Tetrahedron Letters,Vol.24,No.52,pp 5919-5920,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

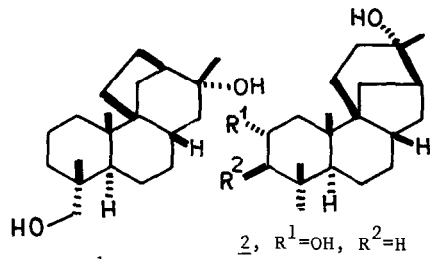
SYNTHESIS OF TRICYCLO[6.2.2.0^{1,6}]DODECANE AND TRICYCLO[6.3.1.0^{1,6}]DODECANE RING SYSTEMS INVOLVING INTRAMOLECULAR CYCLISATION OF DIAZOMETHYL KETONES

Sanat K. Maity and Debabrata Mukherjee*

Department of Organic Chemistry
Indian Association for the Cultivation of Science, Calcutta-700032,India

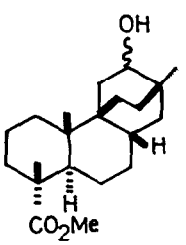
Summary: 2,8-Dimethyltricyclo[6.2.2.0^{1,6}]dodeca-2,5-diene-4,9-dione (6), 2,9-dimethyltricyclo [6.3.1.0^{1,6}]dodeca-2,5-diene-4,10-dione (7) and 2-methyltricyclo[6.3.1.0^{1,6}]dodeca-2,5-diene-4,10-dione (8) have been synthesised for entry into the ring systems of a few tetracyclic diterpenes.

Tricyclo[7.2.1.0^{1,6}]dodecane and tricyclo[6.3.1.0^{1,6}]dodecane ring systems are present in rings B/C/D of the tetracyclic diterpenes stemarin (1) and stemodin (2) respectively. Recently Kelly et al. by their elegant syntheses[1,2] of the diterpenes 1 and 3 demonstrated that both stemodane and stemarin ring systems can be generated from a common tetracyclic intermediate 5 which incorporates 2,8-dimethyl-9-hydroxytricyclo[6.2.2.0^{1,6}]dodecane as rings B/C/D. Furthermore, a tetracyclic intermediate incorporating 2,8-dimethyl-9-oxotricyclo[6.2.2.0^{1,6}]dodecane as B/C/D rings has been utilised recently by van Tamelen et al.[3] for the synthesis of the diterpene maritimol (4). In connection with our interest in bridged carbocyclic systems related to diterpenes, we undertook the synthesis of tricyclo[6.2.2.0^{1,6}]dodecane framework incorporating methyl groups at C-2 and C-8 and oxygen function at C-9. The synthesis of the dienone 6 reported herein involves reductive methylation of the β-naphthoic ester 16 followed by acid-induced intramolecular cyclisation of the diazomethyl ketone 19. From a common starting material 10, we also synthesised

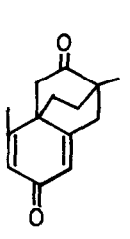


1

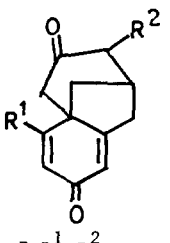
2, R^1=OH, R^2=H
3, R^1=R^2=H
4, R^1=H, R^2=OH



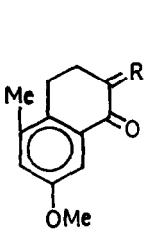
5



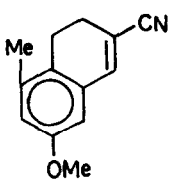
6



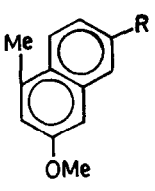
7, R^1=R^2=Me
8, R^1=Me, R^2=H
9, R^1=R^2=H



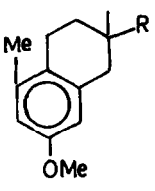
10, R = H_2
11, R=H, CN
12, R=CHOH



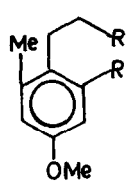
13



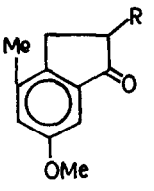
14, R=CN
15, R=CO_2H
16, R=CO_2Me



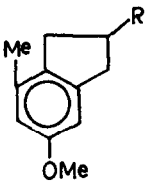
17, R=CO_2Me
18, R=CO_2H
19, R=$COCHN_2$



20, R=CO_2H
21, R=CO_2Me



22, R=CO_2Me
23, R=CHMeCO_2H
24, R=H
25, R=Br
26, R=CH(CO_2Et)$_2$
27, R=CH_2CO_2H



28, R=CHMeCO_2H
29, R=CH_2CO_2H
30, R=CHMeCOCHN$_2$
31, R=CH_2COCHN_2

the dienones 7 and 8 which incorporate rings B/C/D of the stemodane group of diterpenoids (2- 4). Diels-Alder reactions of the dienones 6, 7, 8 with appropriate dienes are expected to give rise to tetracyclic systems related to the aforementioned diterpenes since dienone 9 is known[4] to undergo facile regioselective cycloadditions with dienes. This possibility is currently being explored.

γ-(2-Methyl-4-methoxyphenyl)butyric acid[5] was cyclised with PPA to give the tetralone 10, m.p. 57° in 75% yield. The corresponding β-ketonitrile 11 (m.p. 152-153°), prepared[6] in 77% yield, was reduced with $NaBH_4$ and the crude hydroxy-nitrile on dehydration with toluene-p-sulphonic acid in benzene furnished the unsaturated nitrile 13 (81%), m.p. 93-94°. Dehydrogenation of 13 with 10% Pd-C in refluxing xylene gave rise to 14 (92%), m.p. 136-137°. Base hydrolysis of 14 and subsequent esterification of the acid 15, m.p. 227-228° afforded the ester 16, m.p. 77-78° in 80% overall yield. Reductive methylation of 16 in anhydrous ammonia (a soln. of 16 in THF was stirred with 2.5 equiv Na in distilled liquid ammonia for 3 min and then excess MeI was added) followed by catalytic hydrogenation (H_2, 10% Pd-C) of the product furnished the ester 17 (74%), ^{1}H-NMR ($CDCl_3$): δ1.27 (s,3H), 2.17 (s,3H), 1.6-3.42 (m,6H), 3.63 (s,3H), 3.73 (s,3H), 6.43-6.67 (m,2H). The corresponding acid 18 (80%), m.p. 142-143° was converted[7] into the diazomethyl ketone 19 which underwent intramolecular cyclisation on treatment with trifluoroacetic acid (TFA) in CH_2Cl_2 at -20° to afford the dienone 6 (56% from 18), m.p. 162°; IR (KBr): 1716, 1662, 1623 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ1.13 (s,3H), 2.01 (d,3H,small allylic coupling), 1.38-2.92 (m,8H), 6.05-6.25 (m,2H).

For the synthesis of the dienones 7 and 8, the ketone 10 was condensed with ethyl formate in the presence of NaH and the crude formyl derivative 12 was treated in the cold with alkaline H_2O_2 to give the diacid 20 (74%), m.p. 144-145°. The corresponding dimethyl ester 21 underwent Dieckmann cyclisation in the presence of Na to afford the β-ketoester 22 (84%), m.p. 126-127°. Acid hydrolysis of 22 gave the indanone 24 (86%), m.p. 104°. Alkylation of 22 with ethyl α-bromopropionate and subsequent acid hydrolysis of the crude product gave the keto-acid 23 (73%) as a diastereomeric mixture, m.p. 170-173°. Treatment of the ketone 24 with Br_2 in ether gave the bromo-ketone 25 (90%), m.p. 115-116° which on condensation with diethyl sodiomalonate in benzene gave the keto-diester 26 in 86% yield. Saponification of 26 and subsequent decarboxylation of the resulting diacid gave the keto-acid 27 (85%), m.p. 159-160°. The keto-acids 23 and 27 were reduced with $NaBH_4$ and the crude products subjected to hydrogenolysis (H_2, 10% Pd-C) in AcOH to furnish the acids 28 (85%), m.p. 97-100° and 29 (85%), m.p. 79-80° respectively. The corresponding diazomethyl ketones 30 and 31 were treated with TFA in CH_2Cl_2 at -20° to give the dienones 7 (58%), m.p. 97-99° and 8 (55%), m.p. 144-145° respectively. The dienone 7 was isolated as a ca 1:1 mixture of C-9 epimers; ^{1}H-NMR ($CDCl_3$): δ1.09, 1.27 (2d,3H,J=7 Hz), 2.1 (d,3H, small allylic coupling), 1.70-3.22 (m,8H), 6.03 (bs,2H); IR (KBr) 1710, 1660, 1620 cm^{-1}. Further elaborations of the dienones are in progress.

References:

1. R.B. Kelly, M.L.Harley and S.J.Alward, *Can. J. Chem.*, 58, 755 (1980).
2. R.B. Kelly, M.L.Harley, S.J. Alward, R.N.Rej, G. Gowda, A.Mukhopadhyay and P.S.Manchand, *Can. J. Chem.*, 61, 269 (1983).
3. E.E. van Tamelen, J.G.Carlson, R.K.Russell and S.R.Zawacky, *J. Am. Chem. Soc.*,103, 4615 (1981).
4. K.C. Nicolaou and R.E.Zipkin, *Angew. Chem. Int. Ed. Engl.*, 20, 785 (1981).
5. W.S.Johnson, S. Shulman, K.L. Williamson and R.Pappo, *J. Org. Chem.*, 27, 2015 (1962).
6. W.S.Johnson, J.W.Peterson and C.D.Gutsche, *J. Am. Chem. Soc.*, 69, 2942 (1947).
7. U.R.Ghatak and P.C.Chakraborti, *J. Org. Chem.*, 44, 4562 (1979).

(Received in UK 19 October 1983)