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Reactions of 2,3,19-Trihydroxyurs-12-Triterpenoids: Pinacol Rearrangement of Methyl 2α,3β,19α-Trihydroxyurs-12-en-28-Oate

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Abstract: Pinacol rearrangement of the title group of compounds has been investigated and the structures of the adducts elucidated. Three different A-ring carbonylated compounds were obtained, two of which (**2** and **4**) remained with a six-member ring as in the starting material **1**, and the third one (**3**) with a cyclopentanic ring as a consequence of the A-ring contraction. In addition to normal pinacol rearrangement of ring A, the reaction led to the isomerization of Δ12 double bond in all of the products (**2-4**) with compounds **2** and **3** as dienic triterpenes, and compound **4** with an E-ring γ-lactonic system.
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INTRODUCTION

Methyl tormentate (methyl 2α,3β,19α–trihydroxyurs-12-en-28 oate) has been isolated from the roots of *Potentilla tormentilla* Neck (*Rosaceae*) and its structure established by Potier *et al*[1]. This compound has also been obtained from many Cameroonian species of the family *Cecropiaceae* (*Musanga cecropioides*, *Myrianthus arboreus*, *M. liberecus*, *M. serratus* and *Cecropia peltata*) as its methyl ester and used as starting material for the above reactions. Pinacol rearrangement reactions are acidic medium molecular transpositions of α-diol systems as that in ring A of methyl tormentate **1.**

As previously described by Fittig[2], Gomberg-Bachmann[3] and Zaugg[4], the dehydration of alkyl or aryl substituted α-diols can be followed by the migration of one of these substituents from one carbon to another. In our search of synthetic A-ring contracted pentacyclic triterpene derivatives such as musancropic acids A (**5**) and B (**6**) naturally obtained from *Musanga cecropioides* [5], methyl tormentate was heated for 3 hrs under reflux in benzene in the presence of sulfuric acid to give a mixture which was chromatographed on a silica gel column to afford compounds **2, 3** and **4**. A number of pathways may be suggested in fig.1 for the formation of the A-ring of compounds **2** , **3** and **4** from compound **1.**

RESULTS AND DISCUSSION

The structures of compounds **2, 3** and **4** were established from their IR, UV, ^1H and ^{13}C NMR spectroscopic data and as far as possible by their comparison with those of the starting compound (**1**) .
The NMR (^1H and ^{13}C) and IR spectra of these compounds presented many differences with those of compound **1.** Their IR spectra for instance showed no absorption band characteristic of hydroxyl groups as in the case of the starting compound **1.** This is further more confirmed by their ^{13}C-NMR spectra on which no signal of hydroxylated carbon atom was observed, in addition to the absence in the ^1H-NMR spectra of the signals of H-2 and H-3 protons corresponding to the hydroxylated carbon atoms at these positions in

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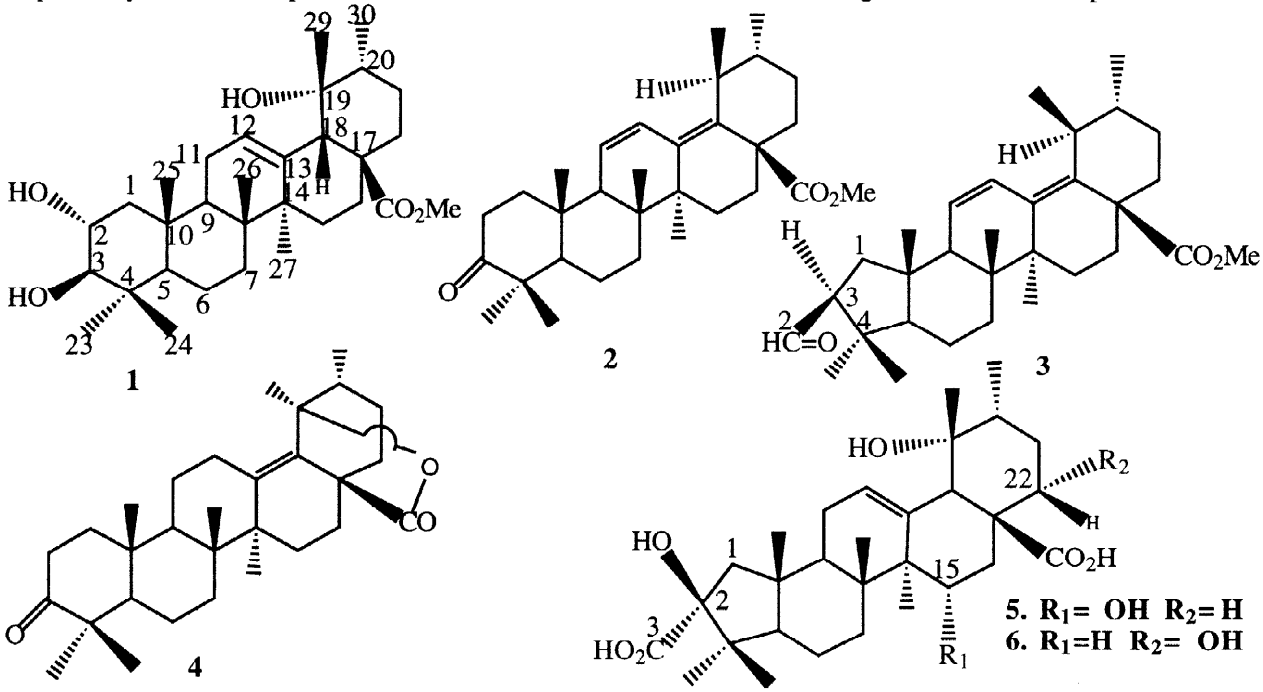
compound **1**. All this suggested that the A-ring of these compounds have been modified comparatively to that of **1**. Secondly the ^{13}C spectra of these compounds revealed that they no longer belonged to the urs-12-en triterpene skeleton[6,7] as compound **1** in which C-12 and C-13 carbon atoms appear at 128.59 and 137.99 ppm respectively. This is compatible with the modification of the C, D and E rings of the above compounds.



Compound **2** was obtained as white crystals from hexane-EtOAc (mp 175-176°C). Its ^{1}H-NMR spectrum exhibited seven three-proton signals between 0.60-1.20 ppm corresponding to seven methyl groups, among which two doublet-like multiplets at 0.98 (CH_3-30) and 1.10 (CH_3-29), a broad doublet at 2.50 ppm corresponding to the allylic proton at C-19 and which exhibited an important NOE effect with the signal at 1.10ppm (CH_3-29). A three-proton singlet was also observed at 3.65ppm corresponding to the carbomethoxyl group at C-28. The disappearance of the signal of the vinylic proton (H-12) at 5.35 ppm of the starting compound (**1**) replaced by the appearance of a three-proton ABX system consisting of two vinylic protons at 5.60 (H-11), and 6.48 (H-12), and an allylic proton at 2.01 (H-9) is compatible with the existence of the 11 and 13(18) conjugated dienic system. This is further supported by the ^{13}C-NMR spectrum of compound **2** (Table 1) which revealed the presence of 4 vinylic carbon atoms consisting of 2 methine carbons at 125.70 corresponding to C-12 and 126.06 attributed to C-11 and finally 2 quaternary carbon atoms at 132.19 (C-13) and 136.22 (C-18). We also reported on this spectrum a signal at 178.50 ppm corresponding to the carbonyl carbon at C-28 and at 217.42 ppm characteristic of the ketone function at C-3 .This is also confirmed by the IR spectrum which revealed two absorption bands at 1718 and 1702 cm^{-1} respectively attributed to the carbonyl functions at these positions.

The structure of compound **2** was further confirmed by the analysis of its uv spectrum which exhibited 3 important absorption maxima at λ_{max} (nm) (log ε): 245 (4.36) (dienic system), 253 (4.40) (C-28 ester carbonyl function) and 265 (4.20) (C-3 ketone). These values are compatible with those found in the literature

for similar chromophores[8], especially for the conjugated dienic system which gave a calculated value of λ_{max} 244 nm on the basis of Woodward and Fieser rules[9].

Compound **3** crystallized as white spangles from hexane (mp 202-204°C). Its ^{1}H- and ^{13}C-NMR spectra were very similar to those of compound **2.** More specifically the ^{1}H-NMR spectrum of the compound showed the same methyl group signals between 0.60-1.20 ppm, as well as the three-proton ABX system (H-12, H-11 and H-9) already described in the case of compound **2**, in addition to the singlet signal at 3.63 ppm attributed to the carbomethoxyl group at C-28. The ^{13}C-NMR spectrum of **3** (Table 1) in turn revealed the presence of the 4 vinylic carbon atoms at 125.73, 126.08, 132.24 and 136.27 ppm attributed to C-12, C-11, C-13 and C-18 respectively as in compound **2** and the signal at 178.60 ppm corresponding to C-28 . All this confirmed the identity of the C, D and E rings in compounds **2** and **3** . The difference between the two was established on the basis ^{13}C-NMR spectrum which showed a carbonyl signal at 203.14 ppm, instead of 217.42 as it is the case in compound **2.** The value of 203.14 ppm is compatible with the resonance of an aldehyde carbonyl group, whereas that of 217.42 in **2** was attributed to a ketonic carbonyl. This was further confirmed by the Fehling liquor test which was positive for compound **3,** but negative for compound **2** . The reaction mechanism (scheme 1) led us to locate the aldehyde function at C-3 confirming the A-ring contraction in **3.**

Compound **4** was obtained as a fine powder from hexane-EtOAc (mp 198-200°C). Its ^{1}H-NMR spectrum exhibited a series of singlets between 0.85-1.15 attributed to quaternary methyl groups. It also presented spectral data similar to those of ring A of compound **2.**Its structure was finally elucidated from interpretation of its ^{13}C-NMR spectral data (Table 1), which showed the presence of the signal at 218.05 ppm, attributed to the ketone in position 3 as in compound **2** in which the corresponding carbon atom resonated at 217.42 ppm, thus establishing the identity of A-ring in both compounds. Apart from this similarity, the other data in the ^{1}H-NMR spectrum of the compound were consistent with a different constitution of C, D and E rings in comparison with the corresponding cycles in **1, 2** and **3.** More specifically the comparison of the ^{1}H-NMR spectrum of **4** with that of the starting compound **1** and of compounds **2** and **3** revealed no vinylic proton, but its ^{13}C-NMR spectrum showed the presence of the signals of two quaternary vinylic carbon atoms at 132.05 and 140.00 ppm, and the absence of the signal of the C-28 carbomethoxyl group at 178 ppm. In addition the comparison of IR spectra of **1** and **4** revealed the absence of the absorption band of a free hydroxyl group in compound **4.** The absence of vinylic proton signals on the ^{1}H-NMR spectrum of compound **4** as well as that of H-18 led us to locate the carbon-carbon double bond between C-13 and C-18. Further analysis of the ^{13}C-NMR spectrum of **4** also led to the identification of a resonance signal at 83.00 ppm which was shown from a DEPT experiment to correspond to an oxygenated quaternary carbon atom. The presence of an absorption band at 1736 cm^{-1}on the IR spectrum of **4** characteristic of a γ-lactonic system coupled to that of the above oxygenated quaternary carbon and the absence of the free hydroxyl group at C-19 were compatible with the formation of a γ-lactone in the E-ring between the C-28 carboxyl (or carbomethoxyl) function and the C-19 hydroxyl group of the starting compound **1.** The signal at 140.00 ppm was attributed to C-13 because of the presence of the lactonic system in the E-ring which resulted in the isomerization of 19-methyl group, which had a β-orientation in the starting compound **1** but an α-orientation in compound **4** . Accordingly the carbon vinylic signal at 132.05 was attributed to C-18.

In addition to structure determination of the three compounds, the mechanism of the reaction which resulted in their formation was discussed . The comparison of the structures of compounds **2,3** and **4** with that

of the starting compound **1** showed not only the involvement of A-ring in the reaction but also that of C, D and E-rings as shown in scheme 1. From the above scheme, four different pathways could be considered for the formation of A-ring in compounds **2**, **3** and **4** from compound **1.**

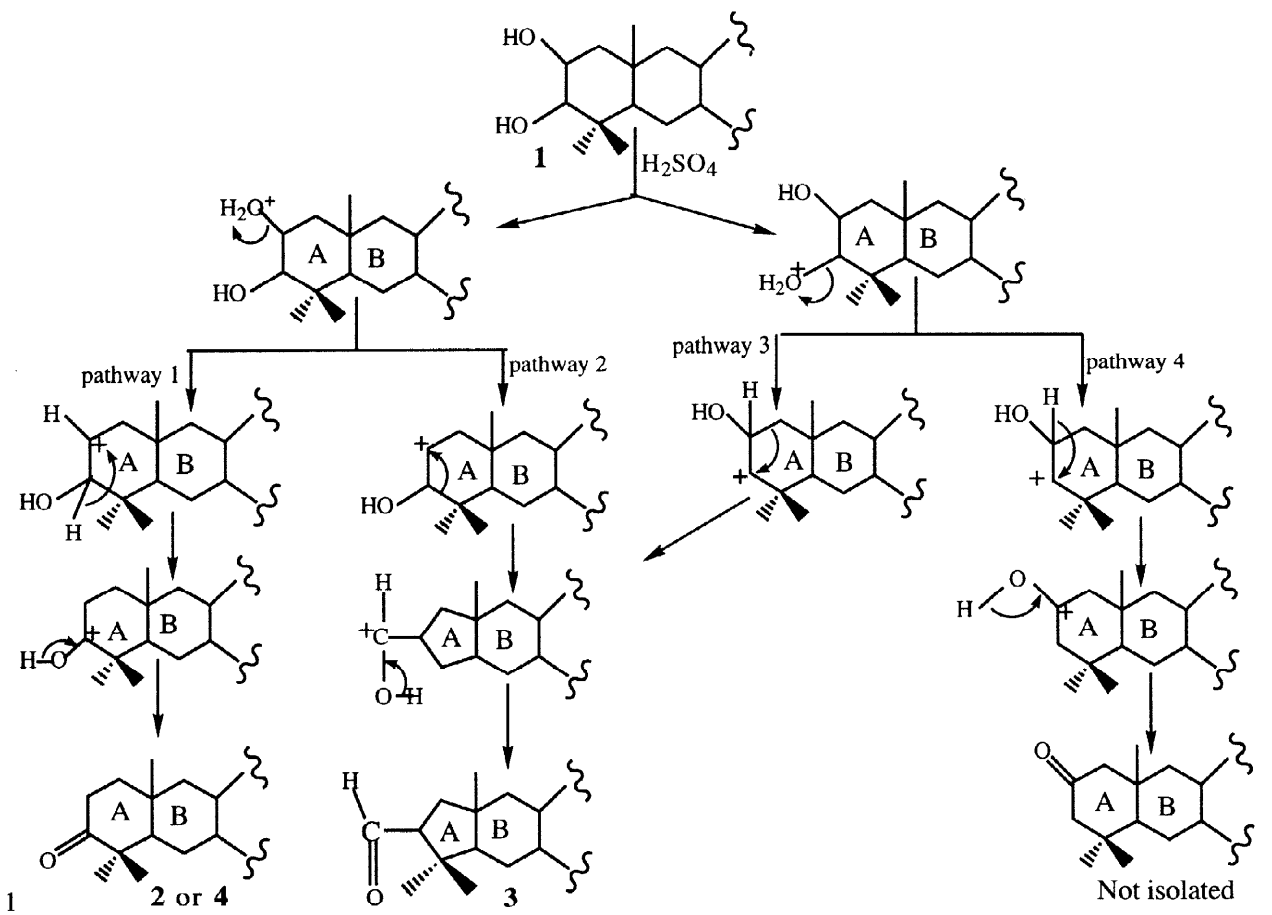
Table 1: ^{13}C-NMR ($CDCl_3$, 300.13 MHz, TMS) spectral data of compounds **1-4**

C n°	1	2	3	4
1	46.34	39.93	53.75	39.77
2	68.47	34.12	42.04	34.28
3	83.25	217.42	203.14	218.05
4	39.14	47.23	47.25	47.12
5	55.05	55.45	55.15	54.73
6	18.28	18.90	18.95	18.66
7	32.44	32.15	32.48	32.78
8	39.74	40.51	40.55	41.36
9	46.95	24.93	25.00	50.19
10	37 94	38.64	38.69	37.04
11	23.54	126.06[a]	126.08[c]	20.29
12	128.59	125.70[a]	125.73[c]	21.96
13	137.99	132.19[b]	132.24[d]	140.00[e]
14	40.99	41.99	42.04	42.44
15	27.99	26.28	26.33	27.94
16	25.23	24.93	25.00	25.27
17	47.68	47.43	47.45	47.22
18	53.02	136.22[b]	136.27[d]	132.05[e]
19	72.83	36.22	35.64	83.00
20	40.99	40.80	40;66	40.35
21	25.83	25.71	25.56	25.27
22	37.24	38.64	38.69	37.04
23	28.55	26.28	26.33	26.83
24	16.72	20.71	20.78	20.29
25	16.36	17.40	17.41	16.50
26	16.42	19.67	19.71	17.61
27	24.34	24.04	24.00	21.00
28	178.26	178.50	178.60	176.01
29	27.18	26.28	26.33	22.36
30	15.97	15.94	15.98	16.45
0Me	51.46	51.74	51.74	

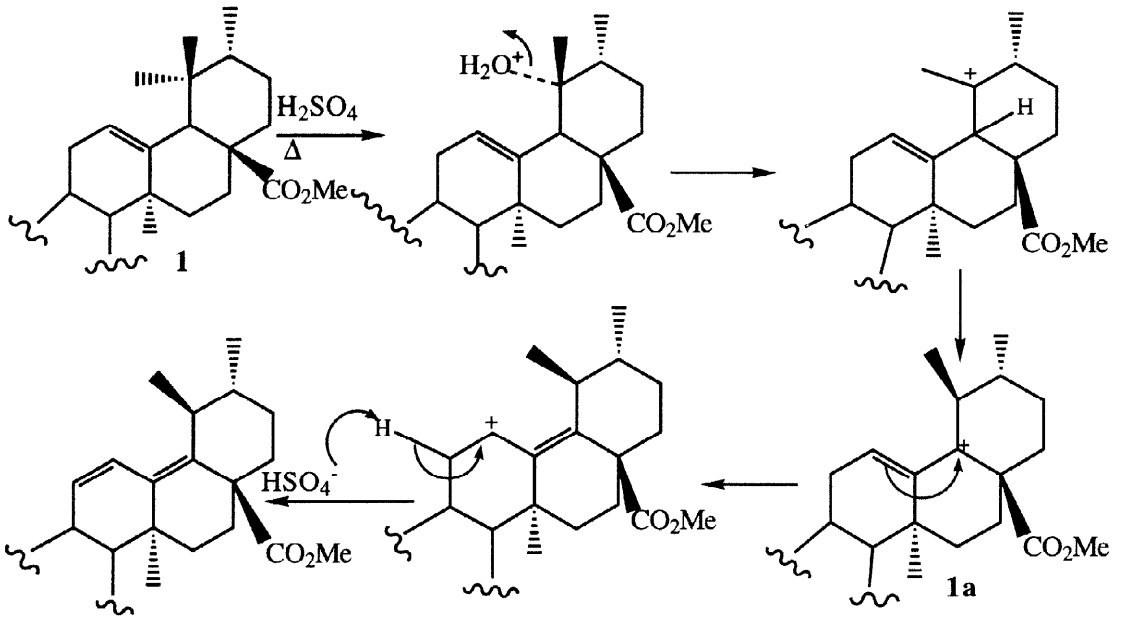
N.B. : a, b, c, d, e : these attributions may be interchanged within the column.

For compounds **2** and **3** we suggested that the formation of the dienic system could arise from the loss of 19α-OH group of **1** through protonation and subsequent elimination of a water molecule, followed by the migration of H-18 from C-18 to C-19 to afford the more stable carbocation (**1a**). The latter intermediate in turn could undergo isomerisation of $\Delta^{12(13)}$ from C-12 - C-13 to C-13- C-18 and which is stabilised by the loss of the proton at C-11 position to afford the dienic system as clearly shown in scheme 2.

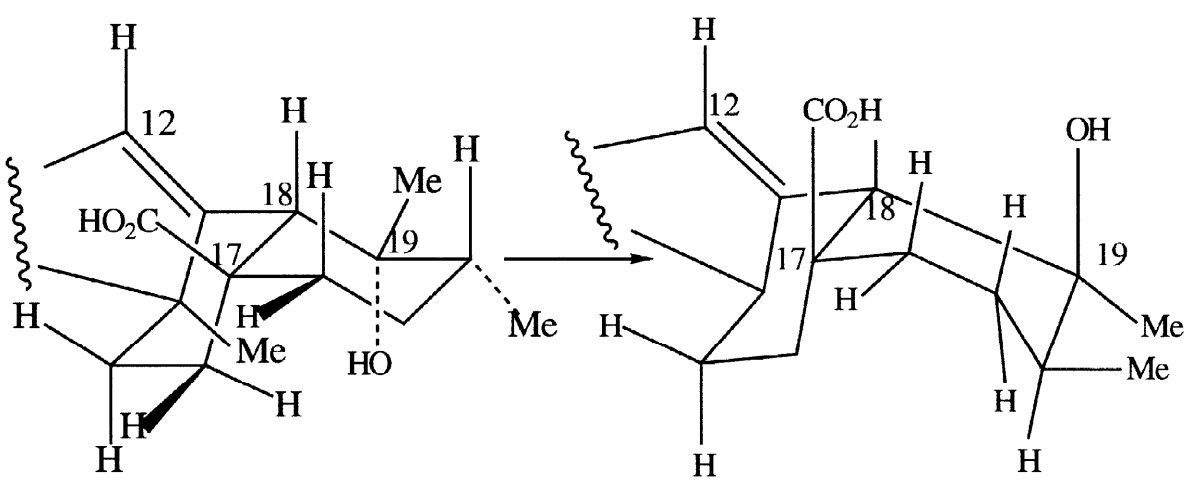
Scheme 1: 3-keto and contracted five membered A-ring formation pathways of compounds **2,3** and **4** from methyl tormentate **1.**



Scheme 2: C- and D-ring dienic system formation pathways in compounds **2** and **3**.



Scheme 3: Perspective drawing of E-ring lactonic system formation pathway in compound **4** where E-ring is converted from chair-1 to inversed boat conformation.



Moreover, concerning the formation of the γ-lactone function in D/E ring in compound **4,** we firstl suggested the hydrolysis of the methyl ester at C-28 to yield a carboxylic group (**1b**).This could be secondl followed by the epimerization at C-19 susceptible of bringing the 19α-OH close to the 28β-COOH, which in tur could lead to the formation of the lactonic system (**1c**), and finally to the isomerisation of $\Delta^{12(13)}$ to $\Delta^{13(18)}$ to give compound **4** as shown in the perspective drawing (scheme 3).

EXPERIMENTAL SECTION

To a solution of 500 mg of methyl tormentate (**1**) (1millimole) in benzene (15ml), 2g of concentrated sulphuric acid were added, and all of which heated under reflux for 3.5 hrs while following the reaction by T.L.C plate. The reaction mixture was further cooled at room temperature and neutralized with 25 ml of a 50% solution of potassium hydroxide , and then extracted twice with 40 ml of diethyl ether .The residue obtained (300mg) after evaporation of the organic phase was chromatographed on a silica gel column (10 g) . Elution with hexane-EtOAc mixture(95/5) yielded 3 compounds which all cristallized in the same mixture of solvents.

Compound 2: Methyl 3-ketoursa-11,13(18) dien-28 oate

(30 mg, 10% yield), white cristals from Hexane-EtOAc(mp 175-176°C), IR (ν_{max}) (KBr) (cm^{-1}): 3000 (C-H),1718 (C=O),1702 ($-CO_2CH_3$),1500. ^{1}H-NMR (300MHz,$CDCl_3$,TMS,δppm) : 0.6-1.20 (seven methyl groups), particularly with δ_H 0.98(3H,d, J=8Hz ,30-CH_3) and 1.10(3H,d, J= 8Hz, 29-CH_3), 2.50 (1H, broad, H-19) , 3.65(3H,s; 28-CO_2CH_3, an ABX system of 3 protons : δ_H 5.60(1 H, d, J= 11.5 Hz, H-11), 6,48 (1H, d, J=11.5 Hz, H-12) and 2.01(1H, d, J=3.5 Hz, H-9) .^{13}C NMR (75MHz, $CDCl_3$, TMS δppm) δ_C 125.70 (C-12), 126.06(C-11), 132,19 (C-13), 136.22(C-18), 178.50(CO2CH), 217.42 (C-3) .UV (EtOH), λ_{max} 245.0, 253.5, 265.0 nm (ε =22700, 25500 and 16400)(Found: C 79.90%, H 9.88%. $C_{31}H_{46}O_3$ requires C 79.83%, H 9.91%).

Compound 3: Methyl A-neo-3-formyl ursa-11,13(18)-dien-28-oate.

(20 mg ,7% yield),m.p. 202-204°C (hexane), gives a positive test with the Fehling liquor reagent which indicates the presence of an aldehyde function .^{13}CNMR (75MHz,CDCL3, TMS, δppm) see Table 1. The ^{1}H- NMR data are almost identical to those of compound (**2**). (Found C 79.86%, H 9.90%. $C_{31}H_{46}O_3$ requires C 79.95%, H 9.98%).

Compound 4: 3-ketours-13,18-en-19,28-olide.

(15mg, 5% yield), M.p. 198-200°C (hexane-EtOAc), IR (ν_{max}, KBr,cm^{-1}): 1736 (carbonyl of the lactone function),1698 (carbonyl of 3-CHO), ^{13}C- NMR (75 MHz, $CDCl_3$, TMS,δppm): (Table 1).(Found C 80.25%, H 9.51%. $C_{31}H_{44}O_3$ requires C 79.97%, H9.66%).

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REFERENCES

1- Potier, P., Das, B.C., Bui, A.M. and Janot , M.M., *Bull. Soc. Chim. Fr.* 1966,**11** 3458.

2- Fittig, R., *Ann. Chem* . 1860, **114** 56.

3- Gomberg, M. and Bachmann, W.E., *J. Amer. Chem. Soc.*1927, **49**, 246.

4- Zaugg, H.E., Freifelder, M. and Horron, B.W., *J .Org. Chem* . 1950, **15** 1191.

5. Lontsi, D., Sondengam, B.L., Martin, M.T. and Bodo, B., *Phytochemistry* . 1991, **30** (7), 2361.

6- Doddrell, D.M., Khong, P.W. and Lewis, K.G. *Tetrahedron Lett.* 1974, **27** 2381.

7- Seo, S, Tomita, Y and Tori, K. ; *Tetrahedron Lett.* 1975, ***1*** , 7.

8- Rao, G.S.R.S., Yadagiri, B, Rao, S.N. and Mallavarapu, G.R., *Phytochemistry* 1984, **23,** 2962.

9- Williams, D.H.and Fleming, L. "Spectroscopic methods in organic chemistry", 3rd ed., pp. 11-20, (1980).