Flexible and Simple Route for the Stereoselective Synthesis of Trisubstituted γ-Butyrolactones: Total Synthesis of (+)-Blastomycinone and its Analogs[1]

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Abstract: A flexible route for the stereoselective synthesis of trisubstituted γ-butyrolactones, namely (+)-blastomycinone and its analogs, is devised by the Sharpless asymmetric epoxidation and the regioselective ring opening reaction with dibutylcopper lithium as the key steps to introduce the requisite alkyl chain.

Key words: (+)-blastomycinone, (–)-3-*epi*-blastomycinone, Sharpless asymmetric epoxidation, dibutylcopper lithium, Wittig olefination

(+)-Blastomycinone[2] (**1**, Figure 1) is a degradation product of the macrocyclic dilactone (+)-Antimycinone A_3, an anti-fungal antibiotic isolated from several members of the *Streptomyces* species. Similar structurally related bioactive trisubstituted butyrolactones like NFX-2,[3a] a Virginamycin inducing factor, NFX-4,[3a] (+)-antimycinone,[3b] and lipid metabolites[3c] are other isolates from different origins with different alkyl chain lengths.

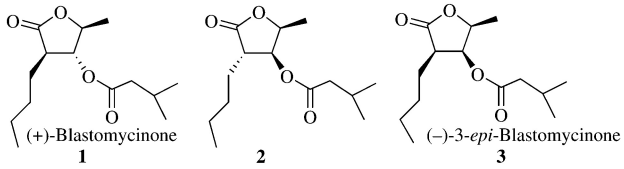
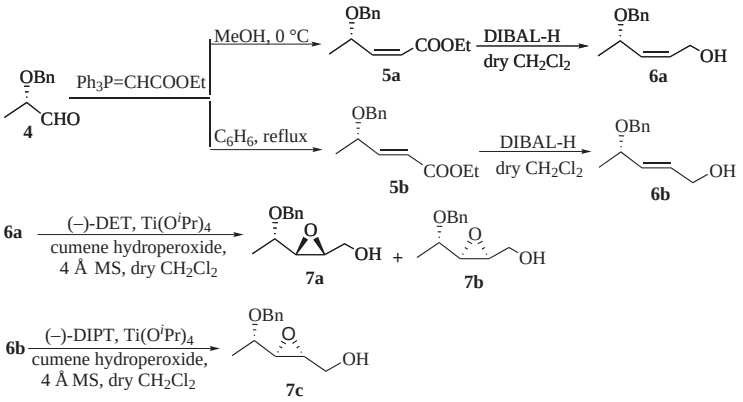


Figure 1

Many syntheses[4] of natural trisubstituted lactones have been directed at (+)-blastomycinone (**1**) and less attention has been given to the synthesis of analogs such as **2** and **3**. To the best of our knowledge only a few flexible approaches[5] for the synthesis of all possible isomers were reported. In this paper we describe stereoselective synthesis of trisubstituted γ-butyrolactones mainly (+)-blastomycinone (**1**), **2** and (–)-3-*epi*-blastomycinone (**3**)[6] by making use of Sharpless asymmetric epoxidation[7] and the regioselective ring opening reaction protocols[8] of the respective epoxides for installing the requisite stereochemistries.

(*S*)-*O*-Benzyllactaldehyde (**4**),[9] prepared from ethyl L-lactate in two steps, on reaction with (ethoxycarbonylmethelene)triphenylphosphorane in MeOH at 0 °C gave the *cis*-olefin **5a** along with *trans* product in a ratio 95:5 in 77% yield, while the same reaction when carried out in benzene at reflux gave *trans*-olefin **5b** (75%) as an exclusive product (Scheme 1). Treatment of **5a** and **5b** with DIBAL-H at –20 °C in anhydrous CH_2Cl_2 led to allylic alcohols **6a** and **6b** in good yields. When **6a** was subjected to Sharpless asymmetric epoxidation it was found to be inert. It was reported in literature[10] that the sterically hindered *cis* allylic alcohols are resistant to epoxidation with DIPT. Consequently, drawing analogy from the literature,[11] the use of (–)-DET was contemplated. Accord-



Scheme 1

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ingly, when **6a** was subjected to SAE with (–)-DET, it gave **7a** (55%) and **7b** (17%) in 19:6 ratio along with some amount of starting material. However, **6b** indeed underwent a facile conversion when subjected to SAE with (–)-DIPT and gave **7c** (71%).

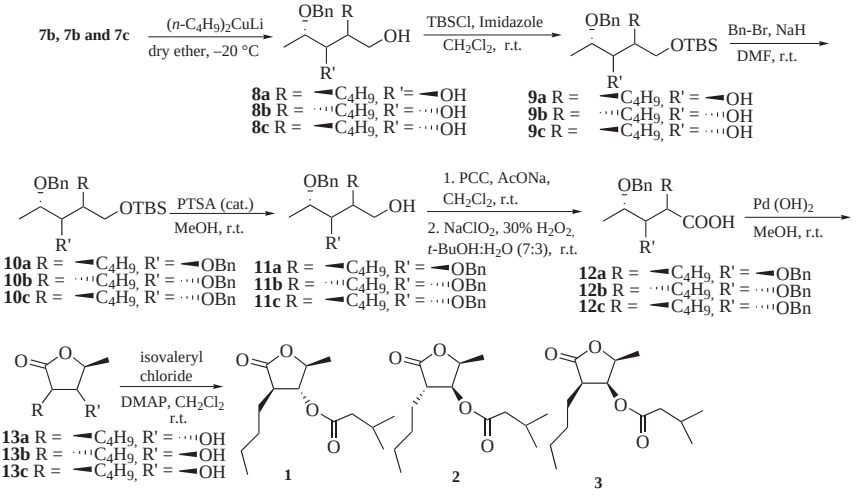
Compounds **7a**, **7b** and **7c** (Scheme 2) on reaction with dibutylcopper lithium in anhydrous Et_2O at –20 °C lead to the regioselective opening of epoxides to give 1,3-diols **8a**, **8b** and **8c** respectively as major products. The traces of 1,2-diol products were eliminated by using oxidative cleavage with $NaIO_4$ to obtain pure alcohols **8a**, **8b** and **8c** in 75%, 73% and 80% yields, respectively. The primary alcohols were selectively protected as silyl ethers with TBSCl to give **9a**, **9b** and **9c** in 80–83% yields. The remaining secondary alcohols were acylated with isovaleryl chloride to obtain isovaleryl esters. The next step was to deblock the silyl ether for further elaboration to acid. However, 1,3-acyl migration was observed while attempting the TBS group deprotection with TBAF in anhydrous CH_2Cl_2. Consequently, it was planned to introduce the ester functionality later in the synthesis. Hence, the 2° alcohols of **9a**, **9b** and **9c** were converted to benzyl ethers (reaction conditions: NaH, BnBr, DMF, r.t.) **10a**, **10b** and **10c** in 88%, 84% and 85% yields, respectively. The TBS deprotection was carried out with PTSA in MeOH to give **11a**, **11b** and **11c** in 82%, 84% and 80% yields, respectively. The primary alcohols **11a**, **11b** and **11c** were then oxidized to acids in a 2-step process, first with pyridinium chlorochromate to give aldehydes, which were later converted (reaction conditions: $NaClO_2$, H_2O_2, *t*-BuOH–H_2O)[12] to acids **12a**, **12b** and **12c** (82%, 82% and 85%), respectively. Deprotection of the benzyl groups [$Pd(OH)_2$ under H_2 atmosphere] in **12a**–**12c** results in simultaneous release of the hydroxy functionality with concomitant lactonization leading to (–)-blastomycinolactol **13a**, (–)-3-*epi*-blastomycinolactol **13b** and **13c** in 86%, 82% and 87% yields, respectively. Finally, the esterification on **13a**–**13c** was carried out with isovaleryl chloride as reported in the literature[5a] to obtain **1**, **2** and **3** in 89%, 91% and 86% respective yields. The spectral data of **1** and **3** were comparable with the known data.[6d] The spectral data of the new isomer **2** was thoroughly analyzed and its structure was unequivocally established as reported in here.

In conclusion, we have described a flexible and efficient route for the preparation of biologically active trisubstituted γ-butyrolactones by using Sharpless asymmetric epoxidation reaction and the regioselective ring opening reaction of the epoxides with 'dibutylcopper lithium' as the main strategy for efficient installation of the stereocenters. *Cis*- and *trans*-olefins along with the choice of Sharpless chiral ligands offers the flexibility and generality to the synthetic strategy for the preparation of a variety of such natural products and their analogs by simple selection or change of reagents.

Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 MHz and 300 MHz) and ^{13}C NMR (50 MHz and 75 MHz) spectra were measured with a Varian Gemini FT-200 M Hz (21 °C) spectrometer and Bruker Avance-300 MHz spectrometers with 7–10 mM solutions in $CDCl_3$ and TMS as internal standards. *J* values are given in Hz. Optical rotations were measured with a JASCO DIP-300 instrument and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}at 25 °C. IR spectra were taken with a Perkin-Elmer 1310 spectrometer. Mass spectra were recorded on CEC-21-11013 or Finnigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system and FAB–MS was measured using VG AUTOSPEC mass spectrometers at 5k or 7k resolution using perfluorokerosene as an internal reference. Elemental analysis was recorded on ELEMENTAR (Vario EL, Germany). Organic solutions were dried over anhyd Na_2SO_4 and concentrated below 40 °C in vacuo. The software ACD/Name Version 1.0, developed by M/s Advanced Chemistry Development Inc., Toronto, Canada, assisted nomenclature used in the experimental section.

Ethyl-4-benzyloxy-(*Z*,4*S*)-2-pentenoate (5a); Typical Procedure

To a stirred solution of **4** (4 g, 24.3 mmol) in MeOH (60 mL) at 0 °C was added (ethoxycarbonylmethylene)-triphenylphosphorane (10.2 g, 29.2 mmol) portion-wise. The reaction mixture was stirred



Scheme 2

at 0 °C for 3 h. The reaction mixture was concentrated under reduced pressure and was purified by column chromatography (silica gel 60–120; EtOAc–hexane, 1:50) to obtain **5a** (4.3 g, 77%) as a colorless liquid; $[\alpha]_D$ –40.5 (*c* = 1.25, $CHCl_3$).

IR (neat): 2940, 1720, 1240, 1180 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.33 (m, 6 H, 2 × CH_3), 4.14 (m, 2 H, OCH_2CH_3), 4.45 (dd, *J* = 12, 23 Hz, 2 H, OCH_2Ph), 5.13 (m, 1 H, CHOBn), 5.82 (d, *J* = 1.2 Hz, 1 H, CH=C*H*COOEt), 6.20 (dd, *J* = 8.2, 11.7 Hz, 1 H, C*H*=CHCOOEt), 7.27 (br s, 5 H, ArH).

FAB–MS: *m*/*z* = 235 (72) [M^+ + 1], 154 (20), 137 (20), 127 (74), 91 (100).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.92.

4-Benzyloxy-(*Z*,4*S*)-2-penten-1-ol (6a); Typical Procedure

DIBAL-H (13.8 mL, 19.4 mmol, 20% solution in toluene) was added dropwise to a solution of **5a** (3.8 g, 16.2 mmol) in anhyd CH_2Cl_2 (40 mL) at –20 °C and stirred for 30 min. After the completion of the reaction MeOH (15 mL) was added, followed by sat. sodium potassium tartrate solution (15 mL), filtered and washed with EtOAc (2 × 100 mL). Organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue was subjected to column chromatography (silica gel 60–120; EtOAc–hexane, 1:4) to obtain **6a** (2.5 gm, 81%) as a colorless liquid; $[\alpha]_D$ –20.9 (*c* = 1.0, $CHCl_3$).

IR (neat): 3400, 3000, 1480, 1080 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 8.6 Hz, 3 H, CH_3), 1.70 (d, 1 H, OH), 4.12 (t, *J* = 8.5 Hz, 2 H, CH_2OH), 4.20–4.38 (m, 1 H, CHOBn), 4.45 (dd, *J* = 10.4, 34.7 Hz, 2 H, OCH_2Ph), 5.50 (dd, *J* = 7.8, 13 Hz, 1 H, C*H*=CHCH_2OH), 5.77 (dt, *J* = 7.8, 13 Hz, 1 H, CH=C*H*CH_2OH), 7.27 (br s, 5 H, ArH).

FAB–MS: *m*/*z* = 215 (72) [M^+ + 23], 193 (100) [M^+ + 1], 175 (32), 154 (38), 91 (54).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.83; H, 8.27.

3-[1-Benzyloxy-(1*S*)-ethyl]-(2*R*,3*S*)-oxiran-2-yl Methanol (7a) and 3-[1-Benzyloxy-(1*S*)-ethyl]-(2*S*,3*R*)-oxiran-2-yl Methanol (7b); Typical Procedure

To stirred anhyd CH_2Cl_2 (10 mL) were added (–)-diethyl tartrate (1.287 g, 6.2 mmol) in CH_2Cl_2 (5 mL) at –20 °C followed by titanium isopropoxide (1.55 mL, 5.2 mmol) and stirred for 20 min. Cumene hydroperoxide (2 mL, 10.3 mmol, 80% solution) was added to the reaction mixture and allowed to stir for 20 min. A solution of **6a** (1.0 g, 5.2 mmol) in CH_2Cl_2 (10 mL) was added and allowed to stir at –20 °C for 15 d. The reaction mixture was quenched with NaOH in aq sat Na_2SO_4 solution (1 g in 10 mL) and stirred for 2 h. The reaction mixture was filtered through celite; the residue washed with EtOAc (4 × 100 mL), the organic layer was washed with water (2 × 50 mL), brine (2 × 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was subjected to column chromatography (silica gel 60–120; EtOAc–hexane, 1:5). The first eluted compound was **6a** (0.25 g) the second elute was the **7a** (0.450 g, 55.5%), the third elute was **7b** (0.140 g, 17%).

Compound 7a

$[\alpha]_D$ +4.37 (*c* = 0.5, $CHCl_3$).

IR (neat): 3400, 2980, 1710, 1340, 1080 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.91 (dd, *J* = 4.15, 7.54 Hz, 1 H, epo-H), 3.15 (dd, *J* = 4.15, 5.6 Hz, 1 H, epo-H), 3.30 (m, 1 H, CHOBn), 3.83 (m, 2 H, CH_2OH), 4.48 (d, *J* = 12.0 Hz, 1 H, CH*H*Ph), 4.57 (d, *J* = 12.0 Hz, 1 H, CH*H*Ph), 7.27 (br s, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.29, 57.16, 59.27, 60.77, 70.53, 71.84, 127.74, 127.89, 128.48.

FAB–MS: *m*/*z* (%) = 231 (34) [M^+ + 23], 207 (100), 181 (30), 154 (50), 137 (74).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.43; H, 7.87.

Compound 7b

$[\alpha]_D$ –3.5 (*c* = 0.5, $CHCl_3$).

IR (neat): 3400, 2980, 1710, 1340, 1080 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.4 Hz, 3 H, CH_3), 3.05 (m, 2 H, epo-H), 3.46 (m, 1 H, CHOBn), 3.60 (dd, *J* = 10.2, 15.3 Hz, 1 H, CH*H*OH), 3.78 (dd, *J* = 5.1, 15.1 Hz, 1 H, C*H*HOH), 4.58 (d, *J* = 12.7 Hz, 1 H, OCH*H*Ph), 4.75 (d, *J* = 12.7 Hz, 1 H, OC*H*HPh), 7.30 (br s, 5 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.58, 54.61, 60.50, 71.07, 73.39, 127.45, 127.61, 128.22.

FAB–MS: *m*/*z* (%) = 231 (34) [M^+ + 23], 207 (100), 181 (30), 154 (50), 137 (74).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.13; H, 7.63.

4-Benzyloxy-2-butyl-(2*S*,3*R*,4*S*)-pentane-1,3-diol (8a); Typical Procedure

To a stirred solution of copper(I) iodide (0.27 g, 1.4 mmol) in anhyd Et_2O (10 mL) was added *n*-BuLi (1.8 mL, 2.8 mmol, 1.6 M solution in *n*-hexane) at –20 °C and stirred for 30 min. Compound **7a** (0.15 g, 0.72 mmol) in anhyd Et_2O (10 mL) was added and stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl (2 mL), treated with NH_3 solution (2 mL) and allowed to stir for 15 min. The organic layer was separated and the water layer was washed with EtOAc (2 × 10 mL). The combined organic layers were washed with water (2 × 5 mL), brine (1 × 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel 60–120, EtOAc–hexane, 1:5) to obtain **8a** (0.143 g, 75.5%) as a colorless liquid; $[\alpha]_D$ +11.6 (*c* = 0.5, $CHCl_3$).

IR (neat): 3420, 2930, 1560 1050, 760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.897 (t, *J* = 6.78, 3 H, CH_2CH_3), 1.16–1.27 (m, 10 H), 1.76 (m, 1 H, C*H*C_4H_9), 3.57 (m, 1 H, CHOBn), 3.66–3.79 (m, 3 H, CH_2OH, C*H*OH), 4.42 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 4.62 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 7.27 (br s, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06, 15.39, 23.04, 24.07, 29.76, 40.82, 64.34, 70.62, 75.31, 77.08, 127.63, 127.79, 128.34, 138.31.

FAB–MS: *m*/*z* (%) = 289 (34) [M^+ + 23], 267 (100) [M^+ + 1], 157 (94), 141 (50), 91 (54).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.37; H, 9.92.

1-[1-Benzyloxy-(1*S*)-ethyl]-2-*tert*-butyldimethyl Silyloxy Methyl-(1*R*,2S)-hexyl Alcohol (9a); Typical Procedure

To a stirred solution of **8a** (0.18 g, 0.67 mmol) in CH_2Cl_2 (4 mL), imidazole (0.092 g, 1.3 mmol) and *t*-butyl dimethylsilyl chloride (0.121 g, 0.8 mmol) were added and allowed to stir at r.t. for 1 h. The reaction mixture was concentrated under reduced pressure and subjected to column chromatography (silica gel 60–120; EtOAc–hexane, 1:50) to obtain **9a** (0.22 g. 81%) as a colorless liquid; $[\alpha]_D$ +19.6 (*c* = 0.6, $CHCl_3$).

IR (neat): 3510, 2960, 2850, 1490, 1280 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, -Si$(CH_3)_2$], 0.864–0.91 [br s, 12 H, Si(*t*-C_4H_9), CH_3], 1.10–1.45 (m, 9 H, CH_3, 3 ×

CH_2), 1.71–1.77 (m, 1 H, C*H*C_4H_9), 3.47–3.55 (m, 1 H, C*H*OH), 3.68 (dd, *J* = 2.64, 10.2 Hz, 2 H, CH_2OTBS), 3.77 (dd, *J* = 3.77, 9.82 Hz, 1 H, CHOBn), 4.38 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 4.60 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 7.27 (br s, 5 H, ArH).

FAB–MS: *m*/*z* (%) = 381 (14) [M^+ + 1], 273 (100), 255 (8), 215 (20), 141 (30).

Anal. Calcd for $C_{22}H_{40}O_3Si$: C, 69.42; H, 10.59. Found: C, 69.55; H, 10.63.

2,3-Di(benzyloxy)-4-*tert*-butyldimethyl Silyloxy-(2*S*,3*R*,4*S*)-octane (10a); Typical Procedure

Sodium hydride (0.02 g, 0.51 mmol, 60% dispersion in paraffin oil) was added to a stirred solution of **9a** (0.2 g, 0.51 mmol) in anhyd DMF (1 mL) at 0 °C and stirred for 15 min. Benzyl bromide (0.065 mL, 0.51 mmol) was added to the reaction mixture and stirred at r.t. for additional 30 min. The reaction mixture was quenched with sat. NH_4Cl (2 mL) and stirred for 10 min, extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was subjected to column chromatography (silica gel 60–120; EtOAc–hexane, 1:50) to afford **10a** (0.22 g, 88%) as a colorless liquid; $[\alpha]_D$ –2.0 (*c* = 0.5, $CHCl_3$).

IR (neat): 2960, 2850, 1570, 1250, 1100 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.06 [s, 6 H, $Si(CH_3)_2$], 0.89–0.97 [br s, 12 H, Si (*t*-C_4H_9), CH_3], 1.18–1.34 (m, 9 H, CH_3, 3 × CH_2), 1.72 (m, 1 H, C*H*C_4H_9), 3.58 (t, *J* = 5.127 Hz, 2 H, CH_2OTBS), 3.67 (t, *J* = 4.39 Hz, 1 H, CHOBn), 3.75 (dd, *J* = 4.39, 5.86 Hz, 1 H, CHOBn), 4.48–4.82 (m, 4 H, OCH_2Bn), 7.27 (br s, 10 H, ArH).

FAB–MS: *m*/*z* (%) = 471 (12) [M^+ + 1], 255 (18), 215 (48) 181 (16) 91 (100).

Anal. Calcd for $C_{29}H_{46}O_3Si$: C, 73.99; H, 9.85. Found: C, 71.08; H, 9.95.

2-[1,2-Di(benzyloxy)-(1*R*,2*S*)-propyl]-(2*S*)-hexan-1-ol (11a); Typical Procedure

PTSA (cat.) was added to a stirred solution of **10a** (0.2 g, 0.42 mmol) in MeOH (2 mL) and stirred at r.t. for 30 min. Reaction mixture was quenched with Et_3N (0.2 mL) and stirred for 5 min. The reaction mixture was concentrated and diluted with EtOAc (10 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel 60–120; EtOAc–hexane, 1:10) to obtain **11a** (0.122 g, 82%) as a liquid; $[\alpha]_D$ +12.5 (*c* = 0.5, $CHCl_3$).

IR (neat): 2960, 2850, 1570 1250, 1190 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.876 (t, 3 H, *J* = 7.17 Hz, CH_3), 1.22–1.31 (br s, 9 H), 1.80–1.89 (m, 1 H, C*H*C_4H_9), 3.51–3.64 (m, 3 H, CHOBn, CH_2OH), 3.67–3.74 (m, 1 H, CHOBn), 4.43–4.7 (m, 4 H, CH_2Ph), 7.28 (br s, 10 H, ArH).

FAB–MS: *m*/*z* (%) = 357 (26) [M^+ + 1], 327 (26), 249 (38), 157 (100), 141 (64).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.63; H, 9.22.

2-[1,2-Di(benzyloxy)-(1*R*,2*S*)-propyl]-(2*R*)-hexanoic Acid (12a); Typical Procedure

To a stirred solution of **11a** (0.075 g, 0.21 mmol) in CH_2Cl_2 (2 mL) was added pyridininum chlorochromate (0.068 g, 0.31 mmol) and NaOAc (0.034 g, 0.42 mmol), and allowed to stir at r.t. for 45 min. The reaction mixture was concentrated under reduced pressure, Et_2O (50 mL) was added and the ether layer was passed through a column (silica gel 60–120), to give aldehyde (0.065 g, 87%) as syrup. The aldehyde thus obtained was subjected to the next reaction without further purification or characterization.

To a stirred solution of aldehyde (0.065 g, 0.18 mmol) in *t*-BuOH–H_2O (7:3, 1 mL), were added sodium chlorite (0.024 g, 0.27 mmol) and H_2O_2 (0.11 mL, 0.98 mmol, 30% aq. sol.), and stirred at r.t. for 6 h. The reaction mixture was concentrated, residue dissolved in EtOAc (10 mL), washed with water (1 × 5 mL), brine (1 × 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel 60–120: EtOAc–hexane, 3:20) to obtain **12a** (0.055 g, 82%) as a colorless liquid; $[\alpha]_D$ +8.0 (*c* = 0.5, $CHCl_3$).

IR (neat): 3300–3000 (br), 2930, 1710, 1280 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.79 Hz, 3 H, CH_3), 1.20–1.33 (m, 9 H), 1.62–1.72 (m, 1 H, C$H_2C_3H_7$), 2.51–2.59 (m, 1 H, C*H*COOH), 3.49–3.55 (m, 1 H, CHOBn), 3.77 (dd, *J* = 4.53, 7.17 Hz, 1 H, CHOBn), 4.43–4.73 (m, 4 H, OCH_2Ph), 7.27 (br s, 10 H, ArH).

FAB–MS: *m*/*z* (%) = 371 (10) [M^+ + 1], 263 (14), 154 (32), 136 (28), 91(100).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.57; H, 8.16. Found: C, 74.42; H, 8.03.

3-Butyl-4-hydroxy-5-methyl-(3*R*,4*R*,5*S*)-tetrahydro-2-furanone [(–)-Blastmycinolactol] (13a); Typical Procedure

$Pd(OH)_2$ (cat.) was added to a stirred solution of **12a** (0.045 g, 0.12 mmol) in MeOH (0.5 mL) and stirred under H_2 atmosphere for 24 h at r.t. The reaction mixture was filtered, filtrate concentrated under reduced pressure and purified by column chromatography (silica gel 60–120, EtOAc–hexane, 1:4) to obtain **13a** (0.018 g, 86%) as a colorless solid: mp 50–51 °C [Lit.[8] mp 49.5–50.5 °C]; $[\alpha]_D$ –17.56 (*c* = 1.0, $CHCl_3$) {Lit.[8] $[\alpha]_D$ –18.0 (*c* = 1.25, $CHCl_3$}.

IR (neat): 3400, 1770, 1190 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 [t, *J* = 6.6, 3 H, $(CH_2)_3CH_3$], 1.35–1.64 (m, 8 H), 1.80–1.92 (m, 1 H), 2.53 (ddd, *J* = 3.77, 7.93 Hz, 1 H, C*H*C_4H_9), 3.78 (t, *J* = 6.68 Hz, 1 H, C*H*CH_3), 4.00–4.22 (m, 1 H, C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.79, 18.17, 22.52, 28.08, 28.75, 48.53, 78.77, 80.23, 178.4.

FAB–MS: *m*/*z* (%) = 173 (10) [M^+ + 1], 99 (63), 82 (48), 71 (26), 57 (84).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 63.05; H, 9.10.

4-Butyl-2-methyl-5-oxo-(2*S*,3*R*,4*R*)-tetrahydro-3-furan-yl 3-Methylbutanoate [(+)-Blastomycinone] (1); Typical Procedure

To a mixture of **13a** (0.050 g, 0.29 mmol) in CH_2Cl_2 (2 mL) and dimethylaminopyridine (0.014 g, 1.16 mmol), isovaleryl chloride (0.21 mL, 1.7 mmol) was added at r.t. and stirred for 24 h. The reaction mixture was quenched with sat. aq $NaHCO_3$ solution (1 mL) and stirred for 15 min and diluted with CH_2Cl_2 (5 mL). The organic layer was washed with water (2 × 5 mL), brine (2 × 5 mL), dried (Na_2SO_4) and residue obtained was purified by column chromatography (silica gel 60–120; EtOAc–hexane, 1:10) to obtain **1** (0.065 g, 89%) as a colorless liquid; $[\alpha]_D$ +11.0 (*c* = 1.2, $CHCl_3$) {Lit.[8] $[\alpha]_D$ +11.5 (*c* = 1.2, $CHCl_3$)}.

IR (neat): 3400, 1770, 1190 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.91–0.98 (m, 9 H), 1.24–1.42 (m, 4 H), 1.45 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.56–1.67 (m, 1 H), 1.78–1.9 (m, 1 H), 2.00–2.14 (m, 1 H), 2.19 (d, *J* = 6.8 Hz, 2 H, $OCOCH_2$), 2.58–2.65 (m, 1 H, C*H*C_4H_9), 4.33 (dq, *J* = 4.8, 6.8 Hz, 1 H, C*H*CH_3), 4.92 (t, *J* = 5.2 Hz, 1 H, C*H*OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 19.42, 22.31, 25.7, 28.92, 29.04, 43.13, 46.46, 78.44, 79.3, 172.34, 175.78.

FAB–MS: *m*/*z* (%) = 173 (10) [M^+ + 1], 99 (63), 82 (48), 71 (26), 57 (84).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 67.57; H, 9.92. Found: C, 67.61; H, 9.78.

4-Benzyloxy-2-butyl-(2*R*,3*S*,4*S*)-pentane-1,3-diol (8b); Typical Procedure

To a stirred solution of copper(I) iodide (0.237 g, 1.25 mmol) in anhyd Et_2O (10 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane, 1.56 mL, 4 mmol) at –20 °C and stirred for 30 min. To this **7b** (0.13 g, 0.625 mmol) in anhyd Et_2O (10 mL) was added and stirred for 1 h. Workup and chromatography as described for **8a** gave **8b** (0.12 g, 73%) as a colorless liquid; $[\alpha]_D$ +11.5 (*c* = 0.5, $CHCl_3$).

IR (neat): 3420, 2930, 1560 1050, 760 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$): δ = 0.910 (t, *J* = 6.9 Hz, 3 H, CH_2CH_3), 1.16–1.60 (m, 11 H), 3.53–3.71 (m, 4 H, CHOBn, CH_2OH, CHOH), 4.42 (d, *J* = 11.89 Hz, 1 H, OCH_2Ph), 4.66 (d, *J* = 11.89 Hz, 1 H, OCH_2Ph), 7.27 (br s, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): 14.01, 15.32, 22.96, 23.72, 29.75, 40.95, 64.18, 70.93, 78.06, 96.04, 127.74, 128.41, 137.99.

FAB–MS: *m*/*z* (%) = 289 (34) [M^+ + 23], 267 (100) [M^+ + 1], 157 (94), 141 (50), 91 (54).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.37; H, 9.96.

1-[1-Benzyloxy-(1*S*)-ethyl]-2-*tert*-butyldimethylsilyloxymethyl-(1*S*,2*R*)-hexyl Alcohol (9b); Typical Procedure

To a stirred solution of **8b** (0.54 g, 2.03 mmol) in CH_2Cl_2 (10 mL), imidazole (0.276 g, 4.0 mmol) and *t*-butyl dimethylsilyl chloride (0.365 g, 2.4 mmol) were added and stirred at r.t. for 1 h. Workup and chromatography as described for **9a** gave **9b** (0.63 g, 80%) as a colorless liquid; $[\alpha]_D$ +20.8 (*c* = 0.6, $CHCl_3$).

IR (neat): 3510, 2960, 2850, 1490, 1280 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, -Si$(CH_3)_2$], 0.88 [s, 12 H, Si(*t*-C_4H_9), CH_3], 1.15 (d, *J* = 5.28 Hz, 3 H, CH_3), 1.17–1.36 [br s, 6 H, $(CH_2)_3$], 1.46–1.52 (m, 1 H, C*H*C_4H_9), 3.53–3.66 (m, 4 H, C*H*OH, CHOBn, CH_2OTBS), 4.47 (d, *J* = 11.33 Hz, 1 H, OCH_2Ph), 4.67 (d, *J* = 11.3 Hz, 1 H, OCH_2Ph), 7.27 (br s, 5 H, ArH).

FAB–MS: *m*/*z* (%) = 381 (14) [M^+ + 1], 273 (100), 255 (8), 215 (20), 141 (30).

Anal. Calcd for $C_{22}H_{40}O_3Si$: C, 69.42; H, 10.59. Found: C, 69.27; H, 10.45.

2,3-Di(benzyloxy)-4-*tert*-butyldimethylsilyloxymethyl-(2*S*,3*S*,4*R*)-octane (10b); Typical Procedure

Sodium hydride (0.037 g, 1.56 mmol, 60% dispersion in paraffin oil) was added to a stirred solution of **9b** (0.6 g, 1.5 mmol) in anhyd DMF (3 mL) at 0 °C and stirred for 15 min. To this benzyl bromide (0.203 mL, 1.7 mmol) was added and stirred at r.t. for 30 min. Workup and chromatography as described for **10a** gave **10b** (0.620 g, 84%) as a colorless liquid; $[\alpha]_D$ –9.3 (*c* = 0.5, $CHCl_3$).

IR (neat): 2960, 2850, 1570, 1250, 1100 cm^{-1}.

^1H NMR: δ = 0.01 [s, 6 H, Si$(CH_3)_2$], 0.90 (br s, 12 H), 1.15–1.38 (m, 9 H, CH_3, 3 × CH_2), 1.59–1.69 (m, 1 H, C*H*C_4H_9), 3.53 (d, *J* = 6.79 Hz, 2 H, CH_2OTBS), 3.63 (dd, *J* = 3.02, 7.55 Hz, 1 H, CHOBn), 3.70 (t, *J* = 6.42 Hz, 1 H, CHOBn), 4.50–4.82 (m, 4 H, OCH_2Bn), 7.27 (br s, 10 H, ArH).

FAB–MS: *m*/*z* (%) = 471 (12) [M^+ + 1], 255 (18), 215 (48) 181 (16) 91 (100).

Anal. Calcd for $C_{29}H_{46}O_3Si$: C, 73.99; H, 9.85. Found: C, 74.12; H, 9.95.

2-[1,2-Di(benzyloxy)-(1*S*,2*S*)-propyl]-(2*R*)-hexan-1-ol (11b); Typical Procedure

PTSA (cat.) was added to a solution of **10b** (0.4 g, 0.84 mmol) in MeOH (4 mL) at r.t. and stirred for 30 min. To the reaction mixture Et_3N was added and stirred for 5 min. Workup and chromatography as described for **11a** gave **11b** (0.25 g, 84%) as a liquid; $[\alpha]_D$ +12.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 2960, 2850, 1570 1250, 1190 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.22–1.34 (br d, 9 H), 1.60–1.72 (m, 1 H, C*H*C_4H_9), 3.40–3.54 (m, 2 H, CH_2OH), 3.67 (dd, *J* = 2.97, 11.15 Hz, 1 H, CHOBn), 3.77 (t, *J* = 6.69 Hz, 1 H, CHOBn), 4.45–4.70 (m, 4 H, 2 × CH_2Ph), 7.28 (br s, 10 H, ArH).

FAB–MS: *m*/*z* (%) = 357 (26) [M^+ + 1], 327 (26), 249 (38), 157 (100), 141 (64).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05; C, 77.67; H, 9.25.

2-[1,2-Di(benzyloxy)-(1*S*,2*S*)-propyl]-(2*S*)-hexanoic Acid (12b); Typical Procedure

To a stirred solution of **11b** (0.25 g, 0.70 mmol) in CH_2Cl_2 (5 mL) were added pyridininum chlorochromate (0.23 g, 1.0 mmol) and NaOAc (0.172 g, 2.1 mmol), and allowed to stir at r.t. for 45 min. The reaction mixture was concentrated under reduced pressure and Et_2O was added (50 mL) and the ether layer was passed through column (silica gel 60–120) to obtain aldehyde (0.23 g, 93%) as syrup, which was used as such for the next reaction.

To a stirred solution of the aldehyde (0.23 g, 0.65 mmol) in *t*-BuOH–water (7:3, 2.5 mL), were added sodium chlorite (0.088 g, 1.5 mmol) and H_2O_2 (0.4 mL, 3.25 mmol, 30% aq solution) and stirred at r.t. for 6 h. Workup and chromatography as described for **12a** gave **12b** (0.055 g, 82%) as a colorless liquid; $[\alpha]_D$ +11.0 (*c* = 0.5, $CHCl_3$).

IR (neat): 3300–3000 (br), 2930, 1710, 1280 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.6 Hz, 3 H, CH_3), 1.19 (d, *J* = 5.8 Hz, 3 H, CH_3), 1.25–1.30 (br d, 6 H), 1.60–1.72 (m, 1 H, C$H_2C_3H_7$), 2.63 (q, 1 H, C*H*COOH), 3.60–3.73 (m, 2 H, CHOBn), 4.51 (d, *J* = 23 Hz, 4 H, OCH_2Ph), 7.27 (br s, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.41, 15.90, 23.94, 28.17, 30.27, 47.34, 72.47, 74.59, 82.65, 129.07, 139.54, 179.98.

FAB–MS: *m*/*z* (%) = 371 (10) [M^+ + 1], 263 (14), 154 (32), 136 (28), 91(100).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.57; H, 8.16. Found: C, 74.62; H, 8.22.

3-Butyl-4-hydroxy-5-methyl-(3*S*,4*S*,5*S*)-tetrahydro-2-furanone (13b); Typical Procedure

$Pd(OH)_2$ (cat.) was added to a stirred solution of **12b** (0.12 g, 0.32 mmol) in MeOH (1 mL) under H_2 atmosphere for 24 h at r.t. Workup and chromatography as described for **13a** gave **13b** (0.45 g, 82%) as a syrup; $[\alpha]_D$ –52.5 (*c* = 0.5, $CHCl_3$).

IR (neat): 3400, 1770, 1190 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.17 Hz, 3 H, CH_3), 1.25–1.60 (m, 8 H), 1.65–1.74 (m, 1 H), 2.49 (ddd, *J* = 3.77, 7.93 Hz, 1 H, C*H*C_4H_9), 4.13 (t, *J* = 4.53 Hz, 1 H, C*H*CH_3), 4.59 (dq, *J* = 6.4, 11.7 Hz, 1 H, C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.39, 28.06, 29.26, 49.2, 73.81, 78.73, 178.4.

FAB–MS: *m*/*z* (%) = 173 (10) [M^+ + 1], 99 (63), 82 (48), 71 (26), 57 (84).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.85; H, 9.47.

4-Butyl-2-methyl-5-oxo-(2*S*,3*S*,4*S*)-tetrahydro-3-furanyl 3-Methylbutanoate (2); Typical Procedure

To a mixture of **13b** (0.02 g, 0.116 mmol) in CH_2Cl_2 (2 mL) and dimethylaminopyridine (0.056 g, 0.46 mmol), isovaleryl chloride (0.085 mL, 0.69 mmol) were added at r.t. and stirred for 24 h. Work-up and chromatography as described for **1** gave **2** (0.026 g, 91%) as a colorless liquid; $[\alpha]_D$ –31.1 (*c* = 1.0, $CHCl_3$).

IR (neat): 3400, 1770, 1190 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.91–0.99 (br s, 9 H), 1.30–1.47 (m, 8 H), 1.62–1.79 (m, 1 H, C*H*C_3H_7), 2.03–2.16 (m, 1 H, C*H*C_3H_7), 2.21 (d, *J* = 5.86 Hz, 2 H, $COCH_2$), 2.52 (ddd, *J* = 2.93, 8.78 Hz, 1 H, C*H*C_4H_9), 4.72 (m, 1 H, C*H*CH_3), 5.12 (dd, *J* = 2.93, 4.39 Hz, 1 H, C*H*OCO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.72, 14.26, 22.32, 25.56, 28.18, 29.07, 43.04, 47.13, 75.22, 76.69, 172.21, 176.63.

FAB–MS: *m*/*z* (%) = 256 (10) [M^+], 200 (16), 184 (2.6), 155 (10), 99 (34), 85 (100).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.78; H, 9.11.

Ethyl 4-benzyloxy-(*E*,4*S*)-2-pentenoate (5b); Typical Procedure

To a stirred solution of (ethoxycarbonylmethylene)-triphenylphosphorane (12.7 g, 36.5 mmol) in benzene (30 mL) at reflux was added **4** (5.0 g, 30.4 mmol) in benzene (20 mL) and allowed to reflux for 1 h. Workup and chromatography as described for **5a** gave **5b** (5.3 g, 75%) as a colorless liquid; $[\alpha]_D$ –40.6 (*c* = 1.25, $CHCl_3$).

IR (neat): 2940, 1720, 1240, 1180 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.30 (m, 6 H, 2 × CH_3), 4.02 (m, 1 H, CHOBn), 4.12 (m, 2 H, $COOCH_2CH_3$), 4.35 (d, 1 H, *J* = 13 Hz, CH_2Ph), 4.50 (d, *J* = 13 Hz, 1 H, CH_2Ph), 5.90 (d, *J* = 17.3 Hz, 1 H, CHCOOEt), 6.78 (dd, *J* = 6.9, 17 Hz, 1 H, C*H*=CHCOOEt), 7.23 (br s, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.21, 20.6, 60.4, 70.67, 73.83, 121.3, 127.5, 127.6, 128.39.

FAB–MS: *m*/*z* = 235 (72) [M^+ + 1], 154 (20), 137 (20), 127 (74), 91 (100).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.47; H, 7.67.

4-Benzoloxy-(*E*, 4*S*)-2-penten-1-ol (6b); Typical Procedure

DIBAL-H (12 mL, 16.9 mmol, 20% solution in toulene) was added to a solution of **5b** (2 g, 8.5 mmol) in ahnyd CH_2Cl_2 (20 mL) at –20 °C dropwise and stirred for 30 min. Workup and chromatography as described for **6a** gave **6b** (1.4 g, 85%) as a colorless liquid; $[\alpha]_D$ –39.2 (*c* = 1.0, $CHCl_3$).

IR (neat): 3400, 3000, 1480, 1080 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 4.6 Hz, 3 H, CH_3), 1.51 (br s, 1 H, OH), 3.91 (t, *J* = 10.3, 14.8 Hz, 1 H, CHOBn), 4.12 (d, *J* = 4.6 Hz, 2 H, C*H*$_2$OH), 4.38 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.52 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 5.60 (dd, *J* = 9.2, 12.6 Hz, 1 H, C*H*=CHCH_2OH), 5.73–5.82 (m, 1 H, CH=C*H*CH_2OH), 7.23 (br s, 5 H, ArH).

FAB–MS: *m*/*z* = 215 (72) [M^+], 193 (100) [M^+ + 1], 175 (32), 154 (38), 91 (54).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.85; H, 8.45.

3-[1-Benzyloxy-(1*R*)-ethyl]-(2*R*)-oxiran-2-yl Methanol (7c); Typical Procedure

To stirred anhyd CH_2Cl_2 (10 mL) was added (–)-diisopropyl tartrate (1.07 g, 4.5 mmol) in CH_2Cl_2 (5 mL) at –20 °C. Later titanium isopropoxide (1.18 g, 4.15 mmol) was added and stirred for 20 min. To the reaction mixture was then added a 80% solution of cumene hydroperoxide (1.6 mL, 8.3 mmol) and stirred for 20 min, followed by the addition of **6b** (0.8 g, 8.3 mmol) dissolved in CH_2Cl_2 (10 mL)and a further stirring at –20 °C for 12 h. Workup and chromatography as described for **7a** gave **7c** (0.61 g, 71%) as a colorless liquid; $[\alpha]_D$ –0.7 (*c* = 1.0, $CHCl_3$).

IR (neat): 3400, 2980, 1710, 1340, 1080 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 5.8 Hz, 3 H, CH_3), 2.92 (m, 1 H, epo-H), 3.05 (dd, *J* = 2.5 Hz, 7.6 Hz, 1 H, epo-H), 3.34 (m, 1 H, CHOBn), 3.91 (dd, *J* = 3, 10 Hz, 2 H, C*H*$_2$OH), 4.58 (d, *J* = 9.1 Hz, 1 H, CH_2Ph), 4.72 (d, *J* = 9.1 Hz, 1 H, CH_2Ph), 7.30 (br s, 5 H, ArH).

FAB–MS: *m*/*z* (%) = 231 (34) [M^+ + 23], 207 (100), 181 (30), 154 (50), 137 (74).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.43; H, 7.83.

4-Benzyloxy-2-butyl-(2*S*,3*S*,4*S*)-pentane-1,3-diol (8c); Typical Procedure

To a stirred solution of copper(I) iodide (1g, 5.2 mmol) in anhyd Et_2O (10 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane, 6.5 mL, 10.5 mmol) at –20 °C and stirred for 30 min. To this solution, **7c** (0.55 g, 2.6 mmol) in anhyd Et_2O (10 mL) was added and stirred for 1 h. Workup and chromatography as described for **8a** gave **8c** (0.56 g, 80%) as a colorless liquid; $[\alpha]_D$ +25.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 3420, 2930, 1560 1050, 760 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.1, 3 H, CH_2CH_3), 1.21 [d, *J* = 4.1 Hz, 3 H, CH(OBn) C*H*$_3$], 1.27–1.53 (m, 8 H), 2.33 (br s, 1 H, OH), 3.46 (dd, *J* = 3.4, 6.8 Hz, 1 H, C*H*OH), 3.54–3.8 (m, 3 H, C*H*$_2$OH, CHOBn), 4.42 (d, *J* = 10.3 Hz, 1 H, OCH_2Ph), 4.70 (d, *J* = 10.3 Hz, 1 H, OCH_2Ph), 7.31 (br s, 5 H, ArH).

^{13}C NMR (75 MHz): δ = 13.97, 15.65, 22.83, 28.74, 29.44, 40.9, 78.62, 127.83, 128.46, 138.0.

FAB–MS: *m*/*z* (%) = 289 (34) [M^+ + 23], 267 (100) [M^+ + 1], 157 (94), 141 (50), 91 (54).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.33; H, 9.79.

1-[1-Benzyloxy-(1*S*)-ethyl]-2-*tert*-butyldimethylsilyloxymethyl(1*S*,2*S*)-hexyl Alcohol (9c); Typical Procedure

To a stirred solution of **8c** (0.50 g, 1.8 mmol) in CH_2Cl_2, imidazole (0.25 g, 3.7 mmol) and *t*-butyldimethylsilyl chloride (0.31 g, 2.0 mmol) were added and stirred at r.t. for 1 h. Workup and chromatography as described for **9a** gave **9c** (0.59 g, 83%) as a colorless liquid; $[\alpha]_D$ +24.5 (*c* = 1.0, $CHCl_3$).

IR (neat): 3510, 2960, 2850, 1490, 1280 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, -Si$(CH_3)_2$], 0.86 [br s, 12 H, Si(*t*-C_4H_9), CH_3], 1.18 (d, *J* = 4.5 Hz, 3 H, CH_3), 1.25 (br s, 5 H, 2 × CH_2, CH), 1.60 (m, 1 H, CHC_4H_9), 2.82 (br s, 1 H, OH), 3.40 (m, 1 H, C*H*OH), 3.56 (dd, *J* = 5.9, 11.8 Hz, 2 H, CH_2OTBS), 3.69 (dd, *J* = 5.9, 11.8 Hz, 2 H, CH_2OTBS), 4.40 (d, *J* = 11.15 Hz, 1 H, C*H*HPh), 4.64 (d, *J* = 11.15 Hz, 1 H, CH*H*Ph), 7.27 (br s, 5 H, ArH).

FAB–MS: *m*/*z* (%) = 381 (14) [M^+ + 1], 273 (100), 255 (8), 215 (20), 141 (30).

Anal. Calcd for $C_{22}H_{40}O_3Si$: C, 69.42; H, 10.59. Found: C, 69.39; H, 10.74.

2,3-Di(benzyloxy)-4-*tert*-butyldimethylsilyloxy-(2*S*,3*S*,4*S*)-octane (10c); Typical Procedure

Sodium hydride (0.02 g, 0.5 mmol, 60% dispersion in paraffin oil) was added to a solution of **9c** (0.2 g, 0.53 mmol) in anhyd DMF (1

mL) at 0 °C and stirred for 15 min. To this solution, benzyl bromide (0.109 g, 0.64 mmol) was added and stirred at r.t. for further 30 min. Workup and chromatography as described for **10a** gave **10c** (0.21 g, 85%) as a colorless liquid; $[\alpha]_D$ +2.1 (*c* = 1.0, $CHCl_3$).

^{1}H NMR: δ = 0.01 [s, 6 H, -Si(CH_3)$_2$], 0.86 (br s, 12 H, *t*-C_4H_9, CH_3), 1.18 (d, *J* = 6.15 Hz, 3 H, CH_3), 1.22–1.32 [br s, 6 H, (CH_3)$_3$], 1.72 (m, 1 H, C*H*C_4H_9), 3.28 (dd, *J* = 4.6, 10.6 Hz, 1 H, CHOBn), 3.53 (dd, *J* = 5.2, 11.2 Hz, 1 H, CHOBn), 3.68–3.84 (m, 2 H, CH_2OTBS), 4.44–4.82 (m, 4 H, OCH_2Bn), 7.27 (br s, 10 H, ArH).

IR (neat): 2960, 2850, 1570, 1250, 1100 cm^{-1}.

FAB–MS: *m*/*z* (%) = 47 (12) [M$^+$ + 1], 255 (18), 215 (48) 181 (16) 91 (100).

Anal. Calcd for $C_{29}H_{46}O_3Si$: C, 73.99; H, 9.85. Found: C, 74.05; H, 9.92.

2-[1,2-Di(benzyloxy)-(1*S*,2*S*)-propyl]-(2*S*)-hexan-1-ol (11c); Typical Procedure

PTSA (cat.) was added to a solution of **10c** (0.2 g, 0.42 mmol) in MeOH (2 mL) at r.t. and stirred for 30 min. Workup and chromatography as described for **11a** gave **11c** (0.12 g, 80%) as a liquid; $[\alpha]_D$ –4.4 (*c* = 1.0, $CHCl_3$).

IR (neat): 2960, 2850, 1570 1250, 1190 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.876 (t, *J* = 5.9 Hz, 3 H, CH_3), 1.17 [d, *J* = 5.94 Hz, 3 H, CH(OBn)C*H*$_3$], 1.25–1.63 (br s, 7 H), 3.45 (dd, *J* = 3.7, 7.4 Hz, 1 H, CHOBn), 3.54 (d, *J* = 4.45, 11.15 Hz, 1 H, CHOBn), 3.80 (dd, *J* = 11.8, 18.5 Hz, 2 H, CH_2OH), 4.50–4.85 (m, 4 H, CH_2Ph), 7.28 (br s, 10 H, ArH).

FAB–MS: *m*/*z* (%) = 357 (26) [M$^+$ + 1], 327 (26), 249 (38), 157 (100), 141 (64).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.52; H, 9.21.

2-[1,2-Di(benzyloxy)-(1*S*,2*S*)-propyl]-(2*R*)-hexanoic Acid (12c); Typical Procedure

To a stirred solution of **11c** (0.1 g, 0.27 mmol) in CH_2Cl_2 (2 mL) were added pyridininum chlorochromate (0.088 g, 0.4 mmol) and NaOAc (0.044 g, 0.54 mmol) and stirring was continued at r.t. for 45 min. The reaction mixture was concentrated under reduced pressure and diluted with Et_2O (50 mL) and the ether layer was passed through column (silica gel 60–120) to obtain aldehyde (0.087 g, 89%) as syrup, which was used as such for the next reaction without further purification.

To a stirred solution of the above aldehyde (0.087 g, 0.24 mmol) in *t*-BuOH–water (7: 3, 1 mL), were added sodium chlorite (0.033 g, 0.36 mmol) and H_2O_2 (0.13 mL, 1.2 mmol, 30% aq solution) and the mixture was stirred at r.t. for 6 h. Workup and chromatography as described for **12a** gave **12c** (0.076 g, 85%) as a colorless liquid; $[\alpha]_D$ +2.5 (*c* = 1.0, $CHCl_3$).

IR (neat): 3300–3000 (br), 2930, 1710, 1280 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.69 Hz, 3 H, CH_3), 1.23 (d, *J* = 5.94 Hz, 3 H, CH_3), 1.30–1.70 (br s, 7 H), 2.61–2.77 (m, 1 H, C*H*COOH), 3.57 (t, *J* = 4.46 Hz, 1 H, CHOBn), 3.69 (t, *J* = 6.69 Hz, 1 H, CHOBn), 4.43–4.73 (m, 4 H, OCH_2Ph), 7.24–7.28 (br s, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.28, 16.78, 23.63, 29.58, 31.03, 49.17, 72.48, 75.65, 76.87, 83.79, 128.85, 129.02,129.52, 129.53, 139.53, 139.84, 180.87.

FAB–MS: *m*/*z* (%) = 371 (10) [M$^+$ + 1], 263 (14), 154 (32), 136 (28), 91(100).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.57; H, 8.16. Found: C, 74.39; H, 8.07.

3-Butyl-4-hydroxy-5-methyl-(3*R*,4*S*,5*S*)-tetrahydro-2-furanone [(–)-3-*epi*-Blastmycinolactol] (13c)

$Pd(OH)_2$ (cat.) was added to a solution of **12c** (0.14 g, 0.395 mmol) in MeOH (1 mL) at r.t. and stirred under H_2 atmosphere for 24 h. Workup and chromatography as described for **13a** gave **13c** (0.058 g, 87%) as syrup; mp 100–101 °C [Lit.[8] mp 99.5–100 °C]; $[\alpha]_D$ –95.5 (*c* = 0.5, MeOH); {Lit.[8] $[\alpha]_D$ –96.0 (*c* = 0.3, MeOH)].

IR (neat): 3400, 1770, 1190 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 6.79 Hz, 3 H, CH_3), 1.34–1.45 (m, 8 H), 1.71–1.81 (m, 1 H), 2.58 (dt, *J* = 4.9, 9.8 Hz, 1 H, C*H*C_4H_9), 4.32 (dt, *J* = 4.9, 9.8 Hz, 1 H, C*H*CH_3), 4.43 (dq, *J* = 3.0, 6.4 Hz, 1 H, C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.67, 13.86, 22.54, 22.97, 29.71, 47.56, 71.16, 78.97, 178.25.

FAB–MS: *m*/*z* (%) = 173 (10) [M$^+$ + 1], 99 (63), 82 (48), 71 (26), 57 (84).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.55; H, 9.44.

4-Butyl-2-methyl-5-oxo-(2*S*,3*S*,4*R*)-tetrahydro-3-furanyl 3-Methylbutanoate [(-)-3-*epi*-Blastomycinone] (3)

To a mixture of **13c** (0.05 g, 0.29 mmol) and dimethylaminopyridine (0.142 g, 1.16 mmol) in CH_2Cl_2 (2 mL), isovaleryl chloride (0.21 mL, 1.7 mmol) was added at r.t. and stirred for 24 h. Workup and chromatography as described for **1** gave **3** (0.063 g, 86%) as a colorless solid; mp 49–50 °C [Lit.[8] mp 48–49 °C]; $[\alpha]_D$ –88.0 (*c* = 1.0, $CHCl_3$); {Lit.[8] $[\alpha]_D$ –89.0 (*c* = 0.9, $CHCl_3$)}.

IR (neat): 3400, 1770, 1190 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.98 (m, 9 H), 1.26–1.46 (m, 8 H), 1.78–1.84 (m, 1 H), 2.03–2.18 (m, 1 H), 2.24 (d, *J* = 6.2 Hz, 2 H, OCOC*H*CH), 2.66 (dt, *J* = 6.2, 5.6 Hz, 1 H, C*H*C_4H_9), 4.54 (dq, *J* = 3.2, 6.4 Hz, 1 H, C*H*CH_3), 5.60 (dd, *J* = 3.2, 5.2 Hz, 1 H, C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.75, 14.07, 22.29, 22.45, 23.39, 25.56, 29.54, 42.95, 45.75, 71.95, 77.38, 172.10, 176.42.

FAB–MS: *m*/*z* (%) = 256 (10) [M$^+$], 200 (16), 184 (2.6), 155 (10), 99 (34) 85 (100).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.48; H, 9.31.

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