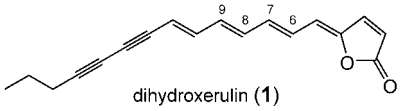
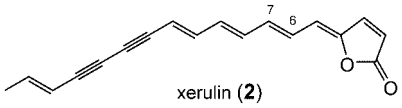
Natural Products Synthesis

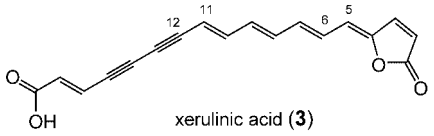
Total Synthesis of Xerulinic Acid**

*Achim Sorg and Reinhard Brückner**

In 1990, Steglich, Anke, and co-workers identified a family of three novel polyenes from the fungus *Xerulina melanotricha* DÖRFELT: dihydroxerulin (**1**), xerulin (**2**), and xerulinic acid (**3**).[1] Dihydroxerulin (**1**) and xerulin (**2**) were characterized



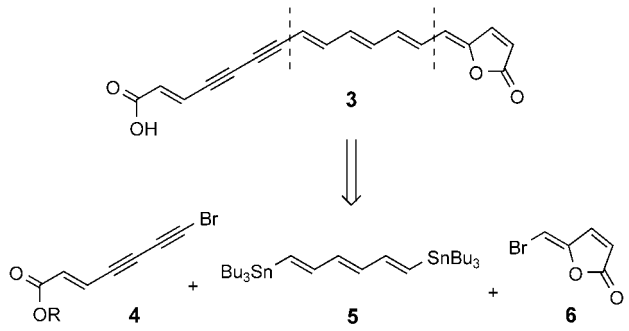




as 90:10–65:35 mixtures, whereas xerulinic acid (**3**) was obtained pure. Each of these compounds inhibited the biosynthesis of cholesterol in HeLa S3 cells by blocking HMG-CoA synthase (EC 4.1.3.5); moreover, in the same cell system, **3** suppressed the synthesis of RNA at $IC_{50} \approx 100$ μM.

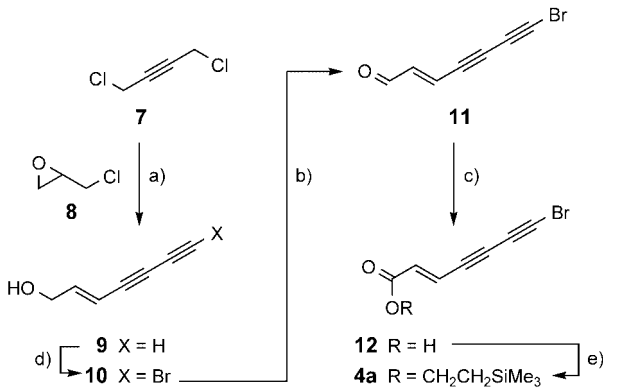
The biological activity and structural uniqueness of the xerulin family stimulated the interest of the synthetic community. The first laboratory syntheses both of dihydroxerulin[2] and xerulin[3] were reported by our group. Rossi et al.[4] completed another synthesis of dihydroxerulin, and Negishi, Alimardanov, and Xu[5] prepared xerulin. Herein we report the first total synthesis of xerulinic acid based on unprecedented disconnections.

Scheme 1 outlines our retrosynthetic analysis. It differs from our routes to dihydroxerulin[2] and xerulin[3] in that we intended to form C–C rather than C=C bonds in the final steps. The latter approach—by Wittig reactions—had been nonstereoselective irrespective of whether the ylides corresponded to the right- or left-hand moiety of the target structure.[2,3] In contrast, the presently adopted approach



Scheme 1. Retrosynthetic analysis of xerulinic acid.

would establish *all* C=C bonds and interconnect them by C–C-forming Stille couplings.[6] This identified the enediyne carboxylate **4**, the hitherto unknown bisstannane **5**, and the novel building block **6**[7]—which ought to be *generally* useful for synthesizing γ-alkylidenebutenolides[8]—as our key precursors. Their syntheses are described in Schemes 2–4,



Scheme 2. a) $LiNH_2$ (6 equiv), NH_3 (l), −35 °C, 15 min; addition of **8**, 3.5 h; →RT, 17% (reference [9]: 21%); b) Dess–Martin periodinane (1.52 equiv), CH_2Cl_2, 0 °C→RT, 2.5 h, 79%; c) $NaClO_2$ (2.1 equiv), KH_2PO_4 (2.5 equiv), 2-methyl-2-butene (3.5 equiv), acetone/H_2O = 3:2, 0 °C, 89%; d) NBS (1.30 equiv), $AgNO_3$ (0.08 equiv), acetone, room temperature, 13 h, 79%; e) $HOCH_2CH_2SiMe_3$ (1.2 equiv), DCC (1.1 equiv), DMAP (0.05 equiv), ethyl acetate, 0 °C→RT, 2 h, 83%. NBS = *N*-bromosuccinimide, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine.

respectively, and their coupling to give xerulinic acid (**3**) is shown in Scheme 5.

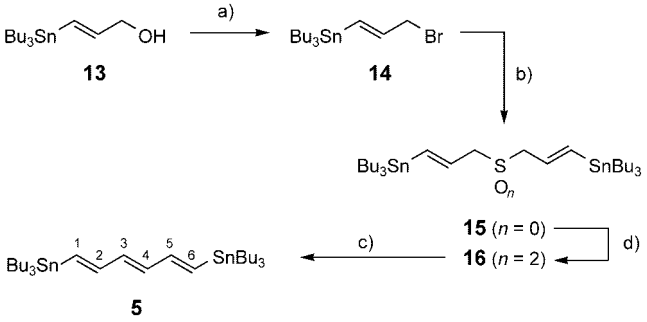
The synthesis of enediyne carboxylate **4a** began with the synthesis of enediynol **9** from epichlorohydrin (**8**) and lithiobutadiyne generated in situ from 1,4-dichlorobut-2-yne (**7**) and excess lithium amide (Scheme 2).[9] Terminal bromination of **9** with NBS/$AgNO_3$[10] led to bromoenediynol **10**.[11] The corresponding aldehyde **11** was generated by a Dess–Martin oxidation[12] of **10** (79% yield) and taken on to the corresponding carboxylic acid **12** by a Lindgren oxidation[13] (89% yield). Esterification with 2-trimethylsilylethanol in the presence of DCC and DMAP provided the unstable ester **4a** in 83% yield.[14]

The synthesis of bisstannane **5** proceeded highly stereoselectively (Scheme 3). It was assembled starting from the tin-

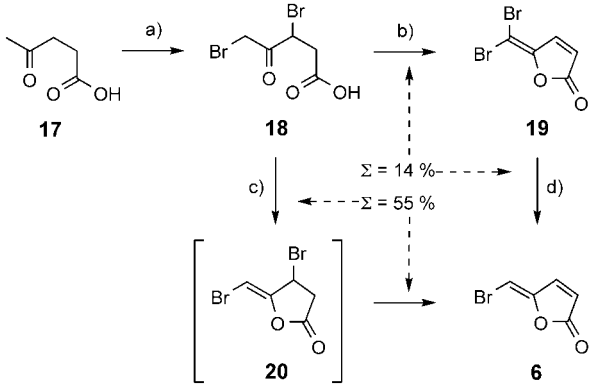
[*] A. Sorg, Prof. Dr. R. Brückner
Institut für Organische Chemie und Biochemie
Universität Freiburg
Albertstrasse 21, 79104 Freiburg (Germany)
Fax: (+49) 761-203-6100
E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de

[**] This work was financially supported by the Fonds der Chemischen Industrie. We are grateful to Dr. Manfred Keller for valuable spectroscopic support and to Melanie Waldrich for technical assistance.

 DOI: 10.1002/anie.200453729



Scheme 3. a) CBr_4 (1.21 equiv), CH_2Cl_2, 0 °C, addition of PPh_3 (1.10 equiv), 1 h, 82% (reference [16]: 81%); b) Na_2S (0.5 equiv), $Bu_4N^+ HSO_4^-$ (0.7 mol%), H_2O/THF, room temperature, 7 h, 90%; c) KOH (30% on Al_2O_3; 20 equiv), CBr_2F_2 (4 equiv), THF, 0 °C, 30 min, 73%; d) $(NH_4)_6Mo_7O_{24}$ (0.2 equiv), H_2O_2 (10 equiv), EtOH, 0 °C→RT, 1 h, 88%.

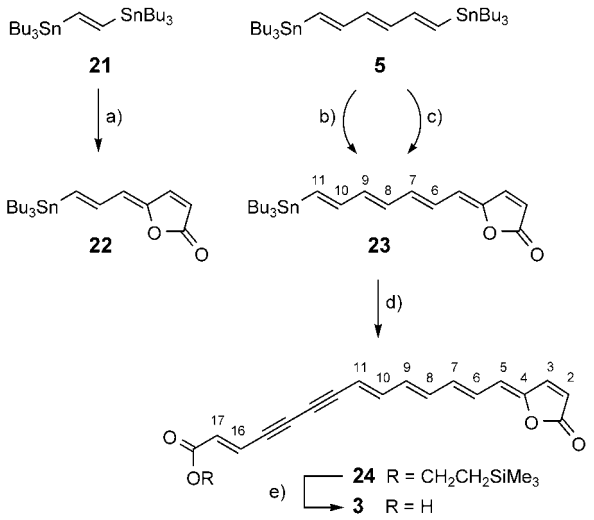


Scheme 4. a) Br_2 (2.1 equiv), CH_2Cl_2, 0 °C→RT, 2 h, 60% (reference [25]: 40%); b) oleum/conc. H_2SO_4 2:1 (v/v), 50–60 °C, 6 min; 28%;[7] c) 1) P_4O_{10} (1.2 equiv), CH_2Cl_2, 0 °C→Δ, 1 h, filtration; 2) NEt_3 (1.03 equiv), CH_2Cl_2, 0 °C→Δ, 1 h, 55%; d) $HSnBu_3$ (1.10 equiv), $[Pd(PPh_3)_4]$ (0.10 equiv), THF, 65 °C, 3 h, 51%.[7]

containing alcohol **13**,[15] which was obtained by cuprostannylation/protonolysis of propargyl alcohol. We transformed compound **13** through nucleophilic attack first into the tin-containing bromide **14** (82%)[16] and subsequently into the tin-containing sulfide **15** (90%).[17] Oxidation with peroxomolybdate provided the corresponding sulfone **16** (88%).[18] Deprotonation of sulfone **16** in the presence of CBr_2F_2 with Al_2O_3-supported KOH[19] induced a Ramberg–Bäcklund reaction[20] to provide triene **5** in 73% yield. The resulting sample of **5** represented a 96:4 mixture of the *trans,trans,trans* and the *trans,cis,trans* isomers. This was inferred from the ratio of the integrals for 2-H and 5-H (*trans,trans,trans*-**5**: $\delta_{2\text{-H}} = \delta_{5\text{-H}} = 6.56$ ppm, *trans,cis,trans*-**5**: $\delta_{2\text{-H}} = \delta_{5\text{-H}} = 7.08$ ppm) and from the magnitudes of the vicinal olefinic H,H coupling constants in the major isomer ($J_{1,2} = J_{5,6} = 18.6$ Hz, $J_{3,4} = 15.1$ Hz).[21] 1,6-Bis(tributylstannyl)hexatriene (**5**) ought to be a valuable conjuctive C_6 reagent in analogy to 1,2-bis(tributylstannyl)ethylene as a conjunctive C_2 reagent[22] and 1,4-bis(methylstannyl)butadiene as a conjunctive C4 reagent.[23,24] The first example of a conjunctive C_6 reagent is provided in the present study (see Scheme 5). Notably, we were able to couple *different* electrophiles at the termini (C1 vs. C6) of **5**. Such a differentiation is more difficult to realize than the C1/C4 differentiation in the single unsymmetrical biscoupling reported for the aforementioned C_4 bisstannane).[23a]

We recently reported the two-step preparation of (bromomethylene)butenolide **6** from dibromolevulinic acid (**18**;[25a] Scheme 4) by oxidative cyclization (→**19**) and stereoselective reduction (→**6**).[7] Since then we have been able to shorten this synthesis by successively treating the same dibromolevulinic acid (**18**) in one pot with two reagents:[26] P_4O_{10} effects a dehydration, presumably giving rise to the enol ester intermediate **20**; thereafter triethylamine (instead of triethylenediamine, which was used in ref. [26]) induces the β-elimination of HBr. This gave four times as much bromobutenolide **6**[27] as our previous synthesis, with the same perfect *Z* selectivity, both of which were prerequisites for **6** to become a viable starting material for our study (we are unaware of previous synthetic applications of this compound[25b]).

To couple bisstannane **5** and butenolide **6** in a 1:1 ratio without too much competitive 1:2 coupling, we considered it safest to perform one Sn→Li exchange per reagent molecule first, a Li→Zn exchange next, and a Negishi coupling[28] thereafter. The model compound 1,2-bis(tributylstannyl)-ethylene (**21**)[22] and butenolide **6** could indeed be combined in this manner, forming 1:1 coupling product **22** in 46% yield (Scheme 5). To our delight, we could extend this procedure to the 1,6-bis(stannyl)hexatriene **5** and butenolide **6** to obtain the desired 1:1 product **23** in 63% yield. By comparison, the combination of the same reagents through a Stille coupling in THF in the presence of $[Pd(dba)_2]$ and $AsPh_3$ led to **23** in only 44% yield. The all-*trans* configuration of **23** was proved by ^1H NMR spectroscopy (499.9 MHz, $CDCl_3$; for the number-



Scheme 5. a) **21** (1.01 equiv), *n*BuLi (1.05 equiv), THF, −78 °C, 70 min; then $ZnCl_2$ (1.05 equiv), →−20 °C, 2 h; then **6**, $[Pd(PPh_3)_4]$ (5 mol%), 0 °C→RT, 45 min, 46%; b) **5** (1.3 equiv), *n*BuLi (1.3 equiv), THF, −78 °C, 20 min; then $ZnCl_2$ (1.3 equiv), 30 min; then **6**, $[Pd(PPh_3)_4]$ (5 mol%), 0 °C, 1 h, 63%; c) **6** (1.1 equiv), $[Pd(dba)_2]$ (5 mol%), $AsPh_3$ (20 mol%) THF, room temperature, 2 h, 44%; d) **4a** (1.08 equiv), $[Pd(dba)_2]$ (6 mol%), $AsPh_3$ (19 mol%), THF, room temperature, 5 h, 73%; e) Bu_4NF (1.5 equiv), THF, 0 °C→RT, 2 h, 61%.

ing see Scheme 5): $J_{6,7} = 14.9$ Hz, $J_{8,9} = 14.7$ Hz, and $J_{10,11} = 18.7$ Hz.

The carbon skeleton of our target molecule **3** was completed by a Stille coupling[6] ([Pd(dba)$_2$],[29] AsPh$_3$[29]) between the brominated enediyne carboxylate **4a** and the stannylated heptatrienylidenebutenolide **23** (Scheme 5). Provided that exposure to atmospheric oxygen and daylight was avoided, the reaction gave xerulinic acid ester **24**[30] in 73% yield. In the final step, this compound was deprotected by treatment with anhydrous Bu$_4$NF in THF to give **3** in 61% yield. The resulting specimen of synthetic xerulinic acid (**3**) was scrutinized by ^{1}H, ^{13}C, and 2D NMR spectroscopy at the same field strengths (500 MHz/126 MHz) and in the same solvent ([D$_6$]DMSO) as the natural product. The juxtaposition of our data and those from Steglich and co-workers[1,31] unambiguously showed that our compound and the natural product are identical.

In summary, we have completed the first, highly convergent synthesis of xerulinic acid (**3**). Although xerulinic acid is perhaps not "complex", its preparation is by no means simple and its tendency to "polymerize" cannot be overestimated. Our synthetic strategy towards **3** is distinct from previous strategies aimed at the xerulin family of compounds.[32] Bisstannane **5** should open a *general* route to polyunsaturated molecules containing a *trans,trans,trans*-hexatriene moiety and lactone **6** should open a *general* route to γ-alkylidenebutenolides.

Received: January 12, 2004 [Z53729]

Keywords: C–C coupling · inhibitors · lactones · natural products · stereoselective synthesis

[1] D. Kuhnt, T. Anke, H. Besl, M. Bross, R. Herrmann, U. Mocek, B. Steffan, W. Steglich, *J. Antibiot.* **1990**, *43*, 1413 – 1420.
[2] K. Siegel, R. Brückner, *Synlett* **1999**, 1227 – 1230.
[3] K. Siegel, R. Brückner, *Chem. Eur. J.* **1998**, *4*, 1116 – 1122.
[4] R. Rossi, F. Bellina, A. Catanese, L. Mannina, D. Valensin, *Tetrahedron* **2000**, *56*, 479 – 487.
[5] E.-i. Negishi, A. Alimardanov, C. Xu, *Org. Lett.* **2000**, *2*, 65 – 67.
[6] For reviews, see: a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504 – 519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508 – 524; b) V. Farina, G. P. Roth in *Advances in Metal-Organic Chemistry*, *Vol. 5* (Ed.: L. S. Liebeskind), JAI, Greenwich, Connecticut, **1996**, pp. 1 – 53; c) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1 – 652.
[7] A. Sorg, K. Siegel, R. Brückner, *Synlett* **2004**, 321 – 325.
[8] a) D. W. Knight, *Contemp. Org. Synth.* **1994**, *1*, 287 – 315; b) E.-i. Negishi, M. Kotora, *Tetrahedron* **1997**, *53*, 6707 – 6738; c) R. Brückner, *Chem. Commun.* **2001**, 141 – 152; d) R. Brückner, *Curr. Org. Chem.* **2001**, *5*, 679 – 718.
[9] S. R. Landor, E. S. Pepper, *J. Chem. Soc. C* **1966**, 2283 – 2285.
[10] Prepared by a procedure analogous to that of: T. V. Bohner, R. Beaudegnies, A. Vasella, *Helv. Chim. Acta* **1999**, *82*, 143 – 160.
[11] All new compounds gave satisfactory ^{1}H and ^{13}C NMR spectra and correct elemental analyses, except acid **12**, unstable ester **4a**, and xerulinic acid (**3**), for all of which, however, correct high-resolution mass spectra were obtained.
[12] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156.
[13] a) B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888 – 890 (resorcinol used as hypochlorite scavenger); b) B. S. Bal, W. E. Childers, Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091 – 2096 (2-methyl-2-butene used as hypochlorite scavenger).
[14] Prepared by a procedure analogous to that of: a) N. Jeker, C. Tamm, *Helv. Chim. Acta* **1988**, *71*, 1895 – 1903; b) G. T. Bourne, D. C. Horwell, M. C. Pritchard, *Tetrahedron* **1991**, *47*, 4763 – 4774.
[15] Prepared by a procedure analogous to that of: J.-F. Betzer, F. Delaloge, B. Muller, A. Pancrazi, J. Prunet, *J. Org. Chem.* **1997**, *62*, 7768 – 7780.
[16] A. S.-Y. Lee, C.-W. Wu, *Tetrahedron* **1999**, *55*, 12531 – 12542.
[17] Method: F. Reimnitz, Ph.D. thesis, Universität Freiburg, **2000**, pp. 71–72, 147 – 148.
[18] The method is same as that described for the oxidation of heterocycle-substituted sulfides en route to Julia–Lythgoe olefins: P. A. Blakemore, P. J. Kocienski, S. Marzcak, J. Wicha, *Synthesis* **1999**, 1209 – 1215.
[19] T.-L. Chan, S. Fong, Y. Li, T.-O. Man, C.-D. Poon, *J. Chem. Soc. Chem. Commun.* **1994**, 1771 – 1772; pure THF was used instead of *t*BuOH/THF (3:1).
[20] For a review, see: L. A. Paquette, *Org. React.* **1977**, *25*, 1 – 71.
[21] **5**: ^{1}H NMR (499.9 MHz, $CDCl_3$, TMS): $\delta = 0.83$–0.97 (m; $6\times SnCH_2CH_2CH_2CH_3$), overlaps with 0.89 (t, $J_{vic} = 7.3$ Hz; $6\times SnCH_2CH_2CH_2CH_3$), 1.31 (tq, both $J_{vic} = 7.3$ Hz; $6\times SnCH_2CH_2CH_2CH_3$), 1.41–1.58 (m; $6\times SnCH_2CH_2CH_2CH_3$), 6.15 ($m_c$, higher order; 3-H, 4-H), 6.29 (d, $J_{1,2} = J_{6,5} = 18.6$ Hz, each peak flanked by Sn isotope satellites as 2 d, $^2J_{^{119}Sn,H} = 70.1$ Hz, $^2J_{^{117}Sn,H} = 67.2$ Hz; 1-H, 6-H), 6.56 ppm (m_c, higher order; 2-H, 5-H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 9.6$ (flanked by Sn isotope satellites as 2 d, $^1J_{^{119}Sn,C1'} = {}^1J_{^{119}Sn,C1''} = 344.8$ Hz, $^1J_{^{117}Sn,C1'} = {}^1J_{^{117}Sn,C1''} = 329.4$ Hz; $SnCH_2CH_2CH_2CH_3$), 13.7 ($SnCH_2CH_2CH_2CH_3$), 27.3 (flanked by Sn isotope satellites as 1 d, $^3J_{^{119}Sn,C3'} = {}^3J_{^{119}Sn,C3''} = {}^3J_{^{117}Sn,C3'} = {}^3J_{^{117}Sn,C3''} = 54.5$ Hz; $SnCH_2CH_2CH_2CH_3$), 29.1 (flanked by Sn isotope satellites as 1 d, $^2J_{^{119}Sn,C2'} = {}^2J_{^{119}Sn,C2''} = {}^2J_{^{117}Sn,C2'} = {}^2J_{^{117}Sn,C1''} = 20.6$ Hz; $SnCH_2CH_2CH_2CH_3$), 134.5 (flanked by Sn isotope satellites as 1 d, $^3J_{^{119}Sn,C3} = {}^3J_{^{119}Sn,C4} = {}^3J_{^{117}Sn,C3} = {}^3J_{^{117}Sn,C4} = 73.6$ Hz; C3, C4), 135.6 (flanked by Sn isotope satellites as 2 d, $^1J_{^{119}Sn,C1} = {}^1J_{^{119}Sn,C6} = 380.0$ Hz, $^1J_{^{117}Sn,C1} = {}^1J_{^{117}Sn,C6} = 363.3$ Hz; C1, C6), 146.9 (flanked by Sn isotope satellites as 1 d, $^2J_{^{119}Sn,C2} = {}^2J_{^{119}Sn,C5} = {}^2J_{^{117}Sn,C2} = {}^2J_{^{117}Sn,C5} = 6.4$ Hz; C2, C5); SELINCOR (S. Berger, *J. Magn. Reson.* **1989**, *81*, 561 – 564; 499.9 MHz/125.7 MHz, $CDCl_3$): $J_{3,4} = 15.1$ Hz, $J_{3,2} = J_{4,5} = 10.1$ Hz; elemental analysis (%): calcd for $C_{30}H_{60}Sn_2$ (656.3): C 54.74, H 9.19; found: C 53.81, H 8.97.
[22] a) K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, *115*, 4419 – 4420; b) J. S. Panek, C. E. Masse *J. Org. Chem.* **1997**, *62*, 8290 – 8291; c) C. E. Masse, M. Yang, J. Solomon, J. S. Panek, *J. Am. Chem. Soc.* **1998**, *120*, 4123 – 4134; d) P. M. Pihko, A. M. P. Koskinen, *Synlett* **1999**, 1966 – 1968.
[23] a) A. Kiehl, A. Eberhardt, M. Adam, V. Enkelmann, K. Müllen, *Angew. Chem.* **1992**, *104*, 1623 – 1626; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1588 – 1591; b) D. Nozawa, H. Takikawa, K. Mori, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2043 – 2046.
[24] A fully conjugated 3,8-dimethyl-C$_{10}$-bis(tributylstannane) has also been synthesized and used as a building block: B. Vaz, R. Alvarez, A. R. de Lera, *J. Org. Chem.* **2002**, *67*, 5040 – 5043.
[25] a) A. J. Manny, S. Kjelleberg, N. Kumar, R. de Nys, R. W. Read, P. Steinberg, *Tetrahedron* **1997**, *53*, 15813 – 15826. b) The aforementioned authors prepared lactone **6** for the first time but the Experimental Section of their study details no more than a 2% yield of **6** separated chromatographically from a 54%:8%:3%:2%:trace mixture of five compounds; accordingly, **6** becomes a synthetically useful reagent only on the grounds of our two-step synthesis (Scheme 5).
[26] N. Kumar, R. W. Read (Unisearch Limited, Australia), PCT Appl. 20020000639 **2002** [*Chem. Abstr.* **2002**, *136*, 69697].

[27] **6**: P_4O_{10} (12.62 g, 44.45 mmol, 1.2 equiv) was added to a solution of **18** (10.15 g, 37.04 mmol) in CH_2Cl_2 (150 mL) at 0 °C. After 30 min, the solution was warmed to room temperature and heated at reflux for 1.5 h. After cooling to room temperature, it was filtered and concentrated in vacuo. A solution of the intermediate (8.094 g) in CH_2Cl_2 (75 mL) was cooled to 0 °C, and NEt_3 (5.29 mL, 3.84 g, 38.0 mmol, 1.02 equiv for **18**) was added. After 1 h, the mixture was first warmed to room temperature and then heated at reflux for 1 h. Aqueous NH_4Cl (40 mL) was added, and the mixture was extracted with CH_2Cl_2 (6×20 mL). The combined organic extracts were dried with Na_2SO_4. Evaporation at reduced pressure and flash chromatography (cyclohexane/EtOAc 20:1→2:1) provided **6** (3.54 g, 55 %) as a slightly yellow solid (m.p. 82–84 °C); ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS): $\delta = 6.11$ (s; 1′-H), 6.32 (d, $J_{3,4} = 5.6$ Hz; 3-H), 7.38 ppm (d, $J_{4,3} = 5.6$ Hz; 4-H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 92.4$ (C1′), 120.8 (C3), 141.7 (C4), 152.4 (C5), 168.2 ppm (C2); elemental analysis (%): calcd for $C_5H_3BrO_2$ (174.4): C 34.32, H 1.73; found: C 34.20, H 1.61.

[28] For reviews, see: a) E. Erdik, *Tetrahedron* **1992**, *48*, 9577 – 9648; b) E.-i. Negishi, F. Liu, in *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 1 – 42; c) P. Knochel in *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 387 – 416.

[29] a) V. Farina, *Pure Appl. Chem.* **1996**, *68*, 73 – 78; b) D. A. Entwistle, S. I. Jordan, J. Montgomery, G. Pattenden, *Synthesis* **1998**, 603 – 612; c) C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, A. N. Ntepe, L. Ricard, *J. Am. Chem. Soc.* **2003**, *125*, 4212 – 4222.

[30] **24**: ^{1}H NMR (499.9 MHz, $CDCl_3$, $CHCl_3$ internal standard): $\delta =$ 0.05 (s; $SiMe_3$), 1.03 (m_c; CH_2SiMe_3), 4.26 (m_c; OCH_2), 5.78 (d, $J_{11,10} = 15.4$ Hz; 11-H), 5.89 (d, $J_{5,6} = 11.7$ Hz; 5-H), 6.20 (d, $J_{2,3} =$ 5.4 Hz; 2-H), 6.32 (d, $J_{17,16} = 16.0$ Hz; 17-H), 6.41–6.56 (m; 7-H, 8-H, 9-H), 6.80–6.88 (m; 6-H, 10-H, 16-H), 7.37 ppm (d, $J_{3,2} =$ 5.2 Hz; 3-H); an edited undecoupled HSQC NMR spectrum ("^{1}H-coupled short-range H,C-COSY spectrum"; 499.9 MHz/ 125.7 MHz, $CHCl_3$ and $CDCl_3$ internal standards in $CDCl_3$, respectively) revealed, amongst others: $\delta = 6.44$ ppm (ddd, $^1J_{H,C} = 156.3$ Hz, $J_{9,8} = 12.8$ Hz, $J_{9,10} = 12.0$ Hz; 9-H), $\delta =$ 6.51 ppm (ddd, $^1J_{H,C} = 156.6$ Hz, $J_{8,9} = 14.6$ Hz, $J_{8,7} = 11.6$ Hz; 8-H), $\delta = 6.53$ (ddd, $^1J_{H,C} = 154.3$ Hz, $J_{7,6} = 15.2$ Hz, $J_{7,8} = 11.3$ Hz; 7-H), 6.82 ppm (dd, $^1J_{H,C} = 168.7$ Hz, $J_{16,17} = 16.1$ Hz; 16-H), $\delta =$ 6.85 ppm (ddd, $^1J_{H,C} = 157.6$ Hz, $J_{10,11} = 15.1$ Hz, $J_{10,9} = 11.1$ Hz; 10-H), $\delta = 6.86$ ppm (ddd, $^1J_{H,C} = 159.2$ Hz, $J_{6,7} = 13.7$ Hz, $J_{6,5} =$ 12.3 Hz; 6-H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = -1.5$ ($Si(CH_3)_3$), 17.3 (C2′), 63.3 (C1′), 78.3, 80.4, 82.5, and 85.3 (C12, C13, C14, C15), 111.1 (C11), 114.4 (C5), 119.1 (C2), 123.6 (C16), 128.4 (C6), 133.0 (C17), 134.6 (C9), 136.6 (C8), 137.5 (C7), 142.5 (C3), 145.3 (C10), 149.7 (C4), 165.5 (C18), 169.2 ppm (C1); elemental analysis (%): calcd for $C_{23}H_{24}O_4Si$ (392.1): C 70.38, H 6.16; found: C 70.15, H 6.13.

[31] W. Steglich, personal communication. We are indebted to Professor Steglich for sending copies of all the original NMR spectra of compound **3**.

[32] A referee suggested that "the possibility of directly obtaining xerulinic acid from xerulin should be commented on". We are unaware of such a possibility; furthermore, during alternative attempts at the synthesis of xerulinic acid, we prepared both the corresponding alcohol ("xerulinol") and aldehyde ("xerulinal") but could not oxidize either to xerulinic acid: K. Siegel, Ph.D. Thesis, Universität Freiburg, **2000**.

