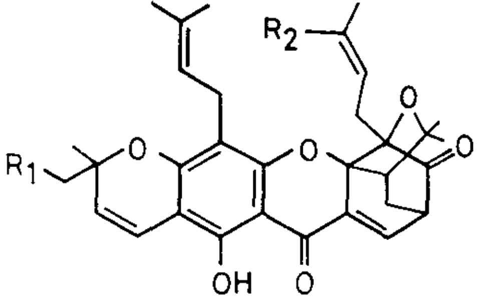
SYNTHESIS OF 5,5-DIMETHYL-7-METHOXY-4-OXATRICYCLO-[4.3.1.$0^{3,7}$]DECAN-2-ONES[1,‡]

Sadagopan Raghavan and G.S.R. Subba Rao[*]

Department of Organic Chemistry, Indian Institute of Science, Bangalore - 560 012, India

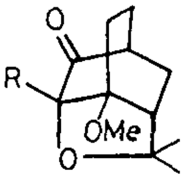
Abstract - *Two new synthetic routes for the preparation of the title compound and its 3-substituted derivatives, a novel ring system present in morellin and other related natural products, are reported from the readily available dihydroanisoles.*

The naturally occurring compounds morellin (1)[2] and gambogic acid (2)[3] have a nucleus consisting of a 4-oxatricyclo[4.3.1.$0^{3,7}$]decane (3) moiety. As part of our synthetic strategy towards *morellin* (1),[4] we describe the synthesis of this novel ring system starting from 2,5-dihydroanisoles.
The adduct[5] (5a, 95%), obtained by heating[6] a mixture of the diene (4a) and *methyl acrylate in a sealed tube, reacted* with MeMgI giving the alcohol (6a, 95%). Reaction of 6a, with *N*-bromosuccinimide (NBS) in CH_2Cl_2, resulted



(1) R_1 = H; R_2 = CHO

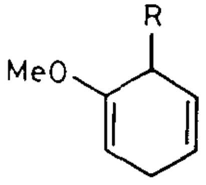
(2) R_1 = $Me_2C{=}CHCH_2$; R_2 = COOH



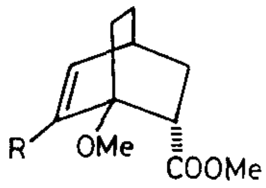
(3) a. R = H
b. R = n-Bu
c. R = $Me_2C{=}CHCH_2$
d. R = $Me_2C(OH)CH_2CH_2$

[‡] Dedicated to Prof. Alan R. Katritzky FRS on his 65th birthday.

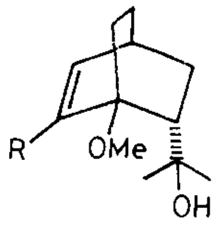
in the bromo ether (7a, 95%). However solvolysis of 7a with silver acetate in acetic acid at 90 °C afforded a mixture from which the tetracyclic compound (8a, 35%) and the acetate (9a, 10%) were separated by chromatography. Hydrolysis of 9a in methanol with 5% sodium hydroxide gave the alcohol (10a) which on oxidation with pyridinium chlorochromate (PCC) in CH_2Cl_2 afforded the tricyclic ketone (3a) in an overall yield of 6% from 4a.



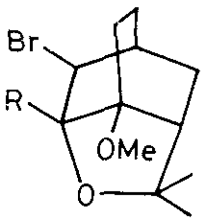
4(a-d)



5(a-e)



6(a-c)

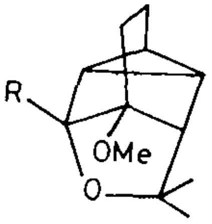


7(a-c)

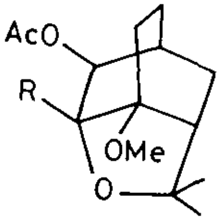
(a) R = H, (b) R = n-Bu, (c) R = $CH_2CH_2CH(OCH_2CH_2O)$,
(d) R = $Me_2C=CHCH_2$,

Similar sequence on the diene (4b), obtained by the alkylation of 4a with 1-bromobutane in presence of KNH_2/NH_3, gave the bromo ether (7b) through the intermediates (5b & 6b). Solvolysis of 7b yielded a mixture of products from which, compound (8b, 40%) was isolated by chromatography. The remaining mixture, on alkaline hydrolysis, furnished the compounds (10b,10%), (11, 10%),(12,10%) and (13,20%). The structures of these compounds were deduced from their spectral data.[†] The structure of 11 was confirmed from X-ray diffraction analysis.[7]

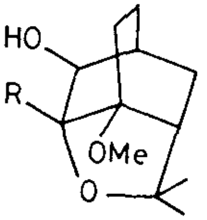
Since the halocyclisation route resulted in a low yield of the tricyclic compounds (3a and 3b), an alternate strategy involving an oxidative cyclisation of the acid (14) was investigated.



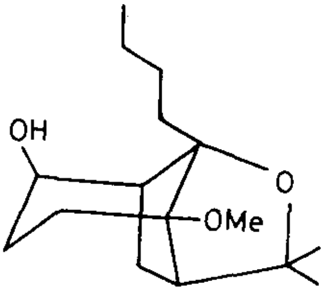
8(a) R = H
(b) R = n-Bu



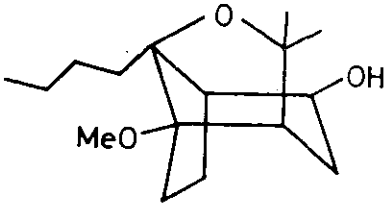
9(a) R = H
(b) R = n-Bu



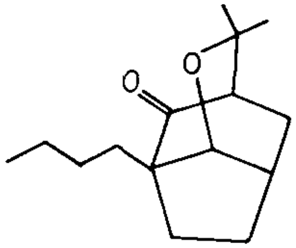
10(a) R = H
(b) R = n-Bu
(c) R = $Me_2C(OH)CH_2CH_2$



(11)



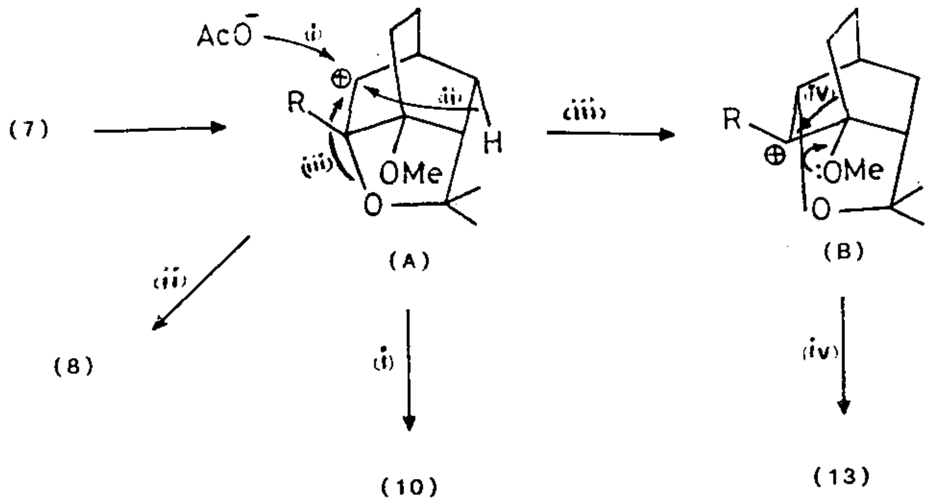
(12)



(13)

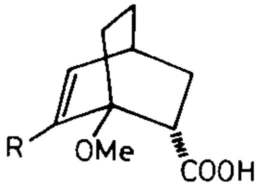
The mechanism of formation of the products (8) and (13) from 7 probably involves the carbocation intermediate (A) which on deprotonation yields the tetracyclic compound (8). Rearrangement of A through the carbocation (B) leads to the formation of the ketone (13) as indicated below.

Hydrolysis of the ester (5a) gave the acid (14a) which was converted to the hydroxylactone (15a, 88%) with performic acid at 60 °C. Reaction of the tetrahydropyranyl ether (15b) with MeMgI yielded a product which was cyclodehydrated[10] with PTS in refluxing benzene to 10a, (80% from 15a), identical



with the product obtained before. PCC oxidation of 10a afforded the tricyclic ketone (3a) in an overall yield of 65% from dihydroanisole (4a). Having demonstrated a strategy to the tricyclic ketone (3a), the synthesis of 5,5-dimethyl-7-methoxy-3-(3'-methylbut-2'-enyl)-4-oxatricyclo-[4.3.1.0^{3,7}]decan-2-one (3c), was attempted by the above methodology.

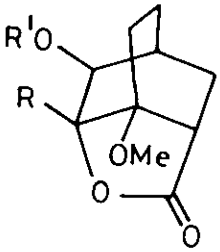
Since direct alkylation of the diene (4a) with 3-methylbut-2-enyl bromide/ KNH_2/ NH_3 did not yield the desired diene (4d), alkylation was carried out using 2-(2'-bromoethyl)-1,3-dioxolane,[8] a potential synthetic equivalent for the prenyl group which afforded the diene (4c) in good yield. The ester (5c, 85%), obtained from the diene (4c) with methyl acrylate, was hydrolysed to the acid (14b, 95%) which was converted to the hydroxy lactone (15c, 95%) with performic acid. Mild hydrolysis with pyridinium *p*-toluenesulphonate[11] in aqueous acetone gave the hemiacetal (16a) which gave the methyl ether (16b) with PTS/methanol. Reaction of 16b with MeMgI afforded the diol which was dehydrated to the compound (17a). Mild acid hydrolysis of 17a with PTS in aq. acetone gave the hemiacetal (17b) which on PCC oxidation yielded the δ-lactone (18). Treatment of the lactone (18) with MeMgI gave the diol (19) which was oxidized with PCC/CH_2Cl_2 to the keto-alcohol (3d). Reaction of 3d with $POCl_3$/DMAP/ pyridine afforded a mixture of olefins which was isomeri-sed with rhodium chloride[12] in isopropanol at 80^{0}C to in the tricyclic ketone (3c) in good yield. Thus a simple route to oxatricyclo[4.3.1.0^{3,7}]decanes is accomplished starting from dihydroanisoles.



(14)

(a) R = H

(b) R = $CH_2CH_2CH(OCH_2CH_2O)$

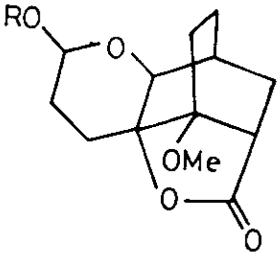


(15)

(a) R = R' = H

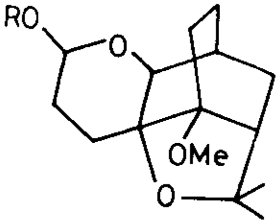
(b) R = H, R' = THP

(c) R = $CH_2CH_2CH(OCH_2CH_2O)$, R' = H



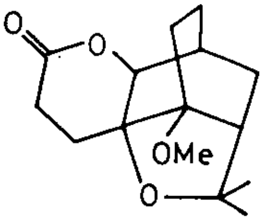
16 (a) R = H

(b) R = Me

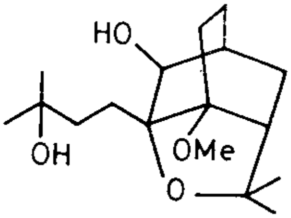


17 (a) R = Me

(b) R = H



(18)



(19)

ACKNOWLEDGEMENTS

This work was supported by a grant from DST, New Delhi under their ILTP programme. SR thanks the CSIR, New Delhi, for a fellowship.

REFERENCES

1. Synthesis Based on Cyclohexadienes Part 7; for Part 6: H. Ramanathan and G. S. R. Subba Rao, *Ind. J. Chem.*, 1991, 30B, 901.
2. G. Kartha, G. N. Ramachandran, H. B. Bhat, P. M. Nair, V. K. V. Raghavan and K. Venkataraman, *Tetrahedron Lett.*, 1963, 459.
3. W. D. Ollis, M. V. J. Ramsay, I. O. Sutherland, and S. Mongkolsuk, *Tetrahedron*, 1965, 21, 1453.
4. A. J. Quillinan and F. Scheinmann, *J. Chem. Soc., Chem. Comm.*, 1971, 966; P. Yates and D. J. Bichan, *Can. J. Chem.*, 1975, 53, 2045, 2054.
5. A. J. Birch and J. S. Hill, *J. Chem. Soc. C*, 1966, 419.
6. A. J. Birch and K. P. Dastur, *Tetrahedron Lett.*, 1972, 4195.
7. This was kindly determined by Prof. K. Venkatesan of our department.
8. G. Büchi and H. Wüest, *J. Org. Chem.*, 1969, 34, 1121.
9. H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 1959, 221.
10. T. R. Kelly, *J. Org. Chem.*, 1972, 37, 3393.
11. R. Sterzycki, *Synthesis*, 1979, 724.
12. S. Torii, T. Inokuchi, and R. Oi, *J. Org. Chem.*, 1983, 48, 1944.

+ All the new compounds gave satisfactory analytical and spectral data. The spectra of some select compounds is indicated below:

3a: ν_{max} 1720,1060 cm^{-1}; δ_H 1.17(s,3H,CH_3),1.45(s,3H,CH_3),1.53–2.37(m,8H), 3.26(s,3H,OCH_3),3.94(d,J=1.7Hz,1H,CHO).

3b: ν_{max} 1725,1105 cm^{-1}; δ_H 0.89(t,3H,CH_3),1.13(s,3H,CH_3),1.23–2.57(m,14H), 1.36(s,3H,CH_3),3.27(s,3H,OCH_3); M^+,266.

3c: ν_{max} 1730,1230 cm^{-1}; δ_H 1.13(s,3H,CH_3),1.36(s,3H,CH_3),1.60–2.71 (m,10H), 1.67(s,3H,CH_3),1.74(s,3H,CH_3),3.26(s,3H,OCH_3),5.05(t,J=7Hz,1H); M^+:278.

3d: ν_{max} 3440,1730,1090 cm^{-1}; δ_H 1.13(s,3H,CH_3),1.22(s,3H,CH_3),1.38(s,3H,CH_3), 1.45(s,3H,CH_3),1.56–2.54(m,12H),3.13(s,3H,OCH_3),3.23(s,1H,OH); M^+: 298.

8a: ν_{max} 1170,1080 cm^{-1}; δ_H 1.35(s,3H,CH_3),1.80–2.86(m,8H),3.21(s,3H,OCH_3), 4.51(d,J=4.1Hz,1H,C$\underline{H}$O); M^+: 194.

8b: ν_{max} 1160,1030 cm^{-1}; δ_H 0.92(s,3H,CH_3),1.24(s,3H,CH_3),1.29(s,3H,CH_3),1.42–2.30(m,14H),3.16(s,3H,OCH_3); M^+: 250.

13: ν_{max} 1725,1240 cm^{-1}; δ_H 0.92(t,3H,CH_3),1.16(s,3H,CH_3),1.28(s,3H,CH_3),1.38–2.47(m,14H),3.90(d,J=4Hz,1H,C$\underline{H}$O–); M^+: 236.

Received, 23rd April, 1993