Natural Product Synthesis

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Total Synthesis of Myrtucommulone A**

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Dedicated to Prof. Dr. Volker Schurig on the occasion of his 70th birthday

Myrtucommulone A (**1**; Figure 1) was first described in 1974 by Kashman and co-workers as a substance found in the common myrtle *Myrtus communis* L.[1a] These authors also

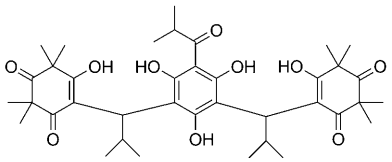

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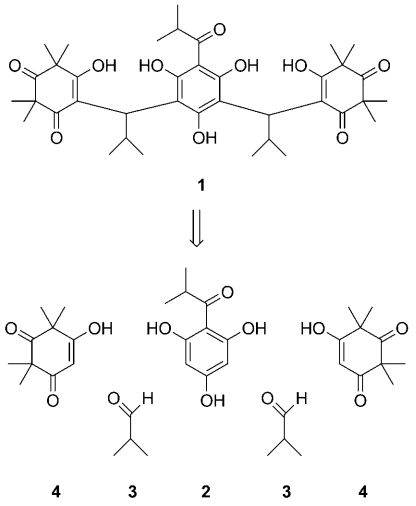
Figure 1. Myrtucommulone A (**1**).

reported that **1** is highly active against Gram-positive bacteria.[1b] Three years later Lounasmaa and co-workers[2] isolated myrtucommulone A from other members of the myrtacea family. After that, interest in myrtle died down until 2002 when Appendino and co-workers[3] re-examined extracts of this Mediterranean shrub and described additional myrtucommulones and their anti-oxidative properties.[4] Shaheen et al.[5] recently isolated the myrtucommulones C to E and other natural products from *Myrtus communis*. Quinn and co-workers[6] examined extracts from *Corymbia scabrida* and could identify **1** and the myrtucommulones F to I.

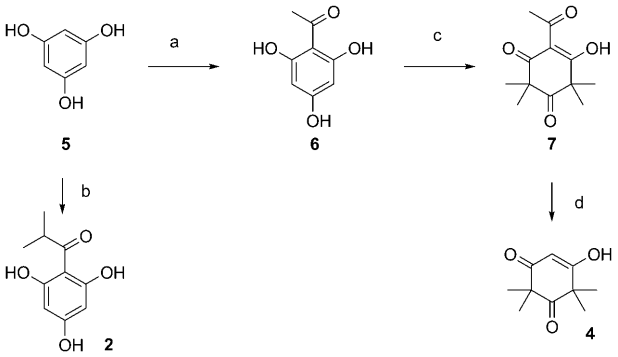
We became interested in the myrtucommulones when it was reported that these compounds show very significant anti-inflammatory activity as well as highly selective apoptosis-inducing activity.[7] For detailed studies of the pharmacological activities of these compounds it seemed reasonable to develop a synthetic strategy leading to myrtucommulone A (**1**) and the other myrtucommulones. Here, we report on our total synthesis[8] of myrtucommulone A (**1**), myrtucommulone F (**13**), myrtucommulone C (**16**), and three analogues thereof. Based on the constitutional symmetry of **1** the retrosynthetic disconnection shown in Scheme 1 seems reasonable. It should be possible to synthesize **1** from isobutyryl phloroglucinol (**2**), isobutyraldehyd (**3**), and syncarpic acid (**4**) in one step.[9]

Isobutyryl phloroglucinol (**2**) is readily available through Friedel–Crafts acylation of phloroglucinol (**5**) in 70–80% yield (Scheme 2).[10] Syncarpic acid (**4**) is described in the



1 ⇓ **4** **3** **2** **3** **4**

Scheme 1. Retrosynthetc disconnection of **1** into isobutyryl phloroglucinol (**2**), isobutyraldehyde (**3**), and syncarpic acid (**4**).



Scheme 2. Synthesis of **2** and **4**. a) Acetyl chloride, $AlCl_3$, CS_2/nitrobenzene, reflux, 70%; b) isobutyric chloride, $AlCl_3$, CS_2/nitrobenzene, reflux, 70%; c) MeI, NaOMe, MeOH, reflux 12 h, 85%; d) 2 N HCl, reflux, 4 h, 95%.

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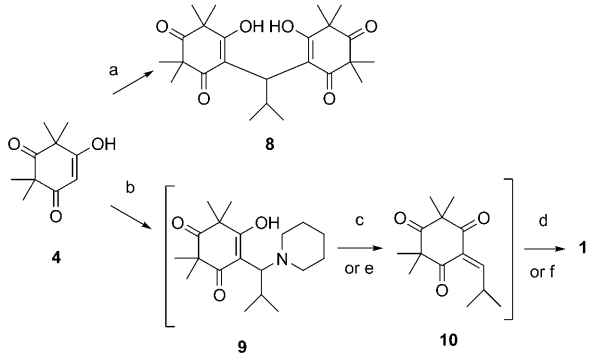
literature[11] and is also available from **5** (Scheme 2). According to reference [11a] **5** is acetylated to give acetyl phloroglucinol (**6**), which is methylated to provide the tetramethyl derivative **7** and finally deacetylated under acidic conditions.

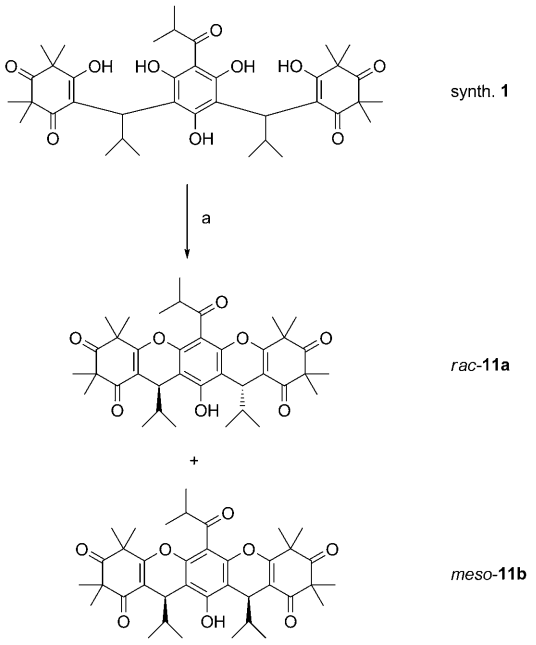
Reactions of syncarpic acid (**4**) with aldehydes were described by Crow and co-workers,[12] by Baltas et al.,[13] and also by André-Barrès and co-workers.[14] According to these authors, syncarpic acid reacts under acidic conditions with aldehydes such as **3** to give compound **8**. To avoid this side reaction, we treated **4** with **3** to obtain the Mannich base **9** , in analogy to the report by Crow et al.[12] Compound **9** was converted in situ into myrtucommulone A (**1**) through the action of anhydrous toluenesulfonic acid (alternatively with trifluoroacetic acid) in approximately 35% yield (yields ranged from 15 to 45%) (Scheme 3, steps b–d). In this synthesis a Mannich reaction (→**9**), an elimination (→**10**), and two acid catalyzed Friedel–Crafts alkylations take place consecutively in one reaction flask.



Scheme 3. Synthesis of myrtucommulone A (**1**). a) **3**, HCl; b) **3**, piperidine, CH_2Cl_2, RT, 10 min.; c) pTsOH, CH_2Cl_2, RT, 10 min.; d) add **2**, then reflux, 24 h, 35%; e) HCl/NH_4Cl, isolate **10** as crude product; f) **2**, NaH (2 equiv), THF, RT, 3 h, quantitative.

The rather low yield of **1** under acidic conditions is a consequence of dehydration to give the pentacyclic derivative **11** (Scheme 4). Therefore we decided to carry out the Friedel–Crafts alkylation under basic conditions,[15] since this should not result in **11**. Running the Friedel–Crafts alkylation under basic conditions required removal of the acid and isolation of **10** as a crude product prior to reaction with **2**, which had been deprotonated with two equivalents of NaH in THF. With this modification, the synthesis of **1** is complete within three hours at room temperature in quantitative yield after chromatographic purification (Scheme 3, steps b, e, and f).

Determination of the structure of **1** directly by NMR spectroscopy was extremely difficult.[16] Therefore we treated our synthetic compound with toluenesulfonic acid to effect cyclization and dehydration (Scheme 4). We obtained the pentacyclic derivatives **11a** and **11b**, which were separated by preparative HPLC and characterized by NMR spectroscopy. The first eluting **11a** was the racemate while the second eluting **11b** was the *meso* compound. Therefore, our synthetic **1** is a mixture of three stereoisomers, one pair of enantiomers and one *meso* form.[18] Additionally, we recrystallized synthetic **1** from acetone to obtain crystals suitable for X-ray analysis[19] (Figure 2). The X-ray structure confirmed our structure determination that was based on the NMR spectra of the pentacyclic derivatives **11a** and **11b**.



Scheme 4. Synthesis of pentacyclic derivatives from myrtucommulone A (**1**). a) *p*TsOH, benzene, reflux, 1 h, 95%.

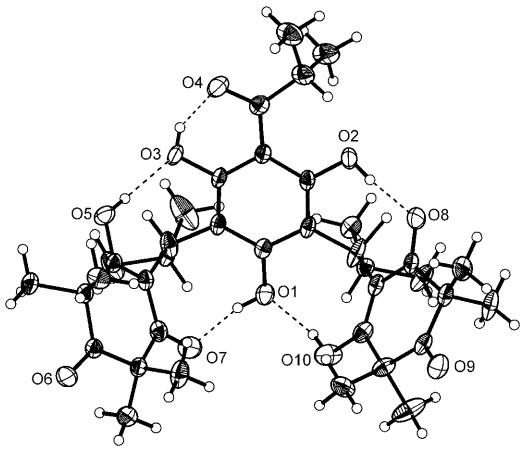
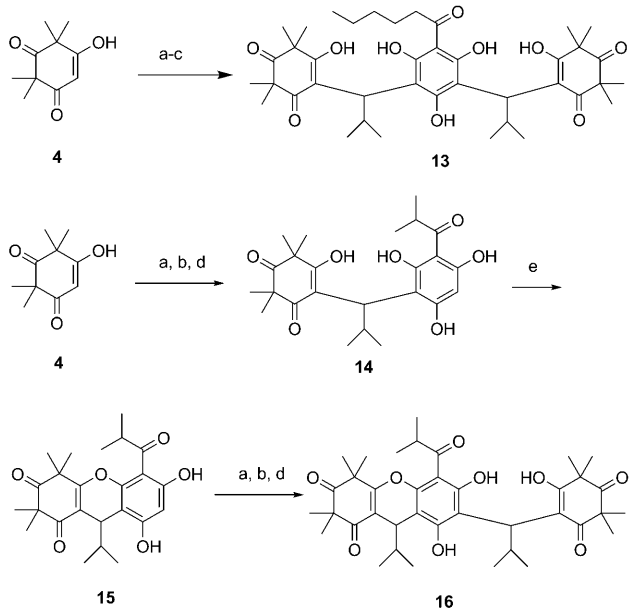


Figure 2. X-ray structure of myrtucommulone A (**1**); ellipsoids at the 50% probability level.

The same synthetic strategy was applied to the starting compounds syncarpic acid (**4**), isobutyraldehyd (**3**), and hexanoyl phloroglucinol (**12**) to prepare myrtucommulone F (**13**), which was recently described by Quinn et al.[6] (Scheme 5). By variation of the equivalents of **10** and **2** it was possible to monoalkylate **2** to yield **14**, which was converted into **15** by acid-catalyzed cyclization and dehydration. When **15** was treated again with the Michael acceptor **10**

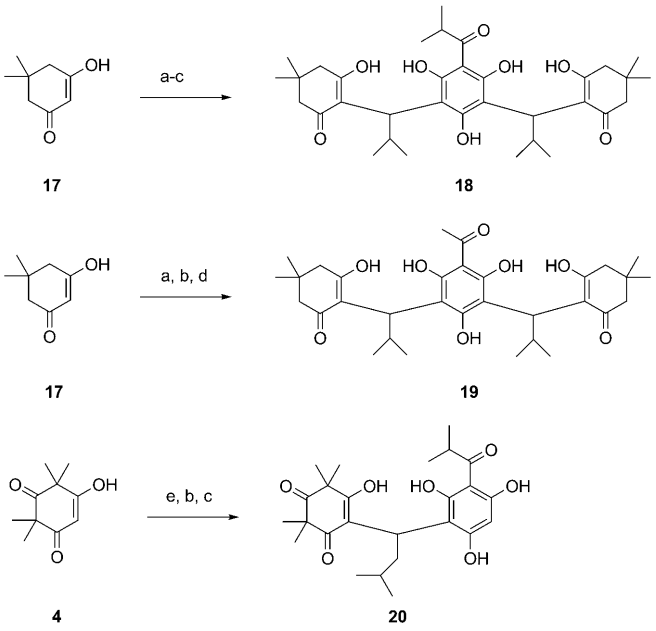


4 13 4 14 15 16

Scheme 5. Syntheses of myrtucommulone F (**13**) and myrtucommulone C (**16**). a) **3**, piperidine, CH_2Cl_2, RT, 15 min; b) HCl/NH_4Cl; c) **12**, NaH (2 equiv), THF, RT, 3 h, quantitative; d) **2**, NaH (2 equiv), THF, RT, 3 h, quantitative; e) *p*TsOH, benzene, reflux, 1 h, 96%.

(Scheme 3) under basic conditions myrtucommulone C (**16**) was obtained, which was recently isolated by Shaheen et al.[5] (Scheme 5).Through the strategy presented here it is possible to vary all three building blocks to synthesize myrtucommulone analogues (Scheme 6).

We determined the efficiency of the synthetic myrtucommulones A and F, and some for inhibition of microsomal prostaglandin E_2 synthase 1 (mPGES-1; anti-inflammatory activity)[20a] and for induction of apoptosis in cancer cells.[20b] In our test systems,[20] myrtucommulone A isolated from myrtle and synthetic myrtucommulone A showed almost identical activity (Table 1).



17 18 17 19 4 20

Scheme 6. Syntheses of the myrtucommulone analogues **18**–**20**. a) **3**, piperidine, CH_2Cl_2, RT, 15 min; b) HCl/NH_4Cl; c) **2**, NaH (2 equiv), THF, RT, 3 h, quantitative; d) acetyl phloroglucinol, NaH (2 equiv), THF, RT, 3 h, 96%; e) isovaleraldehyde, piperidine, CH_2Cl_2, RT, 15 min.

Table 1: IC_{50} values [μM] for suppression of mPGES-1 and EC_{50} values for induction of apoptosis for synthetic and natural myrtucommulone A (**1**), synthetic **13**, derivatives **11a** and **11b**, and myrtucommulone analogues.

Compound	mPGES-1 Inhibition IC_{50} [μM]	Induction of apoptosis EC_{50} [μM]
synthetic **1**	0.7	3.1
natural **1**	1.0	3.2
11a + **11b**	>100	>100
13	0.6	1.3
18	1.8	0.8
19	1.0	n.d.[a]
20	0.4	n.d.[a]

[a] n.d.: not determined.

With our strategy we could synthesize myrtucommulone A (**1**), myrtucommulone F (**13**), and myrtucommulone C (**16**) as mixtures of all stereoisomers. Starting with known compounds, the synthesis consists of only one step (acid-catalyzed reaction) or two steps (base-catalyzed reaction). Research to determine the absolute configuration of natural **1** and to develop a synthesis of enantiomerically pure **1** and further analogues is in progress.

Experimental Section

10: Syncarpic acid (1.1 g, 6 mmol) was suspended in dichloromethane (20 mL) in a 250 mL round-bottom flask. Piperidine (1.2 mL, 2 equiv, 12 mmol) and isobutyraldehyde (822 μL, 1.5 equiv, 9 mmol) were added to this stirred suspension. After 10 min. the reaction mixture was concentrated to dryness (20 Torr, 40 °C). The residue was dissolved in dichloromethane and this solution was stirred vigorously for 15 min with 1N HCl, which had been saturated with NH_4Cl. The phases were separated and the organic layer was dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was removed under reduced pressure. The crude product was filtered through a 5 cm thick pad of silica gel (petroleum ether/acetone 2:1 (v/v)), the eluent was removed by evaporation. The crude product was pure enough to use in the next step and was dissolved in THF (c = 1 mol L^{-1}) under N_2.

1: Sodium hydride (100 mg, 2 mmol, 2 equiv, 60% in mineral oil) was washed two or three times in a dry 50 mL round-bottom flask under N_2, each time with roughly 5 mL THF. The remaining pure NaH was suspended in 5 mL THF. Isobutyryl phloroglucinol (196 mg, 1 mmol, 1 equiv) was added to this suspension, and the mixture was stirred for 5 min at room temperature prior to addition of the solution of the Michael acceptor **10**. Stirring was continued for 3 h, and then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic extracts were dried over $MgSO_4$, the drying agent was removed by filtration, and the volatiles were removed evaporation. The crude product was purified by flash chromatography (silica gel, petroleum ether/acetone 3:2 (v/v), R_f = 0.13). Yield: 665 mg myrtucommulone A (quant.) as a pale yellow solid. Melting range: 150–180 °C.[21] Synthetic and natural myrtucom-

mulone show identical NMR spectra (see the Supporting Information).

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[16] Myrtucommulone A (**1**) is a complex mixture of different rotamers, which are stabilized by intramolecular hydrogen bonds. Additionally, there are probably numerous keto–enol equilibria, which lead to more complex ^{1}H and ^{13}C NMR spectra. Appendino et al.[3a] silylated myrtucommulon A in 23% yield. The silylated derivative could be characterized by NMR spectroscopy. According to these authors, methylation and other derivatization methods led to complete decomposition. Quinn et al.[6] reported recently on detailed 2D NMR studies of **1** and the myrtucommulones F–I. These authors conclude that the relative configuration in **1** for both asymmetric centers is *R**. This is consistent with the formula shown in Ref. [6]. However, later in their publication, these authors state that **1** occurs in the *meso* form and that optical activity is due to atropisomers, which are stabilized by hydrogen bonding. The method for structure elucidation presented here (via **11a** and **11b**) is unambiguous; the derivatization is almost quantitative and thus superior to other methods.

[17] Conditions for preparative HPLC: HPLC setup (Sykam; pump S1521 and detector S3210); column: Macherey–Nagel Nucleodur 100 5C-18 ec, 250 mm length and 21 mm inner diameter; eluent: methanol/water 90:10; flow: 25 mL min^{-1}; room temperature; detection at 210, 254, and 283 nm; retention times t_R(**11a**) = 10.07 min; t_R(**11b**) = 12.58 min. (see the Supporting Information). Interestingly, only linear pentacyclic derivatives formed. Angular derivatives could not be detected.

[18] The ratio between **11a** and **11b** is 54:46 (see the Supporting Information). The double Friedel–Crafts alkylation occurs with low-level simple diastereoselectivity in favor of the chiral myrtucommulone A. To our knowledge, this is the first example of a double intermolecular Friedel–Crafts alkylation, in which a benzylic stereogenic center influences the configuration of the newly formed stereogenic center in *meta* position (see also the Supporting Information and A. J. Lampkins, O. Abdul-Rahim, R. K. Castellano, *J. Org. Chem.* **2006**, *71*, 5815—5818); Diastereoselective Friedel–Crafts alkylations with chiral alkylating reagents have been studied. See for example: a) A. C. Silvanus, S. J. Heffernan, D. J. Liptrot, G. Kociok-Köhn, B. I. Andrews, D. R. Carbery, *Org. Lett.* **2009**, *11*, 1175 – 1178; b) D. Stadler, T. Bach, *Chem. Asian J.* **2008**, *3*, 272 – 284; c) D. Stadler, T. Bach, *Angew. Chem.* **2008**, *120*, 7668 – 7670; *Angew. Chem. Int. Ed.* **2008**, *47*, 7557 – 7559; d) F. Mühlthau, D. Stadler, A. Goeppert, G. A. Olah, G. K. Surya Prakash, T. Bach, *J. Am. Chem. Soc.* **2006**, *128*, 9668 – 9675; e) D. Stadler, F. Mühlthau, P. Rubenbauer, E. Herdtweck, T. Bach, *Synlett* **2006**, 2573 – 2576; f) F. Mühlthau, T. Bach, *Synthesis* **2005**, 3428 – 3436; g) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903 – 2915; h) J. Y. L. Chung, D. Mancheno, P. G. Dormer, N. Variankaval, R. G. Ball, N. N. Tsou, *Org. Lett.* **2008**, *10*, 3037 – 3040; i) *Catalytic Asymmetric Friedel–Crafts Alkylations* (Eds.: M. Bandini, A. Umani-Ronchi), Wiley-VCH, Weinheim, **2009**.

[19] X-ray analysis of **1**: $C_{38}H_{52}O_{10}$, bright yellow crystals, M_r = 667.79 g mol^{-1}; triclinic, space group $P\bar{1}$: a = 10.494(1), b = 12.436(1), c = 14.305(2) Å, α = 81.755(7), β = 89.403(7), γ = 75.669(7)°, V = 1789.5(4) Å^3, Z = 2, μ($Mo_{K\alpha}$) = 1.239 mm^{-1}, T = 120 K, F(000) = 718. Data were collected on a Bruker-AXS X8 Apex diffractometer. 47 122 reflections up to $2\theta_{max}$ = 60° were

registered, of which 10236 independent reflections were used for all calculations. The structure was solved by direct methods and anisotropically refined with all non-hydrogen atoms.[22] The hydrogen atoms were treated as rigid groups with idealized geometry at their carbon atoms. The isopropyl groups C12 and C26 are disordered according to the potential isomers and were refined at split-atom positions. The refinement with $I > 2\sigma(I)$ resulted in a final $R1 = 0.058$, $wR2 = 0.15$. CCDC 640674 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] The catalytic transformation of prostaglandin H_2 to pro-inflammatory prostaglandin E_2 by microsomal prostaglandin E_2 synthase 1 was analyzed in the microsomal preparation of interleukon-1β-stimulated A549 lung epithelial carcinoma cells. See: A. Koeberle, U. Siemoneit, U. Bühring, H. Northoff, S. Laufer, W. Albrecht, O. Werz, *J. Pharmacol. Exp. Ther.* **2008**, *326*, 975–982. The induction of apoptotic cell death of human promyelocytic leukemia cells (HL-60) was analyzed after 24 h incubation by MTT assay. See Ref. [7b].

[21] Recrystallization from methanol yields an amorphous powder with a melting point of 183–185 °C; Ref. [1]: 185–186 °C. Natural **1**, which was not recrystallized from methanol, also showed a melting range from 150–180 °C.

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