Synthesis of (*Z*,*Z*)-Octadeca-10,12-dienoic Acid

C. KELLERSMANN[1], W. FRANCKE[2] and H. STEINHART[1]*

*[1]Department of Food Chemistry, Institute of Biochemistry and Food Chemistry, University of Hamburg, Hamburg, Germany, *E-mail: carolin_kellersmann@gmx.de;*
[2]Institute of Organic Chemistry, University of Hamburg, Hamburg, Germany

Abstract: (*Z*,*Z*)-Octadeca-10,12-dienoic acid was synthesised by coupling (*Z*)-1-bromohept-1-ene with protected undec-10-yne-1-ol. Stereoselective hydrogenation of the triple bond of the obtained enyne-system followed by deprotection yielded (*Z*,*ZZ*)-octadeca-10,12-dienol. The latter can be easily oxidized to the corresponding acid.

Keywords: synthesis of conjugated linoleic acid; CLA; stereoselective hydrogenation

INTRODUCTION

Conjugated linoleic acid (CLA) is a term used for a number of positional and geometrical isomers of octadecadienoic acids showing conjugated double bonds. They are predominantly found in milk and meat with 9*Z*,11*E*-CLA as the main isomer. In ruminants, CLA are formed by Butyrivibrio fibrisolvens in the rumen and also in adipose tissue during bio-hydrogenation/dehydrogenation of unsaturated fatty acids. Since their discovery, there is increasing interest in CLA because of their potential benefits to human health. In various animal experiments during the last decades, CLA showed to be anticarcinogenic, antiatherogenic, antidiabetogenic, and modulators for body composition etc. These studies were conducted mostly by using CLA mixtures, prepared by base-catalysed isomerisation of linoleic acid or with the 9*Z*, 11*E*-CLA or the 10*E*,12*Z*-CLA, which are commercially available. There is evidence that the 10*E*,12*Z*-isomer reduces the uptake of lipids by the adipocytes, whereas the 9Z,11*E*-isomer is active in inhibiting carcinogenesis, both have been shown to inhibit atherogenesis [1]. Because of these differences in biological activities it is important to have pure isomers for further investigations.

During recent years several syntheses of pure isomers were reported. Methyl (*Z*,*E*)-octadeca9,11-dienoate was prepared from methyl ricinoleate in 83% purity [2]. Higher purities could be obtained by alkali-isomerisation of methyl linoleate with low-temperature crystallisation from acetone [3]. A mixture of the 9*Z*,11*E*-isomer and the 9*E*, 11*E*-isomer, labelled with deuterium, was prepared and separated by a combination of reversed-phase and silver resin chromatography in purities of > 95% [4]. Chemoenzymatic synthesis of the butylester of (*Z*,*E*)-octadeca-9,11-dienoic acid with lipase yields the product in purities of 90% [5]. Pure isomers of 9*Z*,11E-, 10*E*,12*Z*- and 10Z, 12*Z*-CLA were synthesised by using 1,2-dichloroethene as a building block [6]. We now report a new and simple method for the synthesis of 10*Z*,12*Z*-octadecadienoic acid.

The building blocks required for our synthesis are (*Z*)-1-bromohept-1-ene 3 and 1-(2′-tetrahydropyranyloxy)-undec-10-yne **5**. (*Z*)-1-bromohept-1-ene **3** was prepared by reaction of catecholborane with hept-1-yne yielding the (*E*)alk-1-enylboronic acid ester. The *trans*-configurated double bond was reacted with bromine, which proceeded with *trans*-addition. The following elimination of the borone-moiety and a bromine produced the desired (*Z*)-1-bromohept-1-ene [7]. Coupling this intermediate to the dihydropyran-derivative of undec-10-yn-1-ol yielded (*Z*)-1-(2′-tetrahydropyranyloxy)-octadeca-10-yn-12-ene **6**. The coupling was catalysed by copper iodide and bis(benzonitrile)dichloropalladium II, furnishing good yields with piperidine as the

ideal solvent [8]. The (Z,Z)-configurated, conjugated system was generated by hydrogenation of the triple bond using dicyclohexylborane **7** [9]. Stereoselective syn-addition of dicyclohexylborane followed by deprotection yielded (*Z*,*Z*)-octadeca-10,12-dienol **8**. The latter was oxidized with Jones reagent (CrO_3 in sulphuric acid) to yield (*Z*,*Z*)-octadeca-10,12-dienoic acid 9.

EXPERIMENTAL

Preparation of (*Z*)-1-bromohept-1-ene (3)

In a dry 25 ml flask were placed 1.7 g hept-1-yne (17.7 mmol) (Fluka) and 2.1 g benzo-1,3,2-dioxaborole (17.7 mmol) (Aldrich). The mixture was heated for two hours at 70°C and cooled to room temperature. After addition of 5 ml dry dichloromethane the solution was cooled to –20°C, and 2 ml bromine, dissolved in 8 ml dry dichloromethane was added dropwise. After the addition was completed, 20 ml 2N sodium hydroxide solution were added carefully at –80°C, and the solution was stirred for 1 h at room temperature. The solution was then extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over anhydrous magnesium sulphate. The solvent was removed in vacuo, and the product was purified by kugelrohr distillation to give 2.27 g (72%) of (Z)-1-bromo-1-heptene. MS: 178 (M^+, 8), 176 (M^+, 8), 136 (1), 134 (1), 121 (7), 119 (7), 97 (19), 70 (31), 55 (100), 41 (62) ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.89 (t, 3H, J = 6.9 Hz, 7-H), 1.24–1.46 (m, 6H, 4-H bis 6-H), 2.16–2.22 (m, 2H, 3-H), 6.05–6.15 (m, 2H, 1-H and 2-H)

Preparation of 1-(2′-tetrahydropyranyl-oxy)-10-undecyne (5)

To a solution of 5 g 10-undecyn-1-ol (Aldrich) (30 mmol), and 0.75 g pyridinium-4-toluenesulfonate (3 mmol) in 60 ml dry, ice-cold dichloromethane was added dropwise a solution of 2.8 g (3 ml, 33 mmol) 2,3-dihydropyran in 15 ml dry dichloromethane. The mixture was stirred over night at 4°C, poured into ice water, and extracted three times with diethyl ether. The combined organic layers were washed with diluted sodium hydrogen carbonate, brine, and dried over anhydrous magnesium sulphate. The solvent was removed in vacuo, and the crude product was purified by flash chromatography over silica (MP Biomedicals, 32-63, 60 Å) using petroleum ether: ethyl acetate (8:1). Yield 5.6 g (74%) MS: 251 (M^+, 1), 101 (17), 95 (11), 85 (100), 67 (23), 55 (25), 41 (26) ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.23–1.43 (m, 12H, 2-H bis 7-H), 1.47–1.63 (m, 6H)/1.66–1.75 (m, 1H)/1.77–1.87 (m, 1H) (3′-H bis 5′-H und 4-H), 1.93 (t, 1H, J = 2.6 Hz, 1-H), 2.17 (dt, 2H, J = 2.5/7.1 Hz, 3-H), 3.38 (dt, 1H, J = 9.4/6.7 Hz, 6′-Ha), 3.46–3.53 (m, 1H, 1-Ha), 3.72 (dt, 1H, J = 9.4/6.7 Hz, 6′-Hb), 3.83–3.90 (m, 1H, 1-Hb).

Preparation of (Z)-1-(2′-Tetrahydropyranyl-oxy)-octadeca-10-yn-12-ene (6)

In a dry 25 ml flask were placed 0.708 g (Z)-1-bromo-1-heptene (4 mmol), 76 mg copper(I)iodide (0.4 mmol), 76 mg bis(benzonitrile)dichloropalladiumII ($PdCl_2[PhCN]_2$, 0.2 mmol) and 12 ml piperidine. To this suspension was added at room temperature 2 g (8 mmol) 1-(2′-tetrahydropyranyl-oxy)-undec-10-yne. After stirring for two hours, saturated aqueous ammonium chloride solution was added and extracted three times with diethyl ether. The combined organic layers were washed with 0.2N hydrochloric acid, saturated sodium hydrogen carbonate solution, and twice with water. The organic layer was dried over anhydrous magnesium sulphate, and the solvent was removed in vacuo. The crude product was purified by flash chromatography over silica using petroleum ether: ethyl acetate (50:1). Yield 1.2 g (86%) MS: 348 (M^+, 2), 264 (1), 219 (2), 205 (1), 177 (1), 163 (1), 121 (4), 101 (5), 85 (100), 79 (21), 55 (32), 41 (60) ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.89 (t, 3H, J = 6.9 Hz, 18-H), 1.26–1.45 (m, 16H, 2-H bis 7-H and 16-H bis 17-H), 1.50–1.62 (m, 8H)/1.67–1.75 (m, 1H)/1.79–1.88 (m, 1H) (3′-H bis 5′-H and 8-H and 15-H), 2.24–2.35 (m, 4H, 9-H and 14-H), 3.38 (dt, 1H, J = 9.7 Hz/6.6 Hz, 1-H_a), 3.47–3.53 (m, 1H, 6′-H_a), 3.73 (dt, 1H, J = 9.66 Hz/6.9 Hz, 1-H_b), 3.83–3.90 (m, 1H, 6′-H_b), 4.53–4.59 (m, 1H, 2′-H), 5.40–5.45 (m, 1H, 12-H), 5.80 (dt, 1H, J = 10.7 Hz/7,4 Hz, 13-H).

Preparation of (*Z*,*Z*)-1-(2′-tetra-hydropyranyloxy)-octadeca-10,12-diene (7)

Dropwise and at 0°C was added 0.43 ml (9 mml) borane dimethyl sulphide complex (Aldrich) to a solution of 0.9 ml (9 mmol) cyclohexene in 21 ml dry hexane. The mixture was stirred until a white precipitate had formed (ca. 10 min).

To 0.348 g (*Z*)-1-(2′-tetrahydropyranyloxy)-octadeca-10-yn-12-ene (1 mmol) dissolved in 20 ml dry hexane were added at 0°C 3.6 ml of the freshly prepared dicyclohexylborane solution. The mixture was stirred for 2 hours at room temperature and diluted with 8 ml dry tetrahydrofuran. After the addition of 0.5 ml acetic acid the mixture was heated to 50°C for three hours. The solution was cooled to room temperature and hydrolysed with 2 ml sodium hydroxide solution (5M) and 0.44 ml hydrogen peroxide solution (30% aqueous). The mixture was stirred for additional 30 min, poured into ice water, and extracted three times with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulphate, and concentrated in vacuo. The crude product was purified by flash chromatography over silica using petroleum ether: ethyl acetate (100:1). Yield 215.7 mg (62%) MS: 350 (M^+, 0,1), 266 (1), 101 (12), 95 (10), 85 (100), 81 (13), 67 (25), 55 (16), 41 (24) ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.89 (t, 3H, J = 6.9 Hz, 18-C), 1.25–1.40 (m, 16H, 2-H bis 7-H and 16-H bis 17-H), 1.48–1.61 (m, 8H)/1.67–1.75 (m, 1H)/1.80–1.86 (m, 1H) (3′-H bis 5′-H and 8-H and 15-H), 2.13–2.20 (m, 4H, 9-H and 14-H), 3.38 (dt, 1H, J = 9.7 Hz/6.6 Hz, 1-H_a), 3.46–3.53 (m, 1H, 6′-H_a), 3.73 (dt, 1H, J = 9.7 Hz/6.9 Hz, 1-H_b), 3.84–3.91 (m, 1H, 6′-H_b), 4.56–4.59 (m, 1H, 2′H), 5.40–5.48 (m, 2H, 10-H and 13-H), 6.20–6.30 (m, 2H, 11-H and 12-H).

Preparation of (*Z*,*Z*)-octadeca-10,12-dienol (8)

215.7 mg (0.62 mmol) (*Z*)-1-(2′-tetrahydropyranyloxy)-octadeca-10-yn-12-ene were dissolved in 10 ml methanol, and catalytic amounts of *p*-toluenesulfonic acid were added. After the mixture was stirred over night at room temperature, solid sodium hydrogen carbonate was added, and the suspension was stirred for additional 15 min. In vacuo, the mixture was reduced to 1/3 of the volume, water was added and extracted three times with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulphate, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica using petroleum ether: ethyl acetate (5:1). Yield 188 mg (~ 100%) MS: 266 (M^+, 4), 248 (1), 149 (2), 135 (7), 121 (11), 109 (14), 95(40), 81 (65), 67 (100), 55 (47), 41 (73) ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.89 (t, 3H, J = 6.9 Hz, 18-C), 1.25–1.40 (m, 20H, 2-H bis 8-H and 15-H bis 17-H), 1.51–1.60 (m, 4H, 9-H and 14-H), 3.63 (t, 2H, J = 6.6 Hz, 1-H), 5.40–5.49 (m, 2H, 10-H and 13-H), 6.20–6.28 (m, 2H, 11-H and 12-H).

Preparation of (*Z*,*Z*)-octadeca-10,12-dienoic acid (9)

To 97.4 mg (0.4 mmol) (*Z*,*Z*)-octadeca-10,12-dienol, dissolved in 5 ml acetone, was added dropwise Jones reagent at 0°C until the reddish-brown colour didn't switch to green. After addition of one drop of 2-propanol, the suspension was filtered. Subsequently the mixture was concentrated in vacuo to ¼ of the volume, and after addition of 10 ml water and 10 ml diethyl ether, the aqueous layer was extracted four times with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulphate, and the solvent was removed in vacuo. The crude product was purified by flash chromatography over silica using petroleum ether: ethyl acetate (2:3). Yield 56 mg (50%) ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.89 (m, 3H, 18-H), 1.24–1.37 (m, 16H, 4-H bis 8-H and 15-H bis 17-H), 1.47–1.55 (m, 2H, 3-H), 1.60–1.67 (m, 4H, 9-H and 14-H), 2.31–2.37 (m, 2H, 2-H), 6.09–6.16 (m, 2H, 10-H and 13-H), 6.81–6.88 (m, 2H, 11-H and 12-H).

References

[1] Banni S., Murru E., Angioni E., Carta G., Melis M.P. (2002): Sci. Alim., **22**: 371.

[2] Berdeaux O., Christie W.W., Gunstone F.D., Sebedio J.-L. (1997): JAOCS, **74**: 1011–1015.

[3] Berdeaux O., Voinot L., Angioni E., Juanéda P., Sébédio J.-L. (1998): JAOCS, **75**: 1749.

[4] Adlof R. (1997): Chem. Phys. Lipids, **88**: 107.

[5] Chen C.-A., Sih C.J. (1998): J. Org. Chem., **63**: 9620.

[6] Loreau O., Maret A., Chardigny J.M., Sébédio J.L., Noël J.P. (2001): Chem. Phys. Lipids, **110**: 57.

[7] Brown H.C., Subrahmanyam C., Hamaoka T., Ravindran N., Bowman D.H., Misumi S., Unni M.K., Somayaji V., Narayan G.J. (1989): Org. Chem., **54**: 6068.

[8] Alami M., Crousse B., Ferri F. (2001): J. Organometal. Chem., **624**: 114.

[9] Brown H.C., Mandal A.K., Kulkarni S.U. (1977): Org. Chem., **42**: 1392.