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BICYCLO[2.2.1]HEPTANE AS CYCLOPENTANE PRECURSOR. PART 4[1]. STEREOCONTROLLED SYNTHESIS OF A POTENTIAL INTERMEDIATE TO CHROMOPHYCANE, DOLASTANE AND CLAVULARANE

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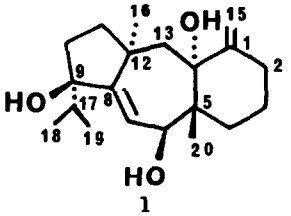
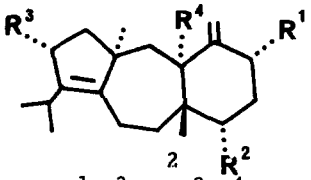
Abstract : The regio- and stereoselective synthesis of the keto-esters **20** and **22** are described, the latter being a potential intermediate to several diterpenes. The key steps involve the Diels-Alder cycloaddition between the benzocycloheptenone **5** and cyclopentadiene followed by a regioselective functionalisation of the adduct **6**. A remarkable reversal of regioselectivity was observed during oxymercuration of the unsymmetric double bond in **6** and its reduced product **11** leading to **8** and **12** which were subsequently transformed to **20** and **22** respectively.

The linearly arrayed 5-7-6 carbocyclic system encountered in marine natural products constitutes three structurally and physiologically interesting families of diterpenoids. The isolation of dolatriol **1**, the first member of the dolastane family from the Dolabella auricularia was reported by Pettit et al[2] in 1976. Subsequently, isolation of many other diterpenes of this family e.g. **2a-d**[3] have been reported. Shortly after the discovery of **1**, the diterpenes **3a-c**[4] belonging to Clavularane family were isolated from Clavularia inflata. More recently, Martin and Clardy reported the isolation of chromophycadiol monoacetate **4**[5], the only chromophycane from Dictyota in Canary Islands. Biogenetically, these three families are interrelated in the sense that

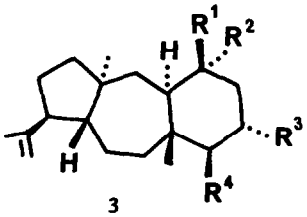


1



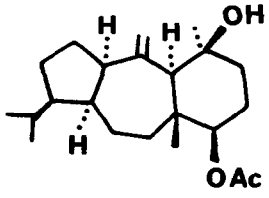
2

a, R^1=R^3=H, R^2=R^4=OH
b, R^1=R^4=OH, R^2=R^3=H
c, R^1=R^3=R^4=H, R^2=OH
d, R^1=H, R^2=R^4=OH, R^3=OAC



3

a, R^1=Me, R^2=R^4=OH, R^3=H
b, R^1, R^2=CH_2, R^3=H, R^4=OH
c, R^1,R^2=CH_2, R^3=R^4=OH

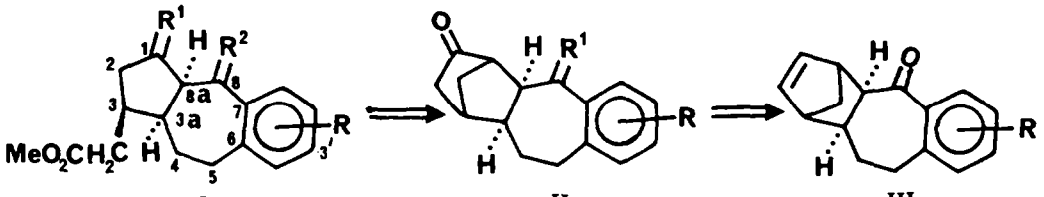


4

both dolastanes and clavularanes are presumably derived from dollabellanes through cationic cyclisation[4] while chromophycane is possibly derived[5] by a methyl migration from C_{12} to C_{13} in dolastane. While clavularanes **3** possess a trans-syn-trans oriented 5-7-6 unit, chromophycane **4** is cis-syn-trans oriented with C_9, C_{12}-substituents in an anti-relationship in both **3** and **4**. However, in dolastanes e.g. in dolatriol **1**, the C_9,C_{12} substituents bear a syn-relationship. In recent years a number of syntheses of dolastanes[6] lacking C_8,C_9 stereocentres as in **2** have been reported. However, to date no effort to synthesise the stereochemically more complex members of these families like **1**, **3** or **4** has been reported. A vital issue in the synthesis of these compounds is the control of stereocentres C_8,C_9 and C_{12}. Herein, we report the results of our synthetic investigation providing a simple solution to this problem of stereoselection for entry into the dolastane, clavularane and chromophycane families.

We envisaged that the keto-ester I could serve as an intermediate to all the three families. The structural and stereochemical features present in I parallel those of chromophycane **4**. An inversion of stereochemistry at C_{8a} of I would permit an approach to dolastane **1** while inversion at C_{8a} and C_3 would allow an entry to clavularanes. A retrosynthesis (Scheme-1) dictates that the ketone I can be derived from II the genesis

Scheme - 1



I

R^1=O, R^2=H_2
or R^1=H_2, R^2=O

II

R^1=H_2 or O

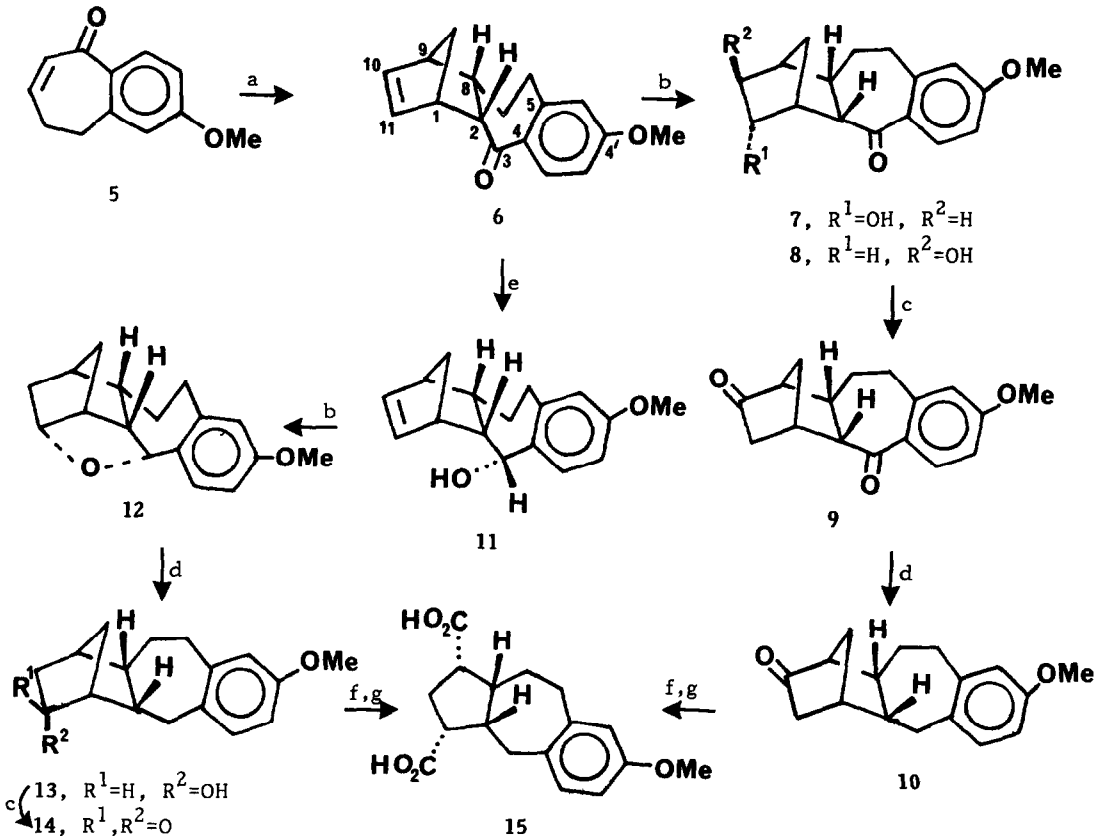
III

of which requires a regioselective functionalisation in III. The enone III may be obtained by a Diels-Alder cycloaddition between cyclopentadiene and a benzocycloheptenone derivative, this key step allowing the annulation of the five membered ring with simultaneous control of stereochemistry at the desired centres.

The cycloaddition of the benzocycloheptenone **5** with cyclopentadiene was achieved to produce the endo-adduct **6** under Lewis acid catalysis (Scheme-2). With $AlCl_3$ (0.75 equivalent) as the catalyst, **6** was obtained only in 54% yield[7]. With increasing amount of $AlCl_3$ (more than one equivalent), the adduct was found to be an inseparable mixture of **6** and its trans epimer. However, when 3 equivalents of $BF_3.Et_2O$ were used as the catalyst, the yield of the adduct **6** was improved dramatically to 98% without causing any epimerisation of **6**. The endo-assignment to the adduct **6** was revealed by the coupling constant[8] between the exo-protons at C_2,C_8. The proton at C_2 appeared at δ 3.38 as a doublet of doublet with $J_{2,8}$ = 10.5 Hz and $J_{1,2}$ = 3 Hz. For the

Regioselective functionalisation at C_{11} of the double bond, we visualised that during oxymercuration of **6**, the carbonyl oxygen at C_3 could be induced to undergo 'RO5 type participation'[9] to lead to the formation of the hydroxy ketone **7**. To our dismay, when the ketone **6** was subjected to oxymercuration using $Hg(OAC)_2$ in aqueous THF containing a catalytic amount of 70% perchloric acid, followed by reduction of the organomercurial the hydroxy ketone **8** was obtained exclusively as a crystalline solid in 90% yield. The exo-assignment of the hydroxy group in **8** followed from the tendency of the norborene derivatives to undergo oxymercuration from the exo face[10]. The formation of **8** from **6** requires the attack by $^{\ominus}OH$ exclusively at C_{10} in the unsymmetrical mercurinium intermediate. As both C_{10} and C_{11} have nearly identical steric environments, the regioselectivity observed in this case is possibly[11] the result of polarisation of the double bond due to the field effect exerted by the nearby carbonyl group. The hydroxy ketone **8** was oxidised to the diketone **9**, which on hydrogenolysis afforded the monoketone **10**.

Scheme-2

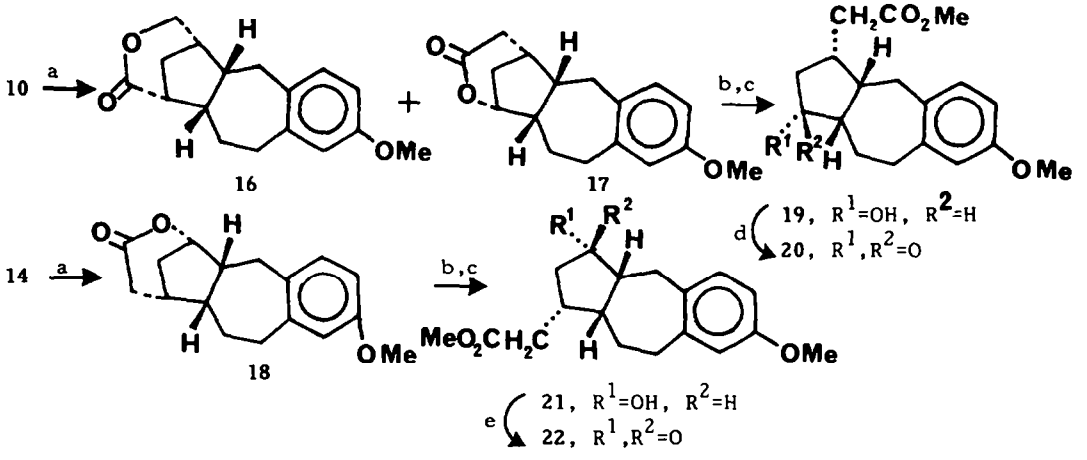


Reagents : a, THF-Cyclopentadiene-$BF_3.Et_2O$,0°C; b, $Hg(OAC)_2$-THF-H_2O-$HClO_4$ then 3MNaOH-$NaBH_4$; c, Jones reagent-acetone, 5°C; d, H_2-Pd/C-EtOH-$HClO_4$; e, $LiAlH_4$-Et_2O, reflux; f, NaH-HCO_2Et-C_6H_6; g, NaOH-30% H_2O_2.

Functionalisation at the desired end (C_{11}) could, however, be achieved through an intramolecular participation of a hydroxy group as follows. The Diels-Alder adduct **6** was reduced with lithium aluminium hydride in refluxing ether to afford **11** in quantitative yield. As expected, the hydride was delivered from the less hindered exo-face to afford the endo alcohol. The stereochemical assignment of the hydroxy group in **11** followed from its subsequent transformation for which an endo alcohol configuration was necessary. When **11** was treated with a suspension of $Hg(OAC)_2$ in aqueous tetrahydrofuran, followed by reduction of the intermediate organomercurial the cyclic ether **12** was obtained in 90% yield. That the oxymercuration product of **11** was not a diol was determined by its resistance to oxidation. Hydrogenolysis of the benzylic ether **12** afforded the hydroxy compound **13** which, after Jones oxidation, gave the ketone **14** in overall excellent yield. The ketone **14** was shown to be different to the ketone **10** by GC analysis as well as by mixed m.p. determination. That the ketone **14** is the regio isomer of the ketone **10** was established by transformation of both the ketone **10** and **14** to the same dicarboxylic acid **15** through formylation and subsequent oxidation of the formyl derivatives. Thus, by simply changing the functional group from carbonyl to hydroxy, the either end of the unsymmetrical double bond of **6**, can be functionalised regioselectivity to afford either the ketone **10** or the ketone **14**.

After successfully achieving the synthesis of the ketones **10** and **14**, both of them were subjected to Baeyer-Villiger oxidation with mCPBA in dichloromethane. While the ketone **10** afforded a mixture of the lactones **16** and **17**, the ketone **14** afforded only the lactone **18** (**Scheme-3**). The lactone **16** and **17** could be separated by fractional crystallisation from their mixture in 18% and 50% yield respectively. The minor lactone obtained from the ketone **10** was found to have the structure **16**, as evident by its transformation to the dicarboxylic acid **15** through hydrolysis and oxidation. The major

Scheme - 3



Reagents : a, mCPBA, CH_2Cl_2, rt; b, KOH-MeOH-H_2O, rt, then HCl; c, CH_2N_2-Et_2O; d, Jones reagent-acetone, 5°C; e, $(COCl)_2$-DMSO-NEt_3-CH_2Cl_2, -60°C.

lactone **17** after saponification and diazomethane treatment afforded the hydroxy ester **19** which was oxidised to the keto-ester **20**. The single lactone **18** obtained from the ketone **14** was saponified and treated with diazomethane to give the hydroxy ester **21** which was oxidised to give the keto-ester **22** in overall good yield. The keto-ester **22** having the desired stereochemistry at the three contiguous stereocentres is properly functionalised for further elaboration to chromophycane. The present approach involving Lewis acid catalysed Diels-Alder reaction for elaboration to chromophycane is complementary to our earlier approach[12] involving photo-induced Diels-Alder reaction for elaboration to dolastanes.

EXPERIMENTAL SECTION

Melting points were recorded in a sulfuric acid bath and are uncorrected. IR spectra were recorded in KBr pellets for solids and in film for liquids on a Perkin-Elmer 298 spectrophotometer. Unless otherwise stated, ^{1}H NMR spectra were recorded at 200 MHz against Me_4Si as an internal standard in $CDCl_3$ solution on a Varian XL-200 spectrometer. Gas chromatography was carried out on a Shimadzu GC-9A model using OV-17 on 1.5% Shimalite W 80-100 silanized column (6m x 3mm). Column chromatography was performed through silica gel (60-200 mesh). Petroleum refers to fraction of petroleum ether boiling in the range 60-80°C. Organic extracts were dried over anhydrous sodium sulfate.

endo-4,5-(4'-Methoxy)benzotricyclo[7.2.1.0^{2,8}]dodec-10-en-3-one (6). To an ice-cooled solution of the enone **(5)** (150 mg, 0.79 mmol) in THF (0.8 mL) was added freshly cracked cyclopentadiene (0.8 mL) in one portion. Freshly distilled $BF_3.Et_2O$ (0.3 mL, 2.5 mmol) was added dropwise to this ice-cold solution with magnetic stirring. Stirring was continued at 0°C for 2.5 h. The reaction mixture was partitioned between saturated $NaHCO_3$ and Et_2O. The aqueous part after separation from the ether layer was extracted with Et_2O (3 x 25 mL). The combined organic extract was washed with brine (2 x 20 mL) and dried. Removal of solvent afforded a viscous liquid which after column chromatography [ethylacetate-petroleum (5:95)] furnished the pure adduct **(6)** (200 mg, 98%), m.p. 80°C; ^{1}H NMR δ 1.11-1.65 (m, 3H), 2.0 (br d, H), 2.42-2.71 (m, H), 2.82 (br s, H), 3.07-3.31 (m, 3H), 3.38 (dd, H, J = 10.5 and 3 Hz), 3.80 (s, 3H), 6.02 (dd, H, J = 5.6 and 2 Hz), 6.51 (dd, H, J = 5.6 and 1.8 Hz), 6.64-6.78 (m, 2H), 7.52 (d, H, J = 8.7 Hz). It was found to be identical by mixture melting point (80°C) with a sample prepared by the $AlCl_3$ method.

exo-10-Hydroxy-endo-4,5-(4'-methoxy)benzotricyclo[7.2.1.0^{2,8}]dodecan-3-one (8). A solution of the ketone **(6)** (540 mg, 2.1 mmol) in THF (5 mL) was added to a magnetically stirred yellow solution of $Hg(OAC)_2$ (760 mg, 2.38 mmol) in H_2O-THF (10 mL, 1:1) containing a drop of $HClO_4$ (70%). The flask was stoppered and stirred at rt for 20 h. Aqueous NaOH (6.5 mL, 3 M) was then added, followed by the addition of a solution of $NaBH_4$ (150 mg, 3.96 mmol) in aqueous NaOH (5 mL, 3M). After stirring for 30 min, the reaction mixture was saturated with NaCl and extracted with ether (3 x 25 mL). The ether extract was washed with brine (2 x 20 mL) and dried. Removal of solvent afforded the hydroxy ketone **(8)** (520 mg, 90%) m.p. 116°C. A small quantity of this solid was recrystallised from ether-petroleum to furnish a pure sample m.p. 122°C. IR: 3380, 1670, 1600 cm^{-1}; ^{1}H NMR δ 1.24-1.52 (m, 3H), 1.66-2.06 (m, 5H), 2.12 (br s, H), 2.86-3.06 (m, 2H), 3.12-3.34 (m, 2H), 3.9 (s, 3H), 4.44 (m, H), 6.78 (br s, H), 6.91 (dd, J = 2 and 8 Hz, H), 8.12 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.89; H, 7.57.

endo – 4 5-(4'-Methoxy)benzotricyclo[7.2.1.0^{2,8}]dodecan-3,10-dione (9). To a magnetically stirred cold (5-10°C) solution of the hydroxy ketone **(8)** (310 mg, 1.15 mmol) in acetone (8 mL), Jones reagent (1 mL) was added dropwise until the colour of the reagent persisted. After stirring for an additional 30 min, the reaction mixture was poured into water (20 mL) and extracted with ether (3 x 25 mL). The ether extract was washed successively with 1% aqueous NaOH, brine and dried. Removal

of solvent gave the diketone **(9)** (260 mg, 83%), m.p. 110°C. Recrystallisation from ether-petroleum furnished an analytical sample, m.p. 113°C; IR: 1745, 1665, 1595 cm^{-1}; ^1H NMR δ 1.6-2.38 (7H), 2.48-2.68 (2H), 2.9-3.22 (2H), 3.41 (br s, H), 3.92 (s, 3H), 6.83 (br s, H), 6.96 (dd, J = 2 and 8 Hz, H), 8.19 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.88; H, 6.86.

endo-4,5-(4'-Methoxy)benzotricyclo[7.2.1.$0^{2,8}$]dodecan-10-one (10). Hydrogenolysis of a solution of the diketone **(9)** (260 mg, 0.96 mmol) in EtOH (8 mL) containing $HClO_4$ (0.05 mL, 70%) was accomplished by stirring over 10% Pd/C (50 mg) under an atmosphere of H_2 for 4 h. After neutralisation of the acid with powdered $NaHCO_3$, the reaction mixture was filtered through a short column of SiO_2. Removal of solvent afforded the ketone **(10)** (230 mg, 93%), m.p. 62-64°C. Recrystallisation from ether-petroleum furnished the analytically pure sample, m.p. 64°C; R_t 2.53 min (270°C); IR: 1740, 1600 cm^{-1}; ^1H NMR δ 1.36-2.82 (12H), 2.90-3.48 (2H), 3.80 (s, 3H), 6.64-6.78 (2H), 7.03 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.72; H, 7.92.

endo-3-Hydroxy-endo-4,5-(4'-methoxy)benzotricyclo[7.2.1.$0^{2,8}$]dodec-10-ene (11). To a refluxing suspension of $LiAlH_4$ (400 mg, 10.67 mmol) in dry ether (68 mL), a solution of the ketone **(6)** (1.35 g, 5.3 mmol) in dry ether (84 mL) was added dropwise with stirring under N_2-atmosphere. Refluxing was continued for an additional 3.5 h. The reaction mixture was then quenched by dropwise addition of saturated aqueous Na_2SO_4 (10 mL) with cooling. The precipitated solid was filtered, the precipitate was washed with Et_2O (3 x 50 mL). The combined filtrate and washing was dried and concentrated to afford the hydroxy compound **(11)** (1.35 g, 100%), m.p. 79°C; IR: 3410, 1605 cm^{-1}; ^1H NMR δ 1.11-2.26 (5H), 2.34-3.32 (6H), 3.8 (s, 3H), 4.97 (br s, H), 6.26-6.46 (2H), 6.64-6.8 (2H), 7.14 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.81; H, 8.02.

endo-3,11-Epoxy-endo-4,5-(4'-methoxy)benzotricyclo[7.2.1.$0^{2,8}$]dodecane (12). Following the procedure described for **(6)**, a solution of the hydroxy compound **(11)** (720 mg, 2.8 mmol) in THF (7 mL) was subjected to oxymercuration using mercuric acetate (950 mg, 2.98 mmol) in THF-H_2O (13 mL, 1:1) containing a drop of 70% perchloric acid to afford the cyclic ether **(12)** (650 mg, 90%) m.p. 170-172°C. A small quantity of this solid was recrystallised from ether-petroleum to furnish a pure sample m.p. 175°C; ^1H NMR: δ 1.3-2.12 (7H), 2.22-2.7 (2H), 2.76-3.06 (3H), 3.82 (s, 3H), 4.43 (t, J = 6 Hz, H), 4.85 (d, J = 4 Hz, H), 6.65 (d, J = 2 Hz, H), 6.74 (dd, J = 2 and 8 Hz, H), 7.27 (d, J = 2 Hz, H), 6.74 (dd, J = 2 and 8 Hz, H), 7.27 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{20}O_2$: C, 79.65, H, 7.86. Found: C, 79.25; H, 8.34.

endo-11-Hydroxy-endo-4,5-(4'-methoxy)benzotricyclo[7.2.1.$0^{2,8}$]dodecane (13). Hydrogenolysis of a solution of the ether **(12)** (450 mg, 1.75 mmol) in EtOH (6 mL) containing 70% $HClO_4$ (0.05 mL) was accomplished by stirring over 10% Pd/C (50 mg) under H_2 atmosphere for 4 h to afford the hydroxy compound **(13)** (400 mg, 88%), m.p. 107-109°C. Recrystallisation from ether-petroleum furnished an analytical sample m.p. 110°C; IR: 3460, 1600 cm^{-1}; ^1H NMR: δ 1.36-2.66 (13H), 2.84-3.06 (H), 3.24-3.4(H), 3.78 (s, 3H), 4.37-4.5 (H), 6.58-6.72 (2H), 6.95 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.17; H, 8.73.

endo-4,5-(4'-Methoxy)benzotricyclo[7.2.1.$0^{2,8}$]dodecan-11-one (14). Following the procedure described above for oxidation of **(8)**, the hydroxy compound **(13)** (240 mg, 0.93 mmol) in acetone (8 mL) was oxidised with Jones reagent (0.8 mL) to afford the ketone **(14)** (220 mg, 92%) m.p. 125°C. Recrystallisation from ether-petroleum afforded an analytical sample m.p. 127°C; R_t 3.3 min (270°C); IR: 1740, 1600 cm^{-1}; ^1H NMR δ 1.66-3.12 (13H), 3.2-3.38 (H), 3.77 (s, 3H), 6.6-6.74 (2H), 6.96 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.42; H, 8.12.

1β,2,3β,3aβ,4,5,8,8aβ-Octahydro-6,7-(3'-methoxy)benzoazulene-1α,3α-dicarboxylic acid (15). A solution of the ketone **(14)** (220 mg, 0.86 mmol) in dry benzene (2 mL) was added to a stirred ice-cold suspension of NaH (50% oil dispersion) (960 mg, 20 mmol) (freed from adhering oil by washing with petroleum) followed by a drop of MeOH under N_2 atmosphere. After stirring for 30 min, ethyl formate (1 mL, 10 mmol) was added dropwise. After stirring at cold for 2 h the reaction mixture was left overnight. MeOH was added to the cold reaction mixture until effervescence stopped. The reaction

mixture was then extracted with Et_2O. The basic aqueous phase after acidification with 10% aq. HCl was extracted with Et_2O (3 x 20 mL) and the organic phase was washed with brine. Removal of solvent afforded a brown viscous liquid (180 mg). The brown mass was dissolved in 10% aqueous NaOH (14 mL) and was oxidised at rt by dropwise addition of H_2O_2 (10 mL, 30%) in two lots with stirring for 5 h. After acidification with 10% aqueous HCl, the reaction mixture was extracted with Et_2O and the organic extract was washed with brine and dried. Removal of solvent afforded the dicarboxylic acid (160 mg, 61%) which was crystallised from ether, m.p. 220°C; ^{1}H NMR (of dimethyl ester): δ 1.05-2.17 (4H), 2.28-3.1 (8H), 3.66 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 6.6-6.74 (2H), 6.98 (d, J = 8 Hz, H). Anal. calcd. for $C_{19}H_{24}O_5$ (dimethyl ester): C, 68.65; H, 7.28. Found: C, 69.09; H, 7.30. Following the above procedure, the ketone **(10)** (50 mg, 0.19 mmol) was transformed to the dicarboxylic acid **(15)** (35 mg, 59%), m.p. and m.m.p. with the dicarboxylic acid prepared from **(14)**, 220°C.

Baeyer-Villiger oxidation of the ketone (10) to the lactones (16) and (17). A solution of the ketone **(10)** (370 mg, 1.44 mmol) in CH_2Cl_2 (10 mL) was stirred with mCPBA (450 mg, 2.6 mmol) and $NaHCO_3$ (800 mg, 9.52 mmol) at rt for 24 h. The reaction mixture was successively washed with 10% aqueous Na_2SO_3 (3 x 10 mL), H_2O (2 x 10 mL), 5% aq. $NaHCO_3$ (3 x 10 mL) and brine (2 x 10 mL) and dried. Removal of solvents afforded a viscous liquid (340 mg, 86%) which was found to be a mixture of two lactones in a ratio of 1:3 by GC with retention times 5.28 and 5.84 min respectively. Purification of the crude lactone mixture by column chromatography [ethyl acetate-petroleum (2:3)] followed by fractional crystallisation from ether - dichloromethane mixture afforded first the lactone **16** (70 mg, 18%), m.p. 148°C; R_t 5.29 min (270°C). IR: 1750, 1730, 1600 cm^{-1}; ^{1}H NMR: δ 1.74-2.08 (6H), 2.2 (br s, H), 2.52-2.82 (4H), 2.96 (m, H), 3.16-3.4 (H), 3.8 (s, 3H), 4.7 (br s, H), 6.70 (m, 2H), 7.04 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.66; H, 7.69 and then the lactone **(17)** (190 mg, 50%), m.p. 103°C, R_t 5.94 min (270°C). IR: 1730, 1600 cm^{-1}; ^{1}H NMR: δ 1.76-2.12 (6H), 2.4 (br s, H), 2.56-2.78 (4H), 2.9-3.06 (H), 3.26 (dd, J = 3.8 and 14.9 Hz, H), 3.82 (s, 3H), 4.56 (s, H), 6.66-6.78 (m, 2H), 7.1 (d, J = 8 Hz, H). Anal. calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.96; H, 7.79.

Transformation of the lactone (16) to the dicarboxylic acid (15). The lactone **(16)** (60 mg, 0.22 mmol) was hydrolysed by stirring with a solution of KOH (50 mg, 0.89 mmol) in MeOH (1.5 mL) and H_2O (1.5 mL) for 12 h. The reaction mixture after dilution with water was extracted with Et_2O. The basic aqueous phase on acidification with cold dil. HCl was extracted with Et_2O to afford the hydroxy acid (60 mg, 93%), m.p. 157°C, which without further characterisation was oxidised in acetone (2 mL) solution with Jones reagent (0.5 mL) to afford the dicarboxylic acid **(15)** (50 mg, 83%), m.p. and m.m.p. with the acid prepared from the ketone **(10)**, 220°C.

1β,2,3β,3aβ,4,5,8,8aβ-Octahydro-1α-carbomethoxymethyl-3α-hydroxy-6,7-(3'-methoxy)benzoazulene (19). The lactone **(17)** (60 mg, 0.22 mL) was hydrolysed by stirring with a solution of KOH (50 mg, 0.89 mmol) in MeOH (1.5 mL) and H_2O (1.5 mL) for 12 h. The reaction mixture after dilution with water was extracted with Et_2O. The basic aqueous phase on acidification with cold dil. HCl was worked up (Et_2O) to afford a solid which was treated directly with excess ethereal diazomethane to furnish the hydroxy ester **(19)** (60 mg, 89%), m.p. 90-91°C. Recrystallisation from ether-petroleum furnished analytical sample, m.p. 91°C. IR: 3440, 1730, 1610 cm^{-1}; ^{1}H NMR: δ 1.08-2.18 (8H), 2.32-2.78 (6H), 2.94-3.06 (m, H), 3.64 (s, 3H), 3.78 (s, 3H), 6.64-6.78 (2H), 7.12 (d, J = 8 Hz, H). Anal. calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.94; H, 7.92.

1β,3aβ,4,5,8,8aβ-Hexahydro-1α-carbomethoxymethyl-6,7-(3'-methoxy)benzoazulen-3(2H)-one (20). Following the procedure described for oxidation of **(8)**, the hydroxy ester **(19)** (70 mg, 0.23 mmol) in acetone (2 mL) was oxidised with Jones reagent (0.25 mL) to afford the keto-ester **(20)** (60 mg, 90%) as a liquid which was purified by column chromatography [ether -petroleum ether (40-60°C) (4:1)]; IR: 1730, 1595 cm^{-1}; ^{1}H NMR: δ1.24-2.98 (12H), 3.25 (d, J = 12 Hz, H), 3.68 (s, 3H), 3.78 (s, 3H), 6.6-6.8 (2H), 7.16 (d, J = 8 Hz, H). Anal. calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.67; H, 7.46.

Baeyer-Villiger oxidation of the ketone (14) to the lactone (18). Following the previous procedure, a solution of the ketone **(14)** (500 mg, 1.95 mmol) in CH_2Cl_2 (40 mL) was treated with mCPBA (730 mg, 4.23 mmol) and $NaHCO_3$ (1.3 g) at rt for 48 h to afford, after chromatography, the lactone **(18)** [160 mg, 30%, based on recovered ketone

(30 mg)] m.p. 136°C. R_t 6.02 min (280°C); IR: 1720, 1590 cm^{-1}; ^1H NMR; δ 1.6-3.4 (13H), 3.78 (s, 3H), 4.8 (br s, H), 6.62-6.8 (2H), 6.98 (d, J = 8 Hz, H). Anal. calcd. for $C_{18}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.58; H, 7.76.

1β,2,3β,3aβ,4,5,8,8aβ-Octahydro-3α-carbomethoxymethyl-1α-hydroxy-6,7-(3'-methoxy)-benzoazulene (21). The lactone **(21)** (60 mg, 0.22 mmol) was hydrolysed as described for **17** by stirring with a solution of KOH (50 mg, 0.89 mmol) in MeOH (1.5 mL) and H_2O (1.5 mL) for 16 h at rt to afford after chromatography the hydroxy ester **(21)** (60 mg, 89%) as a liquid; IR: 3420, 1730, 1595 cm^{-1}; ^1H NMR: δ 1.08-3.10 (14H), 3.66 (s, 3H), 3.74 (s, 3H), 4.38 (m, H), 6.62-6.76 (2H), 7.1 (d, J = 8 Hz, H). Anal. calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.37; H, 7.82.

3β,3aβ,4,5,8,8aβ-Hexahydro-3α-carbomethoxymethyl-6,7-(3'-methoxy)benzoazulen-1(2H)-one (22). To a solution of oxalyl chloride (0.02 mL, 0.23 mmol) in CH_2Cl_2 (0.5 mL) at -60°C, was added DMSO (0.03 mL, 0.42 mmol) dissolved in CH_2Cl_2 (0.09 mL) with stirring under N_2 atmosphere. After 4 min at this temperature a solution of the hydroxy ester **(21)** (50 mg, 0.16 mmol) in CH_2Cl_2 (0.17 mL) was added. Stirring was continued for additional 15 min at -60°C and then Et_3N (0.16 mL, 1.15 mmol) was added, stirred for 5 min and allowed to attain rt. Water (2 mL) was added and the aqueous layer after separation from the organic layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extract were washed successively with aqueous HCl (1%), water, aqueous $NaHCO_3$ (5%), brine and dried. Removal of solvent followed by filtration through short column of neutral Al_2O_3 [ether-petroleum (1:1)] afforded the keto-ester **(22)** (45 mg, 91%) as a viscous liquid. IR: 1730, 1605 cm^{-1}; ^1H NMR: δ 1.3-3.3 (13H), 3.7 (s, 3H), 3.8 (s, 3H), 6.58-6.78 (2H), 7.18 (d, J = 8 Hz, H). Anal. calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.26; H, 7.37.

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