Stereospecific Synthesis of Natural (+)Blastmycinone and Its Three (2*R*)-Diastereomers

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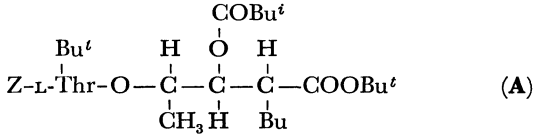
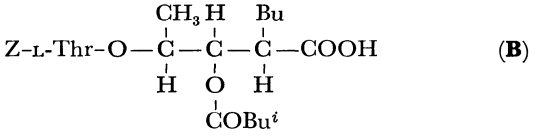
Natural (+)blastmycinone [(+)**1a**] and its three (2*R*)-diastereomers [(+)**1b**, (−)**1c**, and (−)**1d**] were synthesized through stereospecific routes *via* the corresponding (−)blastmycinolactol [(−)**2a**] and its diastereomeric hydroxylactones [(+)**2b**, (−)**2c**, and (−)**2d**] from methyl 4,6-*O*-benzylidene-3-*C*-butyl-3-deoxy-α-D-altropyranoside (**4**) prepared by the Grignard reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**3**) with butylmagnesium chloride. By the synthesis the relative configurations of natural type of racemic blastmycinone and its all diastereomers were completely established.

Natural (+)blastmycinone[1] [(+)**1a**], obtained by saponification of antimycin A_3 (blastmycin) under mild conditions, has recently been synthesized[2] from the synthetic (−)hydroxylactone [(−)**2a**] identical with natural (−)blastmycinolactol.[1] Hydroxylactone [(−)**2a**] was prepared by lithium aluminum hydride-reduction of the optically active (+)diastereomer (**A**) of *t*-butyl 4-(*N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonyloxy)-2-butyl-3-(isovaleryloxy)pentanoate; only this is adequate for the total synthesis of natural antimycin



(**A**)

A_3.[2] The absolute configuration(2*R*,3*R*,4*S*) of the natural (+)blastmycinone [(+)**1a**] has been established on the basis of the absolute configuration of (−)blastmycinolactol [(−)**2a**] which was determined through a stereospecific synthesis of the enantiomeric blastmycinolactol [(+) **2a**].[3] The natural type of racemic blastmycinone and its diastereomers have also been synthesized and characterized by tlc and PMR.[2]* An optically active diastereomer (−)**1b** has been obtained together with the enantiomeric blastmycinone [(−)**1a**] as a byproduct in the lactonization reaction** of (2*S*,3*S*,4*R*)-4-(*N*-benzyloxycarbonyl-L-threonyloxy)-2-butyl-3-(isovaleryloxy)pentanoic acid (**B**) with trifluoroacetic anhydride in benzene.



(**B**)

A recent study by Koyama *et al.*[4] on stereoselective synthesis and relative configurations of the racemic diastereomers of blastmycinone indicates that the configuration of the diastereomer **1b** is 2,3-*cis*: 3,4-*cis*. The diastereomer (−)**1b** appears to be the 3-epimer of the enantiomeric blastmycinone (−)**1a**. However, the possibility of 4-epimerization, which may partly occur on the C-4 of compound **B** under the reaction conditions of lactonization, cannot be excluded. Confirmation of the configuration of **1b** was thus undertaken by an unambiguous method. For this purpose, we attempted a stereospecific synthesis of four optically active diastereomeric blastmycinones [(+)**1a**, (+)**1b**, (−)**1c**, and (−)**1d**], all of which have "2*R*" configuration, similar to that in the natural blastmycinone (+)**1a**, as shown in Fig. 1.

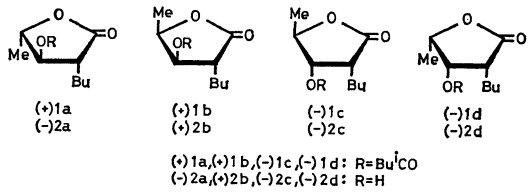


Fig. 1. Absolute configurations of diastereomeric (2*R*)blastmycinones and blastmycinolactols.

Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[5] (**3**) was treated with excess butylmagnesium chloride in ether according to the procedure of Inch and Lewis[6] to afford methyl 4,6-*O*-benzylidene-3-*C*-butyl-3-deoxy-α-D-altropyranoside (**4**) in a 64% yield. Acetylation of **4** with acetic anhydride in pyridine gave the 2-acetate (**5**). The structures of **4** and **5** were confirmed by PMR analysis. Compounds **4** and **5** were treated with *N*-bromosuccinimide[7] in boiling carbon tetrachloride to yield methyl 4-*O*-benzoyl- 6- bromo- 3- *C*- butyl- 3,6- dideoxy- α- D- altropyranoside (**6**) and its 2-acetate (**7**), respectively, in excellent yields.

Lithium aluminum hydride-reduction of **6** in tetrahydrofuran gave methyl 3-*C*-butyl-3,6-dideoxy-α-D-altropyranoside (**8**) in a 76% yield. Acetolysis of **8** with acetic anhydride–sulfuric acid afforded 1,2,4-tri-*O*-acetyl-3-*C*-butyl-3,6-dideoxy-D-altropyranose (**9**) as a syrupy anomeric mixture. Hydrolysis of **9** with methanolic sodium hydroxide gave a free sugar **10**, which was subjected to periodate oxidation to yield 2-*C*-butyl-2,5-dideoxy-3-*O*-formyl-D-ribofuranose (**11**) in an excellent yield. The structure of **11** was supported by its PMR spectral data ($J_{1,2}$=4.7 Hz, $J_{2,3}$=10.0 Hz, $J_{3,4}$=5.8 Hz, and δ($CDCl_3$) 8.23(s, OCHO)]. De-O-formylation of **11** with 2% hydrochloric acid in aqueous dioxane followed by oxidation with bromine–water afforded (−)(2*R*,3*S*,4*R*)-2-butyl-3,4-dihydroxypentanoic acid-1,4-lactone[(−)**2c**] in a 68% yield. Isovalerylation of (−)**2c** with isovaleric anhydride in

* Racemic blastmycinone and its diastereomers were previously designated in order of decreasing R_f-value of tlc with the solvent G (see Experimental) as **1a**, **1b**, **1c**, and **1d**.

** This reaction mainly gave the nine-membered dilactone derivative, from which the diastereomeric antimycin A_3 was synthesized.[2]

Table 1. PMR-spectra data of synthetic (2*R*)blastmycinolactols (in CD_3OD) and blastmycinones (in $CDCl_3$). chemical shifts (δ values) and coupling constants (Hz)

Compounds:	(2*R*)Blastmycinolactols				(2*R*)Blastmycinones			
	(−)**2a**	(+)**2b**	(−)**2c**	(−)**2d**	(+)**1a**	(+)**1b**	(−)**1c**	(−)**1d**
H-3(dd)	3.76	4.18	4.18	4.31	4.95	5.24	5.20	5.68
H-4(dq)	4.20	4.73	4.52	4.56	4.37	4.82	4.51	4.63
4-CH_3(d)	1.41	1.36	1.33	1.38	1.45	1.36	1.40	1.32
$J_{2,3}$	8.2	3.4	5.6	4.7	5.8	3.0	6.0	5.5
$J_{3,4}$	7.5	5.0	1.1	3.3	4.5	5.0	0.7	3.4
J_{4,CH_3}	6.0	6.7	6.8	6.3	6.5	6.5	6.5	6.5

pyridine gave (−)blastmycinone-c [(−)**1c**] in an 86% yield. The synthetic sample showed on tlc (solvent G) a single spot having the same R_f-value as that of the racemic blastmycinone-c (**1c**). The PMR spectrum of (−)**1c** was identical with that of **1c**. (Table 1)

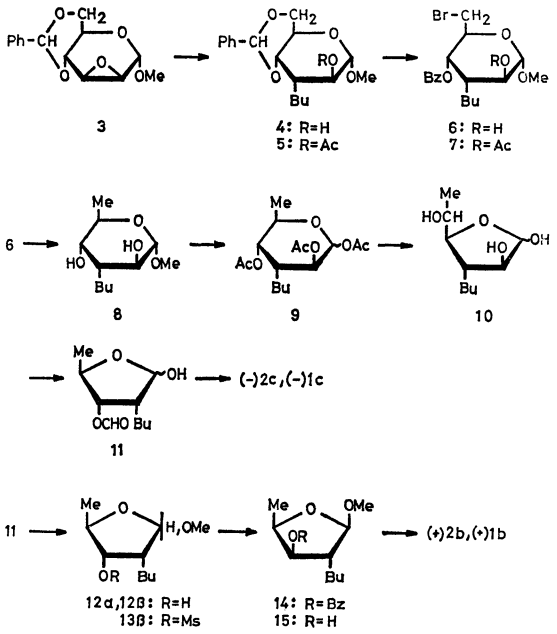


Chart 1.

The periodate-oxidation product **11** was treated with 0.5% methanolic hydrogen chloride to afford an anomeric mixture of the methyl glycoside, which was fractionated on silica gel to give α-anomer (**12**α, 30%) and β-anomer (**12**β, 50%). Treatment of the major product **12**β with methanesulfonyl chloride in pyridine gave 3-mesylate (**13**β), which was subsequently treated with sodium benzoate in dimethylsulfoxide (DMSO) at 140—145 °C for 3 hr to afford the 3-inverted-benzoate (**14**) in a 41% yield. De-O-benzoylated glycoside **15**, obtained by hydrolysis of **14** with 0.1 M methanolic sodium hydroxide, was easily converted into free sugar by treatment with 0.1 M hydrochloric acid in aqueous dioxane at room temperature. The product was then oxidized with bromine-water to afford (+)(2*R*,3*R*,4*R*)-2-butyl-3,4-dihydroxypentanoic acid-1,4-lactone [(+)**2b**] in a 62% yield based on **14**. Isovalerylation of (+)**2b** gave (+)blastmycinone-b [(+)**1b**] in an 88% yield. This showed the same R_f-value as that of the racemic blastmycinone-b (**1b**) on tlc (solvent G), its PMR spectrum also being identical with that of **1b**. (Table 1)

Compound **7** was treated with silver fluoride[8a,8b] in pyridine at room temperature to afford 5-eno-pyranoside (**16**, 91%) as a syrup, whose PMR spectrum showed overlapping narrow multiplets at δ 4.77—4.88 attributed to the terminal methylene protons (H-6, H-6′). Since **16** did not crystallize and showed an R_f-value close to that of **7** on tlc with all solvent systems employed, it was used without further purification for the subsequent synthesis. Hydrogenation of **16** on palladium black followed by removal of some impurities through a silica gel column gave exclusively methyl 2-*O*-acetyl-4-*O*-benzoyl-3-*C*-butyl-3,6-dideoxy-β-L-galactopyranoside (**17**) in a 70% yield. First-order analysis of the PMR spectrum of **17** revealed large ring proton coupling constants ($J_{1,2}$=8.0 and $J_{2,3}$=11.1 Hz), which suggest the preferred conformation of **17** to be 1*C* chair. Acetolysis of **17** with acetic anhydride–sulfuric acid yielded 1,2-di-*O*-acetyl-4-*O*-benzoyl-3-*C*-butyl-3,6-dideoxy-α-L-galactopyranose (**18**) which was contaminated by a small amount of its β-anomer. The protecting groups of **18** were removed with methanolic sodium hydroxide to give **19**, which was then subjected to periodate-oxidation to afford 2-*C*-butyl-2,5-dideoxy-3-*O*-formyl-L-lyxofuranose (**20**) as a semicrystalline anomeric mixture in a 98% yield based on **17**. De-O-formylation of **20** followed by oxidation with bromine–water gave the crystalline diastereomeric hydroxylactone[(−)**2d**, mp 99.0—100.5 °C] in a 51% yield. Isovalerylation of (−)**2d** afforded (−)blastmycinone-d [(−)**1d**, mp 47–48 °C] in an 86% yield, which could be characterized as blastmycinone-d by tlc and PMR.

Subsequently, the natural (+)blastmycinone [(+)**1a**] was synthesized *via* the natural (−)blastmycinolactol [(−)**2a**] as follows. Free sugar **20** was treated with 0.1 M methanolic hydrogen chloride to afford methyl 2-*C*-butyl-2,5-dideoxy-β-L-lxyofuranoside (**21**) as a major product in a 60% yield. The β-glycoside **21** was mesylated and the resulting crystalline mesylate **22** was treated with sodium benzoate in DMSO to give methyl 3-*O*-benzoyl-2-*C*-butyl-2,5-dideoxy-β-L-arabinofuranoside (**23**) in a 42% yield based on **21**, which was proved to be structurally homogeneous by PMR analysis. Debenzoylated product **24** obtained from **23** was hydrolyzed with 0.1 M hydrochloric acid and the resulting free sugar was treated with bromine-water to afford (−)**2a** (mp 49.5—50.5 °C) in an 84% yield.

This product was identical with the authentic sample of natural (−)blastmycinolactol,[2] from which the natural (+)blastmycinone [(+)**1a**] had been derived in an excellent yield.[2]

The configuration of the diastereomer **1b** was unambiguously determined from the above results, the relative configurations of all diastereomeric blastmycinones (**1a**, **1b**, **1c**, and **1d**) being completely established. Configurations [2,3-*cis*:3,4-*cis* for **1b** and 2,3-*trans*:3,4-*cis* for **1d**] proposed by Koyama *et al.*[4] should be revised to 2,3-*trans*:3,4-*cis* for **1b** and 2,3-*cis*:3,4-*cis* for **1d**. Consequently, the byproduct (−)**1b** formed during the lactonization of **B** was proved to be the 4-epimer of the enantiomeric blastmycinone [(−)**1a**].

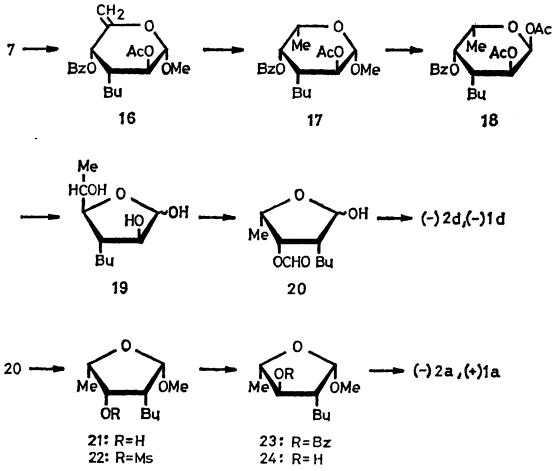


Chart 2.

Finally, we wish to describe the preferred conformations of the optically pure hydroxylactones, (−)**2a**, (+)**2b**, (−)**2c**, and (−)**2d**, in various solvents, which may closely be related to those of the corresponding diastereomeric blastmycinones, (+)**1a**, (+)**1b**, (−)**1c**, and (−)**1d**. The observed ring proton coupling constants ($J_{2,3}$, $J_{3,4}$) of these hydroxylactones in deuteromethanol (Table 1), benzene, pyridine, and deuterochloroform were approximately equal and their CD spectra in methanol measured at room temperature showed no double-humped CD curve[9] but single negative Gaussian curves corresponding to a negative Cotton effect. These evidences indicate that the hydroxylactones in solution may predominantly exist in either nonplaner E_3 or E^3 conformation which is considered to be stable conformation[10] of 1,4-lactone under the preference of co-planarity of the five atoms of lactone group (C–CO–O–C).

Legrand and Bucourt rules[11] on ring chirality allow the negative sign of the Cotton effect to be predicted for the E_3 conformations (Fig. 2) without any conflict with the established correlation between the negative sign of the Cotton effect and the absolute configuration (2*R*) at C_2 of the 1,4-lactone, which has been proposed for the aldono-1,4-lactone by Okuda *et al.*[12] and discussed by Beecham.[13] The prediction was confirmed by PMR data (Table 1) in the following way.

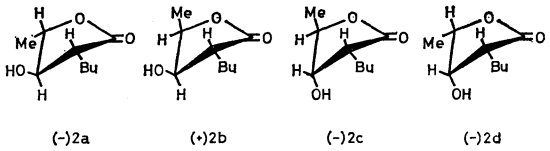


Fig. 2. Preferred conformations of diastereomeric (2*R*)blastmycinolactols.

Coupling constants ($J_{2,3}$, $J_{3,4}$) of (−)**2a** and (−)**2c** could be explained most satisfactorily on the assumption of E_3 conformation (Fig. 2) for the hydroxylactones, (−)**2a** and (−)**2c**. Calculation of the dihedral angles ($\phi_{2,3}$, $\phi_{3,4}$) of (+)**2b** carried out according to the method of Karplus[14] with the coupling constants ($J_{2,3}$, $J_{3,4}$) of (+)**2b** indicates that two conformers, (E^3 $\phi_{2,3}=128°28'$, $\phi_{3,4}=37°54'$) and E^3 ($\phi_{2,3}=48°51'$, $\phi_{3,4}=37°54'$), are possible for (+)**2b**. From a consideration of the Dreiding models, it appears that, in the E_3 conformer, the observed angle (θ *ca.* 20°) of the buckle*** of the lactone ring forces the C-4 methyl group and the C-2 hydrogen atom into a non-parallel axial orientation by which they are kept at a distance, a small 1,3-diaxial interaction between them thus being expected, while is in the E^3 conformation ($\theta \leq 65°$) the bulky C-2 butyl group closely located to the C-4 hydrogen atom which is oriented in an almost parallel axial position to the butyl group, and thus a larger 1,3-diaxial interaction should be expected. In conclusion, the E_3 conformer appears to be more favorable.

On the last hydroxylactone (−)**2d**, the calculated dihedral angles ($\phi_{2,3}=40°00'$ and $\phi_{3,4}=49°32'$) could be applied to both E_3 and E^3 conformers of the lactone. Consideration by means of the model suggests the E^3 conformer (θ *ca.* 45°) to be unfavorable, since a larger 1,3-diaxial interaction between the bulky butyl group in quasi axial position at C-2 and the quasi axial methyl group at C-4 is expected, and the interaction between the hydrogen atoms at C-2 and C-4 in the E_3 conformer might be smaller.

Experimental

Melting points were determined on a micro hot stage and are uncorrected. IR spectra were taken on a Hitachi 225 Spectrophotometer, and PMR spectra on a Varian A-60D Spectrometer using TMS as an internal standard. Optical rotations were measured with a Zeiss Photoelectric Precision Polarimeter. CD spectra were taken on a JASCO J-20 Spectropolarimeter. Tlc was carried out on Wakogel B-5 (Wako Pure Chemical Industries, Ltd.) and silica gel column chromatography on Wakogel C-200 which was activated at 110 °C for 1 hr. The following solvent systems were used: A [hexane–acetone(5 : 1)], B [*ditto*(10 : 1)], C [benzene–ethyl acetate(12 : 1)], D [*ditto*(1 : 1)], E [*ditto*(6 : 1)], F [*ditto*(50 : 1)], and G [petroleum ether–diisopropyl ether (7 : 4)]. In general, all concentrations were carried out at reduced pressure below 40 °C.

*** Extent of the buckle is represented in the angle (θ) between planes $C_{(2)}-\underset{\underset{O}{\|}}{C}_{(1)}-O-C_{(4)}$ and $C_{(2)}-C_{(3)}-C_{(4)}$.[15]

1. *Methyl 4,6-O-Benzylidene-3-C-butyl-3-deoxy-α-D-altropyranoside (4).*[3] Fresh magnesium shavings (11.1 g, 0.457 mol) were covered with dry ether (160 ml) and activated by addition of a piece of iodine. After the activation reaction had started, butyl chloride (47.9 ml, 0.460 mol) was added under stirring at room temperature for 1 hr to form butylmagnesium chloride. After standing for 12 hr, a solution of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**3**)[5] (8.00 g, 30.3 mmol) in dry ether (400 ml) was added to the viscous suspension. The mixture was refluxed for 9 hr under vigorous stirring, then cooled in an ice-bath, and carefully decomposed with ice-water (200 ml). The ether layer was washed with saturated aqueous NaCl, dried and evaporated to give a syrup (11.3 g), which was chromatographed on a silica gel column (1.7 kg) with solvent A to afford a homogeneous sample of **4** as a colorless oil (6.25 g, 64%): $[\alpha]_D^{18}$ +135° (*c* 1.80, chloroform); δ ($CDCl_3$) 3.41 (s, OCH_3), 4.58 (dd, H-1, $J_{1,2}=J_{1,3}=1.0$ Hz), and 5.67 (s, PhC<u>H</u>).

Found: C, 67.36; H, 7.82%. Calcd for $C_{18}H_6O_5$: C, 67.06; H, 8.13%.

2. *Methyl 2-O-Acetyl-4,6-O-benzylidene-3-C-butyl-3-deoxy-α-D-altropyranoside (5).* Acetic anhydride (1.29 ml, 13.6 mmol) was added to a solution of **4** (2.20 g, 6.82 mmol) in dry pyridine (20 ml). After standing overnight at 40 °C, the mixture was poured into cold water (45 ml) and then extracted with chloroform (30 ml×4). The combined organic layers were washed with saturated aqueous $KHSO_4$, $NaHCO_3$, and NaCl, successively. The dried solution was evaporated to give the 2-acetate **5** (2.49 g, 100%) as a pale yellow syrup. A part of this was purified through a silica gel column with solvent B to afford an analytical sample of **5**: $[\alpha]_D^{23}$ +78° (*c* 1.4, chloroform); δ ($CDCl_3$) 2.11 (s, OAc), 3.41 (s, OCH_3), 4.56 (dd, H-1, $J_{1,2}=J_{1,3}=1.0$ Hz), 5.04 (dd, H-2, $J_{2,3}=2.0$ Hz), and 5.68 (s, PhC<u>H</u>).

Found: C, 66.14; H, 7.63%. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74%.

3. *Methyl 4-O-Benzoyl-6-bromo-3-C-butyl-3,6-dideoxy-α-D-altropyranoside (6).* A mixture of **4** (2.80 g, 8.70 mmol), and *N*-bromosuccinimide (NBS) (1.86 g, 10.4 mmol) in carbon tetrachloride (100 ml) containing barium carbonate (2.42 g, 12.3 mmol) was heated for 2.5 hr under stirring at 80 °C. Solids were filtered off, and the filtrate was washed with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$, and NaCl, successively. The dried solution was evaporated to give 6-bromo-4-benzoate **6** (3.49 g, 100%) as a syrup which was suitable for the next synthesis. A part of this was chromatographed on silica gel with solvent C to afford a pure sample of **6**: $[\alpha]_D^{20}$ +19° (*c* 2.02, chloroform); δ ($CDCl_3$) 3.56 (s, OCH_3), 4.66 (d, H-I, $J_{1,2}=4.7$ Hz), and 5.45 (dd, H-4, $J_{3,4}=4.0$, $J_{4,5}=5.2$ Hz).

Found: C, 53.86; H, 6.24; Br, 20.03%. Calcd for $C_{18}H_{25}O_5Br$: C, 53.87; H, 6.28; Br. 19.91%.

4. *Methyl 2-O-Acetyl-4-O-benzoyl-6-bromo-3-C-butyl-3,6-dideoxy-α-D-altropyranoside (7).* A solution of **5** (2.30 g, 6.32 mmol) in dry carbon tetrachloride (100 ml) was treated with NBS (1.35 g, 7.58 mmol) and barium carbonate (1.77 g, 8.95 mmol) in the manner described in the Expt. 3 to afford a practically pure sample of **7** (2.80 g, 100%). A part of this was purified through a silica gel column with solvent C to give a pure sample of **7** as a colorless syrup: $[\alpha]_D^{23}$ +46° (*c* 1.62, chloroform); δ ($CDCl_3$) 2.16 (s, OAc), 4.73 (d, H-1, $J_{1,2}=1.8$ Hz), 5.09 (dd, H-2, $J_{2,3}=4.4$ Hz), and 5.40 (dd, H-4, $J_{3,4}=5.1$, $J_{4,5}=8.6$ Hz)

Found: C, 54.48; H, 6.11; Br, 18.33%. Calcd for $C_{20}H_{27}O_6Br$: C, 54.18; H, 6.14; Br, 18.03%.

5. *Methyl 3-C-Butyl-3,6-dideoxy-α-D-altropyranoside (8).* A suspension of $LiAlH_4$ (2.65 g, 69.6 mmol) in dry tetrahydrofuran (THF) (100 ml) was added in one portion to a stirred and cooled solution of **6** (3.45 g, 8.60 mmol) in dry THF (140 ml). The mixture was refluxed for 1 hr under stirring. To the cooled reaction mixture was slowly added ethyl acetate and water under stirring and solids were then filtered off. The filtrate was washed with water and saturated aqueous NaCl. The dried solution was evaporated and the residue (3.0 g) was purified through a silica gel column (200 g) with solvent D to afford a homogeneous sample of **8** (1.43 g, 76%) as a colorless oil: $[\alpha]_D^{19}$ +24° (*c* 1.31, chloroform); δ ($CDCl_3$) 1.31 (d, 5-CH_3, $J=6.7$ Hz), 3.49 (s, OCH_3), 4.13 (dq, H-5, $J_{4,5}=4.2$ Hz), and 4.51 (d, H-1, $J_{1,2}=6.0$ Hz).

Found: C, 60.64; H, 10.20%. Calcd for $C_{11}H_{21}O_4$: C, 60.52; H, 10.16%.

6. *1,2,4-Tri-O-acetyl-3-C-butyl-3,6-dideoxy-D-altropyranose (9).* To a solution of **8** (1.05 g, 4.82 mmol) in acetic anhydride (25.6 ml, 270 mmol) was added concd sulfuric acid (0.226 ml, 4.24 mmol) under ice-cooling. After being kept for 30 min at room temperature, the reaction mixture was poured into cold water (150 ml) and the solution was neutralized with solid $NaHCO_3$ and then extracted with chloroform (60 ml× 3). The combined extracts were washed with saturated aqueous NaCl, dried and evaporated to give a sample of **9** (1.59 g, 100%) as a yellow syrup: δ ($CDCl_3$) 1.31 (d, 5-CH_3, $J=6.8$ Hz) and 2.1—2.2 (three OAc).

7. *3-C-Butyl-3,6-dideoxy-D-altrofuranose (10).* To a solution of **9** (1.59 g, 4.82 mmol) in methanol (15 ml) was added aqueous 1M NaOH (14 ml) under ice-cooling. After being kept standing for 50 min at room temperature, the solution was neutralized with carbon dioxide and evaporated. To the residue was added acetone. The insoluble matter was filtered off and the filtrate was evaporated to afford the syrupy free sugar **10** (980 mg, 100%) as an anomeric mixture: δ ($CDCl_3$) 1.11 (d, 5-CH_3, $J=6.8$ Hz), 5.29 (d, $J_{1,2}=3.8$ Hz) and 5.40 (s) (each anomeric H-1).

8. *2-C-Butyl-2,5-dideoxy-3-O-formyl-D-ribofuranose (11).* To a solution of **10** (948 mg, 4.64 mmol) in acetone (28 ml) was added a solution of sodium metaperiodate (3.08 g, 14.4 mmol) in water (30 ml). The mixture was stirred for 4 hr at room temperature and the precipitates formed were filtered off and washed with acetone. The combined filtrate and washings were evaporated and the residue was dissolved in chloroform. The solution was washed with saturated aqueous NaCl, dried and evaporated to afford a sample of **11** (940 mg, 100%) as a colorless syrup, which was used for the subsequent synthesis without further purification: δ ($CDCl_3$) 1.28 (d, 4-CH_3, $J=6.8$ Hz), 5.22 (dd, H-3, $J_{2,3}=10.0$ Hz, $J_{3,4}=5.8$ Hz), 5.44 (d, H-1, $J_{1,2}=4.7$ Hz), and 8.23 (s, OC<u>H</u>O).

9. *(−)(2R,3S,4R)-2-Butyl-3,4-dihydroxypentanoic Acid-1,4-Lactone[(−)2c].* A sample of **11** (50 mg, 0.25 mmol) was de-O-formylated with 2% HCl (W/V) in 50% dioxane-water (v/v) (8.8 ml) for 2 hr at room temperature. The reaction mixture was then neutralized with solid $NaHCO_3$. To the mixture containing the de-O-formylated product was added bromine (0.016 ml, 0.32 mmol) and the mixture was stirred at room temperature for 2.5 hr. The oxidation product was extracted with ethyl acetate. The extract was washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, successively, dried and evaporated. The residue (60 mg) was purified through silica gel (6 g) with solvent E to afford a homogeneous sample of (−)**2c** (29.1 mg, 68%) as a colorless syrup: $[\alpha]_D^{17}$ −69° (*c* 0.28, methanol); $[\theta]_{215}^{MeOH}$ −6400; $\nu_{max}^{CCl_4}$ (0.002 M) 3620 (OH) and 1780 cm^{-1} (1,4-lactone).

Found: C, 62.56; H, 9.18%. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

10. *(−)(2R,3S,4R)-2-Butyl-4-hydroxy-3-(isovaleryloxy)-pentanoic Acid-1,4-lactone [(−)blastmycinone-c][(−)**1c**].* Isovaleric anhydride (0.042 ml, 0.20 mmol) was added to a solution of (−)**2c** (18.2 mg, 0.106 mmol) in dry pyridine (0.7 ml). After being kept for 40 hr at room temperature, the reaction mixture was poured into cold water and extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried and evaporated. The residue (31 mg) was chromatographed on silica gel (3 g) with solvent G to afford a pure sample of (−)**1c** (23.1 mg, 86%) as a colorless oil: $[\alpha]_D^{18}$ −88° (*c* 0.97, chloroform); $\nu_{max}^{CCl_4}$ (0.1 M) 1790 (1,4-lactone) and 1742 cm^{-1} (ester); R_f 0.48 (solvent G).

Found: C, 65.66; H, 9.39%. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44%.

11. *Methyl 2-C-Butyl-2,5-dideoxy-β-D-ribofuranoside (**12β**) and Its α-Anomer (**12α**).* Periodate-oxidation product **11** (646 mg, 3.19 mmol) was treated with 0.5% methanolic HCl (32.3 ml) for 1.5 hr at room temperature. The reaction mixture was neutralized with solid $NaHCO_3$ and the insoluble matter was removed by filtration. The filtrate was evaporated and the residue (561 mg) was chromatographed on silica gel (70 g) with solvent E to fractionate α-anomer (**12α**) as a faster-moving component and the β-anomer (**12β**) as a slower migration component. α-Anomer (**12α**): colorless oil, 180 mg (30%); $[\alpha]_D^{18}$ +95° (*c* 0.86, chloroform); δ ($CDCl_3$) 1.19 (d, 4-CH_3, J=6.7 Hz), 3.39 (s, OCH_3), 3.74 (dd, H-3, $J_{2,3}$=5.2 Hz, $J_{3,4}$=0.4 Hz), 4.29 (dq, H-4), and 4.91 (d, H-1, $J_{1,2}$=3.8 Hz).

Found: C, 64.06; H, 10.50%. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71%.

β-Anomer (**12β**): colorless oil, 295 mg (50%); $[\alpha]_D^{18}$ −79° (*c* 1.26, chloroform); δ ($CDCl_3$) 1.30 (d, 4-CH_3, J=6.3 Hz), 3.45 (s, OCH_3), 4.11 (dd, H-3, $J_{2,3}$=5.7 Hz, $J_{3,4}$=2.3 Hz), 4.14 (dq, H-4), and 4.80 (d, H-1, $J_{1,2}$=4.1 Hz).

Found: C, 64.07; H, 10.50%. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71%.

12. *Methyl 2-C-Butyl-2,5-dideoxy-3-O-methanesulfonyl-β-D-ribofuranoside (**13β**).* To a solution of **12β** (120 mg, 0.64 mmol) in dry pyridine (1.2 ml) was added methanesulfonyl chloride (0.06 ml, 0.77 mmol) and the solution was kept for 2 hr at room temperature. After addition of water (15 ml), the mixture was extracted with chloroform and the extract was washed with saturated aqueous NaCl, dried and evaporated to afford 3-mesylate (**13β**) (157 mg, 93%) as a pale yellow syrup, which was used for the subsequent synthesis without further purifications, because of its instability. **13β**: δ ($CDCl_3$) 1.34 (d, 4-CH_3, J=6.7 Hz), 3.06 (s, OMs), 3.44 (s, OCH_3), 4.42 (dq, H-4, $J_{3,4}$=2.3 Hz), 4.83 (d, H-1, $J_{1,2}$=4.4 Hz), and 5.01 (dd, H-3, $J_{2,3}$=5.7 Hz).

13. *Methyl 3-O-Benzoyl-2-C-butyl-2,5-dideoxy-β-D-xylofuranoside (**14**).* A mixture of **13β** (157 mg, 0.59 mmol) and sodium benzoate (255 mg, 1.77 mmol) in dry DMSO (3.1 ml) was heated at 140—145 °C for 3 hr. After being cooled to room temperature, the solids were filtered and washed with ethyl acetate. The combined filtrate and washings were washed with water and saturated aqueous NaCl. The dried solution was evaporated and the residue (210 mg) was chromatographed on silica gel (20 g) with solvent F to afford a homogeneous sample of **14** (70 mg, 41%) as a colorless syrup: $[\alpha]_D^{18}$ −15° (*c* 0.45, chloroform); δ ($CDCl_3$) 1.32 (d, 4-CH_3, J=6.4 Hz), 3.45 (s, OCH_3), 4.52 (dq, H-4, $J_{3,4}$=5.8 Hz), 4.76 (d, H-1, $J_{1,2}$=2.3 Hz), and 5.25 (dd, H-3, $J_{2,3}$=2.7 Hz).

Found: C, 69.61; H, 8.22%. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27%.

14. *Methyl 2-C-Butyl-2,5-dideoxy-β-D-xylofuranoside (**15**).* A solution of **14** (70 mg, 0.24 mmol) in dry methanol (0.29 ml) was treated with 1M methanolic sodium methoxide (0.288 ml) for 1 hr at room temperature. The solution was neutralized with 1M HCl and evaporated to give a sample of **15** (45 mg, 100%) as a pale yellow oil: δ ($CDCl_3$) 1.34 (d, 4-CH_3, J=6.7 Hz), 3.40 (s, OCH_3), and 4.78 (s, H-1).

15. *(+)(2R,3R,4R)-2-Butyl-3,4-dihydroxypentanoic Acid-1,4-Lactone [(+)**2b**].* A sample of **15** (45 mg, 0.24 mmol) was treated with 1M HCl/50% aqueous dioxane (0.45 ml) for 1 hr at room temperature. The reaction mixture containing the free sugar was neutralized with solid $NaHCO_3$, and then treated with bromine (0.015 ml, 0.30 mmol) for 3 hr at room temperature. The reaction mixture was worked up and purified by the procedure described in Expt. 9 to afford a homogeneous sample of (+)**2b** (25.3 mg, 62%) as a colorless oil: $[\alpha]_D^{18}$ +71° (*c* 0.53, methanol); $[\theta]_{216}^{MeOH}$ −3500; $\nu_{max}^{CCl_4}$ (0.002M) 3625 (OH) and 1783 cm^{-1} (lactone).

Found: C, 62.45; H, 9.10%. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

16. *(+)(2R,3R,4R)-2-Butyl-4-hydroxy-3-(isovaleryloxy)-pentanoic Acid-1,4-Lactone [(+)Blastmycinone-b] [(+)**1b**].* By the same procedure as in the preparation of (−)**1c**, the hydroxylactone (+)**2b** (18.5 mg) was isovalerylated to afford (+)**1b** (24.3 mg, 88%) as a colorless oil: $[\alpha]_D^{17}$ +57° (*c* 1.01, chloroform); $\nu_{max}^{CCl_4}$ (0.1 M) 1790 (1,4-lactone) and 1743 cm^{-1} (ester); R_f 0.60 (solvent G).

Found: C, 65.82; H, 9.40%. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44%.

17. *Methyl 2-O-Acetyl-4-O-benzoyl-3-C-butyl-3,6-dideoxy-α-D-arabino-hex-5-enopyranoside (**16**).* Anhydrous silver fluoride (3.40 g, 26.8 mmol) was added to a solution of **7** (2.00 g, 4.52 mmol) in dry pyridine (30 ml), and the mixture was stirred for 1.5 hr at room temperature in the dark. Addition of ether (100 ml) to the reaction mixture gave precipitates, which were filtered and washed with ether. The combined filtrate and washings were washed with saturated aqueous $KHSO_4$, $NaHCO_3$, and NaCl, successively. The dried solution was evaporated to afford a sample of **16** (1.48 g, 91%) as a yellow syrup which was used for the subsequent synthesis without further purification: δ ($CDCl_3$) 2.16 (s, OAc), 3.54 (s, OCH_3), 4.68 (d, H-1, $J_{1,2}$=4.7 Hz), 4.77–4.88 (m, 2H, H-6 and H-6'), 5.24 (dd, H-2, $J_{2,3}$=7.8 Hz), and 5.89 (d, H-4, $J_{3,4}$=3.2 Hz).

18. *Methyl 2-O-Acetyl-4-O-benzoyl-3-C-butyl-3,6-dideoxy-β-L-galactopyranoside (**17**).* To a solution of **16** (1.48 g, 4.08 mmol) in dioxane (50 ml) was added freshly prepared palladium black (*ca.* 300 mg) and the mixture was stirred vigorously for 2 hr under bubbling with hydrogen. The filtered solution was evaporated and the residue (1.60 g) was chromatographed on silica gel (160 g) with solvent B to afford a homogeneous sample of **17** (1.03 g, 70%) as a colorless syrup: $[\alpha]_D^{23}$ −89° (*c* 1.52, chloroform); δ ($CDCl_3$) 1.24 (d, 5-CH_3, J=6.4 Hz), 2.13 (s, OAc), 3.55 (s, OCH_3), 3.91 (dq, H-5, $J_{4,5}$=1.0 Hz), 4.43 (d, H-1, $J_{1,2}$=8.0 Hz), 5.11 (dd, H-2, $J_{2,3}$=11.1 Hz), and 5.44 (dd, H-4, $J_{3,4}$=2.8 Hz).

Found: C, 66.13; H, 7.66%. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74%.

19. *1,2,-Di-O-acetyl-4-O-benzoyl-3-C-butyl-3,6-dideoxy-α-L-galactopyranose (**18**).* A sample of **17** (1.00 g, 2.74 mmol) was treated with acetic anhydride (30 ml, 313 mmol) and concd. sulfuric acid (0.29 ml, 5.46 mmol) for 1 hr at room temperature. The solution was worked up by the procedure described in Expt. 6 to give a sample of **18** (1.08 g, 100%) contaminated by a small amount of its β-anomer, as a yellow syrup: δ ($CDCl_3$) 1.17 (d, 5-CH_3, J=6.6 Hz), 2.07 and

2.18 (each s, OAc), 4.37 (dq, H-5, $J_{4,5}$=0.8 Hz), 5.29 (dd, H-2, $J_{2,3}$=11.8 Hz), 5.57 (dd, H-4, $J_{3,4}$=2.3 Hz), and 6.46 (d, H-1, $J_{1,2}$=3.4 Hz) [β-anomer contaminated, 5.83 (d, H-1, $J_{1,2}$=8.2 Hz)].

20. *2-C-Butyl-2,5-dideoxy-3-O-formyl-L-lyxofuranose (**20**).* A solution of product **18** (1.00 g, 2.55 mmol) in methanol (25 ml) was treated with 1 M NaOH (16.5 ml) for 4 hr at room temperature. The solution was worked up by the procedure described in Expt. 7 to afford 3-*C*-butyl-3,6-dideoxy-L-galactofuranose (**19**) (520 mg, 100%) as a pale yellow syrup. A solution of **19** (500 mg, 2.45 mmol) in acetone (35 ml) was treated with a solution of sodium metaperiodate (1.57 g, 7.35 mmol) in water (40 ml) for 2 hr at room temperature in the dark. The reaction mixture was worked up by the procedure described in Expt. 8 to afford a semicrystalline anomeric mixture of **20** (485 mg, 98%) which was used for the subsequent synthesis without further purification: δ ($CDCl_3$) 1.28 (d, 4-CH_3, J=6.3 Hz), 4.53 (dq, H-4, $J_{3,4}$=3.0 Hz), 5.35 (dd, H-3, $J_{2,3}$=3.0 Hz), *ca.* 5.6 (1H, H-1 in α- and β-anomer), and 8.28 (s, 1H, OCHO).

21. *(−)(2R,3S,4S)-2-Butyl-3,4-dihydroxypentanoic Acid-1,4-lactone [(−)**2d**].* A crystalline sample of (−)**2d** (41.9 mg, 51%) was obtained from **20** (97 mg) by the method described in Expt. 9. Recrystallization of the sample from ethyl acetate-petroleum ether afforded an analytical sample of (−)**2d**: mp 99.5–100.5 °C; $[\alpha]_D^{17}$ −96° (*c* 0.34, methanol); $[\theta]_{214}^{MeOH}$ −5230; $\nu_{max}^{CCl_4}$ (0.002M) 3625 (OH) and 1780 cm^{-1} (lactone).

Found: C, 62.56; H, 9.24%. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

22. *(−)(2R,3S,4S)-2-Butyl-4-hydroxy-3-(isovaleryloxy)-pentanoic Acid-1,4-Lactone [(−)Blastmycinone-d] [(−)**1d**].* The hydroxylactone (−)**2d** (14.5 mg) was isovalerylated by the procedure described in Expt. 10 to afford a crystalline (−)**1d** (18.5 mg, 86%) which was recrystallized from ethyl acetate-petroleum ether: mp 47.0—48.0 °C; $[\alpha]_D^{18}$ −89° (*c* 0.90, chloroform); $\nu_{max}^{CCl_4}$ (0.1 M) 1792 (lactone) and 1748 cm^{-1} (ester); R_f 0.33 (solvent G).

Found: C, 65.82; H, 9.42%. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44%.

23. *Methyl 2-C-butyl-2,5-dideoxy-β-L-lyxofuranoside (**21**).* The periodate oxidation product **20** (300 mg, 1.48 mmol) was treated with 0.5% methanolic hydrogen chloride (15 ml, 2.06 mmol) for 3 hr at room temperature. The solution was worked up by the same procedure as described in Expt. 11 and the product (415 mg) was fractionated on silica gel (40 g) with solvent E. The faster-moving fraction gave the α-anomer showing a positive rotation and the slower-moving fraction afforded β-anomer **21** with a negative rotation as a major product. Since both anomers separated were very unstable, no analytical samples could be obtained. (+)α-Anomer: 15.2 mg (5.5%); δ ($CDCl_3$) 1.32 (d, 4-CH_3, J=6.3 Hz), 3.39 (s, OCH_3), 4.19 (dq, H-4, $J_{3,4}$=3.7 Hz), and 4.85 (d, H-1, $J_{1,2}$=4.0 Hz). (−)β-Anomer (**21**): 167 mg (60%); δ ($CDCl_3$) 1.24 (d, 4-CH_3, J=6.5 Hz), 3.40 (s, OCH_3), 3.98 (dd, H-3, $J_{2,3}$=4.5, $J_{3,4}$=2.5 Hz), 4.19 (dq, H-4), and 4.71 (d, H-1, $J_{1,2}$=5.0 Hz).

24. *Methyl 2-C-Butyl-2,5-dideoxy-3-O-methanesulfonyl-β-L-lyxofuranoside (**22**).* A crystalline sample of **22** (219 mg) was prepared from freshly prepared **21** (155 mg) by the procedure in Expt. 12. It was recrystallized from ether-petroleum ether to afford fine needles which were also very unstable: mp 56—58 °C; δ ($CDCl_3$) 1.37 (d, 4-CH_3, J=6.3 Hz), 3.09 (s, OMs), 3.45 (s, OCH_3), 4.39 (dq, H-4, $J_{3,4}$=2.8 Hz), 4.82 (d, H-1, $J_{1,2}$=4.9 Hz), and 5.17 (dd, H-3, $J_{2,3}$=5.2 Hz).

25. *Methyl 3-O-Benzoyl-2-C-butyl-2,5-dideoxy-β-L-arabinofuranoside (**23**).* A solution of **22** (200 mg, 0.753 mmol) in DMSO (4 ml) was heated with sodium benzoate (326 mg, 2.26 mmol) at 140 °C for 1 hr and the reaction mixture was worked up by the procedure in Expt. 13 to afford a homogeneous sample of **23** (91 mg, 42%) as a colorless syrup: $[\alpha]_D^{22}$ −48° (*c* 1.67, chloroform); δ ($CDCl_3$) 1.42 (d, 4-CH_3, J=6.3 Hz), 3.44 (s, OCH_3), 4.28 (dq, H-4, $J_{3,4}$=5.9 Hz), 4.81 (d, H-1, $J_{1,2}$=1.2 Hz), and 4.88 (dd, H-3, $J_{2,3}$=3.8 Hz).

Found: C, 69.50; H, 8.13%. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27%.

26. *Methyl 2-C-Butyl-2,5-dideoxy-β-L-arabinofuranoside (**24**).* A sample of **24** (29 mg, 100%) was obtained from **23** (45 mg) by the procedure in Expt. 14: δ ($CDCl_3$) 1.32 (d, 4-CH_3, J=6.5 Hz), 3.41 (s, OCH_3), 4.06 (dq, H-4, $J_{3,4}$=5.8 Hz), and 4.74 (d, H-1, $J_{1,2}$=1.5 Hz).

27. *Natural (−)Blastmycinolactol [(−)**2a**].* A crystalline sample of (−)**2a** (22.3 mg, 84%) was obtained by treatment of **24** (29 mg) with 1 M HCl followed by bromine-oxidation by the same procedure as described in Expt. 15. Recrystallization from ether-petroleum ether afforded a pure sample of (−)**2a**: mp 49.5—50.5 °C; $[\alpha]_D^{18}$ −18° (*c* 1.09, methanol); $[\theta]_{217}^{MeOH}$ −5500; $\nu_{max}^{CCl_4}$ (0.002 M) 3635 (OH) and 1785 cm^{-1} (lactone).

Found: C, 62.60; H, 9.22%. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

28. *Natural (+)Blastmycinone [(+)**1a**].* Isovalerylation of (−)**2a** (16.5 mg) in the same manner as described in Expt. 10 afforded (+)**1a** (21.3 mg, 86%) as a colorless oil: $[\alpha]_D^{17}$ +10° (*c* 1.20, chloroform); $\nu_{max}^{CCl_4}$ (0.1 M) 1788 (lactone) and 1745 cm^{-1} (ester); R_f 0.66 (solvent G).

Found: C, 65.72; H, 9.31%. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44%.

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