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Synthesis of novel spiro-isoxazoline and spiro-isoxazolidine derivatives of tomentosin†

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A series of novel enantiomerically pure spiro-isoxazolidines and spiro-isoxazolines were synthesized regioselectively by 1,3-dipolar cycloaddition using respectively two dipoles, nitrones and nitrile oxides, on the exocyclic double bond of the B ring of tomentosin (α-methylene-γ-butyrolactone), a sesquiterpene lactone extracted from *Dittrichia viscosa*.

Introduction

Plants have a long history as therapeutics in the treatment of human diseases and have been a continuous source of inspiration for the development of new medicines. Among them, the genus *Inula* (Asteraceae) comprises more than 100 species, many of which are widely used in traditional medicine for a variety of biological purposes including anti-inflammatory, anti-cancer and antibacterial activities.[1–3] Numerous compounds of interest have been isolated and identified from these plants such as flavonoids, monoterpenes, triterpenoids, and polyphenols. This genus is also a rich source of sesquiterpene acids and lactones. Many studies have focused on sesquiterpene lactones since they exhibit a wide range of biological properties[4–6] and have candidates in different phases of clinical trials such as parthenolide, costunolide, helenalin, and artemisinin (Fig. 1). The cytotoxicity of sesquiterpene lactones was partly attributed to the presence of potential alkylating agents such as the α-methylene-γ-lactone moiety, which are prone to covalently react with biological nucleophiles, *e.g.*, L-cysteine, in a Michael-type addition.[7–12] This highly electrophilic structure may also be the origin of a major contact allergen effect and plants that contain sesquiterpene lactones are held responsible for an increasing number of cases of contact dermatitis.[13–15]

Using this reactive site, various structural modifications have been carried out to obtain less toxic and more reactive candidates and lately the introduction of spiro-heterocyclic molecular frameworks has aroused particular interest among medicinal chemists.[16,17] For example, the Ding and Kumar groups[18–20] recently synthesized spiro-isoxazoline and spiro-isoxazolidine derivatives of parthenin, α-santonin and artemisinin and promising anti-cancer activities were obtained. As part of the Moroccan plant development program,[21–25] *Dittrichia viscosa* L. Greuter, an invasive perennial weed, was particularly examined.[26,27] This plant is used either as extracts or essential oil in traditional Moroccan medicine for its antipyretic, antiseptic and anti-inflammatory properties.[28,29] Easily accessible, it is a renewable source of sesquiterpene lactones such as tomentosin (1),[30,31] also known as xanthalongin. This molecule is straightforwardly isolated in respectively 1.5% with respect to the dry weight of the aerial part of the plant (Fig. 1).[32,33] Tomentosin was already reported to act as a cytotoxic and anti-inflammatory agent[34–36] but despite this biological potential, it has received little pharmacological attention so far. Therefore, we propose herein the introduction of an isoxazoline and an isoxazolidine functionality to form libraries of structurally original spiro-bicyclic analogues of tomentosin by 1,3-dipolar cycloaddition with two dipoles, nitrones and nitrile oxides on the exocyclic double bond of the **B** ring of tomentosin (Fig. 2).

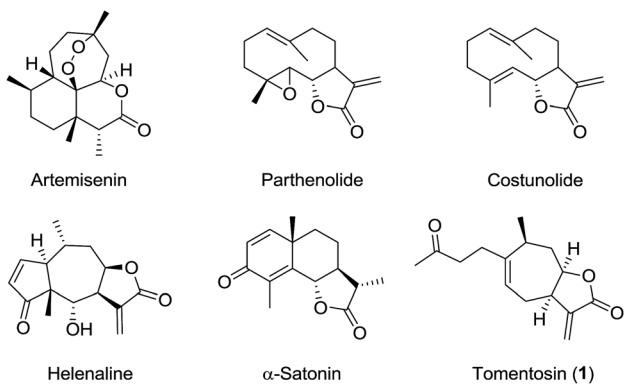

Fig. 1 Examples of biologically active sesquiterpene lactones.

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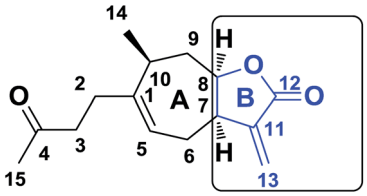


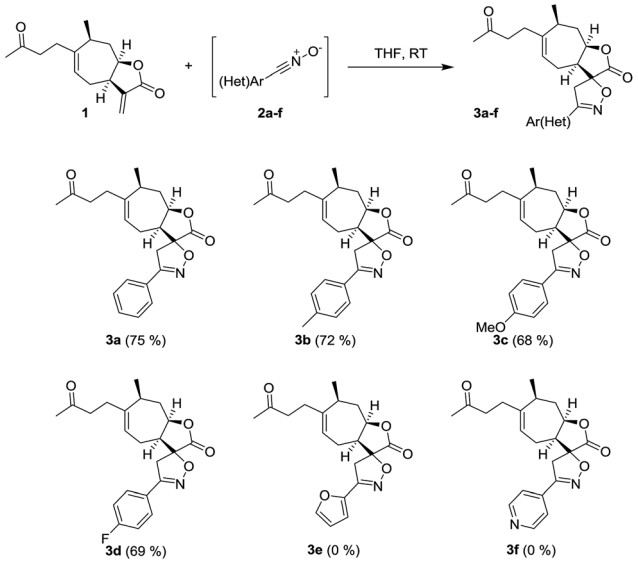
Fig. 2 Sesquiterpene lactones, ring B of tomentosin.

Results and discussion

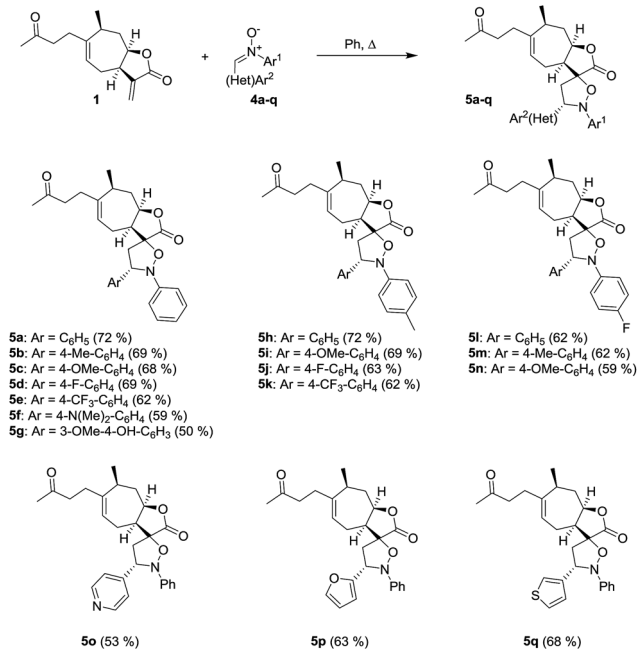
The spiroisoxazoline derivatives of tomentosin were synthesized through a 1,3-dipolar cycloaddition of various aldoximes **2** with the exocyclic ring **B** double bond (Scheme 1).

Nitrile oxides **2** were prepared by converting various aromatic aldehydes to the corresponding oximes *via* the reaction with hypochlorite anion present in bleach. The bleach was used in two steps: initially to produce chlorooxime and then thanks to its basicity to induce dehydrohalogenation, leading to the nitrile oxide. Experimentally, aldoxime was mixed with the tomentosin in THF, and then a bleach solution (14.5% of chlorine) was added dropwise during 12 hours. Only one diastereoisomer was isolated and characterized by NMR spectroscopic analysis and mass spectrometry. The ^{1}H NMR spectra of the spiroisoxazoline derivatives of tomentosin **3a** showed the disappearance of the alkene protons along with the appearance of two doublets at respectively 3.42 and 3.58 ppm that confirm the selectivity of the nitrile oxide cycloaddition. The reaction took place whatever the substituent in the *para* position of the aryl entity, whether electron donating (CH_3, OCH_3) or electron-attracting (F). When a poor or electron-rich heteroaryl was used, the reaction did not take place and only the starting material was recovered.

The spiroisoxazolidine derivatives of tomentosin were obtained through 1,3-dipolar cycloaddition of various nitrones **4**



Scheme 1 Synthesis of spiro-isoxazoline derivatives of tomentosin.



Scheme 2 Synthesis of spiro-isoxazolidine derivatives of tomentosin.

in refluxing dry benzene (Scheme 2).[37–39] Nitrones **4** were straightforwardly obtained according to the literature procedure in which nitroaryls were first reduced in the presence of zinc and acetic acid to obtain the corresponding aryl hydroxylamines that were condensed with various aromatic aldehydes.[40]

The spiro-isoxazolidines **5** were obtained as one diastereomer after purification by flash chromatography. The operating conditions are compatible with the introduction of nitrones with aryl entities bearing electron-donating (CH_3, OCH_3) or electron-attracting (CF_3, F) substituents. The use of nitrones with heteroaryl entities was carried out successfully. It should be noted that the use of toluene instead of benzene, for environmental reasons, did not unfortunately allow us to obtain the products. The structures of the spiroisoxazolidines were confirmed by their ^{1}H, ^{13}C and 2 D NMR spectroscopic data as described for 5q (Fig. 3). The ^{1}H and ^{1}H-COSY data showed the correlation of H-7 with H-8 and H-8 with H-16. Further, the HMBC experiment showed the correlation of H-7 and H-8 with C-17 and H-7 with C-16 (Fig. 3).

In the ^{1}H NMR comparison with the literature data, Reddy *et al.*[18] obtained two diastereomers. Each diastereomer was isolated and the clear chemical shift deviation of the benzylic proton adjacent to the nitrogen atom in the isoxazolidine ring

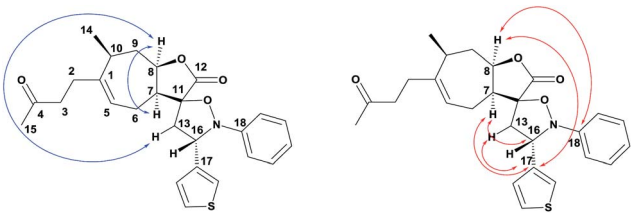


Fig. 3 Selected ^{1}H, ^{1}H–COSY and HMBC correlations of **5q**.

between two diastereomers was observed in ^{1}H NMR. In the major isomer this proton appeared at 5 ppm, but in the minor isomer this signal shifted toward a more shielding region and appeared approximately at 4 ppm.

Experimental section

General information

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 II spectrometer at 250 MHz (^{13}C, 62.9 MHz) and on a Bruker AVANCE III HD nanobay at 400 MHz (^{13}C 101 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) or deuterated solvents (MeOH-d_4, $CDCl_3$) as internal standard. 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.

General procedure for the synthesis of spiro-isoxazolines

The appropriate aldehyde (1 equiv.) was diluted in CH_2Cl_2 (10 mL) and stirred at room temperature. Hydroxylamine (2 equiv.) and NaOH (2 equiv.) were added and the mixture was heated to reflux for 4 h. Ethanol was evaporated under reduced pressure then the crude mixture was diluted with water (10 mL) and AcOEt (10 mL) then extracted with AcOEt (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to lead to the aldoxime intermediate. The aldoxime was diluted in THF (10 mL) then tomentosin (0.2 equiv.) and bleach (5 mL) were added dropwise. The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure providing a crude product, which was purified by flash chromatography on silica gel.

13-[Amino, phenyl-methyl]-11, *N*-epoxy-tomentosin (3a). Following the general procedure, using tomotensin (80 mg, 0.32 mmol), column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **3a** (88 mg, 0.24 mmol, 75%) as a yellow oil; $[\alpha]_D^{20}$ −38.8 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dt, J = 7.6, 1.4 Hz, 2H), 7.46–7.36 (m, 3H), 5.43 (dd, J = 9.4, 3.5 Hz, 1H), 4.91 (ddd, J = 11.3, 6.5, 4.5 Hz, 1H), 3.58 (d, J = 16.8 Hz, 1H), 3.42 (d, J = 16.9 Hz, 1H), 2.84 (ddd, J = 13.1, 6.7, 3.1 Hz, 1H), 2.59–2.15 (m, 7H), 2.13 (s, 3H), 1.94 (ddd, J = 23.2, 11.4, 7.4 Hz, 2H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 173.7 (C), 156.1 (C), 145.1 (C), 130.8 (C), 128.9 (2 CH), 128.5 (CH), 127.0 (2 CH), 120.7 (CH), 89.0 (C), 80.1 (CH), 46.1 (CH), 42.6 (CH_2), 37.6 (CH_2), 36.6 (CH_2), 33.1 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.7 (CH_2), 21.2 (CH_3); HRMS (ESI$^+$): calc. For $C_{22}H_{25}NO_4$ [M + H]$^+$ 368.1856; found 368.1856.

13-[Amino, (*p*-tolyl)-methyl]-11, *N*-epoxy-tomentosin (3b). Following the general procedure, using tomotensin (80 mg, 0.32 mmol), column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **3b** (89 mg, 0.23 mmol, 72%) as a colorless oil; $[\alpha]_D^{20}$ +46.0 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 5.43 (dd, J = 9.4, 3.5 Hz, 1H), 4.90 (ddd, J = 11.4, 6.5, 4.6 Hz, 1H), 3.56 (d, J = 16.8 Hz, 1H), 3.40 (d, J = 17.0 Hz, 1H), 2.84 (ddd, J = 13.0, 6.6, 3.0 Hz, 1H), 2.59–2.39 (m, 3H), 2.38 (s, 3H), 2.36–2.15 (m, 4H), 2.13 (s, 3H), 2.02–1.86 (m, 2H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 173.8 (C), 156.1 (C), 145.1 (C), 141.1 (C), 129.6 (2 CH), 127.0 (2 CH), 125.7 (C), 120.7 (CH), 88.8 (C), 80.1 (C), 46.2 (CH), 42.6 (CH_2), 37.7 (CH_2), 36.6 (CH_2), 33.1 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.7 (CH_2), 21.6 (CH_3), 21.2 (CH_3); HRMS (ESI$^+$): calc. For $C_{23}H_{27}NO_4$ [M + H]$^+$ 382.2012; found 382.2012.

13-[Amino, (4-methoxyphenyl)-methyl]-11, *N*-epoxy-tomentosin (3c). Following the general procedure, using tomotensin (80 mg, 0.32 mmol), column chromatography on silica gel (petroleum ether/ethyl acetate 5/5) provided **3c** (87 mg, 0.22 mmol, 68%) as a colorless oil; $[\alpha]_D^{20}$ +41.9 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 2H), 6.95–6.90 (m, 2H), 5.43 (d, J = 3.7 Hz, 1H), 4.92 (ddd, J = 11.3, 6.6, 4.4 Hz, 1H), 3.85 (s, 3H), 3.56 (d, J = 16.8 Hz, 1H), 3.39 (d, J = 16.8 Hz, 1H), 2.84 (ddd, J = 13.0, 6.6, 3.1 Hz, 1H), 2.61–2.15 (m, 7H), 2.14 (s, 3H), 2.03–1.87 (m, 2H), 1.17 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 173.9 (C), 161.6 (C), 155.7 (C), 145.2 (C), 128.6 (2 CH), 121.1 (C), 120.8 (CH), 114.4 (2 CH), 88.7 (C), 80.1 (CH), 55.5 (CH_3), 46.3 (CH), 42.6 (CH_2), 37.9 (CH_2), 36.6 (CH_2), 33.1 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.8 (CH_2), 21.3 (CH_3); HRMS (ESI$^+$): calc. For $C_{23}H_{27}NO_5$ [M + H]$^+$ 398.1962; found 398.1961.

13-[Amino, (4-fluorophenyl)-methyl]-11, *N*-epoxy-tomentosin (3d). Following the general procedure, using tomotensin (80 mg, 0.32 mmol), column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **3d** (86 mg, 0.22 mmol, 69%) as a colorless oil; $[\alpha]_D^{20}$ +76.0 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 8.6, 5.3 Hz, 2H), 7.10 (t, J = 8.5 Hz, 2H), 5.43 (dd, J = 9.4, 3.5 Hz, 1H), 4.91 (ddd, J = 11.3, 6.6, 4.5 Hz, 1H), 3.54 (d, J = 16.8 Hz, 1H), 3.40 (d, J = 16.9 Hz, 1H), 2.84 (ddd, J = 13.0, 6.6, 3.0 Hz, 1H), 2.60–2.14 (m, 7H), 2.13 (s, 3H), 2.01–1.87 (m, 2H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9 (C), 173.6 (C), 164.1 (d, J = 251.7 Hz, C), 155.2 (C), 145.2 (C), 129.0 (d, J = 8.5 Hz, 2 CH), 124.9 (d, J = 3.5 Hz, CH), 120.6 (CH), 116.1 (d, J = 22.0 Hz, 2 CH), 89.1 (C), 80.14 (CH), 46.1 (CH), 42.6 (CH_2), 37.6 (CH_2), 36.6 (CH_2), 33.1 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.7 (CH_2), 21.2 (CH_3); HRMS (ESI$^+$): calc. For $C_{22}H_{24}FNO_4$ [M + H]$^+$ 386.1762; found 386.1762.

General procedure for the synthesis of spiro-isoxazolidines

The appropriate nitrone (1.1 equiv.) was added to a solution of tomentosin (1 equiv.) in benzene (2 mL). The resulting suspension was heated to reflux for 12 h. Then the reaction mixture was concentrated under reduced pressure and the

crude material was purified by flash chromatography on silica gel to provide the expected spiro-isoxasolidine.

13-[(Phenylamine), phenyl-methyl]-11, *N*-epoxy-tomentosin (5a). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (70 mg, 0.35 mmol), column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5a** (104 mg, 0.23 mmol, 72%) as a yellowish oil; $[\alpha]_D^{20}$ +45.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.8 Hz, 2H), 7.41–7.35 (m, 2H), 7.34–7.28 (m, 1H), 7.21–7.12 (m, 2H), 6.96–6.86 (m, 3H), 5.44–5.37 (m, 1H), 5.14–5.07 (m, 1H), 4.96–4.89 (m, 1H), 2.85 (td, J = 12.3, 11.0, 5.4 Hz, 2H), 2.60–2.17 (m, 7H), 2.15 (s, 3H), 2.13–2.07 (m, 1H), 1.92 (ddd, J = 19.2, 12.8, 7.4 Hz, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2 (C), 174.9 (C), 151.4 (C), 145.0 (C), 140.7 (C), 129.3 (2 CH), 128.9 (2 CH), 128.2 (CH), 126.9 (2 CH), 122.8 (CH), 121.4 (CH), 115.8 (2 CH), 85.6 (C), 80.0 (CH), 70.4 (CH), 46.0 (CH), 43.9 (CH_2), 42.9 (CH_2), 36.9 (CH_2), 33.4 (CH), 31.0 (CH_2), 30.3 (CH_3), 23.1 (CH_2), 21.4 (CH_3); HRMS (ESI^+): calc. For $C_{28}H_{31}NO_4$ $[M + H]^+$ 446.2325; found 446.2325.

13-[(Phenylamine), (*p*-tolyl)-methyl]-11, *N*-epoxy-tomentosin (5b). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (74 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5b** (104 mg, 0.22 mmol, 69%) as a yellowish oil; $[\alpha]_D^{20}$ +59.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.7 Hz, 2H), 7.17 (ddd, J = 13.8, 6.8, 2.7 Hz, 4H), 6.96–6.87 (m, 3H), 5.42 (dd, J = 9.4, 3.5 Hz, 1H), 5.06 (dd, J = 9.5, 6.7 Hz, 1H), 4.91 (ddd, J = 11.4, 6.5, 4.4 Hz, 1H), 2.91–2.76 (m, 2H), 2.60–2.37 (m, 4H), 2.36 (s, 3H), 2.34–2.17 (m, 3H), 2.15 (s, 3H), 2.13–2.06 (m, 1H), 1.93 (dt, J = 14.5, 11.5 Hz, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.8 (C), 151.3 (C), 144.7 (C), 137.8 (C), 137.4 (C), 129.8 (2 CH), 128.7 (2 CH), 126.7 (2 CH), 122.6 (CH), 121.1 (CH), 115.7 (2 CH), 85.3 (C), 79.7 (CH), 70.1 (CH), 45.8 (CH), 43.8 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.2 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.9 (CH_2), 21.2 (CH_3), 21.2 (CH_3); HRMS (ESI^+): calc. For $C_{29}H_{33}NO_4$ $[M + H]^+$ 460.2480; found 460.2482.

13-[(Phenylamine), (4-methoxyphenyl)-methyl]-11, *N*-epoxy-tomentosin (5c). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (80 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 5/5) provided **5c** (103 mg, 0.22 mmol, 68%) as a yellow oil; $[\alpha]_D^{20}$ +38.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.16 (t, J = 7.4 Hz, 2H), 6.97–6.87 (m, 5H), 5.42 (dd, J = 9.3, 3.5 Hz, 1H), 5.03 (dd, J = 9.5, 6.7 Hz, 1H), 4.90 (ddd, J = 11.4, 6.7, 4.5 Hz, 1H), 3.81 (s, 3H), 2.87–2.78 (m, 2H), 2.60–2.17 (m, 7H), 2.15 (s, 3H), 2.10 (dt, J = 13.9, 4.2 Hz, 1H), 1.99–1.84 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.9 (C), 159.4 (C), 151.2 (C), 144.7 (C), 132.1 (C), 128.7 (2 CH), 128.0 (2 CH), 122.8 (CH), 121.1 (CH), 116.0 (2 CH), 114.5 (2 CH), 85.2 (C), 79.7 (CH), 70.0 (CH), 55.4 (CH_3), 45.8 (CH), 43.7 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.2 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.9 (CH_2), 21.2 (CH_3); HRMS (ESI^+): calc. For $C_{29}H_{33}NO_5$ $[M + H]^+$ 476.2429; found 476.2431.

13-[(Phenylamine), (4-fluorophenyl)-methyl]-11, *N*-epoxy-tomentosin (5d). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (76 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5d** (103 mg, 0.22 mmol, 69%) as a yellow oil; $[\alpha]_D^{20}$ −78.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 8.3, 5.3 Hz, 2H), 7.24–7.17 (m, 2H), 7.09 (t, J = 8.4 Hz, 2H), 6.99–6.89 (m, 3H), 5.44 (dd, J = 9.4, 3.4 Hz, 1H), 5.11 (dd, J = 9.4, 6.7 Hz, 1H), 4.94 (ddd, J = 11.4, 6.6, 4.5 Hz, 1H), 2.86 (ddd, J = 19.2, 9.8, 4.8 Hz, 2H), 2.62–2.20 (m, 7H), 2.17 (s, 3H), 2.11 (t, J = 4.2 Hz, 1H), 2.01–1.86 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.7 (C), 162.5 (d, J = 246.4 Hz, C), 151.0 (C), 144.8 (C), 136.1 (d, J = 3.2 Hz, C), 128.8 (2 CH), 128.4 (d, J = 8.0 Hz, 2 CH), 122.9 (CH), 121.1 (CH), 116.0 (d, J = 21.6 Hz, 2 CH), 115.8 (2 CH), 85.4 (C), 79.8 (CH), 69.6 (CH), 45.8 (CH), 43.6 (CH_2), 42.6 (CH_2), 36.7 (CH_2), 33.2 (CH), 30.8 (CH_2), 30.0 (CH_3), 22.9 (CH_2), 21.2 (CH_3); HRMS (ESI^+): calc. For $C_{28}H_{30}FNO_4$ $[M + H]^+$ 464.2228; found 464.2231.

13-[(Phenylamine), (4-trifluoromethylphenyl)-methyl]-11, *N*-epoxy-tomentosin (5e). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (94 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 5/5) provided **5e** (102 mg, 0.20 mmol, 62%) as a colorless oil; $[\alpha]_D^{20}$ +85.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.59 (m, 4H), 7.24–7.15 (m, 2H), 6.98–6.92 (m, 1H), 6.88 (d, J = 7.9 Hz, 2H), 5.40 (dd, J = 9.4, 3.4 Hz, 1H), 5.23–5.16 (m, 1H), 4.94 (ddd, J = 11.4, 6.3, 4.6 Hz, 1H), 2.91–2.80 (m, 2H), 2.59–2.17 (m, 7H), 2.15 (s, 3H), 2.10 (q, J = 4.7, 4.1 Hz, 1H), 2.00–1.82 (m, 2H), 1.15 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.5 (C), 151.0 (C), 144.9 (C), 145.0 (C), 130.4 (d, J = 32.4 Hz, C), 128.9 (2 CH), 127.1 (2 CH), 126.1 (q, J = 3.8 Hz, C), 124.1 (d, J = 273.2 Hz, 2 CH), 122.9 (CH), 121.0 (CH), 115.4 (2 CH), 85.6 (C), 79.9 (CH), 69.6 (CH), 45.8 (CH), 43.4 (CH_2), 42.6 (CH_2), 36.7 (CH_2), 33.1 (CH), 30.8 (CH_2), 30.1 (CH_3), 23.0 (CH_2), 21.3 (CH_3); HRMS (ESI^+): calc. For $C_{29}H_{30}F_3NO_4$ $[M + H]^+$ 514.2197; found 514.2199.

13-[(Phenylamine), (4-dimethylaminophenyl)-methyl]-11, *N*-epoxy-tomentosin (5f). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (85 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 3/7) provided **5f** (93 mg, 0.19 mmol, 59%) as a brown oil; $[\alpha]_D^{20}$ +48.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.7 Hz, 2H), 6.98–6.89 (m, 3H), 6.73 (d, J = 8.4 Hz, 2H), 5.43 (dd, J = 9.3, 3.5 Hz, 1H), 4.98 (dd, J = 9.7, 6.5 Hz, 1H), 4.89 (ddd, J = 11.4, 6.9, 4.3 Hz, 1H), 2.96 (s, 6H), 2.89–2.75 (m, 2H), 2.60–2.18 (m, 7H), 2.15 (s, 3H), 2.10 (dd, J = 10.5, 3.4 Hz, 1H), 1.95 (ddd, J = 21.0, 9.5, 2.7 Hz, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 175.0 (C), 151.3 (C), 150.4 (C), 144.7 (C), 128.6 (2 CH), 127.7 (2 CH), 127.3 (C), 122.7 (CH), 121.2 (CH), 116.2 (2 CH), 112.9 (2 CH), 85.1 (C), 79.6 (CH), 70.2 (CH), 45.8 (C), 43.8 (CH_2), 42.7 (CH_2), 40.7 (2 CH_3), 36.7 (CH_2), 33.3 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.8 (CH_2), 21.2 (CH_3); HRMS (ESI^+): calc. For $C_{30}H_{36}N_2O_4$ $[M + H]^+$ 489.2744; found 489.2747.

13-[(Phenylamine), ((4-hydroxy-3-methoxy)phenyl)-methyl]-11, *N*-epoxy-tomentosin (5g). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (86 mg, 0.35 mmol) column chromatography on silica

gel (petroleum ether/ethyl acetate 3/7) provided **5g** (78 mg, 0.16 mmol, 50%) as an orange oil; $[\alpha]_D^{20}$ −68.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.14 (m, 2H), 7.01 (d, J = 1.9 Hz, 1H), 6.98–6.89 (m, 5H), 5.67 (s, 1H), 5.45–5.39 (m, 1H), 5.03 (dd, J = 9.6, 6.5 Hz, 1H), 4.91 (ddd, J = 11.3, 6.7, 4.3 Hz, 1H), 3.88 (s, 3H), 2.87–2.77 (m, 2H), 2.60–2.17 (m, 7H), 2.14 (s, 3H), 2.10 (dt, J = 13.7, 4.1 Hz, 1H), 1.99–1.88 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1 (C), 174.8 (C), 151.3 (C), 147.1 (C), 145.4 (C), 144.8 (C), 132.1 (C), 128.7 (2 CH), 122.7 (CH), 121.2 (CH), 119.7 (CH), 115.8 (2 CH), 114.8 (CH), 108.9 (CH), 85.3 (C), 79.7 (CH), 70.3 (CH), 56.2 (CH_3), 45.8 (CH), 43.8 (CH_2), 42.6 (CH_2), 36.7 (CH_2), 33.2 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.9 (CH_2), 21.2 (CH_3); HRMS (ESI^+): calc. For $C_{29}H_{33}NO_6$ $[M + H]^+$ 492.2381; found 492.2380.

13-[(*p*-Tolylamine), phenyl-methyl]-11, *N*-epoxy-tomentosin (5h). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (74 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5h** (105 mg, 0.23 mmol, 72%) as a yellowish oil; $[\alpha]_D^{20}$ −34.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.4 Hz, 2H), 7.40–7.33 (m, 2H), 7.33–7.27 (m, 1H), 6.98 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.2 Hz, 2H), 5.41 (dd, J = 9.4, 3.5 Hz, 1H), 5.04 (dd, J = 9.5, 6.6 Hz, 1H), 4.90 (ddd, J = 11.3, 6.8, 4.4 Hz, 1H), 2.89–2.78 (m, 2H), 2.60–2.25 (m, 7H), 2.23 (s, 3H), 2.15 (s, 3H), 2.10 (dt, J = 13.8, 4.1 Hz, 1H), 1.99–1.87 (m, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.9 (C), 148.6 (C), 144.7 (C), 140.1 (C), 132.6 (C), 129.3 (2 CH), 129.0 (2 CH), 128.0 (CH), 126.9 (2 CH), 121.1 (CH), 116.6 (2 CH), 85.2 (C), 79.7 (CH), 70.5 (CH), 45.9 (CH), 43.7 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.2 (CH), 30.8 (CH_2), 30.0 (CH_3), 22.8 (CH_2), 21.2 (CH_3), 20.8 (CH_3); HRMS (ESI^+): calc. For $C_{29}H_{33}NO_4$ $[M + H]^+$ 460.2481; found 460.2482.

13-[(*p*-Tolylamine), (4-methoxyphenyl)-methyl]-11, *N*-epoxy-tomentosin (5i). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (85 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 5/5) provided **5i** (108 mg, 0.22 mmol, 69%) as a brown oil; $[\alpha]_D^{20}$ +94.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 6.88 (dd, J = 10.0, 8.3 Hz, 4H), 5.42 (dd, J = 9.4, 3.5 Hz, 1H), 4.96 (dd, J = 9.7, 6.4 Hz, 1H), 4.88 (ddd, J = 11.4, 6.8, 4.3 Hz, 1H), 3.80 (d, J = 1.1 Hz, 3H), 2.86–2.75 (m, 2H), 2.60–2.25 (m, 7H), 2.23 (s, 3H), 2.15 (s, 3H), 2.09 (dt, J = 13.7, 4.3 Hz, 1H), 1.99–1.86 (m, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 175.1 (C), 159.4 (C), 148.4 (C), 144.7 (C), 132.8 (C), 131.6 (C), 129.3 (2 CH), 128.2 (2 CH), 121.1 (CH), 117.1 (2 CH), 114.4 (2 CH), 85.0 (C), 79.7 (CH), 70.3 (CH), 55.4 (CH_3), 46.0 (CH), 43.7 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.3 (CH), 30.8 (CH_2), 30.0 (CH_3), 22.8 (CH_2), 21.2 (CH_3), 20.8 (CH_3); HRMS (ESI^+): calc. For $C_{30}H_{35}NO_5$ $[M + H]^+$ 490.2586; found 490.2588.

13-[(*p*-Tolylamine), (4-fluorophenyl)-methyl]-11, *N*-epoxy-tomentosin (5j). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (81 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5j** (96 mg, 0.20 mmol, 63%) as a yellowish oil; $[\alpha]_D^{20}$ +55.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 8.4, 5.3 Hz, 2H), 7.05 (t, J = 8.5 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 5.42 (dd, J = 9.4, 3.5 Hz, 1H), 5.02 (dd, J = 9.6, 6.4 Hz, 1H), 4.89 (ddd, J = 11.4, 6.8, 4.4 Hz, 1H), 2.85–2.78 (m, 2H), 2.60–2.25 (m, 7H), 2.23 (s, 3H), 2.15 (s, 3H), 2.10 (dt, J = 13.7, 4.1 Hz, 1H), 1.98–1.86 (m, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.9 (C), 162.5 (d, J = 246.4 Hz, C), 148.3 (C), 144.8 (C), 135.7 (d, J = 3.2 Hz, C), 133.0 (C), 129.4 (2 CH), 128.6 (d, J = 8.1 Hz, 2 CH), 121.1 (CH), 116.9 (2 CH), 115.9 (d, J = 21.5 Hz, 2 CH), 85.2 (C), 79.8 (CH), 70.0 (CH), 46.0 (CH), 43.6 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.2 (CH), 30.8 (CH_2), 30.0 (CH_3), 22.9 (CH_2), 21.2 (CH_3), 20.8 (CH_3); HRMS (ESI^+): calc. For $C_{29}H_{32}FNO_4$ $[M + H]^+$ 478.2387; found 478.2388.

13-[(*p*-Tolylamine), (4-trifluoromethylphenyl)-methyl]-11, *N*-epoxy-tomentosin (5k). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (98 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 5/5) provided **5k** (104 mg, 0.20 mmol, 62%) as a yellowish oil; $[\alpha]_D^{20}$ +98.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, J = 6.1 Hz, 4H), 7.00 (d, J = 8.1 Hz, 2H), 6.83 (d, J = 8.1 Hz, 2H), 5.40 (dd, J = 9.5, 3.4 Hz, 1H), 5.13 (dd, J = 9.4, 6.7 Hz, 1H), 4.91 (ddd, J = 11.3, 6.7, 4.5 Hz, 1H), 2.84 (dd, J = 12.6, 6.6 Hz, 2H), 2.59–2.25 (m, 7H), 2.24 (s, 3H), 2.15 (s, 3H), 2.13–2.06 (m, 1H), 1.91 (dd, J = 13.7, 11.3 Hz, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.7 (C), 148.3 (C), 144.9 (C), 144.5 (C), 133.0 (C), 130.3 (d, J = 32.5 Hz, C), 129.5 (2 CH), 127.2 (2 CH), 126.0 (q, J = 3.7 Hz, 2 CH), 124.1 (d, J = 272.1 Hz, C), 121.0 (CH), 116.5 (2 CH), 85.4 (C), 79.9 (CH), 69.9 (CH), 45.9 (CH), 43.5 (CH), 42.6 (CH), 36.7 (CH_2), 33.2 (CH), 30.8 (CH_2), 30.0 (CH_3), 22.9 (CH_2), 21.2 (CH_3), 20.8 (CH_3); HRMS (ESI^+): calc. For $C_{30}H_{32}F_3NO_4$ $[M + H]^+$ 528.2355; found 528.2356.

13-[(4-Fluorophenylamine), phenyl-methyl]-11, *N*-epoxy-tomentosin (5l). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (76 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5l** (102 mg, 0.22 mmol, 68%) as a yellowish oil; $[\alpha]_D^{20}$ +57.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.40–7.28 (m, 3H), 6.96–6.83 (m, 4H), 5.45–5.37 (m, 1H), 4.99 (dd, J = 9.8, 6.4 Hz, 1H), 4.87 (ddd, J = 11.4, 7.0, 4.1 Hz, 1H), 2.89–2.78 (m, 2H), 2.62–2.18 (m, 7H), 2.15 (s, 3H), 2.10 (dt, J = 13.8, 4.2 Hz, 1H), 2.00–1.83 (m, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 175.1 (C), 159.3 (d, J = 241.6 Hz, C), 147.0 (d, J = 2.5 Hz, C), 144.8 (C), 139.5 (C), 129.1 (2 CH), 128.3 (CH), 127.0 (2 CH), 120.9 (CH), 118.6 (d, J = 8.0 Hz, 2 CH), 115.4 (d, J = 22.6 Hz, 2 CH), 85.1 (C), 79.7 (CH), 71.1 (CH), 45.7 (CH), 43.9 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.5 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.8 (CH_2), 21.2 (CH_3); HRMS (ESI^+): calc. For $C_{28}H_{30}FNO_4$ $[M + H]^+$ 464.2231; found 464.2231.

13-[(4-Fluorophenylamine), (*p*-tolyl)-methyl]-11, *N*-epoxy-tomentosin (5m). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (81 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5m** (95 mg, 0.20 mmol, 62%) as a yellowish oil; $[\alpha]_D^{20}$ +66.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.17 (d, J = 7.8 Hz, 2H), 6.97–6.82 (m, 4H), 5.42 (dd, J = 9.2, 3.7 Hz, 1H), 4.94

(dd, J = 9.9, 6.3 Hz, 1H), 4.85 (ddd, J = 11.4, 7.0, 4.1 Hz, 1H), 2.90–2.75 (m, 2H), 2.60–2.40 (m, 5H), 2.35 (s, 3H), 2.32–2.19 (m, 2H), 2.15 (s, 3H), 2.10 (dt, J = 13.7, 4.2 Hz, 1H), 2.02–1.85 (m, 2H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 175.2 (C), 159.3 (d, J = 241.5 Hz, C), 147.0 (d, J = 2.5 Hz, C) 144.8 (C), 138.1 (C), 136.3 (C), 129.8 (2 CH), 127.0 (2 CH), 120.9 (CH), 118.8 (d, J = 7.9 Hz, 2 CH), 115.3 (d, J = 22.5 Hz, 2 CH), 85.0 (C), 79.7 (CH), 70.9 (CH), 45.7 (CH), 44.0 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.5 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.7 (CH_2), 21.3 (CH_3), 21.1 (CH_3); HRMS (ESI$^+$): calc. For $C_{29}H_{32}FNO_4$ $[M + H]^+$ 478.2386; found 478.2388.

13-[(4-Fluorophenylamine), (4-methoxyphenyl)-methyl]-11, *N*-epoxy-tomentosin (5n). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (86 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 5/5) provided **5n** (94 mg, 0.19 mmol, 59%) as a yellowish oil; $[\alpha]_D^{20}$ +71.0 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 2H), 6.98–6.82 (m, 6H), 5.46–5.40 (m, 1H), 4.93–4.80 (m, 2H), 3.81 (s, 3H), 2.89–2.72 (m, 2H), 2.61–2.18 (m, 7H), 2.15 (s, 3H), 2.10 (dt, J = 13.7, 4.2 Hz, 1H), 2.03–1.85 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 175.3 (C), 159.6 (C), 159.4 (d, J = 241.7 Hz, C), 146.9 (d, J = 2.5 Hz, C), 144.8 (C), 130.9 (C), 128.3 (2 CH), 120.9 (CH), 119.2 (d, J = 8.0 Hz, 2 CH), 115.3 (d, J = 22.5 Hz, 2 CH), 114.5 (2 CH), 84.9 (C), 79.6 (CH), 70.9 (CH), 55.4 (CH_3), 45.7 (CH), 43.9 (CH_2), 42.7 (CH_2), 36.7 (CH_2), 33.6 (CH), 30.8 (CH_2), 30.1 (CH_3), 22.7 (CH_2), 21.1 (CH_3); HRMS (ESI$^+$): calc. For $C_{29}H_{32}FNO_5$ $[M + H]^+$ 494.2336; found 494.2337.

13-[(Phenylamine), (pyridin-4-yl)-methyl]-11, *N*-epoxy-tomentosin (5o). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (70 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 2/8) provided **5o** (76 mg, 0.17 mmol, 53%) as a yellowish oil; $[\alpha]_D^{20}$ +15.1 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66–8.58 (m, 2H), 7.52–7.39 (m, 2H), 7.23–7.15 (m, 2H), 7.01–6.82 (m, 3H), 5.40 (dd, J = 9.2, 3.4 Hz, 1H), 5.14 (dd, J = 9.1, 7.0 Hz, 1H), 4.95 (ddd, J = 11.3, 6.6, 4.5 Hz, 1H), 2.89–2.82 (m, 2H), 2.66–2.17 (m, 7H), 2.14 (s, 3H), 2.13–2.07 (m, 1H), 2.00–1.80 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9 (C), 174.3 (C), 150.8 (C), 150.6 (2 CH), 150.0 (C), 145.0 (C), 129.0 (2 CH), 122.9 (CH), 121.6 (2 CH), 121.0 (CH), 115.1 (2 CH), 85.8 (C), 80.0 (CH), 68.9 (CH), 45.7 (CH), 42.8 (CH_2), 42.6 (CH_2), 36.7 (CH_2), 33.1 (CH), 30.8 (CH_2), 30.1 (CH_3), 23.0 (CH_2), 21.3 (CH_3); HRMS (ESI$^+$): calc. For $C_{27}H_{30}N_2O_4$ $[M + H]^+$ 447.2277; found 447.2278.

13-[(Phenylamine), (furan-2-yl)-methyl]-11, *N*-epoxy-tomentosin (5p). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (66 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5p** (87 mg, 0.20 mmol, 63%) as a yellowish oil; $[\alpha]_D^{20}$ +71.3 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 1.8, 0.9 Hz, 1H), 7.25–7.18 (m, 2H), 6.99 (dd, J = 8.4, 7.1 Hz, 3H), 6.35 (dd, J = 3.3, 1.8 Hz, 1H), 6.31 (dt, J = 3.3, 0.7 Hz, 1H), 5.45 (ddd, J = 7.9, 2.5, 1.2 Hz, 1H), 5.10 (dd, J = 8.2, 7.0 Hz, 1H), 4.93 (ddd, J = 11.3, 6.6, 4.6 Hz, 1H), 2.88–2.72 (m, 2H), 2.60–2.18 (m, 7H), 2.15 (s, 3H), 2.14–2.07 (m, 1H), 2.03–1.90 (m, 2H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 174.6 (C), 151.6 (C), 150.5 (C), 144.7 (C), 142.9 (CH), 128.8 (2 CH), 123.4 (CH), 121.4 (CH), 116.5 (2 CH), 110.7 (CH), 108.5 (CH), 85.7 (C), 80.1 (CH), 64.7 (CH), 46.3 (CH), 42.7 (CH_2), 38.5 (CH_2), 36.7 (CH_2), 33.0 (CH), 30.9 (CH_2), 30.1 (CH_3), 23.0 (CH_2), 21.3 (CH_3); HRMS (ESI$^+$): calc. For $C_{26}H_{29}NO_5$ $[M + H]^+$ 436.2118; found 436.2118.

13-[(Phenylamine), (thiophen-3-yl)-methyl]-11, *N*-epoxy-tomentosin (5q). Following the general procedure, using tomotensin (80 mg, 0.32 mmol) and corresponding nitrone (72 mg, 0.35 mmol) column chromatography on silica gel (petroleum ether/ethyl acetate 6/4) provided **5q** (99 mg, 0.22 mmol, 68%) as a yellowish oil; $[\alpha]_D^{20}$ −17.0 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 5.0, 3.0 Hz, 1H), 7.28 (dt, J = 3.0, 1.0 Hz, 1H), 7.22–7.14 (m, 3H), 6.96 (ddt, J = 8.3, 3.3, 1.7 Hz, 3H), 5.41 (dt, J = 7.8, 2.4 Hz, 1H), 5.16 (dd, J = 9.0, 6.6 Hz, 1H), 4.91 (ddd, J = 11.3, 6.7, 4.4 Hz, 1H), 2.82 (ddd, J = 19.3, 11.2, 4.9 Hz, 2H), 2.60–2.17 (m, 7H), 2.15 (s, 3H), 2.10 (dt, J = 13.8, 4.1 Hz, 1H), 2.00–1.85 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2 (C), 175.0 (C), 151.2 (C), 145.0 (C), 141.3 (C), 129.0 (2 CH), 127.2 (CH), 126.2 (CH), 123.3 (CH), 122.4 (CH), 121.4 (CH), 116.5 (2 CH), 85.6 (C), 80.1 (CH), 67.0 (CH), 46.3 (CH), 42.9 (CH_2), 42.4 (CH_2), 36.9 (CH_2), 33.4 (CH), 31.0 (CH_2), 30.3 (CH_3), 23.2 (CH_2), 21.4 (CH_3); HRMS (ESI$^+$): calc. For $C_{26}H_{29}NO_4S$ $[M + H]^+$ 452.1887; found 452.1890.

Conclusions

In summary, we described here the synthesis of interesting spiro-isoxazolidine and isoxazoline derivatives of tomentosin by a 1,3-dipolar cycloaddition of respectively nitrones and nitrile oxides to the natural compound. We used an enantiomerically pure and natural starting material, thereby limiting the chemical impact on the environment. This procedure allowed us to generate enantiomerically pure spiro compounds in one diastereoisomer form with a limited number of steps.

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