JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

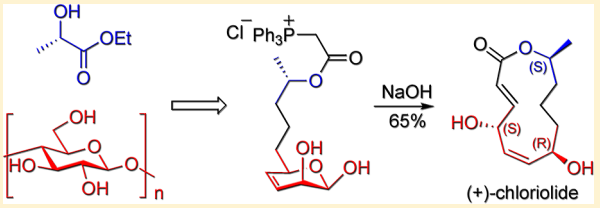
Total Synthesis of (+)-Chloriolide

Michael Ostermeier and Rainer Schobert*

Organic Chemistry Laboratory, University of Bayreuth, 95440 Bayreuth, Germany

Supporting Information

ABSTRACT: (+)-Chloriolide, a metabolite of the ascomycete *Chloridium virescens* var. *chlamydosporum*, was synthesized in 16 linear steps from cellulose as a source of a levoglucosenone that contributed the (*Z*)-alkene and the *R* stereocenter. The attachment of a spacer derived from L-lactate gave an *ω*-hydroxyacetal which was added to the phosphorus ylide Ph_3PCCO. The resulting ester ylide was treated with hydrochloric acid to liberate the hemiacetal shown. Addition of sodium hydroxide regenerated the corresponding ylide, which underwent a spontaneous intramolecular Wittig olefination to afford (+)-chloriolide in 65% yield without the necessity of high-dilution conditions. This is the third synthesis of (+)-chloriolide and the first one ever of a macrolide by a ring-closing Wittig olefination of a stabilized phosphorus ylide bearing an *ω*-hemiacetal. Our synthetic sample exhibited moderate cytotoxicity against cancer cells but no antimicrobial activity against *Staphylococcus aureus*.



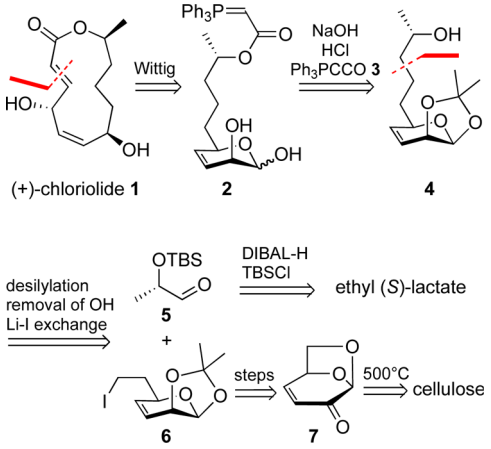
INTRODUCTION

(+)-Chloriolide **1**, a 12-membered macrolide, was obtained in 2006 by Gloer et al. from an isolate of *Chloridium virescens* var. *chlamydosporum* dwelling on decaying hardwood. It was structurally characterized by single-crystal X-ray diffraction, NMR spectroscopy, and the Mosher ester method.[1] Tests for the antibiotic activity of **1** against *S. aureus*, *B. subtilis*, and *E. coli* were negative. Hitherto, two total syntheses of chloriolide were reported by Kirsch et al.[2] and Nanda et al.[3] The first synthesis of **1** by Kirsch et al. in 20 steps and 7% yield was based upon a Yamaguchi lactonization of an *ω*-hydroxycarboxylic acid which was obtained by connecting two silyl ether bridged allyl alcohol precursors via alkene metathesis. Interestingly, attempts by this group to close the macrocycle by formation of the (*E*)-alkene via a Horner–Wadsworth–Emmons reaction or of the (*Z*)-alkene via a ring-closing metathesis reaction failed. Nanda et al. also employed a Yamuguchi lactonization for closing the macrocycle. The required *seco* acid was built up by starting from 1,3-butanediol and installing the other two stereocenters via asymmetric alkyne–aldehyde coupling reactions. This approach afforded **1** in 20 steps and 2% overall yield. Herein we report a third total synthesis of (+)-chloriolide **1** that starts from two cheap enantiopure compounds, lactic acid and cellulose, and uses an *E*-selective intramolecular Wittig olefination for the ring closure.

RESULTS AND DISCUSSION

Our retrosynthetic approach is outlined in Scheme 1. A Wittig-type macrocyclization was to take place spontaneously upon generation of the stabilized phosphorus ester ylide **2** bearing a terminal hemiacetal. Although we had used similar Wittig cyclizations of *ω*-formyl ester ylides in the past for the synthesis of various macrolides with ring sizes ranging from 12 to 18,[4−6] it was unclear at the outset whether enough aldehyde would be present in equilibrium with the hemiacetal at pH values

Scheme 1. Retrosynthetic Approach to (+)-Chloriolide 1

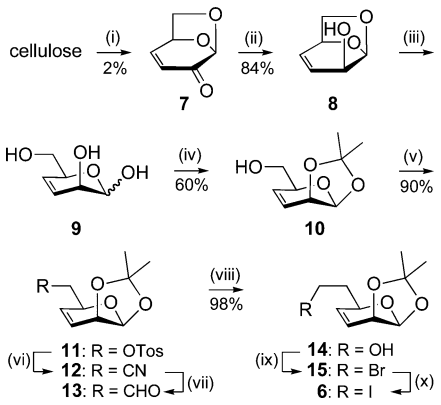


compatible with the ylide form on the other end of **2**. We intended to liberate the hemiacetal–ylide **2** by acidic cleavage of a corresponding acetonide–ylide and subsequent adjustment of the pH with aqueous base. This required acetonide–ylide should be accessible by addition of the secondary alcohol **4** across the C═C bond of the cumulated ylide $Ph_3P{=}C{=}C{=}O$ (**3**).[7,8] Alcohol **4**, which already contains all crucial functional groups and stereocenters, was to be built up by a C_{sp^3}–C_{sp^2} coupling between the silyl-protected lactic aldehyde **5** and an organometallic component derived from iodide **6**. This iodide was reckoned to be accessible from the known pyrolysis product **7** of cellulose by a sequence of reactions, including ketone reduction to the corresponding alcohol, acetonide formation, and elongation of the side chain via the cyanide.

Received: March 5, 2014
Published: April 7, 2014

Levoglucosenone **7** was prepared by pyrolysis of cellulose in 2% yield as reported (Scheme 2).[9,10] The reaction is easy to

Scheme 2. Synthesis of Building Block 6[a]

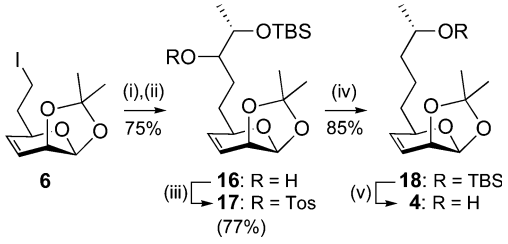


[a]Reagents and conditions: (i) H_3PO_4, ca. 500 °C, 2%; (ii) $NaBH_4$, H_2O, room temperature, 5 min, 84%; (iii) HCl, H_2O/dioxane, reflux, 1.5 h; (iv) *p*TosOH, 2,2-dimethoxypropane, acetone, room temperature, 3 h, 60% (two steps); (v) *p*TosCl, pyridine, CH_2Cl_2, room temperature, 24 h, 90%; (vi) NaCN, DMF, 60 °C, 22 h, 87%; (vii) DIBAL-H, CH_2Cl_2, −65 → −40 °C, 1.5 h, 86%; (viii) $NaBH_4$, EtOH, 0 °C, 1 h, 98%; (ix) CBr_4, PPh_3, THF, 0 °C → room temperature, 24 h, 83%; (x) NaI, acetone, 60 °C, 2 h, 98%.

carry out on a large scale, and thus the low yield is no object. However, an improved synthesis of **7** was reported in 2013.[11] Reduction of **7** with $NaBH_4$ and hydrolytic workup gave the hydroxyacetal **8**[12,13] in 84% yield; addition of hydrochloric acid liberated the triol **9**. Its treatment with 2,2-dimethoxypropane and *p*TosOH afforded the acetonido−acetal **10** (60%, two steps). This was tosylated to give **11**, which was substituted by cyanide, leaving nitrile **12**. The latter was reduced to aldehyde **13** with DIBAL-H in dichloromethane in 86% yield. Quantitative reduction of **13** with sodium borohydride in ethanol furnished alcohol **14**, which was brominated with CBr_4/PPh_3 to leave bromide **15**. This was converted to the corresponding iodide **6** in 98% yield.

Iodide **6** was metalated to the corresponding organolithium derivative with *t*-BuLi and coupled with aldehyde **5**, obtained from ethyl lactate by a known route,[14] to give the product alcohol **16** in 75% yield (Scheme 3). This alcohol was deoxygenated in two steps: tosylation afforded compound **17**, which was reduced with $LiAlH_4$ to give the silyl ether **18** in 65%

Scheme 3. Synthesis of ω-Hydroxyacetal 4[a]

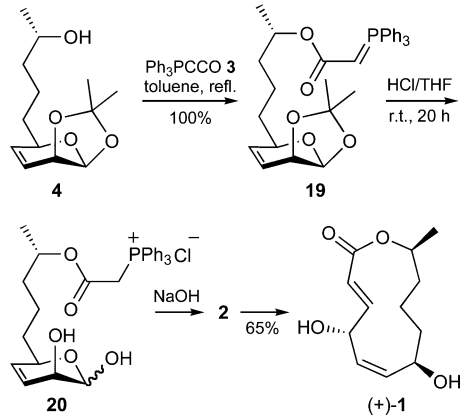


[a]Reagents and conditions: (i) *t*-BuLi (2.2 equiv), Et_2O, −78 °C; (ii) + **5**, −78 °C → room temperature, 20 h, 75%; (iii) *p*TosCl (5 equiv), CH_2Cl_2, pyridine, DMAP, 60 °C, 2 d, 77%; (iv) $LiAlH_4$ (8 equiv), THF, 75 °C, 3.5 h, 85%; (v) TBAF (6.5 equiv), THF, room temperature, 20 h, 100%.

overall yield. Its quantitative desilylation with TBAF in THF afforded the pivotal ω-hydroxyacetal **4**. This strategy for the coupling of the cellulose-derived building block and the side chain containing the *S*-configured secondary alcohol was chosen after initial attempts at Grignard-based $C_{sp^3}-C_{sp^3}$ coupling reactions had all failed. The reason for this might lie in the presence of the three oxygen atoms in the acetonido−acetals, which are ideally positioned to coordinate to magnesium and so interfere with the Grignard process.

The key alcohol **4** was heated with the ylide Ph_3PCCO (**3**) in toluene, affording the air- and moisture-stable ester ylide **19** in quantitative yield (Scheme 4). Ring closure via intramolecular

Scheme 4. Synthesis of Precursor Ylide 19 and Wittig Cyclization to (+)-Chloriolide 1



Wittig olefination requires the presence of a hemiacetal in equilibrium with the free hydroxyaldehyde form on the remote end of the ylide. Thus, acetonido−acetal **19** was dissolved in THF and treated with aqueous HCl to adjust to a pH value of ca. 2.5, allowing cleavage of the acetonide. The resulting solution of hemiacetal−phosphonium salt **20** was layered with CH_2Cl_2 and neutralized with NaOH to generate the ylide **2**, which underwent spontaneous Wittig cyclization to (+)-chloriolide **1** in 65% yield.

Our synthetic (+)-chloriolide showed spectroscopic properties in keeping with those reported in the literature and was void of other diastereomers, as determined by NMR and GC. However, it had a markedly greater specific optical rotation of $[\alpha]_D^{24}$ = 138° (*c* 0.2, $CHCl_3$), possibly since it was painstakingly freed from adherent solvents prior to measurement.

We also tested our sample of **1** for biological activity (cf. Supporting Information). In growth inhibition assays it showed a moderate efficacy against three cancer cell lines, 518A2 melanoma, HCT-116 colon carcinoma, and multidrug-resistant KB-V1/Vbl cervix carcinoma, with IC_{50}(72 h) concentrations ranging from 50 to 90 μM. This cytotoxic effect is presumably not a feature of the macrocyclic lactone but is due to the electrophilic enone and hydroxypentadienyl moieties. In agar diffusion assays synthetic **1** did not inhibit the growth of erythromycin-sensitive *S. aureus* and *E. coli TolC* bacteria at concentrations as high as 20 μg/mL. However, this came as no surprise, since most macrolide aglycones lack antimicrobial activity. We are currently investigating chimeric glycosides of chloriolide with desosamine, the amino sugar causative for the high antibiotic activity of erythromycin.

dx.doi.org/10.1021/jo500527g | J. Org. Chem. 2014, 79, 4038−4042

CONCLUSIONS

The mold metabolite (+)-chloriolide **1** was synthesized in 15 linear steps and 9% overall yield starting from a pyrolysis product of cellulose and ethyl L-lactate. This synthesis is shorter than the previously published methods by the groups of Kirsch and Nanda, and it is also the first synthesis ever of a macrolide by a ring-closing intramolecular Wittig olefination of a stabilized phosphorus ylide bearing an ω-hemiacetal. Since the protection of hydroxy groups is not necessary for this reaction to work, it should be applicable to other carbohydrates as well. This would allow the full exploitation of the abundance of stereocenters and alcohols in sugars for the construction of macrolides which are frequently rich in these features.

EXPERIMENTAL SECTION

General Remarks. IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. Chemical shifts of NMR signals are given in parts per million (δ) downfield from tetramethylsilane for ^{1}H and ^{13}C. Mass spectra were obtained under EI (70 eV) conditions. High-resolution mass spectra were obtained with a UPLC/Q-TOF MS system in ESI mode. For chromatography silica gel 60 (230−400 mesh) was used.

Alcohol 10. A solution of **8**[12,13] (13.1 g, 102.3 mmol) in dioxane (125 mL) and 0.35 M HCl (250 mL) was heated at reflux for 1.5 h. The reaction mixture was cooled to room temperature and neutralized with NEt_3. The volatiles were evaporated, acetone was added, and the precipitate of the ammonium salt was filtered off. The filtrate was concentrated, and the residue of crude **9** was dried under vacuum to leave a yellow oil (14.95 g, 102.3 mmol). This was dissolved in acetone (120 mL) and treated with 2,2-dimethoxypropane (57.5 mL, 463.4 mmol) and *p*TosOH (1.96 g, 10.3 mmol), and the resulting mixture was stirred at room temperature for 3 h. The volatiles were removed under reduced pressure, and the remainder was purified by column chromatography (ethyl acetate/hexane 1/1; R_f = 0.37) to afford **10** (11.4 g, 61.4 mmol, 60% over two steps) as a yellow oil: $[\alpha]_D^{24}$ = 39° (*c* 2.0, $CHCl_3$); IR (ATR) ν_{max} 3457, 2986, 2889, 1678, 1458, 1371, 1316, 1223, 1186, 1163, 1129, 1066, 1043, 981, 882 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3 H), 1.51 (s, 3 H), 2.75 (s, 1 H; OH), 3.57−3.73 (m, 2 H), 4.14−4.24 (m, 2 H), 5.24 (d, *J* = 3.0 Hz, 1 H), 5.94 (d, *J* = 10.3 Hz, 1 H), 5.99−6.10 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4, 28.4, 64.6, 70.3, 73.2, 96.9, 111.5, 123.9, 131.8; MS (EI) *m*/*z* 171 [M$^+$ − CH_3], 155, 111, 98, 83, 69, 59; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_9H_{14}NaO_4^+$ 209.0784, found 209.0783.

{(3a*S*,5*S*,7a*S*)-2,2-Dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo-[4,5-*b*]pyran-5-yl}methyl 4-Methylbenzenesulfonate (11). A solution of **10** (3.45 g, 18.5 mmol) in CH_2Cl_2 (30 mL) was treated with pyridine (30 mL) and *p*-toluenesulfonyl chloride (5.30 g, 27.8 mmol). The mixture was stirred at room temperature for 24 h, and then the reaction was quenched with water (4.5 mL). The volatiles were removed in vacuo, and the residue was purified by column chromatography (methyl *tert*-butyl ether/hexane 1/8) to afford **11** (5.66 g, 90%) as a yellow oil: R_f = 0.27 (hexane/methyl *tert*-butyl ether 3/2); $[\alpha]_D^{24}$ = 22° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 2986, 1598, 1358, 1326, 1174, 1072, 977, 913, 884, 813, 762, 721, 705, 678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3 H), 1.40 (s, 3 H), 2.38 (s, 3 H), 4.00 (dd, *J* = 10.0, 6.0 Hz, 1 H), 4.09 (dd, *J* = 10.0, 6.0 Hz, 1 H), 4.15−4.19 (m, 1 H), 4.30 (m$_c$, 1 H), 5.15 (d, *J* = 3.0 Hz, 1 H), 5.91 (ddd, *J* = 10.2, 1.5, 0.7 Hz, 1 H), 6.03 (ddd, *J* = 10.2, 4.2, 2.2 Hz, 1 H), 7.28 (m$_c$, 2 H), 7.73 (m$_c$, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 26.4, 28.2, 69.8, 70.0, 70.2, 96.7, 111.8, 124.4, 127.9, 129.9, 130.1, 132.4, 144.9; MS (EI) *m*/*z* 340 [M$^+$], 325, 281, 207, 169, 155, 123, 97, 91; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{20}NaO_6S^+$ 363.0873, found 363.0885.

2-{(3a*S*,5*R*,7a*S*)-2,2-Dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo-[4,5-*b*]pyran-5-yl}acetonitrile (12). A solution of tosylate **11** (0.50 g, 1.47 mmol) in DMF (5 mL) was treated with dried NaCN (288 mg, 5.88 mmol), and the resulting suspension was stirred under argon at 60 °C for 22 h. Water was added, and the resulting mixture was extracted three times with methyl *tert*-butyl ether. The combined organic layers were dried and concentrated, and the residue was purified by column chromatography (ethyl acetate/hexane 1/3; R_f = 0.21) to afford 250 mg of **12** (1.28 mmol, 87%) as a white waxy solid; $[\alpha]_D^{24}$ = 43° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 2987, 1382, 1370, 1227, 1178, 1164, 1130, 1069, 1004, 983, 885, 864, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 3 H), 1.53 (s, 3 H), 2.61 (dd, *J* = 16.6, 6.4 Hz, 1 H), 2.68 (dd, *J* = 16.6, 6.0 Hz, 1 H), 4.20−4.25 (m, 1 H), 4.37 (m$_c$, 1 H), 5.25 (d, *J* = 3.0 Hz, 1 H), 6.01 (ddd, *J* = 10.2, 1.5, 0.7 Hz, 1 H), 6.13 (ddd, *J* = 10.2, 4.2, 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.6, 26.3, 28.2, 67.7, 69.8, 96.8, 112.2, 116.2, 124.8, 131.3; MS (EI) *m*/*z* 180 [M$^+$ − CH_3], 155, 139, 137, 122, 107, 97, 79; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{10}H_{13}NNaO_3^+$ 218.0788, found 218.0786.

2-{(3a*S*,5*R*,7a*S*)-2,2-Dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo-[4,5-*b*]pyran-5-yl}acetaldehyde (13). DIBAL-H (2.52 mL of a 1 M solution in hexanes, 2.52 mmol) was slowly added to a solution of **12** (0.41 mg, 2.10 mmol) in CH_2Cl_2 (32 mL) at −65 °C. The mixture was stirred while being warmed from −65 to −40 °C over a period of 90 min. Saturated aqueous potassium sodium tartrate (40 mL) was added, and stirring was continued for another 1 h at room temperature. The phases were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by column chromatography (hexane/ethyl acetate 2/1; R_f = 0.34) to leave 358 mg of **13** (1.81 mmol, 86%) as a colorless oil: $[\alpha]_D^{24}$ = 58° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 2986, 2933, 1724, 1458, 1381, 1225, 1178, 1068, 1050, 984, 883, 865, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 3 H), 1.51 (s, 3 H), 2.64 (ddd, *J* = 17.0, 5.6, 1.8 Hz, 1 H), 2.74 (ddd, *J* = 17.0, 6.6, 2.0 Hz, 1 H), 4.17−4.22 (m, 1 H), 4.56−4.65 (m, 1 H), 5.22 (d, *J* = 3.0 Hz, 1 H), 5.97 (ddd, *J* = 10.2, 1.2, 0.7 Hz, 1 H), 6.04 (ddd, *J* = 10.2, 4.1, 2.1 Hz, 1 H), 9.78 (t, *J* = 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4, 28.4, 47.7, 67.7, 70.2, 97.0, 112.0, 123.3, 133.9, 200.2; MS (EI) *m*/*z* 183 [M$^+$ − CH_3], 153, 139, 123, 112, 97, 83, 67, 59; HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{14}NaO_4^+$ 221.0784, found 221.0768.

(3a*S*,5*R*,7a*S*)-5-(2-Hydroxyethyl)-2,2-dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo[4,5-*b*]pyran (14). A solution of aldehyde **13** (991 mg, 4.99 mmol) in ethanol (45 mL) was treated with $NaBH_4$ (125 mg, 3.30 mmol) and stirred at 0 °C for 1 h. Aqueous $NaHCO_3$ was added, and the resulting mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (ethyl acetate/hexane 1/2) to afford 979 mg of **14** (4.89 mmol, 98%) as colorless crystals with mp 91−92 °C: R_f = 0.23 (ethyl acetate/hexane 1:1); $[\alpha]_D^{24}$ = 90° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 3432, 2985, 1370, 1311, 1224, 1049, 881, 864, 800, 754, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3 H), 1.44 (s, 3 H), 1.69−1.89 (m, 2 H), 2.70 (s, 1 H), 3.63−3.77 (m, 2 H), 4.08−4.13 (m, 1 H), 4.20−4.27 (m, 1 H), 5.10 (d, *J* = 3.0 Hz, 1 H), 5.87−5.96 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3, 28.3, 36.7, 59.3, 70.3, 70.8, 96.8, 111.7, 122.0, 135.4; MS (EI) *m*/*z* 185 [M$^+$ − CH_3], 155, 142, 126, 125, 114, 97, 83, 67, 59; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{16}NaO_4^+$ 223.0941, found 223.0963.

(3a*S*,5*R*,7a*S*)-5-(2-Bromoethyl)-2,2-dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo[4,5-*b*]pyran (15). A solution of alcohol **14** (286 mg, 1.43 mmol) in THF (4.1 mL) was treated with PPh_3 (450 mg, 1.71 mmol) and CBr_4 (568 mg, 1.71 mmol). The resulting mixture was stirred initially at 0 °C for 24 h and then warmed to room temperature. The solvent was removed under vacuum, and the residue was purified by column chromatography (hexane/diethyl ether 10/1; R_f = 0.23) to afford 312 mg of **15** (1.19 mmol, 83%) as a colorless waxy solid: $[\alpha]_D^{24}$ = 144° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 2985, 1435, 1381, 1225, 1186, 1124, 1054, 1007, 973, 883, 865, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3 H), 1.48 (s, 3 H), 2.08−2.17 (m, 2 H), 3.32−3.60 (m, 2 H), 4.13−4.17 (m, 1 H), 4.19−4.26 (m, 1 H), 5.16 (d, *J* = 3.0 Hz, 1 H), 5.89 (ddd, *J* = 10.2, 1.3, 0.7 Hz, 1 H), 5.98 (ddd, *J* = 10.2, 4.2, 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4, 28.5, 29.1, 37.8, 70.0, 70.5, 97.0, 111.8, 123.0, 134.6; MS (EI) *m*/

dx.doi.org/10.1021/jo500527g | J. Org. Chem. 2014, 79, 4038−4042

z 249 (68%) [M(^{81}Br)$^+$ − CH_3], 247 (72%) [M(^{79}Br)$^+$ − CH_3], 219, 207, 187, 176, 155, 135, 123, 109, 97, 81, 59.

(3a*S*,5*R*,7a*S*)-5-(2-Iodoethyl)-2,2-dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo[4,5-*b*]pyran (6). A solution of bromide **15** (145 mg, 0.55 mmol) in dry acetone (4 mL) was treated with dry sodium iodide (248 mg, 1.65 mmol), and the resulting mixture was stirred at 60 °C for 2 h. The solvent was removed, and the residue was divided between CH_2Cl_2 and water. The organic layer was dried over Na_2SO_4 and under vacuum to yield 166 mg of pure **6** (0.54 mmol, 98%) as colorless crystals with mp 49−50 °C: R_f = 0.22 (hexane/diethyl ether 10/1); $[\alpha]_D^{24}$ = 110° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 2983, 1438, 1380, 1224, 1164, 1071, 1048, 1002, 882, 863, 802, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3 H), 1.43 (s, 3 H), 1.98−2.08 (m, 2 H), 3.14−3.29 (m, 2 H), 4.05−4.13 (m, 2 H), 5.12 (d, *J* = 3.0 Hz, 1 H), 5.84 (ddd, *J* = 10.0, 1.3, 0.7 Hz, 1 H), 5.93 (ddd, *J* = 10.0, 4.1, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 1.4, 26.3, 28.3, 38.3, 70.2, 71.5, 97.8, 111.5, 122.9, 134.1; MS (EI) *m*/*z* 310 [M$^+$], 295, 265, 252, 235, 224, 183, 155, 137, 97, 79, 59; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{10}H_{15}INaO_3^+$ 332.9958, found 332.9947.

(3a*S*,5*R*,7a*S*)-5-[(4*S*)-3-hydroxy-4-*tert*-butyldimethylsilyloxypentyl]-2,2-dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo[4,5-*b*]pyran (16). A solution of iodide **6** (692 mg, 2.23 mmol) in diethyl ether (7 mL) was slowly added to a stirred solution of *t*-BuLi (1.6 M in hexanes, 3.07 mL, 4.91 mmol) in diethyl ether (46 mL) kept at −78 °C. After 5 min aldehyde **5**[14] (504 mg, 2.69 mmol) was slowly added and stirring was continued for 25 min at −78 °C. The cooling bath was removed, and the mixture was stirred for a further 20 h. Aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic phases were dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography (diethyl ether/hexane 1/3; R_f = 0.08) to afford 623 mg of **16** (1.67 mmol, 75%) as a colorless oil: $[\alpha]_D^{24}$ = 51° (*c* 1.0; $CHCl_3$); 2.6/1 mixture of two diastereoisomers. *Major diastereoisomer*: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.84 (s, 9 H), 1.03 (d, *J* = 6.3 Hz, 3 H), 1.38 (s, 3 H), 1.52 (s, 3 H), 1.39−1.94 (m, 4 H), 2.34 (s, 1 H), 3.43−3.54 (m, 1 H), 3.71 (m$_c$, 1 H), 4.00−4.19 (m, 2 H), 5.17 (d, *J* = 3.0 Hz, 1 H), 5.93−6.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.9, −4.5, 17.0, 18.0, 25.8, 26.5, 28.5, 30.9, 31.1, 70.7, 71.2, 71.5, 74.9, 97.2, 111.7, 122.4, 135.6. *Minor diastereoisomer*: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.86 (s, 9 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 1.38 (s, 3 H), 1.52 (s, 3 H), 1.39−1.94 (m, 4 H), 2.41 (s, 1 H), 3.20−3.34 (m, 1 H), 3.60 (m$_c$, 1 H), 4.00−4.19 (m, 2 H), 5.16 (d, *J* = 3.0 Hz, 1 H), 5.93−6.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.9, −4.2, 18.0, 20.2, 25.7, 26.5, 28.8, 30.9, 31.1, 70.7, 71.2, 71.7, 75.8, 97.2, 111.7, 122.2, 135.9. *Mixture*: IR (ATR) ν_{max} 3459, 2954, 2358, 2008, 1462, 1370, 1311, 1249, 1185, 1130, 1068, 939, 883, 832, 774 cm^{-1}; MS (EI) *m*/*z* 357 [M$^+$ − CH_3], 297, 281, 257, 239, 221, 211, 187, 159, 145, 119, 115, 85, 75; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{36}NaO_5Si^+$ 395.2224, found 395.2221.

(3a*S*,5*R*,7a*S*)-5-[(4*S*)-3-Tosyloxy-4-*tert*-butyldimethylsilyloxypentyl]-2,2-dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo[4,5-*b*]pyran (17). A solution of alcohol **16** (193 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) and pyridine (0.6 mL) was treated with *p*-toluenesulfonyl chloride (493 mg, 2.59 mmol) and DMAP (63.3 mg, 0.52 mmol). The mixture was heated in a sealed bomb tube at 60 °C for 2 days. Aqueous NH_4Cl was added, the resulting mixture was extracted four times with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4, concentrated, and purified by column chromatography (gradient 25−50% methyl *tert*-butyl ether in hexane) to give 211 mg of **17** (0.40 mmol, 77%) as a colorless oil: R_f = 0.43 (hexane/methyl *tert*-butyl ether 3/1); $[\alpha]_D^{24}$ = 31° (*c* 1.0; $CHCl_3$); 2.6/1 mixture of two diastereoisomers. *Major diastereoisomer:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.04 (s, 3 H), −0.03 (s, 3 H), 0.80 (s, 9 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 1.36 (s, 3 H), 1.48 (s, 3 H), 1.49−1.59 (m, 2 H), 1.69−1.77 (m, 2 H), 2.39 (s, 3 H), 3.88−4.00 (m, 2 H), 4.09−4.17 (m, 1 H), 4.35−4.43 (m, 1 H), 5.10 (d, *J* = 3.0 Hz, 1 H), 5.77 (m$_c$, 1 H), 5.92 (ddd, *J* = 10.0, 4.3, 2.2 Hz, 1 H), 7.23−7.32 (m, 2 H), 7.71−7.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.9, −4.7, 17.9, 19.9, 21.5, 23.3, 25.7, 26.5, 28.5, 29.7, 69.6, 70.6, 70.9, 86.8, 97.1, 111.7, 122.5, 127.7, 129.6, 134.5, 135.3, 144.4. *Minor diastereoisomer*: ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.04 (s, 3 H), −0.03 (s, 3 H), 0.80 (s, 9 H), 1.03 (d, *J* = 6.3 Hz, 3 H), 1.36 (s, 3 H), 1.47 (s, 3 H), 1.49−1.59 (m, 2 H), 1.69−1.77 (m, 2 H), 2.40 (s, 3 H), 3.88−4.00 (m, 2 H), 4.09−4.17 (m, 1 H), 4.24−4.32 (m, 1 H), 5.09 (d, *J* = 3.0 Hz, 1 H), 5.74 (m$_c$, 1 H), 5.92 (ddd, *J* = 10.0, 4.3, 2.2 Hz, 1 H), 7.23−7.32 (m, 2 H), 7.71−7.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.0, −4.9, 17.0, 17.8, 21.5, 23.1, 25.6, 26.5, 28.5, 30.6, 68.0, 70.9, 71.4, 85.4, 97.0, 111.7, 122.4, 127.7, 129.7, 134.2, 135.3, 144.6. *Mixture*: IR (ATR) ν_{max} 2930, 2857, 1599, 1496, 1366, 1188, 1176, 1096, 1073, 1054, 915, 836, 812, 776, 665, 553 cm^{-1}; MS (EI) *m*/*z*: 511 [M$^+$ − CH_3], 411, 341, 279, 229, 211, 165, 159, 113, 91, 73; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{42}NaO_7SSi^+$ 549.2313, found 549.2304.

(3a*S*,5*R*,7a*S*)-5-[(4*S*)-4-*tert*-butyldimethylsilyloxypentyl]-2,2-dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo[4,5-*b*]pyran (18). A mixture of tosylate **17** (332 mg, 0.63 mmol), THF (14 mL), and $LiAlH_4$ (191 mg, 5.04 mmol) was placed in a sealed bomb tube and heated to 75 °C for 3.5 h. After the mixture was cooled, a saturated aqueous potassium sodium tartrate solution (30 mL) was added, and stirring was continued for 1 h. The mixture was extracted twice with ethyl acetate and twice with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and concentrated under vacuum, and the remainder was purified by column chromatography (hexane/methyl *tert*-butyl ether 5/1; R_f = 0.53) to afford 192 mg of **18** (0.54 mmol, 85%) as a colorless oil: $[\alpha]_D^{24}$ = 54° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.01 (s, 6 H), 0.83 (s, 9 H), 1.06 (d, *J* = 6.1 Hz, 3 H), 1.29−1.48 (m, 4 H), 1.36 (s, 3 H), 1.51 (s, 3 H), 1.52−1.68 (m, 2 H), 3.67−3.79 (m, 1 H), 3.99−4.05 (m, 1 H), 4.12−4.15 (m, 1 H), 5.15 (d, *J* = 3.0 Hz, 1 H), 5.92−5.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.7, −4.5, 18.0, 20.8, 23.7, 25.8, 26.5, 28.5, 34.6, 39.6, 68.4, 70.7, 71.9, 97.2, 111.6, 122.1, 135.8; IR (ATR) ν_{max} 2930, 2858, 1473, 1370, 1321, 1237, 1183, 1075, 1052, 1006, 833, 772 cm^{-1}; MS (EI) *m*/*z* 341 [M$^+$ − CH_3], 281, 253, 241, 223, 213, 183, 171, 159, 149, 129, 107, 79, 75; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{36}NaO_4Si^+$ 379.2275, found 379.2275.

(3a*S*,5*R*,7a*S*)-5-[(4*S*)-4-Hydroxypentyl]-2,2-dimethyl-5,7a-dihydro-3a*H*-[1,3]dioxolo[4,5-*b*]pyran (4). A mixture of silyl ether **18** (20.8 mg, 0.06 mmol), THF (3 mL), and TBAF (123 mg, 0.39 mmol) was stirred at room temperature for 20 h. The volatiles were removed in vacuo, and the residue thus obtained was divided between CH_2Cl_2 and brine. The organic layer was dried with Na_2SO_4 and concentrated, and the remainder was purified by column chromatography (hexane/methyl *tert*-butyl ether 10/1) to afford 14 mg of **4** (0.06 mmol, 100%) as a colorless oil: R_f = 0.21 (hexane/ethyl acetate 1/1); $[\alpha]_D^{24}$ = 74° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 3397, 2937, 1459, 1371, 1227, 1189, 1073, 1052, 882 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (d, *J* = 6.2 Hz, 3 H), 1.32 (s, 3 H), 1.35−1.50 (m, 4 H), 1.47 (s, 3 H), 1.51−1.63 (m, 2 H), 2.02 (s, 1 H), 3.65−3.77 (m, 1 H), 3.97−4.06 (m, 1 H), 4.08−4.12 (m, 1 H), 5.11 (d, *J* = 3.0 Hz, 1 H), 5.88−5.91 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 23.3, 26.4, 28.4, 34.3, 38.9, 67.5, 70.5, 71.7, 97.0, 111.5, 122.0, 135.7; MS (EI) *m*/*z* 227 [M$^+$ − CH_3], 167, 155, 138, 109, 97, 81, 68, 59; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}NaO_4^+$ 265.1410, found 265.1390.

(3a*S*,5*R*,7a*S*)-2,2-Dimethyl-5-[(4*S*)-4-(triphenylphosphoranylidenacetoxy)pentyl]-5,7a-dihydro-3a*H*-[1,3]dioxolo-[4,5-*b*]pyran (19). A solution of alcohol **4** (36.0 mg, 0.15 mmol) and Ph_3PCCO (**3**; 44.9 mg, 0.15 mmol) in toluene (3 mL) was heated to reflux for 1 h. The solvent was removed, and the remainder was repeatedly extracted with diethyl ether to remove residual starting materials. Upon drying of the residue under reduced pressure 80.9 mg of ylide **26** (0.15 mmol, 100%) was obtained as a foamy, sticky solid: R_f = 0.13 (rp-18-phase; MeOH/H_2O 3/2, + 1% TFA); $[\alpha]_D^{24}$ = 32° (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 2933, 1611, 1574, 1484, 1368, 1262, 1102, 1071, 1049, 883, 715, 692 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.77−0.88 (m, 3 H), 0.78−1.83 (m, 6 H), 1.33 (s, 3 H), 1.61 (s, 3 H), 3.19−3.33 (m, 1 H), 3.63−3.80 (m, 1 H), 3.86−3.98 (m, 1 H), 5.01 (d, *J* = 3.0 Hz, 1 H), 5.16−5.32 (m, 1 H), 5.54−5.66 (m, 1 H), 5.71−5.85 (m, 1 H), 6.91−7.13 (m, 9 H) 7.51−7.79 (m, 6 H); ^{13}C NMR (C_6D_6, 75 MHz) δ 21.7, 22.0, 27.3, 29.4, 35.4, 37.7, 66.7, 67.4, 71.7, 72.4, 98.2, 112.0, 123.1, 129.0, 129.2, 131.1, 131.2, 132.0, 132.7, 132.8,

dx.doi.org/10.1021/jo500527g | *J. Org. Chem.* 2014, 79, 4038−4042

133.6, 133.8, 136.2, 172.3; ^{31}P NMR (C_6D_6, 121.5 MHz) δ 13.1, 15.2 (rotamers); MS (EI) m/z 544 [M^+], 529, 486, 457, 389, 333, 321, 277, 262, 201, 183, 152, 113, 97, 77; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{33}H_{38}O_5P^+$ 545.2451, found 545.2472.

(+)-Chloriolide 1. A solution of phosphorus ylide **19** (95.0 mg, 0.17 mmol) in THF (1.8 mL) was treated with aqueous HCl (0.15 M, 4 mL), and the resulting mixture was stirred at room temperature for ca. 20 h. The progress and completeness of the cleavage of the acetonide was monitored by TLC on reversed-phase plates. The clear solution finally obtained was poured into an ice-cold, vigorously stirred emulsion of aqueous NaOH (0.25 M, 30 mL) and CH_2Cl_2 (30 mL). The layers were separated immediately, the aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were dried with $MgSO_4$. After it was stirred for another 60 min, the solution was concentrated under vacuum. The crude product thus obtained was purified by column chromatography (hexane/methyl *tert*-butyl ether 1/5; R_f = 0.2) to afford 25 mg of **1** (0.11 mmol, 65%) as a white solid with mp 133−133.5 °C: $[\alpha]_D^{24}$ = 138° (*c* 0.2, $CHCl_3$) (lit.[1] $[\alpha]_D^{25}$ = 107° (*c* 0.2, $CHCl_3$), lit.[2] $[\alpha]_D^{20}$ = 101° (*c* 0.21, CH_2Cl_2), lit.[3] $[\alpha]_D^{25}$ = 105.9° (*c* 0.2, $CHCl_3$)); IR (ATR) ν_{max} 3283, 2924, 2853, 2383, 2342, 2309, 2178, 2151, 2029, 1713, 1456, 1377, 1259, 1173, 1064, 1021, 921, 800, 696, 664, 603, 567 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.26 (d, J = 6.4 Hz, 3 H), 1.35−1.83 (m, 6 H), 4.54 (t, J = 8.8 Hz, 1 H), 4.81−4.86 (m, 1 H), 5.04−5.11 (m, 1 H), 5.52 (dd, J = 11.8, 8.2 Hz, 1 H), 5.67 (ddd, J = 11.8, 7.3, 1.2 Hz, 1 H), 6.10 (dd, J = 16.0, 2.4 Hz, 1 H), 7.24 (dd, J = 16.0, 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 19.7, 21.4, 34.2, 36.2, 68.0, 69.7, 73.9, 119.6, 126.6, 140.4, 152.6, 166.5; MS (EI) m/z 154 [$C_8H_{10}O_3^+$], 125, 97, 84, 55; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{12}H_{18}NaO_4^+$ 249.1097, found 249.1077.

■ ASSOCIATED CONTENT

Supporting Information

Figures and a table giving ^{1}H and ^{13}C NMR spectra of **1**, **4**−**8**, and **10**−**19**, cytotoxicity of (+)-**1**, and the sensitivity of *E. coli* to (+)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for R.S.: Rainer.Schobert@uni-bayreuth.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Ursula Bilitewski (HZI, Braunschweig, Germany) for antimicrobial tests and Katharina Mahal, MSc, in our group for cytotoxicity tests.

■ REFERENCES

(1) Jiao, P.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2006**, *69*, 636−639.
(2) Haug, T. T.; Kirsch, S. F. *Org. Biomol. Chem.* **2010**, *8*, 991−993.
(3) Das, T.; Jana, N.; Nanda, S. *Tetrahedron Lett.* **2010**, *51*, 2644−2647.
(4) Bestmann, H. J.; Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 780−782.
(5) Bestmann, H. J.; Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 791−792.
(6) Bestmann, H. J.; Schobert, R. *Tetrahedron Lett.* **1987**, *28*, 6587−6590.
(7) Bestmann, H. J.; Sandmeier, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634.
(8) Schobert, R.; Boeckman, R. K., Jr.; Pero, J. E. *Org. Synth.* **2005**, *82*, 140−143.
(9) Shafizadeh, F.; Chin, P. *Carbohydr. Res.* **1977**, *58*, 79−87.
(10) Shafizadeh, F.; Laj, Y. *Carbohydr. Res.* **1975**, *40*, 263−274.
(11) Kudo, S.; Zhou, Z.; Yamasaki, K.; Norinaga, K.; Hayashi, J. *Catalysts* **2013**, *3*, 757−773.
(12) Brimacombe, J. S.; Hunedy, F.; Mather, A. M.; Tucker, L. C. N. *Carbohydr. Res.* **1979**, *68*, 231−238.
(13) Zanardi, M. M.; Suárez, A. G. *Tetrahedron Lett.* **2009**, *50*, 999−1002.
(14) Song, L.; Yao, H.; Zhu, L.; Tong, R. *Org. Lett.* **2013**, *15*, 6−9.