this slice had corresponding protons that, in common, gave trNOEs to $H1^{Fuc}$. In addition, scalar coupling partners were easily identified since the ω_1/ω_2 slice reflected TOCSY pathways. The scalar coupling pattern was attributed to protons pro*R*-$H6^{GlcNAc}$, pro*S*-$H6^{GlcNAc}$, and $H5^{GlcNAc}$, as indicated in Figure 2. It should be emphasized that the intraglycosidic trNOEs between $H2^{Fuc}$ and $H3^{Fuc}$ were also present in this spectrum and overlapped with the pro*R*-$H6^{GlcNAc}$/pro*S*-$H6^{GlcNAc}$ pattern. However, the scalar coupling of the latter two protons to $H5^{GlcNAc}$ at $\delta = 3.51$ allowed a clear discrimination. Inspection of Scheme 2 shows that only a $(1 \rightarrow 6)$ linkage between the two sugar residues explains the observed cross peak pattern.

In summary, a 3D-TOCSY-trNOESY experiment allowed unambiguous identification of the bioactive component of a carbohydrate library without prior knowledge of the individual components of the library. Carbohydrates certainly represent an important class of biological macromolecules[7, 8] but, nonetheless, the experimental protocol described here is not limited to carbohydrate derivatives.

Experimental Section

All spectra were acquired on a Bruker DRX 500 MHz spectrometer with a 5 mm TXI probehead at 306 K. TOCSY and STD-TOCSY were measured with 512 increments and 16 transients using a 50 ms MLEV-17 spinlock field of 7.5 kHz. Saturation transfer was achieved by using 40 selective 270° Gaussian pulses of duration 50 ms and spacing 10 ms. The protein envelope was irradiated at 2.8 ppm (on-resonance) and 40 ppm (off-resonance). Subsequent subtraction of on- and off-resonance spectra was achieved via phase cycling.

For the 3D-TOCSY-trNOESY experiment, 124, 256, and 1014 data points in F1, F2, and F3, respectively, were acquired with eight transients each. The acquisition time was 127 ms, which results in a total relaxation delay of 1.6 s. The total measurment time was approximately five days. The mixing time for the NOESY step was 130 ms. Suppression of zero-quantum coherence[9] was achieved by parallel application of a spinlock field (2.5 ms, 7.5 kHz) and a gradient pulse (2.5 ms, approximately 5 $G\,cm^{-1}$) prior to the NOE mixing time. Signals from HDO were suppressed by presaturation with a weak radio-frequency field.

Received: February 2, 2000 [Z14634]

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Natural-Product Hybrids: Design, Synthesis, and Biological Evaluation of Quinone–Annonaceous Acetogenins**

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The acetogenins of *Annonaceae* are a class of natural products with interesting antitumor, immunosuppressive, pesticide, and antimicrobial activities.[1] Their main mode of action is the inhibition of the mitochondrial complex I (NADH-ubiquinone oxidoreductase).[2] Mucocin[3] and squamocin D[4] are two representative members of the *Annonaceae* acetogenins, which show their characteristic structural features: An ether core consisting of tetrahydrofuran (THF) and tetrahydropyran (THP) rings flanked with a left and a right side chain. At the end of the right side chain is located a butenolide unit. The long alkyl chains place at least parts of the compound in the lipophilic interior of the mitochondrial membrane.[5]

It has been proposed that the annonaceous acetogenins act at the terminal electron-transfer step of complex I between the Fe–S cluster N2 and the ubiquinone pool.[2] The butenolide subunit may bind at the quinone binding site of complex I. The reduction potential of an α-alkyl-α,β-unsaturated butyrolactone ($E_p^c = -2.69$ V (irrev.), CH_3CN, versus the saturated calomel electrode (SCE)) is much more negative than the reduction potentials of the quinone group ($E_p^{cI} = -0.75$ V, $E_p^{cII} = -1.48$ V, CH_3CN, versus SCE).[6] Therefore an electron transfer from the Fe–S cluster N2 to the butenolide is unlikely to occur. With the goal to further elucidate the mechanism of action of the acetogenins and to provide molecular probes for complex I studies we designed quinone–mucocin **1** and quinone–squamocin D **2**. In these compounds the butenolide part of mucocin and squamocin D is exchanged against the quinone part of ubiquinone. Here we

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[**] This work was supported by the Deutsche Forschungs-gemeinschaft, Fonds der Chemische Industrie, and ASTA-Medica AG.

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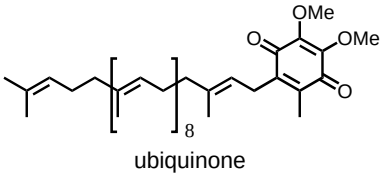
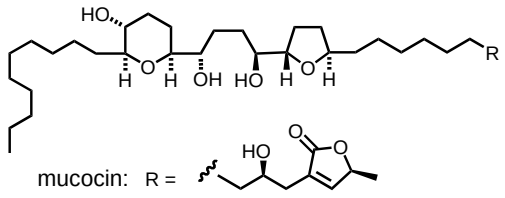
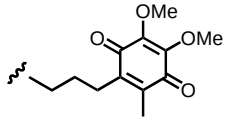


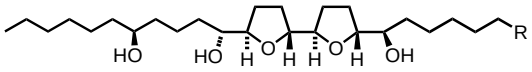
ubiquinone



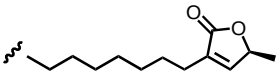
mucocin: R =

1: R =

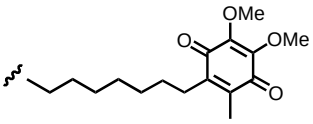


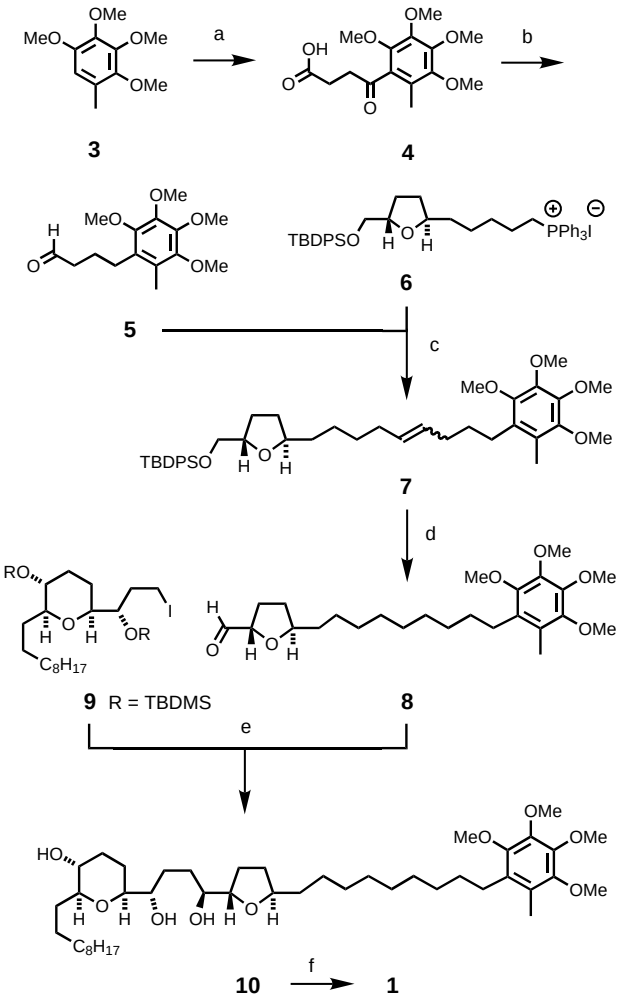


squamocin D: R =



2: R =





Scheme 1. a) *n*BuLi, TMEDA, *n*-hexane, 0 °C, 30 min, succinic anhydride, THF, 2 h, 63 %; b) 1. $LiAlH_4$, THF, 3 h, 72 %; 2. Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 12 h, 88 %; 3. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −40 °C, 2.5 h, 78 %; c) **6**, NaHMDS, THF, 0 °C, 20 min; **5**, 0 °C, 1 h, 87 %; d) 1. Pt/C, H_2, EtOAc, 6 h, 97 %; 2. nBu_4NF, THF, 2.5 h, 95 %; 3. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −40 °C, 1.5 h, 89 %; e) 1. **9** (1.3 equiv), *t*BuLi (2.4 equiv), Et_2O, −105 °C, 4 min, $MgBr_2 \cdot OEt_2$ (2.8 equiv), −100 → −40 °C (2 h) → −78 °C, **8** (1 equiv) → −10 °C, 2 h, 47 %, diastereoselectivity 7:1, chromatographic separation of the epimers; 2. HF, CH_3CN/CH_2Cl_2, 1 h, 90 %; f) 2,6-pyridinedicarboxylic acid, CAN, CH_3CN/H_2O, 0 °C, 4 h, 68 %. TBDPS = *tert*-butyldiphenylsilyl, TMEDA = tetramethylethylenediamine, NaHMDS = sodium hexamethyldisilazide, CAN = Cer(IV) ammonium nitrate.

report on the first synthesis of this novel type of hybrid compounds as well as on their interaction with mitochondrial complex I.

The syntheses of **1** and **2** build upon the modular strategy developed for our total syntheses of mucocin[7] and squamocin D.[8] *ortho*-Lithiation of 2,3,4,5-tetramethoxytoluene (**3**)[9] and reaction with succinic anhydride gave the oxocarboxylic acid **4** (Scheme 1). Reduction with $LiAlH_4$ provided a diol, whose benzyl alcohol function was removed by reduction with $Et_3SiH/BF_3 \cdot OEt_2$.[10] A subsequent Swern oxidation to the aldehyde **5** followed by a Wittig reaction with the phosphonium salt **6**[11] delivered the olefin **7**, which was transformed into the aldehyde **8** by a standard sequence. A chelation-controlled addition of an organomagnesium compound prepared from the iodide **9**[7a,b] by iodine lithium exchange/transmetalation to the aldehyde **8** gave, after removal of the *tert*-butyldimethylsilyl (TBDMS) protecting groups, the triol **10**. Oxidation of the tetramethoxytolyl subunit with ceric ammonium nitrate (CAN)[12] yielded the target compound quinone–mucocin **1** (Table 1).

The starting point for the synthesis of quinone–squamocin D (**2**) was the aldehyde **11** (Scheme 2). Its reaction with lithiated compound **3** gave **12**, which was converted into the iodide **13**. Iodine–metal exchange and addition to the aldehyde **14**[13] gave after oxidation/L-selectride reduction and removal of the TBDMS groups the triol **15**. A CAN oxidation of **15** yielded the target compound quinone–squamocin D (**2**, Table 1).

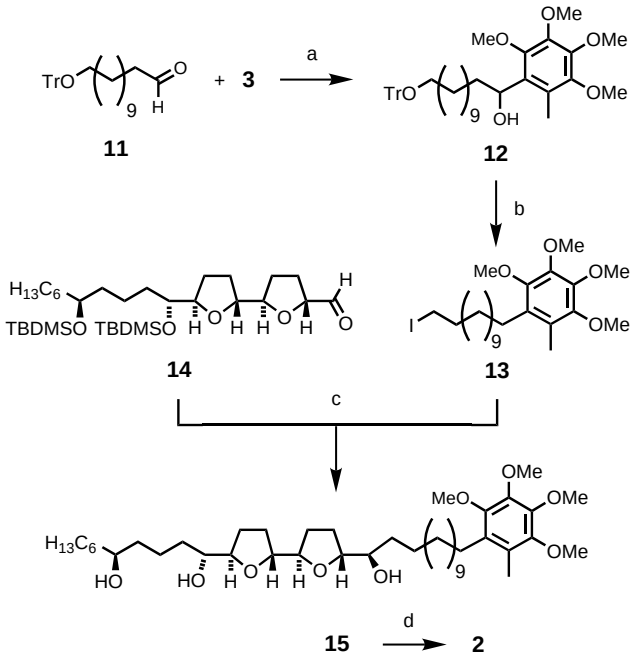
The synthetic compounds **1**, **2**, **10**, and **15** were tested as inhibitors of complex I (bovine-heart mitochondrial; Table 2).[14–16] The known strong inhibitor rotenon (IC_{50} = 1.0 nM) was used as a reference sample.[2] It was found that quinone–mucocin (**1**, IC_{50} = 3.6 nM) was ten times more active than mucocin itself (IC_{50} = 33 nM). In contrast the hydroquinone–mucocin dimethyl ether (**10**) was a weaker inhibitor than the natural product. Quinone–squamocin D (**2**) and its hydroquinone-dimethyl ether (**15**) also displayed activities in the nanomolar range (IC_{50} = 1.7 and IC_{50} = 4.7 nM, respectively). These results show that natural-product hybrids **1** and **2** are very potent inhibitors of mitochondrial

  0570-0833/00/3912-2100 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 12

Table 1. Selected analytical and spectroscopical data of compounds **1** and **2**.

1: $[\alpha]_D^{22} = -20.5$ ($c = 0.044$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.4$ Hz, 3H, 34-H_3), 1.13–1.88 (m, 42H, alkyl), 1.89–2.14 (m, 3H, 13, 14, 22-H_2), 1.99 (s, 3H, 35-Me), 2.42 (t, $J = 6.8$ Hz, 2H, 3-H_2), 2.69 (br s, 1H, OH), 2.82 (br s, 1H, OH), 3.02 (dt, $J = 8.8$, 2.2 Hz, 1H, 24-H), 3.08–3.18 (m, 1H, 20-H), 3.18–3.32 (m, 1H, 23-H), 3.34–3.52 (m, 2H, 16, 19-H), 3.71–3.90 (m, 2H, 12, 15-H), 3.96 (s, 6H, 37, 38-OMe); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.9$ (35-Me), 14.1 (C-34), 22.7, 25.5, 26.2, 26.4, 26.9, 28.3, 28.3, 28.7, 28.7, 29.3, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8, 31.9, 32.0, 32.4, 32.6, 35.6, (C-3 to C-11, C-13, C-14, C-17, C-18, C-21, C-22, C-25 to C-33), 61.1 (37, 38-OMe), 70.6 (C-23), 73.5 (C-19), 73.8 (C-16), 79.3 (C-12), 80.1 (C-20), 81.9 (C-15), 82.0 (C-24), 138.6, 143.1, 144.3 (C-2, C-35, C-37, C-38), 184.2, 184.7 (C-1, C-36); HR-MS (EI): calcd for $C_{41}H_{72}O_9$ ($[M^+ + 2H]$): 708.5176; found: 708.5166.

2: $[\alpha]_D^{22} = +3.1$ ($c = 0.13$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 6.6$ Hz, 3H, 34-H_3), 1.20–1.67 (m, 42H, 4-CH_2 to 14-H_2, 17-H′, 18-H′, 21-H′, 22-H′, 25-H_2 to 27-H_2, 29-H_2 to 33-H_2), 1.89–2.10 (m, 4H, 17-H″, 18-H″, 21-H″, 22-H″), 1.99 (s, 3H, 39-H_3), 2.42 (t, $J = 6.4$ Hz, 2H, 3-H_2), 3.37–3.53 (m, 2H, 15-H, 24-H) overlap with 3.53–3.62 (m, 1H, 28-H), 3.84–3.98 (m, 10H, 16-H, 19-H, 20-H, 23-H, 2 × OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.9$ (CH_3–39), 14.1 (C-34), 21.4 (C-26), 22.6 (C-33), 25.4, 25.7, 26.4, 28.67, 28.74, 29.4, 29.5, 29.6, 29.7, 29.9, 31.9 (C-3 to C-13, C-17, C-18, C-21, C-22, C-30 to C-32), 32.6 (C-25), 33.1 (C-14), 36.8, 37.7 (C-27, C-29), 61.2 (OCH_3), 71.7 (C-28), 74.4, 74.7 (C-15, C-24), 81.7, 81.8, 82.9, 83.0 (C-16, C-19, C-20, C-23), 138.7, 143.1, 144.2 (C-2, C-35, C-37, C-38), 184.2, 184.7 (C-1, C-36); HR-MS: (EI): calcd: 708.5176 ($[M + 2H]^+$); found: 708.5177.



Scheme 2. a) *n*BuLi, TMEDA, *n*-hexane, 0 °C, 2.5 h, 54 %; b) 1. Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 →20 °C, 14 h, 81 %; 2. I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 4 h, 65 %; c) 1. **13**, *t*BuLi, $MgBr_2 \cdot Et_2O$, Et_2O, −100 → −40 → −78 °C, **14**, −78 →0 °C, 3.5 H, 52 %; 2. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −60 → −40 °C, 1.5 h, 96 % ; 3. L-selectride, THF, −100 → −70 °C, 1.5 h, 99 %, diastereoselectivity 88:12, separation of the epimers by chromatography; 4. 5 % HF in CH_3CN, THF, 20 °C, 1.5 h, 77 %; d) CAN, 2,6-pyridinedicarboxylic acid, 0 °C, 4 h, 70 %. Tr = triphenylmethyl.

complex I. The structural similarity between the butenolide and the quinone led to the assumption that both groups interact in a similar way with the ubiquinone reduction site in complex I[2b] and previous studies postulated that the annonaceous acetogenins are competitive inhibitors at the ubiquinone binding site of complex I.[2c] Our data support this hypothesis, although other structural features may also contribute, since the IC_{50} of quinone **2** and hydroquinone dimethyl ether **15** are in the same range. It has been demonstrated that the quinone-binding site in complex I is quite large, probably occupied by both acetogenin subunits, the butenolide as well as the THF/THP part.[14a]

Table 2. Inhibition of mitochondrial complex I by natural acetogenins and synthetic analogues.

Compound	IC_{50} [nm][a]	IC_{50} [μmol/ mg protein][a]	IC_{50} [μmol/ mg protein][b]
mucocin	34	45	33.3
1	3.6	4.9	
10	123	163	
squamocin D	–	–	8.7
squamocin A	1.0	1.3	
2	1.7	2.3	
15	4.7	6.2	
rotenone	1	1.3	

[a] Bovine-heart mitochondria were prepared as described before.[15] The inhibition of oxygen uptake was measured. The respiratory activities were analyzed with a Clark-type oxygen electrode (100 mm sodium phosphate pH = 7.4, 1 mm *N*,*N*,*N*′,*N*′-ethylenediaminetetraacetic acid (EDTA), 1 mm $MgCl_2$, 0.5 mg mL^{-1} protein).[16] [b] Literature data.[14b]

Natural-product hybrids of type **1** and **2** should be useful molecular probes for further investigations of the ubiquinone binding site of complex I. In particular a more detailed look at the redox properties of the system complex I/quinone annonaceous acetogenin seems promising. The new modular synthetic approach presented here allows the efficient access to quinone–annonaceous hybrids with different quinone moieties and different redox properties.

Received: February 14, 2000 [Z 14696]

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Synthesis of Trioxane Using Heteropolyacids as Catalyst

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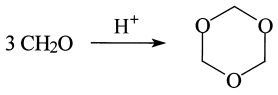
Acetal resin is a term used to describe the high molecular weight polymers and the copolymers of formaldehyde. First commercialized as a homopolymer in 1960 by DuPont, acetal resins are engineering thermoplastics which have found broad use in areas where traditionally metals were applied.[1] Shortly thereafter, researchers at Celanese developed an acetal resin based on the copolymerization of trioxane and cyclic ethers, such as ethylene oxide.[2] In 1962 a commercial plant began producing this acetal copolymer. Since then, a rapid expansion of acetal resin production has occurred worldwide.

Up to 1971 DuPont and Celanese (alone or in joint ventures with other companies) were the sole producers of acetal resins. In 1972 Asahi Chemical started to produce the acetal homopolymer utilizing the world's third type of polyacetal technology.[3] Asahi Chemical also industrialized the acetal copolymer in 1985.[4] At present, the annual demand of acetal resins in the world is about 400000 t per year.

The biggest problem in the case of acetal resins is the energy consumption during its production. The main aspect is the energy requirement in the monomer process. For example, it requires a great deal of energy to get the monomeric trioxane that is needed for the acetal copolymer from aqueous formaldehyde. In the commercial process, trioxane is obtained by heating aqueous formaldehyde in the presence of an acid catalyst like sulfuric acid [Eq. (1)].



(1)

Even though the equilibrium concentration of trioxane is low in the reaction mixture, in the commercial production process trioxane is removed as the distillate from the reaction mixture in the distillation tower.[5] The vapor–liquid equilibrium between trioxane and aqueous formaldehyde is such that when the trioxane concentration in the liquid phase is low, trioxane shows a very high volatility compared to formaldehyde and water in the vapor phase. Thus, almost all the trioxane contained in the vapor phase from the reaction mixture can be concentrated into the distillate in the distillation tower under the proper refluxing conditions. Since the heat of vaporization of the water–formaldehyde mixture is much higher than that of trioxane,[6] most of the energy for trioxane synthesis is consumed in the vaporization of water and formaldehyde.[7] From the viewpoint of the energy requirement, the key point of the trioxane synthesis is the high yield and high selectivity in a one-pass vaporization.

At Asahi Chemical, we developed the *tert*-butyl alcohol process, that is the selective hydration of isobutene using a highly concentrated heteropolyacid as the catalyst.[8] We also developed a new process for producing polyoxytetramethylene glycol with a narrow molecular weight distribution using a heteropolyacid as a catalyst for the polymerization of tetrahydrofuran.[9, 10] With this knowledge, we investigated the catalytic activity of heteropolyacids for the synthesis of trioxane. We observed some interesting phenomena and a superior advantage of heteropolyacids over conventional catalysts like sulfuric acid.

The results for the reaction at atmospheric pressure and 100 °C are shown in Table 1. The best features of using the heteropolyacid, instead of sulfuric acid, as a catalyst for trioxane synthesis were the higher conversion and selectivity. For example, for the same selectivity of 97%, the conversion by sulfuric acid was 20%, while the conversion by the heteropolyacid was 27% (drawn from entries 10 and 6 respectively in Table 1). Heteropolyacids provided a 35% higher yield (yield = conversion × selectivity) than sulfuric acid. A similar result was also obtained for the hydration of isobutene.[8] In this case, high selectivity of heteropolyacids was reported to be related to the big size of their anions.

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