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I_2 Rearrangement Reaction: Synthesis of Isofregenedane Type Diterpenoids

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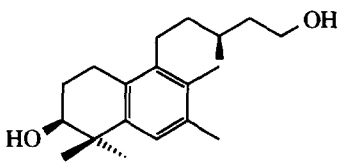
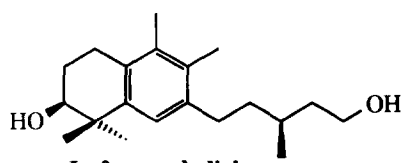
ABSTRACT: The reaction of bicyclic diterpenes either with an allylic grouping or an equivalent function on ring B afforded a simple and rapid synthesis of tetrahydronaphthalenic diterpenes of the isofregenedane type.

Till now only four bicyclic diterpenes with an aromatic ring B have been found in Nature: fregenedadiol,[1] isofregenedadiol,[2] 14-isofregeneden-13-ol[3] and chrysolic acid,[4] although they belong to two isomeric skeleta: fregenedane and isofregenedane.

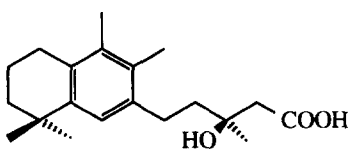
Isofregenedadiol, was isolated from *Halimium viscosum*, and its structure determination has been recently published.[2] Here, we report its synthesis together with a rearrangement reaction that opens up a new avenue for the synthesis of isofregenedane type compounds.



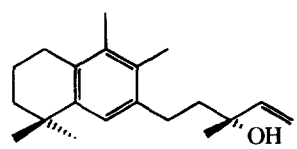
Fregenedadiol



Isofregenedadiol



Chrysolic acid



14-isofregeneden-13(*R*)-ol

In the last few years we have extensively used a rearrangement reaction in the presence of iodine for the isomerization of bicyclic diterpenes with a ring B trisubstituted double bond such as **1** to those with a tetrasubstituted double bond like **2**.[1] When this reaction was applied with other substrates instead of a simple

double–bond isomerization, a tetrahydronaphthalene (THN) product was obtained in good yield.

This reaction with the bicyclic diterpene **3** which possesses an acetoxy allylic group to a disubstituted double bond afforded a 60% yield of the THN derivative **16**,[2] whose structure was determined by comparison with natural isofregenedadiol and by extensive 2D homonuclear and heteronuclear studies of its monoacetyl derivative **20** (3β–acetoxy–isofregenedan–15–ol).[5]

The reaction of **3** in the presence of I_2 always afforded the same compound and yield.[6] This lead us to , apply it to other diterpenic substrates that differ in the ring B functionalization (Figure 1). Some of them, are natural products isolated from diferent species of the *Cistaceae*[7-9] or derivatives, other are substrates substituted or not at C–3 or with different side–chains : *e.g.* three Δ^8 diterpenes subtituted at C–7 with an α–methoxy group **4**, a β–acetoxy group **5**, or a β–hydroxy group **6**, afforded the same result, isofregenedadiol diacetate, **16**.

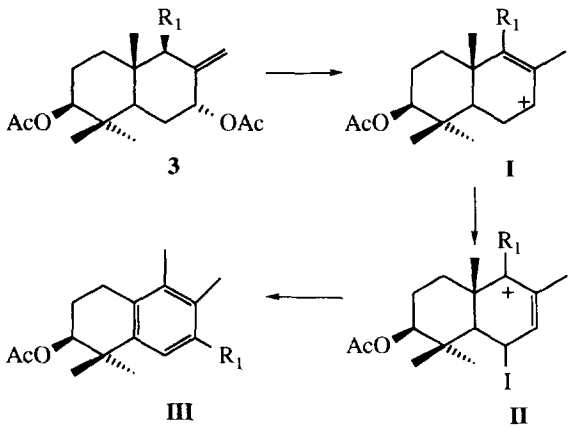
When the oxygenated function is an oxiranic ring the transformations of **7** into **16** and of **15** into **19** are observed, whichever the functionalization at C–15.

Substrates with no functionalization on ring A and that possess a Δ^7 and an oxygenated function either at C–6, **8**, or at C–17, **9**, afforded compound **17**. The same product was obtained when instead of a double bond there is an oxiranic ring on C–7/C–8 (**10** and **11**) no matter its configuration, and also with compound **12** that has a tetrasubstituted Δ^8 double bond and two allylic acetoxy groups at C–7 and C-17.

Analogous results were obtained when the substrate has a shorter sidechain like compounds **13** and **14**, affording the THN derivative **18**.

It is important to say that all the reactions gave more than 60% yield of the THN reaction product after chromatography.

Considering that the reaction is inhibited by Et_3N, it could be supposed that is an acid mediated reaction. The generation of HI *in situ* promotes the formation of an intermediate **I**; further evolution lead to the intermediate **II** probably through a diene and, finally, successive migrations and elimination of HI in the last stage affords product **III**. (Scheme 1)



Scheme 1. In Structure **I** (Δ^8 shown) other allylic cations can be formed: $\Delta^{8,17}$ and Δ^7.

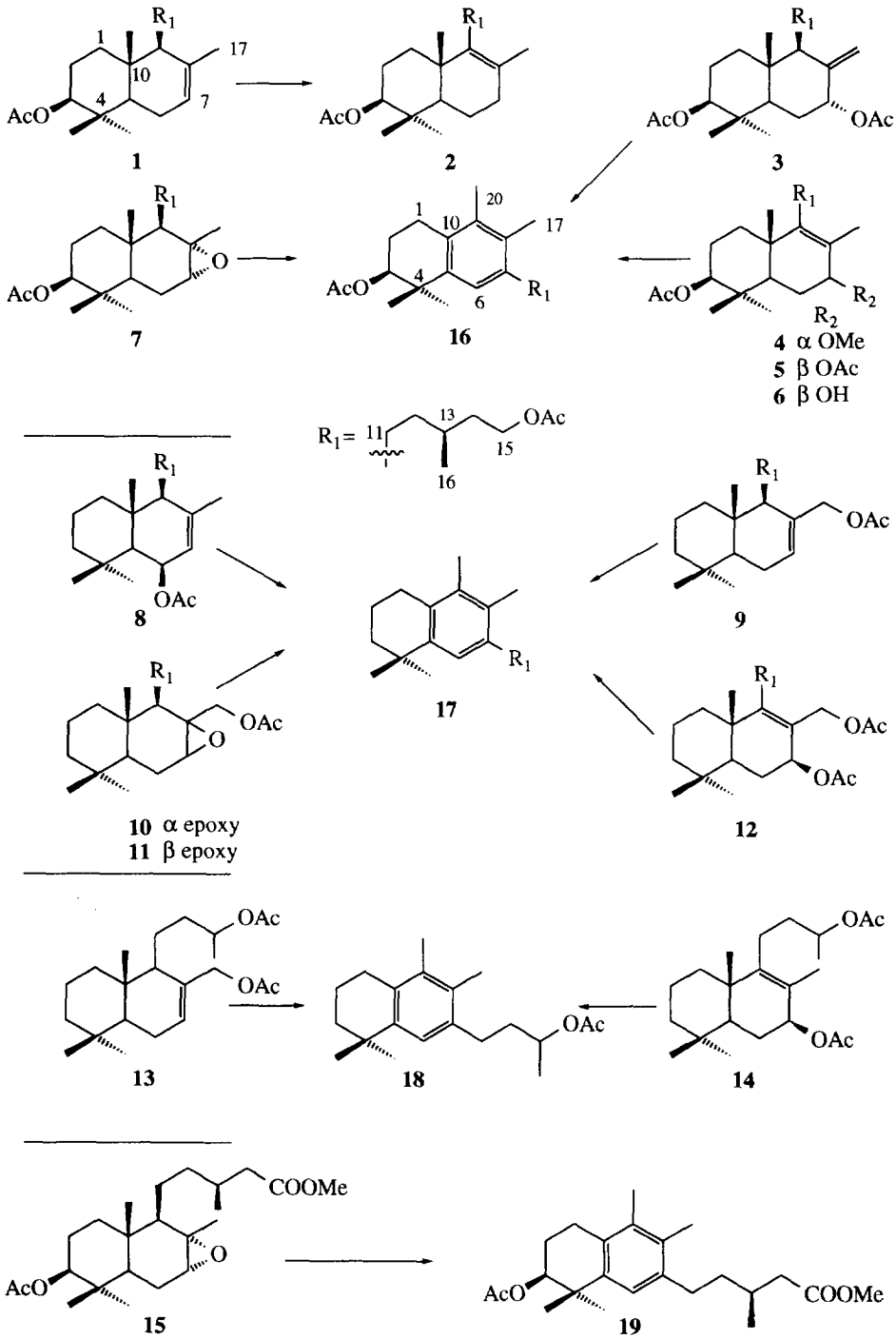

R1
AcO
OAc
R2
O
1
2
3
4 α OMe
5 β OAc
6 β OH
7
16
R1= 11 13 OAc 15 16
8
9
10 α epoxy
11 β epoxy
12
13
14
15
18
19
COOMe

Figure 1

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REFERENCES

1. a. Urones, J.G.; Marcos, I.S.; Basabe, P.; Garrido, N.M.; Jorge, A.; Moro, R.F.; Lithgow, A.M. *Tetrahedron* **1993**, *49*, 6079. b. Urones, J.G.; Marcos, I.S.; Basabe, P.; Garrido, N.M.; Jorge, A.; Moro, R.F.; Lithgow, A.M. *Natural Product Lett.*. **1993**, *3*, 173.
2. Marcos, I.S.; Jorge, A.; Díez, D.; Basabe, P.; Lithgow, A.M.; Sexmero, M.J., Garrido, N.M.; Urones, J.G. *Phytochemistry* , in press.
3. Zdero, C.; Bohlmann, F.; Niemeyer, H.M. *Phytochemistry* **1991**, *30*, 3689.
4. Timmermann, B.N.; Hoffmann, J.J.; Jolad, S.D.; Schram, K.H.; Klenck, R.E.; Bates, R.B. *J. Org. Chem.* **1982**, *47*, 4114.
5. Compound **20** was obtained by alkaline partial hydrolysis with K_2CO_3 of **16.** IR max : 3500, 1740, 1500, 1240. ^1H NMR : 7.03(1H, s, H-6), 4.95(1H, dd, J = 6.8 and 4.3 Hz, H-3), 3.75 (2H, m, H-15), 2.22(3H, s, Me-17), 2.17(3H, s, Me-20), 2.07(3H, s, MeCOO-), 1.32 (6H, s, Me-18 and Me-19), 1.02 (3H, d, J = 6.4 Hz, Me-16); ^{13}C NMR: 24.9(1), 23.9(2), 77.4(3), 37.8(4), 141.5(5), 124.8(6), 138.8(7), 131.9(8), 134.6(9), 130.6(10), 32.1(11), 38.5(12), 30.0(13), 40.0(14), 61.2(15), 19.7(16), 15.4(17), 29.9(18), 26.0(19), 15.6(20), 21.2 and 170.9 (MeCOO). EIMS : 346 (M^+, 20), 286(100), 200(58), 185(92), 183(90), 157(42), 119(70), 83(56), 69(60). The ^1H and ^{13}C NMR data has been unambigously assigned by inverse detected 2D homo and heteronuclear experiments at 500 MHz.
6. A typical procedure is as follows: To 0.5 mmol of **3 – 15** in dry benzene (20 ml) was added 0.5 mmol of I_2. The reaction was heated to reflux 3 to 24 h, monitoring by TLC. Then, benzene was added and the reaction mixture washed with 20% $NaHSO_3$ and H_2O, dried with Na_2SO_4, filtered and evaporated. Compounds **16-18** were separated by Column Chromatography in more than 60% yield.
7. Urones, J.G.; Marcos, I.S.; Basabe, P.; Garrido, N.M. *Phytochemistry* **1988**, *27*, 501.
8. Pascual. J. de; Urones, J.G.; Montes Sánchez, A.; *Anal. Quím.* **1978**, *74*, 959.
9. Urones, J.G.; Marcos, I.S.; Díez, D.; Alonso, C.; Brito–Palma, F.M.S.; Rodilla, J.M.L. *Phytochemistry* **1989**, *28*, 557.

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