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Organoaluminium Induced Ring-Opening of Epoxypyranosides. V.[1] Formal Total Synthesis of Antimycin A_3 and Synthesis of (+)-Blastmycinone.

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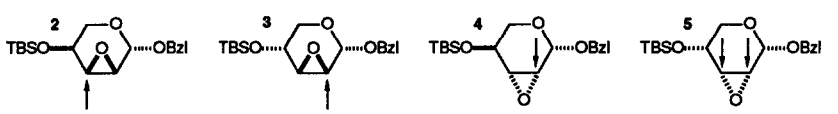
Abstract: *Epoxide ring-opening of the benzyl 2,3-anhydro-α-L-ribopyranoside* ***6*** *with lithium butynyl(trimethyl)-aluminate followed by functional group interconversions gave the dihydroxy thioacetal* ***11****, which was regio-selectively acylated with an L-threonine derivative. Acylation of the remaining hydroxyl group with isovaleryl chloride followed by thioacetal hydrolysis and oxidation of the liberated aldehyde gave* ***14****, an intermediate in Kinoshita's antimycin A_3 synthesis. The stereostructure of* ***11*** *was confirmed by converting it into (-)-blastmycino-lactol (****18****) which was acylated with isovaleryl chloride to give (+)-blastmycinone (****19****).*

The macrolide antibiotic antimycin A_3 (**1**) is one of several cyclic nine-membered dilactones, with different C-2 alkyl chains and C-3 acyl groups, isolated from *Streptomyces* species.[2] Antimycin A_3, like its homologs, inhibits the electron flow in the mitochondrial respiratory chain between cytochromes b and c_1, and has been used extensively to investigate the energy metabolism in eukaryotic organisms, and has also found commercial use as a fungicide.[3]

We have previously described the use of methyl-, alkenyl- and alkynyl-aluminates for the preparation of branched-chain sugars *via* epoxide ring-opening of 2,3-anhydro-pentopyranosides.[4,5]



Scheme 1.[6] Site of attack by "R-" of RMe_3AlLi where R=Me, $TMSC{\equiv}C$, $TBSOCH_2C{\equiv}C$, $n\text{-}PrC{\equiv}C$ etc.

For the transfer of methyl and alkynyl groups to these substrates, organoaluminates seem superior with respect to yield and regioselectivity, to common nucleophilic reagents such as organocuprates, Grignards and

organolithiums. For example, the diastereomeric 2,3-anhydropentosides **2-5**, easily prepared on a large scale from L(+)- or D(-)-arabinose, gave the corresponding 2-C or 3-C-deoxy-alkynyl sugars in 84-95% yields when treated with lithium trimethylsilylethynyl(trimethyl)aluminate (Scheme 1). The high regioselectivity found with **2-4** (>20/1) was lower with **5** (4.8/1 mixture of C-2/C-3 isomers, separable by flash chromatography). Thus a variety of enantiomerically pure, highly functionalized compounds, potentially useful as building blocks in the synthesis of complex, optically active natural products, are conveniently available.

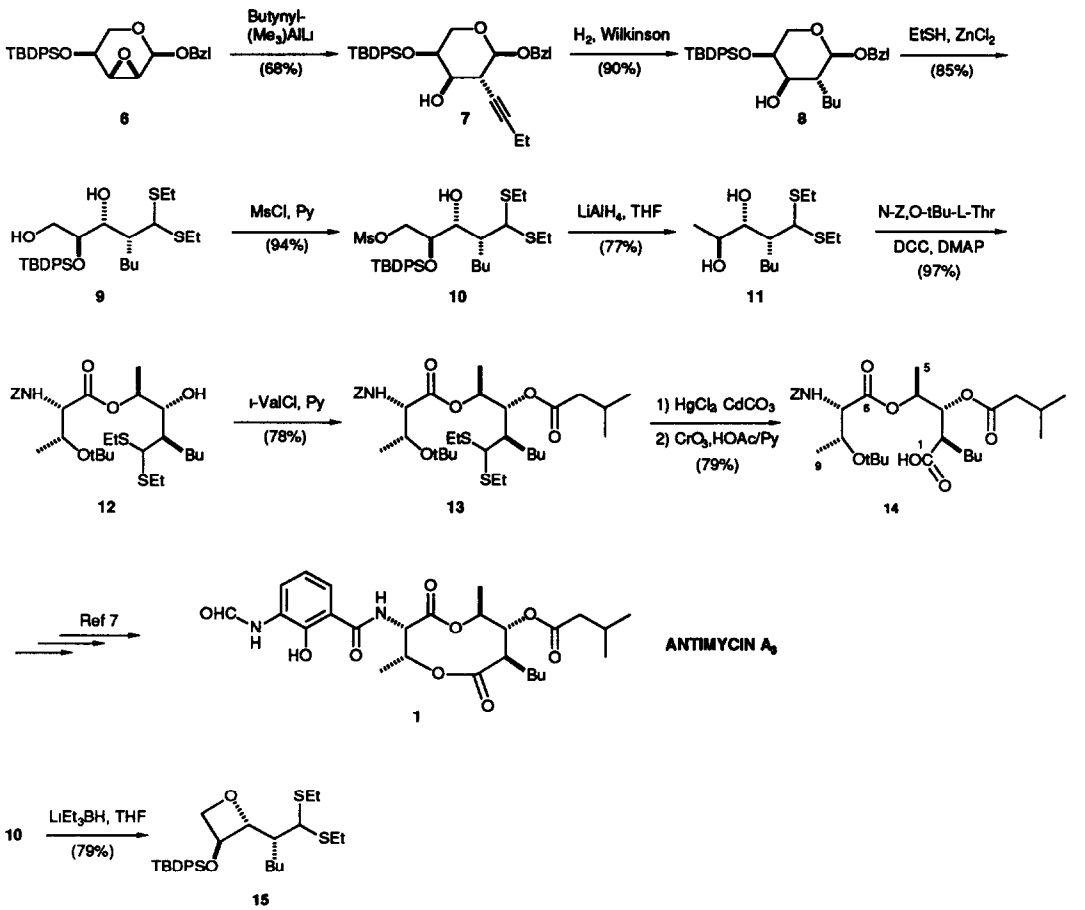
Herein we describe an application of this methodology in an improved synthesis of an advanced intermediate (**14**) in Kinoshita's total synthesis of antimycin A_3.[7] We also have synthesized (+)-blastmycinone (**19**), which is obtained on mild saponification of **1** and which has previously been prepared by several groups both optically active[8] and in racemic form.[9]

RESULTS AND DISCUSSION.

The starting point of our synthesis (Scheme 2) was the 2,3-anhydro-α-L-riboside **6**, prepared from L(+)-arabinose in seven steps (30% overall yield).[4] Reaction of **6** with lithium butynyl(trimethyl)aluminate in hexane afforded the 2-deoxy-2-C-butynyl sugar **7** in 68% yield after removal of the 3-C isomer (~15%) and other minor by-products by flash chromatography. Chemoselective hydrogenation of the triple bond in the presence of a catalytic amount of the Wilkinson catalyst then gave the 2-C-butyl sugar **8**. This two-step procedure efficiently circumvents the difficulty of introducing alkyl groups other than methyl (using Me_4AlLi) regioselectively at C-2 of **6**.[10]

Several methods for the formation of dithioacetals from glycosides have been described.[11] After some experimentation we found that the benzyl glycoside **8**, rather than the corresponding free sugar or 3-O-protected derivatives, was the most suitable precursor for Lewis acid promoted thioacetalisation. We originally used the 4-O-TBS derivative of **8**, but this protecting group was partially removed under a variety of Lewis acidic conditions and therefore we chose the more acid stable TBDPS group. Thus treatment of **8** with 4 equiv. of $ZnCl_2$ in EtSH[12] gave the acyclic diol **9**. This reaction proceeded *via* the thiosugars (α/β mixture).

Selective mesylation of the primary hydroxyl group furnished **10**, which slowly decomposed on standing at room temperature, apparently by way of an intramolecular attack by sulphur on the mesylate.[13] Attempts to reductively remove the mesylate with $NaBH_4$ in DMF or DMSO[14] or with NaI/Zn in DME[15] mainly led to decomposition of the starting material. In fact, this primary mesylate was virtually inert to nucleophilic substitution (*e.g.* 10 equiv. NaI in CH_3CN, 40°C, 24 h), presumably due to steric shielding by the bulky silyl group. In the reaction of **10** with $LiAlH_4$ in THF, on the other hand, Ph_2(t-Bu)SiH was rapidly split off at low temperature, most likely by way of an intramolecular hydride transfer to silicon from the initially formed 3-O trihydridoaluminate, a process to which there are precedents in the literature.[16] At elevated temperature, the intermediate 3,4-bisalcoxy mesylate was further reduced to **11**, possibly *via* an epoxide intermediate. As anticipated, the addition of $LiEt_3BH$ to **10** left the silyl ether unaffected, *i.e.* no ethyl-group transfer to silicon from the 3-O triethylborate took place. No intermolecular hydride substitution of the mesylate occurred however, but instead the oxetane **15** was formed as the major product.

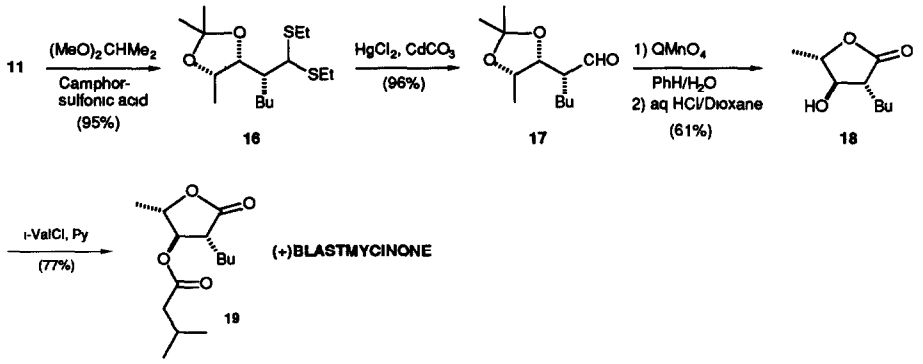


Scheme 2.[6]

The different steric environments of the two secondary hydroxyl groups in **11** allowed regioselective acylation of the more accessible C-4 hydroxyl group with N,O-protected L-threonine to yield the ester **12**. Acylation of the remaining sterically crowded hydroxyl group with isovaleryl chloride (or isovaleric anhydride) in pyridine (with or without 4-dimethylaminopyridine) required prolonged reaction time at elevated temperature and the yield was somewhat reduced due to side reactions. The final transformation of the dithioacetal **13** to the target carboxylic acid **14** was carried out without purification of the intermediate aldehyde, using conventional methodology.[17] Since the conversion of compound **14** into (+)-antimycin A_3 in six steps has been reported,[7,8h] this work constitutes a formal total synthesis of the natural product.

In order to verify the assigned stereostructure of **11**, it was converted into (+)-blastmycinone (**19**) (Scheme 3). Protection of the hydroxyl groups in **11** and subsequent hydrolysis of the dithioacetal gave the known aldehyde **17** which has previously been converted to (-)-blastmycinolactol (**18**) in 38% yield using Jones oxidation followed by treatment with 2N HCl.[8f] We improved that yield to 61% by carrying out the oxidation in a buffered two-phase system with $QMnO_4$[18] as the oxidant and by effecting the lactonisation

with aqueous HCl in 1,4-dioxane. The synthesis was completed by acylation of **18** with isovaleryl chloride to give **19**. The spectral and physical data of **18** and **19** were in agreement with literature data.[8]



Scheme 3.[6]

Our eight step synthesis of the antimycin A_3 precursor **14** in 23% overall yield from **6** compares favourably with Kinoshita's 19 steps in ~1.5% yield, starting from methyl 2,3-anhydro-4,6-di-O-benzylidene-α-D-mannopyranoside.[7,8g] Two additional formal total syntheses of **1** have appeared, both however suffering from low stereoselectivity in the assembly of the C-2 - C-4 asymmetric centra and consequently involving difficult chromatographic separations.[8b,9b]

An important aspect of our synthetic approach, along with brevity and stereoselectivity, is that the other members of the antimycin A family, as well as unnatural stereoisomers and analogues, also should be readily available.

EXPERIMENTAL SECTION.[6]

For general procedures, instrumentation *etc.*, see the preceding paper. NMR spectra were recorded using $CDCl_3$ ($CHCl_3$, 7.26 ppm as internal reference) as solvent unless otherwise indicated. Me_3Al (2.0 M in hexanes) and $LiEt_3BH$ (1.0 M in THF) were purchased from Aldrich. N-Z, O-tBu-L-Thr was obtained from its dicyclohexylammonium salt (Fluka AG) as described in Ref 19. 1-Butyne was prepared according to a literature procedure.[20] Benzyl 2,3-anhydro-α-L-ribopyranoside (mp 96.5-97.5°C; $[\alpha]^{20}_D$=-134.0° (c 0.91, EtOAc)) was prepared as described for its enantiomer.[4] Tetrahydrofuran was distilled from Na/benzophenone under nitrogen.

Benzyl 2,3-anhydro-4-O-(*tert*-butyldiphenylsilyl)-α-L-ribopyranoside (6). Benzyl 2,3-anhydro-α-L-ribopyranoside (5.10 g, 23.0 mmol) was added in portions to a solution of TBDPSCl (6.50 mL, 25.3 mmol) and imidazole (3.40 g, 50.0 mmol) in dry DMF (25 mL). After being stirred at 35°C for 40 min, the reaction mixture was diluted with CH_2Cl_2 (60 mL). The solution was washed with 2M aq. HCl (25 mL), sat. aq. $NaHCO_3$ (25 mL) and water (20 mL), dried and concentrated. Flash chromatography (E/H 1/10) gave **6** as a colourless oil (9.93 g, 94%): TLC(E/H 1/3) Rf = 0.42; $[\alpha]^{20}_D$=-94.8° (c 1.70, $CDCl_3$); ^1H NMR δ 7.75-7.31

(m, 15H, C_6H_5), 4.82 (d, 1H, $J_{1,2}$=3.2 Hz, H-1), 4.78, 4.55 (ABq, 1H each, J_{AB}=12.3 Hz, CH_2Ph), 4.06 (ddd, 1H, $J_{3,4}$=1.6 Hz, $J_{4,5}$=10.0 Hz, $J_{4,5'}$=5.7 Hz, H-4), 3.78 (t, 1H, $J_{5,5'}$=10.8 Hz, H-5), 3.33 (dd, 1H, $J_{2,3}$=4.2 Hz, H-2), 3.30 (ddd, $J_{3,5'}$=1.5 Hz, H-5'), 3.17 (br d, 1H, H-3), 1.08 (s, 9H, tBu).

Anal. Calcd for $C_{28}H_{32}O_4Si$: C, 73.01; H, 7.00. Found: C, 72.95; H, 7.08.

Benzyl 2-C-(1-butynyl)-2-deoxy-4-O-(*tert*-butyldiphenylsilyl)-α-L-arabinopyranoside (7). 1-Butyne (3.01 mL, 37.7 mmol) was transferred with the aid of a cooled, gas-tight syringe into dry hexane (45 mL) at -20°C. BuLi (18.3 mL, 2.06 M in hexane, 37.7 mmol) was slowly added under vigorous stirring. After 10 min, Me_3Al (18.9 mL, 2.0 M in hexanes, 37.6 mmol) was added to the slurry at 0°C. After another 10 min, compound **6** (8.70 g, 18.9 mmol) dissolved in dry hexane (100 mL) was added. After being stirred at 60°C for 1h 45 min, the solution was cooled in an ice-bath. Dry Et_2O (50 mL) was added and this solution was transferred *via* a double tipped needle into cold 2M aq. NH_4Cl with rapid stirring. The mixture was filtered and the solids were washed with EtOAc (3 x 25mL). The combined organic phases were washed with water (2x50 mL), dried and concentrated. Flash chromatography (E/H 1/8) gave **7** as a colourless oil (6.64 g, 68%): TLC(E/H 1/3) Rf = 0.44; $[\alpha]^{20}_D$=-36.7° (c 1.83, $CDCl_3$); ^{1}H NMR δ 7.73-7.32 (m, 15H, C_6H_5), 4.81, 4.56 (ABq, 1H each, J_{AB}=12.4 Hz, CH_2Ph), 4.56 (d, 1H, $J_{1,2}$=3.9 Hz, H-1), 4.07 (m, 1H, H-4), 3.83 (dd, 1H, $J_{5,5'}$=11.7 Hz, $J_{4,5}$=7.4 Hz, H-5), 3.74 (m, 1H, $J_{3,4}$=3.0 Hz, H-3), 3.34 (dd, $J_{4,5'}$=3.6 Hz, H-5'), 2.99 (m, 1H, $J_{2,3}$=6.0 Hz, H-2), 2.96 (d, 1H, $J_{OH,3}$=8.1 Hz, OH), 2.07 (dq, 2H, $J(CH_2CH_3)$=7.5 Hz, $J(CH_2,2)$=2.2 Hz, CH_2CH_3), 1.09 (s, 9H, tBu), 1.02 (t, 3H, CH_2CH_3).

Anal. Calcd for $C_{32}H_{38}O_4Si$: C, 74.67; H, 7.44. Found: C, 74.58; H, 7.49.

Benzyl 2-C-butyl-2-deoxy-4-O-(*tert*-butyldiphenylsilyl)-α-L-arabinopyranoside (8). Compound **7** (6.26 g, 12.2 mmol) was dissolved in benzene (300 mL) and EtOH (99.5%, 150 mL) and $(Ph_3P)_3RhCl$ (1.2 g, 1.2 mmol) were added. The solution was then degassed by repeatedly (three times) evacuating the reaction vessel and filling it with hydrogen gas. (*The solvent composition and the addition of catalyst prior to degassing were important for the outcome of this reaction.*[21]) The homogeneous solution was stirred at room temperature under H_2 (~1 atm) for 16 h. After concentration, the residue was suspended in EtOAc/n-heptane 1/3, filtered and concentrated. Flash chromatography (E/H 1/10) gave **8** as a colourless oil (5.72 g, 90%): TLC(E/H 1/6) Rf = 0.39; $[\alpha]^{20}_D$=-63.1° (c 2.43, $CDCl_3$); ^{1}H NMR δ 7.74-7.32 (m, 15H, C_6H_5), 4.78, 4.48 (ABq, 1H each, J_{AB}=12.1 Hz, CH_2Ph), 4.45 (d, 1H, $J_{1,2}$=2.2 Hz, H-1), 3.91 (t, 1H, $J_{5,5'}$=10.6 Hz, $J_{4,5}$=9.1 Hz, H-5), 3.82 (m, $J_{3,4}$=3.1 Hz, H-4), 3.55 (m, 1H, $J_{2,3}$=3.7 Hz, H-3), 3.37 (dd, 1H, $J_{4,5'}$=4.0 Hz, H-5'), 3.14 (d, 1H, $J_{OH,3}$=8.3 Hz, OH), 1.97 (m, 1H, H-2), 1.10 (m, 15 H, tBu, $(CH_2)_3$), 0.79 (t, 3H, J=6.7 Hz, $(CH_2)_3CH_3$).

Anal. Calcd for $C_{32}H_{42}O_4Si$: C, 74.09; H, 8.16. Found: C, 73.94; H, 8.21.

(2R, 3R, 4S) 2-Butyl-1,1-bis(ethylthio)-3,5-di-hydroxy-4-(*tert*-butyldiphenylsiloxy)-pentane (9). Compound **8** (3.18 g, 6.13 mmol) was dissolved in EtSH (9.0 mL). The solution was cooled to -10°C and $ZnCl_2$ (5.0 g, 36.7 mmol) was added. After being stirred at -10°C for 30 min, and at 0°C for 20 min, the solution was concentrated (-10°C, 12 mm Hg). The residue was dissolved in EtOAc (60 mL) and was added to sat. aq. $NaHCO_3$ (75 mL). The mixture was filtered and the solids were washed with EtOAc (3x15 mL). The aqueous phase was extracted with EtOAc (3x25 mL) and the combined organic phase was washed with

water (25 mL), dried and concentrated. Flash chromatography (E/H 1/5) gave **9** as a colourless oil (2.79 g, 85%): TLC(E/H 1/2) Rf = 0.49; $[\alpha]^{20}_D$=-10.4° (c 1.49, $CDCl_3$); ^{1}H NMR δ 7.74-7.38 (m, 10H, C_6H_5), 4.24 (ddd, 1H, $J_{2,3}$=1.8 Hz, $J_{3,4}$=7.7 Hz, $J_{3,OH}$=3.0 Hz, H-3), 3.98 (d, 1H, $J_{1,2}$=3.4 Hz, H-1), 3.75 (m, 1H, $J_{4,5}$, $J_{4,5'}$=3.7 Hz, 5.2 Hz, H-4), 3.64 (m, 2H, H-5, H-5'), 2.89 (d, 1H, 3-OH), 2.65 (m, 4H, 2x(SCH_2)), 2.40 (dd, 1H, $J_{5,OH}$, $J_{5',OH}$=5.3 Hz, 7.8 Hz, 5-OH), 2.29 (m, 1H, H-2), 1.59-1.03 (m, 6H, $(CH_2)_3CH_3$), 1.26 (m, 6H, 2x(SCH_2CH_3)), 1.07 (s, 9H, tBu), 0.86 (t, 3H, J=6.8 Hz, $(CH_2)_3CH_3$).

Anal. Calcd for $C_{29}H_{46}O_3S_2Si$: C, 65.12; H, 8.67; S, 11.99. Found: C, 65.07; H, 8.76; S, 11.92.

(2R, 3R, 4S) 2-Butyl-1,1-bis(ethylthio)-3-hydroxy-5-(methanesulfonyloxy)-4-(*tert*-butyldiphenyl-siloxy)-pentane (10). Compound **9** (2.56 g, 4.79 mmol) was dissolved in dry pyridine (40 mL) at 0°C and methanesulfonyl chloride (560 µL, 7.18 mmol) was added. After being stirred at 0°C for 15 min, and at room temperature for 70 min, the solution was poured into ice-water (75 mL). The mixture was extracted with CH_2Cl_2 (3x25 mL) and the combined organic phase was dried and co-evaporated with toluene (0.8 mm Hg, 30°C). Flash chromatography (E/H 1/4) gave **10** as a colourless oil (2.77 g, 94%): TLC(E/H 1/2) Rf = 0.46; ^{1}H NMR δ 7.73-7.39 (m, 10H, C_6H_5), 4.28, 4.15 (ABX, each 1H, J_{AB}=10.6 Hz, $J_{4,5}$, $J_{4,5'}$=2.4 Hz, 4.1 Hz, H-5, H-5'), 4.24 (dd, 1H, $J_{2,3}$=2.0 Hz, $J_{3,4}$=8.1 Hz, H-3), 4.00 (d, 1H, $J_{1,2}$=3.4 Hz, H-1), 3.86 (ddd, 1H, H-4), 2.71 (s, 3H, MsO), 2.66 (m, 4H, 2x(SCH_2)), 2.33 (m, 1H, H-2), 1.6-1.0 (m, 6H, $(CH_2)_3CH_3$), 1.27 (m, 6H, 2x(SCH_2CH_3)), 1.07 (s, 9H, tBu), 0.87 (t, 3H, J=6.8 Hz, $(CH_2)_3CH_3$).

This compound slowly decomposed at room temperature and therefore no elemental analysis was performed and no specific rotation was measured.

(2R, 3R, 4S) 2-Butyl-1,1-bis(ethylthio)-3,4-di-hydroxy-pentane (11). Compound **10** (2.36 g, 3.85 mmol), dissolved in cold (-70°C) dry THF (25 mL), was added *via* a double tipped needle into a suspension of $LiAlH_4$ (876 mg, 23.1 mmol) in dry THF (50 mL) at -70°C. After 10 min, the cooling bath was removed and after 1h the mixture was heated to 50°C. After being stirred at this temperature for 3h, the mixture was cooled and then added *via* a double tipped needle into 2M aq. NH_4Cl (150 mL) under argon. The solids were filtered off and were washed with Et_2O. The aqueous phase was extracted with Et_2O (3x30 mL). The combined organic phase was washed with water, dried and concentrated. Flash chromatography (E/H 1/2) gave **11** as a colourless oil (832 mg, 77%): TLC(E/H 1/2) Rf = 0.26; $[\alpha]^{20}_D$=+11.9° (c 2.78, $CDCl_3$); ^{1}H NMR δ 3.97 (d, 1H, $J_{1,2}$=3.4 Hz, H-1), 3.82 (ddd, 1H, $J_{2,3}$=2.0 Hz, $J_{3,4}$=7.0 Hz, $J_{3,OH}$=2.5 Hz, H-3), 3.77 (dq, 1H, H-4), 2.67 (m, 4H, 2x(SCH_2)), 2.50 (d, 1H, 3-OH), 2.24 (m, 1H, H-2), 1.62 (br s, 1H, 4-OH), 1.70-1.25 (m, 6H, $(CH_2)_3CH_3$), 1.28 (m, 6H, 2x(SCH_2CH_3)), 1.28 (d, 3H, $J_{4,5}$=5.9 Hz, H-5), 0.92 (m, 3H, $(CH_2)_3CH_3$).

Anal. Calcd for $C_{13}H_{28}O_2S_2$: C, 55.67; H, 10.06; S, 22.86. Found: C, 55.53; H, 10.13; S, 22.69.

***tert*-Butyldiphenylsilane** (866 mg, 93%) was also isolated: TLC (E/H 1/2) Rf = 0.76; IR(CCl_4) 2110 (Si-H) cm^{-1}. The ^{1}H NMR spectrum was in accordance with published data.[22]

Anal. Calcd for $C_{16}H_{20}Si$: C, 79.93; H, 8.38. Found: C, 80.10; H, 8.47.

(2R, 3R, 4S) 4-(N-Benzyloxycarbonyl-O-*tert*-butyl-L-threonyloxy)-2-butyl-1,1-bis(ethylthio)-3-hydroxy-pentane (12). N-Z, O-tBu-L-Thr (562 mg, 1.82 mmol), DCC (375 mg, 1.82 mmol) and DMAP (22 mg, 182 µmol) were dissolved in CH_2Cl_2 (10 mL). The reaction flask was placed in an ice-bath and

compound **11** (425 mg, 1.52 mmol), dissolved in CH_2Cl_2 (10 mL), was added. After being stirred at 0°C for 15 min, and at room temperature for 6h, the reaction mixture was diluted with Et_2O (20 mL), filtered, washed with sat. aq. $NaHCO_3$ (2x10 mL), dried and concentrated. Flash chromatography (E/H 1/4) gave **12** as a colourless oil (843 mg, 97%): TLC(E/H 1/2) Rf = 0.53; $[\alpha]^{20}_D$=-6.0° (c 1.67, $CDCl_3$); ^{1}H NMR δ 7.37 (m, 5H, C_6H_5), 5.59 (d, 1H, $J_{NH,7}$=8.7 Hz, NH), 5.16, 5.10 (ABq, 2H, J_{AB}=12.2 Hz, CH_2Ph), 5.00 (p, 1H, $J_{3,4}\approx J_{4,5}$=6.0 Hz, H-4), 4.25-4.00 (m, 3H, H-3, H-7, H-8), 3.90 (d, 1H, $J_{1,2}$=3.4 Hz, H-1), 2.66 (m, 4H, 2x(SCH_2)), 1.93 (m, 1H, H-2), 1.7-1.1 (m, 6H, $(CH_2)_3CH_3$), 1.31 (d, 3H, H-5), 1.26 (m, 6H, 2x(SCH_2CH_3)), 1.18 (d, 3H, $J_{8,9}$=6.5 Hz, H-9), 1.16 (s, 9H, tBu), 0.91 (m, 3H, $(CH_2)_3CH_3$).

Anal. Calcd for $C_{29}H_{49}NO_6S_2$: C, 60.91; H, 8.64; N, 2.45; S, 11.21. Found: C, 60.80; H, 8.71; N, 2.52; S, 11.16.

(2R, 3R, 4S) 4-(N-Benzyloxycarbonyl-O-*tert*-butyl-L-threonyloxy)-2-butyl-1,1-bis(ethylthio)-3-isovaleryloxy-pentane (13). Compound **12** (590 mg, 1.03 mmol) was dissolved in dry pyridine (10 mL) at 0°C. Isovaleryl chloride (254 µL, 2.06 mmol) was added and after 15 min, the solution was heated to 40°C. After being stirred at this temperature for 23 h, the solution was poured into ice-water (15 mL) and the mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic phase was washed with water (10 mL), dried and co-evaporated with toluene. Column chromatography (E/H 1/10) gave **13** as a colourless oil (527 mg, 78%): TLC(E/H 1/2) Rf = 0.59; $[\alpha]^{20}_D$=-19.5° (c 2.40, $CDCl_3$); ^{1}H NMR δ 7.37 (m, 5H, C_6H_5), 5.60 (d, 1H, $J_{NH,7}$=9.7 Hz, NH), 5.48 (dd, 1H, $J_{2,3}$=6.4 Hz, $J_{3,4}$=3.5 Hz, H-3), 5.13 (m, 1H, H-4), 5.17, 5.08 (ABq, 2H, J_{AB}=12.3 Hz, CH_2Ph), 4.21 (dq, 1H, $J_{7,8}$=1.5 Hz, $J_{8,9}$=6.3 Hz, H-8), 4.09 (dd, 1H, H-7), 3.82 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 2.62 (m, 4H, 2x(SCH_2)), 2.25-2.08 (m, 3H, $CH_2CH(CH_3)_2$), 2.04 (m, 1H, H-2) 1.8-1.1 (m, 6H, $(CH_2)_3CH_3$), 1.28 (d, 3H, $J_{4,5}$=6.4 Hz, H-5), 1.25 (m, 6H, 2x(SCH_2CH_3)), 1.18 (d, 3H, H-9), 1.14 (s, 9H, tBu), 0.99 (d, 6H, J=6.4 Hz, $CH_2CH(CH_3)_2$), 0.90 (m, 3H, $(CH_2)_3CH_3$).

Anal. Calcd for $C_{34}H_{57}NO_7S_2$: C, 62.26; H, 8.76; N, 2.14; S, 9.78. Found: C, 62.18; H, 8.68; N, 2.21; S, 9.66.

(2R, 3R, 4S) 4-(N-Benzyloxycarbonyl-O-*tert*-butyl-L-threonyloxy)-2-butyl-3-isovaleryloxy-pentanoic acid (14). Compound **13** (346 mg, 527 µmol) was dissolved in CH_3CN/H_2O 8/2 (10 mL). $CdCO_3$ (272 mg, 1.58 mmol) and then $HgCl_2$ (358 mg, 1.32 mmol) were added under vigorous stirring. After 320 min, the mixture was filtered and the solids were washed with Et_2O/hexane 1/1 (10 mL). The organic phase was washed with 0.5 M aq. KI (2x3 mL) and water (3 mL), dried and concentrated. To the residue, a solution of CrO_3 (158 mg, 1.58 mmol) in pyridine/HOAc 30/1 (6 mL) was added. After being stirred at room temperature for 22 h, ice-water and Et_2O (10 mL each) was added and the mixture was filtered. The aqueous phase was extracted with Et_2O (2x5 mL). The combined organic phase was washed with water (2x5 mL), dried and concentrated. Column chromatography (heptane/toluene/acetone/HOAc 40/20/1/2) gave **14** as a colourless oil (235 mg, 79%): TLC(E/H 1/2 with 2% HOAc) Rf = 0.39; $[\alpha]^{20}_D$=+5.4° (c 1.61, $CDCl_3$); (lit.[7] $[\alpha]^{20}_D$=+5.1° (c 1.4, $CHCl_3$)); IR (CCl_4) 3440 (NH), 1730 (CO), 1500 (N-CO) cm^{-1}; ^{1}H NMR δ 7.36 (m, 5H, C_6H_5), 5.65 (d, 1H, $J_{NH,7}$=9.7 Hz, NH), 5.34 (dd, 1H, $J_{2,3}$=9.0 Hz, $J_{3,4}$=5.5 Hz, H-3), 5.21, 5.12 (ABq, 2H, J_{AB}=12.2 Hz, CH_2Ph), 5.03 (m, 1H, H-4), 4.26 (dq, 1H, $J_{7,8}$=1.6 Hz, $J_{8,9}$=6.2 Hz, H-8), 4.14 (dd, 1H, H-7), 2.59 (m, 1H, H-2), 2.25 (d, 2H, J=6.6 Hz, $CH_2CH(CH_3)_2$), 2.14 (m, 1H, $CH_2CH(CH_3)_2$), 1.55 (m, 2H, $CH_2(CH_2)_2CH_3$), 1.4-0.9 (m, 4H, $(CH_2)_2CH_3$), 1.25 (d, 3H, $J_{4,5}$=6.3 Hz, H-5), 1.18 (d, 3H, H-9), 1.11

(s, 9H, tBu), 0.98 (d, 6H, J=6.5 Hz, $CH_2CH(C\underline{H}_3)_2$), 0.88 (m, 3H, $(CH_2)_3C\underline{H}_3$); ^{13}C NMR δ 176.3, 172.0, 170.2 (CO), 157.4 (OCON), 136.1, 128.6, 128.3, 128.2 (Ph), 74.1 ($\underline{C}(CH_3)_3$), 73.3 (C-3), 71.7 (C-4), 67.5 ($C\underline{H}_2Ph$), 67.3 (C-8), 60.1 (C-7), 46.9 (C-2), 43.4 ($\underline{C}H_2CH(CH_3)_2$), 29.0 ($CH_2\underline{C}H_2CH_2CH_3$), 28.5 ($C(\underline{C}H_3)_3$), 28.1 ($\underline{C}H_2(CH_2)_2CH_3$), 25.6 ($CH_2\underline{C}H(CH_3)_2$), 22.5 ($(CH_2)_2\underline{C}H_2CH_3$), 22.4 ($CH_2CH(\underline{C}H_3)_2$), 21.0 (C-9), 15.6 (C-5), 13.8 ($(CH_2)_3\underline{C}H_3$).

The 60 MHz ^1H NMR spectrum of **14** (75 mg in $CDCl_3$ with 1% TMS) was identical with an authentic spectrum kindly provided by M. Kinoshita and M. Nakata.

Anal. Calcd for $C_{30}H_{47}NO_9$: C, 63.70; H, 8.37; N, 2.48. Found: C, 63.72; H, 8.44; N, 2.41.

(2R, 3S, 1'R) 2-1'-Butyl-2',2'-bis(ethylthio)-ethyl-3-*tert*-butyldiphenylsiloxy-oxetane (15). Compound **10** (200 mg, 326 μmol) was dissolved in dry THF (10mL) and the solution was cooled to -70°C. $LiEt_3BH$ (978 μL, 1.0 M in THF, 978 μmol) was added, and after 10 minutes the cooling bath was removed. After being stirred at room temperature for 80 min, the solution was added *via* a double tipped needle into 2M aq. NH_4Cl. The aqueous phase was extracted with Et_2O (2x10 mL). The combined organic phase was dried and concentrated. Flash chromatography (E/H 1/20) gave **15** as a colourless oil (133 mg, 79%): TLC(E/H 1/3) Rf = 0.68; $[\alpha]^{20}_D$=+1.0° (c 1.62, $CDCl_3$); ^1H NMR δ 7.66-7.35 (m, 10H, C_6H_5), 5.05 (t, 1H, $J_{2,3}$=5.3 Hz, $J_{2,H\text{-}1'}$=6.1 Hz, H-2), 4.71 (ddd, 1H, $J_{3,4}$≈$J_{3,4}$=6.2 Hz, H-3), 4.36 (t, 1H, $J_{4a,4b}$=6.2 Hz, H-4a), 4.18 (t, 1H, H-4b), 3.85 (d, 1H, $J_{1',2'}$=3.2 Hz, H-2'), 2.54 (m, 4H, 2x(SCH_2)), 1.83 (m, 1H, H-1'), 1.70-1.15 (m, 6H, $(C\underline{H}_2)_3CH_3$), 1.22 (m, 6H, 2x($SCH_2C\underline{H}_3$)), 1.07 (s, 9H, tBu), 0.83 (m, 3H, $(CH_2)_3C\underline{H}_3$); ^{13}C NMR δ 135.6-127.5 (Ph), 92.0 (C-2), 76.6 (C-4), 69.5 (C-3), 52.5 (C-2'), 47.1 (C-1'), 30.6 ($CH_2\underline{C}H_2CH_2CH_3$), 26.8 ($C(\underline{C}H_3)_3$), 26.5 ($\underline{C}H_2(CH_2)_2CH_3$), 26.2 ($SCH_2$), 22.9 ($(CH_2)_2\underline{C}H_2CH_3$), 19.0 ($\underline{C}(CH_3)_3$), 14.4 ($SCH_2\underline{C}H_3$), 14.0 ($(CH_2)_3\underline{C}H_3$).

Anal. Calcd for $C_{29}H_{44}O_2S_2Si$: C, 67.39; H, 8.58; S, 12.41. Found: C, 67.31; H, 8.51; S, 12.34.

(2R, 3R, 4S) 2-Butyl-1,1-bis(ethylthio)-3,4-di-O-isopropylidene-pentane (16). 2-Methoxy-propene (92 μL, 977 μmol) and camphorsulfonic acid (~1 mg) were added to compound **11** (250 mg, 891 μmol) dissolved in dry CH_2Cl_2 (10 mL),. After being stirred for 1h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and water (5 mL), dried and concentrated. Flash chromatography (E/H 1/10) gave **16** as a colourless oil (272 mg, 95%): TLC(E/H 1/2) Rf = 0.68; $[\alpha]^{20}_D$=-12.0° (c 1.86, $CDCl_3$); ^1H NMR δ 4.32 (m, 2H, H-3, H-4), 3.79 (d, 1H, $J_{1,2}$=3.3 Hz, H-1), 2.63 (m, 4H, 2x(SCH_2)), 1.97 (m, 1H, H-2), 1.79-1.25 (m, 6H, $(C\underline{H}_2)_3CH_3$), 1.44, 1.33 (2 s, each 3H, $C(C\underline{H}_3)_2$), 1.26 (m, 6H, 2x($SCH_2C\underline{H}_3$)), 1.17 (d, 3H, $J_{4,5}$=6.1 Hz, H-5), 0.91 (m, 3H, $(CH_2)_3C\underline{H}_3$).

Anal. Calcd for $C_{16}H_{32}O_2S_2$: C, 59.95; H, 10.06; S, 20.00. Found: C, 60.00; H, 10.12; S, 20.10.

(2R, 3R, 4S) 2-Butyl-3,4-di-O-isopropylidene-pentanal (17). Compound **16** (189 mg, 590 μmol) was dissolved in CH_3CN/H_2O 8/2 (6 mL). $CdCO_3$ (254 mg, 1.47 mmol) and then $HgCl_2$ (352 mg, 1.30 mmol) were added. After being stirred for 20 min, the mixture was filtered and the solids were washed with Et_2O/hexane 1/1 (4x5 mL). The organic phase was washed with 0.5 M aq. KI (3 mL) and water (3 mL), dried and concentrated (20°C). Column chromatography (CH_2Cl_2/Et_2O 40/1) gave **17** as a colourless oil (121 mg, 96%): TLC(E/H 1/2) Rf = 0.58; $[\alpha]^{20}_D$=+76.2° (c 1.23, $CDCl_3$); (lit.[8f] $[\alpha]^{20}_D$=+63.3° (c 1.04, $CHCl_3$)); ^1H NMR δ 9.71 (d, 1H, $J_{1,2}$=1.9 Hz, CHO), 4.38 (m, 1H, H-4), 4.30 (dd, 1H, $J_{2,3}$=9.1 Hz, $J_{3,4}$=5.7 Hz, H-3),

2.60 (m, 1H, H-2), 1.9-1.2 (m, 6H, $(CH_2)_3CH_3$), 1.44, 1.34 (2 s, each 3H, $C(CH_3)_2$), 1.08 (d, 3H, $J_{4,5}$=6.4 Hz, H-5), 0.91 (m, 3H, $(CH_2)_3CH_3$).

This compound slowly decomposed at room temperature which may explain the different optical rotations. No elemental analysis was performed.

(3R, 4R, 5S) 3-Butyl-4-hydroxy-5-methyl-terahydrofuran-2-one ((-)-blastmycinolactol) (18). Compound **17** (113 mg, 527 μmol), dissolved in benzene (4.0 mL), was added to a solution of QBr (19 mg, 53 μmol) in H_2O (4.0 mL) and HOAc (200 μL, 3.5 mmol). $KMnO_4$ (166 mg, 1.05 mmol) was added and the mixture was vigorously stirred for 1h 40 min. The excess oxidant was reduced by addition of 4 M aq. $NaHSO_3$ (0.6 mL) and the aqueous phase was acidified to pH 2 and extracted with Et_2O (2x3 mL). The combined organic phase was washed with water (2 mL) and was then extracted with sat. aq. $NaHCO_3$ (3x3 mL). After acidification (pH 3), this aqueous phase was extracted with Et_2O (3x5 mL). The ethereal extract was dried and concentrated and the residue was dissolved in 1,4-dioxane (5 mL) and 2M aq. HCl (3 mL). After being stirred at room temperature for 80 min, CH_2Cl_2 and H_2O (5 mL each) were added to the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (2x2 mL). The combined organic phase was washed with 1% aq. $NaHCO_3$ (3 mL) and water (2 mL), dried and concentrated. Recrystallisation from Et_2O/petroleum ether (60-70) gave **18** as colourless needles (55.1 mg, 61 %): TLC(E/H 1/1) Rf = 0.47; mp 50-51°C (lit.[8g] 49.5-50.5°C); $[\alpha]^{20}_D$=-18.4° (c 0.98, CD_3OD) (lit.[8g] $[\alpha]^{18}_D$=-18° (c 1.09, MeOH)).

The ^1H NMR spectra (in CD_3OD and $CDCl_3$) were in accordance with literature data.[8g,9a]

(3R, 4R, 5S) 3-Butyl-4-isovaleryloxy-5-methyl-terahydrofuran-2-one ((+)-blastmycinone) (19). Compound **18** (26.0 mg, 151 μmol) was acylated with isovaleryl chloride as described for the preparation of **13**. Column chromatography (hexane/Et_2O 1/3) gave **19** as a colourless oil (29.8 mg, 77 %). TLC(E/H 1/2) Rf = 0.57; $[\alpha]^{20}_D$=+11.0° (c 2.43, $CDCl_3$) (lit.[8g] $[\alpha]^{17}_D$=+10° (c 1.2, $CHCl_3$)).

The ^1H NMR spectrum (in $CDCl_3$) was in accordance with literature data.[8g,9a]

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