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ARTICLE

Structure Determination of Bisacetylenic Oxylipins in Carrots (*Daucus carota* L.) and Enantioselective Synthesis of Falcarindiol

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Although bisacetylenic oxylipins have been demonstrated to exhibit diverse biological activities, the chemical structures of many representatives of this class of phytochemicals still remain elusive. As carrots play an important role in our daily diet and are known as a source of bisacetylenes, an extract made from *Daucus carota* L. was screened for bisacetylenic oxylipins, and, after isolation, their structures were determined by means of LC−MS and 1D/2D NMR spectroscopy. Besides the previously reported falcarinol, falcarindiol, and falcarindiol 3-acetate, nine additional bisacetylenes were identified, among which six derivatives are reported for the first time in literature and three compounds were previously not identified in carrots. To determine the absolute stereochemistry of falcarindiol in carrots, the (3*R*,8*R*)-, (3*R*,8*S*)-, (3*S*,8*R*)-, and (3*S*,8*S*)-stereoisomers of falcarindiol were synthesized according to a novel 10-step total synthesis involving a Cadiot−Chodkiewicz cross-coupling reaction of (*S*)- and (*R*)-trimethylsilanyl-4-dodecen-1-yn-3-ol and (*R*)- and (*S*)-5-bromo-1-penten-4-yn-3-ol, respectively. Comparative chiral HPLC analysis of the synthetic stereoisomers with the isolated phytochemical led to the unequivocal assignment of the (*Z*)-(3*R*,8*S*)-configuration for falcarindiol in carrot extracts from *Daucus carota* L.

KEYWORDS: Carrots; bisacetylenes; polyacetylene; falcarinol; falcarindiol; falcarindiol-3-acetate; enantioselective reduction; hypervalent iodine reagents; panaxydiol

INTRODUCTION

The chemical structures of the bisacetylenic oxylipins falcarinol (**1**), falcarindiol (**2**), and falcarindiol-3-acetate (**3**; **Figure 1**) were reported for the first time about 40 years ago, e.g. falcarinol (**1**) was first isolated from *Falcaria vulgaris* Bernh. (*1*) as well as from Korean ginseng (*2*), and falcarindiol (**2**) and falcarindiol-3-acetate (**3**) were first reported as phytochemicals in carrots (*Daucus carota* L.) (*3*). Later, falcarinol (**1**) and falcarindiol (**2**) were found in several Apiaceae species, e.g. compound **1** in *Petroselinum crispum*, *Aegopodium podagraria*, *Foeniculum vulgare* (*4*, *5*) and compound **2** in *Aegopodium podagraria* L. (*6*), celery (*Apium graveolens* L.), parsnip (*Pastinaca sativa* L.), and parsley (*Petroselinum crispum* L.) (*4*, *5*), respectively. Besides compounds **1**−**3**, other bisacetylenes have been identified in carrots, e.g. falcarinolone, falcarindiol-3,8-diacetate, falcarindione, and 3-acetoxy-falcarin-8-one (*3*, *7*). Whereas falcarindiol (**2**) isolated from *Peucedanum oroselinum*, *Seseli gummiferum*, and *Apium graveolens* was proposed to exhibit a (3*R*,8*S*)-stereochemistry by means of melting point studies of the corresponding hydrogenated alcohols (*4*, *8*) or by means of optical rotation experiments (*9*), the bisacetylenic diol isolated from *Dendropanax arboreus* and *Oplopanax horridus* was reported to exist as the (3*S*,8*S*)-stereoisomer by application of the Mosher method (*10*, *11*). Although some falcarindiol stereoisomers have been earlier prepared in the literature (*13*−*15*), the synthetic routes used are rather tedious and involve up to 20 single reaction steps.

The polyacetylenic oxylipins **1**−**3** gain increasing interest as highly bioactive phytochemicals, and they have been reported to exhibit cytotoxic activities against microorganisms such as *Mycobacterium tuberculosis* and *Candida albicans* (*11*, *12*, *16*) and antifungal activity e.g. against *Botrytis cinerea* and *Aspergillus niger* (*17*−*19*). Antiproliferative activity against leukemia and other cancer cell lines *in vitro* (*4*, *20*−*22*) and *in vivo* (*10*) were found, and more recent studies indicate that synergistic effects between falcarinol and other polyacetylenes in carrots may enhance their bioactivity (*23*). In addition, falcarinol was found to exhibit allergenic activity, thus inducing dermatitis symptoms (*24*). Besides their bioactivity, compounds **1**−**3** were reported to exhibit intense bitter taste and to contribute to the bitter off-taste of fresh carrots as well as processed carrot products (*25*, *26*).

Stimulated by the diverse bioactivities reported for such bisacetylenes, there is growing interest in the chemical structures of previously unknown bisacetylenic phytochemicals in our daily

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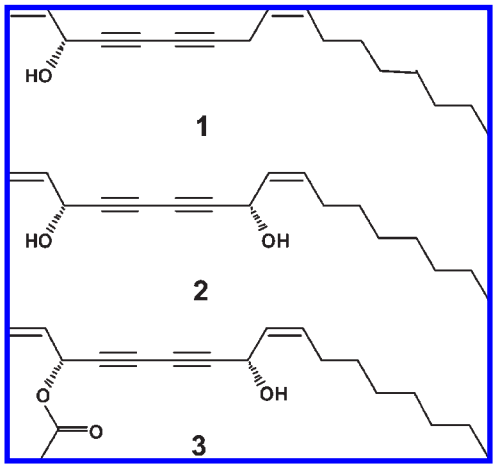

Figure 1. Chemical structures of falcarinol (**1**), falcarindiol (**2**), and falcarindiol-3-acetate (**3**).

diet and, in particular, in carrots, a well-known source of bisacetylenes. In addition, the stereochemistry of the major falcarindiol (**2**) in carrots has not been confirmed by chiral chromatography using enantiopure reference compounds. Therefore, the objective of the present investigation was to screen for new bisacetylenic phytochemicals in carrots (*Daucus carota* L.) by means of UV/vis and LC−MS, to determine their chemical structure by means of 1D/2D NMR spectroscopy, to synthesize all possible stereoisomers of falcarindiol (**2**), and to determine stereochemistry and absolute configuration of the naturally occurring isomer by its comparison with the synthesized stereoisomers by means of chiral liquid chromatography.

MATERIALS AND METHODS

Chemicals. The following compounds were obtained commercially: bromobenzene, *n*-butyllithium, quinoline, copper(I) chloride, dichloromethane, diethyl ether, ethyl acetate, hydroxylamine hydrochloride, magnesium chips, magnesium sulfate, *O*-methylhydroxylamine hydrochloride, *n*-pentane, sodium chloride, sodium thiosulfate, tetrahydrofuran (THF), trimethylboroxine (Merck, Darmstadt, Germany), acetone, acrylic acid chloride, ammonium chloride, borane dimethylsulfide complex, ethanol, hydrochloric acid, Lindlar catalyst, (*R*)- and (*S*)-1-phenyl-2-aminoethanol, trimethylsilyl-acetylene, iodine, pyridine (Sigma-Aldrich, Steinheim, Germany), 2-decyn-1-ol, 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) (ABCR, Karlsruhe, Germany), *N*-bromo-succinimide, petroleum ether, potassium hydroxide, (*R*)- and (*S*)-phenylglycine methyl ester hydrochloride, sodium sulfate, toluene (Fluka, Buchs, Switzerland); solvents were of HPLC grade (Merck, Darmstadt, Germany). Diacetoxyiodosobenzene (DIB) was freshly prepared according to the literature (*27*). Samples of fresh carrots (*Daucus carota* L.) were purchased in a local vegetable store. Falcarinol (**1**), falcarindiol (**2**), and falcarindiol-3-acetate (**3**) were isolated from carrots and purified following the literature protocol (*25*).

UV/Vis-Directed Fractionation of Carrots. Carrots (50 kg) were cut into small pieces by means of a kitchen knife, and aliquots (about 2 kg) were minced in a blender (Retsch, Haan, Germany) and, then, sequentially extracted with *n*-pentane (4 × 800 mL), followed by ethyl acetate (3 × 400 mL) while stirring at room temperature under an atmosphere of argon. After filtration, the combined *n*-pentane extracts and the combined ethyl acetate extracts were separated from solvent in vacuum to afford the *n*-pentane extractables (fraction A; yield: 8.5 g), the ethyl acetate extractables (fraction B; yield: 30 g), and the nonsoluble residue (fraction C; yield: 5600 g). An aliquot (1.2 g) of fraction A was dissolved in a mixture (95/5, v/v; 5 mL) of *n*-pentane and diethyl ether and was then applied onto the top of a water-cooled 400 × 50 mm glass column filled with silica gel (0.063−0.2 mm) conditioned with 5% water. Chromatography was performed by eluting the column with mixtures (600 mL each) of *n*-pentane and diethyl ether in ratios of 95/5 (v/v; fraction A-I), 80/20 (v/v; fraction A-II), 70/30 (v/v; fraction A-III), 50/50 (v/v; fraction A-IV), followed by diethyl ether (fraction A-V). The individual fractions were separated from solvent in vacuum to afford oily residues, which were kept at −20 °C until used. Aliquots of these fractions were analyzed by means of RP-HPLC on a 250 × 4.6 mm i.d., 5 μm, Hyperclone column coupled to a diode array detector, and the effluent was monitored at 232, 244, and 258 nm, previously identified as the UV maxima of the bisacetylene **2** (*3*), thus enabling the detection of a series of bisacetylenes in fractions A-III and A-IV.

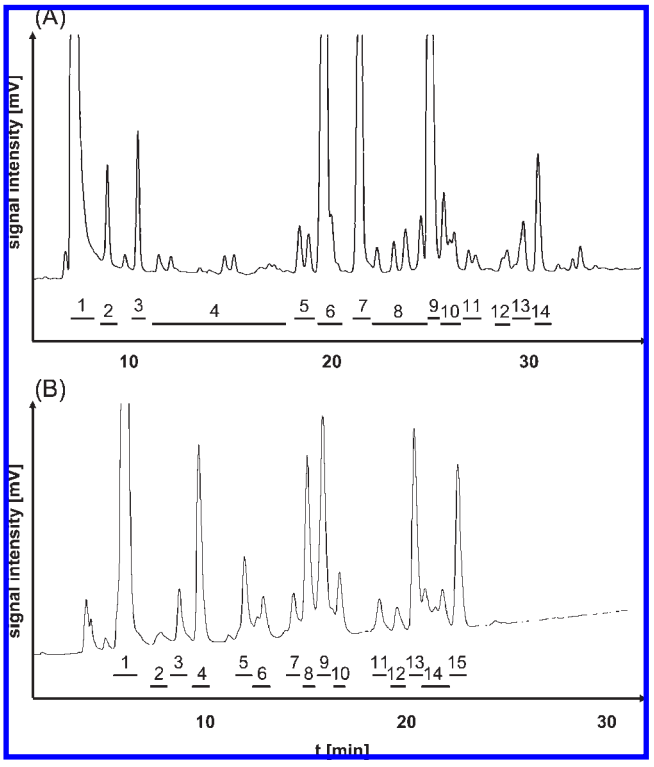

Figure 2. RP-HPLC chromatograms (λ = 200 nm) of fractions A-III (**A**) and A-IV (**B**), respectively.

Identification of Bisacetylenes in Fractions A-III and A-IV. Aliquots (50 mg) of fractions A-III and A-IV, respectively, were dissolved in methanol/water (70/30, v/v; 10 mL) and, after membrane filtration, were fractionated by means of preparative HPLC on a Microsorb RP-18, 250 × 21.2 mm i.d., 5 μm column (Varian, Darmstadt, Germany) using a methanol/water gradient at a flow rate of 18 mL/min. Chromatography was performed using a linear gradient from methanol/water (70/30, v/v) to methanol within 50 min, thereafter, keeping the solvent constant for 10 min. A total of 14 and 15 individual HPLC fractions were collected from fractions A-III and A-IV, respectively (**Figure 2**). Each fraction was finally purified by means of solid phase extraction using C-18 E cartridges (5 g; Phenomenex, Aschaffenburg, Germany) which were preconditioned with methanol (2 × 20 mL), followed by water (3 × 20 mL). After sample application, the cartridge was rinsed with water (30 mL), nitrogen was sucked through the cartridge for 10 min by means of a vacuum pump, and, finally, the unstable target compounds were carefully eluted with methanol (30 mL). After separation of the solvent in vacuum, the individual bisacetylenes were obtained with a purity of more than 98% as confirmed by RP-HPLC connected to a diode array detector (DAD) and an evaporative light scattering detector (ELSD), and their chemical structures were determined by means of LC−MS and 1D/2D NMR spectroscopic experiments.

*Isofalcarinolone, **4**, **Figure 3***. Pale yellow oil (1.5 mg). UV/vis (MeOH): λ_{max} = 284, 268, 256 nm. LC−MS (ESI^+): 281.2 (100, $[M + Na]^+$), 259.4 (56, $[M + H]^+$). LC−TOF-MS: *m*/*z* 259.1690 ($[M + H]^+$, measured), *m*/*z* 259.1693 ($[M+H]^+$, calcd for $C_{17}H_{23}O_2^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 7.18 (1H, dt, *J* = 16.0, 7.3 Hz, H-10), 6.18 (1H, dt, *J* = 16.0, 1.2 Hz, H-9), 5.96 (1H, ddd, *J* = 17.0, 10.2, 5.4 Hz, H-2), 5.51 (1H, ddd, *J* = 17.0, 1.5, 1.0 Hz, H_A-1), 5.32 (1H, ddd, *J* = 10.2, 1.5, 1.0 Hz,

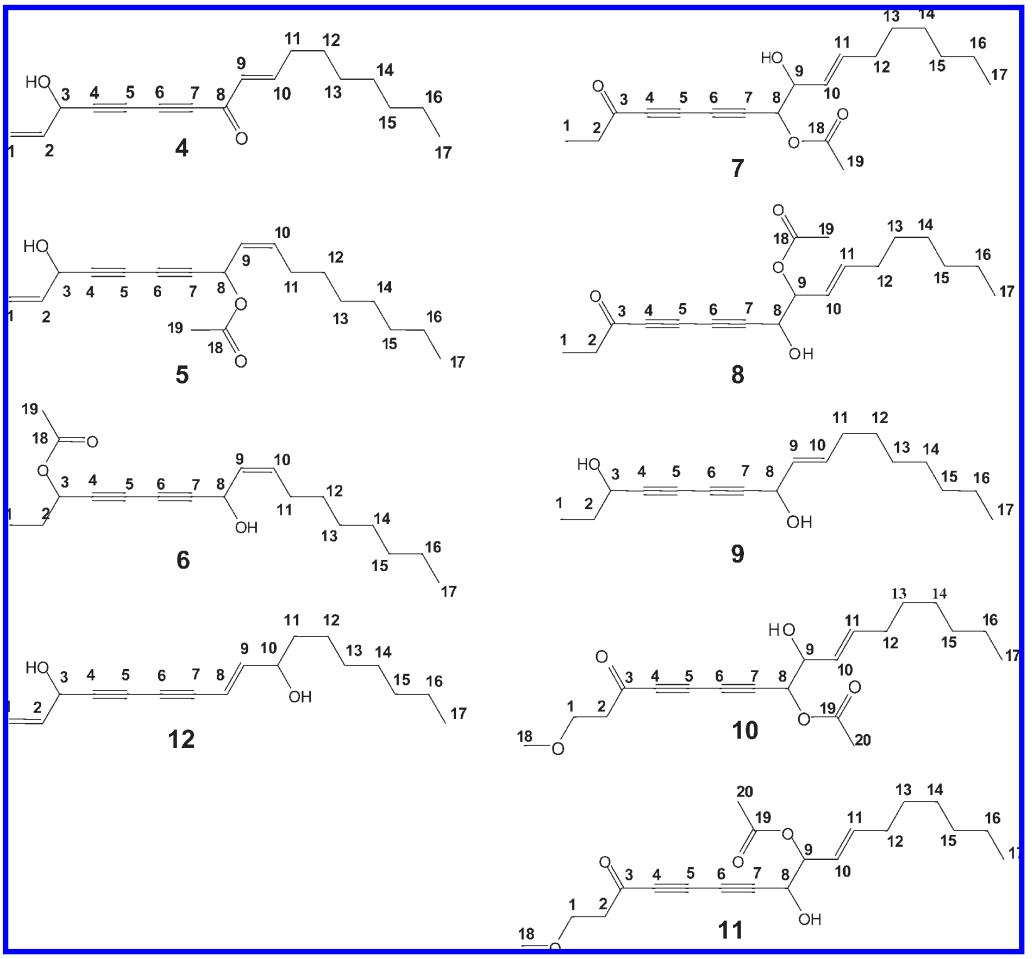

Figure 3. Chemical structures of the bisacetylenic compounds previously not reported in carrots: isofalcarinolone (**4**), falcarindiol-8-acetate (**5**), 1,2-dihydrofalcarindiol-3-acetate (**6**), (*E*)-falcarindiolone-8-acetate (**7**), (*E*)-falcarindiolone-9-acetate (**8**), 1,2-dihydrofalcarindiol (**9**), (*E*)-1-methoxy-falcarindiolone-8-acetate (**10**), (*E*)-1-methoxy-falcarindiolone-9-acetate (**11**), and panaxydiol (**12**).

H_B-1), 5.02 (1H, m, H-3), 2.30 (2H, m, H-11), 1.51 (2H, m, H-12), 1.24−1.42 (8H, m, H-13−16), 0.88 (3H, t, J = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 177.2 (C-8), 156.4 (C-10), 135.3 (C-2), 132.3 (C-9), 118.3 (C-1), 84.7 (C-4), 74.7 (C-7), 74.3 (C-6), 69.3 (C-5), 63.9 (C-3), 32.5 (C-11), 31.8 (C-15), 28.9 (C-13−14), 27.9 (C-12), 22.7 (C-16), 13.9 (C-17) (*34*, *21*).

*Falcarindiol-8-acetate, **5**, **Figure 3***. Colorless oil (2.0 mg). UV/vis (MeOH): λ_{max} = 292, 276, 252. LC−MS (ESI$^+$): 341.5 (46, [M + K]$^+$), 325.4 (100, [M + Na]$^+$), 307.4 (69, [M + Na − H_2O]$^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 6.13 (1H, d, J = 9.0 Hz, H-8), 5.93 (1H, ddd, J = 17.0, 10.1, 5.5 Hz, H-2), 5.65 (1H, dt, J = 10.5, 7.8 Hz, H-10), 5.48 (1H, dd, J = 10.5, 9.0 Hz, H-9), 5.46 (1H, dt, J = 17.0, 1.4 Hz, H_A-1), 5.25 (1H, dt, J = 10.1, 1.0 Hz, H_B-1), 4.93 (1H, dd, J = 5.5 Hz, H-3), 2.13 (2H, m, H-11), 2.08 (3H, s, H-19), 1.37 (2H, m, H-12), 1.24−1.31 (8H, m, H-13−16), 0.88 (3H, t, J = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 169.6 (C-18), 136.5 (C-10), 135.8 (C-2), 123.6 (C-9), 117.2 (C-1), 78.7 (C-4), 76.5 (C-7), 70.2 (C-5), 69.0 (C-6), 63.4 (C-3), 60.1 (C-8), 31.5 (C-15), 28.9 (C-12−14), 27.7 (C-11), 22.6 (C-16), 20.7 (C-19), 13.9 (C-17).

*1,2-Dihydrofalcarindiol-3-acetate, **6**, **Figure 3***. Pale yellow oil (2.0 mg). UV/vis (MeOH): λ_{max} = 284, 268, 256 nm. LC−TOF-MS: m/z 327.1926 ([M + Na]$^+$, measured), m/z 327.1931 ([M + Na]$^+$, calcd for $C_{19}H_{28}O_3Na^+$). ^{1}H NMR (800 MHz, $CDCl_3$; COSY): δ 5.60 (1H, dt, J = 10.0, 7.3 Hz, H-10), 5.50 (1H, ddt, J = 10.0, 8.7, 1.8 Hz, H-9), 5.34 (1H, t, J = 6.4 Hz, H-3), 5.19 (1H, dd, J = 8.7, 4.1 Hz, H-8), 2.10 (2H, m, J = 7.8 Hz, H-11), 2.08 (3H, s, H-19), 1.80 (2H, m, H-2), 1.37 (2H, m, H-12), 1.24−1.31 (8H, m, H-13−16), 1.01 (3H, t, J = 7.7 Hz, H-1), 0.88 (3H, t, J = 6.8 Hz, H-17). ^{13}C NMR (201 MHz, $CDCl_3$; HMQC, HMBC): δ 169.9 (C-18), 134.5 (C-10), 127.3 (C-9), 79.3 (C-7), 77.0 (C-4), 69.3 (C-5), 68.8 (C-6), 65.0 (C-3), 58.4 (C-8), 31.5 (C-15), 28.9 (C-12−14), 27.6 (C-2), 27.4 (C-11), 22.2 (C-16), 20.7 (C-19), 13.9 (C-17), 9.0 (C-1).

*(E)-8,9-Dihydroxy-3-keto-heptadeca-10-en-4,6-diyn-8-acetate, (E)-Falcarindiolon-8-acetate, 7, **Figure 3***. Yellow oil (1.2 mg). UV/vis (MeOH): λ_{max} = 284, 268, 256, 244 nm. LC−MS (ESI$^+$): 351.4 (42, [M + MeOH + H]$^+$), 341.4 (63, [M + Na]$^+$), 336.4 (100, [M + NH_4]$^+$), 319.5 (56, [M + H]$^+$). LC−TOF-MS: m/z 341.1719 ([M + Na]$^+$, measured), m/z 341.1723 ([M + Na]$^+$, calcd for $C_{19}H_{26}O_4Na^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 5.92 (1H, dd, J = 15.4, 7.8 Hz, H-11), 5.50 (1H, dd, J = 7.6, 15.4 Hz, H-10), 5.37 (1H, d, J = 6.8 Hz, H-8), 4.30 (1H, m, H-9), 2.62 (2H, q, J = 7.3 Hz, H-2), 2.12 (3H, s, H-19), 2.08 (2H, m, H-12), 1.42 (2H, m, H-13), 1.24−1.31 (6H, m, H-14−16), 1.16 (3H, t, J = 7.3 Hz, H-1), 0.86 (3H, t, J = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 187.0 (C-3), 169.6 (C-18), 137.5 (C-11), 125.8 (C-10), 82.2 (C-7), 74.7 (C-4), 73.3 (C-9), 69.7 (C-5), 67.3 (C-8), 64.4 (C-6), 39.0 (C-2), 32.5 (C-12), 31.7 (C-16), 29.3 (C-14), 28.9 (C-13), 22.6 (C-15), 21.9 (C-19), 14.8 (C-17), 8.0 (C-1).

*(E)-8,9-Dihydroxy-3-keto-heptadeca-10-en-4,6-diyn-9-acetate, (E)-Falcarindiolone-9-acetate, **8**, **Figure 3***. Yellow oil (1.3 mg). UV/vis (MeOH): λ_{max} = 284, 268, 256, 244 nm. LC−MS (ESI$^+$): 351.4 (42, [M + MeOH]$^+$), 341.4 (63, [M + Na]$^+$), 336.4 (100, [M + NH_4]$^+$), 319.5 (56, [M + H]$^+$). LC−TOF-MS: m/z 341.1719 ([M + Na]$^+$, measured), m/z 341.1723 ([M + Na]$^+$, calcd for $C_{19}H_{26}O_4Na^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 5.96 (1H, dt, J = 15.6, 7.8 Hz, H-11), 5.48 (1H, dd, J = 15.6, 7.6 Hz, H-10), 5.33 (1H, dd, J = 7.6, 7.2 Hz, H-9), 4.52 (1H, m, H-8), 2.62 (2H, q, J = 7.3 Hz, H-2), 2.12 (3H, s, H-19), 2.08 (2H, m, H-12), 1.42 (2H, m, H-13), 1.24−1.31 (6H, m, H-14−16), 1.16 (3H, t, J = 7.3 Hz, H-1), 0.86 (3H, t, J = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 187.0 (C-3), 170.3 (C-18), 140.4 (C-11), 123.8 (C-10), 84.4 (C-7), 76.0 (C-9), 73.8 (C-4), 69.2(C-5), 64.9 (C-8), 64.0 (C-6), 39.0 (C-2), 32.5 (C-12), 31.7 (C-16), 29.3 (C-14), 28.9 (C-13), 22.6 (C-15), 21.9 (C-19), 14.8 (C-17), 8.0 (C-1).

1,2-Dihydrofalcarindiol, ***9****,* ***Figure 3***. Colorless oil (1.3 mg). UV/vis (MeOH): λ_{max} = 268, 246, 233 nm. LC−MS (ESI^+): 301.6 (100, $[M+K]^+$), 245.5 (37, $[M - H_2O + H]^+$), 227.3 (33, $[M - 2H_2O + H]^+$). LC−TOF-MS: *m*/*z* 285.1837 ($[M+Na]^+$, measured), *m*/*z* 285.1825 ($[M+Na]^+$, calcd for $C_{17}H_{26}O_2Na^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 5.65 (1H, dt, *J* = 10.5, 7.8 Hz, H-10), 5.48 (1H, dd, *J* = 10.5, 8.2 Hz, H-9), 5.18 (1H, d, *J* = 8.2 Hz, H-8), 4.36 (1H, t, *J* = 6.1 Hz, H-3), 2.13 (2H, m, H-11), 1.78 (2H, m, H-2), 1.37 (2H, m, H-12), 1.24−1.31 (8H, m, H-13−16), 0.99 (3H, t, *J* = 7.5 Hz, H-1), 0.88 (3H, t, *J* = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 136.5 (C-10), 128.3 (C-9), 80.1 (C-4), 78.5 (C-7), 68.8 (C-5), 68.6 (C-6), 64.5 (C-3), 58.5 (C-8), 32.1 (C-11), 31.7 (C-16), 30.6 (C-2), 29.3 (C-12), 28.9 (C-13−14), 22.6 (C-15), 13.9 (C-17), 9.3 (C-1).

(E)-8,9-Dihydroxy-3-keto-1-methoxy-heptadeca-10-en-4,6-diyn-8-acetate, (E)-1-Methoxy-falcarindiolone-8-acetate, ***10****,* ***Figure 3***. Yellow oil (1.0 mg). UV/vis (MeOH): λ_{max} = 284, 268, 256, 244 nm. LC−MS (ESI^+): 385.1 (18, $[M+K]^+$), 371.3 (100, $[M+Na]^+$), 355.1 (82, $[M - H_2O + Na]^+$). LC−TOF-MS: *m*/*z* 371.1821 ($[M + Na]^+$, measured), *m*/*z* 341.1829 ($[M + Na]^+$, calcd for $C_{20}H_{28}O_5Na^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 5.89 (1H, dt, *J* = 15.5, 6.6 Hz, H-11), 5.50 (1H, dd, *J* = 15.5, 7.6 Hz, H-10), 5.36 (1H, d, *J* = 6.2 Hz, H-8), 4.30 (1H, m, H-9), 3.72 (2H, t, *J* = 6.2 Hz, H-1), 3.35 (3H, s, H-18), 2.82 (2H, *J* = 6.2 Hz, H-2), 2.00 (1H, d, *J* = 7.2 Hz, HO-9), 2.15 (3H, s, H-20), 2.08 (2H, m, H-12), 1.39 (2H, m, H-13), 1.24−1.31 (6H, m, H-14−16), 0.86 (3H, t, *J* = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 183.9 (C-3), 168.6 (C-19), 137.2 (C-11), 125.7 (C-10), 82.4 (C-7), 73.1 (C-9), 69.8 (C-6), 67.3 (C-8), 66.6 (C-1), 58.1 (C-18), 45.1 (C-2), 32.5 (C-12), 31.7 (C-16), 29.3 (C-14), 28.9 (C-13), 22.6 (C-15), 21.9 (C-20), 14.8 (C-17), (C-4, C-5: n.d.).

(E)-8,9-Dihydroxy-3-keto-1-methoxy-heptadeca-10-en-4,6-diyn-9-acetate, (E)-1-Methoxy-falcarindiolone-9-acetate, ***11****,* ***Figure 3***. Yellow oil (1.2 mg). UV/vis (MeOH): λ_{max} = 284, 268, 256, 244 nm. LC−MS (ESI^+): 385.1 (18, $[M+K]^+$), 371.3 (100, $[M+Na]^+$), 355.1 (82, $[M - H_2O + Na]^+$). LC−TOF-MS: *m*/*z* 371.1821 ($[M+Na]^+$, measured), *m*/*z* 341.1829 ($[M+Na]^+$, calcd for $C_{20}H_{28}O_5Na^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 5.92 (1H, dt, *J* = 15.4, 6.6 Hz, H-11), 5.48 (1H, dd, *J* = 15.4, 7.6 Hz, H-10), 5.30 (1H, dd, *J* = 7.6, 5.8 Hz, H-9), 4.52 (1H, dd, *J* = 8.4, 5.8 Hz, H-8), 3.72 (2H, t, *J* = 6.2 Hz, H-1), 3.35 (3H, s, H-18), 2.82 (2H, *J* = 6.2 Hz, H-2), 2.19 (1H, d, *J* = 8.4 Hz, HO-8), 2.12 (3H, s, H-20), 2.08 (2H, m, H-12), 1.39 (2H, m, H-13), 1.24−1.31 (6H, m, H-14−16), 0.86 (3H, t, *J* = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 183.9 (C-3), 170.3 (C-19), 140.4 (C-11), 123.8 (C-10), 84.8 (C-7), 76.0 (C-9), 69.2 (C-6), 66.6 (C-1), 64.9 (C-8), 58.1 (C-18), 45.1 (C-2), 32.5 (C-12), 31.7 (C-16), 29.3 (C-14), 28.9 (C-13), 22.6 (C-15), 21.9 (C-20), 14.8 (C-17), (C-4, C-5: n.d.).

(E)-Heptadeca-1,8-diene-4,6-diyn-3,10-diol, Panaxydiol, ***12****,* ***Figure 3***. Pale yellow oil (1.7 mg). UV/vis (MeOH): λ_{max} = 292, 276, 264. LC−TOF-MS: *m*/*z* 283.1663 ($[M + Na]^+$, measured), *m*/*z* 283.1669 ($[M + Na]^+$, calcd for $C_{17}H_{24}O_2Na^+$). ^{1}H NMR (500 MHz, $CDCl_3$; COSY): δ 6.33 (1H, dd, *J* = 16.0, 5.6 Hz, H-9), 5.94 (1H, ddd, *J* = 17.0, 10.2, 5.4 Hz, H-2), 5.77 (1H, d, *J* = 16.0 Hz, H-8), 5.47 (1H, ddd, *J* = 17.0, 1.5, 1.0 Hz, H_A-1), 5.25 (1H, ddd, *J* = 10.2, 1.5, 1.0 Hz, H_B-1), 4.96 (1H, d, *J* = 5.4 Hz, H-3), 4.18 (1H, ddt, *J* = 6.0, 5.6, 1.5 Hz, H-10), 1.53 (2H, m, H-11), 1.24−1.42 (10H, m, H-12−16), 0.88 (3H, t, *J* = 6.8 Hz, H-17). ^{13}C NMR (125 MHz, $CDCl_3$; HMQC, HMBC): δ 149.8 (C-9), 136.0 (C-2), 117.0 (C-1), 108.2 (C-8), 80.6 (C-4), 77.6 (C-7), 73.7 (C-6), 72.1 (C-10), 70.9 (C-5), 63.5 (C-3), 36.8 (C-11), 31.8 (C-15), 28.9 (C-13−14), 25.3 (C-12), 22.7 (C-16), 13.9 (C-17).

Synthesis of Stereoisomers of Falcarindiol (2). *(R)-2-Amino-1,1,2-triphenylethanol,* ***13a***. Bromobenzene (71.0 g; 47 mL, 452 mmol) was added to magnesium turnings (11.0 g, 458 mmol) in diethyl ether under an atmosphere of nitrogen. After refluxing for 1 h, the mixture was cooled to room temperature, filtrated under an atmosphere of nitrogen, then cooled to 0 °C using an ice/salt bath, and (*R*)-phenylglycine methyl ester hydrochloride (10.08 g, 50 mmol) was added in small portions over about 2 h while stirring. After stirring the mixture overnight at room temperature, the solution was poured on crushed ice (250 g), conc. hydrochloric acid (60 mL) was added slowly and the mixture was vigorously stirred for 1 h. The precipitate formed was isolated by filtration and washed with water (50 mL), followed by diethyl ether (10 mL). The precipitate was dissolved in aqueous NaOH (2 mol/L; 150 mL), stirred for 2 h at room temperature, then diethyl ether (300 mL) was added and the mixture was stirred for another 3 h. The organic phase was isolated and washed with small portions of water (4 × 20 mL) and then dried with $MgSO_4$. After partial removal of the solvent in vacuum, (*R*)-1,1,2-triphenyl-2-aminoethanol (**13a**) crystallized as a colorless solid (7.5 g, 26 mmol, 52% yield). Compound **13a**: mp 130−131 °C. $[\alpha]^{20}_D$ = +248.0° (*c* = 1.00, $CHCl_3$) (*28*). MS (ESI^+): *m*/*z* 312.1 (100, $[M+Na]^+$), 290.1 (2, $[M+H]^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (2H, m), 6.95−7.45 (13H, m), 4.99 (1H, s), 1.64 (3H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.8 (d), 79.6 (s), 126.1 (d), 126.3 (d), 126.6 (d), 127.1 (d), 127.3 (d), 127.4 (d), 127.5 (d), 128.6 (d), 128.7 (d), 140.1 (s), 143.9 (s), 146.6 (s).

(S)-2-Amino-1,1,2-triphenylethanol, ***13b***. The (*S*)-enantiomer **13b** was prepared using the same procedure as detailed for **13a** starting from (*S*)-phenylglycine methyl ester hydrochloride. Compound **13b**: $[\alpha]^{20}_D$ = −256.1° (*c* = 1.00, $CHCl_3$) (*28*). C,H,N-analysis: $C_{20}H_{19}NO$ (289.37 g mol^{-1}): calcd C 83.01, H 6.62, N 4.84; found C 83.00, H 6.59, N 4.55.

(R)-B-Methyl-4,5,5-triphenyl-[1,3,2]oxazaborolidine, ***14a***. Trimethyl-boroxine (292 mg, 2.3 mmol, 0.33 mL) was added to a solution of (*R*)-2-amino-1,1,2-triphenylethanol (**13a**) (1.0 g, 3.46 mmol) in dry toluene (13 mL) at room temperature and stirred for 1 h under nitrogen. The reaction mixture was concentrated to 4 mL in vacuum and dissolved in dry toluene (12 mL). This procedure was repeated twice until the resulting solution of (*R*)-*B*-methyl-4,5,5-triphenyl-[1,3,2] oxazaborolidine (**14a**) turned transparent. This solution was diluted with dry toluene to a total volume of 11 mL (*c* = 0.31 *M* in toluene) and stored at −20 °C under an atmosphere of nitrogen. Compound **14a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.9−7.4 (15H, m), 5.42 (1H, d, *J* = 1.1 Hz), 3.70 (1H, br s), 0.50 (3H, s) (*28*).

(S)-B-Methyl-4,5,5-triphenyl-[1,3,2]-oxazaborolidine, ***14b***. The (*S*)-enantiomer **14b** was prepared using the same procedure as detailed for **14a** starting from (*S*)-2-amino-1,1,2-triphenylethanol (**13b**) (*28*).

(Z)-2-Decen-1-ol, ***15***. Lindlar catalyst (300 mg), quinoline (0.3 mL, 0.0025 mmol), and KOH (8 mg) were added to a solution of 2-decyn-1-ol (1.50 g, 9.74 mmol) in ethanol (7.5 mL). The resulting mixture was evacuated three times and flushed with hydrogen gas and, thereafter, stirred vigorously under an atmosphere of hydrogen (1 atm). After stirring for 7 h, the catalyst was removed by filtration through a plug of Celite 545 (0.5 g, Roth, Germany) and (*Z*)-2-decen-1-ol (**15**) was isolated as an oil (1.51 g, 9.98 mmol, 99% yield) by flash chromatography on silica gel (0.063−0.20 mm) using petroleum ether/ethyl acetate (7/1; v/v) (*27*). Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$): 5.47−5.60 (2H, m), 4.16 (2H, d, *J* = 6.4 Hz), 2.03 (2H, q, *J* = 7.2 Hz), 1.45 (1H, s), 1.20−1.37 (10H, m), 0.85 (3H, t, *J* = 7.0 Hz). MS (EI): *m*/*z* (%) = 156 (M^+), 138 (13); 109 (21), 95 (53), 83 (100), 67 (78), 57 (54).

(Z)-2-Decenal, ***16***. Diacetoxyiodosobenzene (DIB; 2.83 g, 8.79 mmol) was added to a solution of (*Z*)-2-decenol (**15**) (1.25 g, 8.01 mmol) and 2,2,6,6-tetramethyl-piperidinyloxyl (TEMPO) (138 mg, 0.88 mmol) in CH_2Cl_2 (8 mL) and stirred for 2 h at room temperature. Thereafter, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with a saturated, aqueous sodium thiosulfate solution (25 mL). The product was extracted with CH_2Cl_2 (10 mL) and the combined organic phases were washed with a saturated $NaHCO_3$ solution (15 mL), followed by brine (15 mL), and was then dried with $MgSO_4$. The crude product was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (8/1, v/v) to give (*Z*)-2-decenal (**16**) as a colorless oil (1.17 g, 7.61 mmol, 95% yield). Compound **16**: *E*/*Z* ratio 1:32 (determined by chiral GC, system A) (*29*). MS (EI): *m*/*z* (%) = 155 (M^++1, 100), 154 (31), 153 (19), 137 (44), 95 (20), 81 (28). ^{1}H NMR (400 MHz, $CDCl_3$): 10.08 (1H, d, *J* = 8.2 Hz), 6.64 (1H, dt, *J* = 11.1, 8.2 Hz), 5.96 (1H, ddt, *J* = 11.1, 8.2, 1.5 Hz), 2.60 (2H, q, *J* = 7.2 Hz), 1.24−1.55 (10H, m), 0.89 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 153.5, 130.1, 58.5, 31.8 (t), 29.1 (t), 29.0 (t), 28.9 (t), 27.9 (t), 22.6 (t), 14.0 (q).

(±)-(Z)-1-Trimethylsilanyl-4-dodecen-1-yn-3-ol, ***17***. A hexane solution of *n*-BuLi (8.25 mmol, 5.16 mL of 1.6 M solution in hexane) was added to a solution of trimethylsilyl-acetylene (872 mg, 8.9 mmol) in dry THF at −78 °C under an atmosphere of nitrogen. After stirring for 15 min, a solution of (*Z*)-2-decenal (**16**) (1.16 g, 7.53 mmol) in dry THF (2 mL) was added slowly, the mixture was stirred for 2 h, and was then

brought to room temperature. Thereafter, a saturated NH_4Cl solution (6 mL) was added, the reaction mixture was extracted with ethyl acetate (4 × 10 mL) and the combined organic layers were dried with $MgSO_4$. (±)-(*Z*)-1-Trimethylsilanyl-4-dodecen-1-yn-3-ol (**17**) was obtained after removal of the solvent as a pale yellow oil (1.56 g, 6.19 mmol, 82% yield). Compound **17**: *E*/*Z* ratio 1:5 (determined by chiral GC, system B) (*30*). MS (EI): *m*/*z* (%) = 252 ([M]$^+$, 5), 235 (24), 161 (69), 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48−5.58 (2H, m), 5.10 (1H, d, *J* = 7.2 Hz), 2.09 (2H, q, *J* = 7.0 Hz), 1.89 (1H, s), 1.22−1.40 (10H, m), 0.85 (3H, t, *J* = 7.0 Hz), 0.16 (9H, s).

(Z)-Trimethylsilanyl-4-undecen-1-yn-3-one, ***18***. Trimethylsilyl-4-dodecen-1-yn-3-ol (**17**) (505 mg, 2.00 mmol) and TEMPO (41 mg, 0.26 mmol) were dissolved in CH_2Cl_2 (2 mL), and, after the addition of diacetoxy iodosobenzene (838 mg, 2.60 mmol), the reaction mixture was stirred for 2 h at room temperature. The mixture was then diluted with CH_2Cl_2 (4 × 15 mL) and washed with a saturated aqueous sodium thiosulfate solution (6 mL), the aqueous phase was extracted with CH_2Cl_2 (10 mL), and the combined organic phases were washed with small portions of a saturated aqueous $NaHCO_3$ solution (5 mL), followed by brine (5 mL), and then dried with $MgSO_4$. Flash chromatography on silica gel with petroleum ether/ethyl acetate (30/1, v/v) gave (*Z*)-trimethylsilanyl-4-dodecen-1-yn-3-on (**18**) as a colorless oil (475 mg, 95% yield). Compound **18**: E/Z ratio 1:5 (determined by chiral GC, system B) (*29*). MS (EI): *m*/*z* (%) = 251 (M^++1, 24), 235 (26), 221 (19), 205 (44), 153 (57), 139 (100), 125 (90), 97 (43), 75 (91). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (1H, dt, *J* = 11.6, 7.2 Hz), 6.14 (1H, dt, *J* = 11.6, 1.5 Hz), 2.70 (2H, dq, *J* = 7.2, 1.5 Hz), 1.20−1.48 (10H, m), 0.85 (3H, t, *J* = 7.2 Hz), 0.24 (9H, s).

(S)-(Z)-Trimethylsilyl-4-dodecen-1-yn-3-ol, ***19a***. (*S*)-*B*-Methyl-4,5,5-triphenyl-[1,3,2]oxazaborolidine (**14b**) (0.59 mmol 1.97 mL of 0.3 M solution in toluene) and BH_3−SMe_2 (66 μL, 0.56 mmol) were dissolved in dry THF (1.0 mL) under nitrogen and cooled to −5 °C. After addition of (*Z*)-trimethylsilanyl-4-dodecen-1-yn-3-one (**18**) (118 mg, 0.47 mmol) in dry THF (0.5 mL) during 0.5 h, the mixture was stirred for 2 h. Thereafter, methanol (1 mL) was added, the solvent was removed in vacuum, taken up in methanol (1 mL), stirred for 1.5 h, and was again separated from solvents in vacuum. Flash chromatography on silica gel using petroleum ether/ethyl acetate (30/1, v/v) gave (*S*)-(*Z*)-trimethylsilanyl-4-dodecen-1-yn-3-ol (**19a**) as a colorless oil (69 mg, 0.27 mmol, 57% yield; E/Z ratio 1:5, 97% ee, determined by chiral GC, system B) (*15*).

(R)-(Z)-Trimethylsilyl-4-dodecen-1-yn-3-ol, ***19b***. Compound **19b** was prepared using the procedure detailed for **19a** and using (*R*)-*B*-methyl-4,5,5-triphenyl-[1,3,2]oxazaborolidine (**14a**) and BH_3−SMe_2 as reducing reagent. The target compound **19b** was obtained with an ee-value of 93% (GC on a chiral column, system B) (*15*).

N-Methoxy-N-methyl-acrylamide, ***20***. Methylhydroxylamine hydrochloride (5.22 g, 53.54 mmol), dissolved in CH_2Cl_2 (170 mL), was cooled to −5 °C, and acrylic acid chloride (4.53 g, 50.06 mmol) was added. Thereafter, pyridine (8.9 mL, 110.5 mmol) was added over a period of 0.5 h, while the temperature was kept below 0 °C. The reaction mixture was then brought to 20 °C and was cooled down again to 0 °C before brine (170 mL) was added. The solution was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Flash chromatography on silica gel using petroleum ether/ethyl acetate (1:1, v/v) afforded *N*-methoxy-*N*-methylacrylamide (**20**) (2.70 g, 34.48 mmol, 47% yield) as a colorless oil (*31*).

5-Trimethylsilanyl-1-penten-4-yn-3-one, ***21***. Ethyl bromide (0.75 mL, 5 mmol) was added to magnesium turnings (120 mg) suspended in dry THF (3 mL). After 20 min, trimethylsilyl-acetylene (520 mg, 5.30 mmol) was added at −5 °C. This Grignard reagent was added dropwise to a solution of **20** (460 mg, 4.00 mmol) in dry THF (10 mL) at −8 °C over a period of 5 min. The mixture was stirred for 2 h, then aqueous HCl (10% in water; 10 mL) was added and the resulting solution was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (4 mL), followed by brine (4 mL), and dried with Na_2SO_4. Flash chromatography on silica gel using petroleum ether/ethyl acetate (8:1, v/v) gave 5-trimethylsilanyl-1-penten-4-yn-3-one (**21**) as a colorless oil (341 mg, 2.24 mmol, 56% yield) (*32*). Compound **21**: MS (EI) *m*/*z* = 152 (3, M^+), 137 (100), 73 (64). ^{1}H NMR (400 MHz, $CDCl_3$): 6.54 (1H, dd, *J* = 17.4, 1.0 Hz), 6.35 (1H, dd, *J* = 17.4, 10.2 Hz), 6.16 (1H, dd, *J* = 10.2, 1.0 Hz), 0.23 (9H, s).

(R)-5-Trimethylsilanyl-1-penten-4-yn-3-ol, ***22a***. The BH_3−SMe_2 complex (0.95 mmol, 0.09 mL) and (*R*)-*B*-methyl-4,5,5-triphenyl-[1,3,2]oxazaborolidine (**14a**) (0.8 mmol, 2.6 mL of a 0.3 M solution in toluene) were dissolved in dry THF (1.6 mL), and 5-trimethylsilanyl-1-penten-4-yn-3-on (**21**) (120 mg, 0.79 mmol) was added slowly and stirred for 1.5 h at 0 °C. After adding methanol (1.5 mL), the mixture was stirred for 1 h and was then concentrated in vacuum. (*R*)-5-Trimethylsilanyl-1-penten-4-yn-3-ol (**22a**) was obtained by flash chromatography on silica gel using petroleum ether/ethyl acetate (9:1, v/v) as a colorless oil (64 mg, 0.42 mmol, 53% yield, 44% ee, determined by optical rotation ($[\alpha]^{20}_D$)) (*33*). Compound **22a**: MS (EI) *m*/*z* (%) = 154 (M^+, 10), 139 (100), 111 (66), 99 (85), 73 (86). ^{1}H NMR (400 MHz, $CDCl_3$): 5.94 (1H, ddd, *J* = 17.0, 10.1, 5.2 Hz), 5,44 (1H, ddd, *J* = 17.0, 1.6, 1.2 Hz, Hz), 5.20 (1H, ddd, *J* = 10.1, 1.4, 1.2 Hz), 4.85 (1H, m), 0.15 (9H, s).

(S)-5-Trimethylsilanyl-1-penten-4-yn-3-ol, ***22b***. The (*S*)-enantiomer **22b** was prepared following the same procedure reported above for **22a** using (*S*)-*B*-methyl-4,5,5-triphenyl-[1,3,2]oxazaborolidine (**14b**) (*33*).

(R)-5-Bromo-1-penten-4-yn-3-ol, ***23a***. (*R*)-5-Trimethylsilanyl-1-penten-4-yn-3-ol (34 mg, 0.22 mmol) (**22a**) was dissolved in acetone (0.6 mL), silver nitrate (7.5 mg, 0.04 mmol) and *N*-bromo succinimide (59 mg, 0.33 mmol) were added, and the mixture was stirred for 2 h at room temperature. After cooling the solution to 0 °C, water (2 mL) was added, the mixture was stirred for 10 min, then extracted with diethyl ether (3 × 3 mL) and washed with brine (3 mL), and the combined organic layers were dried over $MgSO_4$. (*R*)-5-Bromo-1-penten-4-yn-3-ol (**23a**) was obtained as a colorless oil (35 mg, 0.22 mmol, 99% yield) (*28*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (1H, ddd, *J* = 17.0, 10.1, 5.2 Hz), 5.47 (1H, ddd, *J* = 17.0, 1.6, 1.0 Hz), 5.26 (1H, ddd, *J* = 10.1, 1.4, 1.0 Hz), 4.88 (1H, dt, *J* = 5.4, 1.4 Hz).

(S)-5-Bromo-1-penten-4-yn-3-ol, ***23b***. The (*S*)-enantiomer **23b** was prepared following the same procedure reported above for **23a** starting from (*S*)-5-trimethylsilanyl-1-penten-4-yn-3-ol (**22b**) (*28*).

(3R,8S)-Falcarindiol (***24a***). Butylamine (0.18 mL) and hydroxylamine hydrochloride (1.5 mg, 0.02 mmol) were added to a mixture of (*S*)-(*Z*)-trimethylsilanyl-4-dodecen-1-yn-3-ol (**19a**) (25 mg, 0.10 mmol, *E*/*Z* ratio = 1:5, 97% ee) and copper(I) chloride (0.7 mg, 0.007 mmol) in methanol (0.6 mL). After cooling to 0 °C, (*R*)-5-bromo-1-penten-4-yn-3-ol (**23a**) (35 mg, 0.22 mmol, 44% ee) was added over 30 min and then stirred for 4 h. Water (5 mL) was added, the mixture was extracted with dichloromethane (3 × 5 mL), and the organic phase was washed with brine (4 mL) and, then, dried over $MgSO_4$. Flash chromatography on silica gel using petroleum ether/ethyl acetate (5:1, v/v) gave (*Z*)-(3*R*,8*S*)-falcarindiol, (*Z*)-**24a**, as the major isomer (9 mg, 0.03 mmol, 30% yield). Chiral HPLC revealed that the sample contained the diastereomers (*Z*)-**24a**, (*E*)-**24a**, (*Z*)-**24b**, (*E*)-**24b** in a ratio of 14:1:1:0.1.

(Z)-(3R,8S)-Falcarindiol, (*Z*)-***24a***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (1H, ddd, *J* = 17.0, 10.1, 5.2 Hz, H-2), 5.59 (1H, ddd, *J* = 10.6, 7.6, 1.0 Hz, H-10), 5.50 (1H, ddd, *J* = 8.4, 1.4 Hz, H-9), 5.45 (1H, ddd, *J* = 17.0, 1.6, 1.0 Hz, H_A-1), 5.24 (1H, ddd, *J* = 10.1, 1.6, 1.2 Hz, H_B-1), 5.18 (1H, d, *J* = 8.2 Hz, H-8), 4.92 (1H, d, *J* = 5.0 Hz, H-3), 2.08 (2H, dq, *J* = 8.4, 7.2 Hz, H-11), 1.36 (2H, m, H-12), 1.20−1.31 (8H, m, H-13−16), 0.86 (3H, t, *J* = 7.0 Hz, H-17) (25, 33).

The (3*S*,8*S*)-, (3*S*,8*R*)-, and (3*R*,8*R*)-stereoisomers **24b**−**d** were synthesized following the protocol as detailed above for (3*R*,8*S*)-falcarindiol (**24a**) using the corresponding enantiomers of **19a/b** and **23a/b**, respectively, as the starting components.

(Z)-(3S,8S)-Falcarindiol, (*Z*)-***24b***. The sample obtained contained (*Z*)-**24b**, (*E*)-**24b**, (*Z*)-**24a**, and (*E*)-**24a** in a ratio of 17:1:0.1:0.1 (chiral HPLC).

(Z)-(3S,8R)-Falcarindiol, (*Z*)-***24c***. The sample obtained contained (*Z*)-**24c**, (*E*)-**24c**, (*Z*)-**24d**, and (*E*)-**24d** in a ratio of 3:1:0.2:0.3 (chiral HPLC).

(Z)-(3R,8R)-Falcarindiol, (*Z*)-***24d***. The sample obtained contained (*Z*)-**24d**, (*E*)-**24d**, (*Z*)-**24c**, and (*E*)-**24c** in a ratio of 5:1:0.1:0.1 (chiral HPLC).

Chiral Gas Chromatography. A CP-3900-type gas chromatograph (Varian, Darmstadt, Germany) equipped with a FID and a Chirasil Dex CB 25 m x 0.25 mm, 0.25 μm, column (Varian, Darmstadt, Germany) was used for chiral analysis. Aliquots (2 μL) of the sample was injected using the split/splitless mode and the Varian 8410 autosampler. Data analysis

was performed by means of Galaxy software (Varian, Darmstadt, Germany). System A: The temperature of the oven was kept isothermally at 150 °C at a constant hydrogen gas flow of 0.8 mL/min. Injector and detector were kept at 150 °C. System B: The initial temperature of the oven was 150 °C with a 2 °C/min ramp to 200 °C with a constant hydrogen gas flow of 0.8 mL/min. Injector and detector were kept at 200 °C.

High Performance Liquid Chromatography (HPLC). The HPLC apparatus (Jasco, Gross-Umstadt, Germany) consisted of a MD-2010 plus photodiode array detector and two PU 2087 pumps. Chromatographic separations were performed on 250 × 4.6 mm i.d. stainless-steel columns packed with Hyperclone 5 μm, RP-18 material for analytical scale (1.0 mL/min) and 250 × 21.2 mm i.d. stainless-steel columns packed with Microsorb, 5 μm, RP-18 material (Varian, Darmstadt, Germany) for preparative scale (18 mL/min).

Chiral High Performance Liquid Chromatography (Chiral HPLC). The HPLC apparatus (Varian, Darmstadt, Germany) consisted of ProStar 410 Autosampler, 2 ProStar 215 pumps and ProStar 325 UV-detector monitoring the effluent at 210 nm. Chromatographic separations were performed on 250 × 4.6 mm i.d. stainless-steel columns packed with Daicel Chiralpak AD-H 5 μm material (Daicel Technologies Europe, Bd Gonthier d'Andernach, France) using a gradient of hexane (solvent A) and isopropanol (solvent B) with a flow rate of 0.7 mL/min. The solvent gradient started with 5% B for 70 min, solvent B was then increased to 25% within 1 min and, then, kept constant for 8 min.

Liquid Chromatography/Time-of-Flight Mass Spectrometry (LC−TOF-MS). High resolution mass spectra of the compounds were measured on a Bruker Micro-TOF (Bruker Daltronics, Bremen, Germany) mass spectrometer and referenced to sodium formate.

Liquid Chromatography−Tandem Mass Spectrometry (LC−MS/MS). Electrospray ionization (ESI) mass and product ion spectra were acquired on an API 4000 QTRAP mass spectrometer (Applied Biosystems, Darmstadt, Germany) with direct flow infusion. The ion spray voltage was set at −4500 V in the negative mode and at 5500 V in the positive mode. The mass spectrometer was operated in the full-scan mode detecting positive or negative ions. The MS/MS parameters were tuned to induce fragmentation of the $[M - H]^-$ or $[M + H]^+$ molecular ions into specific product ions after collision with nitrogen as collision gas (4×10^{-5} Torr).

Nuclear Magnetic Resonance Spectroscopy (NMR). ^1H, ^{13}C and 2D NMR experiments were performed using a Bruker DPX-400, a DPX-500 (Bruker BioSpin, Rheinstetten, Germany), and a JEOL-ECA 800 spectrometer (Jeol, Tokyo, Japan), respectively. $CDCl_3$ was used as solvent, and chemical shifts were referenced to the solvent signal. For structural elucidation and NMR signal assignment, COSY, HMQC, and HMBC experiments were carried out using the pulse sequences taken from the Bruker software library. Data processing was performed by using Topspin-NMR software (version 2.1; Bruker, Rheinstetten, Germany) as well as Mestre Nova (Version 5.1.0−2940, Mestrelab Research, Santiago de Compostela, Spain).

RESULTS AND DISCUSSION

Isolation and Identification of Bisacetylenic Oxylipins in Carrots. Aimed at identification of bisacetylenic compounds in carrots, samples of carrots were sequentially extracted with pentane and ethyl acetate, and the solvent was separated from the extracts in vacuum to afford the pentane soluble fraction A, and the ethyl acetate soluble fraction B, and the nonsoluble fraction C. In order to screen for bisacetylenes, aliquots of fractions A and B were analyzed by means of analytical HPLC-DAD monitoring the effluent at 232, 244, and 258 nm, which have been reported as the UV absorption maxima of the bisacetylenic falcarindiol (**2**) (*3*). As fraction A was found to contain a series of compounds exhibiting the expected UV/vis absorption data and fraction B did not seem to contain significant amounts of any bisacetylenes, the pentane solubles in fraction A were further separated by means of column chromatography on silica gel using mixtures of *n*-pentane and diethyl ether as mobile phase to give the five subfractions A-I to A-V. HPLC analysis of the individual fractions revealed the presence of bisacetylenic compounds two fractions, namely A-III and A-IV, which were further separated into 14 and 15 subfractions by means of preparative RP-HPLC (**Figure 2**). A total of seven subfractions exhibiting the UV/vis absorption data expected for bisacetylenes, namely A-III/8 to A-III/10, A-III/14, A-IV/6, A-IV/7, and A-IV/9, were separated from solvent in vacuum and purified by rechromatography on RP-18 material. After checking the purity of the isolates by means of HPLC/DAD and HPLC/ELSD, the chemical structures of the bisacetylenes were determined by means of LC−MS/MS and 1D/2D NMR spectroscopic experiments.

Comparison of chromatographic (RP-HPLC) and spectroscopic data (UV, MS, NMR), as well as cochromatography with the corresponding reference compound led to the unequivocal identification of falcarinol (**1**) and falcarindiol-3-acetate (**3**) as the bisacetylenic compounds in A-III/14 and fraction A-III/9 (**Figure 2**), respectively, which were previously identified in carrots (*25*).

By means of rechromatography, fraction A-III/8 could be separated into four subfractions, namely A-III/8−1 to A-III/8−4. LC−TOF-MS analysis of subfraction A-III/8−3, exhibiting the UV absorption data expected for bisacetylenes, revealed an exact mass of 259.1690 Da for the target compound. Signal integration of the ^1H and ^{13}C NMR spectra exhibited a total of 22 protons and 17 carbon atoms including 5 quarternary carbons, thus suggesting an empirical formula of $C_{17}H_{22}O_2$. Carbon atom C(1) was observed at 118.3 ppm and revealed heteronuclear ^1J-couplings to H_A-C(1) and H_B-C(1) resonating at 5.51 and 5.32 ppm, respectively. Proton H−C(2) was detected as a triplet duplet at 5.96 ppm and exhibited homonuclear ^3J-couplings to H_A-C(1) and H_B-C(1) as well as to proton H−C(3) resonating at 5.02 ppm. The latter proton was found to be bound to carbon C(3) detected with a chemical shift of 63.9 ppm, thus indicating a hydroxyl functionalization of this carbon atom. The proton H−C(2) showed ^3J-coupling to the quaternary carbon C(4) resonating at 84.7 ppm. In addition, the carbon atoms C(5), C(6), and C(7) showed resonance at 69.3, 74.3, and 74.4 ppm, respectively, among which the latter quaternary carbon C(7) showed ^3J-heteronuclear coupling to H−C(9) detected at 6.18 ppm. Taking all these data into account, the carbon sequence C(4)−C(7) could be assigned as a bisacetylene. The keto carbon C(8), resonating at 177.2 ppm, exhibited HMBC-couplings to the olefinic protons H−C(9) and H−C(10) which showed a homonuclear coupling constant of 16.0 Hz, thus indicating a trans-configuration of this double bond. Moreover, carbon C(10) resonating at 156.4 ppm showed heteronuclear couplings to H−C(11) and H−C(12) detected at 2.30 and 1.51 ppm, respectively, both being part of an C_7- alkyl moiety. Taking all these data into account, the compound in fraction A-III/8−3 could be identified as the previously unknown (*E*)-heptadeca-1,9-dien-4,6-diyn-3-ol-8-on, **4** (**Figure 3**). Interestingly, the corresponding (*Z*)-isomer has been reported as a phytochemical in *Aegopodium podagraria* (*6*) and its mono acetate had been isolated from carrots (*3*). In order to check as to whether the (*E*)-isomer might have been formed as an artifact from the corresponding (*Z*)-isomer, during sample workup, a freshly prepared carrot extract was screened by LC−MS/MS for the presence of the (*E*)-isomer without any further sample cleanup steps. Again, the (*E*)-isomer could be detected (data not shown), thus confirming the structure of that bisacetylene as the previously unknown (*E*)-heptadeca-1,9-dien-4,6-diyn-3-ol-8-one, coined (*E*)-isofalcarinolone (**4**, **Figure 3**).

Rechromatography of fraction A-III/10 revealed the two subfractions A-III/10−1 and A-III/10−2, both of which exhibited the typical UV/vis spectrum of a bisacetylene. LC−MS

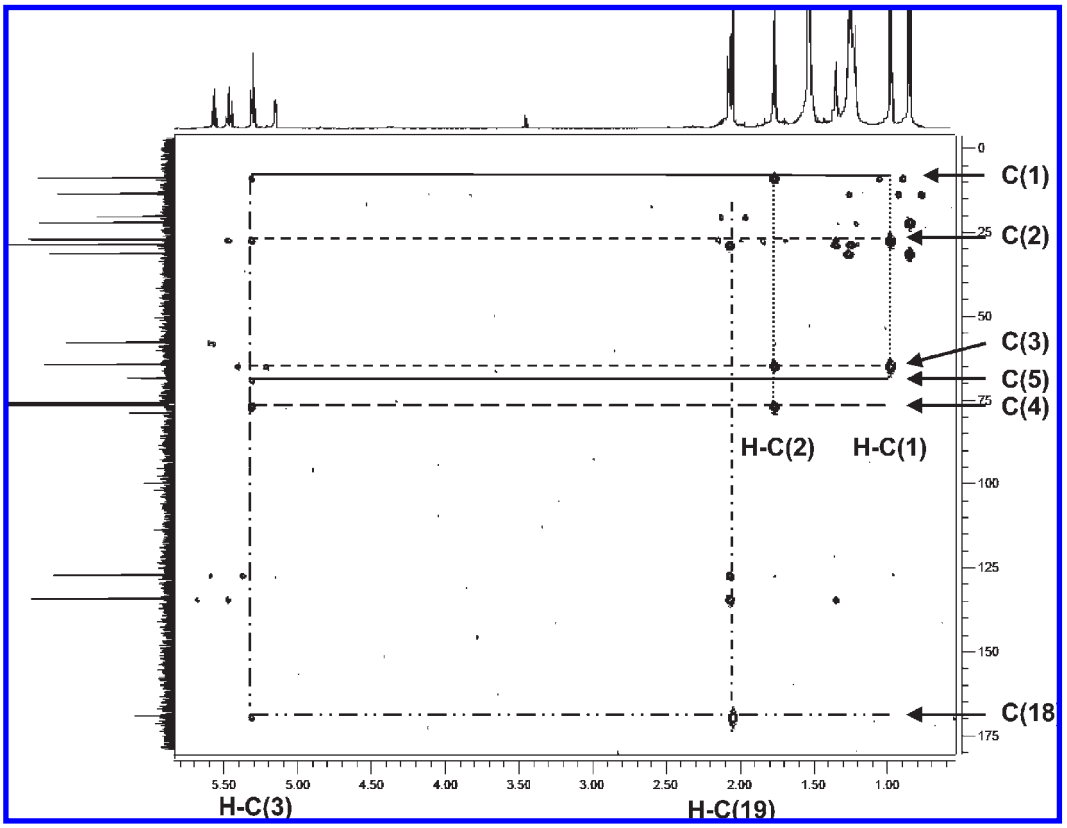

Figure 4. Excerpt of the HMBC spectrum of 1,2-dihydrofalcarindiol-3-acetate (**6**).

analysis of the compound isolated from fraction A-III/10−1 revealed *m*/*z* 325.4 as the pseudomolecular ion $[M+Na]^+$. Signal integration in the ^{1}H NMR spectrum and the number of carbon resonances in the ^{13}C NMR spectrum revealed 26 hydrogen atoms and 19 carbon atoms including five quarternary carbons, thus indicating an empirical formula of $C_{19}H_{26}O_3$. Comparison of the 1D/2D NMR data obtained with the data reported in literature (*21*), the bisacetylenic target compound could be unequivocally identified as falcarindiol 8-acetate, **5** (**Figure 3**). Although compound **5** was identified earlier in *Centella* species (*34*) as well as *Angelica japonica* (*21*), this is the first report on the presence of this bisacetylene in carrots.

LC−TOF-MS analysis of the bisacetylenic compound isolated from subfraction A-III/10−2 revealed an exact mass of 327.1926 Da, fitting well with the formula $C_{19}H_{28}O_3Na$. 1D and 2D NMR spectroscopy confirmed the presence of 28 hydrogen and 19 carbon atoms including 5 quarternary carbons. A triplet integrating for three protons was detected at 1.01 ppm and showed heteronuclear ^1J-coupling to carbon atom C(1) resonating at 9.0 ppm and homonuclear ^3J-coupling to proton H−C(2), which was observed at 1.80 ppm and found to integrate for two protons (**Figure 4**). Proton H−C(2) showed a ^1J-heteronuclear coupling to carbon C(2) at 27.6 ppm and homonuclear connectivity to proton H−C(3) at 5.34 ppm in the COSY spectrum. The latter proton exhibited heteronuclear ^3J-coupling to a carbon atom at 169.9 ppm, that could be assigned as C(18) as a part of an acetate moiety. Carbons C(4)−C(7) resonated at 77.0, 69.3, 68.8, and 79.3 ppm, respectively, and were assigned as the carbon atoms of the bisacetylene substructure. Proton H−C(8), resonating at 5.19 ppm, exhibited a ^1J-heteronuclear coupling to C(8) at 58.4 ppm and a ^3J-homonuclear coupling to H−C(9) at 5.50 ppm. The chemical shift of H−C(8) and C(8) indicated the binding to a free hydroxyl group to C(8). H−C(9) showed ^1J-heteronuclear coupling to C(9) at 127.3 ppm and ^3J-homonuclear connectivity to H−C(10) with a coupling constant of 10.0 Hz, thus indicating the presence of a cis-configured double bond in the target molecule. Taking all these data into account, the target compound in subfraction A-III/10-2 could be identified as 1,2-dihydrofalcarindiol-3-acetate, **6** (**Figure 3**), which to the best of our knowledge has not been reported earlier.

Rechromatography of fraction A-IV/9 revealed the subfractions A-IV/9-1, A-IV/9-2, and A-IV/9-3. LC−TOF-MS analysis of the compound isolated from fraction A-IV/9-1 showed an exact mass of 341.1719 Da, thus fitting well with an empirical formula of $C_{19}H_{26}O_4Na$ and a molecular weight of 318 Da. 1D/2D NMR spectroscopy confirmed the presence of 26 hydrogen atoms and 19 carbon atoms, among which six carbon atoms were found to be quaternary. Proton H−C(1), detected at 1.16 ppm and integrating for three protons, exhibited a ^3J-homonuclear coupling to H−C(2) at 2.82 ppm, a ^2J-heteronuclear coupling to C(2) at 39.0 ppm, and a ^3J-heteronuclear coupling to keto carbon atom C(3) resonating at 187.0 ppm. Proton H−C(8), observed at 5.37 ppm, revealed heteronuclear couplings to C(7), C(6), C(5), and C(4), resonating at 82.2, 64.4, 69.7, and 74.4 ppm, respectively, as well as a weak ^6J-heteronuclear coupling to C(3), thus demonstrating the presence of a bisacetylene substructure C(4)−C(7) in the molecule. In addition, a heteronuclear connectivity was found between proton H−C(8) and carbon C(18), which were found to resonate at 169.6 ppm and was identified as part of an acetic acid moiety. Careful assignment of all proton and carbon signals revealed the binding of a hydroxyl function at carbon C(9) and a (*E*)-configured double bond between H−C(10) and H−C(11) showing a ^3J-homonuclear coupling constant of 15.5 Hz. Taking all spectroscopic data into consideration, the isolated bisacetylene was identified as the previously not reported (*E*)-8,9-dihydroxy-3-keto-heptadeca-10-ene-4,6-diyne 8-acetate, **7** (**Figure 3**), which we name (*E*)-falcarindiolone-8-acetate.

LC−TOF-MS analysis of the compound isolated from subfraction A-IV/9-2 revealed an exact mass of 341.1719 Da, thus fitting well with the empirical formula of $C_{19}H_{26}O_4Na$ and matching the data found for compound **7**. 1D/2D NMR experiments revealed a total of 26 hydrogen atoms and 19 carbons including six quaternary carbons. The signal and coupling pattern exhibited similarities to compound **7**. The chemical shift of H−C(9) and heteronuclear couplings to carbon atoms C(18) and C(19) resonating at 170.3 and 21.9 ppm, respectively, demonstrated the binding of an acetoxy moiety to carbon C(9), whereas the acetoxy moiety in compound **7** was bound at C(8) to the carbon skeleton of the oxylipin. In consequence, the compound isolated from subfraction A-IV/9-2 could be identified as the previously not reported (*E*)-8,9-dihydroxy-3-keto-heptadeca-10-ene-4,6-diyne 9-acetate, **8** (**Figure 3**), coined (*E*)-falcarindiolone-9-acetate.

LC−TOF-MS analysis of subfraction A-IV/9-3 showed an exact mass of 285.1837 Da and indicated an empirical formula of $C_{17}H_{26}O_2Na$. In addition, 1D/2D NMR experiments confirmed the presence of 26 hydrogen atoms and 17 carbon atoms, thus fitting well with the data found for compound **6** without the acetyl moiety. This was confirmed by careful assignment of all protons and carbons by means of 1D/2D NMR spectroscopy and led to the identification of the bisacetylene isolated from subfraction A-IV/9-3 as 1,2-dihydrofalcarindiol, **9** (**Figure 3**). Although this compound has been reported as oplopandiol as a phytochemical in *Oplopanax horridus* (*11*), this bisacetylene has not been previously identified in carrots.

Rechromatography of fraction A-IV/6 gave the two subfractions A-IV/6-1 and A-IV/6-2, both exhibiting an exact mass of 371.1821 Da and an empirical formula of $C_{20}H_{28}O_5Na$. 1D/2D NMR experiments of the bisacetylene isolated from subfraction A-IV/6-1 confirmed the presence of 28 hydrogen atoms and 20 carbon atoms including six quaternary carbons. The homo- and heteronuclear connectivity found by means of COSY, HMQC, and HMBC experiments showed some similarities, but also some differences when compared to compound **7**. Proton H−C(1) resonating at 3.72 ppm and integrating for two protons showed homonuclear coupling to a proton signal at 3.35 ppm integrating for three protons. These protons H−C(18) revealed a ^1J-heteronuclear coupling to C(18) resonating at 58.1 ppm, thus leading to the identification of C(18) as the carbon atom of a methoxy group. In addition, H−C(1) exhibited a ^3J-homonuclear coupling to H−C(2) at 2.82 ppm, a ^2J-heteronuclear coupling to C(2) at 45.1 ppm, and a ^3J-heteronuclear coupling to the keto carbon C(3) resonating at 183.9 ppm. Proton H−C(8) revealed a ^1J-heteronuclear coupling to C(8) at 67.3 ppm and $^{2,3}J$-heteronuclear couplings to C(7), C(6), and C(19) resonating at 82.4, 69.8, and 168.6 ppm, respectively, thus demonstrating the presence of an acetoxy moiety at C(8). In addition, an hydroxyl group was identified to be bound at carbon C(9), e.g. the proton H−C(9) revealed ^3J-homonuclear coupling to a hydroxyl proton observed at 2.00 ppm. Moreover, the olefinic protons H−C(10) and H−C(11) showed homonuclear coupling with a coupling constant of 15.5 Hz, thus indicating the presence of an (*E*)-configuration. Taking all the NMR and LC−MS data into consideration, the structure of the bisacetylene isolated from subfraction A-IV/6-1 was identified as (*E*)-8,9-dihydroxy-1-methoxy-3-keto-heptadeca-10-ene-4,6-diyne 8-acetate, **10** (**Figure 3**). To the best of our knowledge, this compound, coined (*E*)-1-methoxy-falcarindiolone-8-acetate, has not been previously reported in literature.

1D/2D NMR analysis of the bisacetylene isolated from subfraction A-IV/6-2 revealed 28 hydrogen atoms and 20 carbon atoms including six quaternary carbons. The NMR data of that compound were rather similar to those found for compound **10**, just the acetoxy and the hydroxyl group at carbons C(8) an C(9) were found to be reversed. Taking all these data in reference, the structure for the bisacetylene isolated from subfraction A-IV/6-2 was identified as (*E*)-8,9-dihydroxy-1-methoxy-3-keto-heptadeca-10-ene-4,6-diyne 9-acetate, **11** (**Figure 3**). To the best of our knowledge, this compound, coined (*E*)-1-methoxy-falcarindiolone-9-acetate, has not been described in literature previously.

By means of rechromatography on RP-18 material, fraction A-IV/7 could be separated into the two subfractions A-IV/7-1 and A-IV/7-2. Comparison of the spectroscopic data (UV/vis, LC−MS, NMR) led to the unequivocal identification of falcarindiol (**2**, **Figure 2**), which was previously identified in carrots (*25*), as the bisacetylene in subfraction A-IV/7-1.

LC−TOF-MS analysis of subfraction A-IV/7-2 revealed a mass of 283.1663 Da, fitting well with the empirical formula of $C_{17}H_{24}O_2Na$. Signal integration in the ^{1}H NMR spectrum and the number of resonance signals in the ^{13}C NMR spectrum revealed the presence of 24 protons and 17 carbon atoms including four quarternary carbons, thus confirming $C_{17}H_{24}O_2$ as the elemental composition of the target bisacetylene. The 1D/2D NMR data obtained were rather close to those found for falcarindiol (**2**).

In contrast to **2**, the proton H−C(8) was detected at 5.77 ppm and showed a homonuclear coupling to H−C(9) resonating at 6.33 ppm with a coupling constant of 16.0 Hz, thus demonstrating a (*E*)-configured double bond between C(8) and C(9). In addition, proton H−C(9) exhibited an homonuclear coupling to H−C(10) detected at 4.18 ppm and heteronuclear couplings to the carbons C(8) and C(9) at 149.8 ppm and C(10) at 72.1 ppm, respectively, which is well in line with the presence of an hydroxyl function at C(10). Taking all spectroscopic data into consideration, the bisacetylene isolated from subfraction A-IV/7-2 could be unequivocally identified as (*E*)-heptadeca-1,8-diene-4,6-diyn-3,10-diol, **12** (**Figure 3**). Although this compound, also known as panaxydiol, was previously identified in ginseng (*Panax ginseng*) (*35*), fennel (*Apium graveolens*), and parsley (*Petroselinum crispum*) (*4*), this is the first report on the occurrence of that bisacetylene in carrots.

Synthesis of Stereoisomers of Falcarindiol (2). Depending on the botanical source various absolute configurations were proposed for falcarindiol (**2**) in the literature (*4*, *8*). Although previous investigations studied the stereochemistry of **2** isolated from carrots by comparing its optical rotation with literature values for the (3*R*,8*S*)-stereoisomer isolated from other Apiaceae plant species, all possible stereoisomers of falcarindiol should be synthesized and the stereochemistry of the naturally occurring stereoisomer **2** should be verified by means of chiral HPLC. The targeted set of falcarindiol stereoisomers was obtained by Cadiot−Chodkiewicz cross-coupling reactions of (*S*)- and (*R*)-5-bromo-1-penten-4-yn-3-ol and (*S*)- and (*R*)-trimethylsilanyl-4-dodecen-1-yn-3-ol, respectively, as detailed in the total synthetic sequence outlined in **Figure 5**. 2-Decyn-1-ol was partly hydrogenated using the Lindlar catalyst to give (*Z*)-2-decen-1-ol (**15**) in 99% yield, which was then oxidized to the corresponding (*Z*)-2-decenal (**16**) by means of diacetoxy-iodosobenzene (DIB) and catalytic amounts of 2,2,6,6-tetramethyl-piperidinyloxyl (TEMPO) (*33*) (**Figure 5A**). This procedure exhibited a very high degree of selectivity for the oxidation of the primary alcohol function in **15** to the aldehyde **16** (95% yield) without any noticeable over-oxidation to the corresponding carboxylic acid. More importantly, this oxidation method proceeded without significant *E*/*Z*-isomerization (*E*/*Z* ratio of **16** = 1:32, as determined by GC), a major problem encountered with other oxidation methods. Addition of (*Z*)-2-decenal (**16**) to a solution of freshly prepared

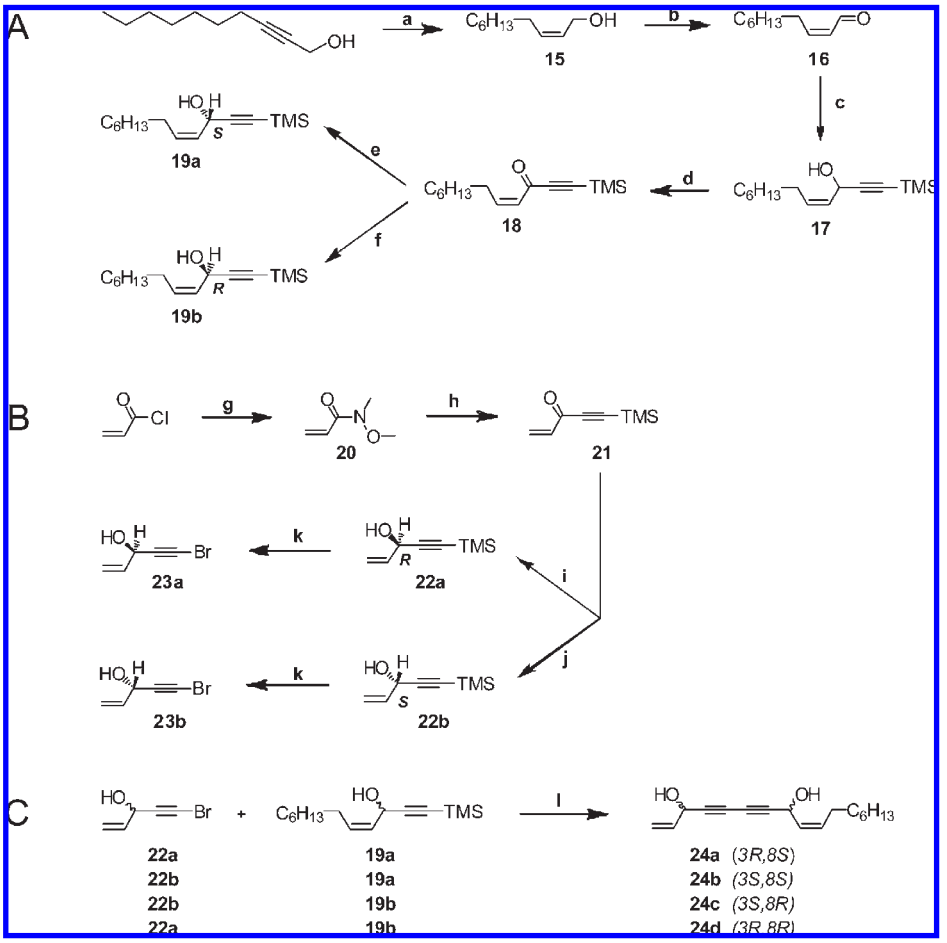

Figure 5. Synthesis of falcarindiol diastereomers **24a**−**d**. Preparation of (**A**) (*S*)- and (*R*)-trimethylsilyl-4-dodecen-1-yn-3-ol (**19a**, **19b**), (**B**) (*R*)- and (*S*)-5-bromo-1-penten-4-yn-3-ol (**23a**, **23b**), and (**C**) Cadiot−Chodkiewicz cross-coupling of **19a/b** and **23a/b**. Reagents and conditions: (**a**) H_2, Pd/C, KOH, quinoline, EtOH, RT, (99% yield); (**b**) $PhI(OAc)_2$, TEMPO (10 mol %), CH_2Cl_2, (95% yield); (**c**) nBuLi, trimethylsilylacetylene, THF, −78 °C, then addition of **16**, (82% yield); (**d**) $PhI(OAc)_2$, TEMPO (10 mol %), CH_2Cl_2, (95% yield); (**e**) (*S*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**14a**), $BH_3 \cdot SMe_2$, THF, 0 °C, (57% yield, 97% ee); (**f**) (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**14b**), $BH_3 \cdot SMe_2$, THF, 0 °C, (57% yield, 93% ee); (**g**) Methylhydroxylamine hydrochloride, pyridine, CH_2Cl_2, 0 °C, 47% yield); (**h**) TMS-acetylene-MgBr, THF, −5 °C, (56% yield); (**i**) (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**14b**), BH_3SMe_2, THF, 0 °C, (53% yield, 44% ee); (**j**) (*S*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**14a**), BH_3SMe_2, THF, 0 °C; (**k**) $AgNO_3$, NBS, acetone, (99% yield); (**l**) CuCl, $NH_2OH \cdot HCl$, butylamine, MeOH, 0 °C, (30% yield).

lithium trimethylsilanylacetylide in THF afforded the trimethylsilanyl-4-dodecen-1-yn-3-ol (**17**) in 82% yield. The latter was thereafter oxidized to trimethylsilanyl-4-dodecen-1-yn-3-on (**18**) (95% yield, *E*/*Z* ratio of **18** = 1:5) by again using the highly effective DIB/TEMPO oxidation method (**Figure 5A**). The next step involved an enantioselective carbonyl reduction of **18** using a borane-mediated, oxazaborolidinine-catalyzed method, which was chosen because of the predictable outcome of the absolute configurations of the corresponding chiral propargylic alcohols (*29*). Therefore, the enantioselective reduction of ketone **18** was performed by the boran−dimethyl sulfide complex in the presence of either (*R*)- or (*S*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine, thus affording (*S*)- or (*R*)-trimethylsilanyl-4-dodecen-1-yn-3-ol (**19a**, **19b**) in a yield of 82% with an enantiomeric excess of 93% (*R*) and 97% (*S*), respectively.

For the synthesis of (*R*)- and (*S*)-5-bromo-1-penten-4-yn-3-ol (**23a**, **23b**), *N*-methoxy-*N*-methylacrylamide (**20**) was prepared from acryloyl chloride and methylhydroxylamine hydrochloride in the presence of pyridine and thereafter it was converted into the trimethylsilyl-4-pentene-1-yn-3-one (**21**) upon treatment with trimethylsilyl-acetylene-MgBr in dry THF (*32*) (**Figure 5B**). Enantioselective reduction of ketone **21** using the boran-dimethyl sulfide complex and either the chiral catalyst (*R*)- or (*S*)-*B*-methyl-4,5,5,-triphenyl-1,3,2-oxazaborolidine (**14a**, **14b**) delivered (*R*)- and (*S*)-trimethylsilyl-4-penten-1-yn-3-ol (**22a**, **22b**) in a yield of 53% and with an enantiomeric excess of 44%. Apparently, a decrease of the steric environment around the carbonyl group from ketone **18** to ketone **21** caused a decrease in the enantioselectivity. On treatment with *N*-bromo-succinimide and silver(I) nitrate, compounds **22a** and **22b** afforded (*R*)- and (*S*)-5-bromo-1-penten-4-yn-3-ol (**23a**, **23b**) in a yield of 99% yield, respectively (**Figure 5B**).

Cadiot−Chodkiewicz cross-coupling of **19a** or **19b** with the enantioenriched **23a** or **23b** (44% ee) afforded the individual falcarindiol diastereomers with the configuration (3*R*,8*S*) (**24a**), (3*S*,8*S*) (**24b**), (3*S*,8*R*) (**24c**), and (3*R*,8*R*) (**24d**), respectively (**Figure 5C**). Each sample of these synthesized stereoisomers contained the expected (*Z*)-isomers as the major product and the corresponding (*E*)-isomer as a minor byproduct.

Assignment of the Stereochemistry of Falcarindiol (2) Isolated from Carrots. In order to elucidate the stereochemistry of falcarindiol isolated from carrots, chiral HPLC analysis has been performed with the naturally occurring compound **2** as well as with the individual synthesized stereoisomers of falcarindiol. As shown in **Figure 6**, the peaks detected were identified as (*Z*)-**24d** (**a**), (*E*)-**24b** (**b**), (*Z*)-**24c** (**c**), (*E*)-**24a** (**d**), (*E*)-**24c** (**e**), (*Z*)-**24b** (**f**),

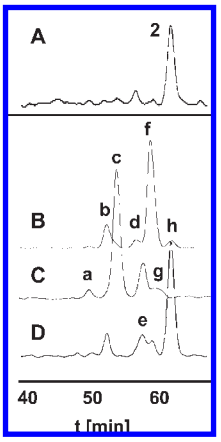

Figure 6. Chiral HPLC analysis of (**A**) a sample of falcarindiol (**2**) isolated from carrots and samples of the synthesized compounds (**B**) (3*S*,8*S*)-falcarindiol (**24b**), (**C**) (3*S*,8*R*)-falcarindiol (**24c**), and (**D**) (3*R*,8*S*)-falcarindiol (**24a**); in addition, the (*Z*)- and (*E*)-stereoisomers have been assigned as follows: (*Z*)-**24d** (**a**), (*E*)-**24b** (**b**), (*Z*)-**24c** (**c**), (*E*)-**24a** (**d**), (*E*)-**24c** (**e**), (*Z*)-**24b** (**f**), (*E*)-**24d** (**g**), (*Z*)-**24a** (**h**).

(*E*)-**24d** (**g**), and (*Z*)-**24a** (**h**). Comparison of the retention times (HPLC), consideration of the diastereomeric ratios of the coupling educts, followed by cochromatography undoubtedly resulted in the assignment of the absolute configuration in falcarindiol (**2**) isolated from carrots as (3*R*,8*S*) (**24a**).

In conclusion, this finding is well in line with the (3*R*,8*S*)-stereochemistry reported for other Apiaceae (*4*, *8*, *9*), and seems to be entirely different from the (3*S*,8*S*) stereochemistry found for bisacetylenes isolated from Araliaceae (*10*, *11*).

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