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Synthetic modification of isocostic acid isolated from *Dittrichia viscosa*: Rapid access to new and know eudesmane acids

M. Zaki[(a,b)*], A. El hakmaoui[(a)], M-A. Hiebel[(b)], S. Berteina-Raboin[(b)], M. Akssira[(a)]

[(a)] Laboratoire de Chimie Physique & Chimie Bioorganique, Département de Chimie, URA C 22, Pôle RéPAM, F. S. T. University Hassan II de Casablanca, B.P. 146 Yasmina, 28800, Mohammedia, Morocco
[(b)] Institut de Chimie Organique et Analytique, University d'Orléans, UMR CNRS 7311, B.P. 6759, 45067 Orléans cedex 2, France

** Corresponding author:*
zaki.smc@gmail.com
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Abstract

The aerial part of *Dittrichia viscosa* is an important renewable source of isocostic acid **1** which was isolated in gram-scale. This isocostic acid **1** is an appropriate starting material for a rapid and efficient synthesis of new eudesmane acids 3,4-epoxy-α-eudesma-12-oic acid **2b,** 3-oxo-4-dehydroeudesma-12-oic acid **4b,** and known eudesmane acids viscic acid **5b**, β-isocostic acid **6b**, 3,5,11(13)-trieneudesma-12-oic acid **7b** and 5-α-hydroxycostic acid **8b** which were isolated from different plants with very low yields.

Keywords: *Isocostic acid; Dittrichia Viscosa; Eudesmane acid.*

1. Introduction

Dittrichia viscosa (L.) W. Greuter is a tough plant that is widespread in the Mediterranean region [1]. It has important anti-inflammatory, antipyretic and anthelmintic properties [2-3]. Considered as an invasive species and particularly abundant in wasteland areas, this perennial plant proved to be a rich source of sesquiterpenes with eudesmane scaffolds. It could accordingly be used as a renewable source of isocostic acid **1** isolated in gram-scale [4-5] (Figure 1). Eudesman acids as viscic acid **5b**, *β*-isocostic acid **6b**, 3,5,11(13)-trieneudesma-12-oic acid **7b** and 5-*α*-hydroxycostic acid **8b** are natural products that have received little pharmacological attention because their very low isolated yields from plants. Viscic acid **5b** was isolated from *Inula viscosa* by A. Ulubelen *et al* [6]. and from *Inula Graveolens* by S. Öksüz [7]. *β*-Isocostic acid **6b** was isolated from *Eupatorium* by Bohlmann *et al* [8]. and from *Laggera alata* by G.-C. Wang [9]. 3,5,11(13)-Trieneudesma-12-oic acid **7b** was reported as a synthetic artifact from bromination of ilicic acid [10-11]. 5-*α*-Hydroxycostic acid **8b** was isolated from *Jasonia Montana* by A. A. Ahmed [12-13]. As a part of our work on the phytochemical study of Moroccan plants as a source of convenient new natural compound based starting materials, we report herein the use of *α*-isocostic acid isolated from *Dittrichia viscosa* (L.) W. Greuter as a starting material for an efficient and rapid synthesis of two new eudesmane derivatives 3,4-epoxy-*α*-eudesma-12-oic acid **2b** and 3-oxo-4-dehydroeudesma-12-oic acid **4b** and for the synthesis of the know eudesmane derivatives viscic acid **5b**, *β*-isocostic acid **6b**, 3,5,11(13)-trieneudesma-12-oic acid **7b** and 5-*α*-hydroxycostic acid **8b** (Figure 1).

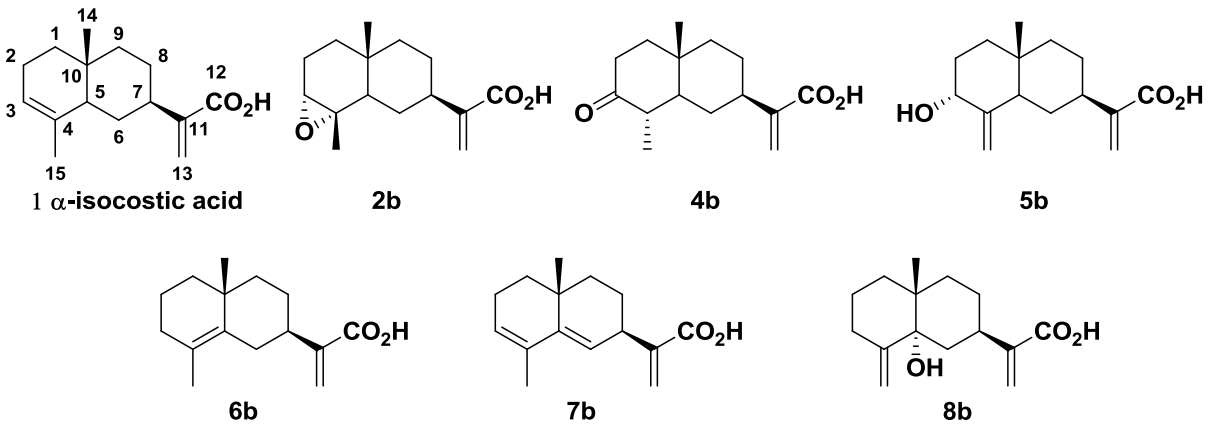


Figure 1. *α*-isocostic acid and its derivatives.

2. Materials and methods

All reagents were purchased from commercial suppliers and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230-400 mesh, 0.040-0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker avance 400.13 (^{13}C, 101MHz), or on a Bruker advance III HD nanobay 400.13 (^{13}C, 101 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiple. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities were determined by the DEPT 135 sequence. High resolution mass spectra (HRMS (ESI)) were performed on a Maxis Bruker 4G by the "Federation de Recherche" ICOA/CBM (FR2708) platform.

3. Results and Discussions

First α-isocostic acid, extracted from *Dittrichia viscosa*, was esterified to facilitate its further manipulation (scheme 1). Then treatment with *m*-chloroperbenzoic acid gave the expected product **2a** in 70 % yield as a unique diastereoisomer. The NOESY NMR (Figure 2) proved unable to determine the relative configuration of the epoxide by the presence of various correlations especially between the protons H-3 and H-15 and between the protons H-15 and H-14. However the broad singlet signal of H-3 at δ 2.86 ppm in ^{1}H NMR corroborates a pseudo equatorial position of this proton. Furthermore, the attack of the epoxidating agent from the less sterically congested side of the double bond opposite to the C-7 unsaturated ester seemed to be the most expected. Finally, this hypothesis was confirmed by comparing our experimental data with the literature [14]. Compound **2a** was next saponified to give 3,4-epoxy-α-eudesma-12-oic acid **2b** in 84 % yield. The ^{13}C NMR confirmed the presence of the acid fonction at δ 172.5 ppm.

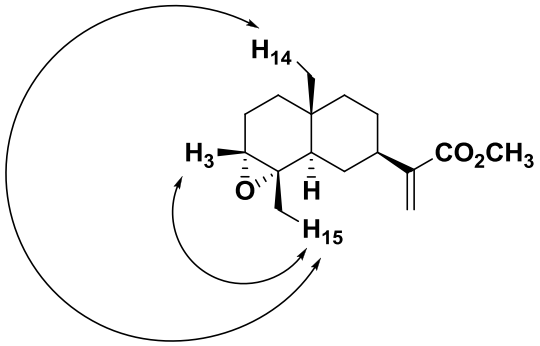
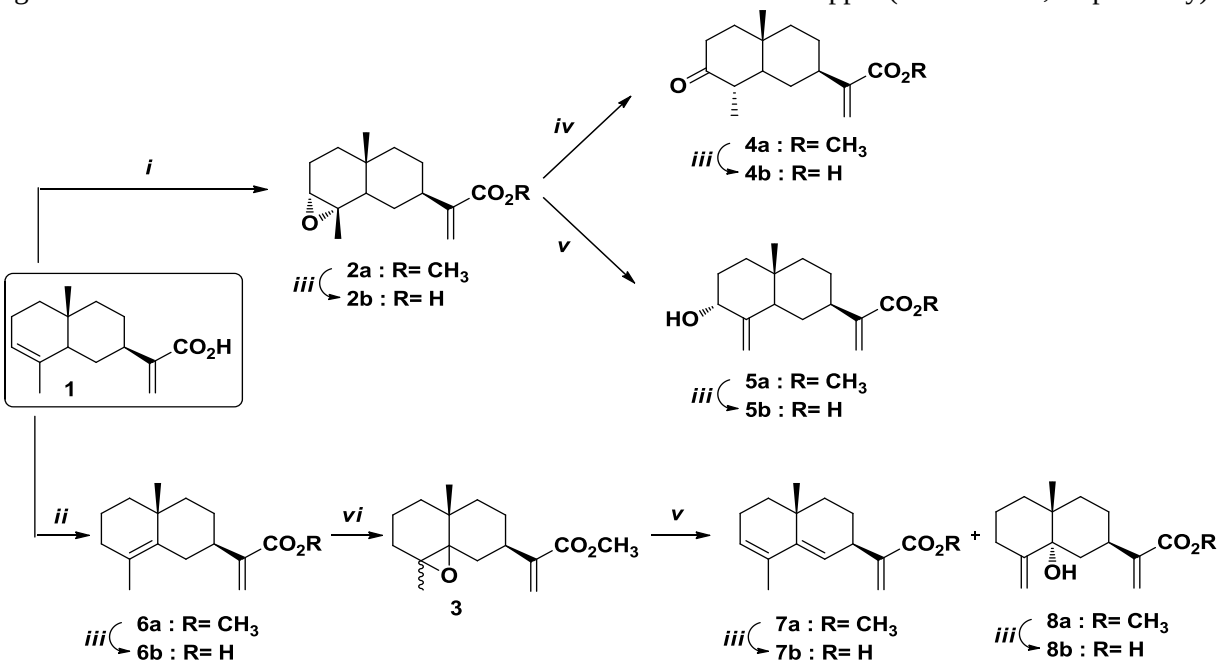


Figure 2.

The treatment of epoxide **2a** with $BF_3.Et_2O$ in CH_2Cl_2 at room temperature for 30 min gave selectively the ketone **4a** in 70 %. The exact configuration was verified by an X-ray diffraction analysis [15]. In the same way the saponification of ketone allows to obtain 3-oxo-4-dehydroeudesma-12-oic acid **4b** in 78 % yield. ^{13}C NMR confirmed the presence of the ketone with a quaternary signal at δ 213.3 ppm and the acid function at δ 172.6 ppm. However, the unsaturated alcohol **5a** was mainly obtained with *p*-toluenesulfonic acid (PTSA) in 72 % yield. Finally, the 3α-hydroxy-β-eudesma-12-oic acid **5b** was obtained in 88 % yield by the saponification of compound **5a**. The structure of **5b** was confirmed by the appearance of an additional double bond signal in ^{1}H NMR spectra (δ 4.57 and 4.94 ppm) and ^{13}C NMR spectra (δ 109.5 and 151.8 ppm). In another way, when the sulfuric acid was used, the esterification of the acid function was accompanied by the migration of the double bond from the position 3-4 to 4-5. The spectral data of the obtained ester are identical with those described in literature [16]. The 4,11-dieneudesma-12-oic acid **6b** was obtained in 78 % yield by the saponification of compound **6a**. Then the same approach was tested on 4,5-epoxy eudesmane scaffold **3** obtained in 70 % yield in presence of *m*-chloroperbenzoic acid. Unfortunately, in this case the epoxidation step gave access to a mixture of two diastereoisomers α:β in 4:3 proportions. Each isomer was clearly identified thanks to ^{1}H NMR comparison with the literature data [17]. Thus; the treatment of epoxide **3** with PTSA in CH_2Cl_2 at room temperature afforded the alcohol **7a** in 60 % yield along with triene **7a** in 38 % yield. The ^{1}H and ^{13}C NMR spectra of **8a** were identical to those reported in the literature [4]. The structure assigned to the eudesma methyl carboxylate **8a** and its absolute configuration were confirmed by X-ray diffraction analysis of a single crystal of **8a** and only the α-OH isomer was isolated [18]. The saponification of compounds **7a** and **8a** afforded the corresponding 3,5,11-trieneudesma-12-oic acid **7b** and 5α-Hydroxy-β-eudesma-12-oic acid **8b** in 80 and 82 % yield, respectively. The structure of the conjugated diene **7b** was established on the basis of its ^{1}H, ^{13}C NMR spectra. Two signals

corresponding to olefinic protons appeared at δ 5.21 ppm (H-6) and 5.60 ppm (H-3). DEPT analysis underlined the presence of two tertiary carbons at δ 75.6 and 69.8 ppm (C-3 and C-6 respectively) and two quaternary carbons indicating the existence of two trisubstituted double bonds at 142.1 and 133.3 ppm (C-5 and C-4, respectively).



Scheme 1. Reagents and conditions: *i*. a) $TMSCHN_2$, PhMe/MeOH, 0°C; b) m-CPBA, rt, 3h; *ii*. H_2SO_4/MeOH, 80°C, 24h; *iii*. NaOH/MeOH, H^+/H_2O; *iv*. $BF_3.Et_2O$, rt, 30 min; *v*. PTSA, rt, 30 min; *vi*. m-CPBA, rt, 3h.

Experimental data

3,4-epoxy-*α*-eudesma-12-oic acid (2b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 5.68 (d, J = 1.4 Hz, 1H), 4.95 (t, J = 1.5 Hz, 1H), 4.57 (t, J = 1.7 Hz, 1H), 4.31 (s, 1H), 2.58 (ddt, J = 12.2, 7.8, 3.7 Hz, 1H), 2.48 – 2.41 (m, 1H), 1.85 – 1.60 (m, 3H), 1.57 – 1.37 (m, 2H), 1.26 – 1.25 (s, 3H), 0.97 – 0.81 (m, 3H), 0.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 151.9, 145.4, 125.2, 109.5, 73.9, 44.0, 41.0, 39.7, 36.1, 35.9, 30.0, 29.9, 27.5, 15.9; HRMS (ESI): calcd. For $C_{15}H_{23}O_3$ $[M + H]^+$ 251.1752; found 251.1753.

3-oxo-4-dehydroeudesma-12-oic acid (4b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 5.67 (s, 1H), 2.58 – 2.38 (m, 2H), 2.34 (ddt, *J* = 14.9, 3.9, 1.9 Hz, 1H), 2.21 (dq, *J* = 12.8, 6.5 Hz, 1H), 1.73 (dddd, *J* = 18.8, 16.8, 9.0, 4.4 Hz, 3H), 1.54 (dtt, *J* = 25.4, 12.6, 3.4 Hz, 3H), 1.33 – 1.13 (m, 3H), 1.10 (s, 3H), 0.97 (dd, *J* = 6.7, 1.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.3, 172.6, 144.9, 125.7, 51.3, 45.7, 41.5, 41.0, 39.5, 38.4, 33.8, 31.5, 27.3, 16.8, 11.6; HRMS (ESI): calcd. For $C_{15}H_{23}O_3$ $[M + H]^+$ 251.1800; found 251.1798.

3*α*-hydroxy-*β*-eudesma-12-oic acid (5b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 5.67 (s, 1H), 4.94 (t, *J* = 1.5 Hz, 1H), 4.57 (t, *J* = 1.7 Hz, 1H), 4.31 (t, *J* = 2.6 Hz, 1H), 2.58 (tt, *J* = 12.2, 3.6 Hz, 1H), 2.47 – 2.40 (m, 1H), 1.87 – 1.60 (m, 5H), 1.56 – 1.36 (m, 3H), 1.32 – 1.21 (m, 3H), 0.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 151.8, 145.6, 125.1, 109.5, 73.9, 44.0, 40.9, 39.7, 36.1, 35.9, 29.9, 29.9, 27.5, 15.9; HRMS (ESI): calcd. For $C_{15}H_{23}O_3$ $[M + H]^+$ 251.1798; found 251.1801.

β-isocostic acid (6b)

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.16 (s, 1H), 5.56 (s, 1H), 2.63 (ddd, 1H, J = 13.6, 3.3, 2.2Hz), 2.32- 2.43 (m, 1H), 1.46-2.04 (m, 10H), 1.22-1.42 (m, 4H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) : δ 170.0, 145.8, 134.4, 125.2,122.5, 42.2, 40.7, 40.3, 34.6, 33.2, 31.5, 28.2, 24.7, 19.4, 19.2 ppm. HRMS (ESI): calcd. For $C_{15}H_{21}O_2$ $[M + H]^+$ 235.1645; found 235.1643.

3,5,11-trieneudesma-12-oic acid (7b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (d, J = 1.4 Hz, 1H), 5.60 (d, J = 1.3 Hz, 1H), 5.21 (d, J = 5.9 Hz, 1H), 4.03 – 3.98 (m, 1H), 3.02 – 2.95 (m, 1H), 2.13 – 2.01 (m, 1H), 1.92 (s, 3H), 1.81 – 1.57 (m, 4H), 1.53 (ddd, J = 13.4, 4.7, 3.4 Hz, 1H), 1.37 – 1.22 (m, 2H), 1.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 142.1, 138.5, 133.3, 121.0, 75.6, 69.8, 41.4, 37.9, 34.1, 33.7, 27.9, 25.2, 24.5, 17.9; HRMS (ESI): calcd. For $C_{15}H_{21}O_2$ $[M + H]^+$ 233.1744; found 233.1743.

5α-hydroxy-β-eudesma-12-oic acid (8b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.69 (s, 1H), 4.80 (t, J = 1.7 Hz, 1H), 4.64 (t, J = 1.5 Hz, 1H), 3.09 (ddt, J = 12.0, 9.2, 4.6 Hz, 1H), 2.63 (tdd, J = 13.3, 6.6, 2.0 Hz, 1H), 2.11 (ddt, J = 13.9, 4.7, 2.0 Hz, 1H), 1.88 (tt, J = 12.9, 4.7 Hz, 2H), 1.80 – 1.50 (m, 6H), 1.27 – 1.17 (m, 2H), 1.15 – 1.02 (m, 1H), 0.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 152.1, 145.4, 125.6, 108.0, 75.9, 38.2, 36.4, 35.2, 34.6, 34.5, 32.0, 26.5, 22.6, 20.3; HRMS (ESI): calcd. For $C_{15}H_{23}O_3$ $[M + H]^+$ 251.1800; found 251.1801.

4. Conclusion

The use of α-costic acid derived from natural extracts of *Dittrichia viscosa* (L.) W. Greuter gave several interesting new and known eudesmons acids in good yields. 4,5- and 3,4-epoxy eudesmane scaffolds appeared to be an interesting source of new chiral intermediates. The convenient of their use are their facile formation from α-isocostic acid, which is readily available from the plant kingdom.

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