ß-Angelica Lactone Epoxide: Chemical Behaviour and some Synthetic Applications

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A new epoxy derivative of ß-angelica lactone has been synthesized. Its chemical behaviour towards nucleophiles has been explored in order to prepare natural products with a trisubstituted ß-hydroxy-γ-methylbutyrolactone-type constitution. Thus, some potential precursors have been obtained and an efficient and stereo-controlled synthesis of (±)-blastmycinone is reported.

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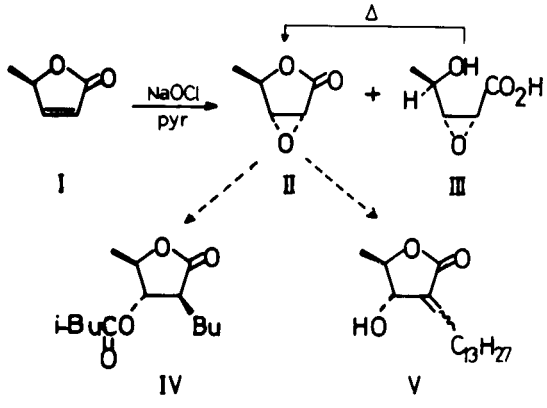
Many interesting substances posess γ-alkyl-γ-lactone structures and we have already reported syntheses of compounds, useful as pheromones and aromas, with this particular structure [1]. More specifically, the α-substituted β-hydroxy-γ-methylbutyrolactone (4-hydroxy-5-methyldihydro-2(3*H*)-furanone)-type cyclic constitution is found extensively in several classes of natural products. Epoxides have proven to be very versatile synthons in the preparation of a variety of compounds [2] and in this sense the unknown epoxy derivative of β-angelica lactone seemed an useful precursor to introduce the α-substituent in the lactone ring in a regio- and stereo-controlled manner.

β-Angelica lactone, **I**, was easily prepared from levulinic acid. Dehydration of this acid under conditions already described [3] gave β-angelica lactone. Conjugation of the double bond, upon the action of triethylamine, afforded **I** in good overall yield.

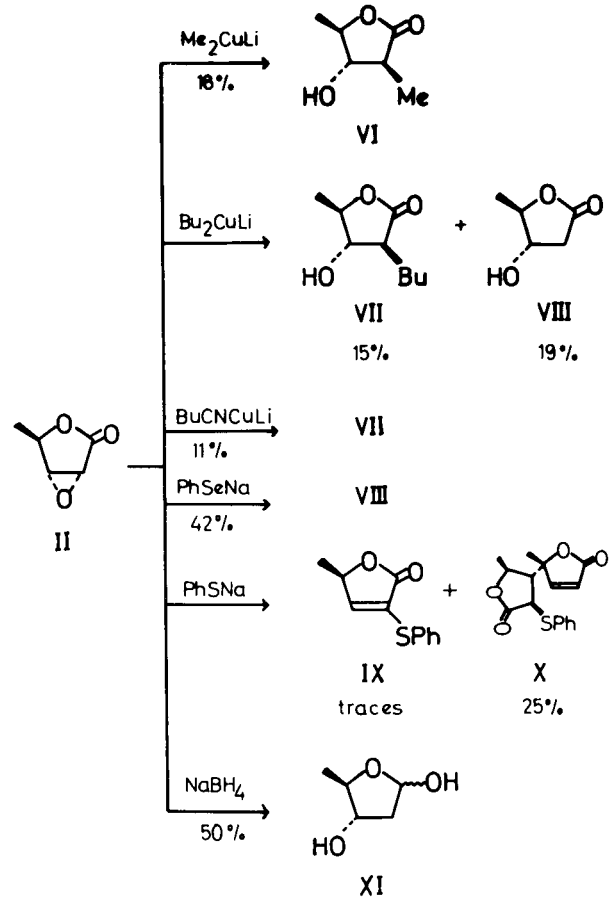
α,β-Butenolides are known to be inert to epoxidation by peracids [4] and the use of hydrogen peroxide as an oxidising agent is precluded since this requires basic conditions which are incompatible with the lactone. Nevertheless, Tishler [4] found that some γ-alkyl-α,β-butenolides gave the corresponding epoxides by the action of sodium hypochlorite in pyridine. We obtained the new epoxylactone derivative **II** by stereospecific epoxidation of β-angelica lactone, **I**, following this method [5]. The hydroxyacid **III** was also obtained along with **II**, but that compound was readily lactonized when the mixture **II** + **III** was distilled off, giving a 54% overall yield of **II** (Scheme I).

Scheme 1



Having in mind the synthesis of products such as blastmycinone, **IV**, (unnatural enantiomer shown), and litsenolides C, **V**, (Scheme 1), we decided to explore the chemical behaviour of the epoxide **II** towards several types of nucleophiles. These must be suitable to introduce alkyl chains

Scheme 2

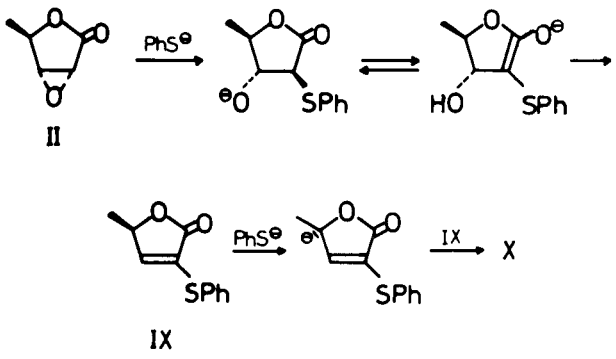


and/or to create the exocyclic double bond of litsenolides C. Some results are shown in Scheme 2. Thus, reactions with cuprates lead to the expected trisubstituted lactones **VI** and **VII**, regio- and stereo-selectively, but in very low yield and in neither case unaltered starting material was recovered.

Blastmycinolactol (3-butyl-4-hydroxy-5-methyldihydro-2(3*H*)-furanone), **VII**, [6] was obtained in 15% yield as well as 4-hydroxy-5-methyldihydro-2(3*H*)-furanone, **VIII** (19% yield), in the reaction of **II** with lithium dibutylcuprate. A similar reductive oxirane ring opening has been already reported [7] for the reactions of α,β-epoxyketones with dialkylcuprates giving β-hydroxyketones; a redox process in which Cu^{I} species are probably involved could be invoked for these kind of reactions. Furthermore, the reduction product **VIII** was also obtained as the only defined compound when **II** was made to react with sodium benzeneselenolate. Since this reagent is prepared by reduction of diphenyldiselenide with sodium borohydride, we thought that the hydride excess was responsible for the epoxide reduction. However, treatment of **II** with sodium borohydride gave the hydroxylactol **XI**, in which both epoxide and carbonyl moieties have been reduced.

On the other hand, a mixture of **IX** and **X** was obtained in 25% yield when sodium benzenethiolate was used as the nucleophile. Compound **X** was identified from spectral data (ir, pmr, cmr and ms) and its formation from **IX** in the presence of the benzenethiolate anion has been verified in a separate experiment. Compound **IX** results from regioselective oxirane ring opening followed by elimination of a hydroxyl ion (Scheme 3). Abstraction of the allylic proton in **IX** by the action of benzenethiolate gives a carbanion, which, by addition to a second mole of **IX**, leads to **X**.

Scheme 3

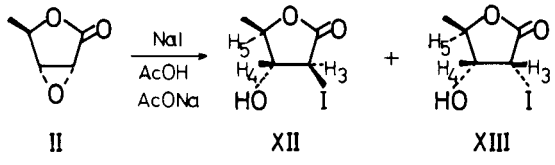


These results made us to think that the presence of the lactone carbonyl has some influence on the behaviour of this epoxide towards nucleophiles. As a matter of fact, very few examples exist in the literature on the nucleophilic ring opening of α-carbonyl oxiranes, and furthermore their behaviour is manifold. For instance, the reaction of α,β-epoxyketones with hydrides affords epoxyalcohols instead of hydroxy ketones [8]; with Grignard reagents, epoxyalcohols are also obtained in the first step, leading to diol formation if conditions permit [9]. Johnson [10] has reported the reaction of ethyl 2,3-epoxybutanoate with several nucleophiles, such as lithium dimethylcuprate, methyllithium and Grignard reagents: with lithium dimethylcuprate the expected ring opening product was obtained but on using the other reagents the desired compounds were never produced. As far as we know, no examples of nucleophilic reactions with α,β-epoxylactones had been reported.

We have carried out MNDO calculations on a variety of α-carbonyl oxiranes and found that the atomic orbital coefficients at the oxiranic carbon atoms in the LUMO are very small and therefore nucleophilic attack would be unlikely from the view point of frontier orbital theory. On the contrary, attack on the carbonyl carbon atom should be easier due to the large contribution of the atomic orbital coefficient and its actual charge. These results will be published fully elsewhere.

In contrast to the results above, epoxylactone **II** underwent reaction with excess sodium iodide in the presence of sodium acetate-acetic acid buffer [11], giving a mixture of diastereoisomeric iodides **XII** and **XIII**, in a 1:1 ratio and 94% yield (Scheme 4). These compounds were chromatographically separated and their stereochemistry was assigned by pmr using the chemical shift reagent Eu(fod)$_3$,

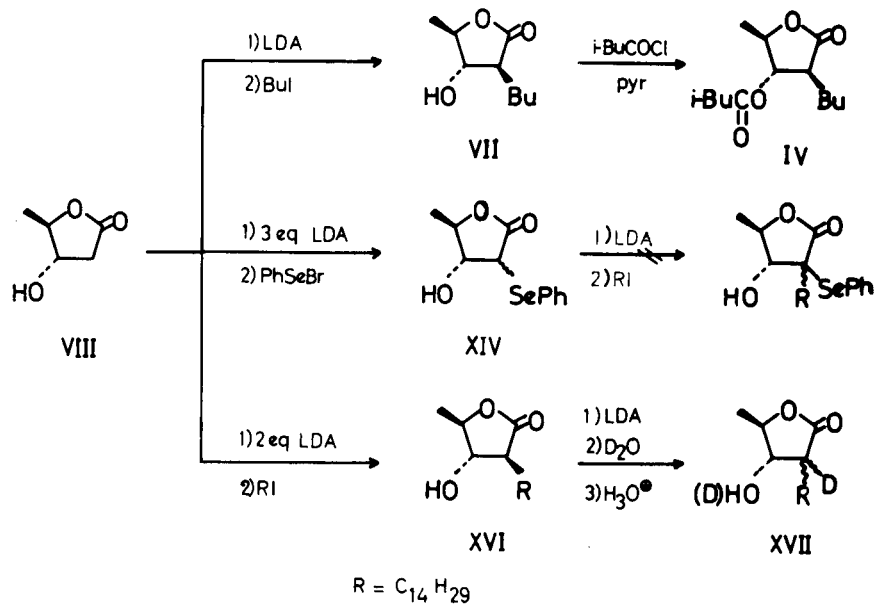
Scheme 4



based on the induced chemical shift on all the protons and considering the hydroxyl group as the main coordination center. (See experimental).

We intended to introduce groups such as phenylseleno and phenylthio by nucleophilic displacement of iodide in **XII** and **XIII**, but reaction of the mixture of iodides **XII** + **XIII** with sodium phenylselenide (1.1 equivalents) gave the hydroxylactone **VIII** in 32% yield and 17% of unaltered starting material as the only defined products (Scheme 4). Compounds **IX** and **X** were exclusively obtained when the mixture **XII** + **XIII** reacted with 1.1 equivalents of sodium benzenethiolate. The same result was found when the reaction was performed with each individual stereoisomer.

Scheme 5



Oxirane **II** was inert under several catalytic hydrogenation conditions namely 10% Pd/C, traces of acetic, hydrochloric or perchloric acids as catalysts, 3-4 atmospheres pressure and in solvents such as dimethoxyethane, ethyl acetate or ethanol. On the contrary, iodides **XII** and **XIII** were readily hydrogenolyzed leading quantitatively to the expected hydroxylactone **VIII**. Introduction of alkyl chains, PhSe, and PhS groups on this substrate should be achieved by reaction with electrophilic reagents. Thus, treatment of **VIII** with 3 equivalents of lithium diisopropyl amide gave a dianion that reacted with phenylselenyl bromide to give **XIV** in good yield (Scheme 5). In the same way, alkylation with myristyl iodide afforded stereoselectively compound **XVI** (already described [12]) and blastmycinolactol, **VII**, in 40% yield, with 40% of unaltered starting material being recovered. This moderate yield is in accordance with previous results reported in the literature [12,13] on the alkylation of β-hydroxy-γ-lactones (4-hydroxydihydro-2(3*H*)-furanones), and the method of alkylation is more convenient than direct reaction of oxirane **II** with dialkylcuprates (Scheme 2).

Introduction of a second substituent in the α-position of lactones **XIV** and **XVI** presented more problems. Thus, attempts to alkylate **XIV** did not succeed since complex mixtures were obtained in which the selenium analogs of **IX** and **X** were detected. Treatment of **XVI** with 2 equivalents of lithium diisopropyl amide followed by phenylselenyl bromide under various conditions lead to recovery of unaltered **XVI**. Difficulty in dianion formation was verified by trying to trap it with deuterated water. The ratio in deuterated product **XVII** (Scheme 5), estimated by pmr and ms, was never higher than ~25%. We concluded from these experiments that the dianion was formed very slowly and decomposes quickly under the reaction conditions even at low temperature, with the slow formation and rapid decomposition being limiting factors in obtaining the precursors of litsenolides C. Preparations of these compounds was then abandoned, since slight changes in the synthetic strategy could overlap with another synthesis published while our work was being carried out [14].

However, synthesis of (±)-blastmycinone, **IV**, was successfully achieved following the sequence which implies that hydroxylactone **VIII** is a key intermediate (Scheme 5). Thus, (±)-blastmycinolactol, **VII**, was easily esterified with isovaleryl chloride in pyridine, affording **IV** in 50% overall yield from the epoxylactone **II**. (+)-Blastmycinone is obtained from natural sources by mild saponification of antimycin A_3, one of the major components of the antibiotic antimycin A complex, which is effective against fungi and yeasts [15], and has been synthesized by several authors [6,16]. The synthetic pathway presented in this work for the racemic mixture is much more efficient than other syntheses reported recently and more practical, since our starting material is levulinic acid, a cheap and readily available substance.

EXPERIMENTAL

Melting points have been determined on a Kofler hot stage and are uncorrected. Distillation of small amounts were effected on a rotational distillator, Buchi model KRV 65/30 (only external or oven temperature

given). The 70 eV electron impact or chemical ionization mass spectra were recorded with a Hewlett-Packard apparatus, model 5985 B. The infrared spectra were recorded on a Perkin-Elmer Spectrophotometer, model 1310. The 80 MHz pmr spectra and 20 MHz cmr spectra were recorded on a Bruker Spectrometer, model WP 80 SY; chemical shifts are given in parts per million relative to TMS (δ scale).

(3*RS*,4*RS*,5*RS*)-3,4-Epoxy-5-methyldihydro-2(3*H*)-furanone (**II**).

To an ice-cooled solution of β-angelica lactone, **I**, (500 mg, 5.1 mmoles) in pyridine (22 ml) aqueous sodium hypochlorite (16.4 ml of a solution containing 55 g/l of chlorine, 12.8 mmoles) was added. The reaction mixture was stirred at 0° for 1 hour and for 1.5 hours at room temperature. Then, aqueous sodium bicarbonate (8 ml of a 1 *M* solution) was added and the resulting solution extracted with methylene chloride (35 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give 90 mg of **II**. The aqueous layer was acidified to *p*H 1 with concentrated hydrochloric acid, saturated with ammonium sulfate and extracted with six 30 ml portions of ethyl acetate, the organic phase was dried and the solvent evaporated to afford a 2:1 mixture of (2*RS*,3*RS*,4*RS*)-2,3-epoxy-4-hydroxypentanoic acid, **III** and epoxylactone **II** (430 mg). The combined crudes were distilled at 90-95°/0.1 torr giving 350 mg of **II** contaminated with some impurity. Chromatography through silica gel (3:7 methylene chloride-hexane as eluent) afforded pure **II** (315 mg, 54% yield) as a liquid, bp 115°/18 torr; ir (film): 1770 cm^{-1} (C=O); pmr (deuteriochloroform): 1.42 (d, 3H, J = 6.7 Hz), 3.79 (dd, 1H, J = 2.5, 0.7 Hz), 3.96 (d, 1H, J = 2.5 Hz), 4.69 (dq, 1H, J = 6.7, 0.7 Hz); cmr (deuteriochloroform): 17.2, 49.5, 58.5, 76.0, 170.0; ms: 114 (M^+, 26.0), 99 (4.0), 71 (9.5), 69 (100), 43 (47.0), 42 (57.4), 41 (69.8), 39 (41.4).

Anal. Calcd. for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.39; H, 5.19.

(3*RS*,4*SR*,5*SR*)- and (3*SR*,4*SR*,5*SR*)-3-Iodo-4-hydroxy-5-methyldihydro-2(3*H*)-furanone (**XII**) and (**XIII**), Respectively.

To an ice-cooled solution of **II** (510 mg, 4.47 mmoles) in acetone (40 ml), sodium iodide (6.7 g, 44.7 mmoles), sodium acetate (1.83 g, 22.4 mmoles) and acetic acid (1.3 ml, 22.4 mmoles) were successively added. The mixture was stirred for 30 minutes at 0° and 2 hours at room temperature. Then ethyl acetate (50 ml) and a 10% aqueous solution of sodium thiosulfate (20 ml) were added, the resulting mixture shaken and the layers separated. The organic layer was washed with two 15 ml portions of saturated aqueous sodium bicarbonate and with 20 ml of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed to give a crude containing a 1:1 mixture of **XII** and **XIII** (1.1 g), that was chromatographed through silica gel (mixtures of hexane-ethyl acetate as eluents), affording **XII**, mp 53-55° (from methylene chloride-pentane) and **XIII**, as a liquid that decomposes by heating (1.03 g, of **XII** + **XIII**, 94% yield). Spectral data of **XII**: ir (chloroform): 3580, 3540 (broad, OH), 1770 (C=O) cm^{-1}; pmr (deuteriochloroform): 1.59 (d, 3H, J = 6.3 Hz), 2.85-3.18 (broad, OH, 1H), 4.26-4.67 (complex absorption, 3H); cmr (deuteriochloroform): 16.9, 18.5, 82.0, 83.1, 172.7; ms: 242 (M^+, 25.1), 170 (5.6), 127 (14.5), 71 (100), 43 (21.9). Spectral data of **XIII**: ir (film): 3650-3080 (broad, OH), 1760 (C=O) cm^{-1}; pmr (deuteriochloroform): 1.50 (d, 3H, J = 6.3 Hz), 2.18-2.52 (broad, OH, 1H), 3.26 (dd, 1H, J = 6.3, 6.1 Hz), 4.32 (dq, 1H, J = 6.3 Hz), 4.75 (d, 1H, J = 6.1 Hz); cmr (deuteriochloroform): 16.8, 25.5, 73.3, 80.9, 172.5; ms: 242 (M^+, 58.2), 198 (17.1), 183 (13.2), 170 (8.9), 127 (25.5), 71 (100), 43 (21.7).

Stereochemical Assignments.

The pmr spectra of **XII** and **XIII**, respectively, in the presence of 0.1, 0.3, and 0.6 equivalents of $Eu(fod)_3$ were registered successively. Induced chemical shifts for all types of protons were plotted *vs* the number of lanthanide equivalents added, resulting straight lines whose slopes are the following: compound **XII**: 8.9 (H_3), 7.4 (H_4), 7.4 (H_5), 2.6 (Me). Compound **XIII**: 7.4 (H_3), 8.8 (H_4), 7.4 (H_5), 3.3 (Me).

Anal. (For the mixture **XII** + **XIII**). Calcd. for $C_5H_7O_3I$: C, 24.82; H, 2.92. Found: C, 24.99; H, 2.91.

(4*RS*,5*SR*)-4-Hydroxy-5-methyldihydro-2(3*H*)-furanone (**VIII**).

From the Mixture **XII** + **XIII**.

The mixture of iodides **XII** and **XIII** (85 mg, 0.35 mmoles) in 10 ml of ethyl acetate was hydrogenated at 2.6 atmospheres in the presence of potassium carbonate (97 mg, 0.70 mmoles) and 10% palladium on charcoal (15 mg). After 72 hours the mixture was filtered and the solvent removed *in vacuo*, affording 48 mg of a residue that was filtered through silica gel to give **VII** (39 mg, 96% yield) as a liquid, bp 125°/12 torr; ir (film): 3680-3020 (broad, OH), 1750 (C=O) cm^{-1}; pmr (deuteriochloroform): 1.35 (d, 3H, J = 6.2 Hz), 2.46 (dd, 1H, J = 17.9, 3.7 Hz), 2.87 (dd, 1H, J = 17.9, 6.1 Hz), 3.66-3.92 (broad, OH, 1H), 4.24 (m, 1H), 4.51 (dq, 1H, J = 6.2, 3.0 Hz); cmr (deuteriochloroform): 18.3, 37.3, 72.6, 84.4, 175.9; ms: 117 (M^+ + 1, 34.9), 99 (7.2), 88 (12.1), 71 (3.2), 57 (19.9), 45 (55), 44 (65.5), 43 (100).

Anal. Calcd. for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.50; H, 6.85.

From **II**.

To a stirred solution of diphenyldiselenide (460 mg, 1.47 mmoles) in absolute ethanol (15 ml), under argon, sodium borohydride (113 mg, 2.99 mmoles) was added in two portions. After stirring for 20 minutes, epoxylactone **II** (300 mg, 2.63 mmoles) in absolute ethanol (3 ml) was added and the mixture stirred for 3 hours at room temperature. Then 4 drops of water were added, the solution was concentrated to 2 ml, diluted with ethyl acetate (30 ml) and finally washed with water (5 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (15 ml). The combined organic layers were dried over anhydrous sodium sulfate and the solvents were removed to afford 640 mg of a residue that was chromatographed through silica gel (mixtures of methylene chloride-hexane and methylene chloride-ether as eluents) to give hydroxylactone **VIII** (128 mg, 42% yield) together with diphenyldiselenide (410 mg).

(3*RS*,4*RS*,5*SR*)-3,5-Dimethyl-4-hydroxydihydrdo-2(3*H*)-furanone (**VI**).

To a stirred suspension of cuprous iodide (725 mg, 3.95 mmoles) in anhydrous ether (8 ml) at −10°, under argon, 4.9 ml (7.84 mmoles) of a 1.6 *M* solution of methyllithium in anhydrous ether was slowly added. After 30 minutes the mixture was cooled at −20° and a solution of epoxide **II** (150 mg, 1.31 mmoles) in anhydrous ether (3 ml) was added dropwise. After stirring for 2 hours at −20° the mixture was hydrolyzed with 1*M* hydrochloric acid (10 ml), stirred for 15 minutes to reach room temperature and then filtered. The layers were separated and the aqueous layer was extracted with three 15 ml portions of ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride (10 ml) and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure to give 130 mg of a crude that was chromatographed through silica gel (mixtures of methylene chloride-hexane as eluents) to afford 75 mg of a complex mixture of unidentified products and 32 mg of **VI** (18% yield) as a liquid, bp 85°/0.15 torr: ir (chloroform): 3600, 3560-3280 (broad, OH), 1775 (C=O) cm^{-1}; pmr (deuteriochloroform): 1.21 (d, 3H, J = 7.4 Hz), 1.36 (d, 3H, J = 6.3 Hz), 1.88-2.20 (broad, OH, 1H), 2.52 (dq, 1H, J = 9.1, 7.4 Hz), 3.64 (dd, 1H, J = 9.1, 7.5 Hz), 4.12 (dq, 1H, J = 7.5, 6.3 Hz); ms (chemical ionization, isobutane): 131 (M^+ + H).

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.38; H, 7.74. Found: C, 55.25; H, 7.86.

(3*RS*,4*RS*,5*SR*)-3-Butyl-4-hydroxy-5-methyldihydro-2(3*H*)-furanone ((±)-blastmycinolactol) (**VII**).

From **VIII**.

To a stirred and ice-cooled solution of diisopropylamine (1.46 ml, 10.4 mmoles) in anhydrous tetrahydrofurane (15 ml) under argon, 7.2 ml (11.51 mmoles) of a 1.6 *M* solution of butyllithium in hexane was added dropwise. After 30 minutes the mixture was cooled to −78° and a solution of **VIII** (550 mg, 4.74 mmoles) in anhydrous tetrahydrofurane (4.5 ml) was added dropwise over a 14 minute period. The mixture was stirred at −78° for 45 minutes and then butyl iodide (1.22 g, 6.64 mmoles) in 4 ml of hexamethylphosphorotriamide and 4 ml of anhydrous tetrahydro-

furan was added. After stirring for 20 minutes at −78° and 5 hours at −40° the mixture was hydrolyzed with 11 ml of 1 *M* hydrochloric acid, allowed to reach room temperature while stirring and diluted with 80 ml of ethyl acetate. The layers were separated and the organic layer was washed twice with 15 ml portions of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the residue was chromatographed through silica gel (mixtures of hexane-ethyl acetate as eluents) to afford 230 mg of unaltered **VIII** and 286 mg of **VII** (60% yield based on the transformed starting material), mp 54-55° (from ether-pentane) (lit [6] mp 50-51°). Spectral data (ir, pmr [6], ms [16d]) for this material are consistent with those published; undescribed cmr (deuteriochloroform): 13.7, 18.2, 22.5, 28.1, 28.7, 48.7, 78.7, 80.7, 177.3.

From **II**.

a) Blastmycinolactol, **VII**, was obtained by reaction at −20° for 2 hours of epoxide II (135 mg, 1.18 mmoles) and lithium dibutylcuprate, prepared from cuprous iodide (451 mg, 2.37 mmoles) and butyllithium (3 ml of a 1.6 *M* solution in hexane, 4.8 mmoles). The crude (190 mg) was chromatographed through silica gel (mixtures of hexane-ethyl acetate as eluents) affording unaltered epoxylactone **II** (11 mg, 8% recovery), compound **VII** (31 mg, 15% yield) and hydroxylactone **VIII** (26 mg, 19% yield).

b) Compound **VII** was also prepared by reaction of epoxide **II** (150 mg, 1.32 mmoles) with lithium butyl cyanocuprate, allowing the reaction mixture to warm-up from −78° to 0° for 2 hours and maintaining it at 0° for an additional 2 hour period. The cuprate reagent was prepared at −40° from cuprous cyanide (236 mg, 2.63 mmoles) and butyllithium (1.64 ml of a 1.6 *M* solution in hexane, 2.62 mmoles). In this way, blastmycinolactol, **VII**, was obtained (27 mg, 11% yield) together with a 11% recovered starting material.

(3*RS*,4*RS*,5*SR*)-3-Tetradecyl-4-hydroxy-5-methyldihydro-2(3*H*)-furanone (**XVI**).

Working as described above for the preparation of blastmycinolactol from **VIII**, compound **XVI** was obtained in 38% yield (60% yield based on transformed starting material) from **VIII** and 1-iodotetradecane, mp 89-90° (from ethyl acetate) (lit [12] mp 91-92°). Spectral data (ir, pmr, cmr, ms) for this material are in agreement with those described in the literature [12].

3-Phenylthio-5-methyl-2(5*H*)-furanone (**IX**).

To a stirred and ice-cooled solution of the mixture of iodides **XII** + **XIII** (150 mg, 0.62 mmoles) in anhydrous dimethoxyethane (7 ml) under argon, sodium benzenethiolate (98 mg, 0.74 mmole) in 5 ml of anhydrous dimethoxyethane was added. After stirring for 1 hour at 0° and 3 hours at room temperature, water (4 drops) was added and the solvents removed. The residue was dissolved in chloroform and dried over anhydrous sodium sulfate. The solvent was evaporated affording 150 mg of a residue that was chromatographed through silica gel to give butenolide **IX** (15 mg, 12% yield), mp 71-72° (from methylene chloride-hexane); ir (film): 3080, 3060, 2980, 2920, 1755 (C=O), 1595, 1590, 1470, 1440 cm^{-1}; pmr (deuteriochloroform): 1.38 (d, 3H, J = 7.2 Hz), 5.03 (dq, 1H, J = 7.2, 2.2 Hz), 6.52 (d, 1H, J = 2.2 Hz), 7.32-7.67 (complex absorption, Ph, 5H); cmr (deuteriochloroform): 19.1, 78.7, 129.2, 129.7, 129.9, 132.5, 133.8, 145.4, 169.6; ms: 206 (M^+, 73.6), 164 (46.1), 163 (24.9), 135 (100), 105 (12.4), 91 (42.3), 77 (10), 51 (12.8), 43 (10.3).

Anal. Calcd. for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89. Found: C, 64.14; H, 4.90.

(4*RS*,5*SR*)-2,4-Dihydroxy-5-methyltetrahydrofuran (**XI**).

A mixture of epoxylactone **II** (105 mg, 0.92 mmole) and sodium borohydride (35 mg, 0.92 mmole) in absolute ethanol (5 ml) was stirred for 3 hours at room temperature. Then water was added (3 drops) and the solvent removed under vacuum without heating. The residue was dissolved in ethyl acetate (20 ml) and the solution washed with 5 ml of water. The aqueous layer was extracted with two 20 ml portions of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated and the residue (90 mg) was chromatographed through silica gel (mixtures of ethyl acetate-hexane as eluents) to give **XI** (55 mg, 50% yield) as a syrup; ir (film): 3650-3000 (broad, OH) cm^{-1}; pmr (deuteriochloroform): 1.38 (d, 3H, J = 6.2 Hz), 2.0-3.4 (complex absorption, 4H), 3.55-4.15 (complex absorption, 3H); cmr (deuteriochloroform): 20.8, 56.4, 60.0, 60.3, 65.4; ms (chemical ionization, methane): 119 ($M + H)^+$), 101 ($(\{M - H_2O_4\} + H)^+$).

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.72; H, 8.80.

(3*RS*,4*SR*,5*SR*)- and (3*SR*,4*SR*,5*SR*)-3-Phenylseleno-4-hydroxy-5-methyldihydro-2(3*H*)-furanone (**XIV**).

To a stirred solution of diisopropylamine (0.4 ml, 2.84 mmoles) in anhydrous tetrahydrofuran (3 ml) cooled at −78° under argon, 2 ml (3.2 mmoles) of a 1.6 *M* solution of butyllithium in hexane were added. After 30 minutes a solution of **VIII** (100 mg, 0.86 mmole) in anhydrous tetrahydrofurane (3.5 ml) was added dropwise and the mixture was stirred for 45 minutes. Then phenylselenyl bromide (244 mg, 1.03 mmoles) in 4 ml of anhydrous tetrahydrofurane was added. After stirring for 3 hours at −78° the mixture was hydrolyzed with 3 ml of 2 *M* hydrochloric acid, allowed to reach room temperature and diluted with ethyl acetate (50 ml). The layers were separated and the organic layer was washed with saturated aqueous sodium chloride (10 ml) and dried over anhydrous sodium sulfate. The solvents were removed at reduced pressure and the residue was chromatographed through silica gel (mixtures of methylene chloride-hexane as eluents) to afford **XIV** as a mixture of diastereoisomers that were not separated (125 mg, 53% yield), recovering 25% of unaltered **VIII** (71% yield of **XIV** based on transformed starting material). The diastereoisomeric mixture was characterized by its spectral data: ir (film): 3660-3100 (broad, OH), 1765 (C=O) cm^{-1}; pmr (deuteriochloroform): 1.36 (d, J = 6.7 Hz) and 1.41 (d, J = 6.9 Hz) (3H), 2.21-2.45 (broad, OH, 1H), 3.86-4.50 (complex absorption, 3H), 7.19-7.80 (complex absorption, 5H); ms 274 (19), 272 (M^+, 100), 270 (50.5), 269 (18.9), 268 (15.3), 158 (51.6), 157 (66.6), 156 (27.9), 155 (25.6), 115 (12.3), 77 (41.5), 71 (59.8), 51 (19.1), 43 (28.3).

Anal. Calcd. for $C_{11}H_{12}O_3Se$: C, 48.72; H, 4.46. Found: C, 49.03; H, 4.52.

(2*RS*,3*RS*,4*SR*)-3-Butyl-4-isovaleryloxy-5-methyl-2(3*H*)-furanone ((±)-blastmycinone) (**IV**).

To a stirred and ice-cooled solution of (±)-blastmycinolactol, **VII**, (118 mg, 0.69 mmole) in anhydrous pyridine (7 ml) isovaleryl chloride (0.25 ml, 2.06 mmoles) was added. After stirring for 24 hours at room temperature the mixture was poured dropwise into ice-water (20 ml) with vigorous stirring and the resulting solution was extracted with ethyl acetate (100 ml). The layers were separated and the organic layer was washed with 2 *M* hydrochloric acid, then with 15 ml of 10% aqueous sodium bicarbonate and finally with saturated sodium chloride (20 ml), and then dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the crude was chromatographed through silica gel (5:95 ethyl acetate-hexane as eluent) to afford (±)-blastmycinone (150 mg, 85% yield) as a colorles oil, bp 95-97°/0.2 torr, whose spectral characteristics (ir, pmr, ms) are identical to those described for an authentic sample [6,16d]; undescribed cmr (deuteriochloroform): 13.5, 19.2, 22.1, 22.2, 25.5, 28.7, 28.8, 43.0, 46.3, 78.4, 79.0, 172.1, 175.4.

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