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STEREOCONTROLLED SYNTHESIS OF DIHYDROPSEUDOCLOVENE-B

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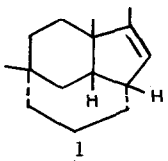
Summary: Aryl participated intramolecular cyclisation of the bromophenol 16 yielded the dienone 17 which was converted into dihydropseudoclovene-B (7) *via* a stereocontrolled route.

Recent reports on the synthesis of the tricyclic sesquiterpene artifacts isoclovene (1)[1,2] and clovene (2)[3] prompted us to disclose a stereocontrolled synthesis of dihydropseudoclovene-B (7) which we accomplished recently in our laboratory. Dehydration of caryolan-1-ol (4) with polyphosphoric acid yields a number of rearranged products from which four sesquiterpene hydrocarbons isoclovene (1), pseudoclovene-A (5), pseudoclovene-B (6) and epi-clovene (3) were isolated and characterised[4]. The structure 6 of pseudoclovene-B was confirmed through X-ray crystallographic analysis[5] of the corresponding dibromide. For entry into the bridged tricyclic framework of pseudoclovene-B, we synthesised earlier the tricyclic dienedione 9[6] involving acid induced intramolecular cyclisation of the diazomethyl ketone 8. However, since a carbonyl group in ring C is not advantageous for further elaboration of 9, we have now



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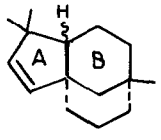
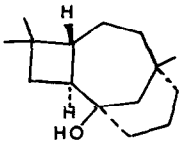


2, A/B-cis
3, A/B-trans



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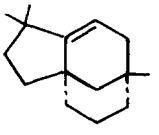

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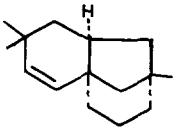

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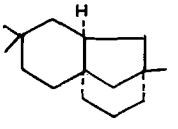

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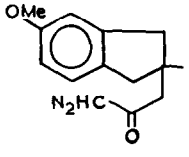

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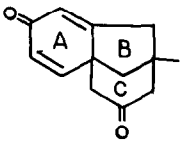

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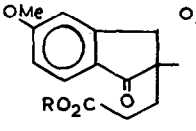
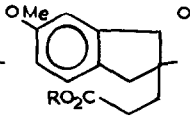
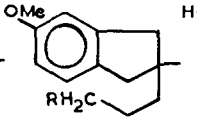


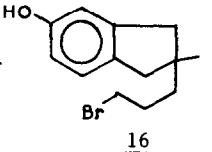
10, R=Me
11, R=H



12, R=H
13, R=Me



14, R=OH
15, R=Br



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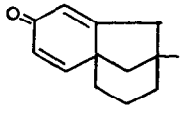

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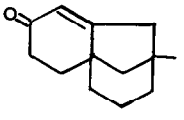

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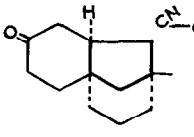

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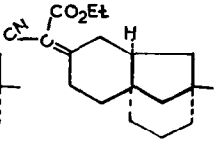

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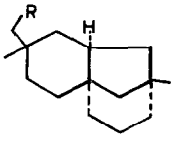
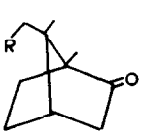


21, R=CN
22, R=CO_2H
23, R=I



24, R=Br
25, R=H

synthesised the dienone 17 utilising aryl participated intramolecular cyclisation of the bromophenol 16 as the key step. Elaboration of the dienone 17 to dihydropseudoclovene-B (7) has been successfully carried out.

Michael reaction of 5-methoxy-2-methyl-indan-1-one with methyl acrylate furnished the keto-ester 10 in 78% yield which on base hydrolysis yielded the corresponding acid 11 (85%), m.p. 103-104°. Reduction of 11 with $NaBH_4$ in aqueous NaOH followed by hydrogenolysis (H_2, 10% Pd on carbon) of the crude product in AcOH afforded the acid 12 (85%), m.p. 66-67°. The corresponding methyl ester 13 was reduced with $LiAlH_4$ and the resulting alcohol 14 (90%) on treatment with PBr_3 was converted into the bromide 15 in 74% yield; ^{1}H-NMR (CCl_4):δ 1.1 (s,3H), 1.37-2.07 (m,4H), 2.67 (bs,4H), 3.32 (t,2H,J=6Hz), 3.73 (s,3H), 6.43-6.67 (m,2H), 6.96 (d,1H, J=8Hz). Demethylation of 15 with BBr_3 in CH_2Cl_2 furnished the bromophenol 16 (82%), m.p.61-62° which was subjected to intramolecular cyclisation (Ar_1-6) with t-BuOK in t-BuOH according to the procedure of Winstein[7]. The dienone 17 was isolated as the only neutral product of the reaction in 64% yield, b.p.110° (bath temp)/0.4 mm; UV (EtOH): 245 nm (log ε 4.16); IR(Film): 1658,1630cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.15 (s,3H), 1.37-2.83 (m,10H), 6.02 (d,1H,J=1.5Hz), 6.07 (d of d,1H,J=10,1.5Hz), 6.93 (d,1H,J=10Hz).

Selective reduction of the disubstituted double bond of 17 furnished the enone 18 [δ ($CDCl_3$): 1.12 (s,3H), 5.72 (t,1H, small allylic coupling)] which was subsequently reduced with Li in liquid ammonia to afford the saturated ketone 19 in 81% overall yield; IR (Film): 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 0.73-2.35 (m,17H), 1.02 (s,3H). The ketone 19 was found homogeneous on TLC and VPC analyses. The stereochemistry at the A/B ring juncture of 19 has been assigned cis since metal-ammonia reduction of closely related enones had generated exclusively cis stereochemistry at 6/5 ring junctures[8,9]. The ketone 19 was condensed with ethyl cyanoacetate in the presence of NH_4OAc to provide the unsaturated cyano-ester 20 (88%). Conjugate addition of CH_3MgI to 20 followed by decarbethoxylation (LiCl, DMSO at 180° for 5 hr) of the resulting product furnished the nitrile 21 in 62% yield (two steps); ^{1}H-NMR ($CDCl_3$): δ 0.71-1.90 (m,17H), 1.0 (s,3H), 1.07 (s,3H), 2.23 (s,2H). Hydrolysis of the nitrile afforded the crystalline acid 22 (89%), m.p. 89-90° which on treatment with $Pb(OAc)_4$ and I_2[10] in the presence of light was smoothly converted into the primary iodide 23 [^{1}H-NMR (CCl_4): δ 0.69-2.0 (m,17H), 0.95 (s,3H), 0.99 (s,3H), 3.09 (s,2H)]. Davis et al.[11] carried out reduction of the bromide 24 with Zn-dust and AcOH to furnish the compound 25 in 71% yield. Following the same procedure the iodide 23 was converted into dihydropseudoclovene-B (7) in 30% (based on 22) yield; b.p. 100° (bath temp)/3 mm; ^{1}H-NMR ($CDCl_3$): δ 0.67-2.0 (m,17H), 0.85 (s,3H), 0.90 (s,3H), 1.02 (s,3H).

A total synthesis of pseudoclovene-B (6) from 19 is under way.

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