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First total syntheses of (*Z*)-15-methyl-10-hexadecenoic acid and the (*Z*)-13-methyl-8-tetradecenoic acid

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Abstract

The first total syntheses for the (*Z*)-15-methyl-10-hexadecenoic acid and the (*Z*)-13-methyl-8-tetradecenoic acid were accomplished in seven steps and in 31–32% overall yields. The (trimethylsilyl)acetylene was the key reagent in both syntheses. It is proposed that the best synthetic strategy towards monounsaturated *iso* methyl-branched fatty acids with double bonds close to the ω end of the acyl chain is first acetylide coupling of (trimethylsilyl)acetylene to a long-chain bifunctional bromoalkane followed by a second acetylide coupling to a short-chain *iso* bromoalkane, since higher yields are thus obtained. Spectral data is also presented for the first time for these two unusual fatty acids with potential as biomarkers and as topoisomerase I inhibitors.

Keywords: (*Z*)-15-Methyl-10-hexadecenoic acid; (*Z*)-13-Methyl-8-tetradecenoic acid; Fatty acids; Synthesis; Biomarkers

1. Introduction

Methyl-branched fatty acids are of interest as biomarkers for alkane-utilizing bacteria in soils and as biomarkers for sulphate-reducing bacteria, such as *Desulfovibrio* species, also found in wetland sediments (Boon et al., 1977; Boon et al., 1996). Particularly interesting fatty acids for the *Desulfovibrio* species are the *iso* methyl-branched fatty acids *i*-15:1 ($n-7$) and *i*-17:1 ($n-7$), which are characteristic for the *Desulfovibrio* and both fatty acids seem to be biosynthetically related by a two carbon extension of the shorter-chain C_{15} analog (Dowling et al., 1988; Edlund et al., 1985). While the *iso* C_{15}–C_{17} ($n-7$) series has been well studied, little is known of another series of odd-chain fatty acids, namely the *iso* C_{15}–C_{17} ($n-6$) series exemplified by the fatty acids (*Z*)-13-methyl-8-tetradecenoic acid (**1a**) and the (*Z*)-15-methyl-10-hexadecenoic acid (**1b**). Acid **1a** has not been isolated from natural sources, but the (*Z*)-15-methyl-10-hexadecenoic acid (**1b**) has been identified before in several organisms, such as in the siphonarid limpet *Siphonaria denticulata* (Carballeira et al., 2001). Because of the nature of the ($n-6$) fatty acids **1a** and **1b**, i.e., C_{15}–C_{17} chain lengths and *iso* ramification, there is a high probability for these compounds to be also of bacterial origin (Kaneda, 1991). In addition, these fatty acids remain under-explored as possible therapeutic agents despite the fact that *iso*-branched fatty acids with similar chain lengths have displayed considerable topoisomerase-I inhibition and also cytotoxicity (Lee et al., 1998; Reyes and Carballeira, 1996). Therefore, in order to provide spectral data so as to aid in their identification in nature and to supply enough material for further biological studies we have developed the first total syntheses for acids **1a** and **1b** following a similar

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synthetic sequence consisting of seven steps and using (trimethylsilyl)acetylene as the key reagent in the syntheses.

2. Materials and methods

2.1. Instrumentation

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker DPX-300 spectrometer. ^{1}H NMR chemical shifts are reported with respect to internal $(CH_3)_4Si$, ^{13}C NMR chemical shifts are reported in parts per million relative to $CDCl_3$ (77.0 ppm). GC/MS analyses were recorded at 70 eV using a Hewlett Packard 5972A MS ChemStation equipped with a 30 m × 0.25 mm special performance capillary column (HP-5MS) of polymethyl siloxane crosslinked with 5% phenyl methylpolysiloxane. IR spectra were recorded on a Nicolet 600 FT-IR spectrophotometer (Thermo-Nicolet, Madison, WI, USA). Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee. High resolution mass spectral data was performed at the Emory University Mass Spectrometry Center.

2.2. General procedure for the protection of the bromo-alcohols

To 4.00 g of either 7-bromo-1-heptanol or 9-bromo-1-nonanol in 12 mL of dichloromethane (CH_2Cl_2) was added dropwise 2,3-dihydro-2*H*-pyran (35.85–41.00 mmol) and catalytic amounts of *p*-toluene sulfonic acid (PTSA). The reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with water (2× 50 mL), $NaHCO_3$ (3× 50 mL), and dried over $MgSO_4$, filtered, and evaporated *in vacuo* affording 5.55–5.59 g (97–100% yield) of either **3a** or **3b**. The products were purified using silica gel column chromatography eluting with hexane/ether (9:1).

2.2.1. 7-Bromo-1-[(tetrahydropyran-2-yl)oxy]heptane (3a)

The 7-bromo-1-[(tetrahydropyran-2-yl)oxy]heptane (**3a**) was obtained as a colorless oil in a 97% yield from the reaction of 7-bromo-1-heptanol (4.00 g, 20.50 mmol) with 2,3-dihydro-2*H*-pyran (35.85 mmol) and catalytic amounts of PTSA in dichloromethane (12 mL) according to the general procedure described above. Compound **3a** presented comparable spectral data to the one previously reported in the literature (Das et al., 2006).

2.2.2. 9-Bromo-1-[(tetrahydropyran-2-yl)oxy]nonane (3b)

The 9-bromo-1-[(tetrahydropyran-2-yl)oxy]nonane (**3b**) was obtained as a colorless oil in a 100% yield from the reaction of 9-bromo-1-nonanol (4.06 g, 18.18 mmol) with 2,3-dihydro-2*H*-pyran (41.00 mmol) and catalytic amounts of PTSA in dichloromethane (12 mL) according to the general procedure described above. Compound **3b** presented comparable spectral data to the one previously reported in the literature (Grube et al., 2006).

2.3. General procedure for the first acetylide coupling reaction

To a stirred solution of (trimethylsilyl)acetylene (5.3–8.1 mL, 38.5–58.2 mmol) in dry THF (18.0 mL) and under argon was added *n*-BuLi (2.5 M, 44.88–67.97 mmol) in hexane at −78 °C. After 5 min HMPA (5.0–7.0 mL) (Caution! HMPA is toxic and safety precautions should be taken when handling this solvent) and either **3a** or **3b** (3.94–5.42 g) were added dropwise to the reaction mixture, maintaining the temperature at −78 °C. After 24 h, the reaction mixture was quenched with water. The organic product was extracted with diethyl ether (2× 15 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo*, affording 4.02–4.74 g (87–98% yield) of either 9-(trimethylsilyl)-1-[(tetrahydropyran-2-yl)oxy]non-8-yne (**4a**) or 11-(trimethylsilyl)-1-[(tetrahydropyran-2-yl)oxy]undec-10-yne (**4b**). The products **4a** and **4b** were purified under vacuum distillation (Kugelrohr) at 100–115 °C/3 mm Hg for 1 h.

2.3.1. 9-(Trimethylsilyl)-1-[(tetrahydropyran-2-yl)oxy]-non-8-yne (4a)

The 9-(trimethylsilyl)-1-[(tetrahydropyran-2-yl)oxy] non-8-yne (**4a**) was obtained as a colorless oil in a 87% yield from the reaction of **3a** (5.42 g, 19.42 mmol) with *n*-BuLi in THF (18 mL) and (trimethylsilyl)acetylene (7 mL) according to the general procedure described above; IR (neat) ν_{max} 2932, 2859, 2174, 1454, 1441, 1352, 1249, 1200, 1137, 1121, 1079, 1034, 843, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.57 (1H, m), 3.86–3.73 (2H, m), 3.50–3.35 (2H, m), 2.21 (2H, t, J = 7.1 Hz, H-7), 1.91–1.52 (10H, m, –CH_2–), 1.33 (6H, m), 0.12 (9H, s, –Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 107.68 (s, C-2), 98.83 (d), 84.45 (s), 67.60 (t, C-1), 62.33 (t), 30.76 (t), 29.66 (t), 28.90 (t), 28.72 (t), 28.54 (t), 26.08 (t), 25.47 (t), 19.81 (t), 19.68 (t), 0.16 (q, –Si(CH_3)$_3$); GC–MS (70 eV) *m/z* (relative intensity) 295 ($M^+ - 1$, 1), 223 (1), 183 (2), 173 (6), 123 (2), 111 (2), 109 (7), 103 (15), 101 (7), 85 (100), 75 (21), 73 (55), 69 (3), 67 (10), 59 (11), 57 (9),

55 (11). HRMS (APCI) Calcd for $C_{17}H_{33}O_2Si$ $[M+H]^+$ 297.2250, found 297.2239.

2.3.2. 11-(Trimethylsilyl)-1-[(tetrahydropyran-2-yl)-oxy]undec-10-yne (**4b**)

The 11-(trimethylsilyl)-1-[(tetrahydropyran-2-yl)-oxy]undec-10-yne (**4b**) was obtained as a colorless oil in a 98% yield from the reaction of **3b** (3.94 g, 12.82 mmol) with *n*-BuLi in THF (18 mL) and (trimethylsilyl)acetylene (5 mL) according to the general procedure described above; IR (neat) ν_{max} 2931, 2855, 2174, 1454, 1352, 1249, 1200, 1136, 1121, 1079, 1033, 843, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.57 (1H, m), 3.89–3.68 (2H, m), 3.51–3.35 (2H, m), 2.20 (2H, t, $J=7.1$ Hz, H-9), 1.80–1.51 (10H, m, $-CH_2-$), 1.31 (10H, m), 0.12 (9H, s, $-Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 107.75 (s, C-10), 98.83 (d), 84.30 (s, C-11), 67.66 (t, C-1), 62.33 (t), 30.76 (t), 29.72 (t), 29.39 (t), 29.00 (t), 28.76 (t), 28.59 (t), 26.20 (t), 25.48 (t), 19.83 (t, C-9), 19.68 (t), 0.16 (q, $-Si(CH_3)_3$); GC–MS (70 eV) *m/z* (relative intensity) 323 (M^+-1, 1), 309 (1), 183 (1), 173 (6), 159 (2), 149 (2), 137 (1), 119 (3), 103 (13), 101 (12), 97 (3), 93 (1), 91 (2), 86 (5), 85 (100), 83 (5), 81 (4), 75 (18), 73 (51), 69 (4), 67 (10), 61 (2), 59 (12), 57 (9), 56 (9), 55 (11). HRMS (APCI) Calcd for $C_{19}H_{37}O_2Si$ $[M+H]^+$ 325.2552, found 325.2563.

2.4. General procedure for the removal of the silyl group

To a mixture of either **4a** or **4b** (2.18–3.67 g, 6.72–12.38 mmol) and dry THF (8.0 mL) was added dropwise tetrabutylammonium fluoride (1 M, 6.72–12.38 mmol) at 0 °C. After 48h at room temperature the reaction was quenched with HCl (2 M), and the organic layer was washed with a brine solution (1 × 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo*, affording 1.48–2.67 g (5.89–11.91 mmol) of the desilylated products **5a** and **5b** in 88–96% isolated yields. The products were used in the next step without further purification.

2.4.1. 1-[(Tetrahydropyran-2-yl)oxy]non-8-yne (**5a**)

The 1-[(tetrahydropyran-2-yl)oxy]non-8-yne (**5a**) was obtained as a colorless oil in a 96% yield in the reaction of 9-(trimethylsilyl)-1-[(tetrahydropyran-2-yl)oxy]non-8-yne (**4a**) (3.68 g, 12.38 mmol) with tetrabutylammonium fluoride (1 M) in THF (8 mL) following the general procedure described above. Compound **5a** presented comparable spectral data to the one previously reported in the literature (Karpinska et al., 2004). HRMS (APCI) Calcd for $C_{14}H_{25}O_2$ $[M+H]^+$ 225.1855, found 225.1846.

2.4.2. 1-[(Tetrahydropyran-2-yl)oxy]undec-10-yne (**5b**)

The 1-[(tetrahydropyran-2-yl)oxy]undec-10-yne (**5b**) was obtained as a colorless oil in a 88% yield in the reaction of 11-(trimethylsilyl)-1-[(tetrahydropyran-2-yl)oxy]undec-10-yne (**4b**) (2.18 g, 6.72 mmol) with tetrabutylammonium fluoride (1 M) in THF (8 mL) following the general procedure described above. Compound **5b** presented comparable spectral data to the one previously reported in the literature (Cryle et al., 2005). HRMS (APCI) Calcd for $C_{16}H_{29}O_2$ $[M+H]^+$ 253.2159, found 253.2168.

2.5. General procedure for the second acetylide coupling reaction

To a solution of either **5a** or **5b** (1.42–2.57 g, 5.64–11.45 mmol) and dry THF (12.0 mL) at 0 °C *n*-BuLi (2.5 M, 19.73–40.01 mmol) in hexane was added while stirring under an argon atmosphere. After 45 min 1-bromo-4-methylpentane (16.91–34.34 mmol) in HMPA (2.5–4.5 mL) (Caution! HMPA is toxic and safety precautions should be taken when handling this solvent) was added to the reaction mixture and the reaction was left stirring for 24 h at room temperature. After this time the reaction mixture was quenched with water and the organic products were extracted with hexane (1 × 50 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*, affording 1.29–2.76 g (3.84–8.94 mmol) of either 13-methyl-1-[(tetrahydropyran-2-yl)oxy]tetradec-8-yne (**6a**) or 15-methyl-1-[(tetrahydropyran-2-yl)oxy]hexadec-10-yne (**6b**) in 68–78% isolated yields. The products were purified by distilling the impurities under vacuum distillation (Kugelrohr) at 110–120 °C/3 mm Hg.

2.5.1. 13-Methyl-1-[(tetrahydropyran-2-yl)oxy]-tetradec-8-yne (**6a**)

The 13-methyl-1-[(tetrahydropyran-2-yl)oxy]tetradec-8-yne (**6a**) was obtained as a colorless oil in a 78% yield from the reaction of 1-[(tetrahydropyran-2-yl)oxy]non-8-yne (**5a**) (2.57 g, 11.45 mmol) with 1-bromo-4-methylpentane (34.34 mmol) in HMPA (4.5 mL) and *n*-BuLi (40.01 mmol) according to the general procedure described above; IR (neat) ν_{max} 2932, 2857, 1466, 1441, 1384, 1366, 1352, 1261, 1201, 1137, 1121, 1078, 1034, 905, 869, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.57 (1H, m), 3.86–3.70 (2H, m), 3.51–3.35

(2H, m), 2.14 (4H, m), 1.84–1.45 (13H, m, $-CH_2-$), 1.34 (8H, m, $-CH_2-$), 0.87 (6H, d, $J = 6.6$ Hz, $-CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 98.83 (d), 80.31 (s), 80.16 (s), 67.63 (t, C-1), 62.32 (t), 38.20 (t, C-12), 30.77 (t), 29.71 (t, C-2), 29.09 (t), 29.01 (t), 28.79 (t), 27.64 (d, C-13), 27.06 (t), 26.16 (t, C-3), 25.49 (t), 22.57 (q, C-14, C-15), 19.68 (t), 18.72 (t, C-10), 18.36 (t, C-7); GC–MS (70 eV) *m/z* (relative intensity) 308 (M^+, 1), 223 (1), 195 (1), 193 (1), 179 (1), 123 (2), 121 (3), 111 (1), 109 (7), 107 (3), 101 (14), 97 (2), 95 (12), 93 (5), 91 (3), 85 (100), 81 (15), 79 (9), 77 (3), 69 (18), 67 (21), 57 (10), 55 (22).

2.5.2. 15-Methyl-1-[(tetrahydropyran-2-yl)oxy]-hexadec-10-yne (**6b**)

The 15-methyl-1-[(tetrahydropyran-2-yl)oxy]hexadec-10-yne (**6b**) was obtained as a colorless oil in a 68% yield from the reaction of 1-[(tetrahydropyran-2-yl)oxy]undec-10-yne (**5b**) (1.29 g, 3.84 mmol) with 1-bromo-4-methylpentane (16.91 mmol) in HMPA (2.5 mL) and *n*-BuLi (19.73 mmol) according to the general procedure described above; IR (neat) ν_{max} 2937, 2856, 1467, 1366, 1255, 1201, 1140, 1121, 1080, 1033, 904, 869, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.57 (1H, m), 3.86–3.70 (2H, m), 3.50–3.35 (2H, m), 2.12 (4H, m), 1.76–1.48 (13H, m), 1.29 (12H, m, $-CH_2-$), 0.87 (6H, d, $J = 6.6$ Hz, $-CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 98.83 (d), 80.10 (s), 80.11 (s), 67.67 (t, C-1), 62.33 (t), 38.19 (t, C-14), 30.77 (t), 29.73 (t, C-2), 29.43 (t), 29.14 (t), 28.82 (t), 27.63 (t), 27.06 (d, C-15), 26.21 (t), 25.48 (t), 22.57 (q, C-16, C-17), 19.68 (t), 18.99 (t, C-12), 18.73 (t, C-9); GC–MS (70 eV) *m/z* (relative intensity) 336 (M^+, 1), 251 (1), 149 (1), 137 (2), 123 (2), 121 (2), 111 (1), 109 (8), 107 (3), 105 (1), 101 (22), 96 (4), 95 (13), 93 (4), 91 (3), 85 (100), 81 (15), 79 (8), 77 (3), 71 (2), 69 (20), 67 (22), 65 (2), 57 (11), 56 (10), 55 (23); analysis calculated for $C_{22}H_{40}O_2$: C, 78.51; H, 11.98; found: C, 79.12; H, 12.67.

2.6. General procedure for the removal of the tetrahydropyranyl protecting group

To a mixture of methanol (10.0 mL) and either **6a** or **6b** (1.23–2.69 g, 3.67–8.73 mmol) was added catalytic amounts of PTSA and the reaction mixture was stirred at 35 °C for 24 h. After this time the organic extract was washed with a saturated solution of sodium bicarbonate (3× 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo*, affording 0.82–1.79 g (3.24–7.96 mmol) of the alkynols **7a** and **7b** for 88–91% yields. The product was used in the next step without further purification.

2.6.1. 13-Methyl-8-tetradecyn-1-ol (**7a**)

The 13-methyl-8-tetradecyn-1-ol (**7a**) was obtained as a colorless oil in a 91% yield from the reaction of 13-methyl-1-[(tetrahydropyran-2-yl)oxy]tetradec-8-yne (2.69 g, 8.73 mmol) with catalytic amounts of PTSA in methanol (10 mL) according to the general procedure described above; IR (neat) ν_{max} 3360 (OH, broad), 2927, 2856, 1466, 1434, 1384, 1367, 1333, 1117, 1058, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, t, $J = 6.6$ Hz, H-1), 2.12 (4H, m, H-7, H-10), 1.60–1.45 (7H, m, $-CH_2-$), 1.35 (8H, m, $-CH_2-$), 0.86 (6H, d, $J = 6.6$ Hz, $-CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 80.34 (s), 80.10 (s), 62.99 (t, C-1), 38.19 (t, C-12), 32.71 (t, C-2), 29.01 (t), 28.91 (t), 28.74 (t), 27.60 (d, C-13), 27.02 (t, C-11), 25.61 (t), 22.56 (q, C-14, C-15), 18.98 (t, C-10),18.70 (t, C-7); GC–MS (70 eV) *m/z* (relative intensity) 224 (M^+, 1), 209 (1), 150 (5), 135 (6), 125 (2), 124 (8), 123 (8), 122 (4), 121 (20), 119 (1), 111 (6), 110 (10), 109 (54), 108 (9), 107 (19), 105 (4), 98 (11), 97 (12), 96 (24), 95 (66), 94 (16), 93 (34), 91 (17), 85 (5), 84 (6), 83 (17), 82 (57), 81 (85), 80 (31), 79 (59), 78 (6), 77 (21), 71 (8), 70 (14), 69 (100), 68 (42), 67 (90), 66 (11), 65 (14), 63 (2), 59 (1), 57 (19), 56 (12), 55 (81), 54 (36). HRMS (APCI) Calcd for $C_{15}H_{29}O$ $[M+H]^+$ 225.2213, found 225.2213.

2.6.2. 15-Methyl-10-hexadecyn-1-ol (**7b**)

The 15-methyl-10-hexadecyn-1-ol (**7b**) was obtained as a colorless oil in an 88% yield from the reaction of 15-methyl-1-[(tetrahydropyran-2-yl)oxy]hexadec-10-yne (1.24 g, 3.67 mmol) with catalytic amounts of PTSA in methanol (10 mL) according to the general procedure described above; IR (neat) ν_{max} 3360 (OH, broad), 2932, 2856, 1467, 1386, 1366, 1320, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, t, $J = 6.6$ Hz, H-1), 2.12 (4H, m, H-9, H-12), 1.55–1.45 (7H, m, $-CH_2-$), 1.29 (12H, m, $-CH_2-$), 0.87 (6H, d, $J = 6.6$ Hz, $-CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 80.29 (s), 80.20 (s), 63.05 (t, C-1), 38.19 (t, C-14), 32.77 (t, C-2), 29.48 (t), 29.36 (t), 29.12 (t), 29.08 (t), 28.81 (t), 27.63 (d, C-15), 27.05 (t), 25.70 (t), 22.56 (q, C-16, C-17), 18.99 (t, C-12), 18.72 (t, C-9); GC–MS (70 eV) *m/z* (relative intensity) 252 (M^+, 1), 237 (1), 196 (1), 178 (1), 163 (1), 153 (1), 151 (1), 149 (3), 137 (2), 136 (3), 135 (7), 121 (11), 111 (5), 110 (12), 109 (59), 107 (12), 97 (10), 96 (29), 95 (62), 94 (10), 93 (23), 91 (11), 83 (17), 82 (54), 81 (77), 80 (20), 79 (40), 77 (14), 70 (11), 69 (100), 68 (37), 67 (81), 65 (10), 57 (16), 55 (75), 54 (31). HRMS (APCI) Calcd for $C_{17}H_{33}O$ $[M+H]^+$ 253.2526, found 253.2525.

2.7. General procedure for the catalytic hydrogenation of the alkynes

Into a 25 mL two-necked round-bottomed flask were placed dry hexane, the alkyne, quinoline (1 mL), and palladium in activated carbon (Lindlar's catalyst). One of the necks was capped with a rubber septum and the other was connected via tygon tubing to a 25 mL graduated pipet ending in a 150 mL beaker with distilled water. While stirring at room temperature a 20 mL syringe with needle was used to withdraw air from the system and to draw water up into the graduated pipet to the 0.0 mL mark. Hydrogen was then introduced into the system using a balloon filled with hydrogen attached to a hose barb-to-luer lock adapter with a stopcock and a needle. The reaction mixture consumed 51.0–54.3 mL of hydrogen during 1 h. The mixture was filtered and the solvent removed *in vacuo* obtaining 0.47–0.51 g (1.99–2.07 mmol) of the desired alkenols **8a** and **8b** accounting for 94–96% yields. The alkenols were purified under vacuum distillation (Kugelrohr) by removing impurities at 110 °C/3 mm Hg.

2.7.1. (Z)-13-Methyl-8-tetradecen-1-ol (*8a*)

The (Z)-13-methyl-8-tetradecen-1-ol (**8a**) was obtained as a colorless oil in a 94% yield from the catalytic hydrogenation, using Lindlar's catalyst, of 13-methyl-8-tetradecyn-1-ol (0.50 g, 2.22 mmol) according to the general procedure described above; IR (neat) ν_{max} 3360 (OH, broad), 3005, 2927, 2856, 1660, 1465, 1384, 1366, 1117, 1058, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.34 (2H, m, H-8, H-9), 3.63 (2H, t, $J = 6.6$ Hz, H-1), 2.00 (5H, m, H-7, H-10, H-13), 1.70 (1H, brs, –OH), 1.68–1.55 (2H, m, H-2), 1.31 (12H, m, $–CH_2–$), 0.86 (6H, d, $J = 6.6$ Hz, $–CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 129.99 (d), 129.75 (d), 63.03 (t, C-1), 38.62 (t, C-12), 32.74 (t, C-2), 29.65 (t), 29.29 (t), 29.21 (t), 27.86 (d, C-13), 27.52 (t, C-10), 27.41 (t, C-7), 27.14 (t), 25.68 (t), 22.60 (q, C-14, C-15); GC–MS (70 eV) *m/z* (relative intensity) 226 (M^+, 1), 208 (3), 180 (1), 152 (2), 137 (4), 124 (7), 123 (10), 111 (5), 110 (15), 109 (23), 97 (16), 96 (45), 95 (53), 83 (32), 82 (80), 81 (61), 79 (10), 69 (74), 68 (40), 67 (73), 57 (40), 56 (53), 55 (100), 54 (39).

2.7.2. (Z)-15-Methyl-10-hexadecen-1-ol (*8b*)

The (*Z*)-15-methyl-10-hexadecen-1-ol (**8b**) was obtained as a colorless oil in a 96% yield from the catalytic hydrogenation, using Lindlar's catalyst, of 15-methyl-10-hexadecyn-1-ol (0.51 g, 1.99 mmol) according to the general procedure described above; IR (neat) ν_{max} 3360 (OH, broad), 3005, 2926, 2854, 1622, 1504, 1467, 1384, 1366, 1120, 1058, 805, 722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.34 (2H, m, H-10, H-11), 3.63 (2H, t, $J = 6.6$ Hz, H-1), 2.00 (5H, m, H-9, H-12, H-15), 1.70 (1H, brs, –OH), 1.58–1.50 (2H, m, H-2), 1.28 (16H, m, $–CH_2–$), 0.86 (6H, d, $J = 6.6$ Hz, $–CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 129.93 (d), 129.85 (d), 63.03 (t, C-1), 38.63 (t, C-14), 32.79 (t, C-2), 29.73 (t), 29.56 (t), 29.46 (t), 29.41 (t), 29.26 (t), 27.87 (d, C-15), 27.54 (t, C-12), 27.42 (t, C-9), 27.18 (t), 25.73 (t, C-3), 22.61 (q, C-16, C-17); GC–MS (70 eV) *m/z* (relative intensity) 254 (M^+, 1), 236 (3), 208 (1), 180 (1), 165 (1), 151 (2), 137 (5), 123 (11), 111 (8), 110 (15), 109 (22), 97 (21), 96 (45), 95 (46), 83 (36), 82 (75), 81 (50), 71 (10), 70 (18), 69 (80), 68 (34), 67 (55), 57 (42), 56 (56), 55 (100), 54 (31); analysis calculated for $C_{17}H_{34}O$: C, 80.24; H, 13.47; found: C, 79.63; H, 12.37.

2.8. General procedure for the oxidation of the alcohols

To a solution of pyridinium dichromate (8.7–10.1 mmol) and 2 mL of dimethylformamide (DMF) was added under argon (or nitrogen) a solution of the alcohol (1.7–2.0 mmol) in 12 ml of DMF and the reaction mixture was left stirring at room temperature for 24 h. After this time, the mixture was washed with water (3 × 15 mL), hexane (1 × 15 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* affording 1.1–1.2 mmol of the corresponding carboxylic acids in 63% yields.

2.8.1. (Z)-13-Methyltetradec-8-enoic acid (*1a*)

The (*Z*)-13-methyltetradec-8-enoic acid (**1a**) was obtained as a colorless oil in a 63% yield from the reaction of (*Z*)-13-methyltetradec-8-en-1-ol (0.46 g, 2.0 mmol) and pyridinium dichromate (3.8 g, 10.1 mmol) in DMF according to the general procedure described above; IR (neat) ν_{max} 3500–2500, 3004, 2925, 2854, 1708 (C=O), 1462, 1412, 1384, 1366, 1169, 1116, 909, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.34 (2H, m, H-8, H-9), 2.34 (2H, t, $J = 7.5$ Hz, H-2), 2.00 (5H, m, H-7, H-10, H-13), 1.56 (2H, m, H-3), 1.35 (10 H, m, $–CH_2–$), 0.86 (6H, d, $J = 6.6$ Hz, $–CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 179.38 (s, C-1), 130.11 (d), 129.61 (d), 38.63 (t, C-12), 33.93 (t, C-2), 29.49 (t, C-6), 28.94 (t, C-5), 28.85 (t, C-4), 27.88 (d, C-13), 27.53 (t, C-10), 27.43 (t, C-7), 27.09 (t), 24.63 (t), 22.61 (q, C-14, C-15); GC–MS (70 eV) *m/z* (relative intensity) 240 (M^+, 8), 222 (3), 207 (1), 185 (2), 179 (3), 167 (9), 161 (2), 149 (6), 143 (1), 137 (4), 129 (2), 125 (5), 123 (7), 115 (3), 111 (11), 109 (10), 101 (5), 98 (12), 97 (21), 87 (4), 85

(8), 84 (25), 83 (33), 81 (23), 73 (14), 71 (13), 70 (31), 69 (97), 67 (34), 60 (15), 57 (52), 55 (100). HRMS (ESI) Calcd for $C_{15}H_{29}O_2$ $[M+H]^+$ 241.2168, found 241.2163.

*2.8.2. (Z)-15-Methylhexadec-10-enoic acid (**1b**)*

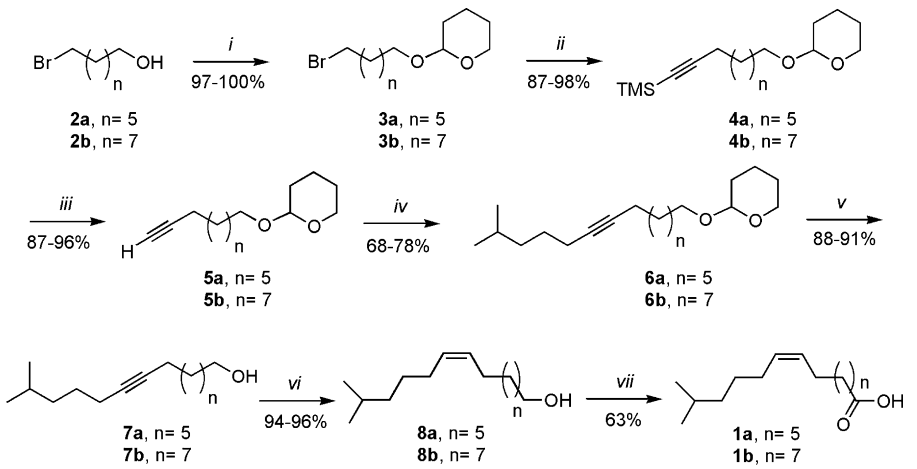
The (*Z*)-15-methylhexadec-10-enoic acid (**1b**) was also obtained as a colorless oil in a 63% yield from the reaction of (*Z*)-15-methylhexadec-10-en-1-ol (0.44 g, 1.7 mmol) and pyridinium dichromate (2.28 g, 8.7 mmol) in DMF according to the general procedure described above; IR (neat) ν_{max} 3500–2500, 3003, 2924, 2853, 1708 (C=O), 1463, 1412, 1384, 1366, 1117, 1089, 1027, 807, 784, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.34 (2H, m, H-10, H-11), 2.34 (2H, t, $J=7.5$ Hz, H-2), 2.01 (5H, m, H-9, H-12, H-15), 1.61 (2H, m, H-3), 1.29 (14H, m, $-CH_2-$), 0.86 (6H, d, $J=6.6$ Hz, $-CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 179.43 (s, C-1), 129.97 (d), 129.81 (d), 38.63 (t, C-14), 33.96 (t, C-2), 29.70 (t), 29.30 (t), 29.20 (t), 29.04 (t), 27.87 (d, C-15), 27.54 (t), 27.42 (t), 27.16 (t), 24.68 (t), 22.61 (q, C-16, C-17); GC–MS (70 eV) *m/z* (relative intensity) 268 (M^+, 6), 250 (4), 235 (1), 213 (2), 207 (2), 195 (5), 177 (3), 165 (2), 161 (1), 151 (3), 149 (1), 143 (1), 137 (4), 129 (3), 125 (6), 123 (5), 115 (3), 111 (13), 109 (7), 101 (4), 98 (12), 97 (24), 95 (14), 87 (4), 85 (8), 84 (22), 83 (36), 81 (19), 73 (12), 71 (11), 70 (29), 69 (85), 67 (28), 60 (18), 57 (51), 55 (100); analysis calculated for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92; found: C, 76.46; H, 12.05; O, 12.25.

3. Results and discussion

Several synthetic approaches have been employed in the synthesis of monounsaturated *iso* methyl-branched fatty acids with double bonds close to the ω end of the acyl chain (Reyes and Carballeira, 1996; Carballeira et al., 2004). A reported methodology employs the Wittig strategy where the best combination for generating the *cis* double bond was using the phosphonium salt of a short-chain *iso* methyl-branched bromoalkane and a long-chain aldehyde bearing a functional group for further transformation into a carboxylic acid. This approach was used in the synthesis of the (*Z*)-15-methylhexadec-11-enoic acid (Reyes and Carballeira, 1996). The synthetic limitations to this approach were the low yields (50%) in the Wittig coupling and obtaining *Z*/*E* mixtures, which can be a serious limitation when only the *Z* isomer is desired.

A more recent approach aiming at a 100% *Z* selectivity involves the use of the versatile reagent (trimethylsilyl)acetylene, as exemplified in the synthesis of the (*Z*)-14-methyl-9-pentadecenoic acid (Carballeira et al., 2004). In this particular synthesis the synthetic approach involved the initial coupling of the (trimethylsilyl)acetylene to a short-chain *iso* bromoalkane resulting in a volatile *iso*-alkyne followed, after removal of the silyl protecting group, by a second acetylide coupling to a longer chain bromoalkane bearing a functional group (e.g., a protected alcohol) that could later be transformed into a carboxylic acid. The advantage of this strategy is that a 100% *Z* stereoselectivity was obtained for the double bond, i.e., after Lindlar hydrogenation of the resulting internal alkyne. However, still a synthetic limitation to this approach is that the initial short-chain *iso*-alkane (in the example giving above the 6-methyl-1-heptyne) is quite volatile, and the yields for the second alkyne-bromide coupling reaction were rather low (33% yields). Therefore, we envisioned that by reversing the coupling order, i.e., initial coupling of the (trimethylsilyl)acetylene to a long-chain bifunctional bromoalkane followed by a second acetylide coupling to a short-chain *iso* bromoalkane would result in higher yields for the second acetylide coupling reaction (Carballeira et al., 2007). This is the strategy we are reporting herein for the seven-step syntheses of the fatty acids (*Z*)-13-methyl-8-tetradecenoic acid (**1a**) and the (*Z*)-15-methyl-10-hexadecenoic acid (**1b**), as outlined in Scheme 1.

Both syntheses started with commercially available (Aldrich) bromo-alcohols, i.e., the 7-bromo-1-heptanol (**2a**) and the 9-bromo-1-nonanol (**2b**), which were protected with 3,4-dihydro-2*H*-pyran (DHP) in the presence of p-toluenesulfonic acid (PTSA) affording the corresponding dihydropyranyl protected alcohols **3a** and **3b**, respectively, in 97–100% isolated yields. The bromo dihydropyranyl protected alcohols **3a** and **3b** were then submitted to the first acetylide coupling reaction with the versatile reagent (trimethylsilyl)acetylene using *n*-BuLi in THF-HMPA affording the trimethylsilyl acetylenic derivatives **4a** and **4b** in 87–98% yields, respectively. Deprotection of the terminal trimethylsilyl group with tetrabutylammonium fluoride (TBAF) afforded the terminal alkynes **5a** and **5b** in 87–96% yields. A second acetylide coupling with 4-methyl-1-bromopentane using *n*-BuLi, THF-HMPA at $-10\,^\circ C$ resulted in the *iso*-branched alkynes **6a** and **6b** in 68–78% isolated yields (Scheme 1). Deprotection of the dihydropyranyl group with PTSA in methanol at $35\,^\circ C$ for 24 h afforded the 13-methyl-8-tetradecyn-1-ol (**7a**) and the 15-methyl-10-hexadecyn-1-ol (**7b**) in 88–91% isolated yields. Catalytic hydrogenation, under Lindlar's conditions of **7a** and **7b**, afforded the *cis*-alkenols (*Z*)-13-methyl-8-tetradecen-1-ol (**8a**) and (*Z*)-15-methyl-10-hexadecen-1-ol (**8b**) in 94–96%



i) DHP, p-TSA, CH_2Cl_2, rt, 24 h; *ii*) *n*-BuLi, HMPA-THF, (trimethylsilyl)acetylene, -78°C, 24h;
iii) TBAF, THF, 0°C, 48h; *iv*) *n*-BuLi, HMPA-THF, 4-methyl-1-bromopentane,-10°C, 24h;
v) p-TSA, MeOH, 35°C, 24h; *vi*) H_2, Lindlar's catalyst, hexane, rt; *vii*) PDC/DMF

Scheme 1. Synthesis of (Z)-13-methyltetradec-8-enoic acid (**1a**) and (Z)-15-methylhexadec-10-enoic acid (**1b**).

yields. Final oxidation of the alcohols with pyridinium dichromate in dimethylformamide (DMF) resulted in the formation of the desired acids **1a** and **1b**, both in 63% yields (Scheme 1). The overall total yields for the seven steps, in both syntheses, were 31–32%.

Acids **1a** and **1b** presented comparable spectral data that confirmed their structures. The *iso* methyl branching was easily identified by both ^{1}H NMR and ^{13}C NMR spectrometry as well as by infrared spectroscopy (IR). In the ^{1}H NMR spectra both terminal isopropyl methyl groups appeared as a doublet at δ 0.86 ppm, while in ^{13}C NMR both methyl groups resonated at δ 22.6 ppm. The IR was more characteristic since the terminal isopropyl group was observed as a doublet at 1384 and 1366 cm^{-1}. The presence of the olefinic hydrogens was easily detected in the ^{1}H NMR spectra by the olefinic signals at δ 5.34 ppm. The ^{13}C NMR spectra were most informative since both allylic methylene carbons resonated at δ 27.4 and 27.5 ppm, confirming the presence of the *cis* double bond. The *cis* double bond stereochemistry was also further confirmed by IR since a strong absorption at 732 cm^{-1} was observed for both acids. The carboxylic acid carbonyl was observed in ^{13}C NMR at δ 179.4 ppm and in IR at 1708 cm^{-1}. The mass spectra of both acids **1a** and **1b** presented a base peak at *m/z* 55 and the typical McLafferty rearrangement at *m/z* 60.

In summary, we have shown that higher yields are indeed obtained in the synthesis of monounsaturated *iso* methyl-branched fatty acids with double bonds close to the ω end of the acyl chain when (trimethylsilyl)acetylene is first coupled to a long-chain bifunctional bromoalkane (87–98% yields) followed by a second acetylide coupling to a short-chain *iso*-bromoalkane (68–78% yields). Complete spectral data is also provided for the first time for the acids **1a** and **1b**. The synthetic methodology presented herein will also certainly furnish enough material for systematic bioassay studies.

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