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Oxidation of Natural Targets by Dimethyl Dioxirane: Regio and Stereospecific Reactions on Enol Double Bond of Bioactive Nor Quinone Methide Triterpenes

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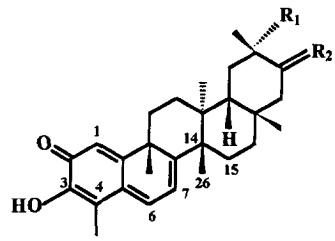
ABSTRACT: Nor quinone methide triterpenes, like pristimerin and tingenone, possess one enol double bond (C_3-C_4). They also have an extended conjugation with an additional double bond (C_7-C_8). When these compounds are treated with dimethyl dioxirane, regio and stereoespecific oxidation occurs only on the enol double bond.

The selective oxidation of a double bond in a hetero conjugated system is a synthetic goal not well resolved. With the advent of dioxiranes on the chemical scene, the combination of high reactivity, neutral pH, and ease of product isolation offered by these reagents has spurred their application to the functionalization of non-natural as well as natural target molecules[1-7]. The results have been encouraging so far in the natural product area: e.g., site selective hydroxylation of estrone acetate[8], cholestane derivatives[8], epoxidation of (all R) vitamin D_3 and vitamin D_3 derivatives[9], epoxidation of flavones[10], arylidene flavanones[11] and their thio-analogues[12]. The recent appearance of chiral dioxiranes[13] widens even more the possibilities for future use.

Dimethyldioxirane (as acetone solution) has been proven as the reagent of choice for the epoxidation of both electron-rich alkenes[10,14] (such as enol ethers, silyl enol ethers and others) an electron-poor alkenes[10,15] (such as α,β-unsaturated acids, esters and ketones, and β-oxo enol ethers).

Various interesting properties of the reactivity of nor quinone methide triterpenes have been noticed by Thomson *et al.*[16]. They reported that these compounds, when treated with nucleophiles, are exclusively attacked at C-6. They obtained phenolic compounds when hydride was used as nucleophile in a reversible pathway in the presence of air oxygen. We have found similar reactivity in compounds with netzahualcoyene skeleton (extended conjugation with a double bond C_{14}-C_{15} and migration of Me-26 from C_{14} to C_{15})[17]. Note that all these compounds are not stable in acid medium, suffering rearrangements[18].



1 R_1=COOCH$_3$ R_2=2H **Pristimerin**
2 R_1=H R_2=O **Tingenone**

Figure 1

The biological significance of nor quinone methide triterpenes[17,19,20], and some of its natural dimeric forms (with an oxirane moiety on C_3-C_4)[21-24] , has stimulated us to get a method for the oxidation of the C_3-C_4 enol double bond of these compounds. Pristimerin **1** and tingenone **2** have a double bond (C_3-C_4) which is part of a dissonant system. We could not oxidize it with the common reagents for this type of functionalization: H_2O_2 in alkaline medium[25], *tert*-butyl hydroperoxide[26] or sodium perborate[27] , which have been successfully used in the epoxidation of benzoquinones[28].

We now report the regio and stereoselective oxidation of C_3-C_4 enol double bond of pristimerin **1** and tingenone **2** using isolated dimethyl dioxirane in acetone solution.

The reactions were carried out by addition of an aliquot of standardized cold solution of ca. 0.1 M dimethyl dioxirane in acetone to stirred solutions of the substrates **1** and **2** in dry CH_2Cl_2 . After the reactions reached a suitable conversion (TLC monitoring), product isolation was achieved by removal of solvent in vacuum followed by TLC preparative chromatography.

Table 1: ^{1}H NMR (200 MHz) of 3-4.

H	3	4
1	6.40 d (1.4)	6.42 s
6	6.66 dd (1.4, 6.5)	6.69 d (6.5)
7	6.09 d (6.6)	6.12 d (6.6)
Me-23	1.60 s	1.61 s
Me-25	1.50 s	1.55 s
Me-26	1.22 s	1.30 s
Me-27	1.09 s	0.99 s
Me-28	1.18 s	1.00 s
Me-30	0.58 s	1.01 d (11.3)

Data (δ, $CDCl_3$)

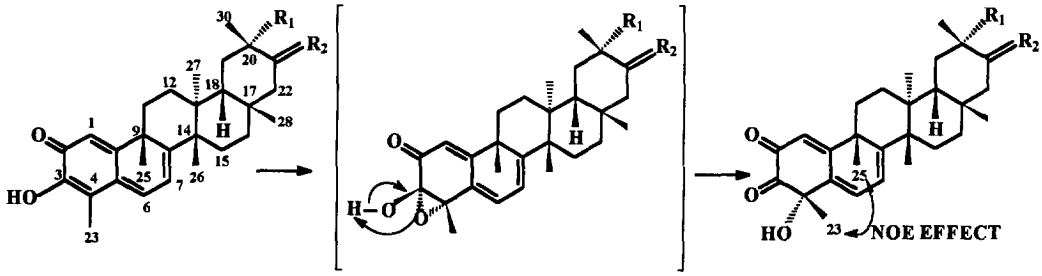
A ^{1}H-nmr analysis of the crudes of reaction before purification revealed that the products were generated as a 9:1 mixture of diastereomers. The main diastereomers were identified as 4α-hydroxy-pristimerin **3** and 4α-hydroxy-tingenone **4**.The minority diastereomers are the corresponding epimers in C-4 of **3** and **4**. The compound **3** (80%) was isolated as a yellow amorphous solid. Its IR spectra showed signals for hydroxyl groups (3500 cm^{-1}) and carbonyl groups (1720, 1650 cm^{-1}). **3** had a M^+ at m/z 480 and a molecular formula $C_{30}H_{40}O_5$. In the ^{1}H-nmr spectrum of **3** (Table 1) appeared a singlet (3H) at δ 1.60, which corresponds to Me-23. This signal was shifted 0.61 ppm upfield with respect to the Me-23 signal in **1**; The spectrum of **3** also showed an ABC system of three vinyl protons , namely, a double doublet at δ 6.66 and two doublets at δ 6.40 and δ 6.09. The three vinyl protons correspond to H-6, H-1 and H-7, which are characteristic of triterpenic quinoids system.

The ^{13} C-nmr spectrum and DEPT experiment (Table 2) of **3** revealed, as most significant signals, the presence of two carbonyl carbons at δ 183.1 (α,β unsaturated carbonyl carbon), and δ 199.2. These signals are attributable to C-2 and C-3 , respectively. The ^{13} C-nmr spectrum also show quaternary carbon linked to an oxygen at δ 81.1, corresponding to C-4. All foregoing data were confirmed by the two-dimensional NMR experiments, HMBC and HMQC.

Table 2: ^{13}C NMR (50 MHz) Data (δ, $CDCl_3$) of 3 and 4.

C	3	4	C	3	4	C	3	4
1	123.0	123.1	**11**	33.1	33.4	**21**	30.9	213.16
2	183.1	183.1	**12**	29.8	32.1	**22**	36.3	52.5
3	199.2	199.2	**13**	38.1	39.4	**23**	26.8	26.8
4	81.1	81.1	**14**	44.8	44.4	**25**	34.5	35.2
5	135.5	133.8	**15**	28.5	28.5	**26**	22.3	22.2
6	126.5	126.3	**16**	34.7	35.4	**27**	18.3	15.1
7	116.1	116.3	**17**	40.5	38.2	**28**	31.5	19.7
8	162.2	161.1	**18**	44.2	41.9	**30**	32.7	32.5
9	42.4	42.1	**19**	29.5	29.8	$\underline{C}OOCH_3$	178.8	-----
10	175.1	174.7	**20**	30.5	43.4	$COO\underline{C}H_3$	51.6	-----

Data based on HMBC and HMQC experiments.



1 R_1=$COOCH_3$ R_2=2H **Pristimerin**
2 R_1=H R_2=O **Tingenone**

3 4α-hydroxy-pristimerin
4 4α-hydroxy-tingenone

Scheme 1

The stereochemistry of the hydroxyl group on C-4 was resolved by a ROESY experiment showing NOE effect between the Me-23 and Me-25 (Scheme 1). Similar spectroscopic results were obtained for **4** (82%). Probably, the major diastereomers are formed via regioselective epoxidation of the reactive double bond (C_3-C_4) of **1** and **2**. For sterics reasons, the epoxides are presumably formed in the α face of **1** and **2**, as C-25 and

most of the Me groups are located in the β face. The intermediate epoxides, which have a singular hemiacetalic carbon C-3, are rearranged to 4α-hydroxy-pristimerin **3** and 4α-hydroxy-tingenone **4**, respectively, via an unknown mechanism. The corresponding 4α-hydroxy-derivatives **3** and **4** also turn out to be excellent heterodienes in Diels-Alder type reactions[29].

Our finding opens a new perspective for the site-selective oxyfunctionalization of molecules with heteroconjugated system.

EXPERIMENTAL

IR spectra were taken on a PE 681 spectrophotometer and ^{1}H and ^{13}C NMR on a Bruker W-200SY at 200 and 50 MHz, respectively, with TMS as internal reference. The HMBC , HMQC and ROESY were run on a Bruker at 400 MHz. MS were recorded on a VG Micromass ZAB-2F and a Hewlett Packard 5995. Schleicher-Schüll F-100/LS 254 and prep. TLC 1510/LS 254 foils were used for TLC. Oxone (potassium monoperoxosulfate), the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, was purchased from Aldrich and was used as received. Dimethyldioxirane (as acetone solution) was prepared according to the published procedure[5], and its peroxide content was determined[30] by oxidation of methyl phenyl sulfide, the latter quantitated by ^{1}H NMR. The solvents were purified by following standard literature methods. The dimethyldioxirane solutions were stored over molecular sieves (4Å) at -20°. The natural compounds **1** and **2** were isolated from *Maytenus canariensis*[31]. The purity of **1** and **2** used in the reactions with DMD, was estimated in 98 % by ^{1}H NMR.

Oxidation of Nor quinone methide triterpenes by Dimethyldioxirane. General Procedure.

The reactions were carried out by rapid addition of an aliquot of standardized cold solution of dimethyl dioxirane in acetone to stirred solutions of the substrates **1** and **2** in dry CH_2Cl_2, at room temperature. After the reactions reached a suitable conversion (TLC monitoring), product isolation was achieved by removal of solvent in vacuum followed by TLC preparative chromatography (AcOEt / n-hex ; (1/1)).

4α-hydroxy-pristimerin 3. Oxidation of **1** (40 mg, 0.08 mmol) with dimethyldioxirane (8 mL of a 0.09 M acetone solution) at room temperature for 4 h gave 32.4 mg (80%) of **3** as amorphous yellow solid; IR ν_{max} ($CHCl_3$) cm^{-1}: 3500, 2950, 1720, 1650, 1530, 1460, 1310, 1210, 1090, 845, 655 ;); EIMS m/z (%): 480 (M^+) (8), 465 (12), 423 (15), 394 (9), 241 (23), 218 (38), 203 (100), 147 (28), 121 (50); HREIMS: calculated for $C_{30}H_{40}O_5$, 480.28757; found 480.29067.

4α-hydroxy-tingenone 4. Oxidation of **2** (50 mg, 0.12 mmol) with dimethyldioxirane (10 mL of a 0.09 M acetone solution) at room temperature for 3 h afforded 41.7 mg (82 %) of **4** as amorphous yellow solid; IR ν_{max} ($CHCl_3$) cm^{-1}: 3500, 2950, 1800, 1650, 1540, 1450, 1370, 1270, 1200, 1080; EIMS m/z (%): 436 (M^+) (3),

380 (12), 366 (10), 351 (13), 215 (25), 187 (52), 149 (100), 121 (31)

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References

1.- Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.*, **1982**, *47*, 2670-2673.

2.- Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.*, **1991**, *124*, 227-232.

3.- Adam, W.; Hadjiarapoglou, L. *Topic in Current Chemistry*; Springer-Verlag: Berlin, Heidelberg. **1993**, *164*, pp. 45-62.

4.- Marples, B.A.; Muxworthy, J.P.; Baggaley, K.H. *Tetrahedron Lett.*, **1991**, *32*, 533-536.

5.- Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.*, **1991**, *124*, 2377.

6.- Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.*, **1989**, *22*, 205.

7.- Curci, R.; Fiorentino, M.; Troisi, L., Edwards, J.O., Pater, R.H. *J. Org. Chem.*, **1980**, *45*, 4758-4760.

8.- Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.*, **1992**, *57*, 5052-5054.

9.- Curci, R.; Detomaso, A.; Prencipe, T.; Carpenter, G.B. *J. Am. Chem. Soc.*, **1994**, *116*, 8112-8115.

10.- Adam, W.; Golsch, D.; Hadjiaraproglou, L.; Patonay, T. *J. Org. Chem.*, **1991**, *56*, 7292-7297.See references therein.

11.- Nemes, C.; Levai, A.; Patonay, T.; Toth, G.; Boros, S.; Halasz, J.; Adam, W.; Golsch, D. *J. Org. Chem.*, **1994**, *59*, 900-905.

12.- Adam, W.; Golsch, D.; Hadjiarapoglou, L.; Levai, A.; Nemes, C.; Patonay, T. *Tetrahedron*, **1994**, *50*, 13113-13120.

13.- Curci R.; D' Accolti L.; Fiorentino M.; Rosa A.; *Tetrahedron Lett.*, **1995**, *36*, 5831-5834.

14.- Troisi, L; Cassidei, L.; Lopez, L.; Mello, R.; Curci, R. *Tetrahedron Lett.*, **1989**, *30*, 257-260.

15.- Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.*, **1991**, *124*, 227-232.

16.- Brown, P.M.; Moir, M.; Thomson, R.H.; King, T.J.; Krishnamoorthy, V.; Seshadri, T.R. *J.C.S. Perkin Trans. I*, **1973**, 2721-2725.

17.- Moujir, L.; Gutiérrez, A.M.; González, A.G.; Jiménez, J. *Biomed. Lett.*, **1991**, *46*, 715.

18.- Nakanishi, K.; Takahashi, Y.; Budsikewicz, H. *J. Org. Chem.*, **1965**, *30*, 1729-1734.

19.- Gutiérrez, A.; Moujir, L.; González, A.G.; Ravelo, A.G.; Luis, J.G. *Antimicrobial Agents and Chemotherapy*, **1991**, *35*, 211-213.

20.- González, A.G.; Ravelo, A.G.; Bazzocchi, I.L.; Mendoza, J.J.; González, C.M.; Luis, J.G.; Ferro, E.A.;

Gutiérrez, A.; Moujir, L.; de Las Heras, F.G. *Il Farmaco*, **1988**, *43*, 501-505.

21.- González, A.G.; Mendoza, J.J.; Luis, J.G.; Ravelo, A.G.; Bazzocchi, I.L. *Tetrahedron Lett.*, **1989**, *30*, 863-866.

22.- González, A.G.; Jiménez, J.S.; Moujir, L.; Ravelo, A.G.; Luis, J.G.; Bazzocchi, I.L.; Gutiengos, A.M. *Tetrahedron.*, **1992**, *48*, 769-774.

23.- González, A.G.; Crespo, A.; Ravelo, A.G.; Muñoz, O. *Nat. Prod. Lett.*, **1994**, *4*, 165-169.

24.- Itokawa, H.; Shirota, O.; Morita, H.; Takeya, K.; Tomioka, N.; Itai, A. *Tetrahedron Lett.*, **1990**, *31*, 6881-6882.

25.- Solladié, G.; Hutt, J.H. *J. Org. Chem.*, **1987**, *52*, 3560.

26.- Sehlessinger, R.H.; Bebernitz, G.R.; Lin, P. *J. Am. Chem. Soc.*, **1985**, *107*, 1777.

27.- Straub, T.S. *Tetrahedron Lett.*, **1995**, *36*, 663-664.

28.- Rashid, A.; Reed, G.; *J. Chem. Soc.* (C), **1967** ,1323.

29.- Alvarenga, N.L.; *Tesis Doctoral.* **1995**, Universidad de La Laguna.

30.- González, A.G.; Alvarenga, N.L.; Rodriguez F.; Ravelo, A.G.; Jiménez, I.A.; Bazzocchi, I.L.; Gupta M. P. *Nat. Prod. Lett.*, **1995**, *7*, 209-218.

31.- Adam, W.; Chan Y.; Cremer D.; Gauss J.; Scheutzow D.; Schindler M. *J.Org. Chem.*, 1987, *52*, 2800-2803.

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