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Molecular rearrangements in derivatives of grandiflorenic acid [(–)-kaur-9(11),16-dien-19-oic acid]

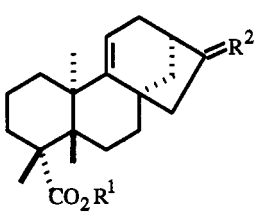
Tatsuhiko Nakano,*[a] María Aracelis Maillo,[a] Antonieta Castaldi Spinelli,[a] Alfonso Martín[a] and Alfredo Usubillaga[b]

[a]Centro de Química, Instituto Venezolano de Investigaciones Científicas (I.V.I.C.), Apartado 21827, Caracas 1020-A, Venezuela

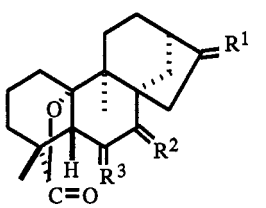
[b]Instituto de Investigación Química, Facultad de Farmacia, Universidad de los Andes, Apartado 143, Mérida, Venezuela

Abstract: Seven new skeletal diterpenes, **4**,**6**,**8**,**9**,**11**,**13** and **14**, were obtained *via* the rearrangements of **1b**,**c**, **3**, **10a**,**b**,**c** and **12**, the derivatives of **1a**, and the structures and stereochemistries of these compounds and also the mechanisms for their formation are described.

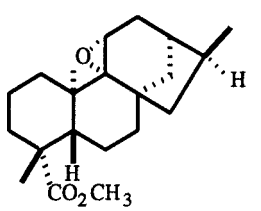
The objective of this work is to study the rearrangements in the derivatives of grandiflorenic acid **1a** [(-)-kaur-9(11),16-dien-19-oic acid] in order to construct diterpenes with new ring systems. Our initial investigation aimed to transform **1a** to the analogs of zoapatlin **2a** (1), eupatalbin **2b**, or eupatoralbin **2c** (2). We first investigated this possibility *via* the rearrangements of the 9,11-epoxide of methyl (-)-kaur-9(11)-en-19-oate **1b**. Epoxidation of **1b** with MCPBA took place stereoselectively at the more accesible α-side and yielded exclusively 9, 11α-epoxide **3**. During this epoxidation we observed that when **1b** contained *N*-nitrosomethylurea as an impurity, the expected **3** was not obtained, but instead **4** was isolated.



1a; R^1=H, R^2=CH_2
b; R^1=CH_3, R^2=β-CH_3,α-H
c; R^1=CH_3, R^2=O



2a; R^1=CH_2, R^2=R^3=H_2
b; R^1=β-CH_3,α-OH, R^2=α-OH,β-H, R^3=H_2
c; R^1=β-CH_3,α-OH, R^2=H^2, R^3=α-OH,β-H



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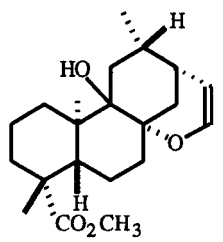
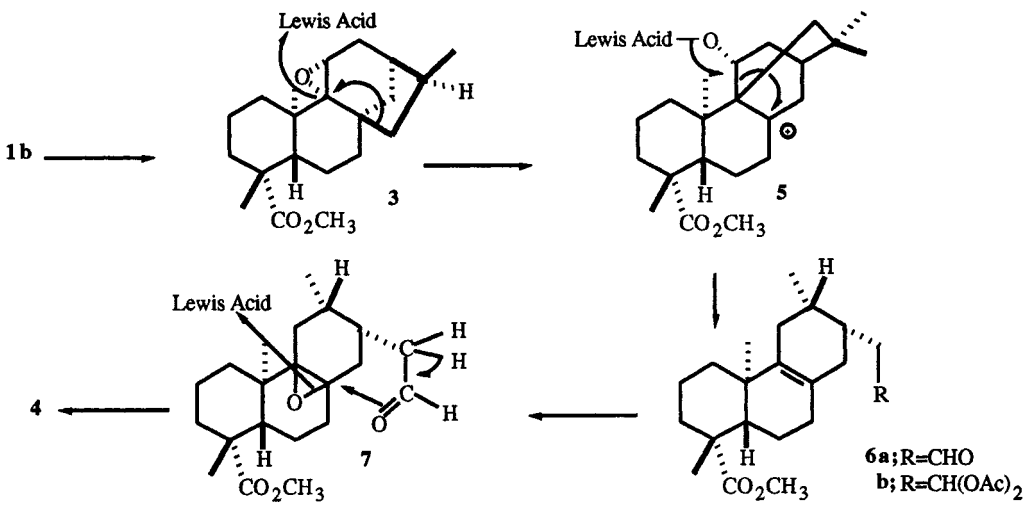


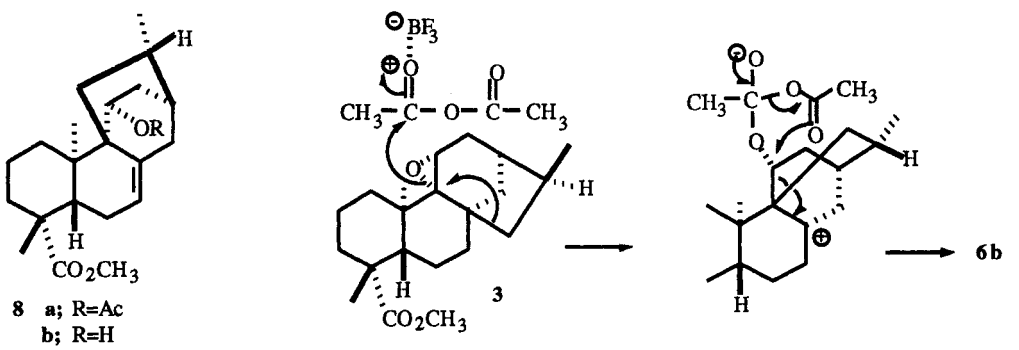
4

We studied in detail how this reaction proceeded. As a consequence it was found that **3** was an intermediate in this reaction pathway and nitrosomethylurea might generate in the presence of MCPBA a catalytic amount of HNO_3 which would act as a Lewis acid to cleave the epoxide ring to form **6a**. **6a** would then react with one mol equiv of MCPBA to give **7**, which upon cleavage of the epoxide ring would afford **4**, as illustrated in Scheme 1.



Scheme 1

That **6a** and **7** were indeed involved in this reaction pathway was demonstrated by an independent experiment in which when **6a**, obtained *via* a different route (see below), was epoxidized and the resulting **7** was treated with a catalytic amount of HCl, **4** was formed. On treatment with BF_3-Et_2O in benzene **3** afforded **6a**. Assuming that in this case the intermediate alcohol **5**, if formed, might be acetylated *in situ* in the presence of Ac_2O to produce **8a*** rather than **6a**, we treated **3** with BF_3-Et_2O in Ac_2O. What we obtained, however, was not the expected **8a** but **6b**, which we presume would be generated by the mechanism shown in Scheme 2.

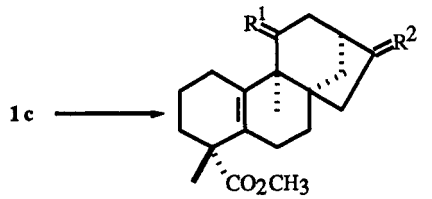


Scheme 2

4 and **6** represent new diterpene skeletons since so far only diterpenes of the pimarane-, cassane- and cleisthanthane-type are known to occur in nature.

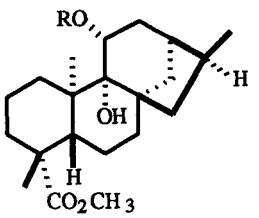
MacMillan, *et al.* (3) reported that on treatment with acetyl hypobromite or Br_2 **1c** underwent 10α→9α-methyl migration to yield 11β-bromo derivative **9a**. This indicated that in this case bromination apparently occurred from the β-side of the molecule. The lack of the sterically shielding 16β-methyl group in **1b** would allow a bromine molecule to attack from the β-side. The β-stereochemistry of the intermediate brominium ion would greatly facilitate subsequent migration of the α-oriented 20-methyl group to C-9. **9b** was synthesized from **9a** by dehydrobromination, followed by hydrogenation of the resulting 11,12-double bond and subsequent Wittig reaction with methylenetriphenylphosphorane.

*Note that this compound is a ring C/D-analog of antheridiogen, A_{AN}, the antheridium-inducing factor from *Anemia phyllitidis* (see ref.4)

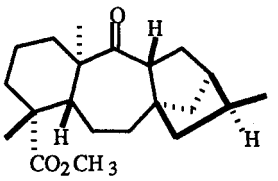


9a; R^1=β-Br,α-H, R^2=O
b; R^1=H_2, R^2=CH_2
c; R^1=O, R^2=β-CH_3,α-H

On treatment with a catalytic amount of H_2SO_4 **10a** rearranged to give **8a** (96%). On the other hand, the rearrangement of **10b** under identical conditions afforded **6a** (13%) and **8b** (8%). Our next interest was directed to a pinacolic type rearrangement of **10b**. Treatment of **10c** with potassium t-butoxide in t-butanol provided 11* (100%).

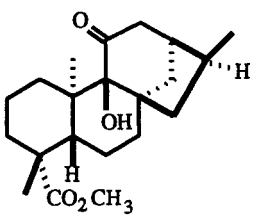


10 **a**; R=Ac
b; R=H
c; R=Ms



11

On treatment with BF_3 - Et_2O in Ac_2O-AcOH **12** did not undergo a pinacolic type rearrangement, but it yielded instead **13** (14%) and **9c** (33%). On the other hand, on treatment with BF_3 - Et_2O in Ac_2O **12** suffered a profound backbone rearrangement to form a new ring B aromatic diterpene **14** (33%). A plausible mechanistic pathway for its formation is depicted in Scheme 3.



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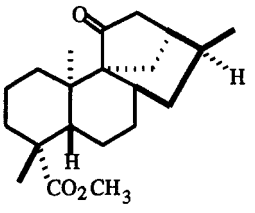

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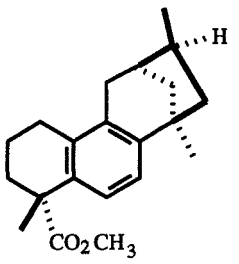

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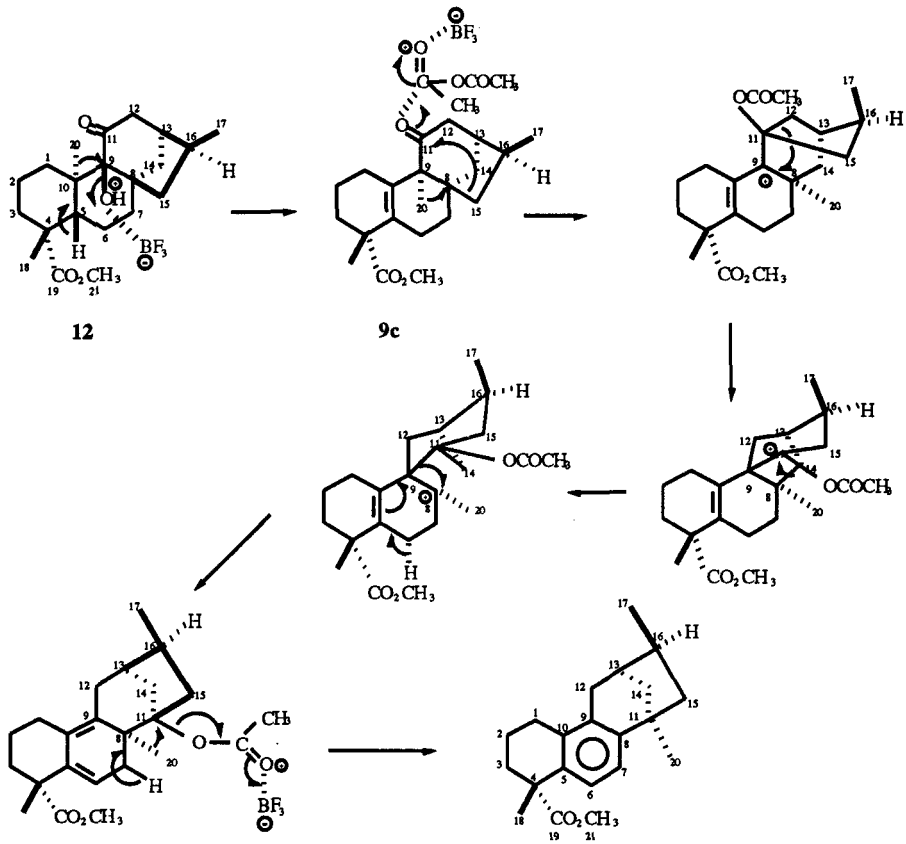
An independent experiment, in which **9c**, obtained *via* a different route (see above), afforded **14** on treatment with BF_3 - Et_2O in Ac_2O, verified that **9c** was indeed an intermediate in this reaction pathway. In Scheme 3 it is shown how each carbon migrates during this rearrangement process by numbering all the carbon atoms in **12**. If C-12 in **12** is labeled by deuterium, then the deuterium must be detected in the same numbered carbon atom in **14**, provided that our postulated mechanistic pathway is correct. On treatment with CD_3OD, D_2O and sodium **12** afforded a mixture of 12-d_0-**12** (66%), 12-d_1-**12** (27%) and 12,12-d_2- **12** (6%). In its broad band proton decoupled ^{13}C n.m.r. spectrum, besides all the carbon resonances in d_0 - **12**, four other carbon signals appeared [δ 44.81 (br t), C-12; δ 40.39 (s), C-13; δ 34.99 (s), C-16] whose signal positions are slightly upfield relative to the corresponding carbons in d_0 - **12**, due to the isotope effect (6). The carbonyl C-11 experienced a downfield shift (7) to δ 215.87 (s). On treatment with BF_3 - Et_2O in Ac_2O under identical conditions, the above mixture of compounds yielded a mixture of d_0 - **14** and its d_1-derivative. Its broad band proton decoupled ^{13}C n.m.r. spectrum was identical with that of d_0-**14** except that in this case three additional carbon signals were observed. A deuterated carbon was found at δ 30. 57 (br t), which was upfield by 0.29 ppm, as compared with the corresponding C-12 in d_0-**14**. Its neighboring C-13 and -16 resonated at δ 39.02 (s) and δ 36.50 (s), respectively, exhibiting an expected upfield

*The toxic substances, grayanotoxins I, II and III are among ring B-homo diterpene analogs with a rearranged kaurane skeleton (see reference 5).

isotope shift. All these n. m. r. results attested to the correctness of the mechanistic pathway which we depicted in Scheme 3 for the formation of **14** from **12**. The structures and stereochemistries of all new compounds obtained were assigned on the basis of spectroscopic data and further confirmed by X-ray crystallographic analysis (**4**, **6b**, **8a**, **13** and **14**).



12 **9c** **14**

Scheme 3

ACKNOWLEDGEMENTS

This paper is a brief summary of the work (8) which we have carried out in our laboratory with a view to constructing new diterpene skeletons and which is also still in progress. We thank Drs. A. T. McPhail, K. D. Onan and D. R. McPhail (Duke University) for X-ray crystallographic analysis.

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