

Communication

Synthesis of Novel Spiro-Isoxazolidine Derivatives of 9 α -Hydroxyparthenolide

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Abstract

The 1,3-dipolar cycloaddition reaction was applied to 9 α -hydroxyparthenolide, an important sesquiterpene component of *Anvillea radiata* that was extracted directly from plant material collected in Morocco. Several new spiro-isoxazolidine derivatives were generated on the B-ring of 9 α -hydroxyparthenolide (α -methylene- γ -butyrolactone (**1**)) by 1,3-dipolar cycloaddition of its exocyclic double bond with various nitrones. These compounds were fully characterized by spectroscopic methods.

Keywords: 9 α -hydroxyparthenolide; spiro-isoxazolidine; sesquiterpene lactones; *Anvillea radiata*

1. Introduction

Plants have been an integral part of the healthcare industry for centuries and form the basis of many traditional and modern pharmaceutical remedies. They contain a wide range of bioactive compounds that can be used to treat a variety of ailments [1]. The study of medicinal plants has led to the discovery of essential medicines such as aspirin, derived from willow bark [2].

Sesquiterpene lactones are a class of natural compounds found in various plants, particularly in the *Asteraceae* family [3,4]. These types of derivatives are of significant importance in medicine due to their diverse biological activities and have candidates in various phases of clinical trials such as parthenolide, costunolide, helenalin, and artemisinin (Figure 1) [5–7]. Parthenolide (**2**) is a sesquiterpene lactone originally purified from feverfew shoots [8]. It is used in the treatment of fever, migraines, and rheumatoid arthritis and as an anti-inflammatory agent [9–11]. It has shown powerful anticancer activity [12,13].

As part of the Moroccan plant development program [14–16], *Anvillea radiata*, an invasive perennial weed, has been particularly studied. Easily accessible, it constitutes a renewable source of sesquiterpene lactones such as 9 α -hydroxyparthenolide [16]. This molecule is directly isolated with good yield from the aerial part of the plant (Figure 2) [16,17].

Here we propose the introduction of an isoxazolidine functionality to form libraries of structurally original spiro-bicyclic analogs of 9 α -hydroxyparthenolide (**1**) by 1,3-dipolar cycloaddition of several nitrones onto the exocyclic double bond of the B-ring of 9 α -hydroxyparthenolide. The numbering system commonly used for this structure is shown in Figure 3.

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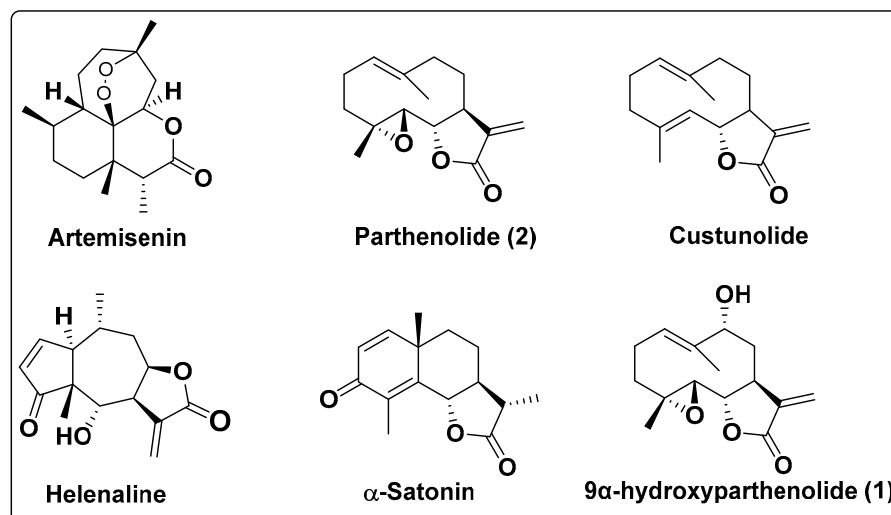


Figure 1. Examples of biologically active sesquiterpene lactones.

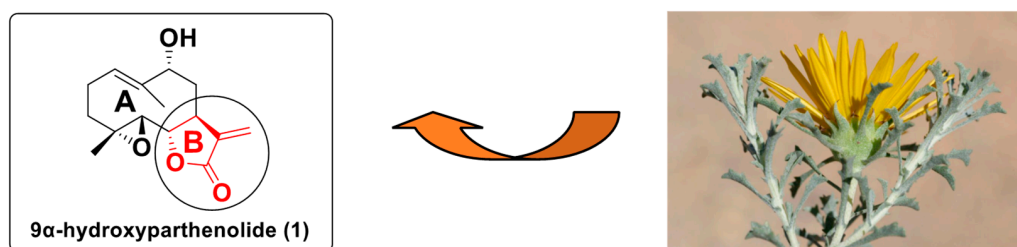


Figure 2. 9 α -Hydroxyparthenolide extracted from *Anvillea radiata*.

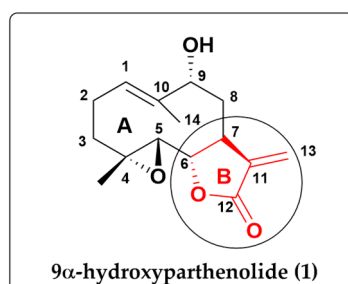


Figure 3. 9 α -Hydroxyparthenolide numbering system.

2. Results and Discussion

Spiro-isoxazolidine derivatives of 9 α -hydroxyparthenolide were successfully synthesized by a 1,3-dipolar cycloaddition reaction using various **3a–h** nitrones. These nitrones **3a–h** were obtained according to the procedure previously reported in the literature. This involves reducing nitroaryls in the presence of zinc and acetic acid to give the corresponding arylhydroxylamines. These were then condensed with various aromatic aldehydes [18].

In order to optimize reaction conditions, initial tests were carried out with nitrone **3b** by adjusting various experimental parameters, including the solvent, nitrone quantity, and reaction time. The results are summarized in Table 1.

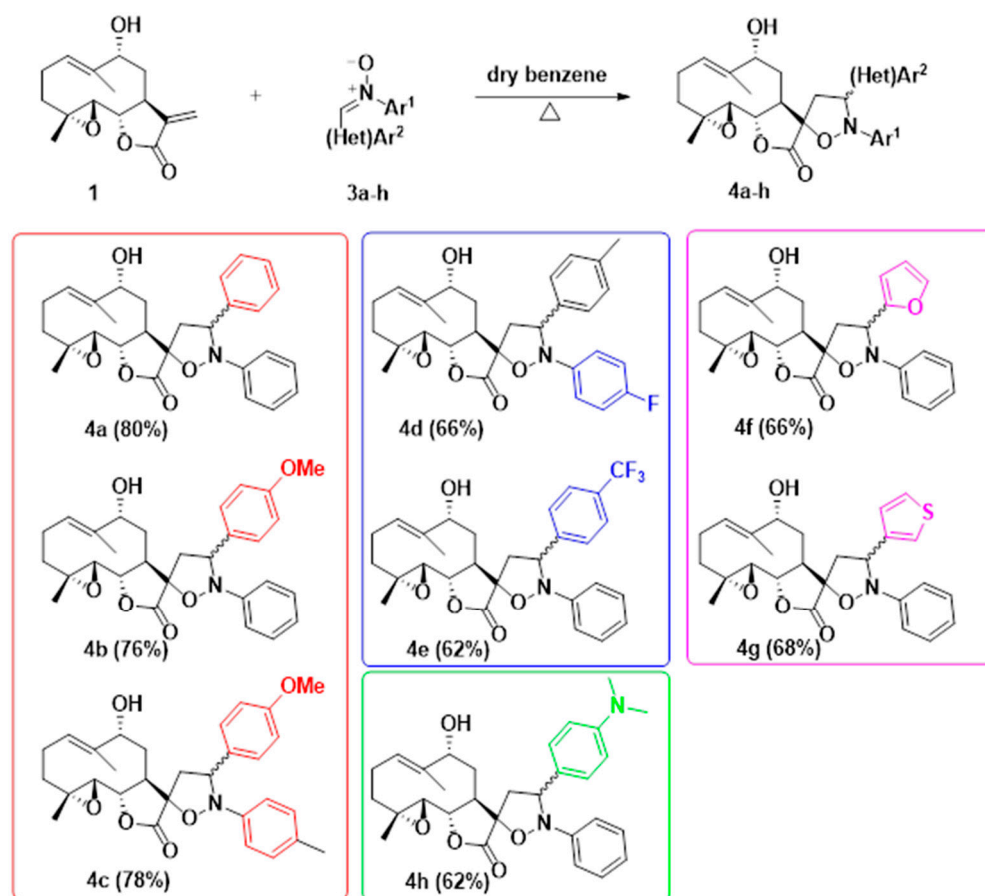
When the reaction was carried out under the same conditions as those reported in the literature, using dry toluene refluxed for 6 h, the desired product was obtained in only 10% yield [19]. Under these conditions, most of the starting material was recovered. Increasing the reaction time and the amount of nitrone (2 equiv.) had little effect on yield and conversion. In view of this modest result, toluene was replaced by benzene, giving the desired product in a much higher yield (76%). A comparable result was obtained using 1.5 equiv. of nitrone instead of 1.1 equiv.

Table 1. Optimization of operating conditions of the 1,3-dipolar cycloaddition reaction.

Entry	Solvent	Time (h)	Nitrone (equiv.)	Yield ^(a) (%)
1	Toluene	6	1.1	10
2	Toluene	12	1.1	20
3	Toluene	12	2	24
4	Benzene	6	1.1	40
5	Benzene	12	1.1	76
6	Benzene	24	1.1	70
7	Benzene	12	1.5	76

^(a) Yield of isolated product after column chromatography.

The optimized conditions were extended to various nitrones and the spiro-isoxazolidine derivatives **4a–h** were isolated in satisfactory yields as two diastereomers (50:50) after purification by flash chromatography (Scheme 1). The diastereomers were not separated by flash chromatography. This 1,3-dipolar cycloaddition reaction is regiospecific but not stereoselective.

**Scheme 1.** Synthesis of spiro-isoxazolidine derivatives of 9α-hydroxyparthenolide.

The operating conditions tolerate various aryl-containing nitrones with electron-donating (CH_3 , OCH_3) or electron-withdrawing substituents (CF_3 , F). Heteroaryl-substituted nitrones were also successfully used under these conditions. The reaction sequence was also successfully applied to *N*-alkyl-substituted aryl derivatives, with an isolated yield of 62% in the case of the dimethylamine substrate.

The synthesized spiro-isoxazolidines were fully characterized by ^1H and ^{13}C NMR spectroscopic techniques, see ^1H and ^{13}C NMR spectra of compounds **4a** to **4h** and 2D MDL molfile in Supplementary Materials. The formation of the spiro-isoxazoline ring was clearly

confirmed by the disappearance of the alkene protons adjacent to the lactone ring and the appearance of the benzyl proton adjacent to the nitrogen atom in the isoxazolidine ring, as well as the appearance of the aromatic proton. The CH chemical shift in the asymmetric center generated is generally between 5.46 and 5.63 ppm. For example, in the case of product **4b**, which enabled us to optimize the reaction, the signal corresponding to the CH proton of the asymmetric center appears at 5.63 ppm.

3. 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). ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE II spectrometer (Billerica, MA, USA) at 250 MHz (^{13}C , 62.9 MHz) and on a Bruker AVANCE III HD nanobay (Billerica, MA, USA) at 400 MHz (^{13}C 101 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as an internal standard, in deuterated solvent (CDCl_3). The following abbreviations were used for the proton spectra multiplicities: b: broad, s: singlet, d: doublet, t: triplet, q: quartet, p: pentuplet, m: multiplet. Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS (ESI)) were performed on a Maxis Bruker 4G (Billerica, MA, USA).

3.1. General Procedure for the Synthesis of Spiro-Isoxazolidines

A solution of 9 α -hydroxyparthenolide (100 mg, 1 equiv.) in benzene (2 mL) was treated with the appropriate nitron (1.1 equiv.). The resulting suspension was refluxed for 12 h, concentrated under reduced pressure, and purified by flash chromatography (silica gel) to afford the desired spiro-isoxazolidine.

3.1.1. Compound **4a**: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-5'-Hydroxy-6',9a'-dimethyl-2,3-diphenyl-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.56 petroleum ether/ethyl acetate 6/4) provided **4a** (80%) as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.52–7.45 (m, 2H), 7.37–7.27 (m, 3H), 7.20–7.11 (m, 2H), 7.03–6.95 (m, 3H), 5.62 (ddt, J = 12.6, 4.0, 1.8 Hz, 1H), 4.33–4.26 (m, 2H), 3.78 (t, J = 9.5 Hz, 1H), 3.18 (t, J = 9.5 Hz, 1H), 2.99 (dd, J = 13.1, 7.9 Hz, 1H), 2.74 (d, J = 9.0 Hz, 1H), 2.57–2.39 (m, 2H), 2.33 (dd, J = 14.5, 6.8 Hz, 1H), 2.28–2.21 (m, 1H), 2.16 (ddd, J = 13.0, 5.5, 2.0 Hz, 1H), 1.89 (dd, J = 14.6, 9.3 Hz, 1H), 1.84–1.80 (m, 1H), 1.70 (s, 3H), 1.62 (s, 1H), 1.28 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.14, 149.25, 139.21, 136.84, 129.36, 128.77, 127.96, 124.12, 122.37, 118.69, 83.10, 79.88, 71.06, 70.75, 66.73, 61.80, 44.64, 39.58, 37.00, 31.68, 23.68, 17.43, 16.63. HRMS (ESI $^+$): m/z [M + H] $^+$ Calcd. for $\text{C}_{28}\text{H}_{32}\text{NO}_5$: 462.2275; found 462.2276.

3.1.2. Compound **4b**: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-5'-Hydroxy-3-(4-methoxyphenyl)-6',9a'-dimethyl-2-phenyl-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.48 petroleum ether/ethyl acetate 6/4) provided **4b** (76%) as a colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, J = 8.4 Hz, 2H), 7.19–7.10 (m, 4H), 7.01 (t, J = 7.1 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 5.63 (dd, J = 13.0, 3.8 Hz, 1H), 4.72 (dd, J = 10.9, 5.8 Hz, 1H), 4.38 (d, J = 6.4 Hz, 1H), 3.80 (s, 3H), 3.28 (t, J = 9.9 Hz, 1H), 2.81–2.72 (m, 2H), 2.68 (d, J = 11.4 Hz, 1H), 2.51 (dtd, J = 47.9, 12.7, 5.5 Hz, 3H), 2.31–2.11 (m, 3H), 2.01 (s, 1H), 1.85 (dd, J = 14.6, 9.8 Hz, 1H), 1.69 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.82, 159.73, 150.31, 136.34, 129.91,

128.65, 128.55, 124.39, 122.18, 119.20, 114.48, 83.97, 79.71, 70.88, 69.68, 66.41, 61.68, 55.44, 43.87, 39.06, 36.86, 31.87, 23.52, 17.23, 16.33.

3.1.3. Compound 4c: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-5'-Hydroxy-3-(4-methoxyphenyl)-6',9a'-dimethyl-2-(p-tolyl)-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.62 petroleum ether/ethyl acetate 6/4) provided **4c** (78%) as a yellowish oil; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, J = 8.7 Hz, 2H), 6.98–6.93 (m, 2H), 6.87 (dd, J = 11.2, 8.6 Hz, 4H), 5.56 (dd, J = 12.5, 3.7 Hz, 1H), 4.79 (dd, J = 10.6, 6.3 Hz, 1H), 4.36 (d, J = 6.6 Hz, 1H), 4.17 (t, J = 9.3 Hz, 1H), 3.80 (s, 3H), 2.97 (dd, J = 12.9, 6.3 Hz, 1H), 2.82 (t, J = 8.6 Hz, 1H), 2.72–2.57 (m, 2H), 2.49 (dd, J = 13.0, 5.4 Hz, 1H), 2.23 (s, 3H), 2.17 (ddd, J = 12.9, 5.6, 1.9 Hz, 1H), 1.95 (dd, J = 15.8, 8.0 Hz, 1H), 1.72 (d, J = 1.2 Hz, 3H), 1.69–1.50 (m, 2H), 1.30 (s, 3H), 1.28–1.14 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.22, 159.36, 147.53, 138.21, 134.00, 130.61, 129.15, 128.52, 121.21, 118.78, 114.18, 84.24, 82.91, 70.83, 70.75, 66.76, 61.31, 55.28, 44.95, 40.01, 36.76, 29.69, 23.32, 20.77, 17.09, 16.43. HRMS (ESI^+): m/z $[\text{M} + \text{H}]^+$ Calcd. for $\text{C}_{30}\text{H}_{36}\text{NO}_6$: 506.2537; found 506.2538.

3.1.4. Compound 4d: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-2-(4-fluorophenyl)-5'-Hydroxy-6',9a'-dimethyl-3-(p-tolyl)-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.29 petroleum ether/ethyl acetate 5/5) provided **4d** (66%) as a colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.29 (m, 2H), 7.12 (d, J = 7.7 Hz, 2H), 6.99 (ddd, J = 6.8, 4.7, 2.4 Hz, 2H), 6.83 (td, J = 8.7, 1.9 Hz, 2H), 5.63–5.56 (m, 1H), 4.34 (d, J = 6.4 Hz, 1H), 4.11 (t, J = 8.7 Hz, 1H), 3.81–3.74 (m, 1H), 3.15 (t, J = 9.5 Hz, 1H), 2.92 (dd, J = 13.2, 7.4 Hz, 1H), 2.71 (dd, J = 9.1, 1.7 Hz, 1H), 2.54–2.36 (m, 3H), 2.35–2.31 (m, 3H), 2.24 (d, J = 13.2 Hz, 1H), 2.18–2.10 (m, 1H), 2.06–1.98 (m, 1H), 1.90 (dd, J = 14.5, 9.4 Hz, 1H), 1.70 (s, 3H), 1.27 (d, J = 1.7 Hz, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.17, 160.97, 158.55, 144.80, 144.78, 138.30, 136.80, 134.69, 129.68, 127.80, 121.96, 121.09, 121.01, 115.14, 114.92, 82.61, 79.60, 71.41, 70.75, 66.45, 61.53, 44.09, 39.18, 36.67, 31.24, 23.34, 21.17, 17.09, 16.31. HRMS (ESI^+): m/z $[\text{M} + \text{H}]^+$ Calcd. for $\text{C}_{29}\text{H}_{33}\text{FNO}_5$: 494.2337; found 494.2340.

3.1.5. Compound 4e: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-5'-Hydroxy-6',9a'-dimethyl-2-phenyl-3-(4-(trifluoromethyl)phenyl)-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.18 petroleum ether/ethyl acetate 5/5) provided **4e** (62%) as a yellowish oil; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 7.8 Hz, 2H), 7.03 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 2H), 5.61–5.54 (m, 1H), 4.31 (t, J = 8.7 Hz, 2H), 4.17 (t, J = 9.3 Hz, 1H), 2.91 (dd, J = 11.5, 8.6 Hz, 3H), 2.64 (d, J = 9.3 Hz, 1H), 2.54–2.35 (m, 2H), 2.30–2.14 (m, 2H), 1.89 (dd, J = 15.8, 8.3 Hz, 1H), 1.73 (s, 4H), 1.57 (s, 1H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 173.73, 148.18, 143.79, 137.95, 130.62, 130.30, 128.74, 128.53, 126.06, 126.02, 124.77, 121.69, 119.18, 83.53, 81.96, 70.92, 70.41, 66.97, 61.44, 43.66, 40.09, 36.93, 30.25, 29.85, 23.47, 17.25, 16.58. HRMS (ESI^+): m/z $[\text{M} + \text{H}]^+$ Calcd. for $\text{C}_{29}\text{H}_{31}\text{F}_3\text{NO}_5$: 530.2149; found 530.2150.

3.1.6. Compound 4f: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-3-(furan-2-yl)-5'-Hydroxy-6',9a'-dimethyl-2-phenyl-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.81 petroleum ether/ethyl acetate 3/7) provided **4f** (66%) as a yellowish oil; ^1H NMR (400 MHz,

CDCl₃) δ 7.46 (s, 1H), 7.27–7.16 (m, 3H), 7.07–6.92 (m, 3H), 6.41–6.23 (m, 1H), 5.63–5.52 (m, 1H), 4.98 (t, J = 8.3 Hz, 1H), 4.35 (d, J = 6.8 Hz, 1H), 4.20 (t, J = 9.2 Hz, 1H), 2.91 (dt, J = 16.3, 7.7 Hz, 3H), 2.63 (dd, J = 16.9, 7.9 Hz, 2H), 2.48 (td, J = 12.8, 5.3 Hz, 1H), 2.37–2.13 (m, 2H), 2.06–1.86 (m, 1H), 1.72 (s, 3H), 1.68–1.43 (m, 2H), 1.29 (d, J = 23.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.85, 150.68, 150.00, 142.89, 138.11, 128.64, 124.18, 121.24, 117.62, 110.48, 108.90, 84.80, 82.92, 70.76, 66.71, 64.94, 61.34, 39.86, 39.74, 36.77, 29.69, 29.52, 23.31, 17.09, 16.38.

3.1.7. Compound 4g: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-5'-Hydroxy-6',9a'-dimethyl-2-phenyl-3-(thiophen-3-yl)-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.75 petroleum ether/ethyl acetate 3/7) provided **4g** (68%) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, J = 5.1, 2.8 Hz, 1H), 7.25–7.15 (m, 4H), 7.01 (d, J = 7.9 Hz, 3H), 5.66–5.57 (m, 1H), 4.44 (t, J = 8.3 Hz, 1H), 4.29 (d, J = 6.5 Hz, 1H), 3.78 (t, J = 9.4 Hz, 1H), 3.19 (t, J = 9.6 Hz, 1H), 2.93 (dd, J = 13.0, 7.7 Hz, 1H), 2.74 (d, J = 8.9 Hz, 1H), 2.58–2.40 (m, 1H), 2.38–2.09 (m, 2H), 1.92–1.76 (m, 2H), 1.70 (s, 3H), 1.64–1.33 (m, 2H), 1.28 (s, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 174.71, 148.83, 139.40, 136.55, 128.45, 126.87, 126.51, 123.99, 123.22, 122.05, 118.44, 82.75, 79.55, 70.75, 66.40, 66.32, 61.45, 42.95, 39.37, 36.67, 31.36, 23.34, 17.10, 16.30.

3.1.8. Compound 4h: (3a'R,5S,5'R,9a'R,10a'S,10b'S,E)-3-(4-(dimethylamino)phenyl)-5'-Hydroxy-6',9a'-dimethyl-2-phenyl-3a',4',5',8',9',9a',10a',10b'-octahydro-2'H-spiro[isoxazolidine-5,3'-oxireno[2',3':9,10]cyclodeca[1,2-b]furan]-2'-one

Following the general procedure. Column chromatography on silica gel (R_f = 0.62 petroleum ether/ethyl acetate 2/8) provided **4h** (62%) as a brown oil; ¹H NMR (250 MHz, CDCl₃) δ 7.47–7.34 (m, 2H), 7.34–7.21 (m, 2H), 7.19–6.82 (m, 3H), 6.76–6.58 (m, 2H), 5.63–5.46 (m, 1H), 4.35–4.01 (m, 3H), 3.86–3.64 (m, 1H), 3.12 (t, J = 9.5 Hz, 1H), 3.02–2.77 (m, 8H), 2.77–1.77 (m, 6H), 1.66 (d, J = 3.7 Hz, 4H), 1.34–1.18 (m, 3H). ¹³C NMR (63 MHz, CDCl₃) δ 174.50, 149.95, 148.97, 136.62, 128.72, 128.36, 123.38, 121.72, 118.11, 112.45, 82.53, 79.55, 70.82, 70.71, 67.10, 66.42, 61.33, 44.10, 40.44, 39.25, 36.74, 31.23, 29.61, 23.30, 17.14, 16.29. HRMS (ESI⁺): m/z [M + H]⁺ Calcd. for C₃₀H₃₇N₂O₅: 505.2697; found 505.2698.

4. Conclusions

Here, we present the synthesis of spiro-isoxazolidine derivatives from naturally occurring 9 α -hydroxypartenolide via 1,3-dipolar cycloaddition. Using a plant-extracted chiral starting synthon, this method takes advantage of the substrate's inherent chirality to efficiently build a new library of spiro-isoxazolidine derivatives. In this respect, the process can be considered sustainable. Indeed, the process requires a minimum of synthetic steps, enabling access to complex molecules of undoubted therapeutic interest.

Supplementary Materials: ¹H and ¹³C NMR spectra of compounds **4a** to **4h** and 2D MDL molfile (in V2000 format) of the 9 α -hydroxypartenolide.

Author Contributions: Conceptualization, M.Z. and M.L.; methodology, M.Z. and M.L.; software, M.Z. and M.L.; validation, M.Z., M.L. and S.B.-R.; formal analysis, M.Z. and M.L.; investigation, M.Z. and M.L.; resources, M.Z. and M.L.; data curation, M.Z. and M.L.; writing—original draft preparation, M.Z. and M.L.; writing—review and editing, M.Z., M.L. and S.B.-R.; visualization, M.Z. and M.L.; supervision, M.Z. and M.L.; project administration, M.Z. and M.L. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

PTL	Parthenolide
SLJ	Sesquiterpene Lactone
NMR	Nuclear Magnetic Resonance

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