Tetrahedron Vol. 41, No. 2, pp. 349 to 355, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

BENZOCYCLOENONES AS DIENOPHILES. STEREOCONTROLLED SYNTHESIS OF BENZOHYDROPENTALENE AND BENZOHYDROAZULENE

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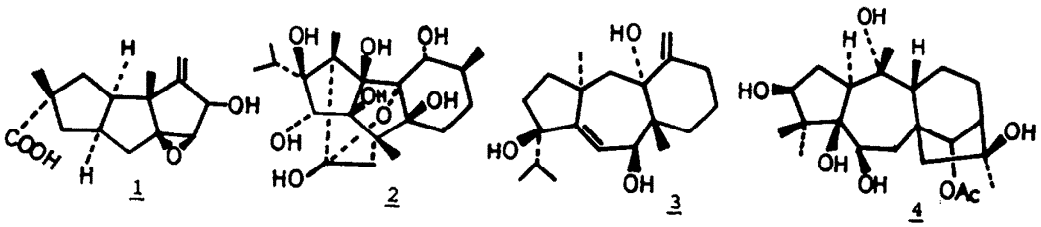
(*Received in UK* 4 *September* 1984)

Abstract - *A convenient route for the synthesis of benzohydropentalene* 14 *and benzohydroazulenes* 21 *and* 22 *is described for entry into a number of tri- and tetracyclic terpenoids.*

The structural complexities and diverse biological activities of several classes of natural products such as the sesquiterpene hirsutic acid[1] 1, the diterpenes ryanodol[2] 2, dolatriol[3] 3, graynotoxins[4] 4 and other related terpenoids have not only attracted the attention of synthetic chemists, but call for development of new synthetic strategies. Structurally, each of these molecules contains a fused 5-n-6 carbocyclic ring system (except 1 , 5-5-5 system). Our approach toward the synthesis of these molecules is based on the construction of 5-n-6 carbocyclic ring system at the initial stage in which the six membered ring is aromatic so that in the final stage the aromatic ring can be used for building up the rest of the molecule. The 5-5-5 ring system be, in principle, derivable from 5-5-6 ring system after reduction of aromatic ring followed by ring contraction[5]. In this paper we wish to report the result of our preliminary investigations leading to a general stereocontrolled route for the construction of 5-n-6 tricyclic ring systems e.g. benzohydropentalene[6] 14 (5-5-6) and benzohydroazulene[7] 21 (5-7-6) for entry into these classes of natural products.

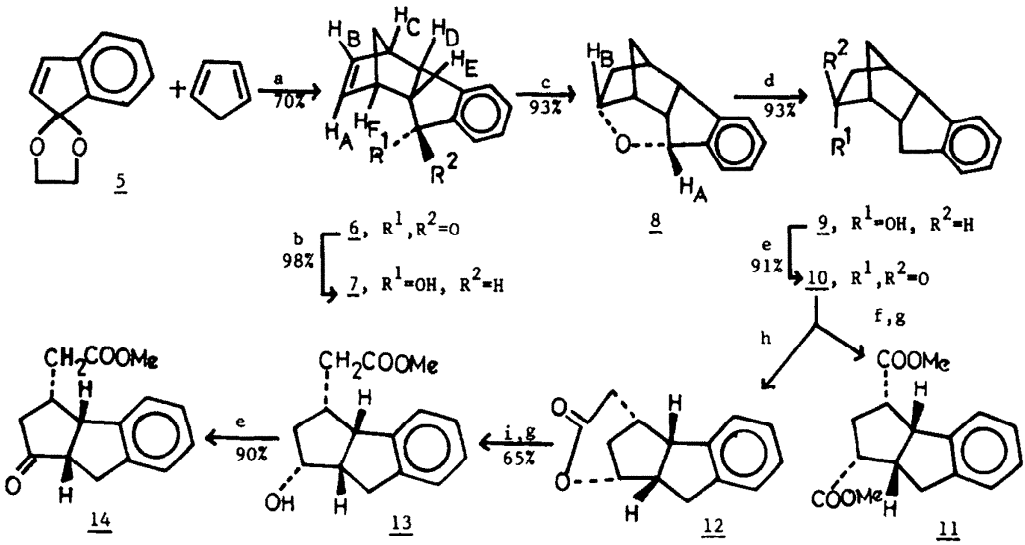


The key concept in our synthetic strategy was the deployment ofthe benzocycloenone, e.g. the ketal 5, the latent indenone, as the dienophile in a stereospecific Diels-Alder cycloaddition with cyclopentadiene to generate the norbornene derivative 6 as delineated in Scheme 1 for the synthesis of benzohydropentalene 14. Instead of normal cleavage of norbornene double bond leading to a cyclopentane ring[8] it was desired to achieve cleavage of the C_1-C_6 bond in 6, so that the ring residues would provide the substituents necessary for building up the natural products. This was achieved by regioselective oxidation of the double bond in 6 to provide the norbornanone 10 through an intramolecular process. Transformation of 10 to 14 was then easy.

RESULTS AND DISCUSSION

The indenone ketal 5[9], on treatment with excess cyclopentadiene in aqueous tetrahydrofuran in presence of trace HCl at room temperature afforded 6[10] (Scheme 1), m.p. 56°C in 70% yield as the only isolable product. The stereochemistry of the Diels-Alder adduct 6 can be readily assigned as endo from the coupling constant[11] of the exo protons H_D, H_E in ^1H NMR spectrum. The characteristic feature of 6 in ^1H NMR was the absorption of the two exo hydrogens H_E and H_D centered at δ 3.13 and 3.85 respectively as doublet of doublet with J_{DE} = 6.6 Hz, J_{EF}= 4.6 Hz and J_{CD}=4.4 Hz. The downfield chemical shift of H_A (δ 5.86) compared to that of H_B (δ 5.43) was

Scheme 1



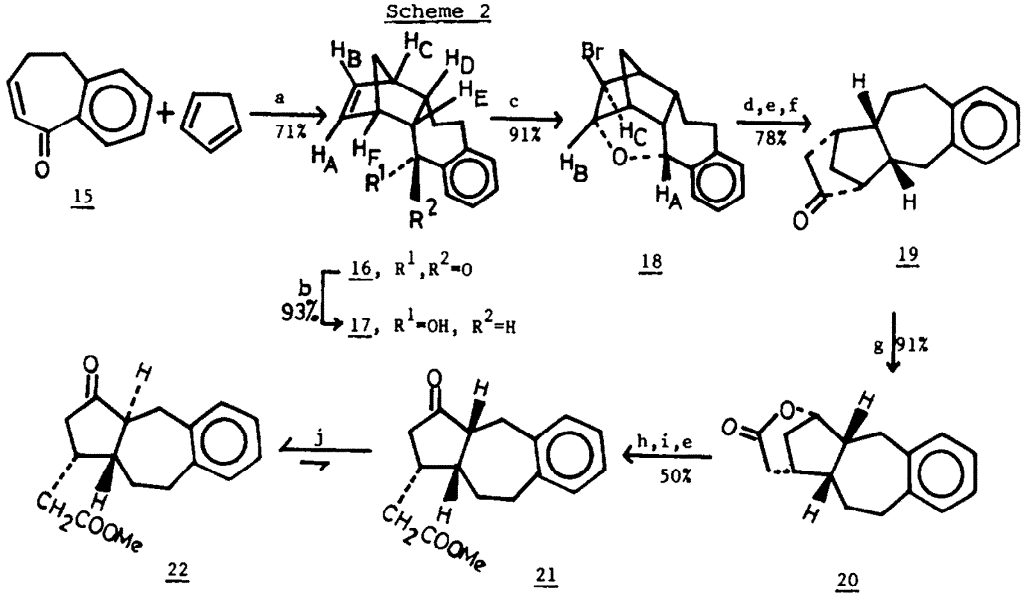
Reagents: a, THF-H_2O-HCl, r.t. b, $NaBH_4$-EtOH. c, $Hg(OAc)_2$-THF-H_2O, $NaBH_4$-NaOH-H_2O. d, H_2, 10% Pd/C-EtOH-$HClO_4$. e, Jones reagent. f, NaH-Bz-HCO_2Et, 30% H_2O_2-NaOH-H_2O. g, CH_2N_2-Et_2O. h, mCPBA-CH_2Cl_2-pTS. i, MeOH-H_2O-KOH.

expected as H_A falls under the deshielding cone of the carbonyl group. Reduction of the ketone 6 with sodium borohydride in ethanol afforded exclusively the syn-ol 7, m.p. 104°C in 98% yield, the hydride being delivered from the less hindered exo face. The syn orientation of the hydroxyl group in 7 was assured from the coupling constant[11] of the C-3 benzylic hydrogen which appeared as a triplet at δ 5.14 (J=8.9 Hz). Attempted oxymercuration of 7 followed by borohydride reduction of

C-Hg bond gave only the cyclic ether 8 as a colourless liquid in very high yield. Hydrogenolysis of 8 afforded the syn-ol 9 as a white crystalline solid which upon Jones oxidation gave the ketone 10, mp 82°C in 91% yield. The structure of the ketone 10 was established by its degradation to the dimethyl ester 11 through formylation followed by oxidation and esterification (CH_2N_2). Thus, the sequence 6 - 10 represents a novel 1 → 4 carbonyl group transposition. Finally, Baeyer-Villiger oxidation of 10 afforded a mixture of the lactone 12 and its regioisomer from which the hydroxy ester 13 was isolated in 65% yield after saponification and esterification followed by crystallisation. Jones oxidation of 13 gave the benzohydropentalene 14 incorporating the tricyclic ring system with three contiguous stereocentres as found in ryanodol 2.

Extension of this concept for the synthesis of benzohydroazulene 21 (Scheme 2) was next realised. The easily accessible benzocycloheptenone 15[12] on treatment with excess cyclopentadiene in anhydrous THF in presence of $AlCl_3$ as catalyst at 0-5°C afforded the ketone 16, mp 66°C in 71% yield as the only isolable product. The endo configuration was again based on the coupling constant of the exo protons H_D, H_E in ^1H NMR spectrum of 16, J_{DE}=10.3 Hz and J_{EF}=3 Hz. Unlike 6, sodium borohydride deduction of 16 afforded, a non separable mixture, of the syn-ol 17 and the anti-ol in 3:2 ratio. However, the syn-ol 17, mp 72°C was obtained exclusively by $LiAlH_4$ reduction of 16. Although the syn orientation of the hydroxyl group in 17 could not be assigned from ^1H NMR spectrum as the C-3 benzylic hydrogen in both the syn and anti-ol exhibited a doublet with identical coupling constant (J=3 Hz), it became evident from subsequent reaction for which a syn orientation of the hydroxyl group in 17 was absolutely necessary.

Scheme 2



Reagents: a, THF-$AlCl_3$, 5°C. b, $LiAlH_4$-Et_2O. c, NBS-DMSO. d, H_2, 10% Pd/C-EtOH-$HClO_4$. e, Jones reagent. f, Zn-HOAc. g, mCPBA-CH_2Cl_2-pTS. h, MeOH-KOH-H_2O. i, CH_2N_2-Et_2O. j, NaOMe-MeOH, Δ.

Oxymercuration of 17 afforded a mixture of diols. However, 17 on treatment with NBS-DMSO underwent smooth bromocyclization to produce the bromo ether 18, mp 98°C in 91% yield. Hydrogenolysis of 18 to the corresponding

bromohydrin followed by Jones oxidation and subsequent Zn-HOAc debromination afforded the solid ketone 19 in 78% overall yield from 18, 19 gave a single lactone 20. Transformation of 20 to the ketone 21 was achieved in 50% overall yield by saponification, esterification and Jones oxidation. Treatment of 21 with a large excess of NaOMe in MeOH afforded an equilibrium mixture of 21 and 22 in a ratio of ca 30:70. The benzohydroazulenes 21 and 22, thus obtained, incorporates the tricyclic skeleton of the antitumor diterpene dolatriol 3 and graynotoxin-I 4.

To conclude, the reaction sequence described in Scheme 1 and Scheme 2 amounts to three carbon attachment to a bicyclic enone leading to a simple cyclopentannulation[1] approach. Application of the ideas delineated here for the synthesis of a tricyclopentanoid and a dolastane diterpene is being actively pursued and will be reported in due course.

EXPERIMENTAL

Compounds described here are racemic mixtures. Melting points were determined for samples in open capillary tubes in a sulphuric acid bath. IR spectra were recorded on Perkin-Elmer model 298 in KBr pellet. UV spectra were recorded on a Beckman DU spectrophotometer for solutions in 95% ethanol. ^{1}H NMR spectra were recorded at 60 MHz and 200 MHz on Varian Associates models T-60A and XL-200 respectively with TMS as internal standard. Microanalyses were performed by Mr. P.P. Bhattacharyya of this laboratory. The procedure for "usual work-up" involved extraction of organic matter with a water-immisicible solvent (3-4 times), washing of the extract with brine, and drying with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the material. Petroleum and light petroleum refer to fractions boiling in the ranges 60-80° and 40-60°C, respectively. Column chromatography was performed on SiO_2 (60-120 mesh).

endo-4,5-Benzotricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (6). To a magnetically stirred ice-cold solution of the indenone ketal 5[9] (1.49 g, 8.56 mmol) in THF (8 mL) containing freshly distilled cyclopentadiene (8 mL), was added H_2O (6 mL) and conc. HCl (0.07 mL). The flask was stoppered and the stirring at room temperature was continued for 16-18 h until disappearance of the ketal 5 in TLC. The reaction mixture was diluted with Et_2O (50 mL) and washed with 5% aq. $NaHCO_3$ solution, brine and dried. Removal of solvents under reduced pressure afforded a yellow oil which after chromatography through a column of SiO_2 afforded a white crystalline solid 6 (1.18 g, 70%). Recrystallisation from ether-petroleum furnished a pure sample, m.p. 56°C; UV λmax 247 and 290 nm (log ε 4.19 and 3.49); IR 1700 and 1600 cm^{-1}; ^{1}H NMR (200 MHz) ($CDCl_3$) δ 1.68-1.79 (m,2H), 3.13 (dd,H_E, J_{DE}=6.6 Hz, J_{EF}=4.6 Hz), 3.22 (br s,H_C), 3.36 (br s,H_F), 3.85 (dd,H_D, J_{DE}=6.6 Hz, J_{CD}=4.4 Hz), 5.43 (dd,H_B, J_{AB}= 5.6 Hz, J_{BC}= 3 Hz), 5.86 (dd, H_A, J_{AB}=5.6 Hz, J_{AF}= 3 Hz), and 7.21-7.56 (m,4H).

endo, syn-4,5-Benzotricyclo[5.2.1.0^{2,6}]dec-8-ene-3-ol (7). A solution of the ketone (6) (420 mg, 2.1 mmol) in EtOH (25 mL) was stirred magnetically with $NaBH_4$ (250 mg, 7 mmol) under N_2 atmosphere at room temperature for 19-20 hrs. The residue after removal of the alcohol under reduced pressure was treated with 1% aq. NaOH solution (20 mL). Usual work up of the alkaline solution with Et_2O afforded a white solid (7) (415 mg, 98%), mp 99-102°C. Recrystallisation from ether-light petroleum furnished a pure sample, mp 104°C; IR 3500, 1635, 1600 cm-1, ^{1}H NMR (200 MHz) ($CDCl_3$) δ 1.53-1.64 (m,2H), 1.70 (d,-OH, J=9 Hz), 3.09-3.26 (m,3H), 3.79 (dd,H_D, J_{DE}= 8.2 Hz, J_{DC}=4.4 Hz), 5.14 [t, CH(OH), J=8.9 Hz], 5.49 (dd, H_B, J_{AB}=5.5 Hz, J_{BC}=3 Hz), 6.01 (dd, H_A, J_{AB}=5.5 Hz, J_{AF}=2.5 Hz), and 7.08-7.27 (m,4H), Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.94; H, 7.19.

Oxymercuration of 7. endo-4,5-Benzo-3,9-epoxytricyclo[5.2.1.0^{2,6}]decane (8). A solution of 7 (850 mg, 4.29 mmol) in THF (9 mL) was added to a magnetically stirred yellow suspension of $Hg(OAc)_2$ (2.85 g, 8.93 mmol) in H_2O (12 mL) and THF (12 mL). The flask was stoppered and stirred at rt for 24 h, 3M aq. NaOH (12 mL) was then added followed by addition of a solution of $NaBH_4$ (250 mg, 6.61 mmol) in 3M aq. NaOH (10 mL). After stirring for 30 min, the reaction mixture was saturated with NaCl and worked up in the usual way with Et_2O to afford a liquid which on sublimation afforded 8 (790 mg, 93%) as a colourless liquid, bp 114°C (bath temp.) (0.5 mm Hg); ^{1}H NMR (60 MHz) (CCl_4) δ 0.65-1.98 (m,4H), 2.21 (brs,1H), 2.61 (brt, J=5 Hz,1H), 2.95-3.51 (m,2H), 4.25 (dd,J=8 and 5 Hz, H_B), 4.95 (d,J=6 Hz, H_A) and 6.93-7.18 (m,4H). Anal Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 85.19; H, 7.10.

endo, syn-4,5-Benzotricyclo[5.2.1.0^{2,6}]decane-9-ol (9). Hydrogenolysis of the compound (8) (790mg, 4 mmol) was accomplished in EtOH (15 mL) using 10% Pd/C (150 mg) in presence of 70% $HClO_4$ (.09 mL) for 7 h. After neutralisation of the acid with powdered $NaHCO_3$, the reaction mixture was filtered throught a short column of SiO_2 to remove the catalyst. Removal of solvent afforded a white solid (9) (740 mg, 93%), mp 122-126°C. Recrystallisation from ether-light petroleum furnished the pure compound, mp 126°C; IR 3220 cm^{-1}; ^1H NMR (60 MHz)(CCl_4) δ 0.46-1.23 (m,3H), 1.46-1.53 (m,2H), 2.33-2.6 (m,2H), 2.73-3.63 (m,4H), 3.99-4.3 (m,-CH-OH), 7.1 (s,4H). Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found : C, 84.08; H, 8.41.

endo-4,5-Benzotricyclo[5.2.1.0^{2,6}]decan-9-one (10). To a magnetically stirred cold (5-10°C) solution of 9 (740 mg, 3.7 mmol) in acetone (20 mL), Jones reagent (2 mL) was added dropwise until the colour of the reagent persisted. After stirring for additional 30 min the reaction mixture was poured into water (60 mL). Usual work up with Et_2O afforded a solid 10 (670 mg, 91%), mp 77-81°C. Recrystallisation from petroleum furnished analytical sample, mp 82°C; IR 1730 cm^{-1}; ^1H NMR (60 MHz)(CCl_4) δ 1.0-1.6 (m,2H), 1.83 (m,2H), 2.46-3.1 (m,5H), 3.70-3.91 (m,1H), and 7.0 (s,4H). Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found : C, 84.97; H, 7.35.

Dimethyl-4,5-benzo-1,2,3,3aβ,6,6aβ-hexahydropentalene-1α,3α-dicarboxylate (11). A solution of the ketone 10 (200 mg, 1 mmol) in dry benzene (2 mL) was added to a stirred ice cold suspension of NaH (50% oil dispersion) (1.4 g, 29 mmol) (freed from adhereing oil by washing with petroleum) followed by a drop of MeOH under N_2 atmosphere. After stirring for 30 min, HCO_2Et (1 mL, 10 mmol) was added dropwise. The reaction mixture was left overnight after stirring at cold for 2 h. MeOH was added to cold reaction mixture until effervescences stopped. This was extracted with Et_2O to remove any unreacted material. The usual work up with Et_2O of the basic aqueous part after acidification (10% aq. HCl) afforded a brown viscous liquid (180 mg).

The brown mass was dissolved in 10% aq. NaOH (14 mL) and was oxidised at rt by adding H_2O_2 (10 mL, 30%) in two lots with stirring for 5 h. Acidification of the reaction mixture followed by usual work up with Et_2O afforded the solid dicarboxylic acid, which on treatment with ethereal diazomethane afforded the dimethyl ester 11 (140 mg, 50%), mp 90°C; IR 1735 cm^{-1}; ^1H NMR (60 MHz) (CCl_4) δ 1.76-3.18 (m,7H), 3.43 (s,3H,CO_2CH_3), 3.66 (s,3H,CO_2CH_3), 3.90-4.06 (m,1H), 6.90-7.06 (m,4H). Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found : C, 70.10; H, 6.50.

Baeyer-Villiger oxidation of the ketone 10 to the lactone 12. A solution of the ketone 10 (630 mg, 3.18 mmol) in CH_2Cl_2 (50 mL) was stirred with mCPBA (2.7 g, 15.6 mmol) and p-TsOH (480 mg, 2.52 mmol) at rt for 40 h. The reaction mixture was successively washed with 5% aq. 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 (Na_2SO_4). Removal of solvent afforded a solid (600 mg, 88%), mp 134-153°C. Repeated crystallisation afforded the lactone 12, in ca.35% Yield, mp 171°C; IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR (200 MHz) ($CDCl_3$) δ 1.97-3.31 (m,8H), 4.02 (brt,1H,J=8 Hz), 4.83 (m,1H), 7.15-7.29 (m,4H). Anal. Calcd. for $C_{14}H_{14}O_2$: C,78.48; H, 6.59. Found : C, 78.17; H, 6.75.

4,5-Benzo-3α-(carbomethoxy methyl)-1,2,3,3aβ,6,6aβ-hexahydropentalene-1α-ol (13). The crude lactone mixture (600 mg, 2.8 mmol) obtained from 10 was hydrolysed by refluxing for 3 h with 2.5% aq. ethanolic KOH (40 mL) under N_2 atmosphere. The reaction mixture after dilution with H_2O was extracted with Et_2O to remove unhydrolysed material. The basic aqueous part on acidification was extracted with Et_2O in the usual way to afford solid hydroxy acid which was directly esterified with ethereal diazomethane. Crystallisation from ether-light petroleum afforded the pure hydroxy ester 13 (450 mg, 65%), mp 100°C; IR 3190 and 1730 cm^{-1}; ^1H NMR (60 MHz) ($CDCl_3$) δ 1.11-3.33 (m,9H), 3.66 (s,3H,CO_2CH_3), 3.76 (brs,1H), 4.15-4.55 (m,1 H), and 7.15-6.96 (m,4H). Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.32. Found : C, 72.99; H, 7.66.

4,5-Benzo-3α-(carbomethoxy methyl)-2,3aβ,6,6aβ-tetrahydropentalen-1-one (14). To a magnetically stirred cold (5-10°C) solution of (13) (100 mg, 0.406 mmol) in acetone (3 mL), Jones reagent (0.4 mL) was added dropwise until the colour of the reagent persisted. After stirring for additional 1 h, the reaction mixture was poured into water (9 mL). Usual work up with Et_2O afforded a liquid 14 (90 mg, 90%). IR (film) 1735 cm^{-1}; ^1H NMR (60 MHz) (CCl_4) δ 1.48-3.08 (m,8H), 3.68 (s,3H,CO_2CH_3), 4.0 (t,1H,J=6 Hz), and 7.1 (brs,4H). Semicarbazone, mp 163°C. Anal. Calcd. for $C_{16}H_{19}O_3N_3$: C, 63.77; H, 6.36. Found : C, 63.97; H, 6.66.

endo-4,5-Benzotricyclo[7.2.1.0^{2,8}]dodec-11-en-3-one (16). Anhydrous $AlCl_3$ (1 g, 7.5 mmol) was added to a stirred ice cold solution of benzocycloheptenone[12] 15 (2.7g,17 mmol) in THF (22 mL) and stirring was continued for 15 min when all $AlCl_3$ went into solution. Cyclopentadiene (ca 15 mL) was directly distilled into this mixture. The

flask was then stoppered and stirring was continued at 0-5°C for 15-16 hrs until the disappearance of 15 in TLC. The reaction mixture was poured into water and worked up in the usual way with Et_2O to afford a light brown liquid. Chromatography of this liquid through SiO_2 afforded a white solid (2.7 g, 71%). Recrystallisation from Et_2O-petroleum afforded a pure sample of 16, mp 66°C; IR 1665 and 1600 cm^{-1}; UV λ_{max} 238 and 282 nm (log ε 3.95 and 3.08); ^1H NMR (200 MHz) ($CDCl_3$) δ 1.09-1.27 (m,1H), 1.33 (d,1H,J=8.2 Hz), 1.49 (d,1H,J=8.3 Hz), 1.99 (brd,1H), 2.55 (complex m,1H), 2.83 (brs,1H), 3.13-3.18 (m,3H), 3.41 (dd,H_E,J_{DE}= 10.3 Hz, J_{EF}=3 Hz), 6.04 (dd, H_B, J_{AB}=5.4 Hz, J_{BC}=2.8 Hz), 6.54 (dd,H_A, J_{AB}= 5.4 Hz, J_{AF}=2.8 Hz), and 7.18-7.52 (m,4H). Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found : C, 86.00; H, 7.29.

endo, syn-4,5-Benzotricyclo[7.2.1.0^{2,8}]dodec-11-en-3-ol (17). A solution of 16 (500 mg, 2 mmol) in anhydrous Et_2O (30 mL) was added dropwise to a refluxing suspension of $LiAlH_4$ (150 mg, 4 mmol) in dry Et_2O (50 mL). After refluxing for 3.5 h, the reaction mixture was decomposed by adding saturated aq. Na_2SO_4 solution at cold. The solid mass was separated by filtration. The filtrate after drying (Na_2SO_4) was concentrated to afford a solid 17 (470 mg, 93%). Recrystallisation from petroleum gave the analytical sample, mp 72°C; IR 3420, 1650 and 1595 cm^{-1}; ^1H NMR (60 MHz) (CCl_4) δ 1.28-3.03 (m,11H), 4.68 (d,1H,J=3 Hz), 5.98 (m,2H), and 6.96 (brs,4H). Anal. Calcd. for $C_{16}H_{18}O$: C, 84.81; H, 8.02. Found : C, 85.10; H, 8.23.

endo-10-Bromo-4,5-benzo-3,11-epoxytricyclo[7.2.1.0^{2,8}]dodecane (18). To a magnetically stirred solution of 17 (450 mg, 2 mmol) in dry DMSO (6 mL), NBS (360 mg, 2 mmol) was added portionwise and stirring was continued for additional 2 h. The reaction mixture was poured into water and worked up with Et_2O in the usual way to afford a solid 18 (550 mg, 91%). Recrystallisation from ether-petroleum afforded a pure sample, mp 98°C; ^1H NMR (60 MHz) (CCl_4) δ 1.58-2.85 (m,10H), 4.05 (d,H_B,J=2 Hz), 4.44 (d,H_A, J=5 Hz), 4.68 (d,H_C,J=2 Hz), and 6.8-7.13 (m,4H); m/z 305 (M^+).

endo-4,5-Benzotricyclo[7.2.1.0^{2,8}]dodecan-11-one (19). Hydrogenolysis of 18 (190 mg, 0.62 mmol) in EtOH (5 mL) was carried out according to the procedure described for 8 using 10% Pd/C (60 mg) in presence of 70% $HClO_4$ (.05 mL) to afford the corresponding bromohydrin (175 mg). A solution of this bromohydrin in acetone (4 mL) was directly oxidised with Jones reagent (0.4 mL) to afford after usual work up the corresponding bromoketone (150 mg), mp 130-132°C; IR 1750 cm^{-1}. Debromination of the bromoketone was carried out by refluxing in glacial HOAc (5 mL) with Zn dust (500 mg, 7.5 mmol) for 4 h. The reaction mixture was diluted with Et_2O and the solid material was filtered off. The ethereal layer was washed with H_2O, saturated aq. Na_2CO_3 and dried (Na_2SO_4). The solvent was removed and the residue was filtered through short column of neutral Al_2O_3 with Et_2O-petroleum as eluent to afford the solid ketone 19 (87 mg, 78%). Crystallisation from petroleum afforded the pure 19, mp 73°C; IR 1740 cm^{-1}; ^1H NMR (60 MHz) ($CDCl_3$). δ 1.68-2.46 (m,12H), 2.85-3.16 (m,2H), and 6.8-6.96 (m,4H). Anal. Calcd. for $C_{16}H_{18}O$: C, 84.81; H, 8.02. Found : C, 84.91; H, 8.14.

Baeyer-Villiger oxidation of 19 to 20. Baeyer-Villiger oxidation of the ketone 19 (200 mg, 0.88 mmol) in CH_2Cl_2 (11 mL) was carried out according to the procedure described for 10 using mCPBA (760 mg, 4.4 mmol) and p-TsOH (40 mg, 0.21 mmol) for 48 h to afford the lactone 20 (195 mg, 91%), mp 98-100°C. Recrystallisation from Et_2O-petroleum gave the pure lactone 20, mp 100°C; IR ($CHCl_3$) 1745 cm^{-1}; ^1H NMR (200 MHz) ($CDCl_3$) δ 1.75-3.44 (m,13H), 4.75 (brs,1H), and 6.98-7.10 (m,4H). Anal. Calcd. for $C_{16}H_8O_2$: C, 79.31; H, 7.49. Found: C, 79.15; H, 7.54.

6,7-Benzo-3α-(carbomethoxy methyl)-2,3,3aβ,4,5,8aβ-hexahydroazulen-1-one (21). The lactone 20 (185 mg, 0.74 mmol) was hydrolysed by refluxing with 2.5% aq. ethanolic KOH (10 mL) for 3 h. Work up of the reaction mixture as described previously afforded a liquid acid which was esterified with ethereal diazomethane to give hydroxy ester as a colourless liquid (110 mg); ^1H NMR (60 MHz) (CCl_4) δ 1.66-3.0 (m,14H), 3.56 (s,3H), 4.08 (brs,1H), 6.96 (s,4H). The crude hydroxy ester in acetone (4 mL) was oxidised with Jones reagent (0.35 mL) according to the procedure described for 13 to afford the keto ester 21 (97 mg, 50%) as a thick liquid; IR (film) 1735 cm^{-1}; ^1H NMR (200 MHz) ($CDCl_3$) δ 1.65-2.00 (m,3H), 2.31-2.47 (m,3H), 2.6-2.88 (m,6H), 3.13 (d,1H,J=4 Hz), 3.72 (s,3H), and 7.02-7.34 (m,4H). Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.91; H, 7.20.

Equilibriation of 21 with NaOMe-MeOH. The keto ester 21 (53 mg, 0.194 mmol) was refluxed with 2% NaOMe in MeOH (2 mL, 0.74 mmol) under N_2 atmosphere for 2 h. The reaction mixture on dilution with H_2O was extracted with Et_2O. No material was obtained after removal of Et_2O. The basic aqueous part after acidification (HCl) was extracted with Et_2O. The residue after removal of Et_2O was treated with ethereal diazomethane to afford 38 mg (72%) of a mixture of 21 and 22 in the ratio of 30:70; ^1H NMR (200 MHz) ($CDCl_3$) of 22 (from the equilibrium mixture δ 3.26 (d,1H,J=14 Hz) and 3.67 (s,3H).

Acknowledgement: We thank Professor U.R. Ghatak of this department for valuable advice and D.S.T. for providing a Varian XL-200 NMR Spectrometer under grant No. 23(3p-8)/81-STP/II.

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