Ring A Functionalization of Terpenoids by the Unusual Baeyer-Villiger Rearrangement of Aliphatic Aldehydes

Alejandro F. Barrero,* [a] E. J. Alvarez-Manzaneda, [a] R. Alvarez-Manzaneda,[b] Rachid Chahboun [a], R. Meneses[a], Marta Aparicio B.[b]

[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada, Spain

[b]Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Almería, 04120 Almería, Spain

Fax +34 58 24 33 18; E-mail: afbarre@goliat.ugr.es

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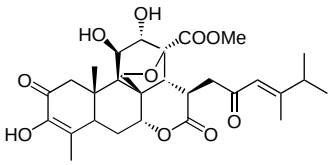
Abstract: A new methodology is described for transforming resinic acids into *nor*-alcohols and *nor*-olefins, *via* the Baeyer-Villiger rearrangement of the derived aldehyde. Based on this methodology 4-hydroxy-18-*nor*-abieta-8,11,13-trien-7-one and 18-*nor*-abieta-8,11,13-triene-4,7α−diol, two new terpenoids recently described, have been synthesized from abietic acid.

Key words: Baeyer-Villiger rearrangement, nor-Terpenes

Some interesting terpenoids, due to their biological activity, have a functionalized A-ring structure. Representative compounds are quassinoids, such as bruceantin (**1**), [1] and the antiherpes *nor*-diterpenes **2** and **3.**[2] Over the last few years the isolation of different natural *nor*-terpenes, e.g. **4-6, 12c** and **20**, has been reported .[3,4]



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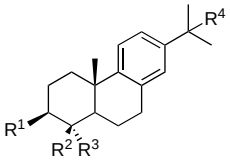
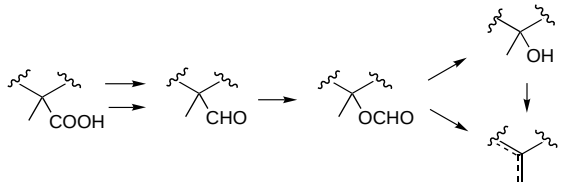


2 R^1: OH; R^2, R^3: $=CH_2$; R^4: H
3 R^1: OH; R^2, R^3: =O; R^4: H
4 R^1: H; R^2: Me; R^3: OH; R^4: H
5 R^1: H; R^2: OH; R^3: Me; R^4: H
6 R^1: H; R^2: Me; R^3: OH; R^4: OH

Following the authors' research into the synthesis of valuable compounds from available natural diterpenes, [5,6] we are now dealing with the synthesis of A-ring functionalized terpenes, such as quassinoids and other *nor*-terpenes, from terpenic acids by removing the carboxylic group through the corresponding aldehyde.

The most common and widely studied reagent for oxidative decarboxylation, lead tetraacetate, usually produces a mixture of unsaturated hydrocarbons with small admixtures of acetates and the corresponding alcohols.[7] The oxidative decarboxylation by hydrogen peroxide and a mercury (II) salt has also been used to transform carboxylic acids into the corresponding *nor*-derivatives.[8] The Barton decarboxylation method has become a suitable procedure for preparing olefins, *nor*-hydroperoxides or *nor*-alcohols from carboxylic acids.[9,11] **2** and **3** were synthesized by applying the Barton decarboxylation protocol.[2]

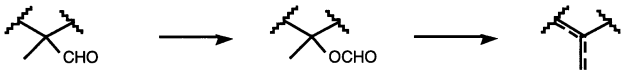
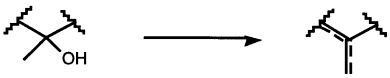
Aldehydes undergo Baeyer-Villiger rearrangement to give carboxylic acids due to preferential migration of hydrogen. Alternative migration of the carbon group to yield formates seldom occurs. Aryl aldehydes having electron-releasing groups are the only exceptions and are converted to aryl formates by the Baeyer-Villiger oxidation. At the present time only a few examples of the preferred migration of a carbon moiety in an aliphatic aldehyde have been reported.[12-14] Recently we have found that aldehyde **7a** is transformed with an excellent yield into the formate **7b** through peroxyacid treatment.[15] In order to elucidate the scope and synthetic applications of this reaction the behaviour of aldehydes **8a-12a** having a variety of carbon skeletons, including mono-, di-, tri- and tetracyclic structures, and different additional functions have been studied. They were efficiently prepared with an 65-70% overall yield from carboxylic acid in a two-step sequence involving reduction with lithium aluminium hydride and further oxidation with pyridinium chlorochromate. Treatment of these aldehydes with peroxyacid afforded the corresponding formates **8b-12b** as the only product in all cases. These esters might easily be transformed into the derived alcohols or olefins (Scheme 1). The complete sequence constitutes a simple and efficient way for transforming terpenic acids into the corresponding *nor*-alcohols and *nor*-olefins.

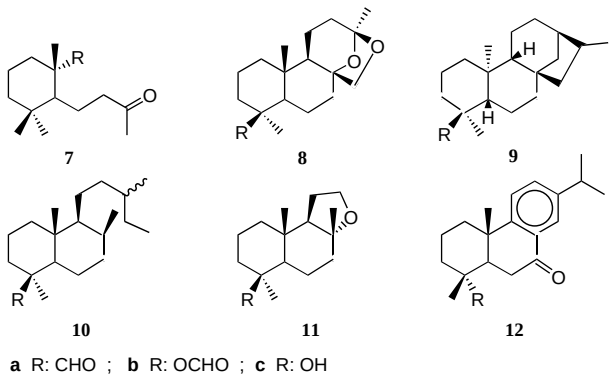


Scheme 1

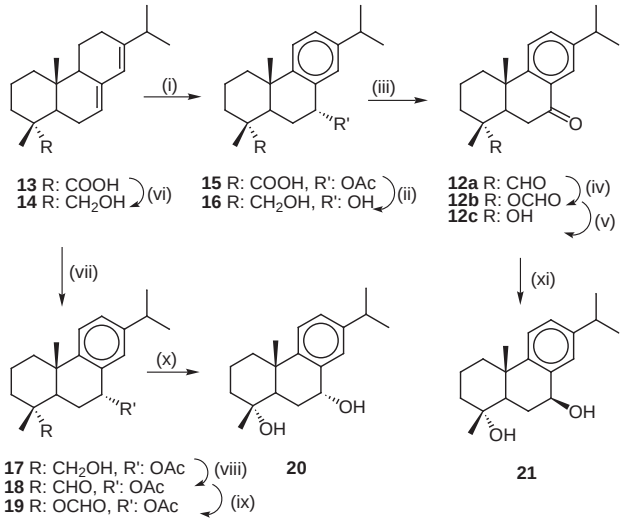
Time reactions and yields of the steps leading from **7a-12a** to the derived *nor*-alcohols and *nor*-olefins are summarized in Table 1.

Table1 Synthesis of *nor*-alcohols and *nor*-olefins from aldehydes

				
	t, %	t, % (exo:endo)	t, %	t, % (exo:endo)
7a	10h, **7b** (85%)	48h, 85% (10:1)	4h, **7c** (95%)	
8a	15h, **8b** (90%)	45h, 90% (1:1)	4h, **8c** (91%)	13h, 90% (9:2)
9a	35h, **9b** (51%)	40h, 93% (2:1)	2h, **9c** (90%)	15h, 89% (10:1)
10a	20h, **10b** (85%)	72h, 70% (1:4)	3h, **10c** (92%)	14h, 91% (5:1)
11a	41h, **11b** (81%)	52h, 90% (5:2)	2h,**11c** (85%)	15h, 93% (4:1)
12a	5h, **12b** (95%)	12h, 90% (7:1)	1h, **12c** (94%)	12h, 90% (4:1)



a R: CHO ; **b** R: OCHO ; **c** R: OH



(i) $Hg(OAc)_2$ (2.2 eq), toluene, reflux, 1h (85 %). (ii) $LiAlH_4$, THF, reflux, 15h (96 %). (iii) PCC (4 eq) , CH_2Cl_2, rt, 45 min (75 %). (iv) MCPBA (2.5 eq), anh. CH_2Cl_2, Na_2HPO_4 (2.75 eq), reflux, 5h, (95%). (v) 2 N KOH-MeOH, reflux, 1h (94%). (vi) $LiAlH_4$, THF, reflux,10h (81 %). (vii) $Hg(OAc)_2$ (2.2 eq), toluene, reflux, 1h (80%). (viii) PCC (2 eq) , CH_2Cl_2, rt, 45 min (71 %). (ix) MCPBA (2.5 eq), anh. CH_2Cl_2, Na_2HPO_4 (2.75 eq), reflux,3h (89 %). (x) 2 N KOH-MeOH, reflux, 1h (95 %). (xi) $NaBH_4$, EtOH, 0 °C,1h (93%).

Scheme 2

The treatment of the aldehyde with *m*-chloroperbenzoic acid in methylene chloride at 50°C afforded the corresponding formate with retention of the configuration, which was converted into a mixture of the exo- and endo-olefins by refluxing in collidine. Alternatively, the formate was quantitatively saponified to the *nor*-alcohol, that gave the olefins by treating with mesyl chloride and pyridine at room temperature. As was to be expected, the Baeyer-Villiger rearrangement of equatorial aldehyde (**12a**) was faster than that of the axial ones. Moreover, in most cases elimination took place in high regioselectivity affording the exo isomer as the main compound.

This procedure may be more advantageous for preparing *nor*-alcohols than the above mentioned radical decarboxylations, since epimerization is avoided.[8] Based on this methodology we have synthesized **12c** and **20**, two new terpenoids isolated from *J. chinensis*[3] and *L. kaempferi*[4] respectively, from abietic acid (**13**) (Scheme 2).

Treatment of **13** with mercuric acetate afforded the 7α-acetoxyderivative **15**, [16] which was reduced to give the diol **16**. Treatment of **16** with PCC afforded the ketoaldehyde **12a** which, when treated with m-chloroperbenzoic acid, gave the ketoester **12b**, which after saponification with refluxing 2N KOH-MeOH yielded **12c**, whose physical and spectroscopic properties were identical to those reported in the literature.[3] **12c** is an immediate precursor of actives terpenoids **2** and **3**.[2]

Alternatively, reduction of **13** with $LiAlH_4$ gave **14**, which after treating with mercuric acetate yielded **17**, which was oxydized with PCC to the aldehyde **18**. This underwent Baeyer-Villiger rearrangement to afford the diester **19** which was saponified to give **20**, whose physical and spectroscopic properties were identical to those reported for the natural compound.[4] Treatment of **12c** with $NaBH_4$ gave the 7β-isomer **21**, which had the expected spectroscopic properties.

Acknowledgement

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(17) For preparation of **7a** see ref 15. The synthesis of **8a** and **11a** is described in ref 6. **9a** was obtained by catalytic (Pd/C) hydrogenation of *ent*-kaur-16-en-18-ol and further oxidation with PCC. **10a** was obtained after hidrogenation over Pd/C of a mixture of methyl *cis*-, *trans*- and mirceocommunate.
Typical Experimental Procedures
*Preparation of aldehydes **8a-12a***
To a stirred solution of carboxylic acid (1 eq) in dry THF was added $LiAlH_4$ and the mixture was stirred under reflux for 15 h. The reaction mixture was poured into ice, then ether was added and filtered under vacuum. The layers were separed and the aqueous phase extracted with ether. After washing the organic layer with brine, it was dried and evaporated to yield the corresponding alcohol which was oxydized without further purification.
To a stirred solution of alcohol (1 eq) in CH_2Cl_2 was added PCC (1.5 eq) and the mixture was stirred at room temperature for 45-60 min. Then it was filtered through a short silicagel column under argon (eluted with ether) and the solvent was evaporated under reduced pressure affording the aldehyde.
*Treatment of aldehydes **8a-12a** with MCPBA: Preparation of formates **8b-12b**.*
To a stirred solution of aldehyde (1 eq) in CH_2Cl_2 was added a solution of MCPBA (2.5 eq) in CH_2Cl_2 and Na_2HPO_4 (2.75 eq) and the mixture was stirred under reflux. The solvent was evaporated under reduced pressure to give a crude which upon silica gel chromatography (hexane-ether as eluent) afforded the formate.
*Treatment of formates **8b-12b** with collidine: Preparation of nor-olefins.*
A solution of formate in collidine was stirred under reflux. The mixture was cooled to room temperature, diluted with ether and washed with 2N HCl and brine. The organic layer was dried and concentrated under reduced pressure to afford the *nor*-olefins.
*Saponification of formates **8b-12b**: Preparation of nor-alcohols **8c-12c**.*
To a solution of formate in MeOH was added a 2N solution of KOH in MeOH and the mixture was refluxed for 1 h. The solvent was evaporated and the crude was diluted with ether and washed with water. The organic layer was dried and concentrated under reduced pressure to afford the *nor*-alcohols **8c-12c**.
*Dehydration of alcohols **8c-12c**: Preparation of nor-olefins.*
To a solution of alcohol in pyridine was added at 0° C MsCl (3 eq) and the mixture was stirred at room temperature. Then the mixture was poured into ice and extracted with ether. The organic layer was washed with 2 N HCl, saturated $NaHCO_3$ and brine, and then it was dried and concentrated under reduced pressure to give the *nor*-olefin.
(18) All new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data.
Selected data:
12a ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.24 (s, 3H, Me-20), 1.25 (d, J= 6.9 Hz, 6H, Me-16, Me-17), 1.29 (s, 3H, Me-19), 1.48 (m, 1H), 1.87 (m, 1H), 2.26 (dd, J= 17.9, 3.5 Hz, 1H, H-6), 2.40 (dt, J= 12.8, 3.2 Hz, 1H), 2.44 (dd, J= 14.2, 3.5 Hz, 1H, H-5), 2.68 (dd, J= 17.9, 14.2 Hz, 1H, H-6), 2.91 (h, J= 6.9 Hz, 1H, H-15), 7.32 (d, J= 8.1 Hz, 1H, H-11), 7.42 (dd, J= 8.14, 2.1 Hz, 1H, H-12), 7.88 (d, J= 2.12 Hz, 1H, H-14), 9.25 (s, 1H, H-18). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$) δ : 37.5* (C-1), 17.3 (C-2), 37.0* (C-3), 49.2 (C-4), 41.7 (C-5), 32.2 (C-6), 197.8 (C-7), 130.6 (C-8), 152.4 (C-9), 36.7 (C-10), 123.6 (C-11), 132.7 (C-12), 147.1 (C-13), 125.2 (C-14), 33.6 (C-15), 23.7 (C-16), 23.7 (C-17), 204.6 (C-18), 14.1 (C-19), 23.7 (C-20) (*: interchangeable signals)
12b ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.25 (s, 3H, Me-20), 1.25 (d, J= 6.9 Hz, 6H, Me-16, Me-17), 1.65 (s, 3H, Me-19), 1.88 (m, 1H), 2.32 (m, 1H), 2.51 (dd, J= 14.1, 3.4 Hz, 1H, H-5), 2.67 (dd, J= 17.7, 14.1 Hz, 1H, H-6), 2.74 (m, 1H), 2.91 (dd, J= 17.7, 3.4 Hz, 1H, H-6), 2.93 (h, J= 6.9 Hz, 1H, H-15), 7.29 (d, J= 8.2 Hz, 1H, H-14), 7.42 (dd, J= 8.2, 2.1 Hz, 1H, H-12), 7.89 (d, J= 2.1 Hz, 1H, H-11), 7.96 (s, 1H, H-18). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$) δ : 36.7 (C-1), 19.7 (C-2), 37.5 (C-3), 85.3 (C-4), 48.1 (C-5), 35.2 (C-6), 198.2 (C-7), 130.5 (C-8), 152.1 (C-9), 38.6 (C-10), 123.8 (C-11), 132.7 (C-12), 147.1 (C-13), 125.0 (C-14), 33.6 (C-15), 23.1 (C-16), 23.8 (C-17), 159.9 (C-18), 26.9 (C-19), 19.9 (C-20).
15 ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.20 (s, 3H, Me-20), 1.23 (d, J=6.9 Hz, 6H, Me-16, Me-17), 1.28 (s, 3H, Me-19), 2.02 (s, 3H, AcO), 2.32 (bd, J=12.4 Hz), 2.64 (dd, J= 12.7, 1.5 Hz), 2.86 (h, J= 6.9 Hz, 1H, H-15), 5.89 (bs, 1H, H-7), 7.04 (d, J=1.8 Hz, 1H, H-14), 7.16 (dd, J= 8.2, 1.8 Hz, H-12), 7.25 (d, J= 8.2 Hz, 1H, H-11).
^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ : 37.6 (C-1), 18.5 (C-2), 36.5 (C-3), 47.0 (C-4), 40.0 (C-5), 28.2 (C-6), 71.0 (C-7), 131.9 (C-8), 147.6* (C-9), 37.3 (C-10), 124.5 (C-11), 128.5 (C-12), 146.6* (C-13), 127.3 (C-14), 33.5 (C-15), 23.8# (C-16), 23.7# (C-17), 184.8 (C-18), 16.1 (C-19), 24.0# (C-20) (* and #: interchangeable signals).
18 ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.15 (s, 3H, Me-20), 1.19 (s, 3H, Me-19), 1.21 (d, J= 7.1 Hz, 6H, Me-16, Me-17), 2.06 (s, 3H, AcO), 2.85 (h, J= 7.1 Hz, 1H, H-15), 5.95 (d, J=2.9 Hz, 1H, H-7), 7.06 (d, J=1.8 Hz, 1H, H-14), 7.17 (dd, J=8.3, 1.8 Hz, 1H, H-11), 7.24 (d, J=8.3 Hz, 1H, H-12). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ : 37.5* (C-1), 17.8 (C-2), 32.1 (C-3), 49.4 (C-4), 49.1 (C-5), 28.3 (C-6), 70.1 (C-7), 131.9 (C-8), 146.9 (C-9), 39.3 (C-10), 124.4 (C-11), 127.3 (C-12), 146.9 (C-13), 128.5 (C-14), 33.5 (C-15), 23.9 (C-16), 24.3 (C-17), 205.8 (C-18), 23.8 (C-19), 14.1 (C-20).

19 ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.14 (s, 3H, Me-20), 1.21 (d, J= 6.9 Hz, 3H, Me-16) 1.22 (d, J=6.9 Hz, 3H, Me-17), 1.54 (s, 3H, Me-19), 2.06 (s, 3H, AcO), 2.40 (dd, J=12.8, 1.9 Hz, 1H), 2.65 (dd, J=9.4, 3.5 Hz, 1H), 2.96 (h, J= 6.9 Hz, 1H, H-15), 5.99 (dd, J=4.3, 1.7 Hz, 1H, H-7), 7.05 (d, J=1.8 Hz, 1H, H-14), 7.17 (dd, J=8.3, 1.9 Hz, 1H, H-11), 7.22 (d, J=8.3 Hz, 1H, H-12), 8.01 (s, 1H, OCHO). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ : 37.1* (C-1), 20.0 (C-2), 37.6* (C-3), 86.3 (C-4), 44.5 (C-5), 25.3 (C-6), 70.4 (C-7), 131.9 (C-8), 146.9(C-9), 38.6 (C-10), 124.7 (C-11), 127.4 (C-12), 146.9 (C-13), 128.5 (C-14), 33.5 (C-15), 23.9 (C-16), 24.3 (C-17), 160.3 (C-18), 23.8 (C-19), 19.9 (C-20), 21.6 (CH_3CO) (*: interchangeable signals).

21 ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.04 (s, 3H, Me-20), 1.18 (s, 3H, Me-19), 1.24 (d, J= 6.9 Hz, 6H, Me-16, Me-17), 2.03 (dt, J=12.6, 5.9 Hz, 1H), 2.22-2.39 (m, 3H), 2.89 (h, J= 6.9 Hz, 1H, H-15), 4.86 (dd, J=9.4, 7.9 Hz, 1H, H-7), 7.10 (dd, J=8.1, 1.9 Hz, 1H, H-11), 7.20 (d, J=8.1 Hz, 1H, H-12), 7.45 (d, J=1.9 Hz, 1H, H-14). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ : 36.1* (C-1), 23.6 (C-2), 38.4* (C-3), 70.7 (C-4), 46.3 (C-5), 32.3 (C-6), 70.4 (C-7), 137.9 (C-8), 144.5(C-9), 39.7 (C-10), 124.9 (C-11), 125.3 (C-12), 146.6 (C-13), 125.7 (C-14), 33.8 (C-15), 23.9 (C-16), 24.1 (C-17), 23.6 (C-19), 22.9 (C-20) (*: interchangeable signals).

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