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SYNTHESIS OF BRIDGED TETRACYCLIC SYSTEMS RELATED TO DITERPENES THROUGH ACID-INDUCED INTRAMOLECULAR CYCLISATION OF DIAZOMETHYL KETONES

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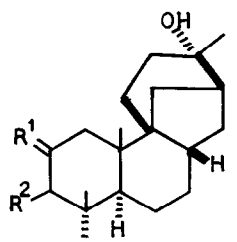
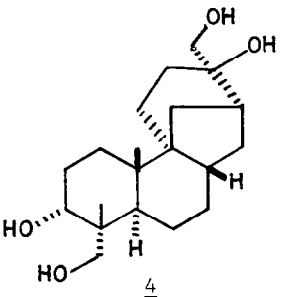
Summary The tetracyclic bridged-ring enones 5, 6 and 23 have been prepared through acid-catalysed intramolecular cyclisation of the diazomethyl ketones 11, 16 and 22 respectively for entry into the ring system of aphidicolin (4) and related diterpenes

Several tetracyclic diterpenes, e g stemodinone (1), 2-desoxystemodinone (2), maritimol (3) and aphidicolin (4) incorporate basic tetracyclo[10 3 1 $0^{1,10}$ $0^{2,7}$]hexadecane framework and have attracted[1,2] much attention of synthetic chemists in recent years Construction of the bicyclo[3 2 1]octane parts (i e rings C and D) of the diterpenes has been accomplished by van Tamelen et al [1,2b] and Kelly et al [2c] through skeletal rearrangement of suitable bicyclo[2 2 2]octanes For synthetic entry into the basic tetracyclic framework of aphidicolin (4) and related diterpenes, we have conveniently synthesised the enones 5, 6 and 23 through acid-catalysed intramolecular cyclisation of the diazomethyl ketones 11, 16 and 22 respectively The rings C and D of 5 and 6 are bicyclo[3 2 1]octanes while 23 incorporates a bicyclo[2 2 2]octane



1, R^1=O, R^2=H
2, R^1=H_2, R^2=H
3, R^1=H_2, R^2=OH



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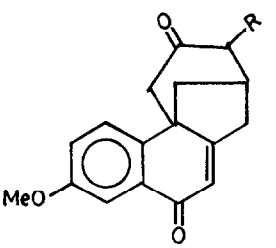
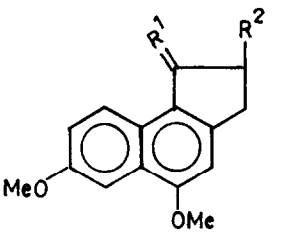
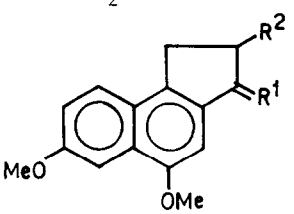


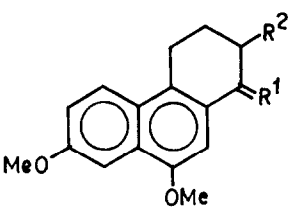
5, R = H
6, R = Me



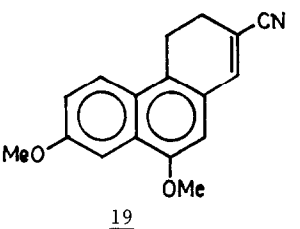
7, R^1=O, R^2=H
8, R^1=O, R^2=CO_2Et
9, R^1=O, R^2=CH_2CO_2H
10, R^1=H_2, R^2=CH_2CO_2H
11, R^1=H_2, R^2=CH_2COCHN_2



12, R^1=O, R^2=H
13, R^1=O, R^2=CO_2Et
14, R^1=O, R^2=$CHMeCO_2H$
15, R^1=H_2, R^2=$CHMeCO_2H$
16, R^1=H_2, R^2=$CHMeCOCHN_2$



17, R^1=O, R^2=H
18, R^1=O, R^2=CN
20, R^1=H_2, R^2=CN
21, R^1=H_2, R^2=CO_2H
22, R^1=H_2, R^2=$COCHN_2$



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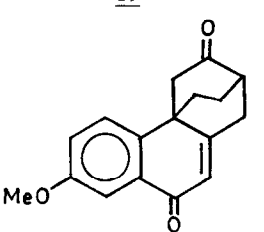

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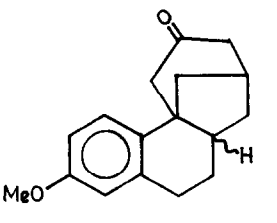

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The benzindanones 7[3] and 12[4] were prepared according to reported procedures The ketone 7 was treated with diethyl carbonate in the presence of NaH to give the β-ketoester 8,m p 156-157° in 85% yield Alkylation of the sodio-enolate of 8 with ethyl bromoacetate in DME afforded an alkylated product (88%),m p 140-141°,which on acid hydrolysis furnished the keto-acid 9,m p 219-220° in 80% yield Similarly, alkylation of the β-ketoester 13,m p 128° with ethyl α-bromopropionate and subsequent hydrolysis of the product (m p 146-148°) furnished the keto-acid 14 (71% from 13) as a diastereoisomeric mixture,m p 206-210°(d) Removal of the carbonyl group from 9 and 14 was accomplished through reduction with $NaBH_4$ in aqueous NaOH followed by catalytic hydrogenation (10% Pd on carbon) in AcOH The acids 10,m p 157-158°, and 15,m p 154-158°, were thus obtained in 84% and 82% yields respectively The diazoketone 11, prepared from the acid chloride of 10 with CH_2N_2,underwent intramolecular cyclisation on treatment with trifluoroacetic acid (TFA) in CH_2Cl_2 at -25° to afford the enone 5 in 50% yield,m p 174-175°, IR(KBr) 1707,1655,1630,1605 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1 9-3 03(m,9H) 3 89(s,3H), 6 31(t,1H,small allylic coupling), 7 12(d of d,1H,J=8, 3 Hz), 7 4(d,1H,J=8 Hz), 7 64(d,1H, J=3 Hz) Similar treatment of 16 afforded 6 (52%),m p 180-181°, IR(KBr) 1708,1658,1638,1600 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1 13 (d,1H,J=6 5 Hz), 1 88-3 02(m,8H), 3 86(s,3H), 6 24(t,1H), 7 08(d of d,1H,J=8, 2 5 Hz), 7 41 (d,1H,J=8 Hz), 7 59(d,1H,J=2 5 Hz)

For the synthesis of the enone 23, the ketone 17[5] was converted into the β-ketonitrile 18, m p 181-182° in 78% yield following the isoxazole procedure[6] of Johnson and coworkers Reduction of 18 with $NaBH_4$ and subsequent dehydration of the crude hydroxy-nitrile with toluene-p-sulphonic acid in benzene afforded the unsaturated nitrile 19 (80%),m p 164-165° Reduction of 19 with Mg and MeOH and subsequent hydrolysis of the saturated nitrile 20 (m p 176°) with 20% methanolic KOH furnished 21,m p 220-221° in 74% overall yield (two steps) The diazoketone 22, prepared from the acid chloride of 21, was treated with TFA in CH_2Cl_2 at -20° to afford the the enone 23 (25%),m p 182-183°, IR($CHCl_3$) 1725, 1658,1630,1605 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1 8-3 2 (m,9H), 3 91(s,3H), 6 46(t,1H), 7 17(d of d,1H,J=8,3 Hz 7 42(d,1H,J=8 Hz), 7 69(d,1H,J=3 Hz) The splitting pattern and relative chemical shifts of the aromatic hydrogens of the enones are similar to those reported[7] for a related system In order to obtain both B/C-trans and B/C-cis fused products we are currently investigating reductions of the enones under different conditions Catalytic hydrogenation (10% Pd on carbon, 3 moles of H_2) of 5 proceeded stereoselectively to yield a pure isomer of 24 in 76% yield, m p 120-121°, IR($CHCl_3$) 1706, 1605,1570 cm^{-1}, ^{1}H-NMR ($CDCl_3$) 0 86-3 1(m,14H), 3 77(s,3H), 6 55-6 79(m,2H), 7 1(d,1H,J=8 Hz) To ascertain the stereochemistry of the B/C ring juncture, X-ray analysis of 24 is under way

References

1 For aphidicolin syntheses, see E E van Tamelen, S R Zawacky, R K Russell and J G Carlson,J Am Chem Soc , 105, 142 (1983) and references cited therein

2 For the syntheses of stemodia diterpenes,see (a) E J Corey, M A Tius and J Das, J Am Chem Soc , 102, 7612 (1980), (b) E E van Tamelen, J G Carlson, R K Russell and S R Zawacky, ibid ,103,4615 (1981), (c) R B Kelly,M L Harley,S J Alward and P S Manchand, Can J Chem , 60, 675 (1982)

3 A Chatterjee, S R Raychoudhuri and S K Chatterjee, Tetrahedron, 37, 3653 (1981)

4 L C Bateman and R Robinson, J Chem Soc ,398 (1941)

5 R A Barnes and W M Bush, J Am Chem Soc , 80, 4714 (1958)

6 W S Johnson, J W Peterson and C D Gutsche, J Am Chem Soc , 69, 2942 (1947)

7 I A Blair, L N Mander and P H C Mundill, Aust J Chem , 34, 1235 (1981)

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