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Total Syntheses of Squamocin A and Squamocin D

Ulrich Emde and Ulrich Koert*

Institut für Chemie, Humboldt Universität, Hessische Straße 1-2, D 10115 Berlin

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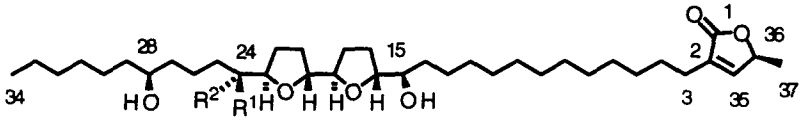
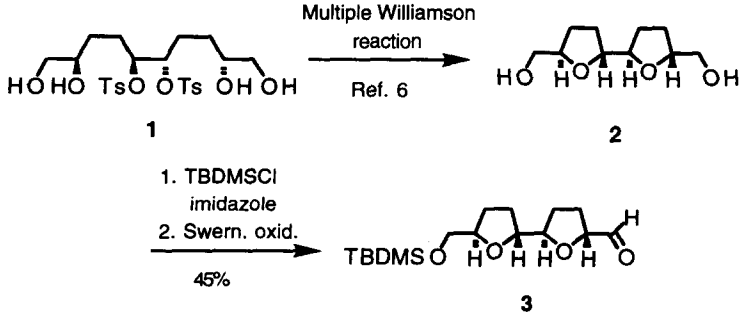
Abstract: The total syntheses of two acetogenins, squamocin A and squamocin D, have been achieved. The adjacent bis-THF subunit was constructed by a multiple Williamson reaction. The left and the right side chain were added by addition of organomagnesium compounds to aldehyde functions. The conversion of a carboxylic acid into the butenolide moiety concluded both syntheses.

Squamocin A and squamocin D belong to a subclass of *Annonaceous acetogenins*[1] with an adjacent bis-THF subunit and an extra hydroxy group in the left side chain (C-28). The relative and absolute configuration of squamocin A[2a] - also called annonin-I[2b] was established by X-ray structural analysis of a degradation product and by spectroscopic studies.[2,3] Squamocin D[4a] - also called asiminacin,[4b] is the C-24 epimer of squamocin A. Its structure was assigned by combined spectroscopic methods.[4] Both natural products show remarkable cytotoxic activity and are interesting antitumor candidates. As mode of action of the *Annonaceous acetogenins* a blockage of mitochondrial complex I is discussed.[1]



Squamocin A R^1 = OH, R^2 = H
Squamocin D R^1 = H, R^2 = OH

The total synthesis of adjacent bis-THF acetogenins is an active field.[5] Here we report on the total syntheses of squamocin A and squamocin D. The bis-THF core with the relative configuration *threo-trans-threo* was constructed by an established multiple Williamson reaction (**1** -> **2**).[6] Monoprotection of **2** followed by oxidation gave the aldehyde **3**.



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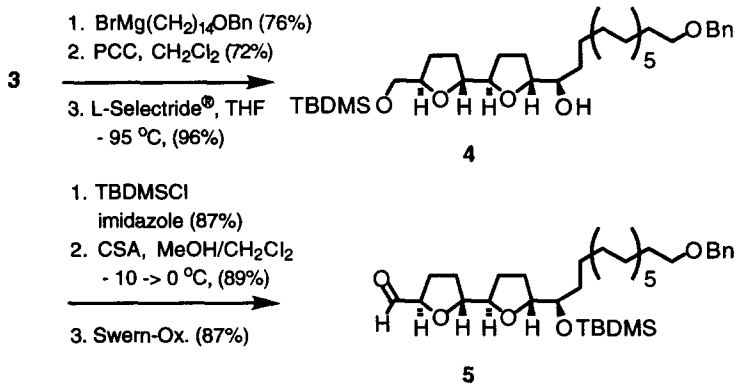
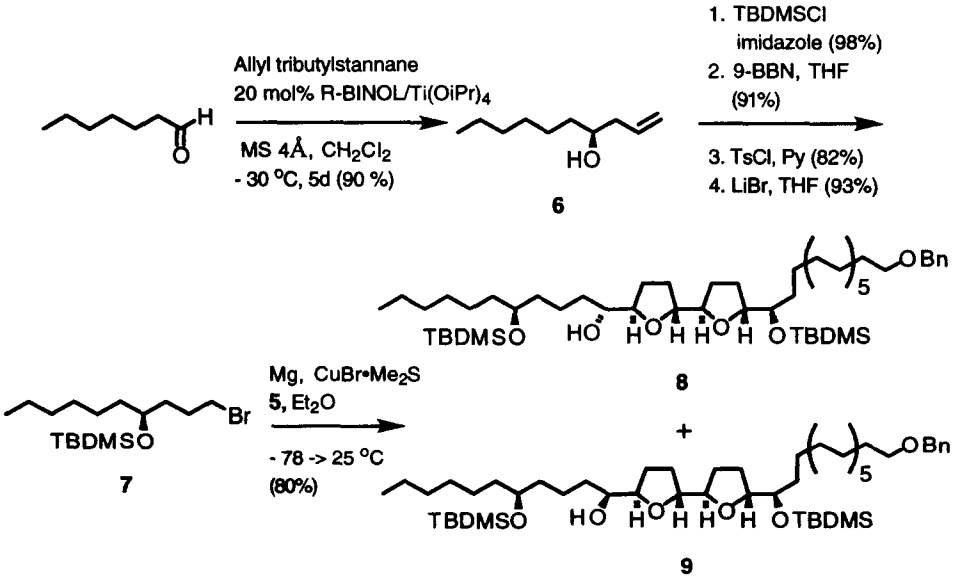
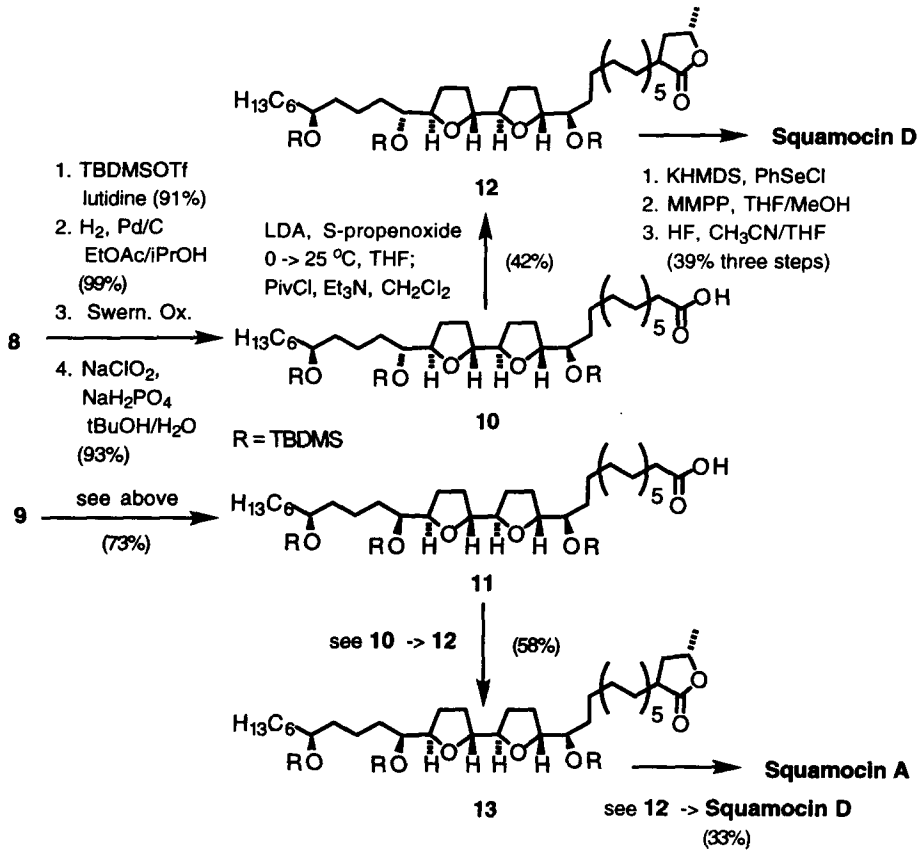
The right side chain was attached by the sequence Grignard addition to **3**, PCC oxidation of the resulting alcohol and stereoselective L-selectride® reduction[7] of the ketone (98:2) leading to the alcohol **4**. The latter could be converted into the aldehyde **5** by standard reactions.



The left side chain with the chiral center at C-28 was addressed next. An enantioselective (96% ee by GC) allylation of heptanal following Keck's procedure[8] produced the alcohol **6**. After TBDMS protection and hydroboration the resulting alcohol was converted into the bromide **7**. The bromide was transformed into the corresponding Grignard reagent, which was allowed to react with the aldehyde **5**. The two epimers **8** and **9**, which were formed in a 2:1 ratio, were separated by SC. The stereochemical assignment of the two epimers was based on the ^{13}C-NMR chemical shift of the new stereocenter (**8**: 74.0 ppm, **9**: 71.2 ppm).



The final synthetic sequence elaborated the butenolide part. Silyl protection of the C-24 hydroxy group and hydrogenolytic cleavage of the benzyl-ether function of **8** and **9** gave two primary alcohols, which were converted into the carboxylic acids **10** and **11**. The dianion of **10** was allowed to react with S-propenoxide. After a mixed anhydride cyclization the γ-lactone **12** was obtained. The C-2-C-35 double bond was introduced by a known selenylation/elimination procedure.[5] Final deprotection of the three silyl ethers gave the target compound squamocin D. Along the same route squamocin A was obtained from the carboxylic acid **11** via the γ-lactone **13**. The spectrocopic data for squamocin A and squamocin D matched the literature data.[9]



In conclusion the total syntheses of two acetogenins, squamocin A and squamocin D, have been achieved. The synthetic strategy allows variations in the left and right side chain and should be useful for the synthesis of pharmacologically interesting analogs.

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9) Spectroscopic data for synthetic squamocin A: $[\alpha]_D$ = + 15; c = 0.08, $CHCl_3$; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86 (t, J = 6.8 Hz, 3H, H-34), 1.22-1.68 (m, 42 H, H-4-14, 25-27, 29-33, H'-17, 18, 21, 22), 1.38 (d, J = 6.8 Hz, 3 H, H-37), 1.91-2.02 (m, 4 H, H''-17, 18, 21, 22), 2.24 (t, J = 7.2 Hz, 2 H, H-3), 3.34-3.42 (m, 1 H, H-15), 3.55-3.66 (m, 2 H, H-24,28), 3.79-3.94 (m, 4 H, H-16, 19, 20, 23), 4.97 (qq, J = 6.8/1.9 Hz, 1 H, H-36), 6.96 (q, J = 1.5 Hz, 1 H, H-35); ^{13}C-NMR (75 MHz, $CDCl_3$): 14.11 (C-34), 19.21 (C-37), 22.00 (C-26), 22.61 (C-33), 25.16 (C-3), 24.82, 25.63, 25.66, 27.39, 28.35, 28.89, 29.1-29.7 signal overlap, 29.72, 31.83 (C-4 to C-13, C-17, C-18, C-21, C-22, C-30 to C-32), 32.52 (C-25), 33.38 (C-14), 37.26, 37.49 (C-27, C-29), 71.38 (C-24), 71.79 (C-28), 74.10 (C-15), 77.4 (C-36), 82.25, 82.50, 82.79, 83.27 (C-16, C-19, C-20, C-23), 134.34 (C-2), 148.83 (C-35), 173.90 (C-1); HRMS:(EI) cal.: 623.4887 (MH^+), found: 623.4897.
Spectroscopic data for synthetic squamocin D: $[\alpha]_D$ = + 20; c = 0.097, $CHCl_3$; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86 (t, J = 6.4 Hz, 3H, H-34), 1.21-1.69 (m, 42 H, H-4-14, 25-27, 29-33, H'-17, 18, 21, 22), 1.38 (d, J = 6.8 Hz, 3 H, H-37), 1.91-2.01 (m, 4 H, H''-17, 18, 21, 22), 2.24 (tt, J = 7.9/1.5 Hz, 2 H, H-3), 3.33-3.42 (m, 2 H, H-15, 24), 3.55-3.60 (m, 1 H, H-28), 3.78-3.89 (m, 4 H, H-16, 19, 20, 23), 4.97 (qq, J = 6.8/1.5 Hz, 1 H, H-36), 6.96 (q, J = 1.5 Hz, 1 H, H-35); ^{13}C-NMR (75 MHz, $CDCl_3$): 14.08 (C-34), 19.22 (C-37), 21.73 (C-26), 22.62 (C-33), 25.17 (C-3), 25.64, 25.65, 27.40, 28.37, 28.93, 28.96, 29.2-29.7 signal overlap, 29.72, 31.84 (C-4 to C-13, C-17, C-18, C-21, C-22, C-30 to C-32), 33.26, 33.45 (C-14, C-25), 37.32, 37.54 (C-27, C-29), 71.80 (C-28), 73.92, 74.10 (C-15, C-24), 77.4 (C-36), 81.76, 81.83 (C-19, C-20), 83.05, 83.20 (C-16, C-23), 134.36 (C-2), 148.82 (C-35), 173.88 (C-1); HRMS:(EI) cal.: 604.4703 (M^+-H_2O), found: 604.4705.