Synthesis and Determination of the Absolute Configuration of Fugomycin and Desoxyfugomycin: CD Spectroscopy and Fungicidal Activity of Butenolides

Manfred Braun,*[a] Andreas Hohmann,[a] Jaykumar Rahematpura,[a] Corinna Bühne,[a] and Stefan Grimme[b]

Abstract: The dibromoalkenes (*S*)-**3** and (*R*)- and (*S*)-**4** are intermediates in the syntheses of the naturally occurring fungicidal butenolides fugomycin (**1**) and desoxyfugomycin (**2**), respectively. The stereoselective bromine–lithium exchange that leads to the carbenoid **12** and the vinyllithium reagent **17a** on the one hand, and palladium-catalyzed coupling reactions of the dibromoalkene **3** and the bromolactone **22** on the other are key steps en route to the butenolides **1** and **2**. The chiral building blocks (*S*)-**3**, (*R*)-**4**, and (*S*)-**4** are readily available from (*R*)-isopropylideneglyceraldehyde **5**, isobutyl (*R*)-lactate **6a**, and ethyl (*S*)-lactate **6b**, respectively. The synthetic procedure adopted here permits the absolute configuration of the natural products fugomycin (**1**) and desoxyfugomycin (**2**) to be assigned by comparison of their chiroptical properties with those of the synthetic products. The CD spectra of the bromolactone **22**, calculated by two different density functional methods (TDDFT, DFT/MRCI), are found to be in good agreement with the measured spectra. On the basis of these calculations, the two CD bands observed could be assigned to n–π* and π–π* transitions, respectively. Fugomycin (**1**) and the synthetic butenolide **20** displayed high fungicidal activity against botrytis in greenhouse experiments, whereas the saturated lactone **21** was practically inactive.

Keywords: chiral pool · configuration determination · density functional calculations · lactones · natural products

Introduction

The butenolide or 2(5*H*)-furanone moiety is frequently present in naturally occurring and biologically active products.[1] A series of these heterocyclic compounds—mostly plant or fungal metabolites—proved themselves as cytotoxic, antitumoral, antiparasitic, or pesticidal agents.[2] This biological activity has given rise to remarkable efforts directed towards the synthesis of this kind of natural product.[3] Recently, two novel butenolides, fugomycin (**1**) and desoxyfugomycin (**2**), were isolated from the strain 63–28 of *Pseudomonas aureofaciens*. They were found to have antifungal activity and their structures were elucidated except for their absolute configurations.[4] Herein, we report a synthesis of the enantiomerically pure butenolides (*S*)-**1**[5] and (*R*)- and (*S*)-**2**, the aim being to determine their absolute configurations.

The synthesis of the butenolides **1** and **2**, which is outlined below, relies on the "ex-chiral-pool" concept[6] in which, by starting from enantiomerically pure building blocks **5**, **6a**, and **6b**, the natural products **1** and **2** have known absolute configurations. According to the retrosynthetic concept outlined in Scheme 1, the dibromoalkenes **3**[7] and **4** were designed to be key intermediates in the syntheses. A prerequisite thereof was the stereoselective carbon–carbon bond formation at their double bonds. Thus, protocols for a controlled halogen–metal exchange of the (*E*)- and (*Z*)-bromide atoms in the dibromoalkenes **3** and **4** had to be elaborated first.

Results and Discussion

Stereoselectivity of halogen–metal exchange in dibromoalkenes 3 and 4: In the halogen–metal exchange reaction[8] of 1,1-dibromoalkenes **7** the halogen atom in either the *Z* or *E* position relative to the bulkier β substituent R can be re-

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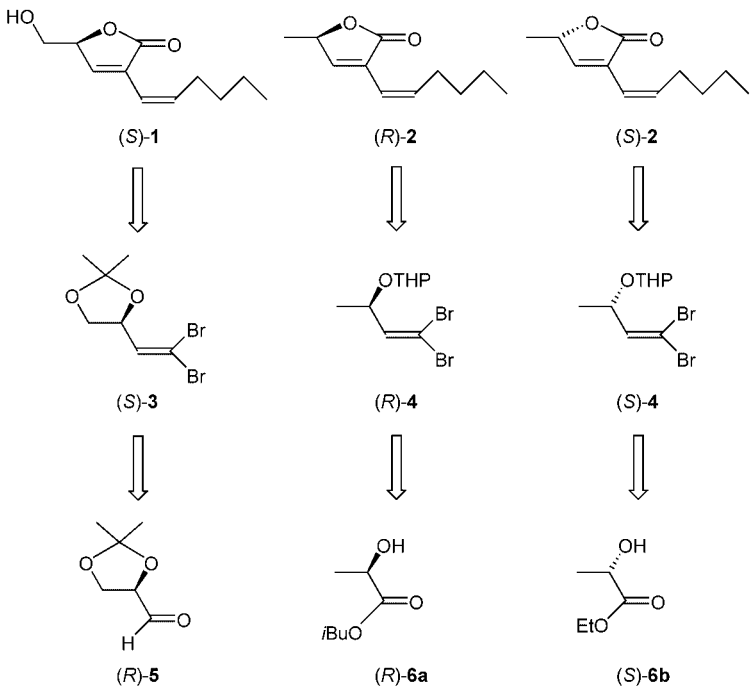
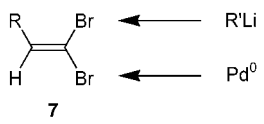


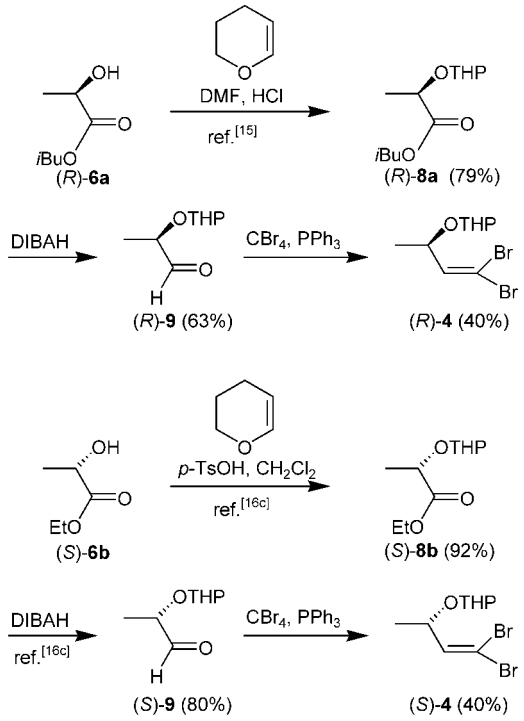
Scheme 1. Retrosynthesis of (*S*)-fugomycin (**1**) and (*R*)- and (*S*)-desoxyfugomycin (**2**). THP = 2-tetrahydropyranyl.

placed. When 1-bromo-1-lithioalkenes are generated from 1,1-dibromalkenes by treatment with alkyllithium reagents, it is predominantly the (*Z*)-bromine atom that is replaced.[9] This outcome has been explained by a release of steric hindrance due to the substitution of the bulky bromine atom by the smaller lithium atom in the *Z* position. On the other hand, enhanced diastereoselectivity in favor of the replacement of the (*Z*)-bromine atom is observed when the residue R carries ether groups that are suitable for chelation to the (*Z*)-lithium atom.[10] In contrast, palladium-catalyzed coupling reactions of dibromoalkenes **7** occur predominantly at the *E* position.[11] Before devising a total synthesis of fugomycin (**1**) and desoxyfugomycin (**2**), it was necessary to investigate whether the two types of protocols—the bromine–lithium exchange and the palladium-catalyzed coupling reactions—would be applicable to the substrates **3** and **4** and whether they would give the anticipated stereochemical outcome.



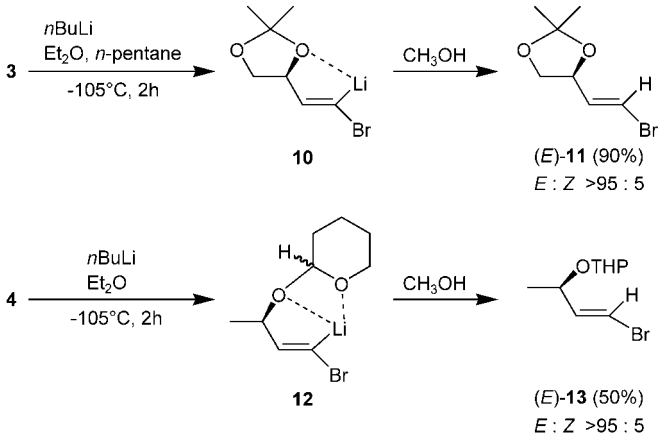
The lithiation of the dibromoalkenes **3** and **4** was investigated first. The former compound is available[7b] from (*R*)-isopropylideneglyceraldehyde **5**[12] according to a modified Corey–Fuchs procedure.[13] To prepare the dibromoalkene **4**, isobutyl (*R*)-lactate **6a** was first protected[14] as the tetrahydropyranyl ether **8a**[15] and reduced to the aldehyde **9** by treatment with diisobutylaluminum hydride. Here again, a Corey–Fuchs protocol permitted the conversion of the aldehyde (*R*)-**9** into the alkene (*R*)-**4** (Scheme 2). The alkene (*S*)-**4** was prepared analogously from commercially available ethyl (*S*)-lactate **6b**. After protection of **6b** as the tetrahydropyranyl ether (*S*)-**8b**,[16] reduction yielded the aldehyde (*S*)-**9**,[16c] which was converted into the dibromoalkene (*S*)-**4** again by using the Corey–Fuchs procedure.[17]

The dibromoalkenes **3** and **4** were treated with *n*-butyllithium in diethyl ether or in mixtures of diethyl ether and *n*-pentane to bring about a bromine–lithium exchange. In both substrates, the (*Z*)-bromine atom was predominantly replaced so that the *E*-configured lithium carbenoids **10** and **12** were formed with high stereoselectivity. This was shown by subsequent protonation that delivered the monobromoalkenes **11** and **13**. In both cases the *E*/*Z* ratio was shown by ^{1}H NMR spectroscopy to surpass 95:5. Remarkably, the stereoselectivity of the bromine-lithium exchange of the lactate-derived dibromoalkene **4** is similar to that of the corresponding (2-methoxyethoxy)methyl (MEM)-protected analogue described previously.[10] Thus,



Scheme 2. Synthesis of (*R*)- and (*S*)-dibromoalkenes **4**.

one may conclude that the chelating effect of the tetrahydropyranyl protecting group is comparable with that of the MEM group. The stereoselectivity of the bromine–lithium exchange was increased when the reaction was performed in less polar solvents. Optimum results in favor of *Z* lithiation of the dibromoalkenes **3** and **4** were obtained in diethyl ether or in mixtures of *n*-pentane and diethyl ether. A distinctly lower *E*/*Z* selectivity was obtained in tetrahydrofuran. It is plausible that intermolecular solvation by this solvent competes with the intramolecular coordination outlined in formulae **10** and **12** (Scheme 3).

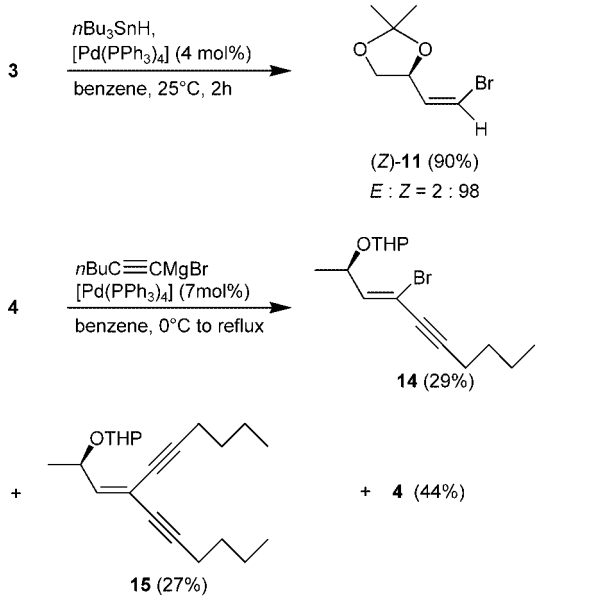


Scheme 3. Stereoselective bromine–lithium exchange in dibromoalkenes **3** and **4**.

To determine the stereochemical outcome of the palladium-mediated replacement of a bromine atom, the dioxolane **3** was first reduced with tributyltin hydride in the presence of $[Pd(PPh_3)_4]$ as catalyst.[18] The reaction occurred with remarkable diastereoselectivity in favor of the *Z* isomer **11** with an *E*/*Z* ratio of 2:98. This result reveals a distinct preference by the palladium to insert into the carbon–bromine bond in the *E* position (Scheme 4).

A Sonogashira-type coupling[19] reaction was chosen to study the stereochemistry of palladium-catalyzed carbon–carbon bond formation in the dibromoalkene **4**; here, the dibromoalkene **4** was allowed to react with hexynylmagnesium bromide in the presence of catalytic amounts of $[Pd(PPh_3)_4]$.[11a] Here again, replacement of the (*E*)-bromine atom predominated, so that the alkyne **14** formed as the major diastereomer. However, double alkynylation occurred to a considerable extent to yield the diyne **15** aside from the unchanged dibromoalkene **4**.

In view of the double alkynylation, a problem that could not be overcome in the palladium-catalyzed coupling reaction of dibromoalkene **4** by changing reaction conditions such as temperature or solvent, this method was not used for stereoselective carbon–carbon bond formation in the synthesis of desoxyfugomycin **2**. Instead, the stereoselective bromine–lithium exchange reaction of dibromoolefin **4** was chosen as the key step. In the synthesis of fugomycin (**1**), on

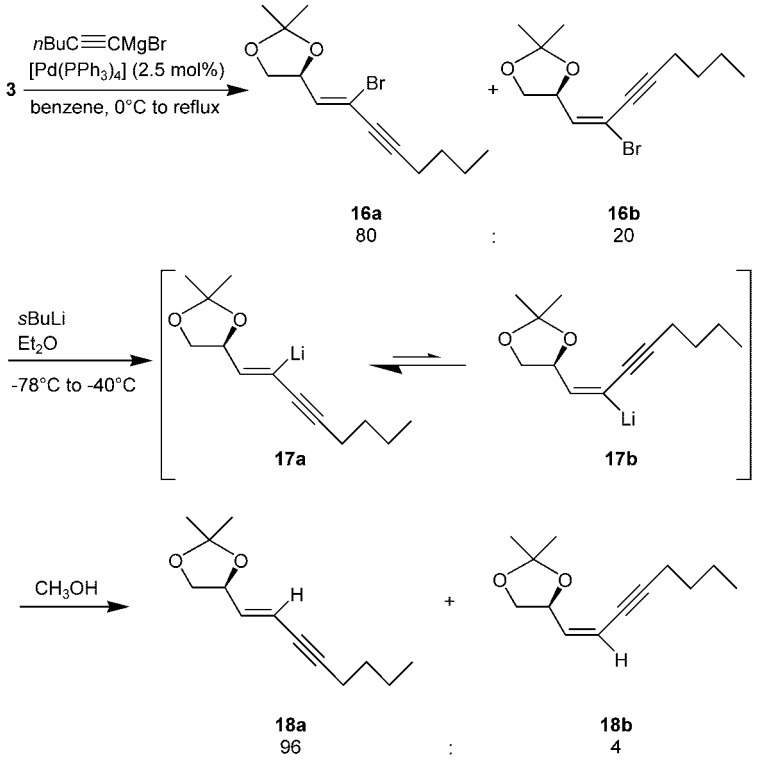


Scheme 4. Palladium-catalyzed substitution reactions of dibromoalkenes **3** and **4**.

the other hand, the stereoselective palladium-catalyzed coupling reaction should be used.

Synthesis of fugomycin: Having shown that stereoselective replacement of the (*E*)-bromine atom in the dioxolane **3** by palladium is feasible, we treated **3** with hexynylmagnesium bromide in the presence of 2.5 mol% of $[Pd[PPh_3)_4]$. The anticipated Sonogashira-type coupling occurred in 82% yield. Remarkably, no double alkynylation product was formed. However, the stereoisomeric products **16a** and **16b** were obtained in a ratio of 80:20,[20] in marked contrast to the high stereoselectivity obtained in the conversion of **3** into the monobromoalkene (*Z*)-**11**. Nevertheless, this drawback could be overcome in the following step. When the mixture of **16a** and **16b** was treated with *sec*-butyllithium at −40 °C to bring about a bromine–lithium exchange reaction, the subsequent protonation gave the enyne **18a** with high stereoselectivity; the ratio of **18a**/**18b** was determined to be 96:4 according to the NMR spectra. The discrepancy between the stereoisomeric ratios of the starting material **16a**/**16b** and the product **18a**/**18b** is explained as follows: it is assumed that there is an equilibrium between the vinyllithium reagents **17a** and **17b**, in which the former compound forms predominantly because it is the thermodynamically more favored isomer. Usually, 1-bromo-1-lithio-1-alkenes are configurationally stable so that they do not form equilibria.[8] In this particular case, however, the propargylic nature of the lithiated alkenes **17a** and **17b** might be the reason for the readily occurring equilibrium (Scheme 5).[21]

Pursuing the synthesis of fugomycin **1**, advantage was taken of the predominant formation of the intermediate **17a**. Thus, this lithioalkene was generated as described above from the mixture of **16a**/**16b** and subsequently treated with methyl chloroformate to deliver the carboxylic ester **19** in quantitative crude yield. The triple bond in the side

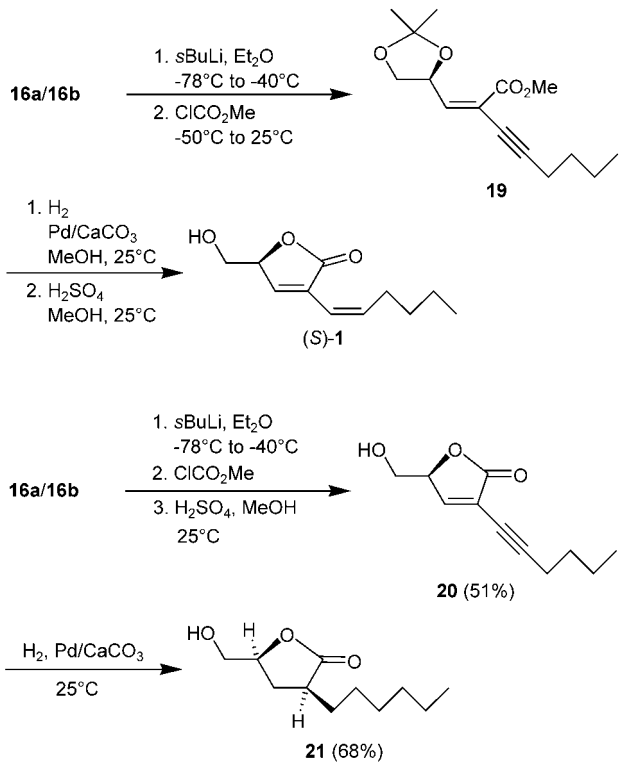


Scheme 5. Stereoselective conversion of dibromoalkene **3** into enynes **18a** and **18b**.

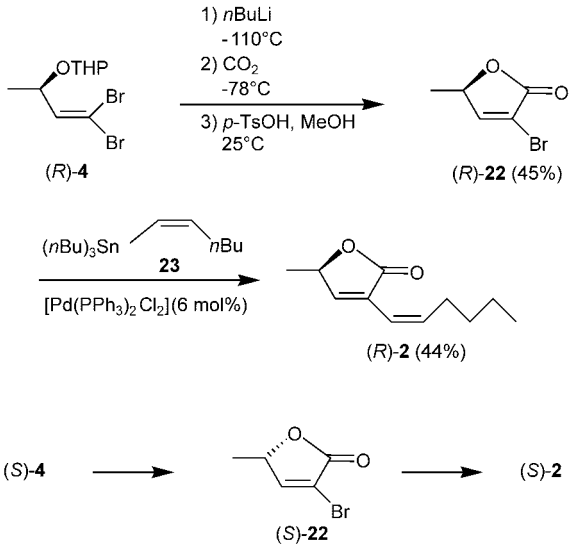
chain was then converted into a *Z* double bond by hydrogenation mediated by Lindlar's catalyst. Finally, cleavage of the dioxolane moiety and lactonization were achieved by treatment with sulfuric acid in methanol.[22] Thus, analytically pure butenolide (*S*)-**1** was obtained in 18% overall yield from the mixture of alkynes **16a**/**16b** (Scheme 6). The relatively low overall yield was mainly caused by partial decomposition during the chromatographic purification of the sensitive compound **1**. It was identical to the natural product according to its spectroscopic data. When, on the other hand, the carboxylic ester **19**, generated from the mixture of **16a**/**16b**, was submitted to in situ lactonization, the butenolide **20** resulted in 51% yield. Its subsequent hydrogenation in the presence of palladium on charcoal gave the saturated lactone **21** that is reported in the literature.[23] In addition, the *cis* configuration was proven by the NOESY spectrum, which displayed a substantial nuclear Overhauser effect exhibited by the 3-H and 5-H atoms of the dihydrofuranone ring of **21**. The enantiomeric purity of this compound was finally proven by conversion into the corresponding Mosher ester,[24] whose ^{1}H NMR spectrum revealed that a single diastereomer had formed.

Synthesis of desoxyfugomycin: As the stereoselective bromine–lithium exchange reaction of the dibromoalkene **4** has been chosen as the key step in the synthesis of desoxyfugomycin, the bromolactones (*R*)- or (*S*)-**22** consequently became the key intermediates.[25] Therefore, the alkene (*R*)-**4** was first treated with *n*-butyllithium to generate the lithium carbenoid **12**, which subsequently was allowed to react with dry ice, and then with *p*-toluenesulfonic acid in methanol to bring about deprotection and lactonization. Thus, this procedure gave the furanone (*R*)-**22** in 45% yield. Starting from dibromoalkene (*S*)-**4**, bromolactone (*S*)-**22** was prepared analogously (Scheme 7).

For the final conversion of the different stereoisomers of the bromolactone **22** into the butenolide **2**, a Stille-type coupling was employed.[26] For this purpose, (*Z*)-alkenylstannane **23** was prepared from 1-hexyne by conversion into 1-iodohexyne, subsequent diimide reduction of the triple bond,[27] and finally stannylation by successive iodine–lithium and lithium–tin exchange. The palladium-catalyzed coupling of the bromolactone **22** with the alkenylstannane **23** gave the expected product **2** in 44% yield. Here again, both enantiomers of the bromolactone **22** were used for the synthesis of (*R*)- and (*S*)-**2**, respectively.



Scheme 6. Conversion of the mixture of bromoalkenes **16a**/**16b** into the lactones **1**, **20**, and **21**.



Scheme 7. Synthesis of the enantiomeric bromolactones **22** and their conversion into (*R*)- and (*S*)-**2**.

Assignment of the absolute configuration to the butenolides 1 and 2: As the route to the butenolides **1** and **2** followed the "ex-chiral-pool" concept, the stereochemistry of the final products could be predicted. Thus the final product **1** unambiguously has the *S* configuration because the dibromoalkene (*S*)-**3** was chosen as the starting material and the stereogenic center has not been touched during the complete reaction sequence. The fact that (*S*)-fugomycin **1** results from (*R*)-isopropylideneglyceraldehyde **5** is due simply to a formal inversion of the configuration by alteration of the priority sequence when converting the aldehyde **5** into the alkene **3**. In an analogous way, the *R* configuration can be assigned to the lactone **2** that was synthesized from the dibromoalkene (*R*)-**4**, itself originating from (*R*)-lactate **6a**. Similarly, (*S*)-**2** results from the synthesis that started from (*S*)-**4**, which was derived from (*S*)-lactate **6b**.

The assignment of the configuration of the natural products **1** and **2** is based on CD spectroscopy and optical rotations. Thus, a crude extract (25 mg) containing among others fugomycin and desoxyfugomycin was submitted to repeated column chromatography to give 1–2 mg of fugomycin (**1**) and 2–3 mg of desoxyfugomycin (**2**). The CD spectra of both synthetic (*S*)-**1** and natural fugomycin are shown in Figure 1. Clearly, both the natural and the synthetic compounds have identical absolute configurations. Each CD spectrum displays two Cotton effects, one corresponding to n–π* transitions, the other to π–π* transitions.[28]

The measurement of the optical rotation proved to be the simplest method for the assignment of the absolute configuration of desoxyfugomycin (**2**). The natural product was reported to have an $[\alpha]_D$ value of +9.6,[4b] which was confirmed by the measurement of the optical rotation of a sample isolated and purified as outlined above. The samples of **2** that were obtained synthetically however had higher specific rotations: the (*S*)-enantiomer of **2** had a $[\alpha]_D$ value of +14.0. There are two remarkable conclusions that can be drawn from these measurements. Firstly, the enantiomer present in excess in natural desoxyfugomycin (**2**) evidently

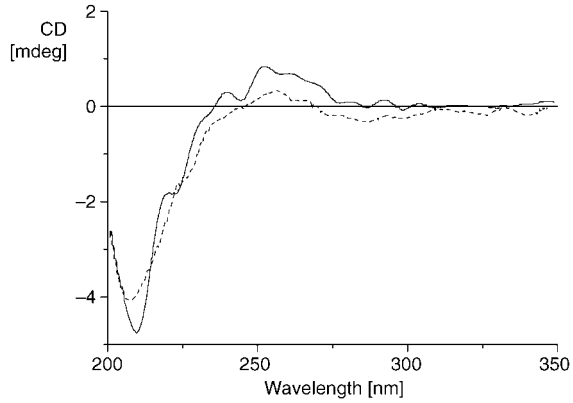


Figure 1. CD spectra of natural fugomycin (——) and synthetic (*S*)-**1** (– – –); solvent: acetonitrile.

has the *S* configuration and natural fugomycin (**1**) has the *S* configuration too (cf. the formal inversion of the configuration). Although both natural products result from the same microorganism, they are not homochiral. Second, with an enantiomeric excess of approximately 70% *ee*, natural desoxyfugomycin has to be considered as a non-optically pure compound. In view of the configurational lability of the stereogenic carbon atom in butenolides,[29] partial racemization of the natural product during the isolation process cannot be excluded.

Measured and calculated CD spectra of bromolactones (*R*)- and (*S*)-22: As the enantiomeric bromolactones **22** are easily accessible in enantiomerically pure form and with unambiguously assigned absolute configurations, we studied their CD spectra. The measured CD spectra of (*R*)- and (*S*)-**22** are shown in Figure 2. As expected, the enantiomeric compounds display opposite Cotton effects.

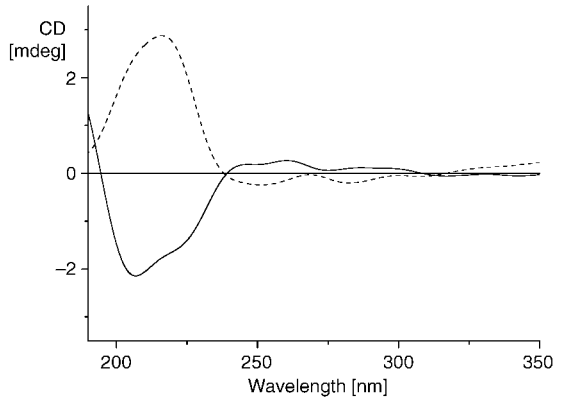


Figure 2. CD spectra of the enantiomeric bromolactones (*R*)-**22** (——) and (*S*)-**22** (– – –); solvent: acetonitrile.

The CD spectrum of *R*-(**22**) was calculated by two different density functional methods (TDDFT, DFT/MRCI) that are based on the BHLYP hybrid exchange correlation functional. All quantum chemical calculations were performed by using the TURBOMOLE suite of programs.[30] The structure of **22** was fully optimized at the density functional

(DFT) level by employing the B3LYP functional[31] and a Gaussian AO basis of valence-triple-zeta quality including polarisation functions (TZVP).[32] The ground state structure was used in subsequent calculations of the CD spectrum in the framework of time-dependent DFT[33] or with the DFT/MRCI[34] method. The BHLYP hybrid density functional[35] and a more extended TZV(2df,2pd) AO basis were used. The results of the simulations together with the experimental spectrum are displayed in Figure 3. The calculated individual transitions shown as black lines have been broadened by Gaussian shape functions and correspond to the DFT/MRCI results.

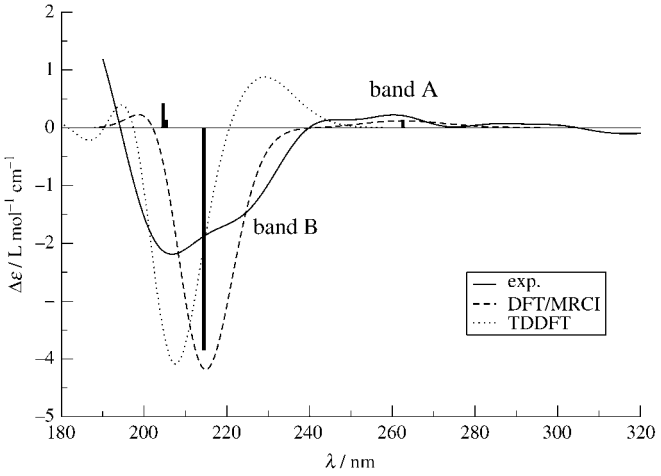


Figure 3. Comparison of experimental and theoretical (see text) CD spectra of *R*-(**22**).

As can be seen from Figure 3, two CD bands (A and B) are observed in the range between 200 and 260 nm. Band A is of very low intensity and close to experimental noise. According to both calculations, however, there is a very weak transition with a positive CD sign in this energy range. The result of the DFT/MRCI treatment is in very good agreement with experiment while the TDDFT excitation energy is blue-shifted and the rotatory strength is too large. On the basis of both calculations, this band could be assigned to an n–π* transition in which the neighboring bromine substituent makes a contribution to the lone-pair orbital. The low intensity can be attributed to the small electric transition dipole moment, the almost planar chromophore (a five-membered ring including a carbonyl oxygen and a bromine atom), and the local character of the transition, which does not significantly involve the asymmetric carbon atom.

The more intense band B is made of a single π–π* excitation. These π orbitals are delocalized over the sp^2 atoms of the chromophore and also receive some contributions from the methyl group. The calculated position (between 208 and 215 nm) and the intensity of this band are described reasonably well by the two methods. As expected for a π–π* excited state which involves significant structural reorganization upon excitation, the observed band is very broad. The observed shoulder at about 225 nm could be tentatively assigned to a vibrational structure.

In vivo fungicidal activity of fugomycin (1) and the synthetic lactones 20 and 21: The natural butenolides fugomycin (**1**) and desoxyfugomycin (**2**) have been described as exhibiting antifungal activity in various culture assays.[4] To find out whether this type of butenolide might be used as fungicides, some of them were submitted to an in vivo study. For this purpose, the enantiomerically pure lactones **1**, **20**, and **21** were submitted to greenhouse tests, in the course of which wheat flour rope, wheat brown rust, rice fire, botrytis and pernospora on vines served as test organisms. Fugomycin (**1**) and the alkynyl-substituted butenolide **20** exhibited a high fungicidal activity against botrytis completely inhibiting the growth of the parasite at a concentration of 250 ppm. On the other hand, the other parasites were only affected insignificantly when treated with those butenolides. The fact that the saturated lactone **21** did not inhibit the growth of any parasites shows that the fungicidal activity hinges on the Michael acceptor unit that is present in the butenolides **1** and **20**, but not in the hydrogenated lactone **21**.

Conclusions

In the synthesis of enantiomerically pure butenolides **1** and **2**, the chiral dibromoalkenes **3** and **4** are key intermediates. Their versatility is obviously caused by the geminal disubstitution pattern of the bromine atoms. Advantage can be taken thereof as protocols for the controlled and predictable replacement of the halogen atoms with alkynyl and alkenyl residues on the one hand and carboxy groups on the other hand have been elaborated. Thus, enantiomerically pure natural products **1** and **2** became readily available, and their absolute configuration could be assigned by synthesis. In addition, the reactive butenolides (*R*)- and (*S*)-**22** could also be obtained. They served as suitable compounds with which to demonstrate a correlation between calculated and measured CD spectra. According to the quantum chemical calculations the CD active part of the chromophore consists of an almost planar five-membered ring that is slightly perturbed by the asymmetric carbon atom. Above 200 nm, the n–π* and π–π* transitions are responsible for the observed CD signals. The fungicidal activity of the butenolides **1** and **20**, disclosed by in vivo tests, is obviously caused by the inherent reactivity of the Michael acceptor in these compounds.

Experimental Section

General: Melting points (uncorrected) were determined with a Büchi melting point apparatus 540. Optical rotations were measured with a Perkin-Elmer 341 polarimeter; $[\alpha]_D$ values are given in units of $10^{-1}\,deg\,cm^2\,g^{-1}$. CD spectra were measured on a Jasco J 600 spectral polarimeter. NMR spectra were recorded in $CDCl_3$ solutions (internal standard) on Varian VXR 200 and 300 spectrometers, and a Bruker DRX 500 spectrometer; chemical shifts are given in ppm. IR spectra were recorded on a Bruker Vector 22 spectrometer. Mass spectra were measured on a Varian MAT 311 spectrometer. UV spectra were recorded on a Perkin-Elmer Lambda 19 spectrometer. TLC silica gel 60 F_{254} plates (Merck) were used for the identification of products. Column chromatography was performed by using Macherey-Nagel Kieselgel 60 and Merck Kieselgel 60, mesh size 0.04–0.063. The GC/MS spectra were measured

on a Hewlett-Packard apparatus 5890/5790 using a HP OV-1-FS capillary column or on a Varian GC 1700 using an Optima 1 capillary column. Elemental analyses were carried out with a Perkin-Elmer CHN-Analysator 263 at the Institut für Pharmazeutische Chemie (Universität Düsseldorf) or by Mikroanalytisches Laboratorium Beller (Göttingen). All reactions involving organometallic compounds were carried out under an atmosphere of anhydrous nitrogen. Tetrahydrofuran (THF) and diethyl ether were predried with KOH and distilled under nitrogen from sodium/benzophenone. They were taken from the distillation flask, which was closed by a septum, with syringes or cannulas. *n*-Butyllithium and *tert*-butyllithium were purchased as solutions in hexane. Reactions at temperatures below 0 °C were monitored by a thermocouple connected to a resistance thermometer (Ebro). For the handling of alkyllithium compounds, see reference [36].

(*S*)-4-(2,2-Dibromoethenyl)-2,2-dimethyl-1,3-dioxolane [(*S*)-3]: Compound (*S*)-**3** was prepared from (*R*)-**5** according to reference [7b].

2-Methylpropyl (*R*)-2-(tetrahydropyran-2-yloxy)propanoate [(*R*)-8a]: A 500-mL flask was charged with (*R*)-**6a** (50.0 mL, 332 mmol) and 3,4-dihydro-2*H*-pyran (35.0 mL, 383 mmol). Whilst stirring, *N*,*N*-dimethylformamide (2 mL), through which a stream of dry hydrogen chloride had been passed, was added to this mixture at room temperature. The flask was closed with a drying tube, filled with anhydrous calcium chloride, and kept at the same temperature overnight. Potassium carbonate (10 g) was then added. The suspension was stirred for 3 h and filtered. The solid residue was washed with diethyl ether (300 mL) and the combined filtrates were concentrated in a rotary evaporator. The residue was purified by a short-path distillation to give (*R*)-**8a** (46.5 g) as a colorless oil; yield: 61 % (lit.[15]: 79 %), b.p. 74–89 °C/0.03 mbar (lit.[15]: 85–90 °C/13 Pa). The product consists of a 1:1 diastereomeric mixture with respect to the stereogenic center in the tetrahydropyranyl ring. ^{1}H NMR (500 MHz): $\delta =$ 0.92–0.9 (m, 6H; $(CH_3)_2CH$), 1.40 (d, $J = 6.62$ Hz) and 1.47 (d, $J =$ 6.94 Hz) (2H; 3-H), 1.5–1.9 (m, 6H; O−CH_2−CH_2−CH_2−CH_2), 1.91–2.01 (m, 1H; $(CH_3)_2CH$−CH_2), 3.43–3.49 (m) and 3.49–3.55 (m) (1H; OC*H*H−CH_2), 3.83–3.98 (m, 3H; O−CH*H*−CH_2 and $(CH_3)_2CH$−CH_2−O), 4.22 (q, $J = 6.73$ Hz) and 4.44 (q, $J = 7.04$ Hz; 1H; CH_3−C*H*(OTHP)), 4.71 (t, $J = 3.63$ Hz; OCHO) and 4.73 ppm (t, $J = 3.47$ Hz; OCHO).

(*R*)-2-(Tetrahydropyran-2-yloxy)propanal [(*R*)-9]: A 1-L three-necked flask was equipped with an overhead stirrer, a pressure-equalizing dropping funnel, a connection to the combined nitrogen/vacuum line, and a septum with a thermocouple. The flask was charged with (*R*)-**8a** (46.0 g, 202 mmol) and dry dichloromethane (250 mL), and the dropping funnel was filled with a 1 M solution of diisobutylaluminum hydride (DIBAH) in dichloromethane (220 mL, 220 mmol). The flask was cooled to −70 °C by means of an ethanol/dry-ice bath. The DIBAH solution was added dropwise at such a rate that the temperature did not exceed −60 °C. Thereafter, stirring was continued at −60 °C to −70 °C for 4 h. After cooling to −75 °C, the solution was treated with a saturated aqueous solution of ammonium chloride (50 mL) and then with 1 N hydrochloric acid to adjust the pH of the mixture to 7. The cooling bath was removed and the mixture was allowed to reach room temperature. The precipitate was removed by filtration through a suction filter and washed several times with diethyl ether. The organic layer of the combined filtrates was separated, and the aqueous phase was extracted with diethyl ether (3× 150 mL). The combined organic layers were washed with brine and dried with magnesium sulfate. After the solvent had been removed in a rotary evaporator, the residue was distilled in vacuo to deliver colorless (*R*)-**9** (20.0 g, 63 %); b.p. 77–82 °C/12 mbar. The product consists of a diastereomeric mixture due to the stereogenic center of the tetrahydropyranyl protecting group. The NMR spectra are in accord with those of (*S*)-**9**, which was prepared from tetrahydropyranyl-protected ethyl(*S*)-lactate.[16c]

(*R*)-1,1-Dibromo-3-(tetrahydropyran-2-yloxy)-1-butene [(*R*)-4]: A solution of triphenylphosphane (89.0 g, 340 mmol) in dry dichloromethane (160 mL) was stirred in a 500-mL three-necked flask equipped with a magnetic stirrer, a thermocouple, a dropping funnel that was closed by a drying tube, and a septum. After the mixture had been cooled to 0 °C, a solution of tetrabromomethane (56 g, 170 mmol) in dry dichloromethane (80 mL) was added through the dropping funnel at such a rate that the temperature did not exceed 15 °C. During this process, the solution was cooled to −10 °C by means of a sodium chloride/ice mixture. Then a solution of (*R*)-**9** (20.0 g, 126 mmol) and triethylamine (18.0 mL, 132 mmol) in dry dichloromethane (20 mL) was added at such a rate that the temperature was kept below 0 °C. Stirring was continued at 0 °C for 30 min, and then the mixture was allowed to reach room temperature. After the addition of *n*-pentane (250 mL), the precipitate was filtered through Celite and washed with diethyl ether (3×30 mL). The combined filtrates were washed with water, dried with magnesium sulfate, and concentrated in a rotary evaporator. The residue was treated with *n*-pentane (250 mL) and filtered. The remaining solid was carefully washed three times with *n*-pentane. The combined filtrates were dried with magnesium sulfate, the solvent was removed under reduced pressure, and the residue was purified by a short-path distillation. The fraction boiling at 75–85 °C/0.021 mbar contained a product (18.28 g) that was partly deprotected. Therefore it was treated with 3,4-dihydro-2*H*-pyran (5.3 mL) and hydrochloric acid/*N*,*N*-dimethylformamide as described above in the preparation of (*R*)-**8a**. The product thus obtained was finally distilled in vacuo to give (*R*)-**4** (16.13 g, 40 %) as a colorless liquid; b.p. 71 °C/0.031 mbar; $[\alpha]_D^{20} = +34.0$ ($c = 1.288$ in chloroform). The product consists of a diastereomeric mixture (ratio: 2.5:1) due to the stereogenic center in the tetrahydropyranyl ring. ^{1}H NMR (500 MHz): $\delta = 1.30$ (d, $J = 6.6$ Hz, 3H; 4-H), 1.50–1.86 (m, 6H; O−CH_2−CH_2−CH_2−CH_2), 3.49–3.55 (m, 1H; O−C*H*H−CH_2), 3.83–3.91 (m, 1H; O−CH*H*−CH_2), 4.54–4.61 (m, 2H; 3-H and OCHO), 6.35 ppm (d, $J = 8.2$ Hz, 1H; 2-H). The minor diastereomer differs in: $\delta = 1.25$ (d, $J = 6.3$ Hz, 1H; 4-H), 4.42 (dq, $J_d = 7.8$ Hz, $J_q =$ 6.6 Hz, 1H; 3-H), 4.69–4.72 (m, OCHO), 6.53 ppm (d, $J = 7.8$ Hz, 1H; 2-H).

After being kept in a refrigerator for several days, the major diastereomer crystallized and could be isolated. ^{13}C NMR (125 MHz): $\delta = 19.7$, 20.1, 25.4, 30.8, 62.9, 71.6, 90.9, 96.4, 104.4 ppm; $[\alpha]_D^{20} = +89.7$ ($c = 0.904$ in chloroform).

Dibromoalkene (*S*)-**4**, prepared according to the same procedure, was obtained in 40 % yield; $[\alpha]_D^{20} = -10.4$ ($c = 0.992$ in chloroform).

(1′*E*,4*S*)-4-(2-Bromoethenyl)-2,2-dimethyl-1,3-dioxolane [(1′*E*,4*S*)-11]: A 50-mL flask, equipped with a magnetic stirrer and a connection to the combined nitrogen/vacuum line was charged with the dibromoalkene (*S*)-**3** (0.953 g, 3.33 mmol) and closed with a septum. The air in the flask was replaced by nitrogen and then diethyl ether (10 mL) and *n*-pentane (5 mL) were injected into the flask. A thermocouple was introduced through the septum and the solution was cooled to −110 °C by means of an ethanol/liquid nitrogen bath. A 1.6 M solution of *n*-butyllithium (2.18 mL, 3.49 mmol) was added dropwise by syringe at such a rate that the temperature did not exceed −105 °C. Thereafter, the mixture was stirred at −105 °C for 2 h. Methanol (2 mL) was injected into the flask by syringe. Then the mixture was allowed to reach room temperature and was washed with a saturated aqueous solution of ammonium chloride (10 mL) and twice with brine (10 mL each). The organic layer was dried with magnesium sulfate, concentrated under reduced pressure and exposed to an oil-pump vacuum for 2 h. The residue was purified by vacuum distillation to give (1′*E*,4*S*)-**11** (0.62 g, 90 %) as a colorless oil. The (*E*)/(*Z*) ratio was determined to surpass 95:5 by ^{1}H NMR spectroscopy; b.p. 65 °C/15 mbar; $[\alpha]_D^{20} = +21$ ($c = 1.45$ in chloroform). ^{1}H NMR (500 MHz): $\delta = 1.38$ (s, 3H; CH_3), 1.42 (s, 3H; CH_3), 3.63 (dd, $J =$ 8.35 Hz, $J = 6.3$ Hz, 1H; 5-H), 4.09 (dd, $J = 8.35$ Hz, $J = 7.1$ Hz, 1H; 5-H), 4.47 (dddd, $J = 7.25$ Hz, $J = 7.09$ Hz, $J = 6.3$ Hz, $J = 0.95$ Hz, 1H; 4-H), 6.19 (dd, $J = 13.55$ Hz, $J = 7.25$ Hz, 1H; 1′-H), 6.43 ppm (dd, $J = 13.55$ Hz, $J = 0.95$ Hz, 1H; 2′-H); ^{13}C NMR (125 MHz): $\delta = 26.11$, 26.94, 69.11, 76.46, 109.9, 110.1, 135.7 ppm; IR (neat): $\tilde{\nu} = 2987$, 2936, 2877, 1625, 1455, 1373, 1223, 1062 cm^{-1}; GC/MS (EI): *m*/*z* (%): 193, 191 (82) $[C_6H_8BrO_2]^+$, 178, 176 (58) $[C_6H_5O_2Br]^+$, 178, 176 (58) $[C_5H_5BrO_2]^+$, 98 (87) $[C_5H_6O_2]^+$, 72 (100).

(1*E*,3*R*)-1-Bromo-3-(tetrahydropyran-2-yloxy)-1-butene [(1*E*,3*R*)-13]: Butene (1*E*,3*R*)-**13** was prepared from (*R*)-**4** (0.400 g, 1.27 mmol) and *n*-butyllithium (0.8 mL of a 1.6 M solution in *n*-hexane, 1.28 mmol) according to the same procedure as that used for the preparation of (1′*E*,4*S*)-**11**. The crude product **13**, which was characterized by its ^{1}H NMR data without further purification, was a 1:1 diastereomeric mixture due to the stereogenic center in the tetrahydropyranyl ring. Yield: 0.15 g (50 %). ^{1}H NMR (500 MHz): (two diastereomers) $\delta = 6.07$ (dd, $J = 13.56$ Hz, $J =$ 7.88 Hz, 1H), 6.26 (dd, $J = 13.24$ Hz, $J = 0.32$ Hz, 1H), 6.28 (dd, $J =$ 13.71 Hz, $J = 5.57$ Hz, 1H), 6.33 (dd, $J = 14.03$ Hz, $J = 0.47$ Hz, 1H).

(1′*Z*,4*S*)-4-(2-Bromoethenyl)-2,2-dimethyl-1,3-dioxolane [(1′*Z*,4*S*)-11]: A 50-mL flask was equipped with a magnetic stirrer, a septum, and a connection to the combined nitrogen/vacuum line and was then charged with $[Pd(PPh_3)_4]$ (0.153 g, 0.132 mmol). Under nitrogen, dibromoalkene (*S*)-**3** (0.948 g, 3.3 mmol), dry benzene (15 mL), and nBu_3SnH (1.1 g, 3.78 mmol) were added successively. After the mixture was stirred at room temperature for 2 h, the solvent was removed by distillation, the residue was treated with *n*-hexane (30 mL), and the resulting mixture was stirred for 5 min. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in diethyl ether (50 mL), a 10% aqueous solution of potassium fluoride (10 mL) was added, and the mixture was stirred overnight. After the precipitate formed thereby had been removed by filtration, the filtrate was dried with magnesium sulfate and concentrated in a rotary evaporator. The residue was purified by distillation under reduced pressure to give (1′*Z*,4*S*)-**11** as a colorless liquid (0.612 g, 90%); b.p. 75°C/21 mbar; $[\alpha]_D^{20}=+17.0$ ($c=0.42$ in chloroform). According to the ^1H NMR spectrum, the (*Z*)/(*E*) ratio of the distilled product is 55:1. ^1H NMR (500 MHz): $\delta=1.33$ (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 3.54 (dd, $J=8.35$ Hz, $J=7.09$ Hz, 1H; 5-H), 4.15 (dd, $J=8.35$ Hz, $J=6.30$ Hz, 1H; 5-H), 4.87 (dddd, $J=7.25$ Hz, $J=7.09$ Hz, $J=6.3$ Hz, $J=1.26$ Hz, 1H; 4-H), 6.17 (t, $J=7.25$ Hz, 1H; 2′-H), 6.26 ppm (dd, $J=7.25$ Hz, $J=1.26$ Hz, 1H; 1′-H); ^{13}C NMR (125 MHz): $\delta=26.26$, 26.95, 69.13, 74.65, 110.05, 110.50, 134.22 ppm; IR (neat): $\tilde{\nu}=3085$, 2987, 2936, 2873, 1625, 1373, 1218, 1062 cm^{-1}; MS (EI): *m*/*z* (%): 193, 191 (76) $[C_6H_8BrO_2]^+$, 178, 176 (28) $[C_5H_5BrO_2]^+$, 97 (90) $[C_5H_5O_2]^+$, 72 (100); elemental analysis calcd (%) for $C_6H_8BrO_2$ (206.01): C 40.78, H 5.38; found: C 40.76, H 5.47.

(1′*Z*,4*S*)- and (1′*E*,4*S*)-4-(2-Bromooct-1-en-3-ynyl)-2,2-dimethyl-1,3-dioxolane [(1′*Z*,4*S*)-16a and (1′*E*,4*S*)-16b]: In a 100-mL two-necked flask, equipped with a magnetic stirrer, a reflux condenser, a connection to the combined nitrogen/vacuum line, and a septum, 1-hexyne (1.97 g, 24.0 mmol) was dissolved in dry THF (5 mL) under nitrogen. The mixture was cooled in an ice bath and a 3 M solution of ethylmagnesium bromide (8.3 mL, 24.9 mmol) in diethyl ether was added dropwise by syringe. Thereafter, the ice bath was removed and the mixture was refluxed for 1 h.

In two different flasks, solutions of $[Pd(PPh_3)_4]$ (0.800 g, 0.692 mmol) in dry benzene (12 mL) and dibromoalkene (*S*)-**3** (5.0 g, 17.48 mmol) in dry benzene (12 mL), respectively, were prepared under nitrogen. The two solutions were combined by means of a cannula and stirred at room temperature for 5 min and then added through a cannula to the solution of hexynylmagnesium bromide, which was stirred at −90°C. The cooling bath was removed and the mixture was allowed to reach room temperature. The yellowish mixture was stirred at room temperature for 2 h and thereafter refluxed for another 12 h, whereby it turned dark brown. After the mixture had been cooled to room temperature, a saturated aqueous solution of ammonium chloride (5 mL) was added and the mixture was diluted with diethyl ether (100 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in a rotary evaporator. The residue was purified by vacuum distillation to give a diastereomeric mixture of **16a**/**16b** (4.12 g, 82%) in a *Z*/*E* ratio of approximately 80:20; b.p. 82–95°C/0.042 mbar; $[\alpha]_{365}^{20}=-1.4$ ($c=1$ in 95% aqueous ethanol). ^1H NMR (500 MHz) of (1′*Z*,4*S*)-**16a**: $\delta=0.92$ (t, $J=7.25$, 3H; CH_3–CH_2), 1.39 (s, 3H; CH_3), 1.42 (s, 3H; CH_3), 1.49–1.56 (m, 4H; CH_3–CH_2–CH_2), 2.28–2.39 (m, 2H; C≡C–CH_2), 3.64 (dd, $J=8.19$ Hz, $J=7.40$ Hz, 1H; 5-H), 4.22 (dd, $J=8.19$ Hz, $J=6.30$ Hz, 1H; 5-H), 4.88 (ddd, $J=7.40$ Hz, $J=7.25$ Hz, $J=6.3$ Hz, 1H; 4-H), 6.24 ppm (d, $J=7.25$ Hz, 1H; 1′-H). The minor stereoisomer (1′*E*,4*S*)-**16b** differs in: $\delta=3.59$ (dd, $J=8.35$ Hz, $J=6.77$ Hz), 4.15 (dd, $J=8.35$ Hz, $J=6.46$ Hz), 5.02 (ddd, $J=8.19$ Hz, $J=6.77$ Hz, $J=6.46$ Hz), 6.08 pm (d, $J=8.19$ Hz); ^{13}C NMR (125 MHz) of (1′*Z*,4*S*)-**16a**: $\delta=13.92$, 19.40, 22.32, 26.03, 26.90, 30.61, 68.77, 76.12, 79.17, 94.36, 105.12, 110.18, 136.49 ppm; IR (film): $\tilde{\nu}=2986$, 2959, 2934, 2873, 2219, 1380, 1371, 1249, 1217, 1060, 860 cm^{-1}; GC/MS (EI): *m*/*z* (%): 288, 286 (4) $[M]^+$, 273, 271 (20) $[C_{12}H_{16}BrO_2]^+$, 258, 256 (32) $[C_{11}H_{13}BrO_2]^+$, 243, 241 (36) $[C_{10}H_{10}BrO_2]^+$, 229, 227 (35) $[C_9H_8BrO_2]^+$, 149 (100) $[C_9H_9O_2]^+$; elemental analysis calcd (%) for $C_{13}H_{19}BrO_2$ (286.08): C 54.37, H 6.67; found: C 54.46, H 6.75.

(1′*E*,4*S*)- and (1′*Z*,4*S*)-4-(Oct-1-en-3-ynyl)-2,2-dimethyl-1,3-dioxolane [(1′*E*,4*S*)-18a and (1′*Z*,4*S*)-18b]: Under nitrogen, the mixture of bromoalkenes **16a**/**16b** (0.276 g, 0.96 mmol) was dissolved in dry diethyl ether (7 mL) in a 50 mL flask equipped with a magnetic stirrer, a connection to the combined nitrogen/vacuum line, a septum, and a thermocouple. The mixture was cooled to −90°C under stirring and a 1.3 M solution of *sec*-butyllithium in cyclohexane (0.9 mL, 1.2 mmol) was added dropwise by syringe at such a rate that the temperature did not exceed −78°C. Thereafter, stirring was continued at −40°C for 2 h. After the addition of methanol (1 mL) the mixture was warmed to room temperature, washed with brine, and dried with magnesium sulfate. The solvent was removed in a rotary evaporator to give a yellow liquid product (0.183 g, 91%), which was characterized by spectroscopy without further purification; $[\alpha]_{546}^{20}=+7.95$ ($c=1.1$ in 95% aqueous ethanol). The ratio of the stereoisomers (*E*)-**18a** and (*Z*)-**18b** was determined to be 24:1 according to the NMR spectra. ^1H NMR (500 MHz) of (1′*E*,4*S*)-**18a**: $\delta=0.91$ (t, $J=7.25$ Hz, 3H; CH_3–CH_2), 1.38 (s, 3H; CH_3), 1.42 (s, 3H; CH_3), 1.46–1.53 (m, 4H; CH_3–CH_2–CH_2), 2.30 (dt, $J_d=2.2$ Hz, $J_t=6.78$ Hz, 2H; C≡C–CH_2), 3.60 (dd, $J=8.16$ Hz, $J=7.53$ Hz, 1H; 5-H), 4.09 (dd, $J=8.20$ Hz, $J=6.31$ Hz, 1H; 5-H), 4.50 (ddd, $J=13.71$ Hz, $J=7.25$ Hz, $J=0.87$ Hz, 1-H; 4-H), 5.76 (ddt, $J_d=15.75$ Hz, $J_d=1.1$ Hz, $J_t=2.2$ Hz, 1H; 2′-H), 5.97 ppm (dd, $J=15.76$ Hz, $J=6.98$ Hz, 1H; 1′-H). The minor stereoisomer (1′*Z*,4*S*)-**18b** differs in: $\delta=2.39$ (dt, $J_d=2.31$ Hz, $J_t=7.09$ Hz), 4.18 (dd, $J=8.16$ Hz, $J=6.27$ Hz), 4.59 (ddt, $J_d=8.82$ Hz, $J_d=2.05$ Hz, $J_t=10.08$ Hz), 5.62 (ddt, $J_d=10.77$, $J_d=1.2$ Hz, $J_t=2.3$ Hz), 5.84 ppm (dd, $J=10.80$ Hz, $J=8.04$ Hz); ^{13}C NMR (125 MHz): $\delta=13.91$, 19.56, 22.30, 26.21, 26.94, 31.06, 69.58, 77.65, 78.42, 92.51, 109.9, 113.8, 138.8 ppm; IR (film): $\tilde{\nu}=2960$, 2935, 2874, 2214, 1600, 1372, 1217, 1064 cm^{-1}; GC/MS (EI): *m*/*z* (%): 208 (72) $[M]^+$, 193 (90) $[C_{12}H_{17}O_2]^+$, 165 (25) $[C_{10}H_{13}O_2]^+$, 151 (48) $[C_9H_{11}O_2]^+$, 121 (59) $[C_8H_9O]^+$, 72 (100) $[C_4H_8O]^+$.

(*S*)-3-(1-Hexynyl)-5-(hydroxymethyl)furan-2(5*H*)-one [(*S*)-20]: A solution of the stereoisomeric mixture (80:20) of **16a** and **16b** (1.33 g, 4.63 mmol) was dissolved in dry diethyl ether (25 mL) under nitrogen in a 100-mL flask equipped with a magnetic stirrer, a connection to the combined nitrogen/vacuum line, a septum, and a thermocouple. The mixture was cooled to −90°C, and a 1.3 M solution of *sec*-butyllithium in cyclohexane (4.3 mL, 5.6 mmol) was added dropwise by syringe. After the mixture had been stirred for 2 h at −50°C, methyl chloroformate (0.656 g, 6.95 mmol) was injected, the mixture was warmed to room temperature and treated with a saturated aqueous solution of ammonium chloride (10 mL). The organic layer was separated and extracted twice with diethyl ether (60 mL). The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dry methanol (20 mL), and concentrated sulfuric acid (20 drops) was added. After stirring at room temperature for 12 h, the solution was neutralized by adding Amberlyst A21 basic ion exchange resin. Thereafter the mixture was stirred with magnesium sulfate for 3 h and then filtered. The solid was washed with dry methanol and the combined filtrates were evaporated to give a brown oily crude product, which was purified by flash column chromatography (*n*-hexane/ethyl acetate, 1:10). The fraction of $R_f=0.83$ was collected to give (*S*)-**20** (0.46 g, 51%) as a colorless solid; m.p. 64–66°C. ^1H NMR (500 MHz): $\delta=0.91$ (t, $J=7.25$ Hz, CH_3–CH_2), 1.40 (m, 2H) and 1.54 (m, 2H) (CH_3–CH_2–CH_2), 2.39 (t, $J=7.1$ Hz, 2H; C≡C–CH_2), 3.74 (dd, $J=12.29$ Hz, $J=5.20$ Hz, 1H; HO–C*H*H), 3.94 (dd, $J=12.29$ Hz, $J=3.78$ Hz, 1H; HO–CH*H*), 5.11 (m, 1H; 5-H), 7.34 ppm (d, $J=2.05$ Hz, 1H; 4-H); ^{13}C NMR (125 MHz): $\delta=12.52$, 18.23, 20.96, 29.19, 61.69, 68.75, 81.18, 98,28, 118.99, 145.54, 169.61 ppm; IR (film): $\tilde{\nu}=3435$, 2959, 2932, 2872, 2237, 2767, 1625, 1459, 1379, 1112, 1082 cm^{-1}; MS (EI): *m*/*z* (%): 194 (1) $[M]^+$, 164 (4) $[C_{10}H_{12}O_2]^+$, 65 (100) $[C_4H_2O_2]^+$; elemental analysis calcd (%) for $C_{11}H_{11}O_3$ (194.07): C 68.02, H 7.27; found: C 68.15, H 7.57.

(3*S*,5*S*)-3-Hexyl-5-hydroxymethyl-3,4-dihydrofuran-2(5*H*)-one [(3*S*,5*S*)-21]: In a hydrogenation apparatus, a mixture of **20** (1.0 g, 5.15 mmol), palladium on charcoal (0.20 g, 10% Pd), and methanol (25 mL) was stirred at room temperature under a hydrogen pressure of 10 bar for 10 h. Thereafter, the solvent was removed and the residue was submitted to column chromatography (*n*-hexane/ethyl acetate, 2:1). The fraction of $R_f=0.35$ was collected to give **21** (0.70 g, 68%) as a colorless oil; $[\alpha]_D^{20}=+12$ ($c=0.5$ in chloroform). The ^1H NMR spectrum is in accord with that described in the literature.[23] ^{13}C NMR (125 MHz): $\delta=14.4$, 22.9, 27.65, 29.4, 29.7, 30.1, 32.0, 41.1, 64.25, 179.1 ppm; IR (film): $\tilde{\nu}=3356$, 2957, 2925, 2854, 1754, 1464, 1208, 1188, 1174, 1098, 957, 900 cm^{-1}; MS

(EI): *m*/*z* (%): 200 (3) $[M]^+$, 169 (49) $[C_{11}H_{19}O_2]^+$, 116 (100) $[C_5H_7O_3]^+$, 81 (24) $[C_5H_5O]^+$.

(1′*Z*,5*S*)-3-(1-Hexenyl)-5-hydroxymethylfuran-2(5*H*)-one, (*S*)-fugomycin [(1′*Z*,5*S*)-1]: Under nitrogen, a mixture (80:20) of the stereoisomers **16a** and **16b** (3.0 g, 10.45 mmol) and dry diethyl ether (40 mL) were stirred in a round-bottomed flask equipped with a magnetic stirrer, a connection to the combined nitrogen/vacuum line, a septum, and a thermocouple. The mixture was cooled to −78 °C, a 1.3 M solution of *sec*-butyllithium in cyclohexane (9.64 mL, 12.53 mmol) was added and stirring was continued at −50 °C for 2 h, After the addition of methyl chloroformate (1.2 mL, 15.5 mmol), the mixture was allowed to reach room temperature and treated with a saturated aqueous solution of ammonium chloride (15 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3×30 mL). The combined organic layers were dried with magnesium sulfate and the solvent was removed under reduced pressure to give crude, oily **19**, which was dissolved in dry methanol (25 mL). Lindlar's catalyst (0.250 g) and quinoline (0.1 mL) were added and the mixture was hydrogenated at room temperature and atmospheric pressure for 12 h. After the mixture had been filtered through Celite, which was subsequently rinsed with methanol, concentrated sulfuric acid (10 drops) was added to the combined filtrates. After the mixture was stirred for 5 h, Amberlyst A21 basic ion-exchange resin was added to neutralize the solution. Drying with magnesium sulfate, filtration, and evaporation of the solvent gave an oily crude product that was submitted to column chromatography (*n*-hexane/ethyl acetate, 2:1). Thus, (*S*)-**1** was obtained as a colorless oil in 18% yield; $R_f = 0.23$. The ^1H and ^{13}C NMR spectroscopic data correspond to those described in the literature.[4a] MS (CI with NBA): *m*/*z* (%): 219 (21) $[M+Na]^+$, 197 (93) $[M+1]^+$, 154 (99) $[C_8H_{13}O]^+$, 139 (25) $[C_7H_7O_3]^+$, 137 (82) $[C_9H_{13}O]^+$, 136 (100) $[C_8H_8O_2]^+$; elemental analysis calcd (%) for $C_{11}H_{16}O_3$ (196.11): C 67.32, H 8.22; found: C 67.42, H 8.19.

(*R*)-3-Bromo-5-methylfuran-2(5*H*)-one [(*R*)-22]: A 250-mL three-necked flask was equipped with a magnetic stirrer, a connection to the combined nitrogen/vacuum line, a septum, and a thermocouple. Under nitrogen, the flask was charged with the dibromoalkene (*R*)-**4** (6.0 g, 19.1 mmol) and dry THF (100 mL). After the solution had been cooled to −120 °C in an ethanol/liquid nitrogen bath, a 1.6 M solution of *n*-butyllithium in *n*-hexane (10.0 mL, 16.0 mmol) was added dropwise to the vigorously stirred mixture at such a rate that the temperature did not exceed −110 °C. After stirring at −120 °C to −110 °C for 1.5 h, another portion of *n*-butyllithium (2.5 mL, 4.0 mmol) was added dropwise. Stirring was continued at the same temperature for 30 min. Thereafter the solution was transferred by a cannula into a mixture of dry ice (approximately 15 g) and dry THF. Stirring was continued at −110 °C for 30 min, and the mixture was warmed to room temperature and concentrated in a rotary evaporator. The remaining solid was partitioned in a mixture of *n*-hexane (100 mL) and a saturated aqueous solution of sodium hydrogen carbonate (100 mL), which was stirred vigorously for 30 min. The layers were separated and the organic phase was extracted twice with a sodium hydrogen carbonate solution (total volume of 200 mL). The combined aqueous alkaline solutions were acidified to pH 2 by careful addition of concentrated sulfuric acid. An equal volume of dichloromethane was added to the aqueous solution and the mixture was stirred vigorously for 3 h. Thereafter, the layers were separated and the aqueous layer was extracted three times with dichloromethane (total volume of 300 mL). The combined organic phases were dried with magnesium sulfate and concentrated in a rotary evaporator. To complete the lactonization, the residue was stirred in methanol (100 mL) with *p*-toluenesulfonic acid (0.38 g) at room temperature for 3 h. Solid sodium carbonate (approximately 5 g) was added, the mixture was filtered, and the solvent was evaporated. The crude **22** (1.52 g, 45%) was sufficiently pure for subsequent transformations. An analytically pure sample was isolated after column chromatography (*n*-hexane/ethyl acetate, 2:1). The NMR data of **22** correspond to those described in the literature[25] for the racemic compound. For (*R*)-**22** $[\alpha]_D^{20} = -46.5$ ($c = 0.9$ in chloroform), whereas (*S*)-**22**, prepared analogously from (*S*)-**4** gave $[\alpha]_D^{20} = +50.3$ ($c = 0.98$ in chloroform).

(*Z*)-1-Hexenyl(tributyl)stannane [(*Z*)-23]: (*Z*)-1-Iodohexane (3.74 g, 17.8 mmol) was dissolved in diethyl ether (20 mL) and the solution was cooled to −78 °C. A 1.7 M solution of *tert*-butyllithium in *n*-pentane (23 mL, 39.1 mmol) was added, and the mixture was stirred for 1 h at −78 °C. Tributyltin chloride (4.8 mL, 17.8 mmol) was added dropwise, and the solution was allowed to reach room temperature. After hydrolysis with a saturated aqueous solution of ammonium chloride the layers were separated and the aqueous phase was extracted three times with diethyl ether. After the mixture had been dried with magnesium sulfate, the solvent was removed to give crude **23** (6.0 g), which was used in the following reaction without further purification. ^1H NMR: $\delta = 0.88$ (t, $J = 0.88$ Hz, 12H; CH_3), 1.3–1.4 (m, 8H; CH_3–CH_2), 1.43–1.55 (m, 8H; CH_3–CH_2–CH_2), 2.02 (br q, $J = 6.83$ Hz, 2H; CH_2–CH=CH), 5.77 (br d, $J = 12.6$ Hz, 1H; CH_2–CH=C*H*), 6.51 ppm (dt, $J_d = 12.4$ Hz, $J_t = 7.01$ Hz, 1H; CH_2–C*H*=CH).

(1′*Z*)-3-(1-Hexenyl)-5-methylfuran-2(5*H*)-one, (desoxyfugomycin) [(1′*Z*)-(2)]: Under nitrogen, $[Pd(PPh_3)_2Cl_2]$ (77 mg, 0.11 mmol) and bromolactone **22** (220 mg, 1.13 mmol) were dissolved in *N*-methylpyrrolidine (10 mL). After the dropwise addition of **23** (632 mg, 1.7 mmol), the mixture was stirred for 100 h at room temperature. After hydrolysis with a saturated aqueous solution of ammonium chloride (5 mL) the solution was extracted with diethyl ether (4×15 mL). The combined organic layers were dried with magnesium sulfate and the solvent was evaporated. The residue was taken up in a 1:1 mixture of *n*-hexane/water (60 mL) and the aqueous phase was extracted with *n*-hexane (2×30 mL). The combined *n*-hexane layers were dried again with magnesium sulfate, and the solvent was removed in vacuo. Column chromatography (*n*-hexane/ethyl acetate 6:1) gave pure desoxyfugomycin **2** (88 mg, 44%). The spectroscopic data correspond to those described in the literature.[4b] (*S*)-**2**: $[\alpha]_D^{20} = +14.0$ ($c = 0.46$ in chloroform); (*R*)-**2**: $[\alpha]_D^{20} = -12$ ($c = 0.42$ in chloroform).

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