Short and Efficient Approach Towards Macrocyclic Lactones Based on a Sonogashira Reaction*

Jürgen Krauss, Doris Unterreitmeier, Christine Neudert, Franz Bracher

Department of Pharmacy, Zentrum für Pharmaforschung, LMU Munich, Germany

Polyketide-derived macrolactones like zearalenone (**1**), zearalane (**2**) or curvularin (**3**) display a wide range of interesting pharmacological activities. Here, we present a short and efficient approach towards this class of natural products by a combination of the Sonogashira and Mitsunobu reactions. The resulting lactone **9** was tested against human cancer cell lines at the NCI.

Keywords: Sonogashira reaction; Mitsunobu reaction; Macrolactones

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Introduction

Polyketide-derived resorcyclic acid lactones like (*S*)-zearalenone (**1**), (*S*)-zearalane (**2**) or (*S*)-curvularin (**3**) (Figure 1) are a well-known group of natural products with interesting pharmacological activities like cytotoxic, antibiotic, antimycotic, anthelmintic, estrogenic, anabolic or immunemodulating action [1–3]. Numerous total syntheses of resorcyclic acid lactones have been described in the literature, but most of these approaches are low-yielding procedures using expensive starting materials.

Results and discussion

In continuation of our work on total synthesis of naturally occurring macrolactones [4, 5], we developed a new approach towards the class of benzolactones. Exemplarily, we describe the synthesis of a simple 15-membered macrolactone instead of the naturally occurring 14-membered lactones and with a primary alcohol instead of the naturally more common secondary alcohols, because these starting materials are commercially available. The Sonogashira reaction and the Mitsunobu reaction [4] are also possible with secondary alcohols. Other methods to build up macrolactones are based on palladium-catalyzed cross-coupling reactions like Suzuki and macrolactonizations by Corey, Gerlach and Thalmann or a Wassermann protocol [6].

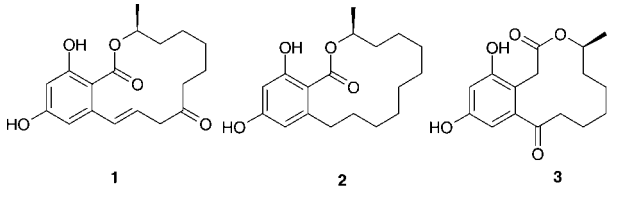

Figure 1. Naturally occurring resorcyclic lactones.

Undec-10-yn-1-ol (**5**) was reacted in a Sonogashira reaction with methyl 2-iodobenzoate (**4**) to the alkyne **6** [7] (Scheme 1). The best solvent for the Sonogashira coupling was ethyldimethylamine (EDMA). After hydrogenation of the triple bond with Pd-catalyst to the alkane **7**, the methyl ester was cleaved with methanolic aqueous KOH to give acid **8**. This acid was readily converted to the lactone **9** under Mitsunobu conditions [8]. Cleavage of the methyl ester of **6** without prior hydrogenation of the triple bond led to the coumarine derivative **10** [9]. In the course of this reaction, the terminal hydroxy group was acetylated by the co-solvent ethyl acetate (Scheme 1).

In an alternative approach, we first prepared the acetylenic ester **12** from 2-iodobenzoyl chloride (**11**) and the alkynol **5** (Scheme 2). The cyclization of **12** in an intramolecular Sonogashira reaction to the acetylenic macrolactone **13** only gave low yields.

The lactone **9** was tested at the NCI against the human cancer cell lines NCI-H460, MCF7, and SF-268, but showed no significant cytotoxic activities [10].

In summary, the preparation of lactone **9** is experimentally very simple by using inexpensive starting materials. The described method allows the preparation of macrolactones in three steps. The total yield of lactone **9** was about 63%.

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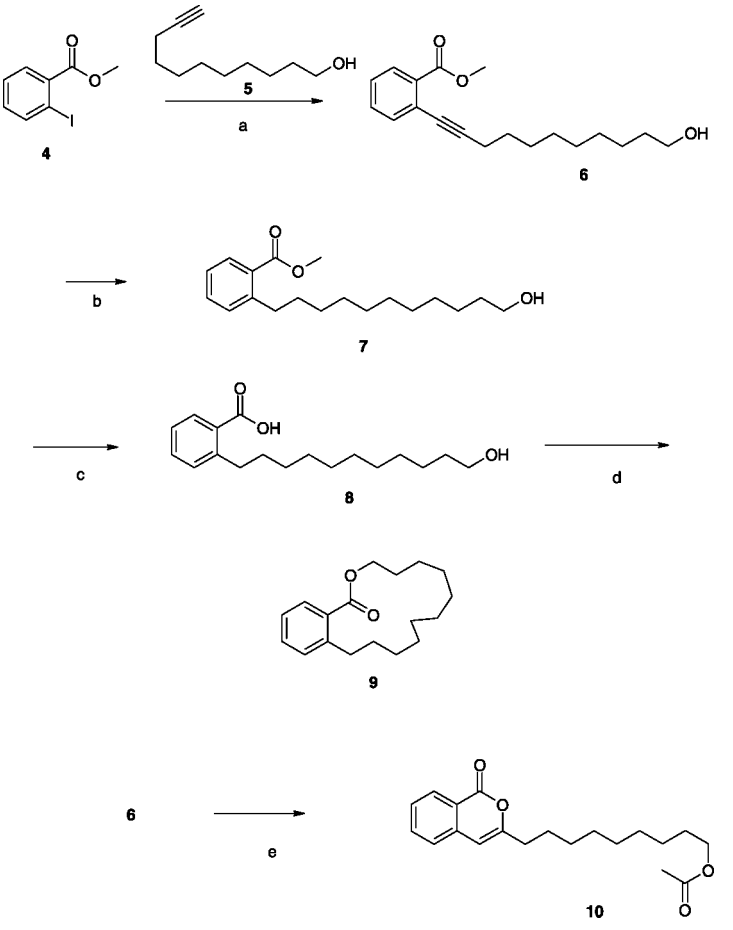
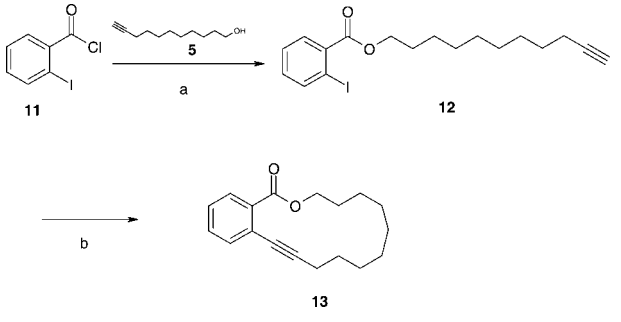
Correspondence: Jürgen Krauss, Department of Pharmacy, Zentrum für Pharmaforschung, LMU München, Butenandtstrasse 5–13, D-81377 München, Germany. Phone: +49-89-218077275, Fax: +49-89-218077171, e-mail: hjkra@cup.uni-muenchen.de

* Dedicated to Prof. Dr. K. Görlitzer on the occasion of his 65th birthday.

Short Communication



Scheme 1. Synthesis of macrolactone **9** and coumarine derivative **10**. (a) EDMA, CuI, $PdCl_2(PPh_3)_2$; (b) H_2/Pd (C), methanol; (c) KOH, methanol, H_2O; (d) $P(Ph)_3$, DEAD, toluene; (e) KOH, methanol, H_2O, EtOAc.



Scheme 2. Alternative synthesis route of cumarine derivative **10**. (a) Toluene, EDMA; (b) EDMA, CuI, $PdCl_2(PPh_3)_2$.

Experimental

General

IR-Spectra: Jasco FT-IR 410 (Jasco, Groß-Umstadt, Germany); MS: Hewlett Packard MS-Engine, electron ionisation (EI) 70 eV, chemical ionisation (CI) with CH_4 (300 eV) (Agilent Technologies, Palo Alto, CA, USA); Shimadzu GC-MS (GC 17A GCMS OP 500) (Shimadzu Deutschland GmbH, Duisburg, Germany), NMR: Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) (Jeol (Germany) GmbH, Eching/München, Germany); flash column chromatography (FCC): silica gel 60 (230−400 mesh, E. Merck, Darmstadt, Germany). HR-MS: Heraeus CHN-Rapid (Heraeus Holding GmbH, Hanau, Germany).

Chemistry

*Methyl (2-(11-hydroxyundec-1-ynyl)benzoate (**6**)*

Methyl-2-iodobenzoate (**4**) (1.0 g, 3.8 mmol) and 640 mg (3.8 mmol) undec-10-yn-1-ol (**5**) were dissolved in 30 mL of a suspension of 200 mg (1.1 mmol) CuI and 200 mg (0.29 mmol) $PdCl_2(PPh_3)_2$ in EDMA. The suspension was stirred for 12 h, the solvent was evaporated and the residue dissolved in 10% $Na_2S_2O_3$ solution. After extraction with diethylether (3 × 30 mL) the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified with FCC (*n*-hexane/ethyl acetate 5:1) to give 1.1 g (96%) of **6**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.32 (m, 8H, 4 × CH_2), 1.39 (s, 1H, OH), 1.46 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.46 (t, J = 7.2 Hz, 2H, CH_2), 3.61 (t, J = 7.3 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 7.29 (ddd, J = 1.3 Hz, J = 7.5 Hz, J = 7.5 Hz, 1H, aromat. CH), 7.40 (ddd, J = 1.3 Hz, J = 7.5

Hz, J = 7.5 Hz, 1H, aromat. CH), 7.49 (dd, J = 1.3 Hz, J = 7.5 Hz, 1H, aromat. CH), 7.89 (dd, J = 1.3 Hz, J = 7.5 Hz, 1H, 6-H). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.64 (CH_2), 25.66 (CH_2), 28.59 (CH_2), 28.86 (CH_2), 29.10 (CH_2), 29.33 (CH_2), 29.41 (CH_2), 32.73 (CH_2), 52.01 (OCH_3), 62.99 (CH_2O), 79.17 (quart. C), 95.99 (quart. C), 124.45 (quart. C), 127.07 (aromat. CH), 130.07 (aromat. CH), 131.42 (aromat. CH), 131.88 (quart. C), 134.16 (aromat. CH), 166.99 (COO). Calcd.: C: 75.46, H: 9.15. Found: C: 75.09, H: 8.74.

*Methyl (2-(11-hydroxyundecyl)benzoate (**7**)*

Of **6**, 500 mg (1.6 mmol) was dissolved in 50 mL methanol, and 100 mg Pd (C) (10%) was added. The suspension was stirred under H_2 atmosphere for 12 h. The catalyst was filtered off and the solvent was evaporated to give 450 mg (92%) of **7**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.28 (m, 14H, 7 × CH_2), 1.47 (s, 1H, OH), 1.57 (m, 4H, 2 × CH_2), 2.93 (t, J = 7.8 Hz, 2H, CH_2), 3.63 (t, J = 6.6 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 7.23 (m, 2H, 2 aromat. CH), 7.40 (ddd, J = 7.5 Hz, J = 7.5 Hz, J = 1.4 Hz, 1H, aromat. CH), 7.84 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H, 6-H).

*2-(11-Hydroxyundecyl)benzoic acid (**8**)*

Of **7**, 400 mg (1.4 mmol) was dissolved in 40 mL 5% KOH solution (methanol/H_2O 1:1) and refluxed for 10 h. The solution was neutralized with 10% HCl solution and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by FCC (*n*-hexane/ethyl acetate 1:1) to give 370 mg (91%) of **8**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.29 (m, 14H, 7 × CH_2), 1.58 (m, 4H, 2 × CH_2), 3.01 (t, J = 7.7 Hz, 2H, CH_2), 3.67 (t, J = 6.7 Hz, 2H, CH_2), 7.26 (m, 2H, 2 aromat. CH), 7.45 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.5 Hz, 1H, aromat. CH), 8.00 (d, J = 7.2 Hz, 1H, 6-H). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 25.63 (CH_2), 29.22 (CH_2), 29.23 (CH_2), 29.24 (2 × CH_2), 29.30 (CH_2), 34.59 (CH_2), 34.61 (CH_2), 34.64 (CH_2), 34.65 (CH_2), 63.21 (CH_2O), 125.83 (aromat. CH), 128.28 (quart. C), 131.23 (aromat. CH), 131.54 (aromat. CH), 132.68 (aromat. CH), 145.79 (quart. C), 171.98 (COOH). MS (EI): *m/z* (%) = 274 (M^+−18, 20), 131 (100), 55 (44). MS (CI): *m/z* (%) = 293 (M^++1, 4), 275 (100). Calcd.: C: 73.93, H: 9.65. Found: C: 73.81, H: 9.63.

*8,9,10,12,13,14,15,16,17−Decahydro-7H-6-oxabenzo-cyclopentadecen-5-one (**9**)*

Of **8**, 200 mg (0.7 mmol) was dissolved in 10 mL toluene and dropped over a period of 4 h to a solution of 520 mg (2.0 mmol) triphenyl phosphine and 400 mg (2.3 mmol) DEAD in 100 mL dry toluene. The mixture was stirred for 12 h. The solvent was evaporated and the residue purified by FCC (*n*-hexane/ethyl acetate 10:1) to give 150 mg (78%) of **9** as a colourless oil. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.27 (m, 6H, 3 × CH_2), 1.37 (m, 4H, 2 × CH_2), 1.52 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 2.96 (t, J = 8.1 Hz, 2H, CH_2), 4.42 (t, J = 5.2 Hz, 2H, CH_2O), 7.22 (m, 2H, 2 aromat. CH), 7.37 (ddd, J = 7.5 Hz, J = 7.5 Hz, J = 1.4 Hz, 1H, aromat. CH), 7.69 (dd, J = 1.6 Hz, J = 7.5 Hz, 1H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 23.78 (CH_2), 24.46 (CH_2), 24.58 (CH_2), 25.64 (CH_2), 26.64 (CH_2), 26.93 (2 × CH_2), 28.89(CH_2), 30.64 (CH_2), 34.15 (CH_2), 64.33 (CH_2), 125.64 (aromat. CH), 129.95 (aromat. CH), 130.82 (aromat. CH), 131.28 (aromat. CH), 143.39 (quart. C), 150.07 (quart. C), 169.11 (COO). MS (EI): *m/z* (%) = 274 (M^+, 35), 148 (100), 55 (95). MS (CI): *m/z* (%) = 275 (M^++1, 100). HR-MS: Calcd.: 274.1933. Found: 274.1919.

*(9-(1-Oxo-1H-isochromen-3-yl)-nonyl) acetate (**10**)*

Of **3**, 200 mg (0.65 mmol) and 0.5 mL ethylacetate were dissolved in 20 mL 5% KOH solution (methanol/H_2O 1:1) and refluxed for 10 h. The solution was neutralized with 10% HCl solution and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by FCC (*n*-hexane/ethyl acetate 5:1) to give 120 mg (56%) of **10**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.30 (m, 10H, 5 × CH_2), 1.60 (m, 2 H, CH_2), 1.69 (m, 2H, CH_2), 2.03 (s, 3H, CH_3), 2.51 (t, J = 7.2 Hz, 2H, CH_2), 4.03 (t, J = 7.1 Hz, 2H, CH_2), 6.24 (s, 1H, aromat. CH), 7.34 (d, J = 7.7 Hz, 1H, aromat. CH), 7.43 (ddd, J = 7.4 Hz, J = 7.5 Hz, J = 1.4 Hz, 1H, aromat. CH), 7.66 (ddd, J = 7.5 Hz, J = 7.9 Hz, J = 7.9 Hz, 1H, aromat. CH), 8.24 (d, J = 7.7 Hz, 1H, 8″-H). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 20.98 (CH_3), 25.85 (CH_2), 26.87 (CH_2), 28.55 (CH_2), 28.94 (CH_2), 29.15 (CH_2), 29.19 (CH_2), 29.31 (CH_2), 33.51 (CH_2), 64.58 (OCH_3), 102.85 (aromat. CH), 120.14 (quart. C), 124.98 (aromat. CH), 127.51 (aromat. CH), 129.49 (aromat. CH), 134.67 (aromat. CH), 137.62 (quart. C), 158.28 (quart. C), 163.06 (quart. C), 171.19 (quart. C). MS (EI): *m/z* (%) = 330 (M^+, 30), 288 (20), 172 (100), 118 (80), 89 45). MS (CI): *m/z* (%) = 331 (100, M^++1), 289 (25), 271 (20).

*Undec-10-yn-1-yl-2-iodobenzoate (**12**)*

Of 2-iodobenzoyl chloride (**11**), 2.6 g (10.0 mmol) and 1.68 g (10.0 mmol) undec-10-yn-1-ol (**5**) were dissolved in toluene, 5 mL EDMA were added and the mixture was stirred for 12 h. The solvent was evaporated, the residue dissolved in 50 mL water and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the the solvent was evaporated. The residue was purified by FCC (*n*-hexane/ethyl acetate 5:1) to give 3.5 g (88%) of **12**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.31 (m, 14H, CH_2), 1.53 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 1.94 (t, J = 2.5 Hz, 1H, CH), 2.18 (dt, J = 2.5 Hz, J = 7.2 Hz, 2H, CH_2), 4.33 (t, J = 6.7 Hz, 2H, CH_2), 7.15 (ddd, J = 1.8 Hz, J = 7.5 Hz, J = 7.9 Hz, 1H, aromat. CH), 7.40 (ddd, J = 1.2 Hz, J = 7.9 Hz, J = 7.5 Hz, 1H, aromat. CH), 7.78 (dd, J = 1.7 Hz, J = 7.9 Hz, 1H, aromat. CH), 7.99 (dd, J = 1.2 Hz, J = 7.9 Hz, 1H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 25.72 (CH_2), 28.48 (CH_2), 28.72 (CH_2), 29.03 (CH_2), 29.36 (CH_2), 29.44 (CH_2), 32.80 (CH_2), 38.93 (CH_2), 42.79 (CH_2), 63.05 (CH_2O), 84.77 (CH), 92.90 (quart. C), 126.88 (aromat. CH), 128.22 (aromat. CH), 129.87 (aromat. CH), 139.16 (aromat. CH), 142.92 (quart. C), 170.07 (CO). MS (EI): *m/z* (%) = 398 (M^+, 6), 248 (100), 231 (63), 203 (18). HR-MS: Calcd.: 398.0743. Found: 38.0739.

*8,9,10,11,12,13,14,15-Octahydro-7H-6-oxa-benzo-cyclopentadecen-16-in-5-one (**13**)*

Of **12**, 680 mg (1.7 mmol) were dissolved in 10 mL EDMA and added dropwise to a stirred suspension of 500 mg (2.6 mmol) CuI and 400 mg (0.6 mmol) $PdCl_2(PPh_3)_2$ in 250 mL dry EDMA and stirred for 12 h. Then, the solvent was evaporated and the residue was dissolved in 30 mL water. The aqueous layer was extracted with diethylether (3 ± 30 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by FCC (*n*-hexane/ethyl acetate 10:1) to give 70 mg (15%) of **13**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.42 (m, 12H, 6 × CH_2), 1.75 (m, 2H, CH_2), 2.51 (dd, J = 5.8 Hz, J = 5.8 Hz, 2H, CH_2), 4.49 (dd, J = 5.3 Hz, J = 5.3 Hz, 2H, CH_2O), 7.29 (ddd, J = 0.9 Hz, J = 7.5 Hz, J = 7.6 Hz, 1H, aromat. CH), 7.38 (ddd, J = 1.1 Hz, J = 7.5 Hz, J = 7.5 Hz, 1H, aromat. CH), 7.50 (dd, J = 1.1 Hz, J = 7.6 Hz, 1H, aromat. CH), 7.69 (dd, J = 0.9 Hz, J = 7.7 Hz, 1H, aromat. CH). ^{13}C-NMR ($CDCl_3$) d (ppm) = 23.56 (CH_2), 25.55 (CH_2), 25.76 (CH_2), 25.86 (CH_2), 27.25 (CH_2), 27.64 (CH_2), 29.52 (CH_2), 33.79 (CH_2), 63.78 (CH_2O), 79.06 (quart. C), 95.27 (quart. C), 123.71 (quart. C), 126.99 (aromat. CH), 129.35 (aromat. CH), 130.76 (aromat. CH), 133.81 (aromat. CH), 167.65 (CO). MS (EI): *m/z* (%) = 270 (M^+, 6), 199 (100), 159 (72).

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