First Synthesis of Xerulin, an Inhibitor of the Biosynthesis of Cholesterol

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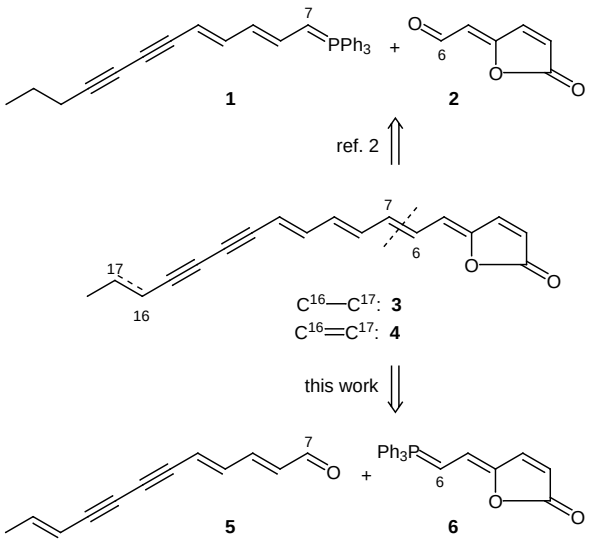
Dedicated to Professor Armin de Meijere (Georg-August-Universität Göttingen) at the occasion of his 60th birthday.

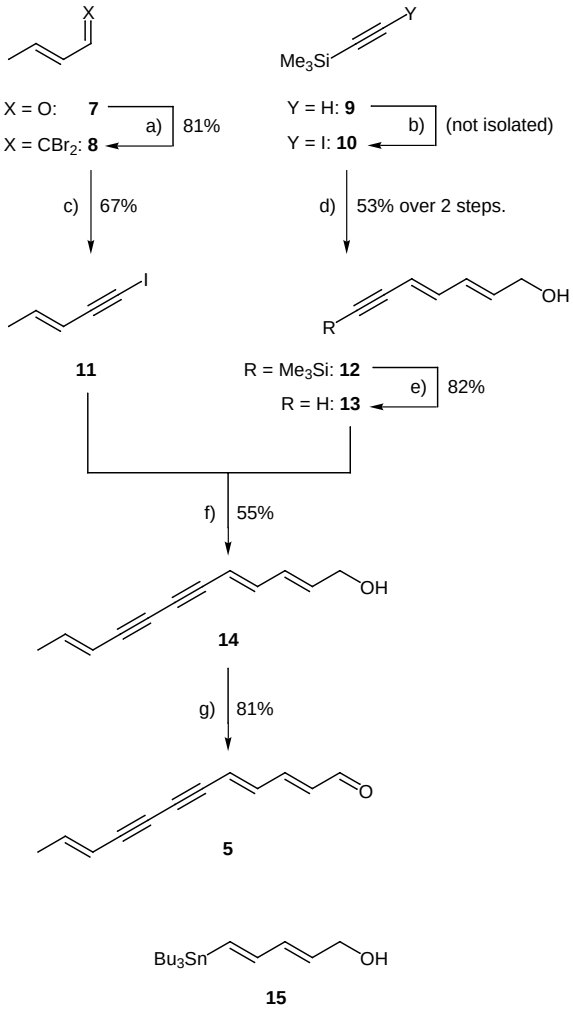
Abstract: Starting from L-ascorbic acid, crotonaldehyde, (trimethylsilyl)acetylene and the stannylated alcohol **15**, the title compound **4** was synthesized for the first time. L-Ascorbic acid was elaborated into phosphonium bromide **19** with a high degree of *Z*-stereoselectivity while the other starting materials were combined for obtaining the unsaturated aldehyde **5**. A Wittig reaction between this aldehyde and the ylide derived from bromide **19** provided xerulin (**4**) along with a mixture of isomers which was readily separable.

Key words: butenolides, butyrolactones, C−C coupling, β-elimination, Wittig reaction

Steglich, Anke, *et al*. isolated and elucidated structurally three unique γ-alkylidenebutenolides from *Xerula melanotricha* Dörfelt (Scheme 1): xerulin (**4**), dihydroxerulin (**3**), and xerulinic acid (which is xerulin with a COOH instead of the CH_3 group).[1] Xerulin (**4**) and dihydroxerulin (**3**) arose as inseparable 90:10 − 65:35 mixtures. They inhibited the biosynthesis of cholesterol in HeLa S3 cells (ID_{50} = 1 μg/g) without being cytotoxic.



Scheme 1



Scheme 2 a) CBr_4 (2.0 equiv), PPh_3 (4.0 equiv.), CH_2Cl_2 °*C*→room temp., 4 h − b) BuLi (1.0 equiv), THF, -78 °C, 5 min, 0 °C, 10 min, -78 °C, I_2 (1.0 equiv), room temp., 10 min; utilized without work-up immediately thereafter. − c) MeLi (2.2 equiv), THF, -78 °C, 20 min, r.t., 10 min, I_2 (1.0 equiv), -78 °C → r.t., 1 h − d) Me_3Si-C≡C-I (1.1 equiv), $Pd(dba)_2$ (2 mol-%), $AsPh_3$ (8 mol-%), **15** (1.0 equiv), THF, r.t., 3 h − e) K_2CO_3 (1.0 equiv), MeOH, r.t., 14 h. − f) $Pd(dba)_2$ (5 mol-%), CuI (15 mol-%), THF/iPr_2NH (5:8, v:v), r.t., 15 min. − g) Dess-Martin periodinane (1.1 equiv), CH_2Cl_2 (not dry), r.t., 5 min.

Recently, we described the first synthesis of dihydroxerulin (**3**).[2] It began with stereoselective preparations of phosphorus ylide **1** and lactone aldehyde **2** and ended with a Wittig reaction between these entities. Irrespective of whether it was effected in the presence or absence of LiBr, it delivered up to 30% of the desired *trans,Z* isomer **3** along with up to 25% of a mixture of at least two stereoisomers. This lack of stereocontrol implies that phophorus ylide **1** is neither "stable" (creating preferentially a *trans*-

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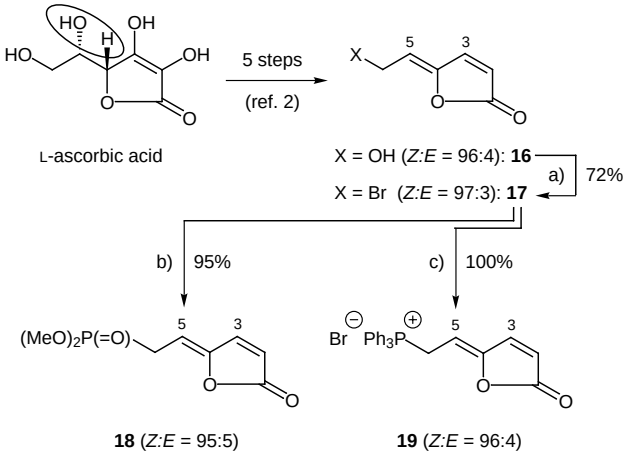
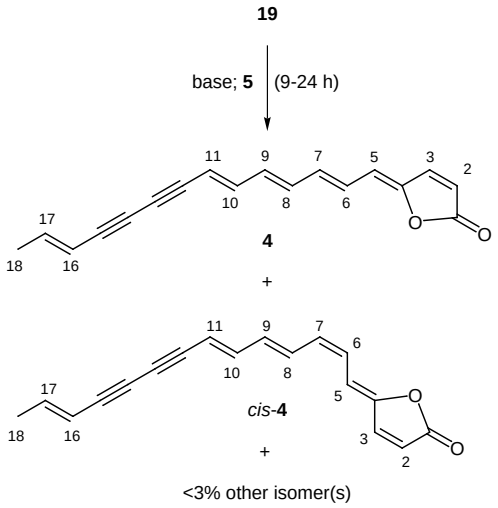
C=C bond) nor "unstable" (creating preferentially a *cis*-C=C bond) but "semistable" which quality almost excludes that a high degree of stereocontrol can be exerted.[3] As a consequence, when we tried to synthesize the next representative of Steglich´s and Anke´s *Xerula* metabolites, namely xerulin (**4**), and chose to rely again upon a Wittig reaction for establishing the C^6=C^7 bond, we decided to switch roles. We introduced the acyclic portion of the target molecule as an aldehyde **5** and the heterocyclic portion as a phosphorus ylide **6** and describe in the following how this was accomplished.

The acyclic portion of xerulin was assembled from crotonaldehyde (**7**), (trimethylsilyl)acetylene (**9**), and the stannylated pentadienol **15**[4] (Scheme 2).[5] Crotonaldehyde (**7**) was C_1-elongated to the dibromodiene **8** (81%) which was subjected to a Fritsch-Buttenberg-Wiechell rearrangement under the Corey-Fuchs conditions[6]. The resulting lithioalkyne was quenched with iodine[7] furnishing the iodopentenyne **11** in 67% yield. Commercial (trimethylsilyl)acetylene (**9**) was oxidized by successive treatment with BuLi and iodine[7] giving a THF solution of the corresponding iodoalkyne **10**. It was used as such for a $Pd(dba)_2$ catalyzed coupling with the stannylalcohol **15**[4] providing the unsaturated alcohol **12** in 53% overall yield.[8] Desilylation in basic methanol[9] furnished the terminal alkyne **13** (82%). It was combined with iodoalkyne **11** in a $Pd(dba)_2$/CuI-catalyzed Cadiot-Chodkiewicz reaction[10] providing the desired diyne **14** and almost no self-coupling products.[11] The sequence of Scheme 2 was terminated by a Dess-Martin oxidation[12] leading to the desired aldehyde **5**[13] in 81% yield.



Scheme 3. a) PPh_3 (2.5 equiv), CBr_4 (2.5 equiv), CH_2Cl_2, 0 °C, 30 min. − b) $P(OMe)_3$ (excess), 80 °C, 2 h − c) PPh_3 (1.0 equiv), MeCN, r.t., 14 h.

Potential precursors of the heterocyclic moiety of xerulin were synthesized from the γ-(hydroxyethylidene)butenolide **16** (96% *Z*; Scheme 3) which we had made accessible from L-isoascorbic acid for synthesizing dihydroxerulin.[2] The OH group of compound **16** was replaced by Br[14] giving the brominated butenolide **17** in 72% yield (97% *Z*).



Conditions	Base	**19**:Base:**5**	Solvent	T [ºC]	Yield **4** [%]	Yield *cis*-**4** + isomer(s) [%]
1	NEt_3	2.0 : 2.0 : 1	CH_2Cl_2	-78 - 20	19	20
2	DBN	2.0 : 2.0 : 1	CH_2Cl_2	-78 - 20	0	0
3	KOtBu	2.0 : 2.0 : 1	THF	-78 - 20	6	5
4	KHMDS	2.0 : 2.0 : 1	THF	-78 - 20	12	12
5	dimsyl-Na	2.0 : 2.0 : 1	DMSO	20	0	0
6	BuLi	1.1 : 1.1 : 1	THF	-78 - 20	12	12
7	BuLi	2.0 : 2.0 : 1	THF	0 - 20	26	27
8	K_2CO_3	1.5 : 1.4 : 1	CH_2Cl_2	20	19	20
9	K_2CO_3	2.0 : 2.0 : 1	CH_2Cl_2	50	16	16
10	K_2CO_3	5.0 : 5.5 : 1	CH_2Cl_2	50	28	27
11	K_2CO_3	5.0 : 5.0 : 1	CH_2Cl_2	90	7	7

Scheme 4

Heating this compound in trimethylphosphite led to the butenolide-containing phosphonate **18** (95% *Z*) in 95% yield while an S_N reaction with triphenylphosphine provided quantitatively the corresponding phosphonium salt **19** (96% *Z*) at room temperature. Configurational assignments of these species are based on the high-field shifted 300 MHz ^{1}H-NMR resonances of protons 3-H (always) and 5-H (except in **19**) in *Z*- compared with *E*-isomers (Table 1);[15] we had observed similar shift differences in γ-alkylidenebutenolides earlier.[2,15]

Table 1 Stereochemically relevant 300 MHz ^{1}H-NMR shifts of γ-alkylidenebutenolides **16**-**19**

	Z isomer		*E* isomer	
	δ(3-H)	δ(5-H)	δ(3-H)	δ(5-H)
16	7.39 [2]	5.48 [2]	7.83 [2]	5.91 [2]
17	7.41	5.55	7.73	6.00
18	7.36	5.28	7.62	5.67
19	7.56	5.86	8.80	5.57

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Table 2 ^{1}H NMR shifts and vicinal coupling constants of natural xerulin (**4**), synthetic xerulin, and the synthetic butenolide *cis*-**4** (500 MHz, $CDCl_3$)

	2-H	3-H	5-H	6-H	7-H	8-H	9-H	10-H	11-H	16-H	17-H	18-H_3
natural **4** [1]	6.17	7.35	5.88	6.81		6.37 - 6.54		6.76	5.75	5.60	6.33	1.83
synthetic **4**	6.19	7.38	5.90	6.83	6.49	6.44	6.40	6.78	5.77	5.62	6.35	1.84
cis-**4**	6.20	7.42	6.27	6.62	6.34	6.78	6.45	6.77	5.78	5.60	6.33	1.83
	$J_{2,3}$	-	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$	$J_{10,11}$	-	$J_{16,17}$	$J_{17,18}$	
natural **4** [1]	5.5	-	11.8	14.5	-	-	10.5	15.5	-	15.8	6.8	
synthetic **4**	5.3	-	11.7	14.2	10.7	14.2	10.5	15.3	-	15.8	7.0	
cis-**4**	5.3	-	12.0	11.6	11.9	14.0	11.4	15.5	-	15.7	6.9	

Exploratory Horner-Wadsworth-Emmons reactions between lithiated phosphonate **18** and aldehyde **5** failed to provide even traces of xerulin. Gratifyingly, Wittig reactions between aldehyde **5** and the ylide derived from butenolide **19** gave the desired olefin under various conditions (Scheme 4). A suspension of K_2CO_3 in CH_2Cl_2 gave up to 55% olefin (entry 10), BuLi in THF 53% (entry 7), and NEt_3 in CH_2Cl_2 39% (entry 1). KHMDS as a base was mediocre (→24% yield; entry 4), KOtBu poor (→11% yield; entry 3) and DBN as well as dimsyl-Na did not lead to products (entries 2, 5).

Unfortunately, irrespective of the reaction conditions the Wittig reactions of Scheme 4 were non-stereoselective. Each of them furnished almost equal amounts of the desired *trans*-olefin **4** (≡ xerulin; up to 28% yield)[16] and its isomer *cis*-**4**.[17] However, the latter was easily separable by chromatography on silicagel (petroleum ether / *tert*-butylmethylether 7:1 → petroleum ether / *tert*-butylmethylether / dichloromethane 4:1:0.2 → 2:1:19; **4** eluted first, *cis*-**4** second).

The 500 MHz ^{1}H-NMR spectrum of synthetic xerulin in $CDCl_3$ was inaccordance with the data of the natural product (Table 2).[1] In addition, it allowed a computer analysis of the previously unresolved multiplet of 7-H, 8-H and 9-H.[16] This analysis revealed a coupling constant $J_{8,9}$ = 14.2 Hz and thereby confirmed the suspected[1] *trans*-configuration of the C^8=C^9 bond. In compound *cis*-**4**, the *cis*-configuration of the newly formed C^6=C^7 bond was deduced from $J_{6,7}$ = 11.6 Hz and the *Z*-configuration of the C^4=C^5 bond from $\delta_{3\text{-H}}$ = 7.42; the latter value is smaller than $\delta \approx$ 7.9 expected[2,15] for an *E* isomer. The *Z*-configuration of the C^4=C^5 bond in compound *cis*-**4** is underlined by the close resemblance of $\delta_{3\text{-H},cis\text{-}4}$ = 7.42 with $\delta_{3\text{-H, natural xerulin}}$ = 7.35 and $\delta_{3\text{-H, synthetic xerulin}}$ = 7.38.

In summary, xerulin (**4**) has been synthesized by a convergent route and was obtained in pure form for the first time. The only reason why this synthesis cannot be called ´stereoselective´ is that the terminating Wittig reaction did not show more stereocontrol than the Wittig reaction − of opposite polarity − used for synthesizing dihydroxerulin (**3**). We are currently looking for modified syntheses of these compounds **4** which allow to construct the C^6=C^7 bond *with* stereocontrol.

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(13) **all-*trans*-2,4,10-Dodecatriene-6,8-diyn-1-al** (**5**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (dd, $J_{12,11}$ = 6.8, $^4J_{12,10}$ = 1.9, 12-H_3), 5.62 (dm_c, $J_{10,11} \approx$ 15.9, 10-H), 6.15 (d, $J_{5,4}$ = 15.4, 5-H), 6.23 (dd, $J_{2,3}$ = 15.5, $J_{2,1}$ = 8.0, 2-H), 6.40 (dq, $J_{11,10}$ = 15.9, $J_{11,12}$ = 7.0, 11-H), 6.87 (dd, $J_{4,5}$ = 15.3, $J_{4,3}$ = 11.5, 4-H), 7.10 (dd, $J_{3,2}$ = 15.5, $J_{3,4}$ = 11.3, 3-H), 9.59 (d, $J_{1,2}$ = 7.5, 1-H).− IR ($CDCl_3$): ν = 3035, 2915, 2825, 2745, 2195, 1680, 1645, 1605, 1445, 1290, 1215, 1160, 1115, 985, 950, 915, 750, 735, 715

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cm^{-1}.– Analysis: calc for $C_{12}H_{10}O$ (170.2): C 84.68, H 5.92; found: C 84.50, H 6.10.

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(16) **Xerulin** (**4**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84 (dd, $J_{18,17}$ = 6.9, $^4J_{18,16}$ = 1.9, 18-H_3), 5.62 (dqd, $J_{16,17}$ = 15.8, $^4J_{16,18}$ = 1.8, $^7J_{16,11}$ = 1.0, 16-H), 5.77 (d, $J_{11,10}$ = 15.3, 11-H), 5.90 (d, $J_{5,6}$ = 11.7, 5-H), 6.19 (d, $J_{2,3}$ = 5.3, 2-H), 6.35 (dq, $J_{17,16}$ = 15.8, $J_{17,18}$ = 7.0, 17-H), 6.40-6.56 (m, 7-H, 8-H, 9-H)*, 6.78 (dd, $J_{10,11}$ = 15.3, $J_{10,9}$ = 10.5, 10-H), in part superimposed by 6.83 (dd, $J_{6,7}$ = 14.2, $J_{6,5}$ = 11.9, 6-H), 7.38 (d, $J_{3,2}$ = 5.2, 3-H). *This spectrum was simulated by the program DAVINX® under WINDOWS® as a 7-spin system comprising 5-H - 11-H. Varying the non-observable δ and *J* values systematically until the calculated spectrum showed the best fit with the experimental spectrum, we found $\delta_{7\text{-H}}$ = 6.49, $\delta_{8\text{-H}}$ = 6.44, $\delta_{9\text{-H}}$ = 6.40, $J_{7,8}$ = 10.7, and $J_{8,9}$ = 14.2.– ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.92 (C-18), 72.54, 79.40, 80.66, and 83.37 (C-12, C-13, C-14, C-15), 109.94 (C-16), 112.18 (C-11), 114.72 (C-5), 118.92 (C-2), 127.78 (C-6), 135.13, 135.60, and 137.87 (C-7, C-8, C-9), 142.59 (C-3), 143.85 (C-10), 144.02 (C-17), 149.53 (C-4), 169.40 (C-1).– IR ($CDCl_3$): ν = 3030, 2960, 2925, 2855, 2250, 2190, 1775, 1750, 1530, 1335, 1215, 1105, 1065, 995, 920, 895, 805, 765, 715 cm^{-1}.– UV (MeOH): λ_{max} (lg ε) = 404 (6.02), 421 (6.02) nm. *m/z* = 262.0993 ($M^{\oplus}$) ±2 mDa confirmed by HRMS (EI, 70 eV).

(17) **Z-5-[(2*Z*,4*E*,6*E*,12*E*)-Tetradecatetraene-8,10-diynylidene)-5*H*-2-furanone** (*cis*-**4**): ^{1}H NMR [500 MHz, $CDCl_3$, contaminated with <10% isomer(s)]: δ = 1.83 (dd, $J_{18,17}$ = 6.9, $^4J_{18,16}$ = 1.9, 18-H_3), 5.60 (dqd, $J_{16,17}$ = 15.8, $^4J_{16,18}$ = 1.6, $^7J_{16,11}$ = 1.2, 16-H), 5.78 (d, $J_{11,10}$ = 15.6, 11-H), 6.20 (d, $J_{2,3}$ = 5.3, 2-H), 6.27 (d, $J_{5,6}$ = 12.4, 5-H), 6.33 (dq, $J_{17,16}$ = 15.7, $J_{17,18}$ = 6.9, 17-H), superimposed by 6.34 (dd, $J_{7,6} \approx J_{7,8} \approx$ 11.5, 7-H), 6.45 (dd, $J_{9,8}$ = 14.1, $J_{9,10}$ = 11.4, 9-H), 6.62 (dd, $J_{6,7} \approx J_{6,5} \approx$ 11.6, 6-H), 6.77 (dd, $J_{10,11}$ = 15.3, $J_{10,9}$ = 11.4, 10-H), superimposed by 6.78 (dd, $J_{8,9}$ = 13.9, $J_{8,7}$ = 12.3, 8-H), 7.42 (d, $J_{3,2}$ = 5.2, 3-H).– ^{13}C NMR [125.7 MHz, $CDCl_3$, contaminated with <10% isomer(s)]: δ = 19.01 (C-18), 72.42, 79.35, 80.53, and 83.37 (C-12, C-13, C-14, C-15), 109.67 (C-5), 109.85 (C-16), 112.56 (C-11), 119.33 (C-2), 123.77 (C-6), 130.00 (C-8), 134.33 (C-7), 135.77 (C-9), 142.84 (C-3), 143.60 (C-10), 144.07 (C-17), 149.69 (C-4), 169.29 (C-1).– IR ($CDCl_3$): ν = 2925, 2855, 2255, 1775, 1750, 1675, 1600, 1530, 1465, 1380, 1335, 1160, 1105, 1065, 995, 925, 890, 755, 720, 705, 650 cm^{-1}.– UV (MeOH): λ_{max} (lg ε) = 405 (6.12), 423 (6.12) nm.– *m/z* = 262.0993 ($M^{\oplus}$) ±2 mDa confirmed by HRMS (EI, 70 eV).

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