Highly Diastereoselective Aldol Reactions of Cobalt-Complexed and Uncomplexed Propynals with an *O*-Silyl Ketene *O,S*-Acetal: Highly Stereoselective Total Syntheses of (±)-Blastmycinone and Its Three Diastereoisomers from 3-(Trimethylsilyl)propynal

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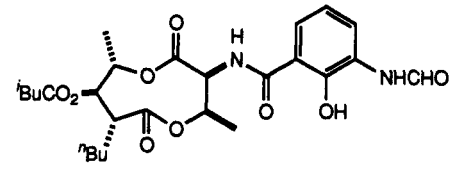
Total syntheses of (±)-blastmycinone (**2**) and its three diastereoisomers (**3–5**) are described. The syntheses involve highly stereoselective aldol reactions of cobalt-complexed propynal **6** and uncomplexed propynal **7** with *O*-silyl ketene *O,S*-acetal **8**, which possesses an *n*-butyl tether, under Mukaiyama conditions. (±)-Blastmycinone (**2**) and its 2-epimer **3** were stereoselectively synthesized through chelation-controlled reduction, whereas (±)-3-epi- and 4-epiblastmycinone (**5** and **4**) were obtained in a highly stereocontrolled manner with bromolactonization as a key step.

Introduction

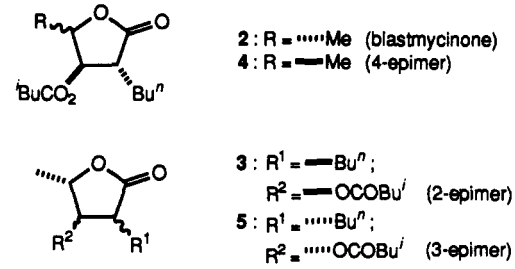
(+)-Antimycin A_3 (blastmycin, **1**) is an antibiotic isolated from a number of *Streptomyces* species[1,2] and has been shown to have antifungal activity.[1b,c,2,3] (+)-Blastmycinone (**2**)[4] has been obtained from the degradation of antimycin A_3 under mild alkaline condition. Many syntheses of both racemic[5] and optically active[6] blastmycinone (**2**) have so far been recorded. Most of the efforts have been directed toward the synthesis of blastmycinone (**2**); far less attention[5g,6b,l,m] has been given to the synthesis of its three stereoisomers **3–5**.

Recently, we have developed a highly diastereoselective aldol reaction[7] of cobalt-complexed propynal **6** (derived from the reaction of 3-(trimethylsilyl)propynal (**7**) with dicobaltoctacarbonyl) with *O*-silyl ketene *O,S*-acetals



1

(+)-Antimycin A_3 [(+)-Blastmycin]



2: R = ·····Me (blastmycinone)
4: R = ▬Me (4-epimer)

3: R^1 = ▬Bu^n; R^2 = ▬OCOBu^i (2-epimer)
5: R^1 = ·····Bu^n; R^2 = ·····OCOBu^i (3-epimer)

Figure 1.

resulting in the exclusive formation of the *syn*-aldol products. In contrast to **6**, uncomplexed propynal **7** has been shown to serve as a suitable substrate for the *anti*-selective aldol reaction with *O*-silyl ketene *O,S*-acetals. These highly stereoselective aldol reactions have been successfully applied to the synthesis of β-lactam antibiotics (±)-PS-5 and (±)-6-epi-PS-5.[7]

In this paper, we describe another successful example of the application of our newly developed aldol reactions to an efficient and highly diastereoselective assembly of all four possible stereoisomers of (±)-blastmycinone (**2–5**) in racemic form from 3-(trimethylsilyl)propynal (**7**).

Results and Discussion

Our strategy for the total syntheses of (±)-blastmycinone (**2**) and its three stereoisomers **3–5** was mainly based on the aldol reactions[7] of *O*-silyl ketene *O,S*-acetals with either cobalt-complexed propynal **6**[8,9] or uncomplexed propynal

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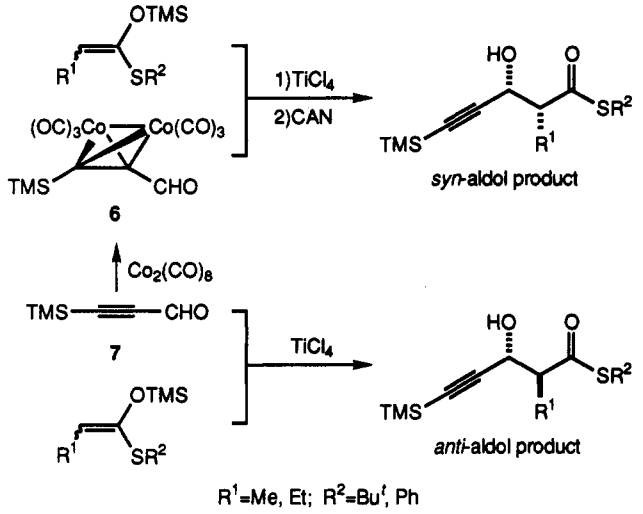
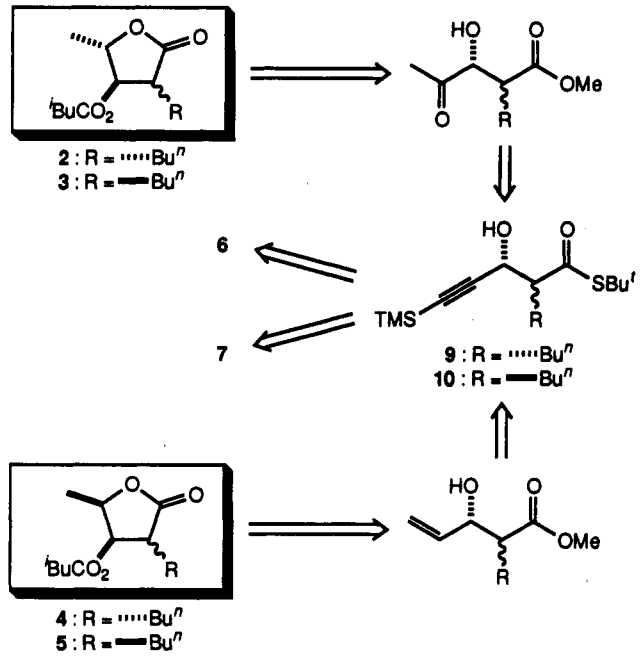
Scheme I



Scheme II



7. Aldol reaction of cobalt-complexed propynal **6** would afford *syn*-aldol condensation product **9**, and uncomplexed propynal **7**, the corresponding *anti*-aldol product **10** in a stereoselective manner. By taking advantage of the hydroxy functionality at the β-stereogenic center of aldol products **9** and **10**, we expected that hydration of the acetylenic moiety, followed by chelation-controlled stereoselective reduction,[10] would lead to the skeleton of blastmycinone (**2**) and the 2-epimer **3**, respectively, with the proper stereochemistry. Alternatively, we expected successive half-reduction of the triple bonds of **9** and **10** to the double bonds and hydroxy group-directed halolactonization[11] to provide the γ-lactones corresponding to the 4-epimer **4** and the 3-epimer **5**, respectively.

Our first concern and the most significant requirement for our diastereoselective syntheses of (±)-blastmycinone (**2**) and stereoisomers **3–5** obviously was the stereoselectivity of the aldol reactions of **6** and **7** with *O*-silyl ketene *O,S*-acetal **8**. Compound **8** was prepared from *S-tert*-butyl hexanethioate according to Gennari's procedure.[12] The ratio of (*Z*)- to (*E*)-**8** was estimated to be 91:9 on the basis of an analysis of its ^{1}H NMR spectrum according to the literature precedent.[12] The aldol reaction was carried out as follows. A solution of cobalt-complexed propynal **6** and *O*-silyl ketene *O,S*-acetal **8** in dry methylene chloride (CH_2Cl_2) was treated at −78 °C with titanium(IV) tetrachloride ($TiCl_4$) in CH_2Cl_2 to provide the aldol product. Exposure of the aldol product to cerium(IV) ammonium nitrate (CAN)[13] in methanol at 0 °C removed the cobalt moiety and produced exclusively *syn*-product **9** in 89% yield. *Anti*-isomer **10** was not detected in the ^{1}H NMR spectrum. The reaction of uncomplexed propynal **7** with *O*-silyl ketene *O,S*-acetal **8**, performed under conditions similar to those described for **6**, except for CAN treatment[13] furnished the corresponding *anti*-product **10** in a highly stereoselective manner (**9**/**10** = 3:97) in 91% yield. The stereochemical assignment[14] of aldol condensation products **9** and **10** was made by comparison of the chemical shifts of the propynyl protons as well as the magnitude of the coupling constant between the α and β protons in the ^{1}H NMR spectra.

As mentioned earlier (Scheme I), we have already disclosed that the reaction[7] of cobalt-complexed propynal **6** with *O*-silyl ketene *O,S*-acetals (R^1 = Me, Et) proceeded in a highly stereoselective manner to give the *syn*-aldol products exclusively. However, when R^1 on the double bond of the *O,S*-acetal was changed to a branched tether such as an isopropyl group, starting aldehyde **6** was recovered completely. In the reaction between uncomplexed propynal **7** and the isopropyl-substituted *O,S*-acetal, a considerable decrease in the *anti* selectivity was observed. In marked contrast to these results, the aldol reactions of **6** and **7** with the *O,S*-acetal **8**, which has a larger but unbranched *n*-butyl group on its double bond, provided aldol condensation products **9** and **10** in a highly stereoselective manner. This result strongly indicates that the aldol reactions of **6** and **7** with the *O,S*-acetal can be generally applicable to stereoselective carbon–carbon bond construction as long as the *O,S*-acetal does not have branched substituents on its vinylic moiety.

With *syn*- and *anti*-aldol products **9** and **10** in hand, we turned our endeavor to an efficient and convenient transformation of **9** and **10** into (±)-blastmycinone (**2**) and isomers **3–5**. We first attempted to convert *syn*-aldol product **9** to (±)-**2** in a stereoselective way. In order to remove the terminal trimethylsilyl (TMS) group,[15] **9** was treated with potassium carbonate in methanol at ambient temperature for 2.5 h to afford desilylated product **11** along with isomerized *anti*-product **12** (66%; **11**/**12** = 90:10), both of which had a methyl ester functionality instead of a *tert*-butyl thioester moiety. Upon treatment with sodium methoxide in methanol at 40 °C for 2 h, **9** gave **11** and a very small amount of **12** (**11**/**12** = 98:2) in 80% yield. The unexpected transesterification that occurred under the mild condition could be explained in terms of the intermediacy of β-lactone **A**, which could have arisen from

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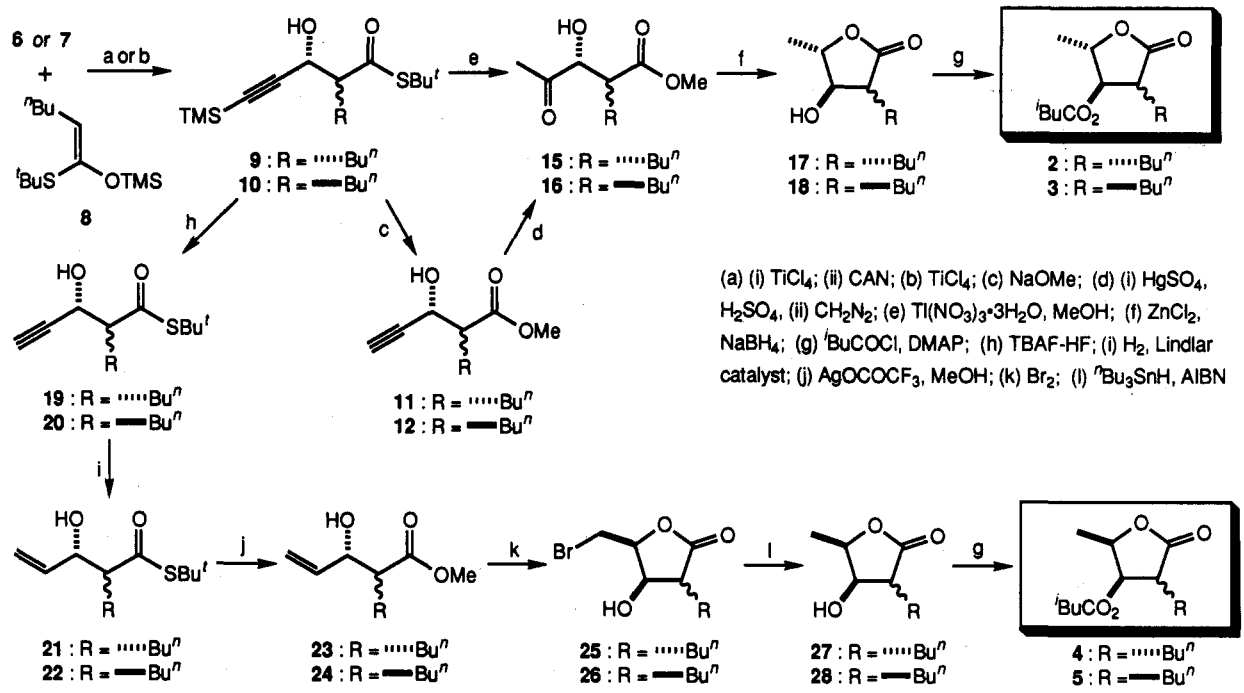
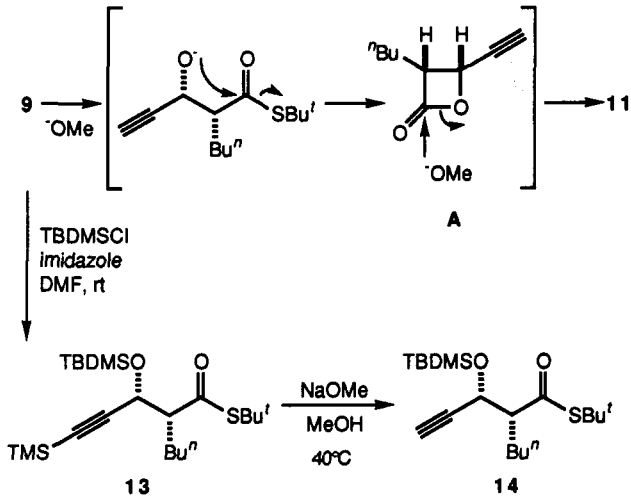
Scheme III



Scheme IV



an intramolecular participation of the free β-hydroxy group as the corresponding hydroxy anion (Scheme IV). Solvolytic cleavage of β-lactone **A** with methoxide anion would result in **11**. This interpretation was supported by the fact that when *O-tert*-butyldimethylsilyl (TBDMS) derivative **13** obtained from **9** was exposed to sodium methoxide in methanol at 40 °C, only the corresponding desilylated compound **14** with the thioester moiety intact was obtained.

Methyl ester **11** thus obtained was hydrated with mercury sulfate[16] and sulfuric acid in aqueous tetrahydrofuran (THF) to furnish, after chromatographic purification, pure γ-keto ester **15** in 76% yield. The isomerization observed during the conversion of **9** to **11** with potassium carbonate and methanol seemed to be mostly supressed by the use of sodium methoxide. However, the ratio of **11** to **12** was sensitive to the reaction time, the reaction temperature, and/or the concentration of sodium methoxide. The above procedure was so capricious that we had difficulty reproducing the results in spite of several attempts. Therefore, we searched for a more reliable, efficient, and convenient alternative for getting γ-keto ester **15**. Treatment of *syn*-aldol product **9** with thallium trinitrate (TTN)[17] in methanol at room temperature effected desilylation, hydration, and transesterification to give straightforwardly **15** as the sole product in 50% yield. Although the chemical yield for this transformation was moderate, the above one-pot procedure was far superior to the stepwise route because exposure of the isomerizable *syn*-aldol product to an alkaline medium could be avoided.

β-Hydroxy-γ-keto ester **15** was reduced with zinc borohydride[10,18] in ether to give the diols, which, when treated with 10% hydrochloric acid solution, afforded (±)-blastmycinolactol (**17**)[5,6] together with 4-epiblastmycinolactol (**27**).[5g,6b,l,m] The ratio of **17** to **27** could not be determined directly because the protons of the two compounds resonated closely to each other in the ^{1}H NMR spectra. Conversion of the mixture of **17** and **27** into the corresponding isovaleryl derivatives, (±)-blastmycinone (**2**)[5,6] and 4-epiblastmycinone (**4**),[5g,6b,l,m] allowed us to use ^{1}H NMR to determine the ratio of **2** to **4** to be 88:12. The ratio indicated that reduction of **15** with zinc borohydride had proceeded in an *anti*-selective manner.[10] The chelation-controlled conditions reported recently by Oshima and Utimoto[19] also worked well for our purpose. The best selectivity (**17**/**27** = 90:10) was achieved when zinc chloride/sodium borohydride in methanol was employed. In this case, the stereoselective *anti*-reduction was followed by a spontaneous cyclization that occurred without the addition of 10% hydrochloric acid. Manganese(II) chloride[19] and calcium chloride[19] could also be employed instead of zinc chloride (see Experimental Section). Pure (±)-blastmy-

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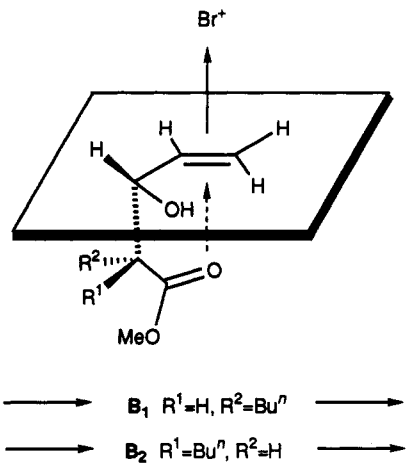
cinolactol (17), obtained from recrystallization of a mixture of 17 and 27, was acylated with isovaleryl chloride and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2 to give (±)-blastmycinone (2)[5,6] in 71% yield.

The method used for the synthesis of 2 from 9 (Scheme III) was used to prepare 3 from *anti*-aldol product 10. The reaction of 10 with TTN[17] in methanol provided β-hydroxy-γ-keto ester 16 in 55% yield, which was subsequently reduced under chelation-controlled conditions with zinc chloride/sodium borohydride[19] to yield exclusively 3,4-*trans*-γ-lactone 18 in 65% yield. Finally, isovalerylation of 18 furnished the desired 2-epiblastmycinone (3)[5g,6b,l,m] in 87% yield. It is noteworthy that reduction of the β-hydroxy-γ-keto ester functionality of 16 was completely stereocontrolled and gave 18 exclusively. The corresponding *syn*-isomer could not be detected in the reaction mixture. The 3,4-*trans*-stereochemistry on the skeleton of the γ-lactones could be constructed stereoselectively by means of chelation-controlled reduction of β-hydroxy-γ-keto esters 15 and 16, derived from aldol products 9 and 10, regardless of the stereochemical relationship between the α- and β-positions in the starting aldol products.

We next transformed aldol products 9 and 10 into 4-epiblastmycinone (4) and 3-epiblastmycinone (5), respectively. The crucial step for the syntheses of 4 and 5 was a highly stereoselective bromolactonization of olefin-ester derivatives 23 and 24. Scheme III shows the protocol for the preparation of 4 and 5. Exposure of *syn*-aldol product 9 to tetra-*n*-butylammonium fluoride (TBAF) in THF removed the TMS group[15] and afforded 19 in 82% yield. Half-reduction of the triple bond of 19 in the presence of Lindlar catalyst left 21. The thioester moiety of 21 was converted into the methyl ester with silver(I) trifluoroacetate[20,21] in methanol to produce 23 in 56% overall yield. Similar sequences for *anti*-aldol product 10 afforded methyl ester 24 in 48% overall yield from 10.

Stereoselective formation of the 3,4-*cis*-γ-lactone structure was realized by treatment of 23 with bromine in chloroform[11] to provide 25 in 57% yield. Complete stereocontrol of the newly generated stereogenic center (the C-4 position of the γ-lactone ring) was attained. The hydroxy group-directed bromolactonization of *anti*-aldol derivative 24 was also highly stereoselective and gave 3,4-*cis*-γ-lactone 26 in 59% yield. These *cis*-selectivity of these bromolactonizations could be tentatively rationalized in analogy to literature precedents[11,22] (see Scheme V). The conformations with planar allylic hydroxy groups (B_1 and B_2) would be susceptible to electrophilic attack from the face of the π-bond *syn* to the allylic hydrogen. In conformers B_1 and B_2, the tether (the nucleophilic part) would be constrained to reside in a nearly ideal position for antiperiplanar attack on the activated π-bond. Antiperiplanar attack would lead to 3,4-*cis*-γ-lactone derivatives 25 and 26, respectively (Scheme V). It should be stated that the high *cis*-stereoinduction observed depends only on the stereogenic center at the allylic position. Debromination of 25 and 26 with tributyltin hydride[23] and 2,2′-azobis(isobutyronitrile) (AIBN), followed by acylation, afforded 4-epiblastmycinone (4)[5g,6b,l,m] and

Scheme V



3-epiblastmycinone (5)[5g,6b,l,m] in 84 and 83% overall yields, respectively.

Conclusion

The aldol reaction of cobalt-complexed aldehyde 6 with *O*-silyl ketene *O*,*S*-acetal 8 having an *n*-butyl appendage gave *syn*-aldol product 9, whereas uncomplexed aldehyde 7 yielded *anti*-aldol product 10 in a highly stereoselective manner. (±)-Blastmycinone (2) and its 2-epimer 3 could be stereoselectively synthesized from aldol products 9 and 10 through highly stereocontrolled reductions carried out under chelation-controlled conditions. Alternatively, the exclusive formation of (±)-4-epiblastmycinone (4) and 3-epiblastmycinone (5) from aldol products 9 and 10 was realized via a hydroxy group-directed bromolactonization. Since 6 can be easily prepared from parent propynal 7 by simple treatment with dicobaltoctacarbonyl, the present syntheses amount to highly stereoselective divergent syntheses of (±)-blastmycinone (2) and all its possible stereoisomers (3–5) from 3-(trimethylsilyl)propynal (7).

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer in $CHCl_3$; mass spectra (MS) and high resolution mass spectra (HRMS) with a Hitachi M-80 mass spectrometer; ^1H NMR spectra with a JEOL JNM-GX 500 spectrometer in $CDCl_3$ with either tetramethylsilane as an internal standard for compounds without a silyl group or $CHCl_3$ (7.26 ppm) for compounds possessing a silyl group; ^{13}C NMR spectra with a JEOL JNM-GX 500 spectrometer in $CDCl_3$ with $CDCl_3$ (77.00 ppm) as an internal standard. All *J* values are in hertz. CH_2Cl_2 was freshly distilled from calcium hydride, and THF from sodium diphenylketyl, prior to use. Aldol reactions were performed in oven-dried glassware under an inert atmosphere of nitrogen. Silica gel (silica gel 60, 230–400 mesh, Nacalai Tesque) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4. *O*-Silyl ketene *O*,*S*-acetal 8 was prepared according to Gennari's procedure.[12] Cobalt-complexed propynal 6 was synthesized from 3-(trimethylsilyl)propynal (7)[24] by our method.[8] Zinc borohydride[18] was prepared from zinc chloride and sodium borohydride in dry diethyl ether.

***S*-*tert*-Butyl (2*R**,3*R**)-2-Butyl-3-hydroxy-5-(trimethylsilyl)-4-pentynethioate (9).** To a solution of 6 (3.3 g, 8.0 mmol) and 8 (4.2 g, 16 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C was added dropwise a solution of $TiCl_4$ in dry CH_2Cl_2 (1.0 M solution; 9.6 mL, 9.6 mmol). The reaction mixture was kept at −78 °C for 30 min with stirring until the starting propynal (6) (monitored by

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TLC) was consumed, and then the reaction was quenched with saturated ammonium chloride solution (1.0 mL). The reaction mixture was washed with water and brine, dried, and concentrated. The residue was dissolved in methanol (50 mL), the MeOH solution was cooled to 0 °C, and CAN (18 g, 34 mmol) was added portionwise. Stirring was continued for 30 min (monitored by TLC), and the methanol was evaporated off. The residue was diluted with water and extracted with ethyl acetate three times. The combined ethyl acetate layers were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane/ethyl acetate (50/1) gave aldol product **9** (2.2 g, 89%) as a colorless oil: MS *m/z* 315 ($M^+ + 1$, 0.2), 258 (29), 127 (18), 107 (18), 99 (50), 73 (82), 57 (100); IR 3470 (OH), 2170 (C≡C), 1660 (C=O) cm^{-1}; ^1H NMR δ 4.51 (t, 1H, *J* = 5.4 Hz, propynyl H), 2.66 (ddd, 1H, *J* = 5.4, 5.4, 8.8 Hz, CHCO), 2.58 (d, 1H, *J* = 5.4 Hz, OH), 1.84–1.21 (m, 6H, CH_2), 1.46 (s, 9H, *t*-Bu), 0.89 (t, 3H, *J* = 7.3 Hz, CH_3), 0.15 (s, 9H, TMS); ^{13}C NMR δ 202.34, 103.80, 90.90, 63.75, 59.78, 48.53, 29.69, 29.44, 27.70, 22.55, 13.77, –0.24. Anal. Calcd for $C_{16}H_{30}O_2SSi$: C, 61.09; H, 9.61. Found: C, 61.49; H, 9.82.

***S*-*tert*-Butyl (2*R**,3*S**)-2-Butyl-3-hydroxy-5-(trimethylsilyl)-4-pentynethioate (10).** To a solution of aldehyde **7** (1.2 g, 9.5 mmol) and **8** (4.9 g, 19 mmol) in dry CH_2Cl_2 (15 mL) at –78 °C was added dropwise a solution of $TiCl_4$ in CH_2Cl_2 (1.0 M solution; 12 mL, 12 mmol). The reaction mixture was stirred at –78 °C for 30 min, quenched with saturated ammonium chloride solution (1.0 mL), and diluted with water. The reaction mixture was extracted with CH_2Cl_2 three times, and the organic layers were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane/ethyl acetate (50/1) gave a mixture of aldol products **9** and **10** (2.7 g, 91%, **9**/**10** = 3:97). *Anti*-product **10** could be easily purified by column chromatography. **10**: a colorless oil; MS *m/z* 315 ($M^+ + 1$, 1.0), 258 (29), 181 (16), 165 (16), 107 (21), 99 (35), 73 (61), 57 (100); IR 3470 (OH), 2160 (C≡C), 1650 (C=O) cm^{-1}; ^1H NMR δ 4.41 (dd, 1H, *J* = 6.4, 8.3 Hz, propynyl H), 2.84 (d, 1H, *J* = 8.3 Hz, OH), 2.68 (ddd, 1H, *J* = 6.4, 6.4, 8.3 Hz, CHCO), 1.77–1.22 (m, 6H, CH_2), 1.47 (s, 9H, *t*-Bu), 0.89 (t, 3H, *J* = 7.3 Hz, CH_3), 0.16 (s, 9H, TMS); ^{13}C NMR δ 203.43, 104.68, 90.62, 63.86, 59.24, 48.68, 29.69, 29.45, 28.97, 22.47, 13.74, –0.23; HRMS calcd for $C_{16}H_{31}O_2SSi$ 315.1813, found 315.1839.

Methyl (2*R,3*R**)-2-Butyl-3-hydroxy-4-pentynoate (11).** To a solution of **9** (74 mg, 0.24 mmol) in methanol (5 mL) was added sodium methoxide (1.0 M solution, 0.75 mL, 0.75 mmol). The reaction mixture was heated at 40 °C for 2 h. Methanol was evaporated off, and the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane/ethyl acetate (3/1) to afford a mixture of **11** and **12** (35 mg, 80%, **11**/**12** = 98:2). **11**: a colorless oil; MS *m/z* 183 ($M^+ - H$, 0.4), 130 (50), 98 (13), 87 (100), 79 (5.7), 69 (7.7), 55 (33); IR 3450 (OH), 3310 (HC≡), 2110 (C≡C), 1720 (C=O) cm^{-1}; ^1H NMR δ 4.57 (ddd, 1H, *J* = 2.4, 5.4, 6.8 Hz, propynyl H), 3.75 (s, 3H, OCH_3), 3.14 (d, 1H, *J* = 6.8 Hz, OH), 2.68 (ddd, 1H, *J* = 5.4, 5.4, 8.8 Hz, CHCO), 2.49 (d, 1H, *J* = 2.4 Hz, HC≡C), 1.86–1.24 (m, 6H, CH_2), 0.91 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C NMR δ 174.05, 82.16, 73.92, 62.86, 51.87, 51.13, 29.47, 27.36, 22.48, 13.77. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.18; H, 8.69. A mixture of **11** and **12** (19 mg, 66%, **11**/**12** = 90:10) was obtained when **9** (49 mg, 0.15 mmol) was treated with a saturated methanolic K_2CO_3 solution (5 mL).

Methyl (2*R,3*S**)-2-Butyl-3-hydroxy-4-pentynoate (12).** Similar treatment of **10** (310 mg, 1.0 mmol) with sodium methoxide (1.0 M methanol solution, 3.0 mL, 3.0 mmol) gave a mixture of **11** and **12** (130 mg, 71%, **11**/**12** = 5:95). Recrystallization of a mixture of **11** and **12** from hexane afforded pure **12** (117 mg, 64%) as a colorless solid: mp 40–42 °C; MS *m/z* 185 ($M^+ + 1$, 3.6), 130 (100), 101 (25), 87 (98), 79 (11), 69 (13), 55 (68); IR 3460 (OH), 3310 (HC≡), 2110 (C≡C), 1715 (C=O) cm^{-1}; ^1H NMR δ 4.49 (dt, 1H, *J* = 2.0, 7.8 Hz, propynyl H), 3.75 (s, 3H, OCH_3), 3.13 (d, 1H, *J* = 7.8 Hz, OH), 2.67 (ddd, 1H, *J* = 5.9, 7.8, 8.8 Hz, CHCO), 2.50 (d, 1H, *J* = 2.0 Hz, HC≡C), 1.81–1.15 (m, 6H, CH_2), 0.90 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C NMR δ 174.85, 82.87, 73.83, 62.95, 51.86, 51.83, 29.11, 28.72, 22.39, 13.75; HRMS calcd for $C_{10}H_{17}O_3$ 185.1177, found 185.1179. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.95; H, 8.50.

***S*-*tert*-Butyl (2*R**,3*R**)-2-Butyl-3-[(*tert*-butyldimethylsilyl)oxy]-5-(trimethylsilyl)-4-pentynethioate (13).** To a solution of **9** (100 mg, 0.34 mmol) and imidazole (27 mg, 0.40 mmol) in DMF at rt was added a solution of *tert*-butyldimethylsilyl chloride (120 mg, 0.77 mmol) in DMF. After stirring for 3 h, the reaction mixture was diluted with water and extracted with ether. The extracts were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane/CH_2Cl_2 (20/1) afforded silyl ether **13** (130 mg, 87%) as a colorless oil; MS *m/z* 429 ($M^+ + 1$, 6.2), 371 (36), 315 (100), 241 (25), 73 (46), 57 (53); IR 2160 (C≡C), 1660 (C=O) cm^{-1}; ^1H NMR δ 4.40 (d, 1H, *J* = 7.8 Hz, propynyl H), 2.66 (ddd, 1H, *J* = 3.9, 7.8, 10 Hz, CHCO), 1.78–1.17 (m, CH_2), 1.46 (s, 9H, *t*-BuS), 0.89 (s, 9H, *t*-BuSi), 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 0.14 (s, 9H, CH_3Si), 0.13 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si); ^{13}C NMR δ 201.09, 105.37, 90.51, 64.50, 61.39, 48.02, 29.74, 29.24, 28.51, 25.74, 22.60, 18.22, 13.82, –0.28, –4.44, –5.05. Anal. Calcd for $C_{22}H_{44}O_2SSi_2$: C, 61.62; H, 10.34. Found: C, 62.01; H, 10.40.

***S*-*tert*-Butyl (2*R**,3*R**)-2-Butyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-pentynethioate (14).** According to the procedure described for the preparation of **11** from **9**, **13** (40 mg, 0.09 mmol) was treated with sodium methoxide (1.0 M methanol solution; 0.30 mL, 0.30 mmol) to give **14** (27 mg, 80%) as a colorless oil; IR 3310 (HC≡), 2110 (C≡C), 1660 (C=O) cm^{-1}; ^1H NMR δ 4.45 (dd, 1H, *J* = 2.0, 7.8 Hz, propynyl H), 2.69 (ddd, 1H, *J* = 4.4, 7.8, 9.8 Hz, CHCO), 2.44 (d, 1H, *J* = 2.0 Hz, HC≡C), 1.75–1.21 (m, 6H, CH_2), 1.46 (s, 9H, *t*-BuS), 0.89 (s, 9H, *t*-BuSi), 0.89 (t, 3H, *J* = 7.3 Hz, CH_3), 0.14 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si); ^{13}C NMR δ 200.90, 83.36, 73.83, 63.94, 61.04, 48.20, 29.69, 29.25, 28.51, 25.68, 22.64, 18.14, 13.82, –4.55, –5.20. Anal. Calcd for $C_{19}H_{36}O_2SSi$: C, 63.99; H, 10.17. Found: C, 63.64; H, 9.99.

Methyl (2*R,3*R**)-2-Butyl-3-hydroxy-4-oxopentanoate (15). Method A**: A solution of **11** (480 mg, 2.6 mmol) in THF (15 mL) was added to a solution of mercury(II) sulfate (460 mg, 1.5 mmol) and sulfuric acid (150 mg, 1.5 mmol) in water (10 mL) at ambient temperature. After stirring for 40 min at rt, the reaction mixture was extracted with chloroform. The extract was washed with water, and brine, dried, and concentrated to dryness. The residue was dissolved in ether, to which a solution of diazomethane in ether was added. The reaction mixture was allowed to stand at room temperature for 10 min, and then the yellow solution was concentrated to dryness. The residue was chromatographed with hexane/ethyl acetate (5/1) to provide **15** (390 mg, 76%) as a colorless oil. **Method B**: To a solution of **9** (31 mg, 0.10 mmol) in methanol (1.5 mL) was added $Tl(NO_3)_3 \cdot 3H_2O$ (73 mg, 0.17 mmol). The reaction mixture was stirred for a day. The precipitates were filtered off by suction, and the filtrate was concentrated. The residue was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated to leave a residue, which was chromatographed with hexane/ethyl acetate (5/1) to afford **15** (9.8 mg, 50%) as a colorless oil: IR 3460 (OH), 1710 (C=O) cm^{-1}; ^1H NMR δ 4.45 (dd, 1H, *J* = 3.9, 4.9 Hz, C*H*OH), 3.75 (s, 3H, OCH_3), 3.62 (d, 1H, *J* = 4.9 Hz, OH), 2.81 (ddd, 1H, *J* = 3.9, 3.9, 10 Hz, CHCOO), 2.26 (s, 3H, CH_3CO), 1.92–1.15 (m, 6H, CH_2), 0.88 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C NMR δ 208.23, 173.82, 77.65, 52.00, 48.18, 29.86, 25.99, 25.96, 22.48, 13.74.

Methyl (2*R,3*S**)-2-Butyl-3-hydroxy-4-oxopentanoate (16).** According to method B described for the preparation of **15** from **9**, **16** (8.2 mg, 55%) was obtained by treatment of **10** (23 mg, 0.07 mmol) with $Tl(NO_3)_3 \cdot 3H_2O$ (49 mg, 0.11 mmol). γ-Keto ester **16** was obtained as a colorless oil: IR 3480 (OH), 1710 (C=O) cm^{-1}; ^1H NMR δ 4.14 (dd, 1H, 2.9, 6.8 Hz, C*H*OH), 3.74 (d, 1H, *J* = 6.8 Hz, OH), 3.65 (s, 3H, OCH_3), 2.94 (ddd, 1H, *J* = 2.9, 7.3, 7.3 Hz, CHCOO), 2.29 (s, 3H, CH_3CO), 1.98–1.31 (m, 6H, CH_2), 0.93 (t, 1H, *J* = 7.3 Hz, CH_3); ^{13}C NMR δ 208.81, 173.33, 77.37, 51.75, 47.73, 29.57, 27.96, 25.62, 22.46, 13.82.

(2*R,3*R**,4*S**)-2-Butyl-3-hydroxy-4-methyl-4-butanolide (Blastmycinolactol, 17).** To a solution of **15** (360 mg, 1.8 mmol) in methanol (20 mL) at rt was added zinc chloride (490 mg, 3.6 mmol). After the reaction mixture stirred for 1.5 h, sodium borohydride (210 mg, 5.4 mmol) was added to the methanol solution at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then the methanol was evaporated off to leave a residue, which was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried, and

concentrated to dryness. Chromatography of the residue with hexane/ethyl acetate (7/1) provided a mixture of **17** and **27** (210 mg, 66%, **17**/**27** = 90:10). Recrystallization of the mixture of **17** and **27** from ether/hexane afforded pure **17** (180 mg, 56%) as a colorless solid: mp 55–56 °C (lit.[6m] mp 49.5–50.5 °C); MS *m/z* 172 (M^+, 1.6), 116 (100), 99 (63), 82 (44), 71 (33), 57 (96); IR 3400 (OH), 1760 (C=O) cm^{-1}; ^1H NMR δ 4.21 (quinlike, 1H, J = 6.4 Hz, C_4-H), 3.85 (ddd, 1H, J = 5.9, 6.8, 8.8 Hz, C_3-H), 2.56 (ddd, 1H, J = 5.9, 7.3, 8.8 Hz, C_2-H), 2.25 (d, 1H, J = 5.9 Hz, OH), 1.92–1.28 (m, 6H, CH_2), 1.45 (d, 3H, J = 6.4 Hz, C_4-CH_3), 0.93 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 176.76, 80.28, 78.78, 48.57, 28.75, 28.09, 22.57, 18.17, 13.78. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.63; H, 9.24. A mixture of **17** and **27** (89:11) was obtained from the reaction of **15** (30 mg, 0.15 mmol) with $MnCl_2$ (38 mg, 0.30 mmol) and sodium borohydride (42 mg, 1.1 mmol). Isovalerylation of a mixture of **17** and **27** afforded **2** and **3** (24 mg, 63% from **15**, **2**/**3** = 89:11). Rather low selectivity [**17**/**27** = 68:32, 31% (after conversion to **2** and **3**)] was observed when **15** was treated with $CaCl_2$ instead of $ZnCl_2$. The reaction of **15** with $Zn(BH_4)_2$[18] was carried out as follows. To a solution of **15** (30 mg, 0.15 mmol) in ether (3 mL) at 0 °C was added a solution of $Zn(BH_4)_2$ in ether (0.06 M solution; 2.4 mL, 0.15 mmol). After stirring for 30 min, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried and evaporated off. The residue was dissolved in methanol (5 mL), and 10% hydrochloric acid (one drop) was added to the methanol solution at rt. The reaction mixture was allowed to stand for 20 min and concentrated to dryness. The residue was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane/ethyl acetate (5/1) provided a mixture of **17** and **27** (88:12, 22 mg, 85%).

(2*R,3*S**,4*R**)-2-Butyl-3-hydroxy-4-methyl-4-butanolide (2-Epiblastmycinolactol, 18).** According to the procedure described for the preparation of **17**, **16** (29 mg, 0.14 mmol) was treated with zinc chloride (56 mg, 0.41 mmol) and sodium borohydride (40 mg, 1.1 mmol) to provide lactone **18** (16 mg, 65%) as a colorless oil: MS *m/z* 173 (M^+ + 1, 100), 172 (M^+, 3.2), 116 (93), 99 (63), 82 (48), 71 (26), 57 (84); IR 3425 (OH), 1755 (C=O) cm^{-1}; ^1H NMR δ 4.52 (dq, 1H, J = 1.0, 6.8 Hz, C_4-H), 4.19 (ddd, 1H, J = 1.0, 4.4, 5.4 Hz, C_3-H), 3.01 (d, 1H, J = 4.4 Hz, OH), 2.59 (ddd, 1H, J = 5.4, 5.4, 9.3 Hz, C_2-H), 1.81–1.28 (m, 6H, CH_2), 1.34 (d, 3H, J = 6.8 Hz, C_4-CH_3), 0.93 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 178.14, 82.88, 73.52, 43.71, 29.68, 22.93, 22.55, 17.92, 13.80; HRMS calcd for $C_9H_{17}O_3$ 173.1176, found 173.1141.

(2*R,3*R**,4*S**)-2-Butyl-4-methyl-3-[(3-methylbutyryl)oxy]-4-butanolide (Blastmycinone, 2).** A solution of **17** (27 mg, 0.16 mmol) and DMAP (38 mg, 0.31 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of isovaleryl chloride (31 mg, 0.25 mmol) in CH_2Cl_2 (1.0 mL) at ambient temperature. After stirring for 2.5 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane/ethyl acetate (7/1) to afford **2** (28 mg, 71%) as a colorless oil: MS *m/z* 256 (M^+, 2.2), 200 (9.5), 184 (2.6), 155 (10), 99 (34), 85 (100), 69 (8.8), 57 (51); IR 1770 (C=O), 1730 (C=O) cm^{-1}; ^1H NMR δ 4.94 (dd, 1H, J = 4.9, 5.9 Hz, C_3-H), 4.36 (dq, 1H, J = 4.9, 6.8 Hz, C_4-H), 2.68 (ddd, 1H, J = 5.3, 5.9, 8.3 Hz, C_2-H), 2.23 (d, 2H, J = 6.8 Hz, CH_2CO), 2.11 (nonetlike, 1H, J = 6.4 Hz, $CHMe_2$), 1.93–1.30 (m, 6H, CH_2), 1.47 (d, 3H, J = 6.8 Hz, C_4-CH_3), 0.97 (d, 6H, J = 6.4 Hz, CH_3), 0.91 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 175.84, 172.37, 79.34, 78.37, 46.39, 43.06, 28.98, 28.87, 25.66, 22.31, 22.26, 19.38, 13.70; HRMS calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1680. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.52; H, 9.34.

(2*R,3*S**,4*R**)-2-Butyl-4-methyl-3-[(3-methylbutyryl)oxy]-4-butanolide (2-Epiblastmycinone, 3).** According to the procedure described for the preparation of **2**, **18** (30 mg, 0.17 mmol) was treated with isovaleryl chloride (32 mg, 0.26 mmol) and DMAP (43 mg, 0.35 mmol) to give **3** (39 mg, 87%) as a colorless oil: MS *m/z* 256 (M^+, 0.7), 200 (48), 184 (14), 155 (22), 99 (100), 85 (100), 69 (10), 57 (61); IR 1770 (C=O), 1725 (C=O) cm^{-1}; ^1H NMR δ 5.14 (d, 1H, J = 5.9 Hz, C_3-H), 4.48 (q, 1H, J = 6.8 Hz, C_4-H), 2.74 (ddd, 1H, J = 5.9, 5.9, 9.8 Hz, C_2-H), 2.25 (dd, 1H, J = 7.3, 15 Hz, CHCO), 2.22 (dd, 1H, J = 6.8, 15 Hz, CHCO), 2.10 (nonetlike, 1H, J = 6.8 Hz, $CHMe_2$), 1.88–1.24 (m, 6H, CH_2), 1.34 (d, 3H, J = 6.8 Hz, C_4-CH_3), 0.97 (d, 6H, J = 6.8 Hz, CH_3), 0.91 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 176.35, 172.40, 80.44, 74.85, 43.16, 41.46, 29.63, 25.67, 23.40, 22.48, 22.31, 22.25, 17.96, 13.75. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.31; H, 9.41.

***S*-*tert*-Butyl (2*R**,3*R**)-2-Butyl-3-hydroxy-4-pentynethioate (19).** To a solution of **9** (703 mg, 2.2 mmol) in dry THF/CH_3CN (1/1, 10 mL) was added a solution of TBAF and hydrofluoric acid in aqueous THF (2.5 mL, prepared from 2.3 mL of 1.0 M TBAF in THF solution and 0.2 mL of 47% hydrofluoric acid) at 0 °C. The reaction mixture was gradually warmed up to rt (30 min). The solvent was evaporated off. The residue was diluted with water and extract with ethyl acetate. The extract was washed with water and brine and concentrated to dryness. Chromatography of the residue with hexane/ethyl acetate (15/1) afforded **19** (442 mg, 82%) as a colorless oil: MS *m/z* 243 (M^+ + 1, 3.5), 186 (100), 153 (79), 129 (19), 107 (9.6), 91 (5.0), 79 (7.8), 67 (6.0), 57 (48); IR 3450 (OH), 3310 (HC≡), 2110 (C≡C), 1650 (C=O) cm^{-1}; ^1H NMR δ 4.56 (dt, 1H, J = 2.0, 5.4 Hz, propynyl H), 2.71 (ddd, 1H, J = 5.4, 5.4, 8.8 Hz, CHCO), 2.70 (d, 1H, J = 5.4 Hz, OH), 2.50 (d, 1H, J = 2.0 Hz, HC≡C), 1.87–1.24 (m, 6H, CH_2), 1.48 (s, 9H, *t*-Bu), 0.91 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 202.33, 82.07, 74.24, 63.28, 59.31, 48.73, 29.66, 29.41, 27.77, 22.59, 13.79; HRMS calcd for $C_{13}H_{23}O_2S$ 243.1417, found 243.1416. Anal. Calcd for $C_{13}H_{22}O_2S$: C, 64.42; H, 9.15. Found: C, 64.84; H, 9.05.

***S*-*tert*-Butyl (2*R**,3*S**)-2-Butyl-3-hydroxy-4-pentynethioate (20).** Similar treatment of **10** (1.0 g, 3.2 mmol) with a solution of TBAF and hydrofluoric acid in aqueous THF (1.2 mL, prepared from 1.1 mL of 1.0 M TBAF in THF solution and 0.1 mL of 47% hydrofluoric acid) gave **20** (0.7 g, 89%) as a colorless oil: MS *m/z* 243 (M^+ + 1, 92), 186 (29), 153 (42), 129 (30), 107 (39), 91 (10), 79 (20), 67 (20), 57 (100); IR 3470 (OH), 3310 (HC≡), 2110 (C≡C), 1650 (C=O) cm^{-1}; ^1H NMR δ 4.46 (ddd, 1H, J = 2.5, 6.4, 8.3 Hz, propynyl H), 2.87 (d, 1H, J = 8.3 Hz, OH), 2.71 (ddd, 1H, J = 6.4, 6.4, 8.3 Hz, CHCO), 2.50 (d, 1H, J = 2.5 Hz, HC≡C), 1.83–1.23 (m, 6H, CH_2), 1.49 (s, 9H, *t*-Bu), 0.90 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 203.27, 82.93, 74.04, 63.35, 59.12, 48.84, 29.97, 29.65, 29.37, 22.52, 13.77; HRMS calcd for $C_{13}H_{23}O_2S$ 243.1418, found 243.1434. Anal. Calcd for $C_{13}H_{22}O_2S$: C, 64.42; H, 9.15. Found: C, 64.73; H, 9.14.

***S*-*tert*-Butyl (2*R**,3*R**)-2-Butyl-3-hydroxy-4-pentenethioate (21).** A solution of **19** (610 mg, 2.5 mmol) in ethanol (5 mL) was hydrogenated over Lindlar catalyst (92 mg) under hydrogen at atmospheric pressure for 1 h (monitored by TLC) at 60 °C. The catalyst was filtered off by suction, and the filtrate was concentrated to dryness. Chromatography of the residue with hexane/ethyl acetate (20/1) provided **21** (520 mg, 85%) as a colorless oil: MS *m/z* 245 (M^+ + 1, 2.1), 188 (28), 155 (16), 126 (43), 109 (78), 99 (75), 83 (13), 71 (18), 57 (100); IR 3490 (OH), 1655 (C=O) cm^{-1}; ^1H NMR δ 5.83 (ddd, 1H, J = 5.4, 11, 17 Hz, vinylic H), 5.29 (dt, 1H, J = 17, 1.5 Hz, vinylic H), 5.18 (dt, 1H, J = 11, 1.5 Hz, vinylic H), 4.34–4.24 (m, 1H, allylic H), 2.56 (ddd, 1H, J = 4.9, 4.9, 9.8 Hz, CHCO), 2.47 (d, 1H, J = 3.4 Hz, OH), 1.78–1.18 (m, 2H, CH_2), 1.46 (s, 9H, *t*-Bu), 0.89 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 203.55, 137.56, 116.20, 73.49, 59.48, 48.54, 29.63, 29.58, 27.04, 22.66, 13.84; HRMS calcd for $C_{13}H_{25}O_2S$ 245.1573, found 245.1604. Anal. Calcd for $C_{13}H_{24}O_2S$: C, 63.89; H, 9.90. Found: C, 63.73; H, 9.71.

***S*-*tert*-Butyl (2*R**,3*S**)-2-Butyl-3-hydroxy-4-pentenethioate (22).** Similar reduction of **20** (135 mg, 0.55 mmol) with Lindlar catalyst (24.0 mg) under a hydrogen atmosphere gave **22** (126 mg, 92%) as a colorless oil: IR 3480 (OH), 1655 (C=O) cm^{-1}; ^1H NMR δ 5.86 (ddd, 1H, J = 5.9, 11, 17 Hz, vinylic H), 5.29 (dt, 1H, J = 17, 1.5 Hz, vinylic H), 5.18 (dt, 1H, J = 11, 1.5 Hz, vinylic H), 4.24–4.15 (m, 1H, allylic H), 2.62 (d, 1H, J = 7.3 Hz, OH), 2.57 (ddd, 1H, J = 5.4, 5.4, 9.3 Hz, CHCO), 1.78–1.23 (m, 6H, CH_2), 1.46 (s, 9H, *t*-Bu), 0.89 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 204.14, 138.59, 116.03, 74.13, 58.88, 48.66, 29.63, 29.49, 29.24, 22.59, 13.83; HRMS calcd for $C_{13}H_{24}O_2S$ 244.1495, found 244.1514.

Methyl (2*R,3*R**)-2-Butyl-3-hydroxy-4-pentenoate (23).** To a solution of **21** (670 mg, 2.7 mmol) in methanol (30 mL) at rt was added silver(I) trifluoroacetate (1.8 g, 8.1 mmol). The reaction mixture was refluxed for 5 h. After the mixture cooled

to ambient temperature, the black precipitates were filtered off by suction, and the filtrate was concentrated to dryness. Chromatography of the residue with hexane/ethyl acetate (3/1) provided methyl ester **23** (340 mg, 66%) as a colorless oil: MS *m/z* 185 ($M^+ - H$, 7.9), 149 (27), 95 (21), 81 (44), 69 (100), 57 (46); IR 3475 (OH), 1715 (C=O) cm^{-1}; ^1H NMR δ 5.86 (ddd, 1H, J = 5.9, 11, 17 Hz, vinylic H), 5.30 (dt, 1H, J = 17, 1.5 Hz, vinylic H), 5.18 (dt, 1H, J = 11, 1.5 Hz, vinylic H), 4.30 (ddt, 1H, J = 4.9, 5.9, 1.5 Hz, allylic H), 3.70 (s, 3H, OCH_3), 2.74–2.28 (brs, 1H, OH), 2.54 (ddd, 1H, J = 4.9, 4.9, 9.8 Hz, CHCO), 1.74–1.18 (m, 6H, CH_2), 0.89 (t, 1H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 175.12, 137.62, 116.37, 73.29, 51.58, 51.16, 29.78, 27.00, 22.54, 13.83; HRMS calcd for $C_{10}H_{18}O_3$ 186.1254, found 186.1274.

Methyl (2*R,3*S**)-2-Butyl-3-hydroxy-4-pentenoate (24).** According to the procedure described for the preparation of **23**, **22** (48 mg, 0.20 mmol) was treated with silver(I) trifluoroacetate (170 mg, 0.77 mmol) in methanol (4 mL) to give methyl ester **24** (22 mg, 59%) as a colorless oil: MS *m/z* 186 (M^+, 3.5), 130 (45), 109 (18), 87 (100), 71 (20), 57 (35); IR 3480 (OH), 1715 (C=O) cm^{-1}; ^1H NMR δ 5.84 (ddd, 1H, J = 6.3, 11, 17 Hz, vinylic H), 5.30 (dt, 1H, J = 17, 1.5 Hz, vinylic H), 5.19 (dt, 1H, J = 11, 1.5 Hz, vinylic H), 4.21 (tt, 1H, J = 1.5, 6.3 Hz, allylic H), 3.71 (s, 3H, OCH_3), 2.73 (brs, 1H, OH), 2.50 (ddd, 1H, J = 5.4, 6.3, 9.3 Hz, CHCO), 1.72–1.19 (m, 6H, CH_2), 0.89 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 175.60, 138.56, 116.45, 73.62, 51.55, 51.11, 29.40, 28.87, 22.47, 13.79; HRMS calcd for $C_{10}H_{18}O_3$ 186.1254, found 186.1234.

(2*R,3*R**,4*S**)-4-(Bromomethyl)-2-butyl-3-hydroxy-4-butanolide (25).** To a solution of **23** (49 mg, 0.26 mmol) in chloroform (2.0 mL) at rt was added a solution of bromine (0.55 M chloroform solution, 0.56 mL, 0.31 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at rt for 1 h. Saturated sodium thiosulfate solution and water were successively added to the reaction mixture, which was then extracted with chloroform. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane/ethyl acetate (10/1) to furnish **25** (39 mg, 57%) as a colorless solid, mp 61–62.5 °C (from hexane); MS *m/z* 253 (M^+ + 1, 10), 251 (M^+ + 1, 11), 194 (77), 115 (31), 100 (62), 82 (45), 71 (31), 57 (100); IR 3400 (OH), 1770 (C=O) cm^{-1}; ^1H NMR δ 4.68 (ddd, 1H, J = 4.9, 5.9, 8.3 Hz, C_4-H), 4.41 (dt, 1H, J = 2.0, 4.9 Hz, C_3-H), 3.68 (dd, 1H, J = 8.3, 10 Hz, CHBr), 3.64 (dd, 1H, J = 5.9, 10 Hz, CHBr), 2.64 (ddd, 1H, J = 2.0, 6.8, 8.8 Hz, C_2-H), 2.61 (d, 1H, J = 4.9 Hz, OH), 1.79–1.31 (m, 6H, CH_2), 0.93 (t, 1H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 177.28, 80.38, 72.66, 49.71, 29.26, 28.24, 27.15, 22.31, 13.73; HRMS calcd for $C_9H_{16}BrO_3$ 253.0262, found 253.0238. Anal. Calcd for $C_9H_{15}BrO_3$: C, 43.05; H, 6.02. Found: C, 43.04; H, 6.02.

(2*R,3*S**,4*R**)-4-(Bromomethyl)-2-butyl-3-hydroxy-4-butanolide (26).** Similar treatment of **24** (16 mg, 0.09 mmol) with bromine (0.80 M chloroform solution, 0.20 mL, 0.16 mmol) furnished **26** (13 mg, 59%) as colorless crystals: mp 70–71 °C (from hexane); MS *m/z* 253 (M^+ + 1, 16), 251 (M^+ + 1, 17), 194 (100), 115 (42), 100 (60), 82 (39), 71 (33), 57 (80); IR 3380 (OH), 1775 (C=O) cm^{-1}; ^1H NMR δ 4.61 (dt, 1H, J = 2.9, 4.9 Hz, C_3-H), 4.51 (dt, 1H, J = 2.9, 7.8 Hz, C_4-H), 3.64 (d, 2H, J = 7.8 Hz, CH_2Br), 2.59 (ddd, 1H, J = 4.9, 4.9, 10 Hz, C_2-H), 2.56 (d, 1H, J = 4.9 Hz, OH), 1.89–1.31 (m, 6H, CH_2), 0.94 (t, 1H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 177.10, 80.81, 69.14, 46.84, 29.54, 26.58, 22.83, 22.48, 13.82; HRMS calcd for $C_9H_{16}BrO_3$ 251.0281, found 251.0271. Anal. Calcd for $C_9H_{15}BrO_3$: C, 43.05; H, 6.02. Found: C, 43.01; H, 6.04.

(2*R,3*R**,4*R**)-2-Butyl-3-hydroxy-4-methyl-4-butanolide (4-Epiblastmycinolactol, 27).** A solution of **25** (25 mg, 0.10 mmol), tributyltin hydride (30 mg, 0.10 mmol), and AIBN (17 mg, 0.10 mmol) in dry toluene (4 mL) was refluxed for 30 min under a nitrogen atmosphere. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated to dryness. Lactone **27** (17 mg, 98%) was obtained by chromatography of the residue with hexane/ethyl acetate (5/1) as a colorless oil; MS *m/z* 172 (M^+, 1.1), 116 (70), 100 (43), 82 (38), 71 (24), 57 (100); IR 3420 (OH), 1760 (C=O) cm^{-1}; ^1H NMR δ 4.64 (dq, 1H, J = 4.9, 6.8 Hz, C_4-H), 4.20 (ddd, 1H, J = 3.4, 3.9, 4.9 Hz, C_3-H), 2.83 (d, 1H, J = 3.9 Hz, OH), 2.54 (ddd, 1H, J = 3.4, 6.4, 8.3 Hz, C_2-H), 1.77–1.30 (m, 6H, CH_2), 1.41 (d, 3H, J = 6.8 Hz, C_4-CH_3), 0.92 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 178.39, 78.69, 73.85, 49.23, 29.27, 28.07, 22.40, 13.83, 13.75; HRMS calcd for $C_9H_{16}O_3$ 172.1098, found 172.1122.

(2*R,3*S**,4*S**)-2-Butyl-3-hydroxy-4-methyl-4-butanolide (3-Epiblastmycinolactol, 28).** According to the procedure described for the preparation of **27** from **25**, **26** (13 mg, 0.05 mmol) was treated with tributyltin hydride (0.02 mL, 0.07 mmol) and AIBN (10 mg, 0.06 mmol) to give lactone **28** (8.4 mg, 96%) as a colorless solid, mp 103.5–105 °C (from hexane) (lit.[6m] mp 99.5–100.5 °C); MS *m/z* 172 (M^+, 2.2), 116 (100), 100 (54), 85 (43), 71 (22), 57 (79); IR 3420 (OH), 1760 (C=O) cm^{-1}; ^1H NMR δ 4.46 (dq, 1H, J = 2.9, 6.8 Hz, C_4-H), 4.31 (dt, 1H, J = 2.9, 4.9 Hz, C_3-H), 2.57 (ddd, 1H, J = 4.9, 4.9, 9.8 Hz, C_2-H), 2.45 (d, 1H, J = 4.9 Hz, OH), 1.86–1.32 (m, 6H, CH_2), 1.43 (d, 3H, J = 6.8 Hz, C_4-CH_3), 0.93 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 178.17, 79.18, 71.08, 47.56, 29.68, 22.96, 22.52, 13.83, 13.64. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.66; H, 9.31.

(2*R,3*R**,4*R**)-2-Butyl-4-methyl-3-[(3-methylbutyryl)oxy]-4-butanolide (4-Epiblastmycinone, 4).** A solution of **27** (17 mg, 0.10 mmol) and DMAP (42 mg, 0.34 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of isovaleryl chloride (32 mg, 0.27 mmol) in CH_2Cl_2 (1.0 mL) at ambient temperature. After stirring for 2.5 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromtographed with hexane/ethyl acetate (7/1) to afford **4** (22 mg, 86%) as a colorless oil: MS *m/z* 256 (M^+, 0.4), 200 (38), 184 (10), 155 (20), 99 (100), 85 (100), 69 (12), 57 (100); IR 1770 (C=O), 1730 (C=O) cm^{-1}; ^1H NMR δ 5.18 (dd, 1H, J = 2.9, 4.9 Hz, C_3-H), 4.77 (dq, 1H, J = 4.9, 6.3 Hz, C_4-H), 2.59 (ddd, 1H, J = 2.9, 6.4, 8.8 Hz, C_2-H), 2.26 (dd, 1H, J = 7.3, 15 Hz, CHCO), 2.23 (dd, 1H, J = 6.8, 15 Hz, CHCO), 2.11 (nonet, 1H, J = 6.8 Hz, $CHMe_2$), 1.82–1.29 (m, 6H, CH_2), 1.34 (d, 3H, J = 6.3 Hz, C_4-CH_3), 0.97 (d, 6H, J = 6.8 Hz, CH_3), 0.92 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 176.62, 172.22, 76.70, 75.25, 47.14, 43.06, 29.08, 28.20, 25.59, 22.33, 14.27, 13.72; HRMS calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1658. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.47; H, 9.21.

(2*R,3*S**,4*S**)-2-Butyl-4-methyl-3-[(3-methylbutyryl)oxy]-4-butanolide (3-Epiblastmycinone, 5).** Similar treatment of **28** (6.3 mg, 0.04 mmol) with isovaleryl chloride (3 drops) and DMAP (22 mg, 0.18 mmol) afforded **5** (8.1 mg, 86%) as a colorless solid: mp 38.5–39.5 °C (from hexane) (lit.[6m] mp 47–48 °C); MS *m/z* 256 (M^+, 0.9), 200 (43), 184 (14), 155 (17), 99 (85), 85 (100), 69 (6.1), 57 (47); IR 1770 (C=O), 1730 (C=O) cm^{-1}; ^1H NMR δ 5.62 (dd, 1H, J = 3.4, 4.9 Hz, C_3-H), 4.57 (dq, 1H, J = 3.4, 6.4 Hz, C_4-H), 2.70 (ddd, 1H, J = 4.9, 4.9, 10 Hz, C_2-H), 2.28 (dd, 1H, J = 7.3, 15 Hz, CHCO), 2.25 (dd, 1H, J = 6.8, 15 Hz, CHCO), 2.18–2.07 (m, 1H, $CHMe_2$), 1.87–1.23 (m, 6H, CH_2), 1.32 (d, 3H, J = 6.4 Hz, C_4-CH_3), 0.98 (d, 6H, J = 6.8 Hz, CH_3), 0.90 (t, 3H, J = 6.8 Hz, CH_3); ^{13}C NMR δ 176.42, 172.10, 77.42, 71.95, 45.75, 43.00, 29.54, 25.56, 23.41, 22.45, 22.33, 22.30, 14.07, 13.75. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.48; H, 9.17.

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Supplementary Material Available: Copies of the ^{13}C NMR spectra of **10**, **15**, **16**, **18**, **19**, **22–24**, and **27** (9 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.