 H, s, CMe), 1.26–2.26 (9 H, m), 2.24 (3 H, s, ArMe), 2.70–3.24 (3 H, m, ArCH$_2$ and ArCOCH), 3.85 (3 H, s, ArOMe), 7.01 (1 H, s, 9-ArH) and 7.22 (1 H, s, 6-ArH); *m*/*z* 286 (M$^+$, 100%), 271 (M$^+$ − Me, 8), 217 (28), 203 (63), 189 (25), 175 (22), 163 (48), 135 (54) and 91 (22).

Reduction of the Mixture of **12** *and* **13** *to the Epimeric Alcohols* **14**.—$NaBH_4$ (0.916 g, 25.4 mmol) was added portionwise to a stirred solution of the ketone mixture **12** and **13** (*ca.* 9:1) (1.19 g, 4.16 mmol) in 95% EtOH (40 cm^3). The mixture was left overnight after which the excess of $NaBH_4$ was decomposed with water. Work-up afforded the solid alcohol **14** (1.0 g, 84%) as an epimeric mixture; ν_{max}/cm^{-1} 3340 (OH); δ_H 0.72 and 0.94 (each s, CMe$_2$, major isomer), 0.88 and 1.08 (each s, CMe$_2$ minor isomer), 1.0–2.0 (8 H, m), 2.20 (3 H, s, ArMe), 2.02–2.28 (2 H, m), 2.50–2.80 (2 H, m, ArCH$_2$), 3.84 and 3.82 (3 H, each s, ArOMe for the major and the minor isomers), 4.66 and 5.02 (d, *J* 6 and br s, 1 H, ArC*H*OH in *ca.* 2:1 ratio respectively), 7.02 and 7.12 (1 H, each s, 9-ArH, for the minor and the major isomer respectively). This epimeric mixture was used directly for the subsequent reactions.

(±)-*Deoxyfaveline Methyl Ether* **15**.—The epimeric mixture of alcohols **14** (1.4 g, 4.8 mmol) was fused with $KHSO_4$ (1.32 g, 9.6 mmol) at 140 °C for 45 min and the resulting mixture was sublimed at 160 °C (0.05 mmHg) to give the methyl ether (±)-**15** (1.17 g, 89%) as a colourless solid, m.p. 86 °C (ether–light petroleum) (Found: C, 84.2; H, 9.7. $C_{19}H_{26}O$ requires C, 84.39; H, 9.69%); ν_{max}/cm^{-1} 1640 (C=C); λ_{max}/nm 220 (log ε 4.38), 264 (log ε 4.21) and 298 (log ε 3.75); δ_H 0.71 (3 H, s, CMe), 0.98 (3

H, s, CMe), 1.20–1.70 (6 H, m), 2.18 (3 H, s, ArMe), 2.08–2.48 (3 H, m), 2.50–2.70 (2 H, m, $ArCH_2$), 3.80 (3 H, s, ArOMe), 6.36 (1 H, br s, C=CH), 6.64 (1 H, s, 11-ArH) and 6.82 (1 H, s, 14-ArH).

(±)-*Deoxofaveline Acetate* **16**.—EtSH (1 cm^3, 11.76 mmol) was added dropwise to a stirred suspension of NaH (40% dispersion in oil; 425 mg, 7.4 mmol) in dry DMF (10 cm^3) under N_2. The ether **15** (250 mg, 0.93 mmol) was added to the mixture which was then refluxed for 4 h. After this it was cooled, diluted with water, acidified with HCl (2 mol dm^{-3}) and extracted with ether. Work-up of the extract afforded the crude phenol **1** (235 mg, 99%); ν_{max}/cm^{-1} 3360 (br, phenolic OH). The phenol **1** (235 mg, 0.92 mmol) was stirred with pyridine (15.3 cm^3) and Ac_2O (7.6 cm^3) overnight after which the mixture was diluted with water and extracted with ether. Work-up of the extract gave the acetate **16** (240 mg, 87.7%), m.p. 159–160 °C (ether–light petroleum) (Found: C, 80.5; H, 8.75. $C_{20}H_{26}O_2$ requires C, 80.49; H, 8.75%); ν_{max}/cm^{-1} 1755 (phenolic ester) and 1640 (C=C); λ_{max}/nm 264 (log ε 4.32) and 213 (log ε 4.33); δ_H 0.72 (3 H, s, CMe), 1.00 (3 H, s, CMe), 1.18–2.00 (6 H, m), 2.12 (3 H, s, ArMe), 2.27 (3 H, s, ArOCOMe), 2.00–3.00 (5 H, m), 6.23 (1 H, s, C=CH), 6.76 (1 H, s, 14-ArH) and 6.89 (1 H, s, 11-ArH).

(±)-*Deoxofaveline* **1**.—The acetate **16** (200 mg, 0.67 mmol) in Et_2O (30 cm^3) was stirred at room temperature with $LiAlH_4$ (110 mg) for 30 min, decomposed with cold saturated aqueous Na_2SO_4 and finally extracted with ether. Work-up of the extract afforded (±)-**1** (140 mg, 81%) as a colourless solid, m.p. 148–149 °C (lit.,[2] m.p. 149–151 °C; for the optically active **1**) $\nu_{max}(CHCl_3)/cm^{-1}$ 3590, 3360br, 2930, 2860sh, 2840, 1615 and 1585; $\nu_{max}(KBr)/cm^{-1}$ 3540, 3520, 2970sh, 2940, 2900sh, 2860, 2840, 1635, 1615 and 1585; λ_{max}/nm 302 (log ε 3.52), 263 (log ε 4.07) and 223 (log ε 4.2); δ_H(300 MHz; $CDCl_3$) 0.69 (3 H, s, CMe), 0.97 (3 H, s, CMe), 1.32–1.65 (6 H, m), 2.11–2.39 (3 H, m, CH and $ArCHCH_2$), 2.18 (3 H, s, ArMe), 2.52–2.68 (2 H, m, $ArCH_2$), 4.44 (1 H, s, ArOH), 6.23 (1 H, s, C=CH), 6.54 (1 H, s, 11-ArH) and 6.76 (1 H, s, 14-ArH). The spectral data for **1** are identical with those of the naturally occurring optically active deoxofaveline.[2]

Demethylation of the O-*Methyl Ether* **15** *with Aluminium Chloride–Ethanethiol: The Tetracyclic Dienone* **17**.—Anhydrous $AlCl_3$ (124 mg, 0.93 mmol) was added to a stirred solution of compound **15** (250 mg, 0.93 mmol) and EtSH (0.93 cm^3) in CH_2Cl_2 (10 cm^3) with cooling in an ice-bath. The mixture was stirred at 0 °C for an additional 4 h and then left overnight. It was then poured into HCl (6 mol dm^{-3}) and extracted with ether. Work-up of the extract afforded the crude dienone **17**. The residue was chromatographed on silica gel and eluted with ether–light petroleum (1:5 to 1:4) to afford the dienone **17** (230 mg, 97%), m.p. 86–87 °C (ether–light petroleum) (Found: C, 84.2; H, 9.4. $C_{18}H_{24}O$ requires C, 84.32; H, 9.44%); ν_{max}/cm^{-1} 1665 (dienone) and 1625 (C=C); λ_{max}/nm 255 (log ε 4.13); δ_H 0.96 (3 H, s, CMe), 1.06 (3 H, s, CMe), 1.79 (3 H, d, *J* 2, vinyl Me), 1.10–2.24 (13 H, m). 6.10 (1 H, s, 11-H) and 6.42 (1 H, d, *J* 2 14-H).

5-*Acetoxy*-7-*methoxy*-1,1,8-*trimethyl*-2,3,4,4a,5,10,11,11a-*octahydro*-1H-*dibenzo*[a,d]*cycloheptene* **18**.—The epimeric mixture of alcohols **14** (720 mg, 2.5 mmol) was treated with pyridine (41.6 cm^3) and Ac_2O (20.8 cm^3) and the mixture stirred overnight. Dilution of the mixture with water and extraction with ether afforded the acetate **18** (700 mg, 85%) as a liquid (Found: C, 76.2; H, 9.1. $C_{21}H_{30}O_3$ requires C, 76.32; H, 9.15%); ν_{max}/cm^{-1} 1730 (acetate); δ_H 0.75 (s, CMe_2, minor isomer), 0.84 and 1.00 (each s, CMe_2, major isomer), 1.08–2.00 (9 H, m), 2.06 and 2.19 (3 H, each s, OCOMe for the major and the minor isomer, partially overlapped with ArMe), 2.16 (3 H, s, ArMe), 2.38–3.26 (2 H, m, $ArCH_2$), 3.83 (3 H, s, ArOMe), 5.66 and 5.8 (br s, and d, *J* 6, 1 H, CHOCOMe, in *ca.* 1:2 ratio respectively), 6.84 (1 H, s, 6-ArH) and 6.90 (1 H, s, 9-ArH).

5-*Acetoxy*-7-*methoxy*-1,1,8-*trimethyl*-1,2,3,4,4a,5,11,11a-*octahydrodibenzo*[a,d]*cyclohepten*-10-*one* **19**.—To a well stirred solution of the acetate **18** (200 mg, 0.6 mmol) in dichloromethane (10 cm^3), was added a finely powdered and a homogenised mixture of PCC (800 mg, 3.6 mmol) and Celite (800 mg).[17] The reaction mixture was refluxed for 15 h and then diluted with ether (10 cm^3), filtered through a short pad of alumina, dried (Na_2SO_4) and evaporated to give the crude keto acetate **19**. This was chromatographed over neutral alumina (15 g) and eluted with light petroleum–ether (5:1 to 4:1) to give the keto acetate **19** (124 mg, 60%) as a gummy liquid (Found: C, 73.0; H, 8.2. $C_{21}H_{28}O_4$ requires C, 73.22; H, 8.19%); ν_{max}/cm^{-1} 1665 (benzylic CO) and 1730 (acetate); λ_{max}/nm 276 (log ε 3.92) and 226 (log ε 4.13); δ_H 0.88 (s, CMe_2, major isomer), 0.92 s, CMe_2, minor isomer), 1.00–2.40 (8 H, m), 1.96 and 2.20 (3 H, each s, OCOMe for the major and the minor isomer, partially overlapped with ArMe), 2.22 (3 H, s, ArMe), 2.60–2.90 (2 H, m, $ArCOCH_2$), 3.90 (3 H, s, ArOMe), 5.60 and 6.18 (s and d, *J* 6, 1 H, CHOAc, in *ca.* 1:2 ratio respectively) 6.68 and 6.84 (1 H, each s, 6-ArH for the minor and the major isomer respectively) and 7.48–7.56 (1 H, br s, 9-ArH for both the isomers).

5-*Hydroxy*-7-*methoxy*-1,1-8-*trimethyl*-1,2,3,4,4a,5,11,11a-*octahydrodibenzo*[a,d]*cyclohepten*-10-*one* **20**.—The diastereoisomeric mixture of the keto acetates **19** (440 mg, 1.27 mmol) was heated under reflux with methanolic KOH (0.36 mol dm^{-3}; 20 cm^3) for 2 h. The cooled reaction mixture was diluted with water and most of the methanol removed *in vacuo*. The product was extracted with ether and the extract worked up to afford the keto alcohol **20** (0.378 g, 98%) as a thick gum (Found: C, 75.4; H, 8.7. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67%); ν_{max}/cm^{-1} 1660 (benzylic CO); λ_{max}/nm 275 (log ε 4.19) and 225 (log ε 4.4); δ_H 0.86 (6 H, s, CMe_2), 1.00–2.00 (8 H, m), 2.19 (3 H, s, ArMe), 2.30–3.00 (2 H, m, $ArCOCH_2$), 3.88 and 3.90 (3 H, each s, ArOMe for both the isomers), 4.51 and 5.06 (br s and d, *J* 6, 1 H, ArC*H*OH, in *ca.* 2:1 ratio respectively), 6.57 and 7.00 (1 H, each s, 6-ArH, for the major and the minor isomer respectively) and 7.49 (1 H, br s, 9-ArH, for both the isomers).

(±)-*Faveline Methyl Ether* **2**.—The keto alcohol **20** (400 mg, 1.32 mmol) was fused with $KHSO_4$ (363 mg, 2.64 mmol) at 140 °C for 45 min and the resulting mixture was sublimed to give (±)-**2** (360 mg, 96%), m.p. 139–140 °C (lit.,[2] m.p. 135–136 °C for the optically active **2**); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930br, 2840, 1660 (benzylic CO) and 1600; $\nu_{max}(KBr)/cm^{-1}$ 2970, 2940sh, 2920, 2850, 1655 (benzylic CO) and 1600; λ_{max}/nm 344 (log ε 3.80), 301 (log ε 3.95), 260 (log ε 4.74), 254sh ((log ε 4.51) and 202 (log ε 4.05); δ_H(300 MHz; $CDCl_3$) 0.76 (3 H, s, CMe), 1.12 (3 H, s, CMe), 1.42–1.62 (2 H, m), 1.64–1.76 (2 H, m), 2.18 (3 H, s, ArMe), 2.28–2.37 (3 H, m), 3.01–3.03 (2 H, m, $ArCOCH_2$), 3.87 (3 H, s, ArOMe), 6.29 (1 H, s, C=CH), 6.59 (1 H, s, 11-ArH) and 7.62 (1 H, s, 14-ArH). The spectral data are identical with those of the naturally occurring optically active faveline methyl ether.[2]

Demethylation of **2** *with* DMF–NaH–EtSH: 7,10-*Diacetoxy*-1,1,8-*trimethyl*-2,3,4,5-*tetrahydro*-1H-*dibenzo*[a,d]*cycloheptene* **22**.—The keto ether **2** (250 mg, 0.88 mmol) was subjected to dimethylation with EtSH (0.8 cm^3, 9.4 mmol) and NaH (40% dispersion in oil; 400 mg, 6.2 mmol) in dry DMF (10 cm^3) as described for the preparation of **1**, to give the diol **21** (213 mg, 90%) as a poorly soluble amorphous white solid, which was treated with pyridine (12.9 cm^3) and Ac_2O (6.5 cm^3). The mixture was stirred overnight, and then diluted with water and

extracted with ether. Work-up of the extract gave **22** (248 mg, 89%) as a colourless solid, m.p. 159–160 °C (ether–light petroleum) (Found: C, 74.6; H, 7.4. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.39%); ν_{max}/cm^{-1} 1750–1760 (acetates) and 1635 (C=C); λ_{max}/nm 286 (log ε 3.84) and 210 (log ε 4.47); δ_H 1.02 (6 H, s, CMe_2), 1.32–1.60 (6 H, m), 2.16 (3 H, s, ArMe), 2.28 (3 H, s, 10-OCOMe), 2.32 (3 H, s, 7-ArOCOMe), 2.96 (2 H, s, $ArCH_2$), 6.4 (1 H, s, C=CH), 6.84 (1 H, s, 9-ArH) and 7.20 (1 H, s, 6-ArH).

cis-*and*trans-7-*Hydroxy*-1,1,8-*trimethyl*-1,2,3,4,4a,10,11,11a-*octahydrodibenzo*[a,d]*cyclohepten*-5-*one* **23**.—The mixture of the epimeric ketones (*ca.* 9:1) **12** and **13** (400 mg, 1.4 mmol) was demethylated with EtSH (1.18 cm^3, 13.8 mmol) and NaH (40% dispersion in oil; 699 mg, 10.9 mmol) in dry DMF (13.9 cm^3) in the same way as described for compound **15**, to give the keto phenol **23** (361 mg, 95%) as a solid, m.p. 200–217 °C (ether–light petroleum) (Found: C, 79.4; H, 8.85. $C_{18}H_{24}O_2$ requires C, 79.37; H, 8.88%); ν_{max}/cm^{-1} 3400 (phenolic OH), 1655 (CO) and 1605; λ_{max}/nm 229 (log ε 4.16), 262 (log ε 3.84) and 315 (log ε 3.4); δ_H 0.76 and 0.92 (each s, CMe_2, for the minor isomer), 1.00 (s, CMe_2, for the major isomer), 1.13–2.20 (9 H, m), 2.24 (3 H, s, ArMe), 2.60–3.24 (3 H, m, $ArCH_2$ and CHCOAr), 5.96 (1 H, br, ArOH), 6.93 (1 H, br s, 9-ArH), 7.30 and 7.46 (1 H, each s, 6-ArH for the major and the minor isomers); *m/z* 272 (M^+, 98%) 257 (M^+ − Me, 8), 203 (44), 189 (100), 176 (41), 161 (42), 150 (45), 121 (82) and 91 (59).

5,7-*Diacetoxy*-1,1,8-*trimethyl*-2,3,4,4a,5,10,11,11a-*octahydro*-1H-*dibenzo*[a,d]*cycloheptene* **25**.—The diastereoisomeric mixture of the keto phenol **23** (575 mg, 2.1 mmol) was reduced with $NaBH_4$ (462 mg, 12.0 mmol) in EtOH (15 cm^3) following the same procedure as described for the preparation of compound **14**, to give **24** (506 mg) as a liquid. This was directly acetylated with pyridine (34.4 cm^3) and Ac_2O (17.2 cm^3) by the method described for the preparation of compound **16**, to give **25** (632 mg, 95%) as a semi-solid liquid. (Found: C, 73.8; H, 8.5. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%); ν_{max}(neat)/cm^{-1} 1735 (acetate) and 1760 (phenolic ester); δ_H 0.71 and 0.74 (each s, CMe of minor *cis*-ring isomer), 0.93 and 0.97 (each s, CMe_2 major *cis*-ring isomer), 0.82 and 1.02 (very small signals, possibly due to CMe_2 of *trans*-isomer), 1.08–2.00 (10 H, m), 2.02 and 2.10 (3 H, each s, OCOMe, for the minor and the major *cis*-ring isomer respectively), 2.14 (3 H, s, ArMe), 2.28 and 2.30 (3 H, each s, ArOCOMe of minor and major *cis*-ring isomer respectively), 2.18 and 2.34 (very small signals, possibly due to OCOMe and ArOCOMe respectively of the *trans* isomer), 2.50–3.10 (2 H, m, $ArCH_2$), 5.62 and 5.84 (br s and d, *J* 6, 1 H, CHOAc, in *ca.* 1:2 ratio) and 6.94 (2 H, br s, 6 and 9-ArH).

5,7-*Diacetoxy*-1,1,8-*trimethyl*-1,2,3,4,4a,5,11,11a-*octahydrodibenzo*[a,d]*cyclohepten*-10-*one* **26**.—To a well stirred suspension of PCC (1 g, 4.5 mmol) and Celite (1 g) in benzene (6 cm^3) a solution of the diacetate **25** (250 mg, 0.69 mmol) in benzene (2 cm^3) was added. The mixture was refluxed for 18 h, and then the reaction mixture was worked-up as described for the preparation of compound **19**. Chromatography of the crude product on neutral alumina (30 g) and elution with ether–light petroleum (1:9 to 1:4) gave the keto diacetate **26** (110 mg, 42%) as a semi-solid (Found: C, 70.9; H, 7.6. $C_{22}H_{28}O_5$ requires C, 70.94; H, 7.58%); ν_{max}/cm^{-1} 1675 (CO), 1730 (acetate) and 1750 (phenolic ester); λ_{max}/nm 250 (log ε 3.85) and 215 (log ε 4.2); δ_H 0.86 (s, CMe_2, major isomer), 0.90 (s, CMe, minor isomer), 1.00–2.04 (8 H, m), 1.92 and 2.16 (3 H, each s, CHOCO*Me* for the major and the minor isomer, partially overlapped with ArMe), 2.20 (3 H, s, ArMe), 2.32 (3 H, s, ArOCOMe), 2.50–2.90 (2 H, m, $ArCOCH_2$), 5.56 and 6.10 (br s and d, *J* 6, 1 H, CHOAc in *ca.* 2:1 ratio respectively), 6.96 and 7.08 (1 H, each s, 6-ArH, for the major and the minor isomer respectively) and 7.53 (1 H, br s, 9-ArH for both the isomers).

5,7-*Dihydroxy*-1-(1,8-*trimethyl*-1,2,3,4,4a,5,11,11a-*octahydrodibenzo*[a,d]*cyclohepten*-10-*one* **27**.—(*a*) *Hydrolysis of the diastereoisomeric mixture of the keto diacetates* **26**. The keto diacetate **26** (220 mg, 0.59 mmol) was hydrolysed with methanolic KOH (0.36 mol dm^{-3}; 30 cm^3) by the procedure described for compound **19**, to give compound **27** (160 mg, 94%) m.p. 154 °C (ether–light petroleum) (Found: C, 75.0; H, 8.4. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%); ν_{max}($CHCl_3$)/cm^{-1} 1675 (CO) and 1600; λ_{max}/nm 280 (log ε 3.84), 230 (log ε 4.03) and 215 (log ε 3.97); δ_H 0.86 (6 H, br s, CMe_2), 1.16–2.08 (8 H, m) 2.21 (3 H, s, ArMe), 2.40–2.80 (2 H, m, $ArCOCH_2$), 4.46 and 5.00 (br s and d, *J* 6, 1 H, ArC*H*OH, in *ca.* 2:1 ratio), 6.48 and 6.82 (1 H, each s, 6-ArH for the major and the minor isomers respectively) and 7.42 and 7.46 (1 H, each s, 9-ArH, for the major and the minor isomers respectively).

(*b*) *Demethylation and deacetylation of* **19** *with boron tribromide*. To a well stirred solution of the acetate **19** (200 mg, 0.58 mmol) in dry dichloromethane (5 cm^3), boron tribromide (0.3 cm^3) in dry dichloromethane (5 cm^3) was added dropwise at 0 °C. After addition was completed the reaction mixture allowed to stand at the same temperature for a further 2 h and finally for overnight at room temperature. The mixture was poured into ice and extracted with ether to afford compound **27** (130 mg, 78%) identical (IR, ^{1}H NMR) with the sample described above.

(±)-*Faveline* **3**.—The keto diol **27** (200 mg, 0.694 mmol) was fused with $KHSO_4$ (190 mg, 1.38 mmol) at 140 °C for 45 min and the resulting mixture was sublimed at 180 °C (0.05 mmHg) to give (±)-faveline **3**, m.p. 194–196 °C (lit.,[2] 192–194 °C for optically active **3**); ν_{max}($CHCl_3$)/cm^{-1} 3580, 3260br, 2930, 2850, 1660 (CO) and 1605; ν_{max}(KBr)/cm^{-1} 3240br, 2960sh, 2930, 2850, 1655 (CO) and 1590; λ_{max}/nm 301 (log ε 3.6) and 260 (log ε 4.2); δ_H(100 MHz; $CDCl_3$) 0.75 (3 H, s, CMe), 1.10 (3 H, s, CMe), 1.30–2.30 (6 H, m), 2.21 (3 H, s, ArMe), 2.36 (1 H, m, CH), 3.00–3.07 (2 H, m, $ArCOCH_2$), 6.20 (1 H, s, C=CH), 6.60 (1 H, s, 11-ArH) and 7.64 (1 H, s, 14-ArH). The spectral data for **3** are identical with those of the naturally occurring optically active faveline.[2]

Acknowledgements

We gratefully acknowledge Professor S. Nozoe for the generous samples and spectra of deoxofaveline, faveline methyl ether and faveline. We thank C.S.I.R., New Delhi for the award of S.R.F. to A. K. G. and financial support through grant No. 02(368)/92/EMR-11.

References

1 Part 18, S. Deb, G. Bhattacharjee and U. R. Ghatak, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1453.
2 Y. Endo, T. Ohta and S. Nozoe, *Tetrahedron Lett.*, 1991, **32**, 3083.
3 S. F. Kimbu, F. Keumedjio, L. B. Sondengam and J. D. Connolly, *Phytochemistry*, 1991, **30**, 619.
4 X. A. Dominguez, H. Sanchez V., S. Garcia G., G. Espinosa B., H. J. Williams, C. Ortiz, A. I. Scott and J. H. Reibenspies, *J. Nat. Prod.*, 1992, **55**, 221.
5 T. Kametani, H. Kondoh, M. Tsubuki and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1990, 5.
6 T. Matsumoto, S. Imai, T. Yoshinari and S. Maisuno, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3103.
7 E. R. Koft, *Tetrahedron*, 1987, **43**, 5775.
8 G. Majetich, Y. Zhang, T. L. Feltman and S. Duncass, Jr., *Tetrahedron Lett.*, 1993, **34**, 445.
9 Preliminary communiation: A. K. Ghosh, C. Ray and U. R. Ghatak, *Tetrahedron Lett.*, 1992, **33**, 655.

10 B. K. Banik, S. Ghosh and U. R. Ghatak, *Tetrahedron*, 1988, **44**, 6947.
11 J. M. Conia and J. C. Limasset, *Bull. Soc. Chim. Fr.*, 1967, **6**, 1936.
12 H. O. House, W. E. Hanners and E. J. Reach, *J. Org. Chem.*, 1972, **37**, 985.
13 A. Bowers, T. C. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.
14 A. Chatterjee, D. Banerjee and R. Mallik, *Tetrahedron*, 1977, **33**, 85.
15 G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1970, 1327.
16 M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji and E. Fujita, *Chem. Lett.*, 1979, 97.
17 (*a*) R. Rathore, N. Saxena and S. Chandrasekaran, *Synth. Commun.*, 1986, **16**, 1493; (*b*) J. L. Maurer, F. Berchier, A. J. Serino, C. B. Knobler and M. F. Hawthorne, *J. Org. Chem.*, 1990, **55**, 838; (*c*) S. Ghosh, B. K. Banik and U. R. Ghatak, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3195.
18 U. R. Ghatak, S. K. Alam and J. K. Ray, *J. Org. Chem.*, 1978, **43**, 4598.
19 M. V. Bhatt and J. R. Babu, *Tetrahedron Lett.*, 1984, **25**, 3497.
20 U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravarty and R. E. Moore, *J. Org. Chem.*, 1969, **34**, 3739.

Paper 3/04116F
Received 13*th July* 1993
Accepted 1*st September* 1993