First Total Synthesis of Dihydroxerulin, a Potent Inhibitor of the Biosynthesis of Cholesterol**

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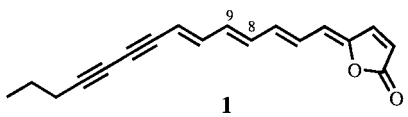
Dedicated to Professor Wolfgang Steglich on the occasion of his 65th birthday

Abstract: Dihydroxerulin (**1**) is a noncytotoxic inhibitor of cholesterol biosynthesis. In spite of being achiral and devoid of OH groups, it was synthesized efficiently (12 steps, 6 steps in the longest linear sequence) from the optically active, polyhydroxylated sugar lactone **6**. Our synthesis follows the strategy of Scheme 2 and illustrates with the β-elimination **10** $\rightarrow$ (*Z*)-**9** a novel general approach to γ-alkylidenebutenolides with stereopure C_β=C bonds. The enol triflate (*Z*)-**9** was hydrogenolyzed to lactone (*Z*)-**11** under very mild conditions. A Wittig reaction with the derived aldehyde (*Z*)-**13** delivered 30% of the title compound. Its 800 MHz ^{1}H NMR spectrum revealed that the C^8=C^9 bond of synthetic, and therefore also natural, **1** is *trans*-substituted.

Keywords: butenolides · lactones · natural products · stereoselective synthesis · structure elucidation

Introduction

Many natural products are γ-alkylidenebutenolides[1, 2] but only a few of them contain no additional ring substituent.[3] A prominent example of such a compound is dihydroxerulin (**1**; Scheme 1). It was isolated from *Xerula melanotricha* Dörfelt and structurally elucidated (except for the configuration of the C^8=C^9 double bond) by Steglich, Anke, et al.[4] Dihydroxerulin is a noncytotoxic inhibitor of cholesterol biosynthesis ($ID_{50} = 1\ \mu g\,g^{-1}$), preventing the incorporation of [^{14}C]acetate, but not of [^{14}C]mevalonic acid, into cholesterol produced from HeLa S3 cells.[4] Dihydroxerulin was only isolated in 90:10 – 65:35 mixtures with xerulin (**2**). Nonetheless, 500 MHz ^{1}H NMR spectra of these mixtures in $CDCl_3$ allowed to determine the constitution of the major component entirely and in addition almost all of its stereochemistry. The only unknown remained the configuration of the C^8=C^9 bond, due to severe signal overlap. However, this configuration was suspected to be *trans*, because compounds **1** and **2** cooccurred with xerulinic acid (**3**).[4] The latter displays nonsuperimposed signals for 8-H and for 9-H and a mutual first-order splitting by $J_{8,9} = 14.9$ Hz; this is a typical value for J_{trans}.



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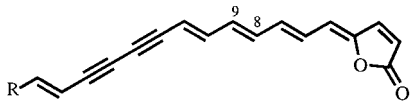

2: R = CH_3 **3**: R = CO_2H

Scheme 1. Dihydroxerulin (**1**) and its derivatives, with numbering scheme.

The unique structure of the presently known members **1** – **3** of the xerulin family, the pronounced depression of cholesterol levels which they cause, and the hope that structural analogues might turn out to be even more biologically active make these and similar compounds attractive targets for synthetic chemists. We initiated such a program ourselves and present in the following the first laboratory synthesis of dihydroxerulin (**1**). In addition, a computer analysis of the 800 MHz ^{1}H NMR spectrum of synthetic **1** in C_6D_6 corroborated the hitherto only suspected (vide supra) 8-*trans* configuration.

It is important that our synthesis makes the particular target molecule **1** accessible by an approach that we hope will become a general strategy for the stereocontrolled production of γ-alkylidene butenolides with or without α-substituents.[5] The key steps are stereospecific *anti*-selective eliminations of water from the γ-(1-hydroxyalkyl)-substituted 2(5*H*)-furanones **4** or *iso*-**4**, be they racemic or enantiopure, depicted in

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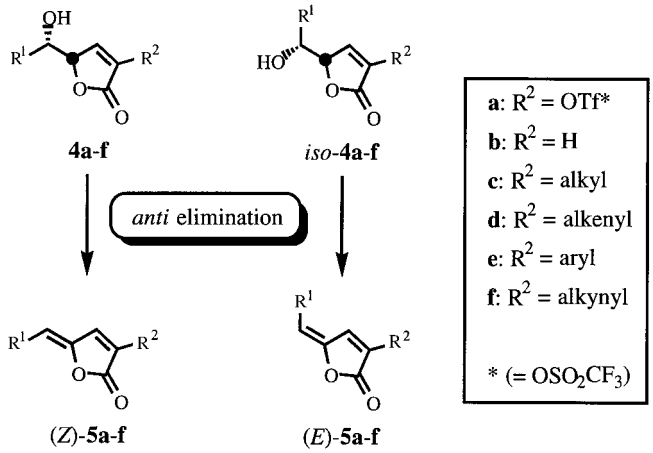
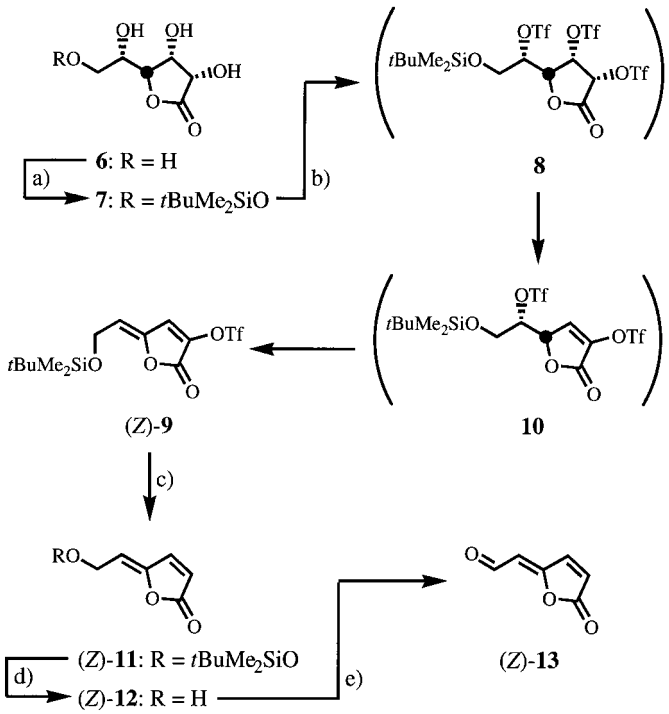
Scheme 2. Furanones of generic structure **4** give γ-alkylidenebutenolides (*Z*)-**5** if they eliminate *anti* while, under the same proviso, the diastereomeric furanones *iso*-**4** give the isomeric butenolides (*E*)-**5**. To the best of our knowledge, β-eliminations have so far only allowed access to γ-alkylidenebutenolides with little[6] or with no stereoselectivity at all[7] (exception: ref. [8]); it did not matter whether the elimination step was performed separately[6b, 7a,c] or took place in situ.[6a,c,d, 7b]



Scheme 2. Stereospecific *anti*-selective eliminations of water from the γ-(1-hydroxyalkyl)-substituted 2(5*H*)-furanones **4** and *iso*-**4**.



Scheme 3. a) tBuMe$_2$SiCl (0.95 equiv), imidazole (2.0 equiv), DMF, $-30\,^{\circ}$C, 1 h; $\rightarrow$RT, 2 h; 58%; b) pyridine (5.0 equiv), Tf_2O (3.3 equiv), CH_2Cl_2, $-85\,^{\circ}$C, 40 min; $\rightarrow -20\,^{\circ}$C, 80 min; $\rightarrow -10\,^{\circ}$C, 90 min; 85% (*Z*:*E* > 99:1); c) LiCl (3.0 equiv), $NiCl_2(PPh_3)_2$ (2 mol%), THF, RT, 15 s; Bu_3SnH (1.1 equiv), RT, 30 s; 83% (*Z*:*E* = 94:6); d) HF pyridine complex (11.2 equiv), THF, 0 °C, 3 h; addition of silica gel powder (for flash chromatography) under continued stirring at 0 °C, 15 min; 80% (*Z*:*E* = 96:4); e) Dess–Martin periodinane (1.1 equiv), CH_2Cl_2, RT, 5 min; 90% as a 95:5 mixture, recrystallized from EtOAc/pentane at $-78\,^{\circ}$C as a 98:2 *Z*:*E* mixture; 82%.

Results and Discussion

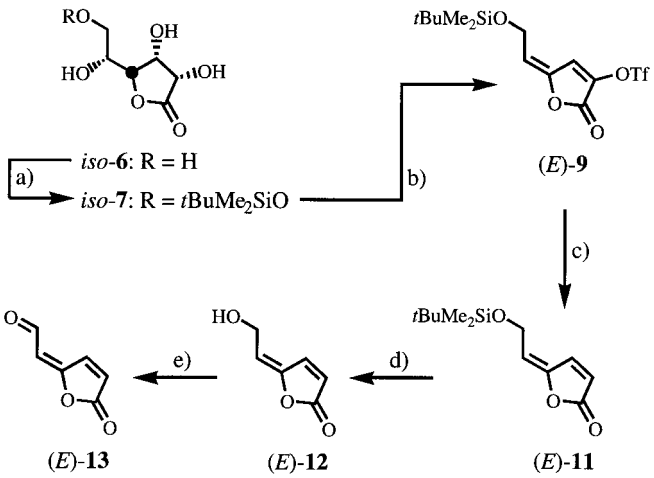
Our synthesis of dihydroxerulin started from L-gulono-1,4-lactone (**6**; Scheme 3).[9] Protection of the primary alcohol function[10] delivered the silylated lactone **7**. All free OH groups of this compound were sulfonylated and two of them subsequently eliminated by treatment with 3.3 equiv of triflic anhydride in the presence of pyridine. We assume that the tris(triflate) **8** formed as a short-lived intermediate. It must have suffered two spontaneous β-eliminations. In all likelihood the first elimination gave rise to the endocyclic C=C bond of a butenolide triflate **10**[11] whereas the second elimination introduced the crucial stereogenic semicyclic C=C bond, thus furnishing the alkylidenebutenolide triflate (*Z*)-**9**.[12] This compound was isolated in 85% yield and with a *Z*:*E* ratio of >99:1 (after flash chromatography on silica gel[13]).

At this point, two subgoals had been reached: the γ-carbon of butenolide (*Z*)-**9** was incorporated into a correctly and homogeneously configured C=C bond and the α-carbon was poised for a desoxygenation. The latter was realized through a transition metal complex catalyzed hydrogenolysis of the C–OTf bond with Bu_3SnH (Scheme 3). Using $NiCl_2(PPh_3)_2$ for this purpose for the first time, the reduction of (*Z*)-**9** went to completion at room temperature within only 30 s and provided 83% (*Z*)-**11**. The nickel catalyst was vastly superior to $[PdCl_2(PPh_3)_2]$, $[Pd(PPh_3)_4]$[14] or $[Pd_2(dba)_3 \cdot CHCl_3]$, each of which required 100 times longer for hydrogenolysis (60 min) and still rendered only half the yield ($\leq$43%). The only drawback is that we could not entirely suppress an isomerization of the semicyclic double bond: (*Z*)-**11** showed an isomer ratio of *Z*:*E* = 94:6 (determined, as are all other isomer ratios of this study, from ^{1}H NMR integrals). The

Abstract in German: *Dihydroxerulin (**1**) ist ein nichtcytotoxischer Inhibitor der Cholesterin-Biosynthese. Obwohl diese Verbindung achiral ist und keine OH-Gruppen enthält, wurde sie in sehr effizienter Weise (12 Stufen, 6 Stufen in der längsten linearen Sequenz) aus dem optisch aktiven und hochhydroxylierten Zuckerlacton **6** synthetisiert. Die von uns realisierte Route folgt der in Schema 2 dargelegten Synthesestrategie. Sie illustriert am Beispiel der β-Eliminierung **10** $\rightarrow$(Z)-**9** einen neuartigen generellen Zugang zu γ-Alkylidenebutenoliden, die eine stereochemisch definierte C_γ=C-Bindung von frei wählbarer Konfiguration enthalten. Das Enoltriflat (Z)-**9** wurde unter sehr milden Bedingungen zum triflatfreien Lacton (Z)-**11** hydrogenolysiert. Eine Wittig-Reaktion mit dem davon abgeleiteten Aldehydolacton (Z)-**13** und dem Ylid des stark ungesättigten Phosphoniumsalzes **21** lieferte die Titelverbindung in 30% Ausbeute. Deren 800-MHz-^{1}H-NMR-Spektrum zeigte, daß die C^8=C^9-Bindung von synthetischem und mithin auch von natürlichem **1** trans-substituiert ist.*

ensuing steps were a desilylation with the HF pyridine complex[15] to 80% of alcohol (*Z*)-**12**, which possessed a 96:4 *Z*:*E* composition, and a Dess–Martin oxidation.[16] These provided 90% of aldehyde (*Z*)-**13** as a *Z*:*E* 95:5 mixture or, after recrystallization, 82% of almost isomerically pure material (*Z*:*E* = 98:2) (Scheme 3).

The presently achieved degree of configurational control of the semicyclic C=C bond of our synthetic intermediates (*Z*)-**9**, (*Z*)-**11**, (*Z*)-**12**, and (*Z*)-**13** of Scheme 3 surpasses our initial results considerably. Indeed, an undesired isomerization of this C=C bond threatened every step of the described sequence. In order to be sure that we dealt with *Z*-configured semicyclic C=C bonds throughout Scheme 3 we prepared all *E* isomers by the conceptually identical series of transformations depicted in Scheme 4 starting from D-mannono-1,4-lactone (*iso*-**6**). After monosilylation[10] (→**7**) the tandem

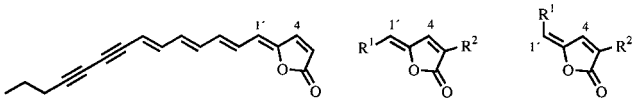


Scheme 4. a) *t*BuMe$_2$SiCl (1.0 equiv), imidazole (2.0 equiv), DMF, −30 °C, 1 h; →RT, 2 h; 62%; b) pyridine (5.0 equiv), Tf$_2$O (3.3 equiv), CH$_2$Cl$_2$, −78 °C; →0 °C, 120 min; 60% (*E*:*Z* > 99:1); c) LiCl (3.0 equiv), NiCl$_2$(PPh$_3$)$_2$ (2 mol%), THF, RT, 15 s; Bu$_3$SnH (1.1 equiv), RT, 30 s; 79% (*E*:*Z* = 83:17); d) HF pyridine complex (11.2 equiv), THF, 0 °C, 3 h; addition of silica gel powder (for flash chromatography) under continued stirring at 0 °C, 15 min; 76% (*E*:*Z* = 81:19); e) Dess–Martin periodinane (1.1 equiv), CH$_2$Cl$_2$, RT, 10 min; 81% (*E*:*Z* = 79:21).

triflation/β-elimination reaction with triflic anhydride and pyridine provided the butenolide triflate (*E*)-**9** in 60% yield as a single isomer (*E*:*Z* > 99:1). This transformation constitutes one of our first realizations[5] of the Scheme 2 approach to γ-alkylidenebutenolides (*E*)-**5** from γ-(α-hydroxyalkyl)butenolides *iso*-**4**.[12] The [NiCl$_2$(PPh$_3$)$_2$]-catalyzed hydrogenolysis of triflate (*E*)-**9** with Bu$_3$SnH delivered compound (*E*)-**11** in 82% yield. However, we observed a competing isomerization of the semicyclic double bond lowering the *E*:*Z* ratio to 83:17. Desilylation of ether (*E*)-**11** by HF/pyridine[15] gave 76% of the alcohol (*E*)-**12** (*E*:*Z* = 81:19). It was oxidized (81% yield) with Dess–Martin periodinane[16] giving aldehyde (*E*)-**13** as a 79:21 *E*:*Z* mixture.

Having compounds **9** and **11**–**13** now as pairs of isomers in our hands, it was evident that each compound originating from the synthesis of Scheme 3 belonged to one configurational series and each compound emerging from a reaction of Scheme 4 to the *opposite* configurational series. This followed from the groupwise similarities of the 300 MHz ^{1}H NMR shifts of the protons 1′-H and 4-H, respectively (Table 1). In *Z* vs. *E* isomers, these resonances were shifted upfield by about 0.5 ppm.[17]

Table 1. ^{1}H NMR shifts (at 300 MHz in CDCl$_3$) distinguishing between *Z*- and *E*-configured γ-alkylidenebutenolides.



	R^1	R^2	$\delta_{Z\text{-isomer}}$ 1′-H	4-H	$\delta_{E\text{-isomer}}$ 1′-H	4-H	$\delta_Z - \delta_E$ 1′-H	4-H
9	*t*BuMe$_2$SiO–CH$_2$	OTf	5.64	7.26	6.02	7.91	−0.38	−0.65
11	*t*BuMe$_2$SiO–CH$_2$	H	5.41	7.36	5.83	7.85	−0.42	−0.49
12	HO–CH$_2$	H	5.48	7.39	5.91	7.83	−0.43	−0.44
13	(O=)CH	H	5.63	7.59	6.18	8.13	−0.55	−0.54
1 (synthetic)	–	–	5.90	7.38	–	–	–	–
1 (natural)[4]	–	–	5.88	7.35	–	–	–	–

The highly unsaturated side-chain of dihydroxerulin (**1**) was prepared as shown in Scheme 5. Two 1,4-eliminations of HCl from the dichlorobutyne **14** gave the butadiyne dianion.[18] Propylation of one of its termini[18] and iodination of the other provided the iododiyne **17**.[19] It was Stille-cross-coupled[20] with the stannane **18** obtained from the pentenynol **15**[21] and Bu$_3$SnH in one step.[22] The resulting alcohol **19** was transformed via bromide **20**[23] into the triphenylphosphonium salt **21**.[24] The Wittig reaction between the ylid derived therefrom and the aldehyde (*Z*)-**13** brought the first synthesis of dihydroxerulin (**1**) to an end (Scheme 5). The target compound was initially obtained in a mixture with at least two isomers (55% total yield). Careful purification by repetitive passages through silica-gel-filled flash chromatography columns[13] led to 30% of pure dihydroxerulin (**1**). Our synthesis encompasses 2 × 5 consecutive steps in the two linear sequences which converge in the last, single, eleventh step. Our synthetic specimen of dihydroxerulin (**1**) was identical with the natural product,[4] as evidenced by coinciding 500 MHz ^{1}H NMR shift values and coupling constants (in CDCl$_3$; Table 2).

What we felt remained to be proved from first NMR principles were the configurations of the stereogenic C^4=C^5, C^6=C^7, C^8=C^9, and C^{10}=C^{11} bonds of dihydroxerulin. Clearly, the route by which we obtained **1** already implies that the C^4=C^5, C^8=C^9, and C^{10}=C^{11} bonds of **1** possess the same configuration as the correponding double bonds in the precursor aldehyde (*Z*)-**13** and phosphonium salt **21**. Independently, the *Z* configuration of the C^4=C^5 bond follows unequivocally from the ^{1}H NMR shift criterion established in entries 1–4 of Table 1 (compare with entries 5, 6). The C^6=C^7 and C^{10}=C^{11} bonds of **1** are clearly *trans* configured because of the magnitude of the vicinal coupling constants $J_{6,7}$ (14.3 Hz) and $J_{10,11}$ (15.5 Hz). However, we could not tell right away the configuration of the C^8=C^9 bond, since under the Steglich/Anke[4] measuring conditions (500 MHz, CDCl$_3$) the 8-^{1}H/9-^{1}H NMR subspectrum of **1** is higher-order. Because signal spreading in the 8-^{1}H/9-^{1}H range was slightly larger in C$_6$D$_6$

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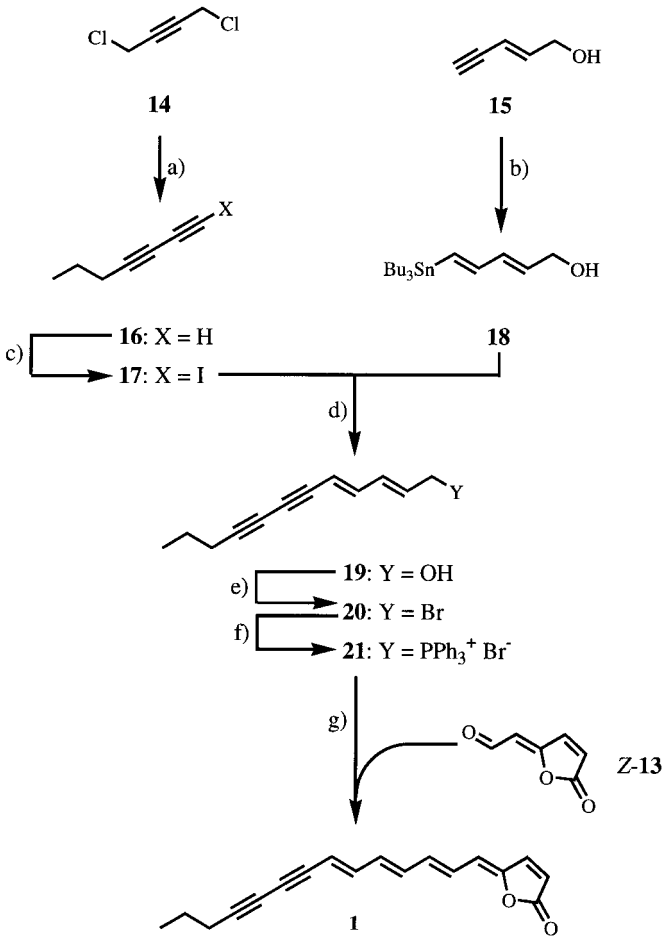
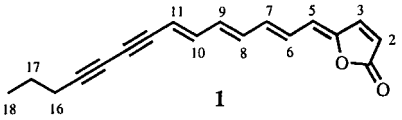


Scheme 5. a) $NaNH_2$ (3.0 equiv), PrBr (1.1 equiv), NH_3/DMSO (6:1), −33 °C, 4 h; used crude (ref. [18] 58–62%); b) CuCN (1.1 equiv), BuLi (2.2 equiv), THF, −78 °C→RT, 30 min; →−78 °C, Bu_3SnH (1.1 equiv), then **15**, −78 °C, 2.5 h; 78% (ref. [22] 67%); c) I_2 (1.0 equiv), morpholine (3.0 equiv), THF, 45 °C, 10 h; 43% over the two steps; d) LiCl (3.0 equiv), $PdCl_2(PPh_3)_2$ (2 mol%), THF, RT, 5 h; 81%; e) NaBr (1.5 equiv), $BF_3 \cdot OEt_2$ (1.5 equiv), MeCN, RT, 6 h; 61%; f) PPh_3 (1.0 equiv), MeCN, RT, 12 h; 99%; g) *n*BuLi (1.0 equiv), THF, −83 °C, 3 min; (*Z*)-**13** (1.0 equiv), −83 °C, 6 h; →RT, 2 h; after repeated chromatography 30% **1** and 25% mixtures of other isomers.

Table 2. Comparison of ^1H NMR data at 500 MHz in $CDCl_3$ between synthetic and natural dihydroxerulin (**1**);[4] chemical shifts in ppm, coupling constants in Hz.



proton	2	3	5	6	7–9	10	11	16	17	18
chemical shift										
natural **1**[4]	6.17	7.35	5.88	6.80	6.37–6.54	6.74	5.69	2.32	1.57	0.99
synthetic **1**	6.19	7.38	5.90	6.82	6.39–6.56	6.77	5.72	2.35	1.59	1.01
couplings	$^3J_{2,3}$	$^5J_{2,5}$	$^3J_{5,6}$	$^3J_{6,7}$	$^3J_{9,10}$	$^3J_{10,11}$	$^7J_{11,16}$	$^3J_{16,17}$	$^3J_{17,18}$	
natural **1**[4]	5.5	0.5	11.8	14.5	10.5	15.5	1.2	7.0	7.5	
synthetic **1**	5.4	–	11.9	14.3	10.5	15.5	1.0	7.1	7.3	

than in $CDCl_3$ we used the former for recording a 800 MHz 8-^1H/9-^1H NMR subspectrum of **1** as our ultimate means (Figure 1, top half). We then calculated (trial and error method) this subspectrum from the values $\delta_{7H} = 5.9725$, $\delta_{10H} = 6.5190$, $J_{7,8} = 10.3$ Hz, and $J_{9,10} = 10.4$ Hz which were directly accessible from the first-order resonances of 7-H and 10-H. We varied δ_{8H} in 0.000125-ppm steps between 5.8381 ± 0.0025 ppm, δ_{9H} in 0.000125-ppm steps between 5.8606 ± 0.0025 ppm, and $J_{8,9}$ first in 0.5-Hz steps between 10.0 and 14.0 Hz and then in 0.2-Hz steps between 14.0 and 16.0 Hz until the calculated (Figure 1, top half) and experimental 8-^1H/9-^1H subspectrum (Figure 1, top half) coincided. In this case, $\delta_{8H} = 5.84$, $\delta_{9H} = 5.86$, and $J_{8,9} = 14.8$ Hz. The last value proves that the $C^8{=}C^9$ bond of dihydroxerulin (**1**) is *trans*-configured.

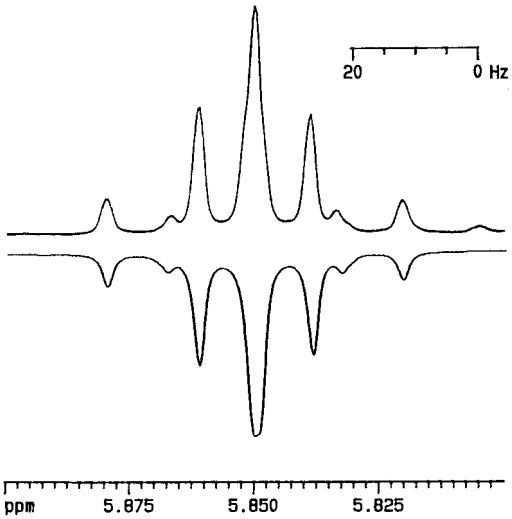


Figure 1. Experimental (top) and calculated (bottom) 8-^1H/9-^1H subspectrum of dihydroxerulin (**1**) at 800 MHz in C_6D_6.

We are currently trying to expand the scope of our γ-(α-hydroxyalkyl)butenolide **4**→γ-alkylidenebutenolide **5** strategy to obtain xerulin (**2**) and xerulinic acid (**3**) by variations of our approach to dihydroxerulin (**1**) presented here.

Experimental Section

General methods: All reactions were performed in oven-dried (110 °C) glassware under N_2. Reactions with light-sensitive compounds were performed in brown glassware or in ordinary glassware wrapped by aluminum foil. THF was freshly distilled from K, CH_2Cl_2 and pyridine from CaH_2, MeCN from P_4O_{10}. Products were purified by flash chromatography[13] on Merck silica gel 60 (eluents given in brackets; volume of each collected fraction (mL)/column diameter (cm): 1.3/1.0, 4/1.5, 8/2.0, 14/2.5, 20/3.0, 30/4, 50/5, 80/6, 125/75; which fractions contained the isolated product is indicated in each description as product in fractions *xx*–*yy*). Yields refer to analytically pure samples. Isomer ratios were derived from suitable ^1H NMR integrals. ^1H [$CHCl_3$ ($\delta = 7.26$) as internal standard in $CDCl_3$ or C_6HD_5 ($\delta = 7.16$) as internal standard in C_6D_6] and ^{13}C NMR [C_6D_6 ($\delta = 128.00$) as internal standard in C_6D_6]: Bruker AMX300 and Varian VXR500S; integrals in accord with assignments; coupling constants in Hz. The assignments of ^1H and ^{13}C NMR resonances refer to the IUPAC nomenclature and primed numbers belong to the side-chain, except for dihydroxerulin which was numbered as shown in Table 2. Combustion analyses: M. Beller and F. Hambloch, Institute of Organic Chemistry, University of Göttingen; MS: Dr. G. Remberg, Institute of Organic Chemistry, University of Göttingen; IR spectra: Perkin–Elmer 1600 Series FT-IR; UV spectra: Perkin–Elmer Lambda 2; melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected.

Dihydroxerulin (**1**): *n*BuLi (2.5 M in hexane, 487 μL, 1.22 mmol, 1.0 equiv) was added to phosphonium salt **21** in THF (20 mL) at −83 °C. The

aldehyde (*Z*)-**13** (151 mg, 1.22 mmol) precooled at −83 °C in THF (5 mL) was added to this solution after 3 min. The reaction was allowed to proceed at −83 °C for 6 h and at room temp for 2 h. The solvent was removed in vacuo. The crude product was purified by flash chromatography (5 cm, fractions 1–9 petroleum ether:*t*BuOMe:CH_2Cl_2 10:1:1, fractions 10–19 petroleum ether:*t*BuOMe:CH_2Cl_2 5:1:1, product in fractions 7–19) yielded the title compound as a mixture of isomers (177 mg, 55 %). Dihydroxerulin (**1**) could be separated from it by repeated flash chromatographies (3 cm, fractions 1–29 petroleum ether:*t*BuOMe:CH_2Cl_2 6:1:0.2, fractions 30–49 petroleum ether:*t*BuOMe:CH_2Cl_2 4:1:0.2, fractions 50–84 petroleum ether:*t*BuOMe:CH_2Cl_2 3:1:0.2, product in fractions 52–84). The pure title compound (96 mg, 30 %) was isolated as an orange solid [m.p. 132–135 °C (decomp), ref. [4] 143–154 °C for a mixture with xerulin]. ^{1}H NMR (500 MHz): $\delta = 1.01$ (t, $J_{18,17} = 7.3$, 18-H_3), 1.59 (tq, $J_{17,18} = J_{17,16} = 7.2$, 17-$H_2$), 2.35 (td, $J_{16,17} = 7.0$, $^7J_{16,11} = 1.0$, 16-H_2), 5.72 (d, $J_{11,10} = 15.4$, 11-H), 5.90 (d, $J_{5,6} = 11.9$, 5-H), 6.19 (d, $J_{2,3} = 5.5$, 2-H), 6.39–6.56 (m, 7-H, 8-H, 9-H), 6.77 (dd, $J_{10,11} = 15.5$, $J_{10,9} = 10.5$, 10-H), 6.82 (dd, $J_{6,7} = 14.3$, $J_{6,5} = 11.8$, 6-H), 7.38 (d, $J_{3,2} = 5.3$, 3-H); ^{1}H NMR (800 MHz, C_6D_6, C_6HD_5 as internal standard): $\delta = 0.73$ (t, $J_{18,17} = 7.4$, 18-H_3), 1.22 (qt, $J_{17,18} = J_{17,16} = 7.2$, 17-$H_2$), 1.91 (dt, $J_{16,17} = 7.0$, $^7J_{16,11} = 0.8$, 16-H_2), 5.08 (d, $J_{5,6} = 11.7$, 5-H), 5.45 (d, $J_{11,10} = 15.5$, 11-H), 5.48 (d, $J_{2,3} = 5.3$, 2-H), 5.78–5.88 (m, 8-H, 9-H)*, 5.97 (dd, $J_{6,7} = 14.8$, $J_{7,8} = 10.3$, 7-H), 6.23 (d, $J_{3,2} = 5.3$, 3-H), 6.52 (dd, $J_{10,11} = 15.4$, $J_{10,9} = 10.4$, 10-H), 6.57 (dd, $J_{6,7} = 15.1$, $J_{6,5} = 11.7$, 6-H); (* a computer analysis was done because these signals were higher-order; cf. body of the text). A $^3J_{1H,1H}$ correlation spectrum (500 MHz, C_6D_6) shows cross-peaks between the following resonances: 2-H ⇔ 3-H; 5-H ⇔ 6-H; 6-H ⇔ 7-H; 7-H ⇔ 8-H/9-H; 8-H/9-H ⇔ 7-H/10-H; 10-H ⇔ 8-H/9-H; 10-H ⇔ 11-H; 16-H_2 ⇔ 17-H_2; 17-H_2 ⇔ 18-H_3. A $^{n\geq3}J1_H1_H$ correlation spectrum (500 MHz, C_6D_6) shows cross-peaks between the following resonances: 2-H ⇔ 3-H, 5-H; 3-H ⇔ 2-H, 5-H; 5-H ⇔ 2-H, 3-H, 6-H, 7-H; 6-H ⇔ 5-H, 7-H; 7-H ⇔ 5-H, 6-H, 8-H/9-H; 8-H/9-H ⇔ 7-H, 10-H; 10-H ⇔ 5-H, 8-H/9-H; 11-H ⇔ 16-H_2; 16-H_2 ⇔ 11-H, 17-H_2; 17-H_2 ⇔ 16-H_2, 18-H_3; 18-H_3 ⇔ 17-H_2; ^{13}C NMR (125.7 MHz, C_6D_6; C_6D_6 as internal standard): $\delta = 13.37$ (C-18), 21.68 (C-16), 21.91 (C-17), 66.74 and 80.80 (C-13, C-14), 75.64 (C-12), 87.58 (C-15), 112.20 (C-11), 113.64 (C-5), 118.81 (C-2), ≈128 (C-6)*, 134.78 and 135.70 (C-8, C-9), 137.35 (C-7), 141.83 (C-3), 144.19 (C-10), 149.79 (C-4), 168.49 (C-1) (* signal superimposed by C_6D_6 and therefore not unambiguously identifiable). A $^1J_{H,^{13}C}$ correlation spectrum (500 MHz and 125.7 MHz, respectively, C_6D_6) shows cross-peaks between the following resonances: 2-H ⇔ C-2; 3-H ⇔ C-3; 5-H ⇔ C-5; 6-H ⇔ C-6; 7-H ⇔ C-7; 8-H/9-H ⇔ C-8, C-9; 10-H ⇔ C-10; 11-H ⇔ C-11; 16-H_2 ⇔ C-16; 17-H_2 ⇔ C-17; 18-H_3 ⇔ C-18. A $^{n\geq1}J_{^1H,^{13}C}$ correlation spectrum (500 MHz and 125.7 MHz, respectively, C_6D_6) shows cross-peaks between the following resonances: 2-H ⇔ C-1, C-3, C-4; 3-H ⇔ C-1, C-2, C-4; 5-H ⇔ C-3, C-4, C-7; 6-H ⇔ C-4; 7-H ⇔ C-9; 8-H/9-H ⇔ C-7, C-10; 10-H ⇔ C-8; 11-H ⇔ C-9, C-10, C-12; 16-H_2 ⇔ C-12, C-13/C-14, C-15; 17-H_2 ⇔ C-15, C-16, C-18; 18-H_3 ⇔ C-17; IR ($CDCl_3$): ν = 3155, 2965, 2930, 2255, 1775, 1750, 1530, 1465, 1380, 1335, 1105, 1065, 995, 910, 735, 650 cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 396 (5.61), 413 (5.64) nm; $C_{18}H_{16}O_2$ (264.3): calcd C 81.79, H 6.10; found C 81.98, H 6.08; m/z = 264.1150 ± 2 mDa (M^+) confirmed by HRMS (EI, 70 eV).

(−)-L-6-(*tert*-Butyldimethylsilyl)-gulono-1,4-lactone (**7**): A solution of *tert*-butyldimethylsilyl chloride (1.05 g, 7.00 mmol, 0.95 equiv) in CH_2Cl_2 (5 mL) was added to a mixture of L-gulono-1,4-lactone (**6**; 1.31 g, 7.30 mmol) and imidazole (0.94 g, 13.9 mmol, 1.9 equiv) in DMF (15 mL) at −40 °C over 2 h. The mixture was stirred at −30 °C for 1 h and at RT for 2 h. It was poured into ice water (50 mL) and extracted with *t*BuOMe (3 × 50 mL). The organic layers were dried over Na_2SO_4. After removal of the solvent, flash chromatography (4 cm, fractions 1–5 petroleum ether:*t*BuOMe 1:1, fractions 6–12 *t*BuOMe, product in fractions 8–12) yielded the title compound (1.25 g, 58 %) as a glassy solid. $[\alpha]_D^{20} = -29.6$ ($c = 0.96$ in acetone); ^{1}H NMR (300 MHz): $\delta = 0.12$ [s, Si(CH_3)$_2$], 0.91 (s, *t*Bu), 2.84 (d, $J_{5,5\text{-OH}} = 3.4$, 5-OH), 3.21 (d,$J_{2,2\text{-OH}} = 7.3$, 2-OH), AB signal ($\delta_A = 3.75$, $\delta_B = 3.84$, $J_{AB} = 10.5$, in addition split by $J_{A,5} = 7.9$, $J_{B,5} = 4.9$, 6-H_2), superimposes 3.71 (d, $J_{3,3\text{-OH}} = 2.2$, 3-OH), 4.15 (m_c, 5-H), 4.39 (dd, $J_{4,5} = 5.7$, $J_{4,3} = 3.0$, 4-H), 4.46 (dd, $J_{2,2\text{-OH}} = 7.0$, $J_{2,3} = 5.1$, 2-H), 4.54 (m_c, presumably hardly resolved ddd, $J_{3,2} \approx 5.0$, $J_{3,3\text{-OH}} \approx J_{3,4} \approx 2.5$, 3-H); IR ($CHCl_3$): $\tilde{\nu}$ = 3550, 2955, 2860, 1780, 1465, 1255, 1195, 1120, 840, 790, 765 cm^{-1}; $C_{12}H_{24}O_6Si$ (292.4): calcd C 49.29, H 8.29; found C 49.29, H 8.40.

(−)-D-6-*O*-(*tert*-Butyldimethylsilyl)-mannono-1,4-lactone (*iso*-**7**) was prepared from *tert*-butyldimethylsilyl chloride (50 wt % in toluene, 9.00 mL, 3.91 g, 25.9 mmol, 1.0 equiv), D-mannono-1,4-lactone (*iso*-**6**; 4.614 g, 25.93 mmol), and imidazole (3.531 g, 51.86 mmol, 2.0 equiv) as a glassy solid (4.723 g, 62 %) analogously as described for the preparation of compound **7**. $[\alpha]_D^{20} = -15.6$ ($c = 0.77$ in $CHCl_3$); ^{1}H NMR (300 MHz, contains 4 mol % = 1 wt % *t*BuOMe): $\delta = 0.10$ [2 × s, Si(CH_3)$_2$], 0.91 (s, *t*Bu), 3.28 (br s, 3 × OH), AB signal ($\delta_A = 3.80$, $\delta_B = 3.88$, $J_{AB} = 10.7$, in addition split by $J_{A,5} = 3.7$, $J_{B,5} = 3.6$, 6-H_2), 4.04 (ddd, $J_{5,4} = 8.7$, $J_{5,6H(A)}$ approx $J_{5,6H(B)} = 3.9$, 5-H), 4.32 (dd, $J_{4,5} = 8.7$, $J_{4,3} = 2.7$, 4-H), 4.51 (d, $J_{2,3}$ = 4.5, 2-H), 4.64 (dd, $J_{3,2} = 4.7$, $J_{3,4} = 2.9$, 3-H); IR ($CHCl_3$): ν = 2975, 1790, 1465, 1365, 1230, 1210, 1075, 845, 780, 765, 750 cm^{-1}; $C_{12}H_{24}O_6Si$ (292.4): calcd C 49.29, H 8.27; found C 49.41, H 8.07.

5-[(*Z*)-2-(*tert*-Butyldimethylsiloxy)ethylidene]-3-(trifluoromethanesulfonyloxy)-2(5*H*)-furanone [(*Z*)-**9**]: Triflic anhydride (3.219 g, 1.42 mmol, 3.3 equiv) was added to a solution of triol **7** (1.000 g, 3.420 mmol) and pyridine (1.353 g, 17.10 mmol, 5.0 equiv) in CH_2Cl_2 (40 mL) at −78 °C over 40 min. The mixture was allowed to warm to −20 °C over 80 min and subsequently stirred between −20 and −10 °C for 90 min. It was recooled to −78 °C and poured without workup onto a flash chromatography column (5 cm, CH_2Cl_2, product in fractions 6–9). The title compound (1.135 g, 85 %) was eluted as a white solid (m.p. 45 °C). Small signals of (*E*)-**9** at $\delta = 6.02$ (1′-H) and $\delta = 7.91$ (4-H) showed *Z*:*E* selectivity of > 99:1. ^{1}H NMR (300 MHz): $\delta = 0.08$ [s, Si(CH_3)$_2$], 0.89 (s, *t*Bu), 4.54 (d, $J_{2',1'} = 6.4$, 2′-H_2), 5.64 (t, $J_{1',2'} = 6.4$, 1′-H), 7.26 (s, 4-H)* (* this signal was caused by (*Z*)-**9**, as proved by integration); IR ($CDCl_3$): ν = 2930, 2860, 1800, 1610, 1440, 1230, 1135, 1075, 1050, 900, 840, 760, 715, 650 cm^{-1}. $C_{13}H_{19}F_3O_6SSi$ (388.4): calcd C 40.20, H 4.93; found C 40.49, H 4.79.

5-[(*E*)-2-(*tert*-Butyldimethylsiloxy)ethylidene]-3-(trifluoromethanesulfonyloxy)-2(5*H*)-furanone [(*E*)-**9**] was prepared from triflic anhydride (3.322 g, 11.78 mmol, 3.3 equiv), triol *iso*-**7** (1.032 g, 3.530 mmol), and pyridine (1.394 g, 17.65 mmol, 5.0 equiv) as a colorless liquid (816 mg, 60 %) as described for the preparation of compound (*Z*)-**9**. Here, (*Z*)-**9** was not detectable by ^{1}H NMR. ^{1}H NMR (300 MHz): $\delta = 0.13$ [s, Si(CH_3)$_2$], 0.94 (s, *t*Bu), 4.56 (d, $J_{2',1'} = 4.5$, 2′-H_2), 6.02 (t, $J_{1',2'} = 4.7$, 1′-H), 7.91 (s, 4-H); IR ($CDCl_3$): $\tilde{\nu}$ = 2960, 2930, 2895, 2860, 1800, 1785, 1610, 1440, 1225, 1175, 1135, 1110, 1070 cm^{-1}; $C_{13}H_{19}F_3O_6SSi$ (388.4): calcd C 40.20, H 4.93; found C 40.31, H 4.93.

5-[(*Z*)-2-(*tert*-Butyldimethylsiloxy)ethylidene]-2(5*H*)-furanone [(*Z*)-**11**]: A mixture of LiCl (460 mg, 10.8 mmol, 3.0 equiv) and $NiCl_2(PPh_3)_2$ (46 mg, 70 μmol, 2 mol %) was added to a solution of the triflate (*Z*)-**9** (1.400 g, 3.605 mol) in THF (15 mL). After 15 s Bu_3SnH (1.158 g, 3.969 mmol, 1.1 equiv) was added dropwise while stirring in a water bath maintained at 25 °C. The color of the reaction mixture changed from blue via green to brown. The reaction was finished after 30 s (TLC). The crude product obtained after removal of the solvent in vacuo was purified by flash chromatography (3 cm, fractions 1–9 petroleum ether:*t*BuOMe 10:1, fractions 10–30 petroleum ether: *t*BuOMe 5:1, product in fractions 17–30). The title compound (720 mg, 83 %) was obtained as a colorless oil. It was contaminated with 6 % of (*E*)-**11** [calculated from ^{1}H integrals of 4-H ($\delta_{E\text{-}11} = 7.85$), 1′-H ($\delta_{E\text{-}11} = 5.83$), and 2′-H ($\delta_{E\text{-}11} = 4.47$)]. ^{1}H NMR (300 MHz): $\delta = 0.09$ [s, Si(CH_3)$_2$], 0.90 (s, *t*Bu), 4.54 (d, $J_{2',1'} = 6.4$, 2′-H_2), 5.41 (t, $J_{1',2'} = 6.4$, 1′-H), 6.21 (d, $J_{3,4} = 5.2$, 3-H), 7.36 (d, $J_{4,3} = 5.3$, 4-H); IR (film): $\tilde{\nu}$ = 2930, 2855, 1780, 1465, 1255, 1205, 1105, 990, 930, 835, 780 cm^{-1}. $C_{12}H_{20}O_3Si$ (240.4): calcd C 59.96, H 8.39; found C 59.86, H 8.46.

5-[(*E*)-2-(*tert*-Butyldimethylsiloxy)ethylidene]-2(5*H*)-furanone [(*E*)-**11**] was prepared from LiCl (71 mg, 1.7 mmol, 3.0 equiv), $NiCl_2(PPh_3)_2$ (7.2 mg, 11 μmol, 2 mol %), triflate (*Z*)-**9** (217 mg, 0.559 mmol), and Bu_3SnH (180 mg, 0.615 mmol, 1.1 equiv) as a colorless oil (106 mg, 79 %) analogously as described for the preparation of compound (*Z*)-**11**. It was contaminated with 17 % of (*Z*)-**11** [calculated from ^{1}H integrals of 4-H ($\delta_{Z\text{-}11} = 7.36$), 1′-H ($\delta_{Z\text{-}11} = 5.41$), and 2′-H ($\delta_{Z\text{-}11} = 4.54$)]. ^{1}H NMR (300 MHz, contains 2 wt % *t*BuOMe): $\delta = 0.11$ [s, Si(CH_3)$_2$], 0.92 (s, *t*Bu), 4.47 (d, $J_{2',1'} = 6.1$, 2′-H_2), 5.83 (incompletely resolved tdd, $J_{1',2'} = 5.7$, $^5J_{1',3} = 1.9$, $^4J_{1',4} = 1.0$, 1′-H), 6.22 (ddm$_c$, $J_{3,4} = 5.6$, $^5J_{3,1'} = 1.9$, 3-H, superimposed by the corresponding signal of the *Z* isomer), 7.85 (incompletely resolved dd, $J_{4,3} = 5.6$, $^4J_{4,1'} = 0.7$, 4-H); IR ($CDCl_3$): ν = 2930, 2855, 1780, 1675, 1460, 1390, 1255, 1100, 1070, 990, 835, 780 cm^{-1}; $C_{12}H_{20}O_3Si$ (240.4): calcd C 59.96, H 8.39; found C 59.99, H 8.03.

5-[(*Z*)-2-Hydroxyethylidene]-2(5*H*)-furanone [(*Z*)-**12**]: HF pyridine complex (1.50 mL, 1.36 g, 36.1 mmol, 11.2 equiv) was added to a solution of the silylether (*Z*)-**11** [contaminated with 6 % of (*E*)-**11**; 770 mg, 3.21 mmol] in THF (20 mL) at 0 °C. After stirring at 0 °C for 3 h silica gel for flash

0947-6539/98/0406-1120 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 6

chromatography (300 mg) was added. The mixture was filtered through a pad of Celite® after stirring at 0 °C for 15 min. The crude product obtained after removal of the solvent in vacuo was purified by flash chromatography (3 cm, fractions 1–9 petroleum ether:*t*BuOMe 1:1, fractions 10–3 *t*BuOMe, product in fractions 15–23). The title compound (325 mg, 80 %) was obtained as colorless oil. It was contaminated with 4 % of (*E*)-**12** [calculated from ^{1}H integrals of 4-H ($\delta_{E\text{-}12} = 7.83$), and 1′-H ($\delta_{E\text{-}12} = 5.91$]. ^{1}H NMR (300 MHz): $\delta = 1.74$ (t, $J_{2',OH} = 5.9$, OH), 4.54 (br t, $J_{2',1'} \approx J_{2',OH} = 6.4$, 2′-H$_2$), 5.48 (t, $J_{1',2'} = 6.5$, 1′-H), 6.25 (d, $J_{3,4} = 5.7$, 3-H), 7.39 (d, $J_{4,3} = 5.2$, 4-H); IR ($CDCl_3$): $\nu = 3610$, 3150, 2975, 1775, 1750, 1675, 1560, 1465, 1385, 1315, 1215, 1115, 1060, 965, 920, 900, 880, 765, 705 cm^{-1}; $C_6H_6O_3$ (126.1): calcd C 57.14, H 4.80; found C 57.08, H 4.75.

5-[(*E*)-2-Hydroxyethylidene]-2(5*H*)-furanone [(*E*)-**12**] was prepared from HF pyridine complex (0.110 mL, 100 mg, 2.91 mmol, 14.0 equiv) and silylether (*E*)-**11** [contaminated with 17 % of (*Z*)-**11**, 50 mg, 0.20 mmol) as a colorless oil (20 mg, 76 %) as described for the preparation of compound (*Z*)-**12**. It was contaminated with 19 % of (*E*)-**12** [calculated from ^{1}H integrals of 4-H ($\delta_{Z\text{-}12} = 7.39$), and 1′-H ($\delta_{Z\text{-}12} = 5.48$]. ^{1}H NMR (300 MHz, contains 8 wt % *t*BuOMe): $\delta = 2.00$ (br s, OH), 4.47 (d, $J_{2',1'} = 6.8$, 2′-H$_2$), 5.91 (td, $J_{1',2'} = 6.9$, $^5J_{1',3} = 1.6$, 1′-H), 6.27 {dd, $J_{3,4} = 5.7$, $^5J_{3,1'} = 1.5$, 3-H [partly superimposed by the corresponding signal of (*Z*)-**12**]}, 7.83 (d, $J_{4,3} = 5.7$, 4-H); IR ($CDCl_3$): $\tilde{\nu} = 3335$, 3135, 3100, 2930, 1745, 1670, 1555, 1420, 1305, 1195, 1120, 1065, 1010, 975, 910, 820 cm^{-1}; $C_6H_6O_3$ (126.1): calcd C 57.14, H 4.80; found C 57.63, H 5.51.

5-[(*Z*)-Formylmethylene]-2(5*H*)-furanone [(*Z*)-**13**]: Dess–Martin periodinane (1.082 g, 2.540 mmol, 1.1 equiv) was added to a solution of the alcohol (*Z*)-**12** [contaminated with 4 % of (*E*)-**12**, 291 mg, 2.31 mmol] in CH_2Cl_2 (3 mL, not dry). The solution was diluted with *t*BuOMe (30 mL) and filtered through a pad of Celite after 5 min. The crude product obtained after removal of the solvent in vacuo was purified by flash chromatography (3 cm, fractions 1–7 petroleum ether:*t*BuOMe 1:1, fractions 8–20 *t*BuOMe, product in fractions 13–20). The title compound (258 mg, 90 %) was obtained as a yellow solid. Recrystallization from EtOAc/pentane at −78 °C yielded (*Z*)-**13** (235 mg, 82 %, m.p. 58 °C) as yellow crystals contaminated with 2 % of (*E*)-**13** [calculated from ^{1}H integrals of 2′H ($\delta_{E\text{-}13} = 10.01$), 4-H ($\delta_{E\text{-}13} = 8.13$), 3-H ($\delta_{E\text{-}13} = 6.66$), and 1′H ($\delta_{E\text{-}13} = 6.18$)]. ^{1}H NMR (300 MHz): $\delta = 5.63$ (d, $J_{1',2'} = 7.9$, 1′-H), 6.51 (dd, $J_{3,4} = 5.7$, $J_{3,1'} = 0.8$, 3-H), 7.59 (d, $J_{4,3} = 5.3$, 4-H), 10.24 (d, $J_{2',1'} = 7.9$, 2′-H); IR ($CDCl_3$): $\nu = 2925$, 2855, 1795, 1675, 1645, 1620, 1560, 1190, 1100, 1080 cm^{-1}; $C_6H_4O_3$ (124.1): calcd C 58.07, H 3.25; found C 58.20, H 3.46.

5-[(*E*)-Formylmethylene]-2(5*H*)-furanone [(*E*)-**13**] was prepared from Dess–Martin periodinane (751 mg, 1.76 mmol, 1.1 equiv) and alcohol (*E*)-**12** [contaminated with 19 % of (*Z*)-**12**, 202 mg, 1.60 mmol] as a yellow oil (162 mg, 81 %) analogously as described for the preparation of compound (*Z*)-**13**. It was contaminated with 21 % of (*Z*)-**13** [calculated from ^{1}H integrals of 2′H ($\delta_{Z\text{-}13} = 10.24$), 4-H ($\delta_{Z\text{-}13} = 7.59$), 3-H ($\delta_{Z\text{-}13} = 6.51$), and 1′-H ($\delta_{Z\text{-}13} = 5.63$)]. ^{1}H NMR (300 MHz): $\delta = 6.18$ (hardly resolved dd, $J_{1',2'} = 6.3$, $^5J_{1',3} = 0.9$, 1′-H), 6.66 (dd, $J_{3,4} = 5.6$, $^5J_{3,1'} = 1.9$, 3-H), 8.13 (d, $J_{4,3} = 5.7$, 4-H), 10.01 (d, $J_{2',1'} = 6.4$, 2′-H); IR ($CDCl_3$): $\nu = 3115$, 2855, 2765, 2260, 1800, 1680, 1560, 1405, 1360, 1305, 1190, 1100, 955, 900, 855, 745 cm^{-1}; $C_6H_4O_3$ (124.1): calcd C 58.07, H 3.25; found C 57.84, H 3.47.

1,3-Heptadiyne (**16**): Na (10.35 g, 450 mmol, 3.0 equiv) and a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ (100 mg) were dissolved in liquid NH_3 (300 mL). After stirring at −33 °C for 60 min the dichloride **14** was added at −55 °C over 60 min. Subsequently, propyl bromide (27.2 mL, 299 mmol, 1.1 equiv) was added at −33 °C over 15 min and DMSO (50 mL) was added at once. The reaction was allowed to proceed at −33 °C for 4 h; then the mixture was poured into ice-water (1000 mL), filtered, and extracted with pentane (3 × 300 mL). The organic layers were dried over $MgSO_4$ and concentrated to 50 mL by distilling off the solvent through a Vigreux column. Distillation yielded **16** as a colorless liquid (26 %, b.p. (64 mbar) 64 °C, ref. [18] 58–62 %). Higher overall yields resulted when we worked with a concentrated solution of **16** in pentane. ^{1}H NMR (300 MHz): $\delta = 1.00$ (t, $J_{7,6} = 7.4$, 7-H$_3$), 1.57 (tq, $J_{6,5} = J_{6,7} = 7.2$, 6-H$_2$), 1.96 (hardly resolved d, $^6J_{1,5} = 1.2$, 1-H), 2.23 (td, $J_{5,6} = 7.0$, $^6J_{5,1} = 1.0$, 5-H$_2$).

1-Iodo-1,3-heptadiyne (**17**): Morpholine (38.55 mL, 38.55 g, 442.5 mmol, 3.0 equiv) was added to a solution of I_2 (38.1 g, 150.1 mmol, 1.0 equiv) in THF (150 mL) at 45 °C. The solution of 1,3-heptadiyne (**16**) in pentane obtained as described above was added to the reaction mixture at 45 °C after 30 min. The reaction was allowed to proceed for 10 h. The mixture was washed with a satd. aqueous solution of $Na_2S_2O_3$ (2 × 200 mL). The aqueous layers were re-extracted with *t*BuOMe (3 × 150 mL). The combined organic layers were dried over $MgSO_4$. The crude product obtained after removal of the solvent in vacuo was purified by flash chromatography (3 cm, petroleum ether, product in fractions 4–10). The title compound (13.98 g, 43 % over the two steps) was obtained as a yellow oil. ^{1}H NMR (300 MHz): $\delta = 0.99$ (t, $J_{7,6} = 7.4$, 7-H$_3$), 1.56 (qt, $J_{6,7} = J_{6,5} = 7.2$, 6-H$_2$), 2.28 (t, $J_{5,6} = 7.2$, 5-H$_2$); IR (film): $\nu = 2985$, 2930, 2230, 1725, 1460, 1035 cm^{-1}; C_7H_7I (218.0): calcd C 38.56, H 3.24; found C 38.29, H 3.37.

5-(Tributylstannyl)-2,4-dien-1-ol (**18**): *n*BuLi (1.2 M in hexane, 93.0 mL, 110 mmol, 2.2 equiv) was added to a suspension of CuCN (4.92 g, 55.0 mmol, 1.1 equiv) in THF (150 mL) at −78 °C. The clear solution was allowed to warm to RT over 30 min and subsequently cooled to −78 °C. Bu_3SnH (32.12 g, 110 mmol, 2.2 equiv) was added over 10 min. After 15 min the alkyne **15** (4.10 g, 50.0 mmol) was added over 5 min. The reaction was allowed to proceed at −78 °C for 2.5 h, then the mixture was poured into a buffer of conc. aqueous NH_3 (20 mL) and satd. aqueous NH_4Cl (180 mL) and extracted with *t*BuOMe (3 × 150 mL). The organic layers were dried over Na_2SO_4. The crude product obtained after removal of the solvent in vacuo was purified by flash chromatography (5 cm, petroleum ether:*t*BuOMe 10:1+1 % NEt_3, product in fractions 10–20). The title compound (14.520 g, 78 %) was obtained as a colorless liquid. ^{1}H NMR (300 MHz): $\delta = 0.87$-0.94 (m, 3 × *CH*$_2$-CH$_2$-CH$_2$-CH$_3$), superimposed by 0.89 (t, $^3J = 7.4$, 3 × CH$_2$-CH$_2$-CH$_2$-*CH*$_3$), 1.31 (tq, both of $^3J = 7.2$, 3 × CH$_2$-CH$_2$-*CH*$_2$-CH$_3$), 1.44–ca. 1.58 (m, CH$_2$-*CH*$_2$-CH$_2$-CH$_3$, OH), 4.20 (br d, $J_{1,2} = 5.6$, 1-H$_2$), 5.80 (dt, $J_{2,3} = 15.6$, $J_{2,1} = 5.9$, 2-H), 6.24 (ddm$_c$, $J_{3,2} \approx 15$, $J_{3,4} \approx 10$, 3-H), superimposed by 6.26 (d, $J_{5,4} = 18.8$, 5-H), 6.54 (dd with extra peaks caused by transition to higher-order spectrum, $J_{4,5} = 18.9$, $J_{4,3} = 9.7$, 4-H); $C_{17}H_{34}OSn$ (373.2): calcd C 54.72, H 9.18; C 54.97, H 9.14.

***trans,trans*-2,4-Dodecadiene-6,8-diyn-1-ol** (**19**): A mixture of LiCl (1.938 g, 45.81 mmol, 3.0 equiv) and $PdCl_2(PPh_3)_2$ (215 mg, 0.304 mmol, 0.02 equiv) was added to a solution of the iodide **17** (3.300 g, 15.17 mmol) in THF (20 mL). The stannane **18** (6.790 g, 18.20 mmol, 1.2 equiv) was added after 2 min. The reaction mixture was washed with saturated aqueous $Na_2S_2O_3$ (3 × 100 mL) after 5 h. The aqueous phases were re-extracted with *t*BuOMe (3 × 80 mL). The combined organic layers were dried over $MgSO_4$. The crude product obtained after removal of the solvent in vacuo was purified by flash chromatography (4 cm, petroleum ether (300 mL), fractions 1–9 petroleum ether:*t*BuOMe 10:1, fractions 10–14 petroleum ether:*t*BuOMe 5:1, fractions 15–19 petroleum ether:*t*BuOMe 2:1, fractions 20–48 petroleum ether:*t*BuOMe 1:1, product in fractions 32–48). The title compound (2.130 g, 81 %) was obtained as a yellow solid (m.p. 68 °C). ^{1}H NMR (300 MHz): $\delta = 1.00$ (t, $J_{12,11} = 7.4$, 12-H$_3$), 1.39 (t, $J_{OH,1} = 5.9$, OH), 1.58 (qt, $J_{11,12} = J_{11,10} = 7.2$, 11-H$_2$), 2.32 (t, $J_{10,11} = 7.0$, 10-H$_2$), 4.24 (br dd, $J_{1,OH} = J_{1,2} = 5.5$, 1-H$_2$), 5.62 (br d, $J_{5,4} = 15.5$, 5-H), 5.96 (dt, $J_{2,3} = 15.4$, $J_{2,1} = 5.5$, 2-H), 6.32 (ddm$_c$, $J_{3,2} \approx 15.0$, $J_{3,4} \approx 11.0$, 3-H*), 6.68 (dd, $J_{4,5} = 15.4$, $J_{4,3} = 10.9$, 4-H*) (* the distinction of 3-H vs 4-H is based on an increment calculation[25] which predicts $\delta_{3H} = 6.24$ and $\delta_{4H} = 6.87$); IR (KBr): $\nu = 3125$, 1620, 1400, 1090, 985 cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 226 (5.40), 235 (5.56), 292 (5.48), 310 (5.41) nm; $C_{12}H_{13}O$ (174.2): calcd C 82.72, H 8.10; found C 82.65, H 8.31.

***trans,trans*-1-Bromo-2,4-dodecadiene-6,8-diyne** (**20**): $BF_3 \cdot OEt_2$ (264 mg, 2.59 mmol, 1.5 equiv) was added to a suspension of alcohol **19** (300 mg, 1.72 mmol) and NaBr (266 mg, 2.59 mmol, 1.5 equiv) in MeCN (15 mL). After 6 h the solution was filtered through a column for flash chromatography (5 cm, filled 4 cm by height, petroleum ether: *t*BuOMe 10:1, product in fractions 2–6). The title compound (248 mg, 61 %) was obtained as a yellow oil. ^{1}H NMR (300 MHz; contains 2 wt % CH_2Cl_2): $\delta = 1.00$ (t, $J_{12,11} = 7.4$, 12-H$_3$), 1.58 (tq, $J_{11,10} = J_{11,12} = 7.2$, 11-H$_2$), 2.33 (t, $J_{10,11} = 7.0$, 10-H$_2$), 4.02 (d, $J_{1,2} = 7.9$, 1-H$_2$), 5.67 (br d, $J_{5,4} = 15.8$, 5-H), 5.99 (td, $J_{2,3} = 15.1$, $J_{2,1} = 7.6$, 2-H), 6.31 (dd, $J_{3,2} = 14.7$, $J_{3,4} = 11.0$, 3-H*, 6.66 (ddm$_c$, $J_{4,5} = 15.5$, $J_{4,3} = 11.0$, 4-H*) (* distinction of 3- vs. 4-H in analogy to compound **19**); $C_{12}H_{13}Br$ (237.1): calcd C 60.78, H 5.53; found C 58.48, H 5.58. No better CH analysis could be obtained.

(*trans,trans*-2,4-Dodecadiene-6,8-diynyl)triphenylphosphonium bromide (**21**): PPh_3 (282 mg, 1.07 mmol, 1.0 equiv) was added to a solution of the bromide **20** (253 mg, 1.07 mmol) in MeCN (10 mL). The solvent was removed in vacuo after 12 h. The title compound (530 mg, 99 %) was obtained as red rubbery mass. ^{1}H NMR (300 MHz): $\delta = 0.98$ (t, $J_{12,11} = 7.4$, 12-H$_3$), 1.56 (qt, $J_{11,12} = J_{11,10} = 7.2$, 11-H$_2$), 2.30 (t, $J_{10,11} = 7.0$, 10-H$_2$), 4.96 (dd, $^2J_{1,P} = 16.2$, $J_{1,2} = 7.5$, 1-H$_2$), 5.55 (dd, $J_{5,4} = 15.5$, $^6J_{5,P} = 2.3$, 5-H),

superimposes the two high-field branches of 5.62 (dtd, $J_{2,3} = 14.3$, $J_{2,1} = {}^3J_{2,P} = 7.3$, 2-H), AB signal [$\delta_A = 6.49$, $\delta_B = 6.61$, $J_{AB} = 11.6$, in addition split by $J_{A,5} = 15.1$, ${}^5J_{A,P} = 0.8$ (only recognizable in two of the four main branches of this signal), $J_{B,2} = 14.4$, ${}^4J_{B,P} = 4.9$, A: 4-H, B: 3-H], 7.65 – 7.72 and 7.77 – 7.89 (2m, of 6 and 9H, respectively, ArH); IR (film): $\nu = 3055$, 2960, 1635, 1435, 1110, 995, 745, 725, 690 cm^{-1}; $C_{30}H_{28}BrP$ (499.4) calcd C 72.15, H 5.65; found C 71.90, H 5.57.

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