Easy Access to 5-Alkyl-4-bromo-2(5*H*)-furanones: Synthesis of a Fimbrolide, an Acetoxyfimbrolide, and Bromobeckerelide

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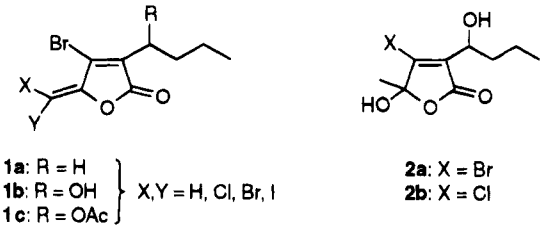
Treatment of γ-monosubstituted allenic esters with *N*-bromosuccinimide in water yields 5-alkyl-4-bromo-2(5*H*)-furanones, that can be transformed into 5-alkylidene-4-bromo-2(5*H*)-furanones in good overall yields. Starting with a simple allenic ester these transformations have been applied to a new synthesis of fimbrolide (**1a**), acetoxyfimbrolide (**1c**), and bromobeckerelide (**2a**).

Introduction

In the past few years a great deal of research has focused on the isolation, identification, and synthesis of marine origin secondary metabolites. There are some striking differences between terrestrial and marine metabolites: halogen atoms appear frequently as substituents in the metabolites of algae or sponges. Fimbrolides **1**[1] and beckerelides **2**,[2] isolated in 1977 from the red marine algae *Delisea fimbriata* and *Beckerella subcostatum*, respectively, are halogenated α,β-butenolides with interesting antifungal and antimicrobial properties (Chart 1). Lactones **1** and **2a** present the structure of 4-bromo-5-methylene(or methyl)-2(5*H*)-furanone with a butyl chain linked at the α-position of the carbonyl group. Later on, six new compounds related to the structure of fimbrolides were isolated from *Delisea elegans*,[3] and very recently several new halogenated furanones have been isolated from *Delisea pulchra*.[4]

Due to their pharmacological properties, several approaches to the synthesis of these novel highly functionalized secondary metabolites have been described. Two syntheses of fimbrolide (**1a**, X = H, Y = Br) were reported before 1985,[5] two preparations of bromobeckerelide (**2a**) have been published in the last years,[6] and the only reported synthesis of an acetoxyfimbrolide (**1c**, X = H, Y = Br) was described very recently in a research report without an experimental part.[7] Finally, syntheses of analogues of these metabolites lacking the bromine atom at the 4-position have also been published.[8] Most of these syntheses construct the furanone ring in the last steps by an oxidation reaction of a properly polysubstituted furan derivative using molecular oxygen or peracids,[6-8] while other strategies to build the heterocyclic system use very strong acid (100% sulfuric acid)[5a] or basic (2 equiv of *n*-BuLi)[5b] conditions.

Chart 1



1a: R = H
1b: R = OH
1c: R = OAc
} X,Y = H, Cl, Br, I

2a: X = Br
2b: X = Cl

In relation to our research on structurally simple α,β-butenolides we initiated some years ago a program with the aim to open an easy and smooth access to γ-monoalkyl(idene)-β-bromo-α,β-butenolides compatible with the functional groups present in the natural products **1** and **2**. A first approach based on the bromination–dehydrobromination of α,β-butenolides failed,[9] but we have been successful on the bromolactonization of γ-monosubstituted allenic esters, **3** (R^2 = H).[10] We report herein the full results related with this reaction, that has allowed us to synthesize, in short sequences using a common allenic ester, fimbrolide (**1a**, X = H, Y = Br), acetoxyfimbrolide (**1c**, X = H, Y = Br), and bromobeckerelide (**2a**).

Results and Discussion

The reaction of allenic acids and esters **3** with several electrophiles, including bromine, is a widely used route for the synthesis of β-substituted-α,β-butenolides[11] (Scheme 1). Nevertheless, reaction with bromine is described only when R^1 = Ph, R^2 = H, alkyl[11a,b] or R^1 and R^2 = alkyl.[11c,d] No report for allenes when R^1 = alkyl, R^2 = H was found in the literature. Methyl 2,3-pentadienoate (**4**) was prepared by a Wittig olefin synthesis[12] and was used as a model compound for the bromolactonization reaction. When **4** was submitted to the conventional ionic bromination conditions using molecular bromine, a very com-

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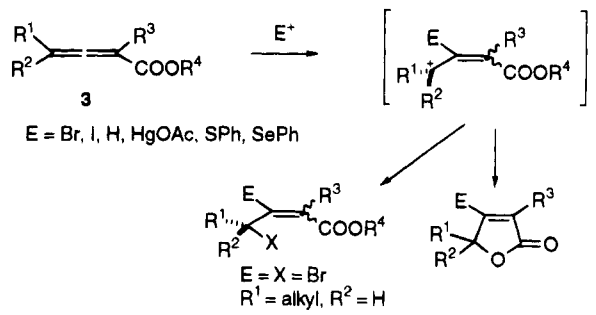
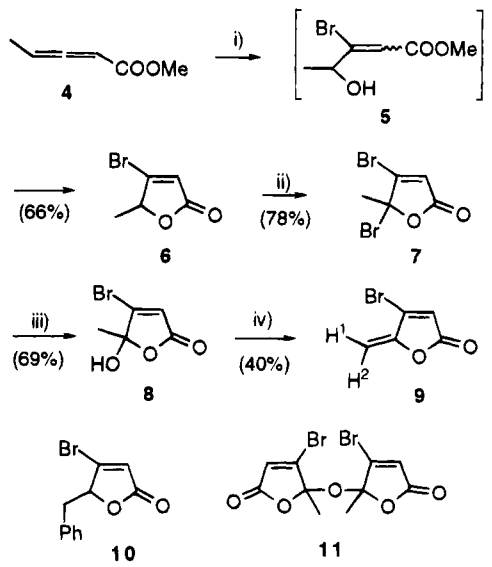
Scheme 1



Scheme 2[a]



[a] (i) NBS, water; (ii) NBS, CCl_4, hν; (iii) THF, water; (iv) P_2O_5, benzene, reflux.

plex mixture was obtained containing small proportions of bromolactone **6**,[13] the main isolated products resulting from the addition of bromine to the β,γ-double bond of **4**. From this result it was concluded that the lactonization outlined in Scheme 1 when E is bromine works satisfactorily only when the positive charged intermediate is stabilized by inductive or resonance effects, otherwise addition products are formed.[13] Taking into account this fact, we visualized that bromohydrin **5**, an addition product, could be a useful intermediate for the synthesis of β-bromolactone **6** (Scheme 2).

When allene **4** was allowed to react with *N*-bromosuccinimide (NBS) as brominating agent, in water[14] and in the darkness, lactone **6**[13] was isolated in 66% yield. Only 4% of the new methyl (*Z*)-3-bromo-4-hydroxy-2-pentenoate ((*Z*)-**5**) was obtained as a byproduct. The *Z*-configuration of the double bond was based on the chemical shift of the methinic proton (δ 4.43) as well as those of C_2 and C_3 (δ 117.5 and 145.4, respectively). The mentioned proton is not deshielded by the carbonyl group, and the absorptions of the olefinic carbon atoms confirm this stereochemical assignment by comparison with other previously reported β-halogeno-α,β-unsaturated carboxylic acid derivatives.[13,15]

For the synthesis of metabolites **1** and **2**, strategies for further functionalization of C_5, *i.e.* preparation of 5-alkylidene-4-bromo-2(5*H*)-furanones and 5-alkyl-4-bromo-5-hydroxy-2(5*H*)-furanones were needed. Following the model sequence this would represent the formation of 4-bromo-5-hydroxy-5-methyl-2(5*H*)-furanone (**8**) and 4-bromo-5-methylene-2(5*H*)-furanone (**9**) through oxidation of lactone **6**. It is reported that the allylic bromination of γ-crotonolactone using NBS affords 5-bromo-2(5*H*)-furanone in high yields,[16] although the same reaction on β-angelica lactone gives dibromolactones.[16b] With these precedents in mind, lactone **6** was allowed to react with NBS under irradiation with an incandescent lamp and **7**[13] was isolated (78% yield) as a moisture sensitive substance, like other γ-bromo-α,β-butenolides.[16a] All our attempts to perform the dehydrobromination of dibromolactone **7** using basic conditions (Na_2CO_3, DABCO, DBU) failed. The use of LiBr in DMF at reflux, a method already applied to other bromolactones,[17] led to lactone **9** in fair yields, but always contaminated with compound **8**. Finally, pure lactone **9** was prepared in two steps: treatment of dibromo derivative **7** with THF/water which allowed the isolation of the new pseudoacid **8** (63% yield from **6**), followed by dehydration of **8** with phosphorus pentoxide in benzene at reflux.[5b,8] It is worth mentioning that the ^{1}H NMR spectrum of butenolide **8** does not show the existence of the acyclic carbonyl tautomer, observed in other γ-hydroxybutenolides.[18] Methylenebutyrolactone **9** was obtained as a white solid (mp 59–61 °C dec) after column chromatography purification with important loss of product and was unstable, as was its simple analogue, γ-methylene-α,β-butenolide or protoanemonin (**30**).[19] Its ^{1}H NMR spectrum shows two double doublets at δ 5.21 and 5.32 with J = 3.1 and 0.8 Hz and J = 3.1 and 1.8 Hz corresponding to H^1 and H^2, respectively (Scheme 2). Two minor compounds, furanone **10** and ether **11**, were also isolated from the reaction with P_2O_5. Butenolide **10** should be the result of a Friedel–Crafts alkylation of benzene, used as solvent, and its ^{1}H NMR spectrum shows two double doublets at δ 2.94 and 3.35 due to the diastereotopic protons of the methylene group. Summing up, this sequence describes an easy conversion of the model allene **4** into the new and highly functionalized lactones 4-bromo-5-hydroxy-5-methyl-2(5*H*)-furanone (**8**) and 4-bromo-5-methylene-2(5*H*)-furanone (**9**) in 42 and 17% yields, respectively. Both lactones contain already the functionalized heterocyclic system present in natural products **1** and **2**.

The new bromolactonization reaction was extended to other γ-monosubstituted allenic esters. Improving significantly the previous described synthesis,[20] allene **12** was synthesized in 68% yield using the Wittig reaction between isovaleryl chloride and (methoxycarbonyl)methylenetriphenylphosphorane. Reaction of compound **12** with NBS/water afforded a crude product whose ^{1}H NMR spectrum revealed the presence of bromohydrin **13** as a major component (δ 3.78 for a MeO group) (Scheme 3). Heating this material in chloroform with a trace of

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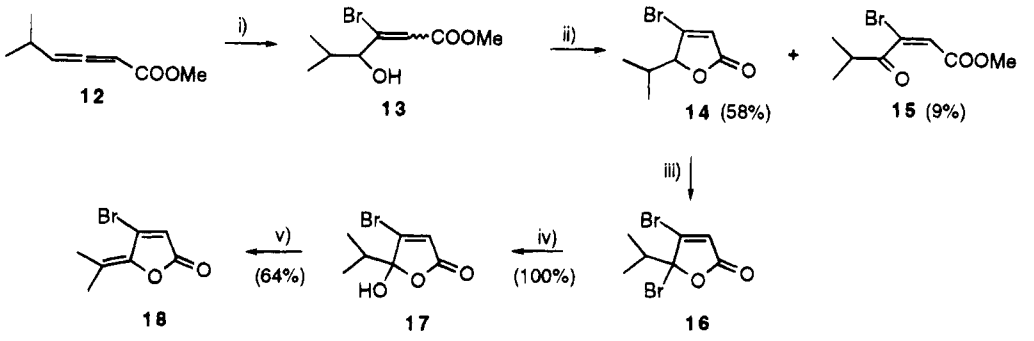
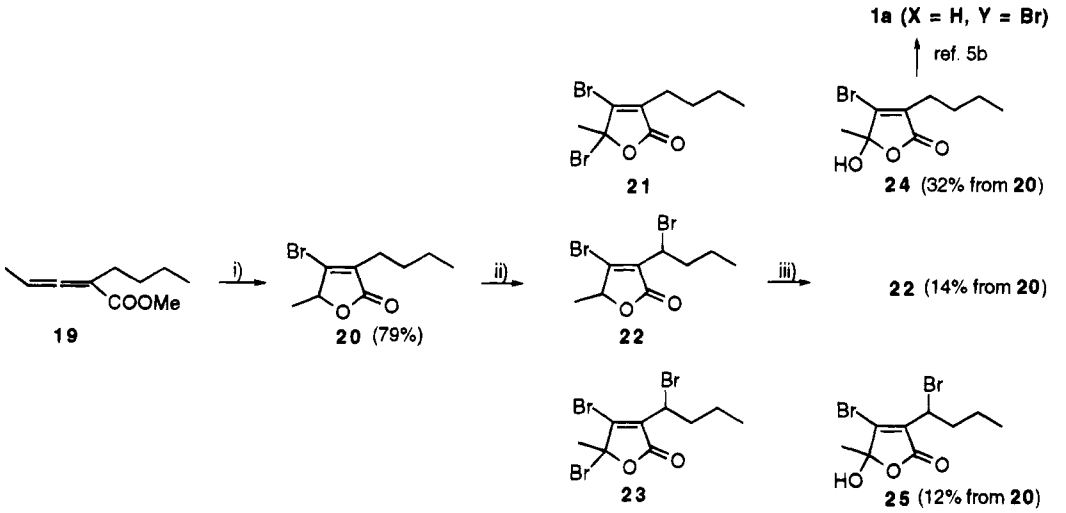
Scheme 3[a]



[a] (i) NBS, water; (ii) *p*-TsOH, $CHCl_3$, reflux; (iii) NBS, CCl_4, hν; (iv) THF, water; (v) P_2O_5, benzene, reflux.

Scheme 4[a]



[a] (i) NBS, water; (ii) 1 equiv of NBS, CCl_4, hν; (iii) THF, water.

p-toluenesulfonic acid gave pure bromolactone **14** (58% overall yield) and methyl 3-bromo-5-methyl-4-oxo-2-hexenoate (**15**) as a byproduct (9% yield). The spectroscopic data of **15** indicate that the carbonyl group is out of the plane of the α,β-unsaturated ester. The 1709 cm^{-1} absorption in the IR spectrum and the chemical shift of δ 203.5 in the ^{13}C NMR spectrum[21] are in agreement with a nonconjugated ketone. This lack of coplanarity can be explained assuming an (*E*)-configuration of the double bond with an important steric hindrance.

The allylic bromination of lactone **14** under the above described conditions afforded dibromofuranone **16** in high yield. This compound was completely characterized by its spectroscopic data and correct elemental analysis. There is no absorption at $5.1 > \delta > 4.8$ in the ^1H NMR spectrum, which indicates the absence of a γ-methinic proton of an α,β-butenolide. Hydrolysis of compound **16** yielded the new pseudoacid **17** quantitatively. Its ^1H NMR spectrum does not show the presence of the corresponding acyclic tautomer as was also the case for lactone **8**. Finally, its dehydration using phosphorus pentoxide allowed the isolation of product **18** in 64% yield. This alkylidenebromobutenolide was very unstable, although we could characterize it by its spectroscopic data. Among them, the mass spectrum showed the molecular ions at m/z = 204, 202.

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Having resolved the transformation of γ-monoalkyl allenic esters into the corresponding β-bromo-γ-hydroxy-α,β-butenolides and γ-alkylidene-β-bromo-α,β-butenolides we decided to apply this short sequence to the syntheses of fimbrolides and bromobeckerelide. For these purposes methyl 2-butyl-2,3-pentadienoate (**19**) was prepared as starting material (Scheme 4). The corresponding acid had been already described,[22] although it was prepared in a very low yield. Instead, the ester was obtained through a Wittig reaction between propionyl chloride and [1-(methoxycarbonyl)pentylidene]triphenylphosphorane.[23] The required methyl 2-bromohexanoate was prepared by conventional methods from hexanoic acid.[24] The structure of allene **19** was confirmed by the absorptions at 1962 cm^{-1} and δ 210.4 in the IR and ^{13}C NMR spectra, respectively. The vinylic proton absorbs as a quadruple triplet (J = 7.3 and 2.8 Hz) at δ 5.49 in the ^1H NMR spectrum as the result of its coupling with the methyl group and a long-range coupling across five bonds to the allylic methylene group. The new bromolactone **20** was isolated in pure state in 79% yield when allene **19** was treated with NBS in water. A 3% of pseudoacid **24** (*vide infra*) was also identified in this reaction.

Lactone **20** presents already the carbon skeleton of the target natural products, and its structure was established

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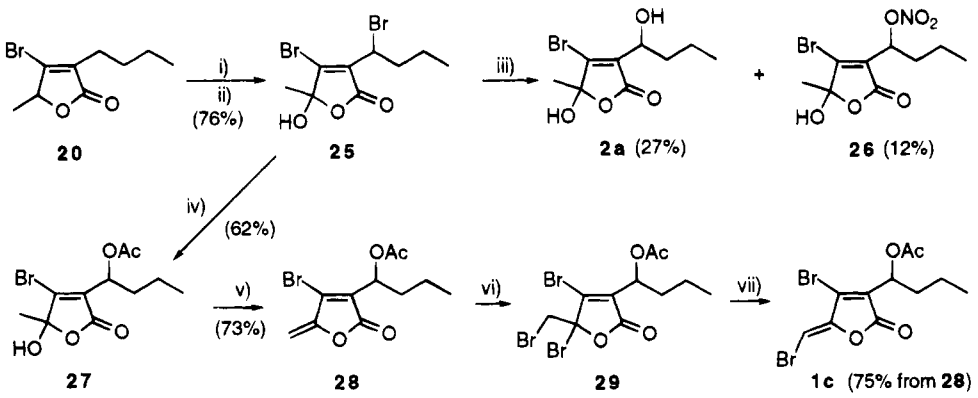
Scheme 5[a]



[a] (i) 2.4 equiv of NBS, CCl_4, hν; (ii) THF, water; (iii) $AgNO_3$, THF, water; (iv) AgOAc, HOAc; (v) P_2O_5, benzene, reflux; (vi) Br_2, CH_2Cl_2; (vii) DBU, CH_2Cl_2.

by the absorptions at 1761 and 1653 cm^{-1} in its IR spectrum that correspond to the carbonyl group and to the carbon–carbon double bond of the α,β-butenolide, respectively. The methinic proton (δ 4.93) absorbs as a quadruple triplet presenting again a long-range coupling with the allylic methylene group. The olefinic carbons resonate at δ 132.3 and 145.1 (C_3 and C_4, respectively) which confirms the structure of 4-bromo-2(5*H*)-furanone.

The photochemical allylic bromination of **20** with 1 equiv of NBS unfortunately did not work in this case as nicely as with the other substrates **6** and **14**, because of the presence of two allylic positions. The crude product contained starting material, dibromolactones **21** and **22**, and tribromolactone **23**. Since γ-bromobutenolides are unstable against moisture making the purification of the desired lactone **21** very difficult, it was decided to follow the synthetic sequence, submitting the crude bromination material to hydrolysis. Under these conditions pseudoacid **24** was isolated in 32% yield, and since this lactone is an advanced intermediate in the synthesis of fimbrolide (**1a**, X = H, Y = Br) described by Caine and co-workers[5b] our results constitute a new formal synthesis of this secondary metabolite. The presence of intermolecular hydrogen bonds in the bulk pseudoacid **24** was indicated by an absorption at 1747 cm^{-1} in the neat IR spectrum and a maximum at 1778 cm^{-1} in the IR spectrum registered in carbon tetrachloride.[5b] We report for the first time the complete ^{13}C NMR data for this compound. During the process of purification of these crude materials pure lactone **22** as a 1:1 diastereoisomeric mixture was also isolated, from which we were able to crystallize one isomer. In a further attempt, the reaction of lactone **20** with molecular bromine followed by hydrolysis gave also several products from which lactone **24** could be isolated in 26% yield. The lack of selectivity in the allylic bromination of lactone **20** opened the possibility to functionalize the butyl chain as in acetoxyfimbrolide **1c** and bromobeckerelide (**2a**) and therefore to prepare these products.

For this purpose β-bromobutenolide **20** was treated with 2.4 equiv of NBS, and the obtained crude material was submitted without any purification to hydrolysis. Flash chromatography of the residue afforded 76% yield of the pseudoacid **25** with the allylic position of the butyl chain already functionalized (Scheme 5). Substitution of the bromine atom by a hydroxyl group was achieved by the reaction of compound **25** with water/THF in the presence of silver nitrate.[25] Preparative TLC of the crude material led to the isolation of bromobeckerelide (**2a**) and the new bromobeckerelide nitrate (**26**). Melting point and spectral properties of synthetic **2a** were in agreement with those previously published.[2,6] The ^{13}C NMR (100 MHz) of the product distinguished two signals for each carbon, except for the carbonyl group, due to the presence of diastereoisomers, in contrast to the data registered by Katsumura *et al.*[6b] Its electron impact spectrum, not described before, did not show the molecular ion, the highest signal being at m/z = 223, 221, which should correspond to the loss of a propyl chain. The structural assignment of nitrate **26** was unambiguous since the chemical ionization mass spectrum using ammonia as reagent gas indicated molecular ions at m/z = 346, 344 $(C_9H_{12}BrNO_6 + 35)^+$ and 329, 327 $(C_9H_{12}BrNO_6 + 18)^+$, while in the ^1H NMR spectrum the methinic proton was downfield shifted (δ 5.63) in comparison to lactone **25** and **2a**, and the IR spectrum presented intense absorptions at 1643 and 1280 cm^{-1}: the first band corresponding to the superposition of the absorption of the C=C bond and the asymmetric vibration of the nitro group and the second band to the symmetric vibration of the later group.[26]

For the synthesis of acetoxyfimbrolide (**1c**, X = H, Y = Br) from pseudoacid **25**, the introduction of an acetoxy group in the allylic position and a bromomethylene group in γ-position were needed. The second transformation is satisfactorily well documented in the literature for analogous compounds,[5b,8] and therefore the allylic substitution was performed in the first place. The new acetate **27** was prepared in 62% yield when derivative **25** was reacted with glacial acetic acid in the presence of silver acetate.[27] This product was also obtained as a 1:1 diastereoisomeric mixture as evidenced by its ^1H and ^{13}C NMR: two double doublets (δ 5.38 and 5.41) are observed for the methinic proton and two signals were observed for many carbon atoms. The IR spectrum indicated the presence of all the functional groups: the C=C bond (1660 cm^{-1}), two carbonyl groups (1748 and 1771 cm^{-1}), and a hydroxyl group (3600–3000 cm^{-1}).

Reaction of derivative **27** with a large excess of P_2O_5 in benzene at reflux[5b] led to a crude material consisting

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Chart 2

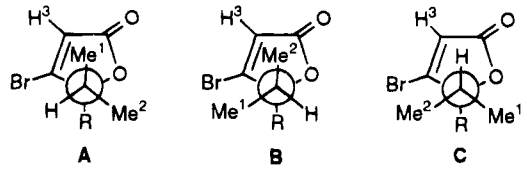


Table 1. NMR Data for Compounds 14, 16, and 17

	δ values for CH_3		% NOE on H^3			
	^1H (δ)	^{13}C (δ)	*a*	*b*	% conf A	% conf B
14	0.79, 1.22	13.2, 19.2	1.6	0.2	89	9
16	0.87, 1.38	15.7, 18.0	1.3	0.6	95	3
17	0.86, 1.19	15.2, 16.0	1.9	0.6		

[a] Upfield shifted methyl group was irradiated. [b] Downfield shifted methyl group was irradiated.

mainly of the dehydrated and deacetylated product. The reaction was repeated using only 1 equiv of P_2O_5,[28] and the desired methylenebutenolide **28** was isolated (73% yield) whose ^1H NMR spectrum indicated the presence of the acetoxy group (singlet at δ 2.08) and the exocyclic double bond (two doublets at δ 5.19 and 5.28). The carbonyl group of the ester and the terminal methylene group resonate at δ 170.1 and 97.4, respectively, in the ^{13}C NMR spectrum. Addition of bromine to the methylene group followed by dehydrobromination of the tribromo derivative **29** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave acetoxyfimbrolide (**1c**, X = H, Y = Br) in 75% yield from **28**. In one operation we also isolated lactone **29** in pure state as a solid, and it was characterized by its ^1H NMR spectrum. Synthetic acetoxyfimbrolide showed identical ^1H and ^{13}C NMR to those previously reported.[1]

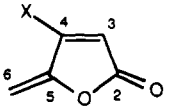
In conclusion we report a new easy, short, and elegant entry not only to γ-alkyl-β-bromo-γ-hydroxy-α,β-butenolides, but also to γ-alkylidene-β-bromo-α,β-butenolides using allenic esters as starting material. This strategy has been successfully applied to a formal synthesis of fimbrolide (**1a**, X = H, Y = Br) and to new syntheses of acetoxyfimbrolide (**1c**, X = H, Y = Br) and bromobeckerelide (**2a**) using a common intermediate, namely 4-bromo-3-butyl-5-methyl-2(5*H*)-furanone (**20**).

Conformational Analysis of the Isopropyl Derivatives 14, 16, and 17. The diastereotopic methyl groups of lactones **14**, **16**, and **17** absorb significantly differentiated in both ^1H and ^{13}C NMR spectra as shown in Table 1. This fact prompted us to carry out a conformational analysis of these compounds using homonuclear $^1H\{^1H\}$ NOE studies and semiempirical calculations.

The NOE measurements were performed in d_6-DMSO solutions at 300 K at a concentration of 10 mg of product in 0.5 mL. Two experiments were run for each compound presaturating both methyl groups. No information was deduced from the NOE measured on the methinic proton of the isopropyl group or the nonirradiated methyl group, but the NOE observed on H^3 was relevant (Chart 2). The results (Table 1) show that in the three compounds the major conformer presents the olefinic proton H^3 closer to the upfield shifted methyl group. Only conformers A and B can present a nuclear Overhauser effect between this proton and the methyl groups, and conformer A should be the more populated for steric reasons (interaction Br/H *vs* Br/Me^1). In this conformation the upfield shifted methyl group is placed above the lactone ring and it is influenced by the anisotropic effect of the π-electron system of the butenolide that causes the observed upfield shift. These considerations are reinforced by the NOE observed on H^5 for compound **14**: in conformer A (R = H^5) the downfield shifted methyl group is much closer to this proton (10.9% NOE) than the other methyl group (1.3% NOE).

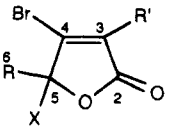
Semiempirical calculations using the MNDO program[29] for compounds **14** and **16** indicate also that conformer A is the more populated (89 and 95%, respectively) followed by conformer B (9% and 3%, respectively).

Table 2. ^{13}C NMR (δ) for Lactones 30 and 9



	C-2	C-3	C-4	C-5	C-6
30 (X = H)	169.8	121.5	143.7	154.9	98.0
9 (X = Br)	166.4	121.9	137.0	153.9	97.4

Table 3. Comparison of the Chemical Shift of C-6 (^{13}C NMR δ) for Several 5-Substituted 4-Bromo-α,β-butenolides



	X = H	X = Br	X = OH
R = Me	≈18 (**6**, **20**)	≈30 (**7**)	≈23 (**2a**, **8**, **24**, **25**, **27**)
R = *i*-Pr	≈30 (**14**)	≈38 (**16**)	≈33 (**17**)

^{13}C NMR Data. We include in this paper the ^{13}C NMR spectrum of the simplest unfunctionalized 5-methylene-2(5*H*)-furanone, protoanemonin (**30**) prepared following the method described by Shaw.[30] To the best of our knowledge this spectrum had not been previously reported, and it was important for the structural elucidation of a variety of compounds reported herein. For instance, the chemical shifts of the carbon atoms of butenolide **30** and **9** are similar except for C-4: in **9** this carbon atom is upfield shifted in comparison to **30** (Table 2).

Also the comparison of these spectra and the use of the technique of SEFT has allowed us to assign the chemical shifts of all the carbon atoms (see Experimental Section). Worth mentioning is the influence of the substituent at C-5 position (H, Br, OH) on the chemical shift of C-6. A bromine atom at C-5 shifts the absorption of C-6 around 10 ppm downfield with respect to the hydrogen atom. By contrast, a hydroxyl group induces only a ≈5 ppm downfield effect (Table 3).

Experimental Section

Commercial grade solvents were used without further purification unless otherwise stated. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15–20 mmHg. Flash chromatographies were performed on silica gel (230–400 mesh). Distillation of small amounts of substances were performed on a Büchi KRV 65/30 rotational distiller (only oven

(28) We thank Prof. H. Kotsuki for sending us the experimental part of ref 8.

(29) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907.

(30) Shaw, E. *J. Am. Chem. Soc.* **1946**, *68*, 2510–2513.

temperature given). GC analysis were performed on a Hewlett-Packard 5890 instrument with a capillary column Hewlett-Packard Ultra 1 (crosslinked methyl silicone gum, 12 m × 0.2 mm × 0.3 μm), T_{inj} = 210 °C, T_1 = 80 °C, t_1 = 3 min, r = 10 °C/min, T_2 = 200 °C. Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. NMR spectra were recorded on 80-, 250-, or 400-MHz Bruker WP80SY, AC250, and AM400WB instruments. $CDCl_3$ was used as solvent for NMR experiments, with chemical shifts reported in δ ppm relative to residual $CHCl_3$ (7.24 ppm) for proton NMR or $CDCl_3$ (77.0 ppm) for carbon-13 NMR. Mass spectra (70-eV ionizing voltage for electron impact and ammonia as reagent gas for chemical ionization) were performed on a Hewlett-Packard 5985 instrument; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments. Some of the bromine-containing products described below proved too reactive or unstable for satisfactory elemental analysis, although good spectroscopic data are included as supplementary material.

Methyl Pentadienoate (4). Compound **4** was prepared following the method described by Lang.[12]

4-Bromo-5-methyl-2(5*H*)-furanone (6). A light-protected and magnetically stirred suspension of allene **4** (3.47 g, 31 mmol) and NBS (6.06 g, 34 mmol) in water (75 mL) was allowed to react for 16 h at 25 °C. When the stirring was stopped after this time, two phases were observed. The mixture was extracted with methylene chloride (2 × 50 mL), and the organic phase was washed successively with 25 mL of 0.5 M sodium bisulfite solution and 25 mL of saturated NaCl solution. Flash chromatography of the crude product afforded the following fractions: (i) lactone **6**[13] (3.63 g, 21 mmol, 66% yield) with hexane–ether (3:1) as eluent; (ii) methyl (*Z*)-3-bromo-4-hydroxy-2-pentenoate, (*Z*)-**5** (260 mg, 1.2 mmol, 4% yield), using ether as eluent. Fractions containing lactone **6** should be concentrated at 0 °C. (*Z*)-**5**: bp 120–125 °C/0.02 mmHg; IR (film) 3700–3100, 2982, 2950, 1720, 1637, 1433, 1288, 1194, 1173 cm^{-1}; ^1H NMR (80 MHz) 1.43 (d, J = 6.3 Hz, 3 H), 2.13 (s, 1 H, OH), 3.77 (s, 3 H), 4.43 (dq, J = 6.3 Hz, J = 1.0 Hz, 1 H), 6.68 (d, J = 1.0 Hz, 1 H); ^{13}C NMR (20 MHz) 22.0, 51.6, 73.0, 117.5 (CH=), 145.4 (CBr=), 165.0 (CO); MS m/z 211, 209 (M^+ + 1, 11, 13), 210 (4), 208 (3), 195 (7), 193 (13), 179 (9), 177 (11), 129 (59), 97 (100), 69 (29), 53 (20), 43 (20). Anal. Calcd for $C_6H_9BrO_3$: C, 34.47; H, 4.34; Br, 38.23. Found: C, 34.13; H, 4.16; Br, 38.42.

4,5-Dibromo-5-methyl-2(5*H*)-furanone (7). A stirred mixture of NBS (1.55 g, 8.7 mmol) and bromolactone **6** (1.54 g, 8.7 mmol) in anhydrous carbon tetrachloride (70 mL) was irradiated with a 500 W incandescent lamp for 2.5 h at such a distance to maintain the temperature of the mixture at 55–60 °C. The mixture was filtered, and the precipitate was washed with CCl_4 (3 × 10 mL). The filtrate was successively washed with 0.5 M sodium bisulfite and saturated NaCl solution. The organic phase was dried, and the solvent was removed to give dibromolactone **7** (1.73 g, 6.8 mmol, 78% yield) as a white solid.[13]

4-Bromo-5-hydroxy-5-methyl-2(5*H*)-furanone (8). A solution of lactone **7** (811 mg, 3.17 mmol) in THF (15 mL) and water (50 mL) was stirred at room temperature for 24 h. The mixture was extracted with ether (3 × 80 mL), and the organic phase was washed with saturated NaCl solution. The crude product (590 mg) was purified by flash chromatography using hexane–ether (2:1) as eluent to give pseudoacid **8** as a colorless oil (421 mg, 2.18 mmol, 69% yield): bp 125–130 °C/0.1 mmHg; IR (film) 3600–3000, 1749, 1613, 1265, 1201, 1133, 1079, 936, 862 cm^{-1}; ^1H NMR (80 MHz) 1.71 (s, 3 H), 3.85 (br s, 1 H), 6.24 (s, 1 H); ^{13}C NMR (20 MHz) 23.5, 107.2 (C(OH)), 122.4 (CH=), 152.1 (CBr=), 168.8 (CO); MS m/z 195, 193 (M^+ + 1, 2, 2), 179 (8), 177 (15), 175 (9), 134 (5), 132 (5), 106 (3), 104 (4), 85 (65), 83 (100), 47 (30), 43 (29); MS m/z (CI, NH_3) 229, 227 (M^+ + 35), 212, 210 (M^+ + 18). Anal. Calcd for $C_5H_5BrO_3$: C, 31.12; H, 2.61; Br, 41.40. Found: C, 30.96; H, 2.72; Br, 40.99.

When the crude product obtained by bromination of lactone **6** (725 mg, 4.1 mmol) was submittted without purification to hydrolysis, lactone **8** (499 mg, 2.59 mmol) was obtained in 63% overall yield.

4-Bromo-5-methylene-2(5*H*)-furanone (9). A suspension of pseudoacid **8** (458 mg, 2.37 mmol) and phosphorus pentoxide (6.0 g) in benzene (70 mL) was heated at reflux temperature under argon atmosphere until no more **8** was present by TLC analysis using hexane–ether (2:1) as eluent (45 min). The precipitate was filtered off through Celite, and the solid was washed with benzene (3 × 20 mL). The organic phase was washed with water, and the solvent was removed under reduced pressure at 0 °C to afford slightly impure lactone **9** (338 mg) as a solid. Flash chromatography of this crude product yielded the following fractions: (i) 166 mg of pure **9** (0.95 mmol, 40% yield) using hexane–ether (9:1) as eluent; (ii) 25 mg of 5-benzyl-4-bromo-2(5*H*)-furanone (**10**) (0.1 mmol, 4% yield) using hexane–ether (1:1) as eluent; and (iii) a solid identified as compound **11** (17 mg, 0.05 mmol, 4% yield) with ether as eluent. **9**: mp 59–61 °C dec (hexane/ether); IR (KBr) 3138, 3086, 1790, 1754, 1650, 1561, 1230, 1119, 968, 879, 853 cm^{-1}; ^1H NMR (80 MHz) 5.21 (dd, J = 3.1 Hz, J = 0.8 Hz, 1 H), 5.32 (dd, J = 3.1 Hz, J = 1.8 Hz, 1 H), 6.45 (dd, J = 1.8 Hz, J = 0.8 Hz, 1 H); ^{13}C NMR (20 MHz) 97.4 (CH_2=), 121.9 (CH=), 137.0 (CBr=), 153.9 (=CO), 166.4 (CO); MS m/z 176, 174 (M^+, 68, 64), 148 (17), 146 (16), 134 (32), 132 (29), 106 (72), 104 (69), 79 (20), 67 (100), 53 (99), 51 (21), 50 (58), 42 (78). Anal. Calcd for $C_5H_3BrO_2$: C, 34.32; H, 1.73; Br, 45.67. Found: C, 34.38; H, 1.65; Br, 45.37. **10**: IR (film) 3113, 3064, 3032, 2957, 2926, 2853, 1762, 1604, 1321, 1150, 701 cm^{-1}; ^1H NMR (80 MHz) 2.94 (dd, J = 14.6 Hz, J = 6.0 Hz, 1 H), 3.35 (dd, J = 14.6 Hz, J = 4.1 Hz, 1 H), 5.13 (ddd, J = 6.0 Hz, J = 4.1 Hz, J = 1.6 Hz, 1 H), 6.12 (d, J = 1.6 Hz, 1 H), 7.22 (s, 5 H); ^{13}C NMR (20 MHz) 37.6, 85.1, 123.0 (CH=), 127.4, 128.5, 129.8, 133.4, 149.4 (CBr=), 169.8 (CO); MS m/z 254, 252 (M^+, 76, 77), 163 (45), 161 (45), 133 (20), 129 (25), 128 (100), 127 (52), 116 (21), 115 (58), 107 (80), 106 (28), 105 (85), 104 (28), 102 (37). **11**: IR (KBr) 3120, 2956, 1764, 1611, 1241, 1143, 1086, 928 cm^{-1}; ^1H NMR (80 MHz) 1.73 (s, 6 H), 6.42 (s, 2 H); MS m/z 177, 175 (M^+ − 191, 100, 79), 134 (19), 132 (19), 106 (17), 104 (17).

Methyl 5-Methyl-2,3-hexadienoate (12). The same procedure described for the synthesis of allene **19** was used, but acetonitrile was employed as solvent. Ester **12** was purified by rapid distillation (bp 105–115 °C/21 mmHg), and the yield was 68%. IR (film) 2971, 2874, 1948, 1719, 1444, 1415, 1270, 1176, 1050 cm^{-1}; ^1H NMR (80 MHz) 1.09 (d, J = 7.0 Hz, 6 H), 2.43 (m, 1 H), 3.74 (s, 3 H), 5.61 and 5.73 (2 H); ^{13}C NMR (20 MHz) 22.1, 22.3, 27.7, 51.9, 88.9 (=*C*HCO$_2$Me), 102.6 (=*C*HCH), 166.7, 211.4 (=*C*=); MS m/z 140 (M^+, 8), 139 (7), 125 (100), 109 (26), 97 (27), 81 (89), 80 (54), 79 (62), 66 (26), 65 (32), 63 (20), 59 (54), 53 (51), 51 (23), 43 (25), 41 (52). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.72; H, 8.62.

4-Bromo-5-isopropyl-2(5*H*)-furanone (14). A light-protected and magnetically stirred suspension of allene **12** (0.84 g, 6.0 mmol) and NBS (1.07 g, 6.0 mmol) in water (15 mL) was allowed to react for 16 h. When the stirring was stopped after this time, two phases were observed. The mixture was diluted with water (25 mL) and extracted with chloroform (2 × 25 mL). The organic phase was successively washed with 0.5 M sodium bisulfite and saturated NaCl solutions and dried. A catalytic amount of *p*-toluenesulfonic acid was added to the resulting chloroform solution and it was heated to reflux for 100 min. Flash chromatography of the crude product (1.24 g) using hexane–ether (9:1) as eluent afforded the following fractions: (i) 127 mg (0.54 mmol, 9% yield) of a yellow oil identified as methyl (*E*)-3-bromo-5-methyl-4-oxo-2-hexenoate (**15**); (ii) 717 mg (3.5 mmol, 58% yield) of 4-bromo-5-isopropyl-2(5*H*)-furanone (**14**) as a colorless oil. **14**: bp 120–130 °C/20 mmHg; mp 31–33 °C; IR (film) 3109, 2969, 2935, 2878, 1785, 1759, 1603, 1249, 1155, 1006, 943 cm^{-1}; ^1H NMR (80 MHz) 0.79 (d, J = 6.9 Hz, 3 H), 1.22 (d, J = 6.9 Hz, 3 H), 2.33 (d sept, J = 6.9 Hz, J = 2.4 Hz, 1 H), 4.90 (dd, J = 2.4 Hz, J = 1.8 Hz, 1 H), 6.34 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (20 MHz) 13.2, 19.2, 29.6, 89.0, 122.4 (CH=), 149.7 (CBr=), 170.2 (CO); MS m/z 207, 205 (M^+ + 1, 31, 29), 164 (32), 162 (41), 53 (23), 43 (100), 41 (53). Anal. Calcd for $C_7H_9BrO_2$: C, 41.00; H, 4.42. Found: C, 40.82; H, 4.26. **15**: bp 60–65 °C/1.5 mmHg; IR (film) 2976, 1722, 1709, 1617, 1325, 1215, 1005 cm^{-1}; ^1H NMR (80 MHz) 1.19 (d, J = 6.7 Hz, 6 H), 2.95 (sept, J = 6.7 Hz, 1

H), 3.64 (s, 3 H), 6.34 (s, 1 H); ^{13}C NMR (100 MHz) 18.2 (2 × Me), 39.3, 52.3, 124.0 (CH=), 137.3 (CBr=), 163.7 (COO), 203.5 (CO); MS *m/z* 237, 235 (M^+ + 1, 54, 58), 205 (46), 203 (47), 193 (81), 191 (86), 155 (77), 95 (20), 85 (27), 81 (32), 71 (39), 59 (41), 53 (56), 43 (100), 41 (90).

4,5-Dibromo-5-isopropyl-2(5*H*)-furanone (16). The same procedure described for the bromination of **6** was applied to bromolactone **14**. The process gave dibromolactone **16** (88% yield) as a yellowish oil that solidified in the freezer: mp 35–40 °C (ether/pentane); IR (KBr) 3114, 2979, 1805, 1764, 1594, 1204, 921 cm^{-1}; ^{1}H NMR (80 MHz) 0.87 (d, J = 6.8 Hz, 3 H), 1.38 (d, J = 6.8 Hz, 3 H), 2.49 (sept, J = 6.8 Hz, 1 H), 6.35 (s, 1 H); ^{13}C NMR (20 MHz) 15.7, 18.0, 38.0, 100.5 (CBr), 121.0 (CH=), 154.2 (CBr=), 166.7 (CO); MS *m/z* 287, 285, 283 (M^+ + 1, 4, 10, 6), 244 (2), 242 (5), 240 (2), 205 (47), 203 (42), 81 (60), 53 (39), 43 (100). Anal. Calcd for $C_7H_8Br_2O_2$: C, 29.61; H, 2.84; Br, 56.28. Found: C, 29.76; H, 2.71; Br, 56.11.

4-Bromo-5-hydroxy-5-isopropyl-2(5*H*)-furanone (17). A solution of lactone **16** (284 mg, 1.0 mmol) in THF (5 mL) and water (20 mL) was stirred at room temperature for 30 h at 25 °C. The mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the solvent was removed to give pseudoacid **17** as a white solid (220 mg, 1.0 mmol, 100% yield): mp 84–85 °C (CH_2Cl_2/pentane); IR (KBr) 3560–3280, 3114, 2973, 2934, 1746, 1605, 1237, 1183, 1105, 1063, 938, 859, 747 cm^{-1}; ^{1}H NMR (80 MHz) 0.86 (d, J = 6.8 Hz, 3 H), 1.19 (d, J = 6.8 Hz, 3 H), 2.31 (sept, J = 6.8 Hz, 1 H), 3.76 (br s, 1 H), 6.31 (s, 1 H); ^{13}C NMR (20 MHz) 15.2, 16.0, 33.1, 110.3 (C(OH)), 123.1 (CH=), 151.5 (CBr=), 169.1 (CO); MS *m/z* 223, 221 (M^+ + 1, 0.5, 0.3), 205 (2), 203 (1), 194 (1), 192 (1), 179 (28), 177 (26), 141 (39), 71 (53), 69 (24), 53 (62), 43 (100), 41 (55). Anal. Calcd for $C_7H_9BrO_3$: C, 38.03; H, 4.10; Br, 36.15. Found: C, 38.16; H, 4.07; Br, 35.90.

4-Bromo-5-isopropylidene-2(5*H*)-furanone (18). The same dehydration procedure described for pseudoacid **8** was applied to compound **17**. The reaction was completed after 30 min affording slightly impure ylidenebutenolide **18** in 64% yield as a solid. Purification of this material by flash chromatography using hexane–ether (9:1) as eluent gave pure **18** (44% yield): mp 62–64 °C; IR (CCl_4) 3139, 2918, 1773, 1745, 1659, 1549, 1249, 1181, 1103, 983 cm^{-1}; ^{1}H NMR (80 MHz) 2.07 (s, 3 H), 2.28 (s, 3 H), 6.32 (s, 1 H); ^{13}C NMR (100 MHz) 18.6, 21.6, 121.6 (CH=), 128.1 (*C*Me$_2$), 133.3 (CBr=), 142.5 (=CO), 166.8 (CO); MS *m/z* 204, 202 (M^+, 94, 100), 162 (69), 160 (64), 134 (54), 132 (48), 123 (24), 106 (27), 104 (27).

Methyl 2-Butyl-2,3-pentadienoate (19). A solution of triethylamine (3.40 mL, 25 mmol) in methylene chloride (25 mL) was added to a stirred solution of [(1-methoxycarbonyl)-pentylidene]triphenylphosphorane[23] (9.64 g, 25 mmol) in CH_2Cl_2 (80 mL) at 25 °C under Ar. The mixture was stirred for 15 min, and a solution of freshly distilled propionyl chloride (2.20 mL, 25 mmol) in the same solvent (25 mL) was slowly added during 25 min. The reaction was stirred 70 min further. The solvent was removed under reduced pressure at 0 °C, and the residue was treated with pentane (125 mL) and stirred for 2 h. The precipitate was filtered off and washed with cold pentane (3 × 30 mL). The organic solution was concentrated at 0 °C to a volume of 20 mL, and the formed precipitate was again filtered. Removal of the volatiles *in vacuo* was performed at low temperature. Flash chromatography of this material (2.95 g) using hexane–ether (9:1) as eluent yielded pure **19** (2.14 g, 13 mmol, 52% yield). This allene could also be purified by distillation: bp 65–68 °C/0.45 mmHg; IR (film) 2970, 2939, 2872, 1962, 1717, 1445, 1269, 1243, 1133 cm^{-1}; ^{1}H NMR (400 MHz) 0.88 (t, J = 7.1 Hz, 3 H), 1.30–1.45 (m, 4 H), 1.76 (d, J = 7.3 Hz, 3 H), 2.15–2.29 (m, 2 H), 3.73 (s, 3 H), 5.49 (tq, J = 7.3 Hz, J = 2.8 Hz, 1 H); ^{13}C NMR (20 MHz) 13.1, 13.7, 22.0, 28.1, 30.2, 51.7, 89.4 (CH=), 99.8 (=*C*CO$_2$Me), 168.0, 210.4 (=C=); MS *m/z* 168 (M^+, 9), 153 (5), 126 (100), 111 (78), 109 (21), 94 (27), 93 (34), 79 (48), 77 (34), 67 (69), 66 (29), 65 (33), 59 (32), 55 (20), 51 (25), 41 (49). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.62.

4-Bromo-3-butyl-5-methyl-2(5*H*)-furanone (20). The same procedure described for the synthesis of bromolactone **6** was applied to allene **19** (1.81 g, 10.8 mmol). Flash chromatography of the crude product (2.40 g) afforded the following fractions: (i) starting material (71 mg, 4% yield) using hexane–ether (19:1) as eluent; (ii) bromolactone **20** (1.99 g, 79% yield) as a colorless oil with hexane–ether (9:1) as eluent; and (iii) 4-bromo-3-butyl-5-hydroxy-5-methyl-2(5*H*)-furanone (**24**) as a yellow oil (85 mg, 3% yield) using ether as eluent. **20**: bp 60–65 °C/0.02 mmHg; IR (film) 2965, 2940, 2873, 1761, 1653, 1453, 1320, 1274, 1117, 1048, 925 cm^{-1}; ^{1}H NMR (400 MHz) 0.93 (t, J = 7.3 Hz, 3 H), 1.35 (m, 2 H), 1.51 (d, J = 6.7 Hz, 3 H), 1.55 (m, 2 H), 2.33 (t, J = 7.3 Hz, 2 H), 4.93 (tq, J = 6.7 Hz, J = 1.1 Hz, 1 H); ^{13}C NMR (20 MHz) 13.5, 18.5, 22.2, 24.7, 28.8, 79.7, 132.3 (=*C*CH$_2$), 145.1 (CBr=), 170.2 (CO); MS *m/z* 235, 233 (M^+ + 1, 1.2, 1.2), 234 (1), 232 (1), 219 (1), 217 (1), 192 (45), 190 (48), 153 (100), 111 (32), 107 (33). Anal. Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.28. Found: C, 46.27; H, 5.66; Br, 34.55. **24**:[5b] bp 155–160 °C/0.04 mmHg; ^{1}H NMR (400 MHz) 0.93 (t, J = 7.4 Hz, 3 H), 1.36 (m, 2 H), 1.55 (m, 2 H), 1.72 (s, 3 H), 2.33 (t, J = 7.4 Hz, 2 H), 3.48 (br s, 1 H); ^{13}C NMR (100 MHz) 13.7, 22.3, 23.8 (*C*H$_3$C(OH)), 24.5, 28.8, 105.2 (C(OH)), 133.6 (=*C*CH$_2$), 145.5 (CBr=), 169.5 (CO), SEFT; MS *m/z* (CI/NH$_3$) 285, 283 (M^+ + 35), 268, 266 (M^+ + 18).

Reaction of Bromolactone 20 with 1 Equiv of NBS. A stirred mixture of NBS (385 mg, 2.2 mmol) and bromolactone **20** (504 mg, 2.2 mmol) in anhydrous carbon tetrachloride (20 mL) was irradiated with a 500 W incandescent lamp for 5.5 h at such a distance to maintain the temperature of the mixture at 40–45 °C. The mixture was filtered, and the precipitate was washed with CCl_4 (3 × 10 mL). The filtrate was successively washed with 0.5 M sodium bisulfite and saturated NaCl solution. The organic phase was dried, and the solvent was removed to give an orange oil (657 mg). GC analysis of this crude product indicated the presence of **20** (t_r = 8.6 min, 16%), **21** (t_r = 10.3 min, 43%), **22** (t_r = 11.6 min, 20%), and **23** (t_r = 12.9 min, 10%). Flash chromatography of this material through silica gel afforded the following fractions: (i) 4,5-dibromo-3-butyl-5-methyl-2(5*H*)-furanone (**21**) and 4,5-dibromo-3-(1-bromobutyl)-5-methyl-2(5*H*)-furanone (**23**) in a 3:1 ratio using hexane–ether (9:1) as eluent (143 mg, 15 and 5% yield, respectively); (ii) starting material (48 mg, 10% yield) with the same eluent; (iii) 4-bromo-3-(1-bromobutyl)-5-methyl-2(5*H*)-furanone (**22**) (95 mg, 14% yield) with hexane–ether (9:1) as eluent; and (iv) 4-bromo-3-butyl-5-hydroxy-5-methyl-2(5*H*)-furanone (**24**) and 4-bromo-3-(1-bromobutyl)-5-hydroxy-5-methyl-2(5*H*)-furanone (**25**) in a 3:1 ratio using hexane–ether (1:1) as eluent (132 mg, 17 and 5% yield, respectively). Repeated flash chromatography of the third fraction allowed the isolation of a pure sample of the less polar diastereoisomer **22**. **21**: ^{1}H NMR (80 MHz) from the mixture of **21** and **23** 0.92 (t, J = 7.3 Hz, 3 H), 1.08–1.86 (m, 4 H), 2.13 (s, 3 H), 2.33 (t, J = 7.6 Hz, 2 H). Less polar diastereoisomer **22**: ^{1}H NMR (400 MHz) 0.94 (t, J = 7.3 Hz, 3 H), 1.22–1.64 (m, 5 H with δ 1.52, d, J = 6.7 Hz), 2.10–2.40 (m, 2 H), 4.75 (t, J = 7.8 Hz, 1 H), 4.94 (q, J = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz) 13.1, 18.5, 21.2, 36.9, 41.4 (CHBr), 79.8 (CHO), 131.3 (=C), 147.2 (CBr=), 167.5 (CO). Diastereoisomers **22**: IR (film) 2963, 2935, 2874, 1768, 1643, 1453, 1317, 1054 cm^{-1}; ^{1}H NMR (400 MHz) 0.94 (t, J = 7.3 Hz, 3 H), 1.22–1.64 (m, 5 H with δ 1.52, d, J = 6.7 Hz and δ 1.53, d, J = 6.7 Hz), 2.10–2.40 (m, 2 H), 4.75 and 4.76 (2 × t, J = J = 7.8 Hz, 1 H), 4.94 and 4.96 (2 × q, J = J = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz) 13.1, 18.2/18.5, 21.2, 36.8/36.9, 41.4 (CHBr), 79.8 (CHO), 131.2/131.3 (=C), 147.1/147.2 (CBr=), 167.4/167.5 (CO); MS *m/z* 313, 311, 309 (M^+ − 1, 0.4, 0.7, 0.4), 233 (17), 231 (19), 107 (39), 91 (31), 79 (32), 77 (25), 65 (21), 53 (20), 51 (21), 43 (100), 41 (30); MS *m/z* (CI/NH$_3$) 349, 347, 345 (M^+ + 35), 332, 330, 328 (M^+ + 18). Anal. Calcd for $C_9H_{12}Br_2O_2$: C, 34.65; H, 3.88. Found: C, 34.65; H, 3.85. For spectroscopic data of **23**–**25** see below.

Hydrolysis of the Crude Mixture Obtained in the Reaction of 20 with 1 Equiv of NBS. The crude mixture obtained from the bromination of **20** (1.00 g, 4.3 mmol) with NBS (767 mg, 4.3 mmol) was dissolved in THF (70 mL). Water was added (100 mL), and the mixture was stirred at room temperature for 20 h. The mixture was extracted with ether

(3 × 75 mL), the organic phase was washed with saturated NaCl solution and dried, and the solvent was removed at room temperature. Flash chromatography of the residue (1.36 g) through silica gel gave the following fractions: (i) starting lactone **20** (71 mg, 7% yield) with hexane–ether (19:1) as eluent; (ii) diastereoisomers **22** (185 mg, 14% yield) using hexane–ether (9:1) as eluent; and (iii) **24** and **25** (515 mg) with hexane–ether (1:1) as eluent. Careful crystallization of the third fraction with ether–pentane yielded a 1:1 mixture of the diastereoisomers of lactone **25** (172 mg, 0.5 mmol, 12% yield) as a white solid. The mother liquor contained lactone **24** (343 mg, 1.4 mmol, 32% yield) with ≈8% of **25**. Pure **24** was obtained by flash chromatography using hexane–ether (4:1) as eluent. **24**: bp 155–160 °C/0.04 mmHg; IR (film) 3600–3000, 2961, 2933, 2871, 1747, 1659, 1258, 1210, 1045, 908 cm^{-1}; ^1H NMR (400 MHz) 0.93 (t, J = 7.4 Hz, 3 H), 1.36 (m, 2 H), 1.55 (m, 2 H), 1.72 (s, 3 H), 2.33 (t, J = 7.4 Hz, 2 H), 3.48 (br s, 1H); ^{13}C NMR (100 MHz) 13.7, 22.3, 23.8, 24.5, 28.8, 105.2 (C(OH)), 133.6 (C=), 145.5 (CBr=), 169.5 (CO), SEFT; MS m/z (CI/NH_3) 285, 283 (M^+ + 35), 268, 266 (M^+ + 18). **25**: mp 109–115 °C (ether/pentane); IR (KBr) 3650–3000, 2958, 2929, 2870, 1729, 1645, 1218 cm^{-1}; ^1H NMR (250 MHz) 0.93 (t, J = 6.7 Hz, 3 H), 1.15–1.60 (m, 2 H), 1.70 and 1.72 (2 × s, 3 H), 2.05–2.35 (m, 2 H), 3.80 (d, J = 14.0 Hz, 1 H, OH), 4.70 (t, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz) 13.1, 21.2, 23.7/23.9, 36.8/37.0, 41.1/41.3 (CHBr), 105.0 (COH), 132.3/132.4 (C=), 146.8/147.0 (CBr=), 166.5 (CO), SEFT; MS m/z 329, 327, 325 (M^+ − 1, 0.1, 0.2, 0.1), 249 (4), 247 (4), 231 (2), 229 (3), 43 (100); MS m/z (CI/NH_3) 365, 363, 361 (M^+ + 35), 348, 346, 344 (M^+ + 18). Anal. Calcd for $C_9H_{12}Br_2O_3$: C, 32.96; H, 3.69. Found: C, 32.99; H, 3.59.

Reaction of Bromolactone 20 with Bromine and Subsequent Hydrolysis. A 1.46 M solution of bromine in CCl_4 (0.85 mL, 1.24 mmol) was added to a light-protected mixture of bromolactone **20** (188 mg, 0.81 mmol) and a catalytic amount of sodium bicarbonate in CCl_4 (5 mL). The mixture was heated at 70–75 °C for 130 h. Chloroform (15 mL) was added, and the solution was washed with water (20 mL). GC analysis of this crude product (276 mg) indicated the presence of **20** (9%), **21** (31%), **22** (19%), **23** (17%), and 4,5-dibromo-5-bromomethyl-3-butyl-2(5*H*)-furanone (**31**) (20%). Hydrolysis of this mixture using the same conditions described in the aforementioned experiment yielded a residue of 249 mg. Flash chromatography through silica gel of this material afforded several fractions, one of them containing lactone **24** (52 mg, 26% yield). Another fraction consisted in a mixture of lactones **23** and **31**. Preparative TLC of this fraction using hexane–ether (9:1) as eluent allowed the isolation of pure **23** (R_f = 0.38) and pure **31** (R_f = 0.56). **23**: mp 53–56 °C (hexane); ^1H NMR (80 MHz) 0.92 (t, J = 7.3 Hz, 3 H), 1.08–1.86 (m, 2 H), 2.05–2.54 (m, 5 H with δ 2.15, s), 4.72 (t, J = 7.7 Hz, 1 H). **31**: ^1H NMR (80 MHz) 0.92 (t, J = 6.2 Hz, 3 H), 1.12–1.86 (m, 4 H), 2.39 (t, J = 6.9 Hz, 2 H), 4.05 (d, J = 11.8 Hz, 1 H), 4.18 (d, J = 11.8 Hz, 1 H).

4-Bromo-3-(1-bromobutyl)-5-hydroxy-5-methyl-2(5*H*)-furanone (25). A stirred mixture of NBS (2.03 g, 11.4 mmol) and bromolactone **20** (1.11 g, 4.8 mmol) in anhydrous carbon tetrachloride (25 mL) was irradiated with a 500 W incandescent lamp for 5 h at such a distance to maintain the temperature of the mixture at 40–45 °C. The mixture was filtered, and the precipitate was washed with CCl_4 (3 × 10 mL). The solvent was removed to give an orange oil. This residue was dissolved in water (80 mL) and THF (60 mL) and was stirred at room temperature for 30 h. The mixture was extracted with ether (2 × 50 mL), the organic phase was washed with saturated NaCl solution and dried, and the solvent was removed at room temperature. Flash chromatography of the residue (1.65 g) through silica gel gave the following fractions: (i) tribromolactone **23** (157 mg, 0.40 mmol, 8% yield) with hexane–chloroform (1:1) as eluent; and (ii) pseudoacid **25** (1.23 g, 3.64 mmol, 76% yield) using hexane–chloroform (1:4) as eluent. Recrystallization from pentane–ether afforded pure **25** (643 mg, 1.96 mmol, 41% yield). For spectroscopic data of **25** see above.

4-Bromo-5-hydroxy-3-(1-hydroxybutyl)-5-methyl-2(5*H*)-furanone, Bromobeckerelide (2a). A light-protected mixture of lactone **25** (36 mg, 0.11 mmol) and silver nitrate (23 mg, 0.14 mmol) in water (1 mL) and THF (0.5 mL) was stirred at room temperature for 2 d. TLC analysis using hexane–ether–ethyl acetate (2:1:1) as eluent indicated the presence of starting material. Silver nitrate (23 mg, 0.14 mmol) was added and this addition was repeated after 4 and 6 d. After a week of reaction time the precipitate was filtered off and washed with THF (5 × 5 mL), and the solvent was removed to afford 118 mg of a white solid. This product was extracted with ether (3 × 1 mL) to yield a yellow oil (30 mg). Preparative TLC of this material using hexane–ether–ethyl acetate (2:1:1) as eluent allowed the isolation of two fractions: (i) R_f = 0.22 identified as bromobeckerelide (**2a**) (8 mg, 27% yield); and (ii) R_f = 0.53 identified as the nitrate of bromobeckerelide (**26**) (4 mg, 12% yield). **2a**: mp 84–87 °C (lit.[6a] 83–86 °C); IR (film) 3700–3000, 2962, 2933, 2874, 1754, 1654 cm^{-1}; ^1H NMR (80 MHz) 0.92 (t, J = 6.7 Hz, 3 H), 1.11–2.22 (m, 7 H with 2 × s at δ 1.68 and 1.72), 3.4–4.0 (br absorption, 2 H), 4.47 (t, J = 6.9 Hz, 1 H); ^{13}C NMR (100 MHz) 13.6/13.7 (CH_3), 18.57/18.61 (CH_2), 23.7/23.8 (CH_3COH), 37.6/38.0 (CH_2CHOH), 67.5/67.6 (CHOH), 105.2/105.5 (COH), 133.3/133.8 (C=), 147.3/148.2 (CBr=), 169.7 (CO); MS m/z 223, 221 (M^+ − 43, 9, 8), 205 (6), 203 (5), 177 (5), 175 (5), 43 (78), 41 (100). **26**: IR ($CHCl_3$) 3500–3100, 2971, 2935, 2888, 1768, 1643, 1280, 1240 cm^{-1}; ^1H NMR (80 MHz) 0.96 (t, J = 6.5 Hz, 3 H), 1.17–2.26 (m, 7 H with δ 1.72, s), 3.54 (br s, 1 H), 5.63 (t, J = 6.9 Hz, 1 H); MS m/z (CI/NH_3) 346, 344 (M^+ + 35), 329, 327 (M^+ + 18).

3-(1-Acetoxybutyl)-4-bromo-5-hydroxy-5-methyl-2(5*H*)-furanone (27). Dibromolactone **25** (106 mg, 0.32 mmol) was dissolved in glacial acetic acid (7 mL) in a 10 mL light-protected flask. Silver acetate (88 mg, 0.53 mmol) was added in four portions along 7 h; during this time the mixture was heated at reflux. After this period no starting material was present according to TLC analysis (hexane–ether 1:1). The mixture was neutralized (pH = 7–8) with 10% NaOH solution, the precipitate was filtered off, and the solution was extracted continuously with ether (200 mL) for 20 h. The organic phase was dried, and the solvent was removed affording an oil (72 mg). This product was purified through a silica gel column using hexane–ether (3:1) as eluent. The first fraction contained mainly (*E*)-4-bromo-3-(1-butenyl)-5-hydroxy-5-methyl-2(5*H*)-furanone (**32**) (9 mg, 11% yield), and the second contained both diastereoisomers of acetoxylactone **27** (62 mg, 62% yield). **27**: IR (film) 3600–3000, 2964, 2939, 2876, 1771, 1748, 1660, 1374, 1231, 1042, 956 cm^{-1}; ^1H NMR (400 MHz) 0.95 (t, J = 7.4 Hz, 3 H), 1.28–1.47 (m, 2 H), 1.68 and 1.69 (2 × s, 3 H), 1.83–1.98 (m, 2 H), 2.10 and 2.11 (2 × s, 3 H), 5.17 (br s, 1 H), 5.38 and 5.41 (2 × dd, J = 8.0 Hz, J = 6.2 Hz, and J = 8.1 Hz, J = 5.6 Hz, 1 H); ^{13}C NMR (100 MHz) 13.6, 18.4, 20.6/20.7 (CH_3CO), 23.5/23.8 (CH_3COH), 33.6/33.8, 69.0, 104.9/105.1 (COH), 130.7 (C=), 146.2/147.1 (CBr=), 166.1/166.5 (CO), 171.1/171.4 (CH_3CO); MS m/z (CI/NH_3) 343, 341 (M^+ + 35), 326, 324 (M^+ + 18). **32**: ^1H NMR (80 MHz) 1.07 (t, J = 7.2 Hz, 3 H), 1.71 (s, 3 H), 2.01–2.46 (m, 2 H), 3.11 (br s, 1 H), 6.04 (dt, J = 15.9 Hz, J = 1.6 Hz, 1 H), 7.15 (dt, J = 15.9 Hz, J = 6.6 Hz, 1 H).

3-(1-Acetoxybutyl)-4-bromo-5-methylene-2(5*H*)-furanone (28). A stirred and light-protected suspension of pseudoacid **27** (38 mg, 0.12 mmol) and phosphorus pentoxide (17 mg, 0.12 mmol) in anhydrous benzene (4.5 mL) was heated at 70 °C for 16 h. The insoluble material was filtered off, and the solvent was removed at room temperature. Flash chromatography of the crude product through silica gel using hexane–ether (3:1) as eluent afforded the following fractions: (i) unidentified product (7 mg); (ii) lactone **28** (26 mg, 73% yield); and (iii) starting material (2 mg). **28**: IR (film) 2966, 2938, 2875, 1778, 1743, 1651, 1616, 1370, 1230, 1025 cm^{-1}; ^1H NMR (250 MHz) 0.93 (t, J = 7.3 Hz, 3 H), 1.22–1.44 (m, 2 H), 1.73–1.99 (m, 2 H), 2.08 (s, 3 H), 5.19 (d, J = 2.9 Hz, 1 H), 5.28 (d, J = 2.9 Hz, 1 H), 5.54 (dd, J = 8.2 Hz, J = 5.7 Hz, 1 H); ^{13}C NMR (64 MHz) 13.5, 18.4, 20.5 (CH_3CO), 33.7, 68.3, 97.4 (CH_2=), 131.1, 133.0, 152.4 (CBr=), 164.9 (CO), 170.1 (CH_3CO).

(*E*)-3-(1-Acetoxybutyl)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone, Acetoxyfimbrolide, (1c, X = H, Y = Br). To a light-protected solution of lactone **28** (11.8 mg, 0.04 mmol)

in anhydrous methylene chloride (0.5 mL) containing a small amount of hydroquinone at −4 °C was added a 0.1 M solution of bromine in the same solvent (0.8 mL, 0.08 mmol). The mixture was stirred for 15 min at −4 °C and then at room temperature for 24 h. Then a 0.17 M solution of DBU in CH_2Cl_2 (0.4 mL, 0.07 mmol) was introduced at −15 °C, and stirring was continued for 1 h. Methylene chloride (10 mL) was added, and the mixture was successively washed with 5% HCl (5 mL) and saturated NaCl solution (5 mL). The organic layer was dried, the solvent was removed at room temperature, and the crude product was purified by silica gel flash chromatography using pentane−ethyl acetate (3:1) as eluent to afford 11.2 mg (75% yield) of acetoxyfimbrolide (**1c**, X = H, Y = Br): IR (film) 3085, 2973, 2938, 2882, 1782, 1743, 1651, 1609, 1230, 1033 cm^{-1}; ^1H NMR (250 MHz) 0.93 (t, J = 7.3 Hz, 3 H), 1.15−1.48 (m, 2 H), 1.71−2.07 (m, 2 H), 2.05 (s, 3 H), 5.51 (dd, J = 8.3 Hz, J = 6.1 Hz, 1 H), 6.36 (s, 1 H); ^{13}C NMR (64 MHz) 13.5, 18.4, 20.5 (CH_3CO), 33.7, 68.2, 93.3 (CHBr=), 130.5, 131.3, 149.7 (CBr=), 163.7 (CO), 170.1 (CH_3CO).

3-(1-Acetoxybutyl)-4,5-dibromo-5-bromomethyl-2(5*H*)-furanone (29). In one operation the crude product from the bromination of lactone **28** was purified by silica gel flash chromatography using pentane−ether (3:1) as eluent and yielded pure tribromolactone **29**: mp 58−62 °C; ^1H NMR (250 MHz) 0.94 (t, J = 7.3 Hz, 3 H), 1.18−1.50 (m, 2 H), 1.75−2.05 (m, 2 H), 2.09 (s, 3 H), 4.02 and 4.03 (2 × d, $J = J$ = 11.0 Hz, 1 H), 4.18 and 4.19 (2 × d, $J = J$ = 11.0 Hz, 1 H), 5.49 (t, J = 7.3 Hz, 1 H).

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Supplementary Material Available: Copies of ^1H NMR spectra of **10**, **11**, **15**, **18**, **23**, **26-29**, and **31**, and ^{13}C NMR spectra of **10**, **15**, **18**, **27**, and **28** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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