The Anionic [1,3]-H-Shift Applied in Synthesis: A Novel Access to (+)-Citreoviral

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Dedicated to my Dear Friend Professor Horst Kunz on the Occasion of his 60th Birthday

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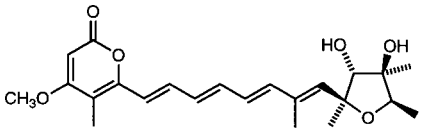
Abstract. In this paper we present a highly stereoselective and concise synthesis of the tetrahydrofuran derivative **3** and thus, a formal synthesis of the mycotoxin metabolite (+)-citreoviral (**2**). In our route we made use of a novel anionic [1,3]-H-shift to convert the homoallylic alcohol **9** into the allylic benzyl ether **10**. Another key step was the regio- and stereocontrolled cyclization of epoxide **18b** to tetrahydrofuran **19b**, which was then converted into ester **3**.

The polyene pyron mycotoxin citreoviridin (**1**) was isolated as early as 1947 by Hirata from the fungus *Penicillium citreo-viride* B in rice-plants [1]. It causes the cardial Beriberi sickness [2] by inhibiting mitochondrial F_1, F_0-ATPase activity [3]. Its metabolite citreoviral (**2**), which is far less toxic, was first isolated and characterized in 1984 by Yamamura *et al*. [4].



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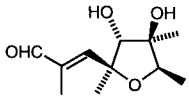
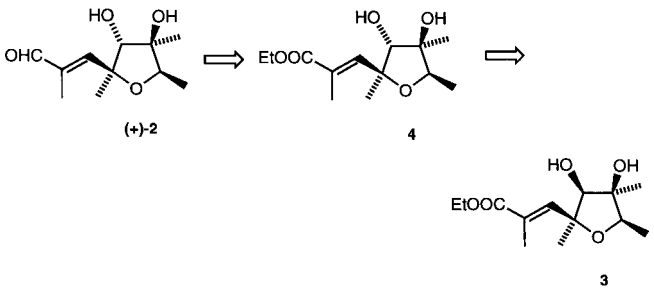


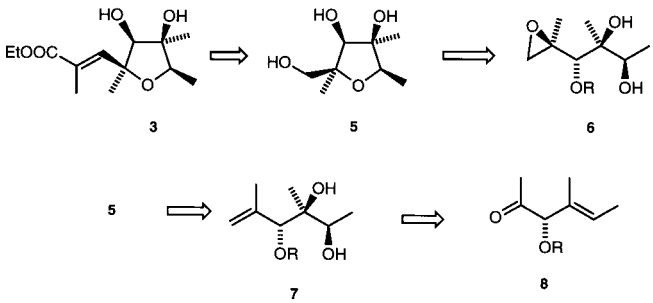
2

The interesting physiological properties of **1** and **2** together with the fascinating tetrahydrofuran core structure of these molecules have stimulated a number of synthetic approaches which cumulated in the total synthesis of racemic **1** [5] and of the natural enantiomer (–)-1 [6]. **2** has been synthesized in form of the racemate [7] and of the natural enantiomer (+)-**2** by several groups [8]. The route by Takano [8c] proceeds *via* the tetrahydrofuranyl enoate **3** which had previously been converted into **2** by inversion at C-3 and reduction of the ester to the aldehyde by Yamamura [7a] (Scheme 1).



Scheme 1 Takano's route to (+)-2 [8b,c]

In this paper we present a novel and efficient access to **3** (Scheme 2). Our synthesis of **3** starts from ketone **8** which, in the synthetic direction, had to be converted into the ketodiol **7** and subsequently into epoxide **6**. Williamson type cyclization should convert **6** stereoselectively and regioselectively *via* a favourable 5-exo-trig-cyclization [9] into tetrahydrofuran **5** which had to be transformed into the enoate **3** eventually.



Scheme 2 Our retrosynthetic pathway to **3**

The synthesis of ketone **8** is based on a novel anionic [1,3]-H-shift we described recently [10]. Thus, on heating with sodium hydride and benzylchoride in DMF, the known [11] homoallylic alcohol **10** underwent *O*-benzylation followed by a strictly intramolecular [1,3]-H shift to form the trisubstituted (*E*)-olefin **11** in quantitative yield. By this reaction, a homoallylic alcohol such as **10**, which is readily available by diastereocontrolled crotylation [12] of the corresponding aldehyde (**9**), is converted into an allylic benzyl ether such as **11**,

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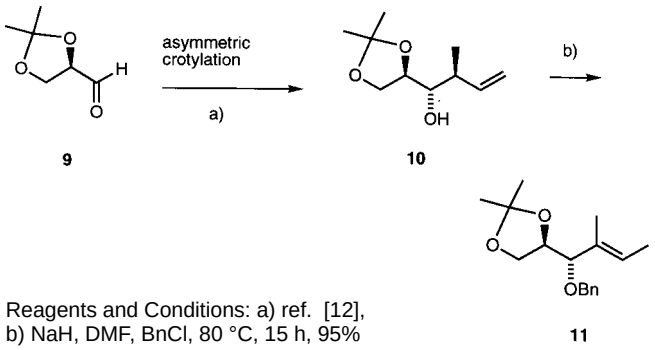
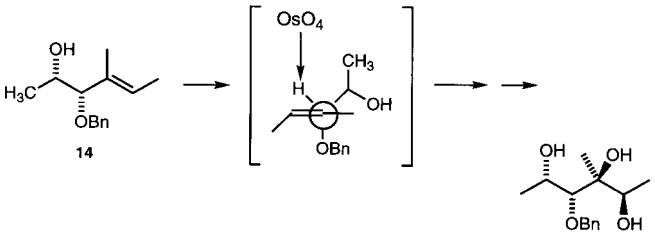
which is difficult to prepare in an diastereocontrolled fashion by direct methods, *e.g.* addition of the corresponding vinyl Grignard reagent to **9**.



Reagents and Conditions: a) ref. [12], b) NaH, DMF, BnCl, 80 °C, 15 h, 95%

Scheme 3 Key intermediate **11** is formed from **10** by a novel anionic [1,3]-H-shift [10]

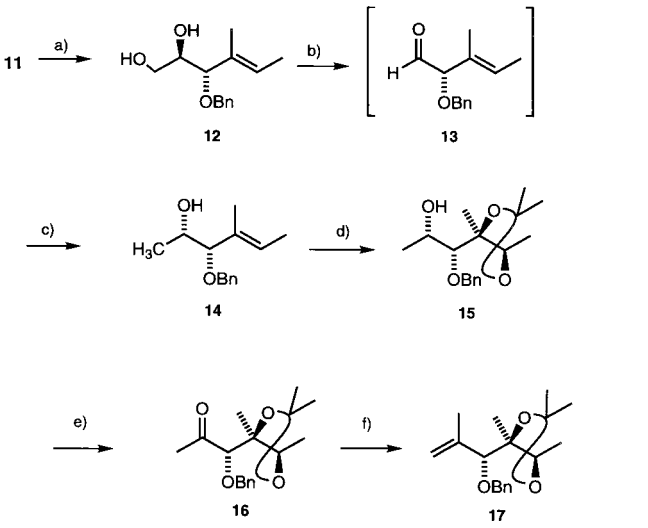
The conversion of olefin **11** into triol **17** is shown in Scheme 5. Diol deprotection and glycol cleavage with lead tetraacetate afforded aldehyde **13** which was immediately subjected to a chelate Cram controlled Grignard reaction [13] with methyl magnesium iodide. Diol **14** was formed without noticable racemization and with excellent (97:3) diastereoselectivity. The combined 1,3-induction of the hydroxy group and the 1,2-induction of the benzyl ether, was obviously the reason for the excellent diastereoselectivity (93:7) of the following osmylation, which is in accord with the Kishi-model [14] (Scheme 4) in which the osmium tetroxide approaches the double-bond antiperiplanarly to the OBn-moiety across the small hydrogenatom.



Scheme 4 The osmylation of olefin **14** follows kishi's rule [14]

After converting the diol into the acetonide the major diastereomer **15** was separated by HPLC and oxidized to the ketone **16**. After conversion of **16** into olefin **17** *via* Wittig reaction epoxidation with *m*-chloroperbenzoic acid furnished a 2:1-mixture of the epoxides **18a**/**b** which were treated without separation with acid to form the tetrahydrofurans **19a**/**b** (Scheme &).

In accordance with our expectation (Scheme 2), the epoxide was opened at the teriary position by the acid to form the more stable carbenium ion at C-2 which



Reagents and Conditions: a) TFA, MeOH, 3 d, 95%; b) $Pb(OAc)_4$, CH_2Cl_2, 0 °C, 20 min; c) MeMgI, Et_2O, 22 °C, 72%; d) i) 4% OsO_4, NMO, CH_3CN, 60 °C, 24 h; ii) DMP, CSA, CH_2Cl_2, 22 °C, 3 h, 58%; e) DMSO, iPr_2EtN, CH_2Cl_2, −50 °C, 91%; f) Ph_3PMeBr, DMSO, NaH, 22 °C, 45%

Scheme 5 Synthesis of the key intermediate **17**

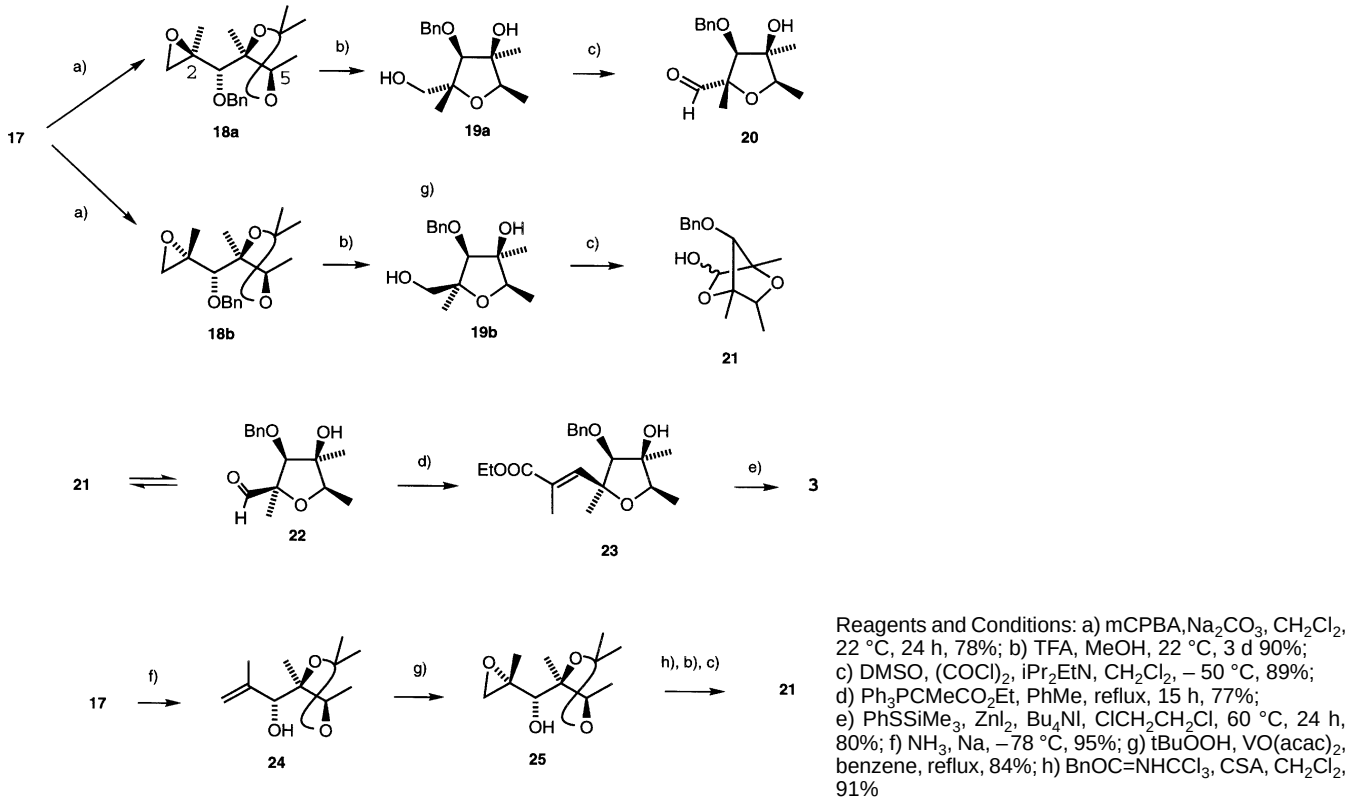
was then intercepted by the 5-hydroxy function with inversion of configuration. After Swern oxidation of the primary alcohol function to the aldehyde the isomers behaved differently. Whereas aldehyde **20** was formed from **19a**, stereoisomer **19b** gave the bicyclic hemiacetal **21**, which could easily be separated from aldehyde **20** by chromatography. *Via* a mobile ring chain equilibrium small amounts of the aldehyde **22** were formed from **21** which underwent smooth Wittig reaction to generate the (*E*)-enoate **23** stereoselectively. **23** was debenzylated with Hanessian's reagent [15] to give **3** eventually, which was identical with Takano's compound [8c] in the ^1H NMR spectrum and the optical rotation.

To remedy the unsatisfactory stereoselectivity in the epoxidation of **17**, the benzyl group was removed reductively and the resulting alcohol **24** was now subjected to a Sharpless epoxidation [16] with *t*-BuOOH/VO $(acac)_2$. The desired diastereomer **25** was formed as the only product in 84% yield. Rebenzylation of **25** with Bundle's reagent [17] furnished stereopure **18b** as expected which was converted into **21** directly.

In conclusion, we have reported a concise stereocontrolled approach to nonracemic ester **3** in **12** steps from **8** which constitutes a formal synthesis of (+)-**2**. Key steps are the anionic [1,3]-H-shift from **9** to **10**, and the epoxide → tetrahydrofuran rearrangement of **18** to **19**.

Experimental

NMR: Bruker AC 250. IR Perkin Elmer 257. MS: Varian MAT 711. Optical rotation: Perkin Elmer P 241.Column chroma-



Scheme 6 Synthesis of the Relay Intermediate **3**

tography: Merck silicagel 60, particle size 0.06–0.2 mm). HPLC: nucleosil 5 µm.

1.1.2 E-(2R,3S)-1,2-O-Isopropylidene-3-benzyloxy-4-methyl-hex-4-ene-1,2-diol (**11**)

A suspension of sodium hydride (6.3 g, 260 mmol) in 500 ml DMF was treated dropwise under argon with 24.44 g (131 mmol) alcohol 10 at 0 °C. After 1 h at 0 °C 22.6 ml (195 mmol) benzyl chloride were added. The mixture was stirred 15 h at 80 °C. H_2 gas was evolved and the mixture turned dark brown. After cooling the mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried with $MgSO_4$ and evaporated to dryness. Column chromatography (hexane/ethyl acetate 10:1) furnished 33.35 g (95%, 121 mmol) of **11**. – H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.34 (s, 3H), 1.39 (s, 3H), 1.58 (d, 3H, J = 6.5 Hz), 1.67 (s, 3H,); 3.61 (d, 1H, J = 7.5 Hz); 3.95 (dd, 1H, J = 8 Hz, J = 5 Hz); 4.09 (dd, 1H, J = 8 Hz, J = 6 Hz); 4.15 (m, 1H); 4.23 + 4.46 (je: d, 1H, J = 11.5 Hz,); 5.54 (q, 1H, J = 6.5 Hz,); 7.30 (m, 5H). – ^{13}C NMR ($CDCl_3$): δ/ppm = 10.99; 13.20; 25.28; 26.68; 67.52; 69.63; 75.69; 85.91; 109.11; 125.61; 127.39; 127.58; 128.19; 132.45; 138.38 . – IR (film): 3090 w; 3030 m; 2995 s; 2930 s; 2929 s; 2860 s; 1670 m; 1450 s; 1377 s; 1366 s; 1248 m; 1215 m; 1155 s; 1071 s; 1045 s; 1026 m; 960 m; 910 w; 846 s; 733 s; 695 s cm^{-1}. – MS (EI, 80 eV, 40 °C): m/z = 276 (M; 1,75); 175 (M–$C_5H_9O_2$; 51,64); 101 ($C_5H_9O_2$; 30,06); 91 (Bn, 100). $[\alpha]_D^{20}$ = + 56.7 (c = 1.9; $CHCl_3$).

$C_{17}H_{24}O_3$ (276.38) Calcd.: C 73.88 H 8.75 Found: C 73.98 H 8.27.

1.1.3 E-(2R,3S)-3-Benzyloxy-4-methyl-hex-4-ene-1,2-diol (**12**)

15.0 g (54 mmol) allylic ether **11** in 150 ml methanol was treated with 10 ml trifluroacetic acid and 10 ml of water. After 48 h at 22 °C the solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane/ethyl acetate 1:1) to furnish 11.81 g (93%, 50 mmol) diol **12** as a colourless viscous oil. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.65 (s, 3H); 1.70 (d, 3H, J = 7 Hz); 3.10 (s, 2H, 1-OH); 3.60 (m, 4H, H-1); 4.20 + 4.40 (2×d, 1H, J = 12 Hz); 5.50 (q, 1H, J = 7 Hz); 7.30 (m, 5H). – ^{13}C NMR ($CDCl_3$, 67.5 MHz: δ/ppm = 10.89; 13.15; 63.78; 69.89; 70.07; 70.94; 85.66; 127.55; 127.68: 128.30; 138.09. – IR (film): 3500–3200 s; 3089 s; 3030 s; 2977 s; 2862 s; 1673 s; 1606 m; 1380 s; 1070 s; 736 s, 698 s cm^{-1}. – MS (EI, 80 eV, 80 °C): m/z = 236 (M; 4.49); 175 (M–$C_2H_5O_2$; 60,70); 91 (Bn; 100). $[\alpha]_D^{20}$ = + 41.5 (c = 1.3; $CHCl_3$).

$C_{14}H_{20}O_3$ (236.31) Calcd.: C 71.16 H 8.53 Found: C 70.84 H 8.60.

1.1.4 E-(2S,3S)-3-Benzyloxy-4-methyl-hex-4-ene-2-ol (**14**)

17.81 g (75 mmol) of diol **12** in 250 ml dichloromethane were treated in small portions with 33.42 g (75 mmol) of lead tetraacetate at 22 °C. The solution turned yellow orange. After

15 min 30 g of potassium carbonate were added and the mixture was stirred for 10 min. After filtration over sodium sulfate and washing of the residue with 500 ml dichloromethane the filtrate was epovaporated to dryness and the residue was diluted with 30 ml diethylether. This solution was added dropwise to a solution of the Grignard reagent prepared from 14.2 g (100 mmol) methyl iodide and 2.43 g (100 mmol) magnesium turnings. The mixture was stirred at 22 °C for 20 h and then quenched with 20 saturated aqueous ammonium chloride. The organic layer was separated, washed with water, dried with $MgSO_4$ and evaporated. Column chromatography (hexane/ethyl acetate 3:1) furnished 12.1 g (72%, 55 mmol) 14 as a yellow oil with a diastereomeric ratio of 95:5 (NMR). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.02 (d, 3H, J = 7 Hz); 1.15 (dd, 3H, J = 7 Hz, J = 7 Hz); 1.58 (s, 1H); 3.41 (d, 1H, J = 8 Hz); 3.82 (m, 1H); 4.23 + 4.48 (2 × d, 1H, J = 11 Hz,); 5.54 (q, 1H, J = 6 Hz); 7.34 (m, 5H). – IR (film): 3600–3200 s; 3109 s; 3060 s, 3030 m; 2974 s; 2862 s; 1497 m; 1454 s; 1393 m; 1368 m; 1062 s; 735 s; 697 s cm^{-1}. – MS (EI, 80 eV, 60 °C): *m/z* = 220 (M; 1.17); 175 (M–C_2H_5O; 35.93); 91 (Bn; 100).

1.1.5 (2R,3S,4S,5S)-2,3-O-Isopropylidene-4-benzyloxy-3-methyl-hexane-2,3,5-triol (**15**)

3.31 g (15 mmol) olefin **14** were dissolved together with 8.12 g (60 mmol) 4-methylmorpholine-*N*-oxide-monohydrate (NMO) and 0.165 g (0.65 mmol) osmium tetroxide in a mixture of 132 ml acetonitrile and 33 ml water. The mixture was stirred 24 h at 80 °C. 11.4 g (60 mmol) sodium thiosulfate was added under ice cooling and the mixture was stirred for 1 h. Filtration through celite and concentration of the filtrate furnished a mixture of triols, which was dissolved in 60 ml 2,2-dimethoxypropane and acidified with camphorsulfonic acid to pH 3. After stirring the mixture for 24 h at 22 °C 100 ml of diethylether were added and the organic layer was washed with 50 ml aqueous sodium bicarbonate, 50 ml brine, dried over $MgSO_4$ and evaporated. Column chromatography (hexane/ethylacetate 1:1) and subsequent separation of the diastereomers by HPLC (2% isopropanol/hexane) revealed a diastereomeric ratio of 93:7. 2.58 g (58%; 8.76 mmol) of the pure diastereomer **15** were obtained as a colourless oil. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.14 (s, 3H); 1.26 (m, 6H, H-1); 1.35 (s, 3H); 1.43 (s, 3H); 2.45 (d, 1H, J = 9 Hz); 3.26 (s, 1H); 3.90 (m, 1H); 4.25 (q, 1H, J = 6 Hz); 4.67 + 4.88 (2 × d, 1H, J = 11 Hz); 7.35 (m, 5H). – ^{13}C NMR ($CDCl_3$): δ/ppm = 15.07; 18.43; 22.50; 26.50; 28.67; 31.52; 66.51; 76.32; 84.65; 86.39; 106.45; 127.77; 127.81; 128.34; 137.93. – IR (film): 3600–3200 s; 3031 m; 2982 s; 2935 s; 2881 s; 1497 m; 1454 m; 1376 s; 1195 s; 1099 s; 1004 s; 850 s; 734 s; 698 s cm^{-1}. – MS (EI, 80 eV, 60 °C): *m/z* = 294 (M; 0.18); 279 (M–CH_3; 7.03); 148 ($C_{10}H_{12}O$; 54,19); 129 ($C_7H_{13}O_2$; 97,48); 91 (Bn; 100). $[\alpha]_D^{20}$ = – 2.7 (c = 2.2; $CHCl_3$).

$C_{17}H_{26}O_4$	Calcd:	C 69.36	H 8.90
(294.39)	Found:	C 69.50	H 8.38.

1.1.6 (3S,4S,5R)-4,5-O-Isopropylidene-3-benzyloxy-4,5-dihydroxy-4-methyl-hexane-2-one (**16**)

A solution of oxalyl chloride (1.0 ml, 11.4 mmol) in 15 ml dichloromethane was treated dropwise at –60 °C with 1.87 g (24 mmol) dimethylsulfoxide. Then 2.58 g (8.76 mmol) of alcohol **15** in 30 ml dichloromethane was added. The temperature was raised to –35 °C and 8.7 ml (50 mmol) Hünig's base were added and the mixture was stirred for 30 min and then warmed to room temperature under stirring. 30 ml of water and 30 ml of diethylether were added and the organic phase was washed with aqueous ammonium chloride and brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (hexane/ethyl acetate 3:1) to furnish 2.07 g (81%; 7.08 mmol) of ketone **16** as a colourless oil. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.08 (s, 3H); 1.22 (d, 3H, J = 6 Hz); 1.28 (s, 3H); 1.41 (s, 3H); 2.26 (s, 3H); 3.73 (s, 1H); 4.05 (q, 1H, J = 6 Hz); 4.32 + 4.66 (2 × d, 1H, J = 12 Hz); 7.33 (m, 5H). – ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 14.84; 17.57; 26.20; 28.49; 28.98; 66.50; 72.94; 82.12; 88.26; 107.54; 128.13; 128.42; 128.61; 136.89; 209.14. – IR (film): 3030 s; 2985 s; 2935 s; 2880 s; 1723 s; 1495 m; 1455 m; 1381 s; 1195 s; 1097 s; 1004 s; 850 s; 735 s; 696 s cm^{-1}. – MS (EI, 80 eV, 60 °C): *m/z* = 292 (M; 1.76); 279 (M–CH_3; 11.44); 129 ($C_7H_{13}O_2$; 85,61); 91 (Bn; 100). $[\alpha]_D^{20}$ = –13.4 (c = 1.5; $CHCl_3$).

$C_{17}H_{24}O_4$	Calcd:	C 69.84	H 8.27
(292.38)	Found:	C 69.53	H 8.14.

1.1.7 (2R,3S,4S)-2,3-O-Isopropylidene-4-benzyloxy-3,5-dimethyl-hex-5-ene-2,3-diol (**17**)

240 mg (10 mmol) sodium hydride in 5 ml dimethylsulfoxide were heated for 45 min to 75 °C. 3.6 g (10 mmol) Methyltriphenylphosphonium bromide in 10 ml warm dimethylsulfoxide were added under ice cooling and the mixture was stirred for 10 min at 22 °C. To the dark yellow solution 2.07 g (7.1 mmol) of ketone **16** in 2 ml dimethysulfoxide were added and the mixture was stirred at 50 °C for 1 h . After cooling 30 ml of water were added and the solution was extracted with diethylether. The organic phase was dried over $MgSO_4$ and evaporated to give after column chromatography (hexane/ethyl acetate 6:1) 930 mg (45%, 3.2 mmol) olefin **17** as a colourless oil. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.07 (s, 3H); 1.24 (d, 3H, J = 6 Hz); 1.26 (s, 3H); 1.29 (s, 3H,); 1.40 (s, 3H, 2-CH_3); 3.63 (s, 1H); 4.10 (q, 1H, J = 6 Hz); 4.23 + 4.58 (2 × d, 1H, J = 12 Hz,); 5.00 (s, 1H); 5.14 (s, 1H); 7.34 (m, 5H). – ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 15.42; 17.25; 20.80; 26.40; 28.61; 70.72; 78.40; 83.29; 87.11; 106.79; 110.23; 114.78; 127.84; 127.92; 128.29; 137.51. – IR Film: 3029 s; 2995 s; 2987 s; 2938 s; 2882 s; 1495 m; 1457 m; 1381 s; 1277 s; 1195 s; 1097 s; 1004 s; 850 s; 735 s; 696 s cm^{-1}. – MS (EI, 80 eV, 60 °C): *m/z* = 290 (M; 9.46); 129 ($C_7H_{13}O_2$; 85.61); 91 (Bn; 100). $[\alpha]_D^{20}$ = –6.7 (c = 1.3; $CHCl_3$).

$C_{18}H_{26}O_3$	Calcd.:	C 75.46	H 8.70
(290.40)	Found:	C 75.61	H 8.70.

1.1.8 (2'R,1R,2S,3R)- and (2'S,1R,2S,3R)-2,3-O-Isopropylidene-1-benzyloxy-2-methyl-1-(2-methyl-oxiran-2-yl)-butane-2,3-diol (**18a** and **18b**)

210 mg (0.7 mmol) olefin **17** was treated in 10 ml dichloromethane with 0.5 g sodium hydrogencarbonate and 300 mg (0.87 mmol) mCPBA (55%). The mixture was stirred for 24 h at 22 °C and then washed with 5 ml water, dried over $MgSO_4$ and evaporated. Column chromatography (hexane/ethyl acetate 3:1) furnished 173 mg (78%; 0.56 mmol) of a 2:1 mixture of **18a** and **18b**.

1.1.9 (2R,3S,4S,5S)- and (2R,3S,4S,5R)-4-Benzyloxy-5-hydroxymethyl-2,3,5-trimethyl-tetrahydrofuran-3-ol (**19a** and **19b**)

173 mg (0.56 mmol) of the mixture of **18a**/**b** was stirred in 10 ml methanol with 1 ml water and 1 ml trifluoroacetic acid for 48 h at 50 °C. The mixture was concentrated and purified by column chromatography (hexane/ethyl acetate 1:1) to furnish **19a** and **19b** as a 2:1 mixture (135 mg , 90%; 0.51 mmol).

1.1.10 (1R,3R,4R,6R,7R)-7-Benzyloxy-1,4,6-trimethyl-2,5-dioxa-bicyclo-[2,2,1]-heptane-3-ol (**21**) and *(2R,3S,4S,5R)-4-Benzyloxy-5-formyl-2,3,5-trimethyl-tetrahydrofuran-3-ol* (**20**)

The mixture of **19a**/**b** (125 mg (0.47 mmol) was subjected to Swern oxidation as described for alcohol **15** using 0,17 ml (2.4 mmol) DMSO, 0.1 ml (1.15 mmol) oxalylchloride and 0.9 ml (5 mmol) Hünig's base. A mixture of **20** and **21** was obtained which was separated by column chromatography (hexane/ethyl acetate 5:1) to furnish **21** (50 mg, 41%; 0.19 mmol) and **20** (46 mg, 38%; 0.17 mmol).

21: ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.14 (d, 3H, J = 7 Hz); 1.27 + 1.39 (2 × s, 3H); 1.71 (s, 1H); 3.58 + 3.74 (2× s, 1H); 3.87 (q, 1H, J = 7 Hz); 4.65 + 4.74 (2×d, 1H, J = 12 Hz); 7.35 (m, 5 H). – ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 12.60; 13.03; 14.25; 73.19; 73.66; 78.08; 79.33; 82.47; 84.43; 85.87; 102.31; 127.52; 127.89; 128.37; 135.66. – IR (film): 3600–3200 s; 3029 m; 2985 s; 2935 s; 2883 s; 1495 m; 1454 m; 1376 s; 1195 s; 1099 s; 1004 s; 850 s; 734 s; 698 s cm^{-1}. – MS (EI, 80 eV, 100 °C): *m/z* = 262 (M–H_2; 1.96); 235 (M–CHO; 18.34); 111 ($C_7H_{11}O$; 45.58); 105 ($C_6H_7O_2$; 31.17); 91 (Bn; 100). $[\alpha]_D^{20}$ = – 15.1 (c = 1.2; $CHCl_3$).
$C_{15}H_{20}O_4$ Calcd.: HRMS ($C_{14}H_{19}O$): 235.1334
(258.31) Found: HRMS ($C_{14}H_{19}O_3$): 235.1330.

20: ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.10 (s, 3H); 1.28 (d, 3H, J = 6 Hz); 1.32 (s, 3H,); 2.55 (s, 1H); 3.52 (q, 1H, J = 6 Hz); 3.90 (s, 1H); 4.61 + 4.75 (2×d, 1H, J = 17 Hz); 7.38 (m, 5H); 9.66 (s, 1H). – ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 12.70; 14.09; 17.39; 22.52; 29.68; 73.39; 77.20; 79.82; 83.52; 128.28; 128.31; 128.55; 136.97; 203.91.

1.1.11 Ethyl E-(2R,3S,4S,5R)-3-(3-Benzyloxy-4-hydroxy-2,4,5-trimethyl-tetrahydrofuran-2-yl)-2-methyl-acrylate (**23**)

40 mg (0.15 mmol) hemiacetal **21** in 5 ml toluene was refluxed with 1.0 g (3 mmol) 1-carboethoxyethylidene-triphenylphosphorane for 24 h . The mixture was purified by column chromatography (hexane/ethyl acetate 10:1) to furnish 40 mg (77%; 0.12 mmol) of ester **23**. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.20 (s, 3H); 1.21 (t, 3H, J = 6 Hz); 1.28 (d, 3H, J = 7 Hz); 1.35 (s, 3H); 2.07 (s, 3H); 2.28 (s, 1H); 3.59 (s, 1H); 3.79 (q, 1H, J = 6 Hz); 4.19 (q, 2H, J = 7 Hz); 4.74 (s, 2H); 7.02 (s, 1H); 7.26 (m, 5H). – ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 13.08; 13.74; 14.31; 20.57; 26.03; 60.86; 77.67; 77.82; 81.78; 85.55; 127.79; 127.85; 128.34; 129.21; 138.13; 141.70; 168.88. – IR (film): 3600–3200 s; 3029 m; 2985 s; 2935 s; 2883 s; 1718 s; 1645 s; 1495 m; 1454 m; 1376 s; 1270 s; 1195 s; 1099 s; 1004 s; 910 m; 850 s; 735 s; 695 s cm^{-1}. – MS (EI, 80 eV, 60 °C): *m/z* = 258 (M; 2.68); 243 (M–CH_3; 6.22); 113 ($C_6H_9O_2$; 21.53); $[\alpha]_D^{20}$ = +18.5 (c = 0.9; $CHCl_3$).
$C_{20}H_{28}O_5$ Calcd.: C 68.94 H 8.10
(348.43) Found: C 68.72 H 8.32.

1.1.12 Ethyl E-(2R,3S,4R,5R)-3-(3,4-Dihydroxy-2,4,5-trimethyl-tetrahydrofuran-2-yl)-2-methyl-acrylate (**3**)

30 mg (0.09 mmol) of the benzylether **22** in 5 ml 1,2-dichloroethane was treated with 3.8 ml (20 mmol) phenylthiotrimethylsilane, 110 mg (0.3 mmol) tetrabutylammoniumiodide and 312 mg (1 mmol) zinc iodide and warmed for 24 h to 60 °C. The mixture was filtered and the residue was washed with dichloromethane. The filtrate was washed with barium hydroxide (5%) and water, dried over $MgSO_4$ and evaporated to give after column chromatography (hexane/ethyl acetate 3:1) 18 mg (0.070 mmol; 80%) ester **3** as a colourless oil. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.21 (d, 3H, J = 7 Hz); 1.22 (s, 3H); 1.30 (t, 3H, J = 7 Hz); 1.43 (s, 3H); 2.06 (d, 3H, J = 1Hz); 2.58 (d, 1H, J = 10 Hz); 3.73 (d, 1H; J = 10 Hz,); 3.84 (q, 1H, J = 7 Hz); 4.19 (q, 2H, J = 7 Hz); 6.91 (q, 1H, J = 1Hz). – ^{13}C-NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 13.08; 13.74; 14.31; 20.57; 26.03; 60.86; 77.67; 77.82; 81.78; 85.55; 129.21; 141.70; 168.88. – IR (film): 3600–3200 s; 3029 m; 2985 s; 2935 s; 2883 s; 1715 s; 1640 s; 1495 m; 1376 s; 1195 s; 1099 s; 1004 s; 910 m; 865 m cm^{-1}. – MS (EI, 80 eV, 100 °C): *m/z*= 258 (M; 2.68); 243 (M–CH_3; 6.22); 113 ($C_6H_9O_2$; 21.53). $[\alpha]_D^{20}$ = +10.4 (c = 0.2; $CHCl_3$) Lit. [8c]; $[\alpha]_D^{22}$ = +11.4 (c = 0.51, $CHCl_3$).
$C_{13}H_{22}O_5$ Calcd.: HRMS (C13H22O5): 258.1467
(258.31) Found: HRMS ($C_{13}H_{22}O_5$): 258,1452.

1.1.13 (2R,3S,4S)-2,3-O-Isopropylidene- -3,5-dimethyl-hex-5-ene-2,3,4-triol (**24**)

1.1.14 930 mg (3.2 mmol) benzyl ether **17** were dissolved in 15 ml ammonia and 10 ml THF at –78 °C and treated with 100 mg (4.3 mmol) sodium. After 15 min ammonium chloride was added and the ammonia was evaporated at room temperature. The residue was evaporated and purified by column chromatography (hexane/ethyl acetate 1:1) to give 600 mg (95%, 3 mmol) of the alcohol **24**. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.12 (s, 3H); 1.25 (d, 3H, J = 7 Hz); 1.36 (s, 3H); 1.42 (s, 3H); 1.91 (s, 3H); 2.10 (s, 1H); 3.91 (s, 1H); 4.38 (q, 1H, J = 7 Hz); 5.10 (m, 2H). – ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 15.64; 18.17; 19.03; 25.58; 28.02; 75.64; 79.33; 81.91; 103.54; 113.88; 114.92. – IR (film): 3600–3300 s; 2995 s; 2972 m; 2941 m; 1460 m; 1277 s; 1221 s; 1193 s; 1097 s; 1075 m; 1024 m; 1004 m; 910 m; 863 m cm^{-1}. – MS (EI, 80 eV, 40 °C): *m/z* = 200 (M; 16.16); 129 ($C_7H_{13}O_2$; 70.24); 86 ($C_4H_6O_2$; 41.72); 71 (C_4H_7O; 78.92); 59 (C_3H_7O; 58.31); 43 (C_3H_7; 100). $[\alpha]_D^{20}$ = –6.8 (c = 1.7; $CHCl_3$).
$C_{11}H_{20}O_3$ Calcd.: C 65.97 H 10.07
(200.28) Found: C 66.41 H 9.93.

1.1.15 (2'R,1S,2R,3R)-2,3-O-Isopropylidene-2-methyl-1-(2-methyl-oxiran-2-yl)-butane-1,2,3-triol (**25**)

600 mg (3 mmol) olefin **24** in 10 ml benzene were refluxed with 0.8 ml (6 mmol) *tert*-butylhydroperoxide (70% in water) and 42 mg (0.16 mmol) vanadyl acetylacetonate for 15 h. After cooling the mixture was washed with aqueous sodium hydrogensulfite, water and dried over $MgSO_4$ and evaporat-

ed. Column chromatography (hexane/ethyl acetate 95:5) furnished 545 mg (84%, 2.5 mmol) epoxide **25** (diastereomeric ratio 93:7 according to analytical HPLC (hexane/ethyl acetate 95:5)) as a colourless oil. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ/ppm = 1.01 (s, 3H); 1.28 (d, 3H, J = 6 Hz); 1.35 (s, 3H,); 1.42 (s, 3H); 1.46 (s, 3H); 2.39 (s, 1H); 2.66 (d, 1H, J = 6 Hz); 2.95 (d, 1H, J = 6 Hz); 3.64 (s, 1H); 4.18 (q, 1H, J = 6 Hz). – ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ/ppm = 15.22; 16.18; 19.96; 26.44; 28.61; 50.39; 57.59; 77.01; 79.82; 81.94; 107.13. – IR (film): 3600–3200 s; 2997 s; 2969 s; 2915 m; 1487 m; 1455 m; 1359 s; 1211 s; 1093 s; 1020 m; 1002 s; 905 m cm^{-1}. – MS (EI, 80 eV, 60 °C): *m/z* = 201 (M–CH_3; 0.61); 129 ($C_7H_{13}O_2$; 78.20); 107 (BnO; 18.32); 91 (Bn; 100). $[\alpha]_D^{20}$ = –7.3 (c = 1.0; $CHCl_3$).

$C_{11}H_{20}O_4$ Calcd.: C 61.09 H 9.32
(216.27) Found: C 61.21 H 9.28.

540 mg (2.5 mmol) epoxide **25** in 10 ml dichloromethane was treated with 756 mg (3.0 mmol) benzyltrichloroacetimidate and 50 mg camphorsulfonic acid at 0 °C. After stirring the mixture overnight the solvent was evaporated and the crude product was cyclized to **19b** and oxidized to **21** as described before. 422 mg (63%) of **21** was obtained.

References

[1] Y. Hirata, J. Chem. Soc. Jpn **1947**, *65*, 63

[2] a) Y. Uleno in Mycotoxines, Hrsg.: I. F. H. Purchase, Elsevier, New York 1974, 283; b) Ch. Zink, Pschyrembel Klinisches Wörterbuch, 256. ed., W. de Gruyter, Berlin 1990, 194

[3] P. Mitchell, FEBS Lett. **1977**, *78*, 1

[4] Y. Shizuri, S. Nishiyama, D. Imai, S. Yamamura, Tetrahedron Lett. **1984**, *25*, 4771

[5] D. R. Williams, F. H. White, Tetrahedron Lett. **1985**, *26*, 2529, J. Org. Chem. **1987**, *52*, 5067

[6] a) S. Nishiyama, Y. Shizuri, S. Yamamura, Tetrahedron Lett. **1985**, *26*, 231; b) Shizuri, H. Suh, C. S. Wilcox, J. Am. Chem. Soc. **1988**, *110*, 470; c) K. Wang, H. Venkataraman, Y. G. Kim, J. K. Cha, J. Org .Chem. **1991**, *56*, 7174

[7] a) S. Nishiyama, H. Shigemori, S. Yamamura, J. Chem. Soc., Chem. Commun. **1985**, 292; b) M. C. Bowden, P. Patel, G. Pattenden, Tetrahedron Lett. **1985**, *26*, 4793; c) M. J. Begley, M. C. Bowden, P. Patel, G. Pattenden, J. Chem. Soc., Perkin Trans. I **1991**, 1951; d) W. Ebenezer, G. Pattenden, Tetrahedron Lett. **1992**, *33*, 4053

[8] a) B. M.Trost, J. K. Lynch, S. R. Anlge, Tetrahedron Lett. **1987**, *28*, 375; b) S. Hatakeyama, Y. Matsui, M. Suzuki, K. Sakurai, S. Takano, Tetrahedron Lett. **1985**, *26*, 6485; c) S. Hatakeyama, K. Sakurai, H. Numata, N. Ochi, S. Takano, J. Am. Chem. Soc. **1988**, *110*, 5201; d) N. Hanaki, J. T. Link, D. W. C. MacMillan, L. E. Overman, W. G. Trankle, J. A. Wurster, Org. Lett. **2000**, *2*, 223

[9] J. Baldwin, J. Chem. Soc., Chem. Commun. **1976**, 734

[10] J. Mulzer, G. Wille, J. Bilow, D. Arigoni, B. Martinoni, K. Roten, Tetrahedron Lett. **1997**, *38*, 5469; cf. also J. Gigg, R. Gigg, J. Chem. Soc. C. **1968**, 1903

[11] J. Mulzer, P. deLasalle, A. Freißler, Liebigs Ann. Chem. **1986**, 1152

[12] a) W. R. Roush, M. A. Adams, A. E. Walts, D. J. Harris, J. Am. Chem. Soc. **1986**, *108*, 3422; b) J. Garcia, B. M. Kim, S. Masamune, J. Org. Chem. **1987**, *52*, 4831

[13] W. C. Still, J. McDonald III, Tetrahedron Lett. **1980**, *21*, 1031; Review: R. M. Devant, H. E. Radunz in Houben-Weyl, Methods of Organic Chemistry, Vol. 21 b, Stereoselective Synthesis, (G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, editors), Thieme, Stuttgart, New York 1995, p. 1151 ff

[14] J. K. Cha, W. J. Christ, Y. Kishi, Tetrahedron Lett. **1983**, *24*, 3943

[15] a) S. Hanessian, Y. Guindon, Tetrahedron Lett. **1989**, *21*, 2305; b) K. C. Nicolaou, M. R. Pavia, S. P. Seitz, J. Am. Chem. Soc. **1982**, *104*, 2027

[16] K. B. Sharpless, R. C. Michaelson, J. Am. Chem. Soc. **1973**, *95*, 6136

[17] T. Iversen, K. R. Bundle, J. Chem. Soc., Chem. Commun. **1981**, 1240

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