

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

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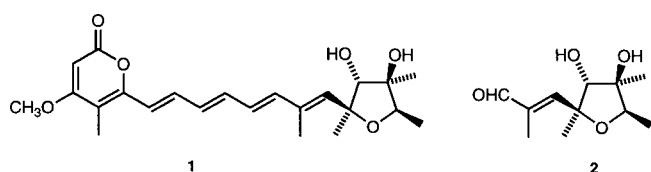
Dedicated to my Dear Friend Professor Horst Kunz on the Occasion of his 60th Birthday

Keywords: Cyclizations, Natural products, Synthetic methods, Citreooviral, Tetrahydrofuran synthesis

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 (+)-citreooviral (**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**.

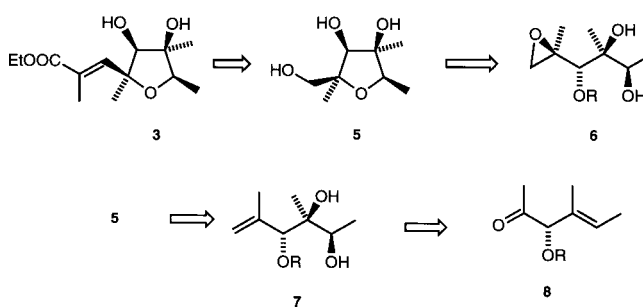
The polyene pyron mycotoxin citreoviridin (**1**) was isolated as early as 1947 by Hirata from the fungus *Penicillium citreo-viride* B in rice-plants [1]. It causes the cardiac Beriberi sickness [2] by inhibiting mitochondrial F_1 , F_0 -ATPase activity [3]. Its metabolite citreooviral (**2**), which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



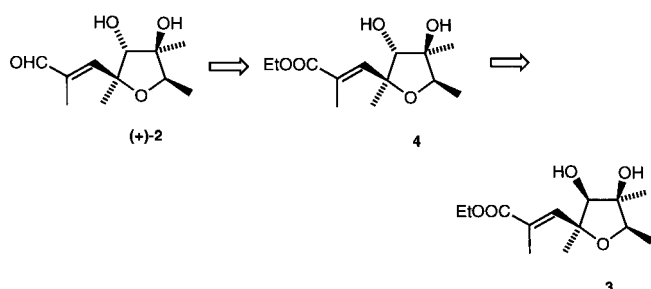
The interesting physiological properties of **1** and **2** together with the fascinating tetrahydrofuran core structure of these molecules have stimulated a number of synthetic approaches which cumulated in the total synthesis of racemic **1** [5] and of the natural enantiomer (–)-**1** [6]. **2** has 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).

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.



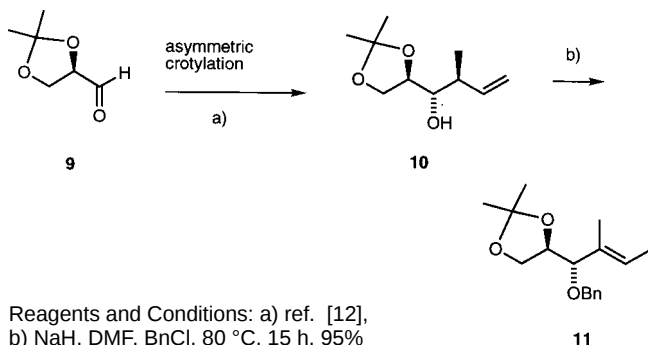
Scheme 2 Our retrosynthetic pathway to **3**



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

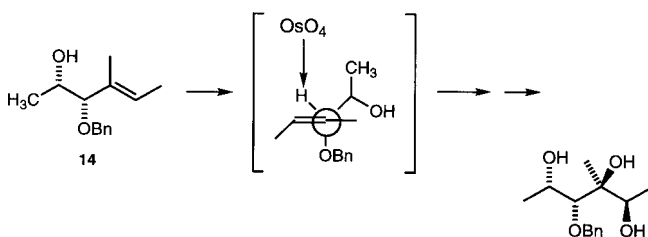
The synthesis of ketone **8** is based on a novel anionic [1,3]-H-shift we described recently [10]. Thus, on heating with sodium hydride and benzylchloride in DMF, the known [11] homoallylic alcohol **10** underwent *O*-benzylation followed by a strictly intramolecular [1,3]-H shift to form the trisubstituted (*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**,

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



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

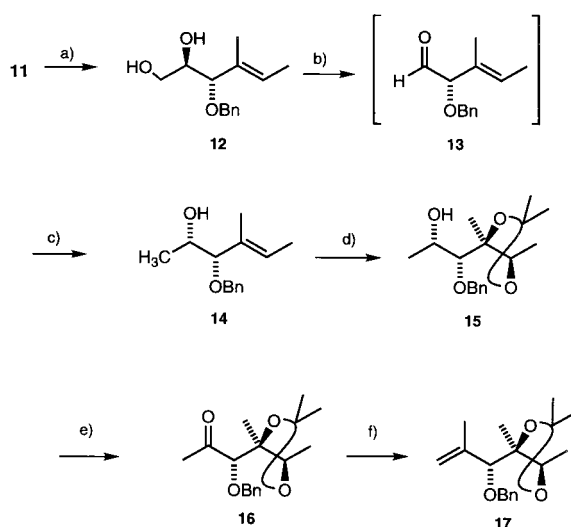
The conversion of olefin **11** into triol **17** is shown in Scheme 5. Diol deprotection and glycol cleavage with lead tetraacetate afforded aldehyde **13** which was immediately subjected to a chelate Cram controlled Grignard reaction [13] with methyl magnesium iodide. Diol **14** was formed without noticeable 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 antiperiplanar to the OBn-moiety across the small hydrogen atom.



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*-chloroperoxybenzoic 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 tertiary 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, CH₂Cl₂, 0 °C, 20 min; c) MeMgI, Et₂O, 22 °C, 72%; d) i) 4% OsO₄, NMO, CH₃CN, 60 °C, 24 h; ii) DMP, CSA, CH₂Cl₂, 22 °C, 3 h, 58%; e) DMSO, iPr₂EtN, CH₂Cl₂, -50 °C, 91%; f) Ph₃PMeBr, DMSO, NaH, 22 °C, 45%

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

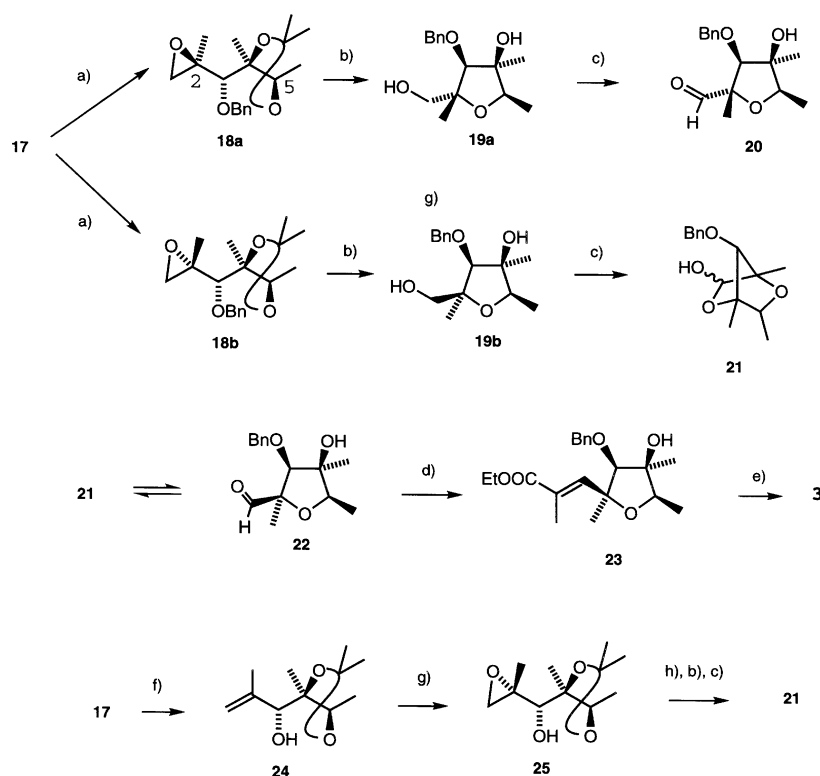
was then intercepted by the 5-hydroxy function with inversion of configuration. After Swern oxidation of the primary alcohol function to the aldehyde the isomers behaved differently. Whereas aldehyde **20** was formed from **19a**, stereoisomer **19b** gave the bicyclic hemiacetal **21**, which could 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-



Reagents and Conditions: a) mCPBA, Na₂CO₃, CH₂Cl₂, 22 °C, 24 h, 78%; b) TFA, MeOH, 22 °C, 3 d 90%; c) DMSO, (COCl)₂, iPr₂EtN, CH₂Cl₂, –50 °C, 89%; d) Ph₃PCMeCO₂Et, PhMe, reflux, 15 h, 77%; e) PhSSiMe₃, ZnI₂, Bu₄NI, ClCH₂CH₂Cl, 60 °C, 24 h, 80%; f) NH₃, Na, –78 °C, 95%; g) tBuOOH, VO(acac)₂, benzene, reflux, 84%; h) BnOC=NHCCl₃, CSA, CH₂Cl₂, 91%

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*-(2*R*,3*S*)-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. H₂ 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 MgSO₄ and evaporated to dryness. Column chromatography (hexane/ethyl acetate 10:1) furnished 33.35 g (95%, 121 mmol) of **11**. – ¹H NMR (CDCl₃, 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). – ¹³C NMR (CDCl₃): 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–C₅H₉O₂; 51,64); 101 (C₅H₉O₂; 30,06); 91 (Bn, 100). [α]_D²⁰ = + 56.7 (c = 1.9; CHCl₃).

C₁₇H₂₄O₃ Calcd.: C 73.88 H 8.75
(276.38) Found: C 73.98 H 8.27.

1.1.3 *E*-(2*R*,3*S*)-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 trifluoroacetic 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. – ¹H NMR (CDCl₃, 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). – ¹³C NMR (CDCl₃, 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–C₂H₅O₂; 60,70); 91 (Bn; 100). [α]_D²⁰ = + 41.5 (c = 1.3; CHCl₃).

C₁₄H₂₀O₃ Calcd.: C 71.16 H 8.53
(236.31) Found: C 70.84 H 8.60.

1.1.4 *E*-(2*S*,3*S*)-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 evaporated 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). – ^1H 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 $\times$ 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 ($\text{M}-\text{C}_2\text{H}_5\text{O}$; 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/ethyl acetate 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. – ^1H 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 $\times$ 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 ($\text{M}-\text{CH}_3$; 7.03); 148 ($\text{C}_{10}\text{H}_{12}\text{O}$; 54.19); 129 ($\text{C}_7\text{H}_{13}\text{O}_2$; 97.48); 91 (Bn; 100). $[\alpha]_D^{20}$ = –2.7 (c = 2.2; CHCl_3). $\text{C}_{17}\text{H}_{26}\text{O}_4$ 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. – ^1H 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 $\times$ 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 ($\text{M}-\text{CH}_3$; 11.44); 129 ($\text{C}_7\text{H}_{13}\text{O}_2$; 85.61); 91 (Bn; 100). $[\alpha]_D^{20}$ = –13.4 (c = 1.5; CHCl_3). $\text{C}_{17}\text{H}_{24}\text{O}_4$ 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 dimethylsulfoxide 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. – ^1H 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 $\times$ 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 ($\text{C}_7\text{H}_{13}\text{O}_2$; 85.61); 91 (Bn; 100). $[\alpha]_D^{20}$ = –6.7 (c = 1.3; CHCl_3). $\text{C}_{18}\text{H}_{26}\text{O}_3$ 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-Benzoyloxy-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-Benzoyloxy-1,4,6-trimethyl-2,5-dioxo-bicyclo-[2,2,1]-heptane-3-ol (**21**) and (2R,3S,4S,5R)-4-Benzoyloxy-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: ^1H NMR (CDCl_3 , 250 MHz): δ/ppm = 1.14 (d, 3H, J = 7 Hz); 1.27 + 1.39 (2 $\times$ s, 3H); 1.71 (s, 1H); 3.58 + 3.74 (2 $\times$ s, 1H); 3.87 (q, 1H, J = 7 Hz); 4.65 + 4.74 (2 $\times$ d, 1H, J = 12 Hz); 7.35 (m, 5H). – ^{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–H₂; 1.96); 235 (M–CHO; 18.34); 111 (C₇H₁₁O; 45.58); 105 (C₆H₇O₂; 31.17); 91 (Bn; 100). $[\alpha]_D^{20}$ = –15.1 (c = 1.2; CHCl_3). C₁₅H₂₀O₄ Calcd.: HRMS (C₁₄H₁₉O): 235.1334 (258.31) Found: HRMS (C₁₄H₁₉O₃): 235.1330.

20: ^1H 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 $\times$ 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-Benzoyloxy-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**. – ^1H 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–CH₃; 6.22); 113 (C₆H₉O₂; 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) phenylthiotri-methylsilane, 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 MgSO₄ and evaporated to give after column chromatography (hexane/ethyl acetate 3:1) 18 mg (0.070 mmol; 80%) ester **3** as a colourless oil. – ^1H -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 = 1 Hz); 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 = 1 Hz). – ^{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–CH₃; 6.22); 113 (C₆H₉O₂; 21.53). $[\alpha]_D^{20}$ = +10.4 (c = 0.2; CHCl_3) Lit. [8c]; $[\alpha]_D^{20}$ = +11.4 (c = 0.51, CHCl_3).

C ₁₃ H ₂₂ O ₅	Calcd.: HRMS (C ₁₃ H ₂₂ O ₅): 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**. – ^1H 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 (C₇H₁₃O₂; 70.24); 86 (C₄H₆O₂; 41.72); 71 (C₄H₇O; 78.92); 59 (C₃H₇O; 58.31); 43 (C₃H₇; 100). $[\alpha]_D^{20}$ = –6.8 (c = 1.7; CHCl_3). C₁₁H₂₀O₃ 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 MgSO₄ and evaporated.

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. – ^1H 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 ($\text{M}-\text{CH}_3$; 0.61); 129 ($\text{C}_7\text{H}_{13}\text{O}_2$; 78.20); 107 (BnO ; 18.32); 91 (Bn ; 100). $[\alpha]_{\text{D}}^{20}$ = –7.3 (c = 1.0; CHCl_3).

$\text{C}_{11}\text{H}_{20}\text{O}_4$ 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.

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