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Total Synthesis of 3-Oxo- and 3β-Hydroxytauranin via Negishi Coupling of a Bis(*ortho*-oxy)-Functionalized Benzyl Chloride

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The first asymmetric synthesis of the sesquiterpene quinones 3-oxo- and 3β-hydroxytauranin (**1**, **2**) was achieved and the originally proposed structure of 3α-hydroxytauranin was revised. The protected benzyl chloride **5** was obtained in six steps starting from 4-bromo-3,5-dihydroxybenzoic acid (**8**) via a highly scalable approach. The troublesome Negishi coupling of the benzyl chloride **5** with alkenyldimethylalane **6** was optimized to furnish *all-trans*-farnesylarene **14** in very good yield. This prenylated arene was transformed in six additional steps to 3β-hydroxytauranin (**2**). Finally, a new convenient access to propargylated terpenes without using dry cryogenic ammonia and gaseous allene or propyne is described.

Introduction

Sesquiterpene quinones and hydroquinones possess many of interesting pharmacological activities. Avarol and avarone inhibit the reverse transcriptase of the HIV-virus and in this way the replication of the AIDS virus is suppressed.[1a] Ilimaquinone shows an inhibition of the RNase-H-function of the HIV-1 reverse transcriptase[1b] and the tubulin-polymerization.[1c] Bolinaquinone, 21-dehydrobolinaquinone, and dysidine possess inhibitory activity against hPTP1B, a potential drug target for treatment of type-II diabetes and obesity.[1d] Yahazunol, cyclozonarone, spongiaquinone and hyatellaquinone show good cytostatic/cytotoxic activity against the tumour cell lines HM02 (gastric adenocarcinoma), HepG2 (hepatocellular carcinoma), and MCF7 (breast carcinoma).[1e] Wiedendiol B exhibits a strong and selective cyclooxygenase-2 (COX2) inhibition. COX2 inhibitors are drugs with antiphlogistic and antirheumatic activities.[1f]

Gunatilaka's group claimed to have isolated the sesquiterpene quinones tauranin, 3-oxotauranin (**1**), 3α-hydroxytauranin, and 14-hydroxytauranin (Figure 1) from *Phyllostigta spinarum*, a fungal strain endophytic in *Platycladus orientalis* from the Sonoran Desert. Tauranin shows apoptotic activity toward several human solid tumor cell lines.[1g] Analyzing the ^{1}H NMR spectroscopic data of 3α-hydroxytauranin[1g] it is obvious that the reported coupling constants of the proton in position 3 (δ = 3.29 ppm, dd, $J_{2ax,3ax}$ = 11.3 Hz, $J_{2eq,3ax}$ = 4.3 Hz) are in agreement with the 3β-epimer of **2** (Figure 1). The 3-H signal of 3β-

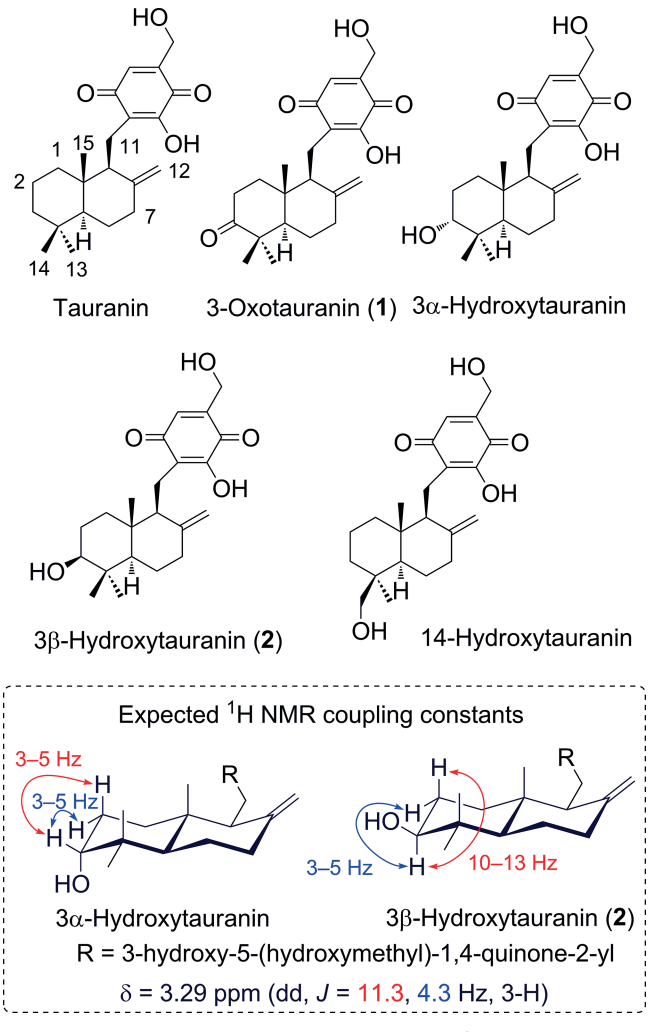

Figure 1. Structures of tauranins and expected ^{1}H NMR coupling constants.

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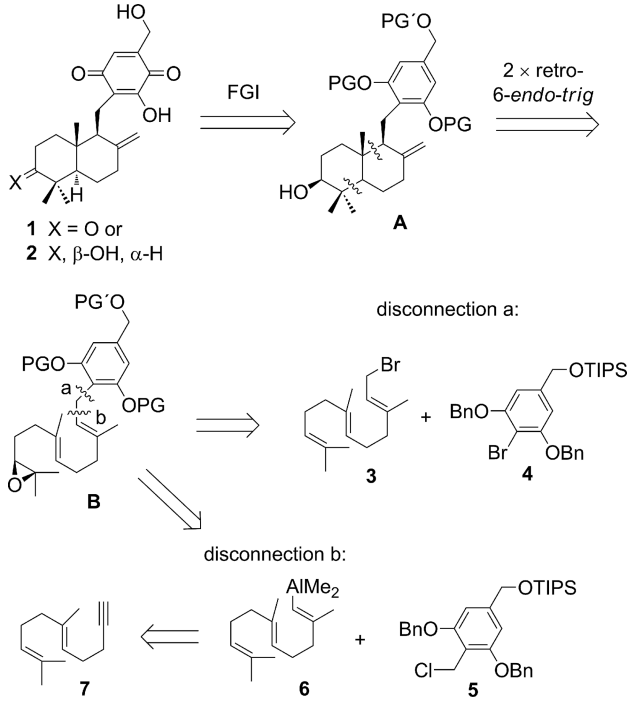
hydroxyalbicanyl acetate shows very similar coupling constants (δ = 3.25 ppm, dd, $J_{2ax,3ax}$ = 11.4 Hz, $J_{2eq,3ax}$ = 4.3 Hz).[1h] Our goal was to develop a straightforward synthesis of both 3-oxo- and 3β-hydroxytauranin (**1**, **2**). The NMR spectroscopic data and optical rotations of compounds **1** and **2** should be compared with those of the natural products to confirm their correct structures and absolute configurations. Furthermore, 3-oxo- and 3β-hydroxytauranin (**1**, **2**) should be tested for their pharmacological activities as cytostatic/cytotoxic, antiphlogistic, antirheumatic, and anti-inflammatory.

Almost all total syntheses of sesquiterpene quinones use the direct disconnection between an arene chore and the bicyclic sesquiterpene moiety.[2] This approach usually demand a protected terpenoid, whose asymmetric de novo synthesis is often cumbersome. Commonly functional group interconversions (FGI) or deprotections are necessary to manipulate the sesquiterpene chore in the desired manner. This is especially difficult in the case of in position 3 functionalized terpenes.

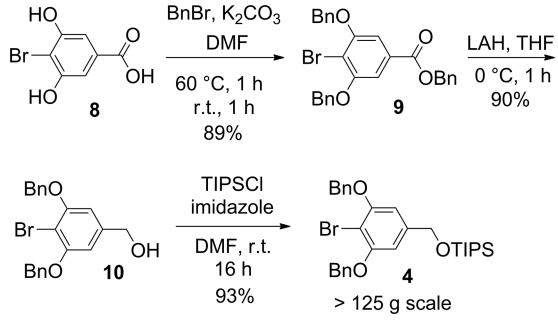
Results and Discussion

We employed a bioinspired and more convenient approach and retrosynthetically reduced the quinonic chore to the orthogonally protected 3β-hydroxyalbicanylresorcin **A** (Scheme 1). Double retrosynthetic ring opening between the positions 4,5 and 9,10 of **A** resulted in (*S*)-epoxide **B**. Our methodology offers two further disconnections as shown in Scheme 1. Disconnection a leads to farnesylbromide (**3**) and aryl bromide **4** and disconnection b to alkenyldimethylalane **6** and benzyl chloride **5**.



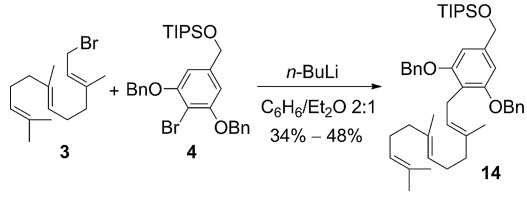
Scheme 1. Retrosynthesis of 3-oxo- and 3β-hydroxytauranin (**1**, **2**).

Pursuing disconnection a we examined the lithiation of aryl bromide **4**. The required aryl bromide **4** was prepared from 4-bromo-3,5-dihydroxybenzoic acid (**8**) by benzylation to yield the ester **9**[3a–3c] (Scheme 2). Reduction of **9** with $LiAlH_4$ gave benzylic alcohol **10**[3a] which was protected with TIPSCl to **4**.[3c,3d] This procedure is highly scalable as no chromatography is needed and all intermediates can be purified by crystallization on a multigram scale. All conversions are almost quantitative and the overall yield of 74% over three steps is justified by waste of product due to crystallization.



Scheme 2. Synthesis of the aryl bromide **4**.

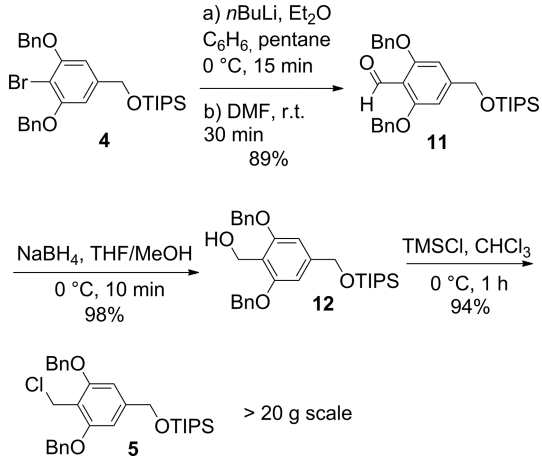
Many attempts to lithiate the benzyl-protected arene **4** showed that *n*BuLi in a very apolar solvent mixture (benzene and Et_2O) is crucial for a clean conversion.[3e] Subsequent coupling with farnesyl bromide (**3**) led mainly to elimination products besides the desired prenylated arene **14** in 34% to 48% yield (Scheme 3).



Scheme 3. Synthesis of the coupling product **14**.

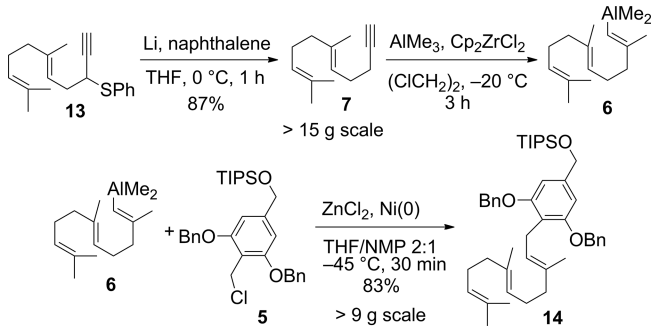
For this reason disconnection b was chosen (Scheme 1). The Pd-catalyzed Negishi coupling of benzyl chlorides has been explored by Negishi.[4a] Lipshutz studied and improved it by using a Ni^0 catalyst and broadened the scope to highly electron rich benzyl chlorides, which could be coupled in excellent yields.[4b–4g] For this approach the necessary benzyl chloride **5** could be obtained via an optimized lithium–halogen exchange of the aryl bromide **4** with *n*BuLi and subsequent reaction with DMF to provide the aldehyde **11** (Scheme 4).[5a] The formyl group of **11** was reduced with $NaBH_4$ to the benzylic alcohol **12**[5b] which was transformed with TMSCl to the benzyl chloride **5**.[5c] The elaborated approach is also highly scalable since all products were purified by crystallization on a multigram scale.

The most frequently applied method to obtain propargylated prenyls is the elongation of the corresponding prenyl halide with lithiated 1-(trimethylsilyl)propyne and subsequent desilylation[4e] or nucleophilic substitution of the latter halide with a dilithiated species derived from gaseous allene[6a] or propyne.[4g] The former reaction leads to byproducts which are difficult to separate.[4g] Concerning the



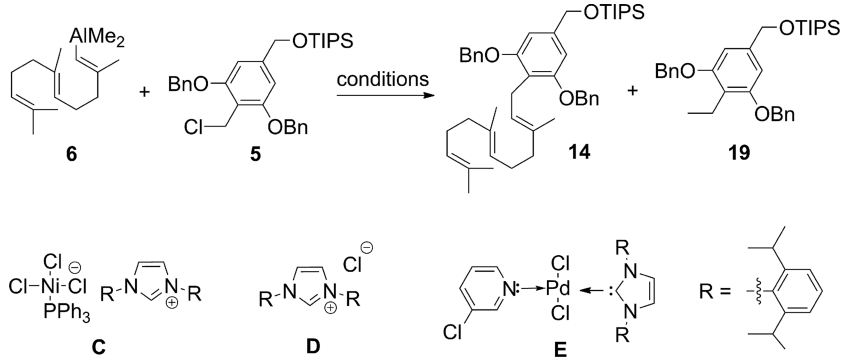
Scheme 4. Synthesis of the benzyl chloride **5**.

latter reaction, the handling and availability of gaseous allene or propyne is difficult, so we attempted to improve a protocol developed by Negishi, which exploits dilithiated phenyl propargyl thioether as a nucleophile.[6b] This procedure uses a reductive desulfurization of the anion derived from **13** (Scheme 5) with lithium in anhydrous ammonia.[6b] Since the drying of cryogenic liquid ammonia is cumbersome and the water content is crucial for a clean conversion of the phenyl thioether **13** to the alkyne **7**, we looked for a more appropriate procedure. We found that the reductive desulfurization with catalytic amounts of naphthalene and lithium dust[6c] resulted in a clean conversion and gave the desired alkyne **7** (Scheme 5) after 1 h at 0 °C with a 87% yield after distillation on a 100 mmol scale.



Scheme 5. Synthesis of the Negishi coupling product **14**.

Table 1. Screening of Negishi coupling conditions.



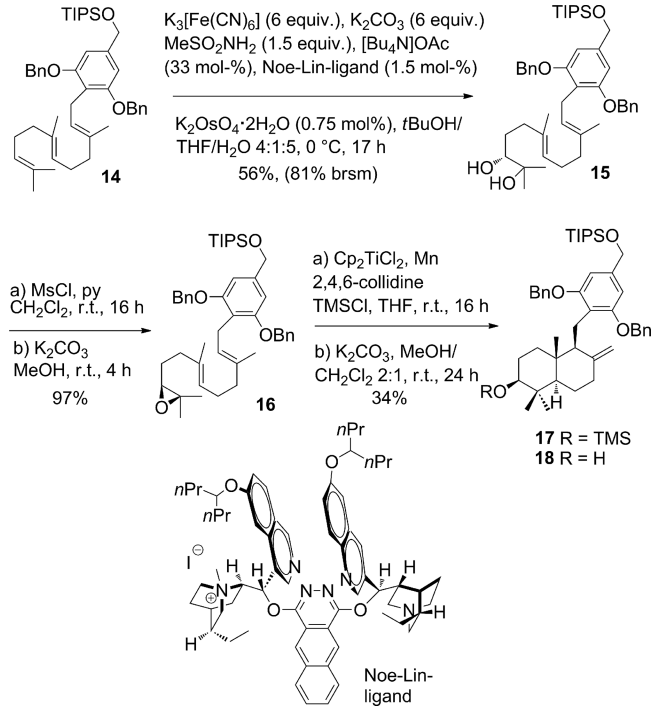
Entry[a]	MX[b]	Conditions, catalyst [mol-%][c]	Conversion[d]
1	none	$Pd(PPh_3)_4$ (5)	2%
2	none	$Ni(PPh_3)_2Cl_2$, 2 BuLi (5)	69% (30%)
3	none	Ni(dppp)[e]Cl_2, 2 BuLi (5)	11% (10%)
4	$ZnCl_2$[f]	$Ni(PPh_3)_2Cl_2$, 2 BuLi (5)	55% (8%)
5	$ZnCl_2$	$Ni(PPh_3)_2Cl_2$, 2 BuLi (5)	66%
6	$ZnCl_2$	$Ni(acac)_2$, 2 PPh_3, 2 DIBAL (5)	67%
7	$InCl_3$	$Ni(acac)_2$, 2 PPh_3, 2 DIBAL (5)	49%
8	$ZnCl_2$	$Ni(acac)_2$, 2 PPh_3, 2 DIBAL (2)	55%
9	$ZnCl_2$	$Ni(acac)_2$, 2 P(*o*-tol)$_3$, 2 DIBAL (2)	18%
10	$ZnCl_2$	**C** (3)	32%
11	$ZnCl_2$	$Ni(acac)_2$, 2 IPr·HCl (**D**), 4 DIBAL (3)	28%
12	$ZnCl_2$	$Pd(PPh_3)_2Cl_2$, 2 BuLi (5)	8%
13	$ZnCl_2$	Pd(dppf)[g]Cl_2, 2 DIBAL (3)	19%
14	$InCl_3$	Pd(dppf)Cl_2, 2 DIBAL (3)	3%
15	$ZnCl_2$, LiBr[h]	PEPPSI-IPr (**E**) (3) in THF/NMP 2:1	14% (4%)
16	$ZnCl_2$	$Ni(acac)_2$, 2 PPh_3, 2 DIBAL (25)	72%
17	$ZnCl_2$	$Ni(acac)_2$, 2 PPh_3, 2 DIBAL (40)	40%
18	$ZnCl_2$	$Ni(acac)_2$, 2 PPh_3, 2 DIBAL (40) in THF/NMP 2:1	54%
19	$ZnCl_2$	$Ni(acac)_2$, 2 PPh_3, 2 DIBAL (15) in THF/NMP 2:1 at –45 °C	83%

[a] All reaction were performed with 1 mmol benzyl chloride **5** and 1.4 mmol carboaluminated alkyne **6** in 5 mL of THF at room temp. (unless otherwise stated). [b] Added metal salt (MX) based on amount of alane **6**. Unless stated otherwise 1.05 equiv. $ZnCl_2$ respectively 0.34 equiv. $InCl_3$ were used. [c] Amount of catalyst based on amount benzyl chloride **5** is given in parenthesis. [d] Determined by ^{1}H-NMR of the crude reaction mixture, yield of ethylbenzene **19** is given in parenthesis. [e] dppp = 1,3-bis(diphenylphosphanyl)propane. [f] 0.45 equiv. $ZnCl_2$ were used. [g] dppf = 1,1-bis(diphenylphosphanyl)ferrocene. [h] 2.0 equiv. LiBr was added.

Thus we developed a new convenient method for the multigram preparation of propargylated terpenes without using time-consuming manipulations. Compound **7** reacted with $Cp_2ZrCl_2/AlMe_3$ to the alkenyldimethylalane **6**.[4a]

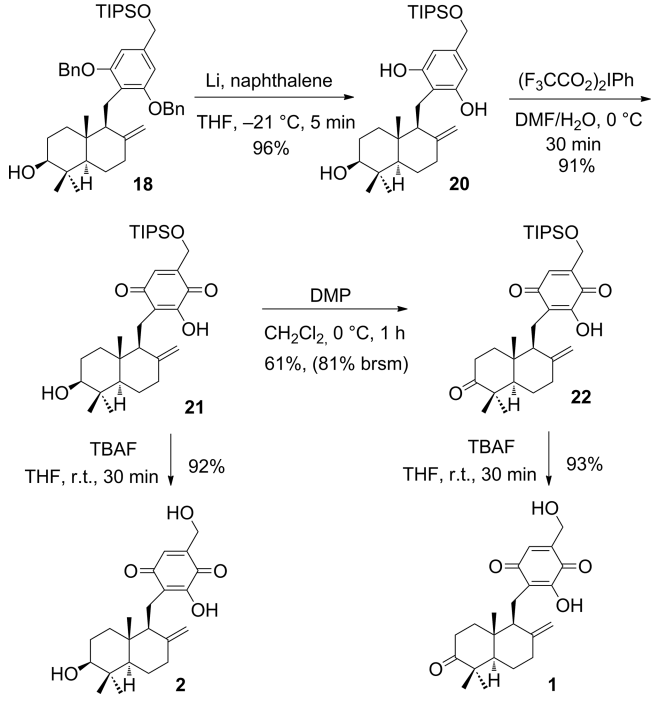
With the two building blocks **5** and **6** in our hands we performed the standard Negishi coupling protocol of Lipshutz[4d] to obtain the prenylated arene **14** (Scheme 5). We observed that in our case a large amount of the corresponding ethylbenzene derivative **19** is produced via methyl transfer from the alkenyldimethylalane **6** to the benzyl chloride **5** (Table 1, entry 2). This is the first bis(*ortho*-oxy)-substituted benzyl chloride coupled in a Negishi fashion as well as the first described methyl transfer in such a case. Since the ethylbenzene **19** has the same polarity as the required prenylated arene **14** and is not separable by standard column chromatography, it was highly desirable to suppress its formation. Therefore we screened different catalyst systems and reaction conditions. As Lipshutz already stated $Pd(PPh_3)_4$ catalysis (entry 1) is less efficient.[4b,4c] The use of Ni^0 catalyst obtained by treatment of $Ni(dppp)Cl_2$ with BuLi led to the formation of the ethylbenzene derivative **19** together with the prenylated arene **14**, both of them with poor yields of 10% and 11% (entry 3). Changes introduced in the preparation of the Ni^0 catalyst either by addition of PPh_3, tri(*o*-tolyl)phosphane [P(*o*-tol)$_3$][7a] (entry 9) or and reducing agents such as DIBAL,[4b–4d] transmetallation of the carboalumination product either by addition of $ZnCl_2$[7b] or $InCl_3$,[7c,7d] or the addition of precatalysts **C**,[7e] **D**, **E**[7f,7g] (entries 10, 11, 15) did not provide any better results in the first attempts, but suppressed the formation of the unwanted ethylbenzol **19**. However, larger amounts of Ni^0 catalyst derived from $Ni(acac)_2$, PPh_3 and DIBAL, increased the yields to a certain extent (entries 16–17). Moreover, the change of solvent from THF to THF/NMP, 2:1 at –45 °C[4f] gave the desired product **14** with an acceptable yield of 83% (entry 19).

The asymmetric Sharpless dihydroxylation[8a] of **14**[8b] with Noe-Lin-ligand[8c–8e] to **15** was difficult because of solubility problems and produced 26% of (*R*)-glycol **15** plus a huge amount of overoxidized byproducts after 2 d under standard conditions (Scheme 6). After numerous efforts, we found that making use of THF as less polar cosolvent, tetrabutylammonium acetate as a phase-transfer catalyst,[8f] and the addition of K_2CO_3 (6 equiv.), $K_3[Fe(CN)_6]$ (6 equiv.) and methanesulfonamide (1.5 equiv.) furnished the desired (*R*)-glycol **15** with a 56% yield, which represented 81% yield based on the recovered starting material (brms) with an enantiomeric ratio of 95:5.[8g] Mesylation of the secondary alcohol function of **15** and basic cyclization with K_2CO_3 in MeOH furnished the desired (*S*)-10,11-epoxyfarnesylarene **16** in a one pot reaction with 97% yield.[8d] The resulting (10*S*,2*E*,6*E*)-10,11-epoxyfarnesylarene **16** was subjected to a known bioinspired Ti^{III}-mediated cyclization cascade[9a–9j] to give 3β-trimethylsilyloxyalbicanylarene **17**.[9i,9j] Since the TIPS group was partially removed via the standard deprotection protocol with TBAF,[9a–9j] we used a selective TMS deprotection method making use of K_2CO_3 in MeOH/DCM to afford **18** with 34% yield.



Scheme 6. Synthesis of 3β-hydroxyalbicanylarene **18**; yields in parenthesis are based on the recovered starting material.

The debenzylation of **18** under gentle conditions with lithium naphthalide at –21 °C yielded the desired resorcine **20**[10] (Scheme 7) in an almost quantitative yield. Attempts to oxidize the resorcine moiety to the 2-hydroxyquinone motif with salcomine [*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II)] in DMF,[11a,11b] MeCN or MeOH under



Scheme 7. Synthesis of 3-oxo- and 3β-hydroxytauranin (**1, 2**); yields in parenthesis are based on the recovered starting material.

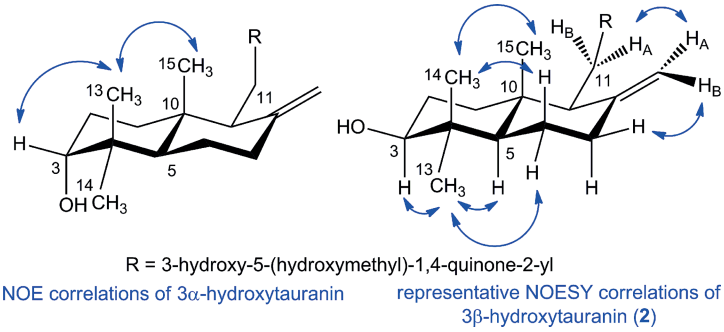


Figure 2. NOE correlations of 3α-hydroxytauranin and NOESY correlations of 3β-hydroxytauranin (2).

an O_2 atmosphere were disappointing and afforded **21** with 10–40% yields after 36 h in addition to several overoxidized byproducts. Several attempts to perform the oxidation with IBX (2-iodoxybenzoic acid) in DMF,[11c] CAN in MeCN/H_2O,[11d] PCC/H_5IO_6 in MeCN,[11e,11f] were not satisfying and showed a tendency towards oxidative destruction of the already formed quinonic moiety. Oxidation with PIFA [(bis(trifluoroacetoxy)iodo)benzene] in MeCN/H_2O, 2:1 at 0 °C[11g] was more promising, but led to several byproducts. Fortunately, changing the solvent system to DMF/H_2O furnished the desired quinone **21** with an excellent yield (91%).

Finally, TBAF promoted TIPS[12a] deprotection led to the isolation of 3β-hydroxytauranin (**2**) with 92% yield. No oxidation of an alcohol function besides the oxidation labile 2-hydroxyquinone moiety is reported in literature. The Dess–Martin-periodinan (DMP) oxidation[12b] of the secondary alcohol moiety of **21** to ketone **22** was stopped after a reaction time of 1 h at 0 °C due to oxidative destruction of the quinonic motif. In this way, the TIPS protected ketone **22** could be obtained with 61% yield, which represented 81% yield brsm (based on the recovered starting material). Treatment of the isolated ketone **22** with TBAF in THF furnished 3-oxotauranin (**1**) with an excellent yield (93%).

NOE correlations of 3α-hydroxytauranin were obtained in the Gunatilaka group by 1D NOE measurements.[1g] Irradiation of the signal at δ = 0.98 ppm (CH_3-13) showed enhancements of the signals at δ = 0.76 ppm (CH_3-15) and 3.29 ppm (3-H_{eq}) indicating that the both methyl groups and 3-H are on the same side of the molecule. Since CH_3-15 is β-oriented, CH_3-13 and 3-H must also be β-oriented (Scheme 2). The chemical shifts for the signals of CH_3-15 and CH_3-14 are δ = 0.76 ppm and δ = 0.77 ppm. This means, the assumed NOE CH_3-15/CH_3-13 is actually the NOE CH_3-13/CH_3-14. The NOESY correlations CH_3-13/5-H and CH_3-13/6-H_{eq} of 3β-hydroxytauranin (2) showed the α-orientation of CH_3-13. Due to the NOESY correlation CH_3-13/3-H_{ax} the hydroxy group of 2 is β-oriented (Figure 2).

Conclusions

We developed a bioinspired approach for the straightforward synthesis of 3-oxo- and 3β-hydroxytauranin (**1**, **2**). The NMR spectroscopic data of both compounds **1** and **2** matched those reported by Wijeratne et al.[1g] The optical rotation of 3-oxotauranin (**1**) ($[\alpha]_D^{23}$ = –160, $CHCl_3$) showed reasonable agreement with the value reported in the literature ($[\alpha]_D^{23}$ = –130.2, $CHCl_3$). The absolute value for 3β-hydroxytauranin (**2**) ($[\alpha]_D^{23}$ = –149, $CHCl_3$) is similar to that reported by Wijeratne et al.[1g] ($[\alpha]_D^{23}$ = +139.5, $CHCl_3$) but of opposite sign. Since compounds **1** and **2** were derived from the same precursor **21**, the sign of the optical rotation of the natural product **2** must be wrong. In summary we showed that the natural product isolated from *Phyllostigta spinarum* has indeed a 3β-configuration and is not 3α-hydroxytauranin as proposed by Wijeratne et al.[1g] According to our interpretation of NMR spectroscopic data for 3-oxotauranin (**1**) and 3β-hydroxytauranin (**2**) the revised NMR assignments for both natural products can be found in the supplement. The incorrect assignment of both methyl groups 13 and 14 in compound **1** and 3α-hydroxytauranin suggests also, that the postulated natural product has to be 13- and not 14-hydroxytauranin (Figure 1). Furthermore, a new convenient access to propargylated terpenes on a multigram scale without using dry cryogenic ammonia and gaseous allene or propyne has been demonstrated.

Experimental Section

General: All moisture or oxygen sensitive reactions were performed in oven-dried glassware under an argon atmosphere using standard Schlenk techniques. Unless otherwise stated silica gel (Macherey–Nagel, particle size 40–63 μm) was used for column chromatography. The oxidation labile 2-hydroxyquinones were handled under an inert gas atmosphere and frozen in a benzene matrix at –21 °C for longer storage. Optical rotations of these compounds have to be measured direct after purification. Melting points were determined in open capillary tubes with a Büchi M-565 melting point apparatus. Mass spectra were measured on an Orbitrap Elite (Thermo Fisher Scientific) mass spectrometer (HRMS, ESI). NMR spectroscopic data were recorded under conditions as indicated with a Bruker Avance 300 and a Bruker Avance-III-HD 500 spectrometer. Solvent signals were used as internal standard (^1H = 7.26 ppm and ^{13}C = 77.0 ppm for $CDCl_3$; ^1H = 2.05 ppm and ^{13}C = 29.8 ppm for [D_6]acetone). Multiplicity m_c = centered multiplet.

Benzyl 3,5-Bis(benzyloxy)-4-bromobenzoate (9): A solution of **8** (69.90 g, 300.0 mmol) in DMF (250 mL) was prepared in a three-

neck flask equipped with a dropping funnel and a KPG stirrer under an inert gas atmosphere. Finely divided K_2CO_3 (165.8 g, 1.200 mol) was added in small portions. Then benzyl bromide (121.3 mL, 1.020 mol) was added under vigorous stirring in a manner to keep the reaction temperature at about 60 °C (0.5–1 h). After one further hour of stirring at room temperature a highly viscous suspension has formed due to crystallization of the product **9**. To induce further crystallization H_2O (300 mL) was added within 15 min whilst stirring and the resulting suspension was poured into H_2O (1 L). The white solid was collected by suction filtration and washed with H_2O (3 × 500 mL) and pentane (2 × 300 mL). After drying at 40 °C and 7 mbar the crude product was recrystallized from hexanes/MTBE/$CHCl_3$ to yield the title compound **9** (134.9 g, 266.9 mmol, 89%). R_f = 0.24 (10% EtOAc/hexanes), m.p. 134.1 °C (hexanes/MTBE/$CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 5.21 (s, 4 H), 5.36 (s, 2 H), 7.33–7.37 (m, 4 H), 7.38–7.45 (m, 9 H), 7.49–7.53 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 67.0, 70.9, 107.3, 108.3, 127.0, 128.0, 128.1, 128.3, 128.5, 128.6, 129.9, 135.7, 136.1, 156.1, 165.7 ppm. ESI-HRMS: calcd. for $[C_{28}H_{23}O_4{}^{79}Br + H]^+$: *m*/*z* = 503.0852; found *m*/*z* = 503.0853.

[3,5-Bis(benzyloxy)-4-bromophenyl]methanol (10): A solution of **9** (121.8 g, 242.3 mmol) in THF (600 mL) was chilled in an ice bath and LAH (14.47 g, 381.3 mmol) was added in small portions. After stirring for 1 h Me_2CO (50 mL) was added and the reaction was stirred for further 15 min. Then MTBE (800 mL) was added and the reaction was quenched by addition of 5 M HCl (400 mL, 2.00 mol). After the precipitate has dissolved H_2O (400 mL) was added and the layers were separated. The aqueous phase was extracted one further time with MTBE (500 mL), the combined organic phases were washed with brine and dried with $MgSO_4$. After removal of the solvent the obtained crude product was purified by recrystallization from hexanes/MTBE/$CHCl_3$ to furnish the desired benzyl alcohol **10** (87.14 g, 218.2 mmol, 90%). R_f = 0.29 (40% EtOAc/hexanes), m.p. 123.0 °C (hexanes/MTBE/$CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.95 (t, *J* = 5.7 Hz, 1 H), 4.56 (d, *J* = 5.7 Hz, 2 H), 5.14 (s, 4 H), 6.61 (s, 2 H), 7.33 (m_c, 2 H), 7.40 (m_c, 4 H), 7.49 (m_c, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 64.9, 70.7, 101.1, 104.6, 126.9, 127.8, 128.5, 136.4, 141.6, 156.2 ppm. ESI-HRMS: calcd. for $[C_{21}H_{19}O_3{}^{79}Br + H]^+$: *m*/*z* = 399.0590; found *m*/*z* = 399.0592.

[3,5-Bis(benzyloxy)-4-bromobenzyloxy]triisopropylsilane (4): To a solution of benzyl alcohol **10** (99.82 g, 250.0 mmol) and imidazole (18.72 g, 275.0 mmol) in DMF (250 mL) TIPSCl (57.33 mL, 270.0 mmol) was added. After stirring for 16 h at room temperature the reaction mixture was partitioned between hexanes (750 mL) and H_2O (750 mL) and the aqueous phase was extracted with hexanes (500 mL). The combined organic phases were washed with brine (250 mL) and dried with $MgSO_4$. After evaporation of the solvent the crude product was crystallized from hexanes to furnish the title compound **4** (129.5 g, 233.1 mmol, 93%). R_f = 0.42 (5% MTBE/hexanes), m.p. 66.6 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.13 (d, *J* = 6.6 Hz, 18 H), 1.17–1.25 (m, 3 H), 4.80 (s, 2 H), 5.21 (s, 4 H), 6.72 (s, 2 H), 7.35 (m_c, 2 H), 7.43 (m_c, 4 H), 7.54 (m_c, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.9, 17.9, 64.5, 70.6, 100.2, 103.7, 126.7, 127.6, 128.4, 136.6, 142.4, 156.0 ppm. ESI-HRMS: calcd. for $[C_{30}H_{39}O_3{}^{79}BrSi + H]^+$: *m*/*z* = 555.1925; found *m*/*z* = 555.1912.

2,6-Bis(benzyloxy)-4-[(triisopropylsilyloxy)methyl]benzaldehyde (11): Aryl bromide **4** (25.25 g, 45.44 mmol) was dissolved in Et_2O (100 mL), C_6H_6 (35 mL) and pentane (250 mL). *n*BuLi (19.8 mL, 2.41 M in hexane, 47.7 mmol) was added dropwise within 10 min under an inert gas atmosphere at 0 °C. After stirring for 15 min DMF (4.11 mL, 53.4 mmol) was added dropwise during 5 min. The reaction mixture was allowed to come to room temperature within 25 min and then half saturated NH_4Cl solution (250 mL) was added. After separation of phases the aqueous phase was extracted with MTBE (250 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After evaporation of all volatiles the crude product was filtered through a plug of silica (h = 5 cm) eluting with 15% MTBE/hexanes. Removal of solvent and fractional crystallization from hexanes yielded the desired benzaldehyde **11** (20.42 g, 40.46 mmol, 89%). R_f = 0.27 (15% MTBE/hexanes), m.p. 60.7 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.08 (d, *J* = 6.7 Hz, 18 H), 1.13–1.20 (m, 3 H), 4.80 (s, 2 H), 5.20 (s, 4 H), 6.69 (s, 2 H), 7.32 (m_c, 2 H), 7.40 (m_c, 4 H), 7.48 (m_c, 4 H), 10.65 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.8, 17.9, 64.6, 70.3, 102.2, 113.6, 126.8, 127.8, 128.5, 136.3, 150.7, 161.2, 188.8 ppm. ESI-HRMS: calcd. for $[C_{31}H_{40}O_4Si + H]^+$: *m*/*z* = 505.2769; found *m*/*z* = 505.2763.

{2,6-Bis(benzyloxy)-4-[(triisopropylsilyloxy)methyl]phenyl}methanol (12): To a solution of benzaldehyde **11** (35.38 g, 70.10 mmol) in THF/MeOH (60 mL, 5:1) $NaBH_4$ (2.686 g, 70.10 mmol) was added at 0 °C. After stirring for 10 min at 0 °C the reaction mixture was concentrated and partitioned between MTBE (500 mL) and half saturated NH_4Cl (300 mL). After separation of the phases the aqueous phase was extracted once more with MTBE (150 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After removal of solvent the crude product was crystallized from hexanes to furnish the title compound **12** (34.86 g, 68.79 mmol, 98%). R_f = 0.36 (20% EtOAc/hexanes), m.p. 51.2 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.13 (d, *J* = 6.8 Hz, 18 H), 1.17–1.25 (m, 3 H), 2.60 (br. s, 1 H), 4.84 (s, 2 H), 4.93 (s, 2 H), 5.15 (s, 4 H), 6.72 (s, 2 H), 7.36 (m_c, 2 H), 7.42 (m_c, 4 H), 7.47 (m_c, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.9, 18.0, 55.0, 64.8, 70.2, 102.4, 116.0, 127.1, 127.8, 128.5, 136.8, 143.3, 157.4 ppm. ESI-HRMS: calcd. for $[C_{31}H_{42}O_4Si + Na]^+$: *m*/*z* = 529.2745; found *m*/*z* = 529.2726.

[3,5-Bis(benzyloxy)-4-(chloromethyl)benzyloxy]triisopropylsilane (5): Benzylic alcohol **12** (20.94 g, 41.32 mmol) was dissolved in $CHCl_3$ (30 mL) and chilled in an ice bath. TMSCl (12.09 mL, 95.02 mmol) was added within 5 min under an inert gas atmosphere and the reaction mixture was stirred for 1 h. The turbid reaction mixture was partitioned between hexanes (500 mL) and half saturated $NaHCO_3$ (300 mL) solution. After separation of the phases the organic phase was washed with brine and dried with $MgSO_4$. Removal of all volatiles yielded the desired benzyl chloride **5** (21.70 g, 41.32 mmol, 100%) as a highly viscous oil or a white solid in quantitative yield. This crude product is pure enough and can be used directly for the next step. Due to its limited shelf life in the liquid state it is recommended to crystallize the title compound. Crystallization from pentane afforded benzyl chloride **5** as colorless crystals (20.36 g, 38.77 mmol, 94%), which were stored in a brown glass flask for half a year, without any notable decomposition. R_f = 0.55 (5% MTBE/hexanes, decomposition), m.p. 71.2 °C (pentane). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.11 (d, *J* = 6.8 Hz, 18 H), 1.15–1.24 (m, 3 H), 4.82 (s, 2 H), 4.93 (s, 2 H), 5.18 (s, 4 H), 6.68 (s, 2 H), 7.35 (m_c, 2 H), 7.43 (m_c, 4 H), 7.51 (m_c, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.9, 18.0, 36.1, 64.8, 70.1, 102.2, 113.1, 127.0, 127.8, 128.5, 136.9, 144.6, 157.5 ppm. ESI-HRMS: calcd. for $[C_{31}H_{41}ClO_3Si - Cl]^+$: *m*/*z* = 489.2819; found *m*/*z* = 489.2812 CHN-Analysis: calcd. C 70.89%, H 7.87%; found C 70.97%, H 7.875.

(*E*)-6,10-Dimethylundeca-5,9-dien-1-yne (7): To a vigorous stirred mixture of lithium dust (11.10 g, 1.600 mol) and naphthalene

(1.025 g, 8.000 mmol) in THF (150 mL) propargyl phenyl thioether **13** (28.45 g, 100.0 mmol) in THF (25 mL) was added over 30 min at 0 °C under an inert gas atmosphere. After stirring for 1 h the starting material was consumed (TLC or GC judgment) and the reaction mixture was decanted into a vigorous stirred suspension of ice cold hexanes (600 mL) and half saturated NH_4Cl (350 mL). The surplus lithium dust was washed twice with MTBE (2 × 50 mL) and the supernatant liquid was added to the hexane suspension. After separation of the phases the organic phase was washed twice with 1 M KOH (2 × 250 mL) and then with brine (250 mL). The crude extract was dried with $MgSO_4$ and all volatiles were removed under reduced pressure. Distillation (78 °C at 10^{-3} mbar) of the residue yielded the desulfurized alkyne **7** (15.39 g, 87.29 mmol, 87%). $R_{f'}$ = 0.22 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.60 (m_c, 3 H), 1.62 (m_c, 3 H), 1.68 (m_c, 3 H), 1.94 (t, J = 2.5 Hz, 1 H), 1.97–2.02 (m, 2 H), 2.04–2.11 (m, 2 H), 2.17–2.26 (m, 4 H), 5.09 (m_c, 1 H), 5.18 (tq, J = 6.8, 1.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 16.0, 17.6, 18.9, 25.6, 26.5, 27.1, 39.6, 68.1, 84.4, 122.4, 124.1, 131.3, 136.6 ppm.

{3,5-Bis(benzyloxy)-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl]benzyloxy}triisopropylsilane (14): Cp_2ZrCl_2 (1.637 g, 5.600 mmol) was dissolved in 1,2-dichloroethane (20 mL) under an inert gas atmosphere and cooled to 0 °C. $AlMe_3$ (3.225 mL, 33.60 mmol) was added dropwise followed by addition of H_2O (4.2 μL, 233 μmol). After stirring at room temperature for 15 min the mixture was cooled to –20 °C and alkyne **7** (3.949 g, 22.40 mmol) was added. After 2–3 h the carboalumination is complete (TLC or GC-judgment) and all volatiles were removed in vacuo (10^{-3} mbar, 30 °C). To ensure that all $AlMe_3$ has been removed hexanes (15 mL) were added and the solvents evaporated. To isolate the obtained alane **6** pentane (15 mL) was added and the obtained suspension filtered under an inert gas atmosphere to remove the zirconium salts. After removal of solvent a freshly prepared $ZnCl_2$ solution (26.0 mL, 1.0 M in THF, 26.0 mmol) was added at 0 °C. Meanwhile Ni(acac)$_2$ (616.6 mg, 2.400 mmol) and PPh_3 (1.259 g, 4.80 mmol) was dissolved in THF (16 mL) and DIBAL (4.00 mL, 1.2 M in PhMe, 4.80 mmol) was added dropwise at 0 °C under an inert gas atmosphere to obtain the active catalyst as a deep red-brown solution. A solution of benzyl chloride **5** (8.403 g, 16.00 mmol) in THF (10 mL) was added dropwise and the now deep green-blue solution was stirred for 5 min. The reaction mixture was cooled to –45 °C and NMP (28 mL) was added. The previously prepared solution containing the organometallic species **6** was added dropwise and the solution was warmed to room temperature within 30 min. After stirring for 15 min at room temperature the reaction was carefully aborted by addition of aqueous citric acid solution (200 mL, 30% m/v). After the precipitate has dissolved the mixture was partitioned between hexanes (500 mL) and H_2O (250 mL). The aqueous phase was extracted with hexanes (250 mL) and the combined organic extracts were washed with brine and dried with $MgSO_4$. After removal of solvents flash chromatography (silica gel, 15% to 40% C_6H_6/hexanes) yielded the desired title compound **14** (9.062 g, 13.31 mmol, 83%). $R_{f'}$ = 0.28 (25% C_6H_6/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.29 (d, J = 6.6 Hz, 18 H), 1.31–1.39 (m, 3 H), 1.75–1.79 (m, 6 H), 1.85 (m_c, 3 H), 1.87 (m_c, 3 H), 2.11–2.31 (m, 8 H), 3.71 (d, J = 7.0 Hz, 2 H), 4.98 (s, 2 H), 5.25–5.34 (m, 6 H), 5.53 (tq, J = 7.0, 1.2 Hz, 1 H), 6.84 (s, 2 H), 7.46 (m_c, 2 H), 7.53 (m_c, 4 H), 7.61 (m_c, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 12.0, 15.9, 16.1, 17.6, 18.0, 22.5, 25.6, 26.7, 39.7, 39.8, 65.0, 70.0, 102.5, 117.3, 123.1, 124.4, 127.0, 127.5, 128.3, 130.9, 134.2, 134.5, 137.5, 140.6, 157.1 ppm. ESI-HRMS: calcd. for $[C_{45}H_{64}O_3Si + H]^+$: m/z = 681.4697; found m/z = 681.4670.

(*R*,6*E*,10*E*)-12-{2,6-Bis(benzyloxy)-4-[(triisopropylsilyloxy)-methyl]phenyl}-2,6,10-trimethyldodeca-6,10-diene-2,3-diol (15): A mixture of finely divided K_2CO_3 (9.81 g, 71.0 mmol), finely grounded $K_3[Fe(CN)_6]$ (23.4 g, 71.1 mmol), methanesulfonamide (1.69 g, 17.8 mmol), tetrabutylammonium acetate (1.19 g, 3.95 mmol), Noe-Lin-ligand (210 mg, 178 μmol) and $K_2OsO_4{\cdot}2H_2O$ (34.7 mg, 88.8 mmol) was chilled in an ice bath and H_2O (59 mL) and *t*BuOH (47.2 mL) was added. After stirring for 5 min the ligand has dissolved and a solution of farnesyl arene **14** (8.06 g, 11.8 mmol) in THF (11.8 mL) was added. After vigorous stirring at 0 °C for 17 h saturated solutions of Na_2SO_3 (150 mL) and $Na_2S_2O_3$ (150 mL) were added. The reaction mixture was warmed to room temperature and stirring was continued for further 45 min. The reaction mixture was extracted three times with ethyl acetate (500 mL, 2 × 150 mL) and the combined organic phases were washed with brine. Evaporation of all volatiles yielded a highly viscous crude product, which was put on a plug of silica (ø = 6 cm, h = 5 cm) and eluted with 40% Me_2CO/hexanes (500 mL) to obtain a fraction containing residual starting material, product, and overoxidized byproducts. Elution with (25% MeOH/NH_4OH [9:1]/$CHCl_3$) recovered Noe-Lin-ligand (197 mg, 167 μmol, 93%). Flash chromatography of the product **15** containing fraction (silica gel, 7.5% Me_2CO/hexanes to 15% Me_2CO/hexanes) yielded the starting material **14** (2.50 g, 3.67 mmol) besides the desired glycol **15** (4.72 g, 6.60 mmol, 56%, 81% brsm). $R_{f'}$ = 0.28 (25% Me_2CO/hexanes). $[\alpha]_D^{23}$ = +6.9 (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.09–1.24 (m, 27 H), 1.42 (m_c, 1 H), 1.51–1.67 (m, 7 H), 1.93–2.55 (m, 8 H), 3.34 (dd, J = 10.4, 2.0 Hz, 1 H), 3.50 (d, J = 7.0 Hz, 2 H), 4.81 (s, 2 H), 5.12 (s, 4 H), 5.20 (tq, J = 10.4, 2.0 Hz, 1 H), 5.32 (tq, J = 7.0, 1.3 Hz, 1 H), 6.67 (s, 2 H), 7.29–7.49 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 12.0, 15.9, 16.0, 18.0, 22.4, 23.2, 26.6, 29.6, 36.7, 39.8, 65.0, 70.1, 72.9, 78.2, 102.6, 117.3, 123.1, 125.2, 127.1, 127.6, 128.3, 134.2, 134.6, 137.5, 140.6, 157.1 ppm. ESI-HRMS: calcd. for $[C_{45}H_{66}O_5Si + Na]^+$: m/z = 737.4572; found m/z = 737.4541.

[3,5-Bis(benzyloxy)-4-{(2*E*,6*E*)-9-[(2*S*)-3,3-dimethyloxiran-2-yl]-3,7-dimethylnona-2,6-dienyl}benzyloxy]triisopropylsilane (16): To a solution of glycol **15** (5.45 g, 7.62 mmol) in CH_2Cl_2 (36.5 mL) and pyridine (14.6 mL) methanesulfonyl chloride (1.15 mL, 14.9 mmol) was added at 0 °C under an inert gas atmosphere. The reaction was warmed to room temperature and stirred for 16 h. After dilution with MeOH (170 mL) finely divided K_2CO_3 (4.74 g, 34.3 mmol) was added and the suspension was vigorously stirred at room temperature for 4 h. After the bulk of volatiles were removed the mixture was partitioned between MTBE (250 mL) and H_2O (200 mL). The aqueous phase was extracted with MTBE (150 mL) and the combined organic phases were dried with $MgSO_4$. After evaporation of the solvent the crude product was filtered through a plug of silica gel (h = 5 cm, ø = 4 cm) eluting with 12.5% MTBE/hexanes to obtain the title compound **16** (5.14 g, 7.37 mmol, 97%). $R_{f'}$ = 0.45 (12.5% MTBE/hexanes). $[\alpha]_D^{23}$ = –2.1 (c = 0.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.11 (d, J = 6.8 Hz, 18 H), 1.15–1.22 (m, 3 H), 1.26 (s, 3 H), 1.31 (s, 3 H), 1.55–1.62 (m, 4 H), 1.64–1.69 (m, 4 H), 1.96–2.01 (m, 2 H), 2.03–2.17 (m, 4 H), 2.70 (t, J = 6.3 Hz, 1 H), 3.50 (d, J = 7.0 Hz, 2 H), 4.81 (s, 2 H), 5.12 (s, 4 H), 5.17 (tq, J = 7.0, 1.2 Hz, 1 H), 5.32 (tq, J = 7.0, 1.2 Hz, 1 H), 6.67 (s, 2 H), 7.33 (m_c, 2 H), 7.39 (m_c, 4 H), 7.46 (m_c, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 12.0, 15.9, 16.1, 18.0, 18.7, 22.4, 24.9, 26.7, 27.4, 36.2, 39.8, 58.2, 64.2, 65.0, 70.1, 102.6, 117.3, 123.1, 125.1, 127.1, 127.6, 128.4, 133.8, 134.2, 137.6, 140.7, 157.1 ppm. ESI-HRMS: calcd. for $[C_{45}H_{64}O_4Si + Na]^+$: m/z = 719.4466; found m/z = 719.4445.

(2*S*,4a*R*,5*S*,8a*R*)-5-{2,6-Bis(benzyloxy)-4-[(triisopropylsilyloxy)-methyl]benzyl}-1,1,4a-trimethyl-6-methylenedecahydronaphthalen-2-ol (18): A mixture of Mn-dust (3.141 g, 57.17 mmol) and Cp_2TiCl_2 (355.8 mg, 1.429 mmol) in carefully degassed THF (90 mL) was prepared under an inert gas atmosphere at room temperature. The resulting deep red suspension was stirred for about 20 min until the color faded to greyish green. TMSCl (3.62 mL, 28.6 mmol) and 2,4,6-collidine (6.62 mL, 50.0 mmol) were added simultaneously and the resulting greyish brown suspension was stirred for 5 min. A solution of epoxide **16** (4.981 g, 7.146 mmol) in degassed THF (5 mL) was prepared at room temperature and added to the reaction mixture. The flask was rinsed twice with THF (2× 2 mL) to ensure complete transfer and the suspension was stirred for further 16 h. After chilling the reaction mixture in an ice bath 1 M HCl (125 mL, 125 mmol) was added slowly to dissolve the surplus Mn and the reaction mixture was partitioned between MTBE (500 mL) and H_2O (350 mL). After extraction with MTBE (3× 250 mL) the combined organic extracts were washed with brine and dried with $MgSO_4$. All volatiles were removed under reduced pressure and the obtained highly viscous oil was redissolved in MeOH/DCM (2:1, 30 mL) and finely divided K_2CO_3 (9.876 g, 71.46 mmol) was added. After vigorous stirring at room temperature for 24 h TLC analysis showed disappearance of the nonpolar TMS protected intermediate and the reaction mixture was partitioned between MTBE (300 mL) and H_2O (150 mL). The aqueous phase was extracted with MTBE (2× 250 mL), the combined organic extracts were washed with brine and dried with $MgSO_4$. After evaporation of all volatiles the crude product was purified by flash chromatography (Merck LiChroprep® Si 60 [15–25 μm], 12.5% to 20% MTBE/hexanes) to furnish the title compound **18** (1.712 g, 2.456 mmol, 34%). $R_{f'}$ = 0.17 (20% MTBE/hexanes). $[a]_D^{23}$ = –21.3 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.73 (s, 3 H), 0.74 (s, 3 H), 0.88–0.97 (m, 2 H), 0.95 (s, 3 H), 1.11 (d, *J* = 6.7 Hz, 18 H), 1.14–1.23 (m, 3 H), 1.35 (dddd, *J* = 12.9, 12.9, 12.9, 4.1 Hz, 1 H), 1.40–1.50 (m, 2 H), 1.63–1.71 (m, 2 H), 1.89 (ddd, *J* = 12.9, 12.9, 4.7 Hz, 1 H), 2.29 (ddd, *J* = 12.9, 3.9, 2.3 Hz, 1 H), 2.62 (dd, *J* = 9.8, 3.4 Hz, 1 H), 2.69 (dd, *J* = 13.8, 3.4 Hz, 1 H), 2.92 (dd, *J* = 10.5, 5.6 Hz, 1 H), 2.97 (dd, *J* = 13.8, 9.8 Hz, 1 H), 4.69 (d, *J* = 1.1 Hz, 1 H), 4.81 (s, 2 H), 5.07 (s, 5 H), 6.66 (s, 2 H), 7.36 (m_c, 2 H), 7.41 (m_c, 4 H), 7.47 (m_c, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.9, 14.1, 15.3, 18.0, 19.2, 24.0, 27.8, 28.2, 35.8, 38.4, 39.0, 39.7, 53.9, 54.4, 64.9, 70.3, 78.5, 102.4, 106.8, 117.2, 127.7, 128.4, 137.2, 140.4, 149.1, 157.5 ppm. ESI-HRMS: calcd. for $[C_{45}H_{64}O_4Si + H]^+$: *m*/*z* = 697.4647; found *m*/*z* = 697.4635.

2-{[(1*S*,4a*R*,6*S*,8a*R*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl]methyl}-5-[(triisopropylsilyloxy)methyl]benzene-1,3-diol (20): To a solution of naphthalene (796 mg, 6.21 mmol) in THF (12 mL) lithium granules (43.1 mg, 6.21 mmol) were added and the mixture was sonicated for 5 min under an inert gas atmosphere at room temperature. The mixture was stirred with a SmCo-stir bar for about 3 h until all lithium disappeared and THF (13 mL) was added. After cooling to –21 °C a solution of the benzyl protected resorcine **18** (555 mg, 796 μmol) in THF (10 mL) was added dropwise under vigorous stirring within 5 min and the reaction mixture was warmed to room temperature. The reaction mixture was partitioned between MTBE (250 mL) and half saturated NH_4Cl (200 mL) and the aqueous phase was extracted with MTBE (100 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and all volatiles were removed under reduced pressure. Column chromatography (silica gel, 25% Me_2CO/hexanes) provided the desired resorcine **20** (396 mg, 766 μmol, 96%). $R_{f'}$ = 0.27 (25% Me_2CO/hexanes). $[a]_D^{23}$ = –7.2 (*c* = 0.64, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.80 (s, 3 H), 0.81 (s, 3 H), 0.99 (s, 3 H), 1.07 (d, *J* = 6.6 Hz, 18 H), 1.11–1.19 (m, 4 H), 1.31 (td, *J* = 13.5, 3.8 Hz, 1 H), 1.41 (dddd, *J* = 12.9, 12.9, 12.9, 4.2 Hz, 1 H), 1.54–1.79 (m, 4 H), 2.00 (dd, *J* = 12.9, 5.0 Hz, 1 H), 2.04 (dt, *J* = 13.5, 3.8 Hz, 1 H), 2.27 (dd, *J* = 7.4, 3.6 Hz, 1 H), 2.40 (ddd, *J* = 12.5, 4.2, 2.4 Hz, 1 H), 2.64 (dd, *J* = 14.9, 7.4 Hz, 1 H), 2.88 (dd, *J* = 14.9, 3.6 Hz, 1 H), 3.28 (dd, *J* = 11.7, 4.5 Hz, 1 H), 4.66 (s, 2 H), 4.88 (m_c, 1 H), 5.10 (m_c, 1 H), 5.55 (br. s, 2 H), 6.32 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.9, 14.1, 15.3, 18.1, 18.8, 24.1, 27.6, 28.2, 36.2, 38.3, 39.1, 40.4, 54.6, 55.6, 64.3, 79.2, 105.1, 107.0, 114.0, 140.8, 150.6, 154.8 ppm. ESI-HRMS: calcd. for $[C_{31}H_{52}O_4Si + H]^+$: *m*/*z* = 517.3708; found *m*/*z* = 517.3708.

3-Hydroxy-2-{[(1*S*,4a*R*,6*S*,8a*R*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl]methyl}-5-[(triisopropylsilyloxy)methyl]cyclohexa-2,5-diene-1,4-dione (21): A solution of resorcine **20** (254 mg, 491 μmol) in DMF (20 mL) and H_2O (5 mL) was chilled in an ice bath and a solution of bis(trifluoroacetoxy)iodobenzene (429 mg, 998 μmol) in DMF (8.5 mL) and H_2O (2.5 mL) was added dropwise during 30 min under an inert gas atmosphere. The reaction mixture was partitioned between hexanes/MTBE (3:1, 200 mL) and half saturated NH_4Cl (100 mL) and the aqueous phase was extracted with hexanes/MTBE (3:1, 100 mL). After the combined organic phases were washed with brine and dried with $MgSO_4$ the solvent was evaporated. The crude product was purified by column chromatography (silica gel, 3% *i*PrOH/$CHCl_3$) to obtain the quinone **21** (238 mg, 448 μmol, 91%). $R_{f'}$ = 0.31 (3% *i*PrOH/$CHCl_3$). $[a]_D^{23}$ = –101 (*c* = 0.18, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.77 (s, 3 H), 0.78 (s, 3 H), 0.99 (s, 3 H), 1.06 (d, *J* = 6.9 Hz, 18 H), 1.11–1.19 (m, 4 H), 1.38 (dddd, *J* = 12.9, 12.9, 12.9, 4.2 Hz, 1 H), 1.44 (br. s, 1 H), 1.51–1.66 (m, 2 H), 1.68–1.78 (m, 2 H), 1.83 (m_c, 1 H), 1.92 (ddd, *J* = 12.9, 12.9, 5.0 Hz, 1 H), 2.31 (ddd, *J* = 12.9, 4.0, 2.5 Hz, 1 H), 2.35 (br. d, *J* = 10.9 Hz, 1 H), 2.50 (dd, *J* = 13.9, 2.8 Hz, 1 H), 2.67 (dd, *J* = 13.9, 10.9 Hz, 1 H), 3.31 (dd, *J* = 11.2, 4.2 Hz, 1 H), 4.61 (d, *J* = 2.4 Hz, 2 H), 4.69 (m_c, 1 H), 4.73 (m_c, 1 H), 6.73 (t, *J* = 2.4 Hz, 1 H), 7.09 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.8, 14.0, 15.4, 17.9, 19.0, 23.9, 27.9, 28.2, 36.6, 38.0, 39.1, 39.8, 54.1, 54.5, 58.8, 78.7, 107.1, 121.5, 133.2, 143.9, 148.2, 151.0, 182.9, 187.9 ppm. ESI-HRMS: calcd. for $[C_{31}H_{50}O_5Si + H]^+$: *m*/*z* = 531.3500; found *m*/*z* = 531.3502.

3β-Hydroxytauranin (2): To a solution of quinone **21** (60.0 mg, 113 μmol) in THF (5 mL) TBAF (120 mg, 429 μmol) was added and the reaction mixture was stirred under an inert gas atmosphere at room temperature for 30 min. The reaction mixture was partitioned between MTBE (50 mL) and half saturated NH_4Cl (25 mL) and the aqueous phase was extracted with MTBE (25 mL). After the combined organic phases were washed with brine and dried with $MgSO_4$ the solvent was evaporated. The crude product was purified by column chromatography (silica gel, 6.5% MeOH/$CHCl_3$) to obtain 3β-hydroxytauranin (**2**; 38.8 mg, 104 μmol, 92%) as deep orange crystals. $R_{f'}$ = 0.28 (6.5% MeOH/$CHCl_3$), m.p. 185–190 °C ($CHCl_3$, decomposition). $[a]_D^{23}$ = –149 (*c* = 0.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): see supplement. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): see supplement. ESI-HRMS: calcd. for $[C_{22}H_{30}O_5 + H]^+$: *m*/*z* = 375.2166; found *m*/*z* = 375.2167.

3-Hydroxy-5-[(triisopropylsilyloxy)methyl]-2-{[(1*S*,4a*R*,8a*R*)-5,5,8a-trimethyl-2-methylene-6-oxodecahydronaphthalen-1-yl]methyl}-cyclohexa-2,5-diene-1,4-dione (22): A solution of quinone **21** (74.4 mg, 140 μmol) in DCM (6 mL) was chilled in an ice bath under an inert gas atmosphere. Dess–Martin-periodinan (DMP, 62.4 mg, 147 μmol) was added and the reaction mixture was stirred

at 0 °C for 1 h. Then the mixture was diluted with hexanes (90 mL) and filtered through a pad of silica (h = 4 cm, ø = 3 cm). The quinones stayed at the baseline and were separated via Dry Column Vacuum Chromatography (DCVC, silica gel, 5% to 15% Me_2CO/hexanes) yielding the desired ketone **22** (44.9 mg, 84.9 μmol, 61%, 81% brsm) besides recovered starting material **21** (18.7 mg, 35.2 μmol). R_f = 0.34 (15% $Me_2CO/CHCl_3$). $[\alpha]_D^{23}$ = –97 (*c* = 0.13, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.95 (s, 3 H), 1.03 (s, 3 H), 1.06 (d, *J* = 6.9 Hz, 18 H), 1.10 (s, 3 H), 1.11–1.19 (m, 3 H), 1.49 (dddd, *J* = 13.2, 13.2, 13.2, 4.2 Hz, 1 H), 1.64–1.72 (m, 2 H), 1.94–2.01 (m, 2 H), 2.10 (ddd, *J* = 13.2, 6.6, 3.9 Hz, 1 H), 2.36 (ddd, *J* = 12.7, 3.8, 2.5 Hz, 1 H), 2.41–2.48 (m, 2 H), 2.50 (dd, *J* = 13.9, 2.7 Hz, 1 H), 2.65 (ddd, *J* = 15.2, 12.4, 6.6 Hz, 1 H), 2.75 (dd, *J* = 13.9, 11.0 Hz, 1 H), 4.62 (d, *J* = 2.4 Hz, 2 H), 4.76 (d, *J* = 0.7 Hz, 1 H), 4.81 (d, *J* = 0.7 Hz, 1 H), 6.75 (t, *J* = 2.4 Hz, 1 H), 6.95 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 11.8, 13.7, 17.9, 19.3, 21.7, 25.1, 26.0, 34.8, 37.2, 37.7, 39.7, 47.7, 53.4, 55.0, 58.8, 108.0, 121.0, 133.2, 144.0, 147.4, 151.0, 182.9, 187.8, 217.0 ppm. ESI-HRMS: calcd. for $[C_{31}H_{48}O_5Si + H]^+$: *m*/*z* = 529.3344; found *m*/*z* = 529.3346.

3-Oxotauranin (1): To a solution of quinone **22** (43.2 mg, 81.1 μmol) in THF (5 mL) TBAF (80.0 mg, 286 μmol) was added and the reaction mixture was stirred under an inert gas atmosphere at room temperature for 30 min. The reaction mixture was partitioned between MTBE (50 mL) and half saturated NH_4Cl (25 mL) and the aqueous phase was extracted with MTBE (25 mL). After the combined organic phases were washed with brine and dried with $MgSO_4$ the solvent was evaporated. The crude product was purified by column chromatography (silica gel, 5% MeOH/$CHCl_3$) to obtain 3-oxotauranin (**1**; 28.0 mg, 75.2 μmol, 93%). R_f = 0.22 (5% MeOH/$CHCl_3$). $[\alpha]_D^{23}$ = –160 (*c* = 0.13, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 298 K): see supplement. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): see supplement. ESI-HRMS: calcd. for $[C_{22}H_{28}O_5 + H]^+$: *m*/*z* = 373.2010; found *m*/*z* = 373.2009.

Supporting Information (see footnote on the first page of this article): Revised NMR-assignments of 3β-hydroxytauranin (**2**) and 3-oxotauranin (**1**), figures of ^1H and ^{13}C NMR spectra of products, the determination of the enantiomeric purity of glycol **15**, and synthesis of *O6′*-(4-heptyl)dihydrocupreidine.

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