2-Benzoylamino-2-deoxy-2-hydroxymethyl-D-hexono-1,4-lactones: Synthesis from D-Fructose and utilization in the Total Synthesis of Thermozymocidin (Myriocin)

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2-Benzoylamino-2-deoxy-2-hydroxymethyl-D-mannonic (6) and -D-gluconic (13) acids have been synthesized from D-fructose by the following route: (i) a hydrocyanation reaction of fructosyl-*p*-tolylamine, (ii) acid hydrolysis of the nitrile produced, and (iii) hydrogenolysis of the tolylamino group then formed. The stereochemistry of the hydrocyanation reaction has been studied by changing both the solvents and other reaction conditions. The major (gluconic) and the minor (mannonic) epimers have been separated and characterized by chemical and spectroscopic methods.

Upon *N*-acylation the amino acids (6) and (13) cyclized to the corresponding 1,4-lactones (5) and (12). One of these 2-benzoylamino-2-deoxy-2-hydroxymethyl-D-hexono-1,4-lactones [the mannonic (5)], was transformed in six steps into the 2-benzoylamino-2-benzoyloxymethyl-2-deoxy-3-*O*-benzoyl-5-*O*-(4-tolylsulphonyl)-D-lyxono-1,4-lactone (3), which is a key intermediate in the convergent total synthesis of the antibiotic thermozymocidin (1).

Thermozymocidin (myriocin), an antibiotic, was isolated from the thermophilic fungus *Myriococcum albomyces* in 1972.[1] Structure elucidation required, in addition to a combination of chemical degradations, n.m.r., i.r., and mass spectral techniques,[2] an *X*-ray analysis,[3] and synthetic studies [4] to establish its relative configuration, and the synthesis of the optical antipode of anhydrothermozymocidin [5] to determine the absolute configuration as (1).

The first total synthesis of (+)-(1) was achieved using D-fructose (7) as a source of chirality for the asymmetric centres of thermozymocidin (Scheme 1).[6]

Our retrosynthetic approach involved fission of (2) to give the tosylate (3) and the cuprate (4), compounds likely to couple in a stereoselective way, as mentioned earlier by other workers.[7] Alternatively, it was thought that the *E* double bond in (2) could be formed *via* a Corey-Kwiatkowski reaction [8] between a suitable phosphonamide and the aldehyde (14). The intermediate (3) was thought to be available by derivatization of the *N*-benzoylated 1,4-lactone (5), the expected product of cyclization of the amino acid (6), in conformity with the behaviour of thermozymocidin itself.[2] Finally we planned to obtain (6) from the easily available D-fructose.

Here we describe details of the synthesis of 2-benzolyamino-2-deoxy-2-hydroxymethyl-D-hexono-1,4-lactones from D-fructose and their utilization in the total synthesis of thermozymocidin. The transformation of D-fructose into 2-amino-2-deoxy-2-hydroxymethyl-D-mannonic acid (6) was of critical importance for success (see Scheme 2). Initial attempts to synthesize this amino-acid using Strecker, Bucherer, or Bucherer-Bergs reactions were unsuccessful. D-Fructose was then converted into fructosyl-*p*-tolylamine [9] and treated with an excess of liquid hydrogen cyanide in ethanol–water (1 : 0.74) following the general Kuhn procedure.[10] Two epimeric 2-deoxy-2-hydroxymethyl-2-*p*-tolylamino-hexononitriles were obtained (80% yield): the 2*R*-epimer (9) precipitated, while the desired 2*S*-epimer (8) was obtained from the mother liquors. Unfortunately the relative ratio 2*R* : 2*S* was 3.5 : 1, but 2*R*-epimer was partially converted into the 2*S*-epimer by equilibration in ethanol–water in the presence of an excess of liquid hydrogen cyanide. The stereochemical outcome is consistent with the trend observed by Kuhn [10] in the hydrocyanation reaction of four aldopentosyl-*p*-tolylamines.

In order to attain a more favourable stereochemical course, we tried to carry out the reaction in a solvent causing no precipitation of the gluconic epimer (9). The use of a different ethanol : water ratio (1 : 1.36) in the hydrocyanation reaction, although improving the epimer ratio to 1 : 1, reduced the total yield considerably (3%). In our opinion the low yields obtained result from the presence of water. Further attempts to use liquid hydrogen cyanide, dimethylformamide, or dimethylformamide–ethanol, as solvents instead of water, were similarly unsuccessful.

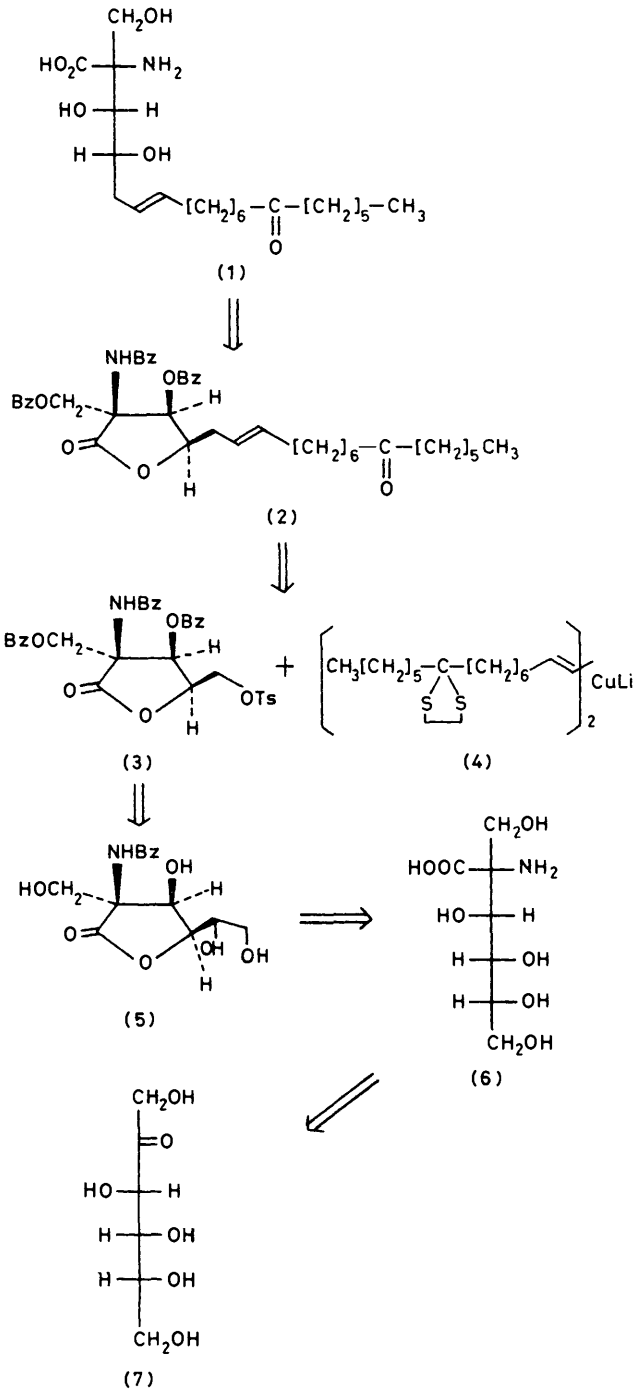
According to the general results of Kuhn,[10] which demonstrate that phenylamines are less stereoselective than the corresponding tolylamines, we synthesized the fructosylphenylamine.[9] The results were, however, disappointing since this compound seems to be very unstable in aqueous solution and not reactive in dimethylformamide, dimethylformamide–ethanol, or pure HCN.

Hydrolysis with concentrated hydrochloric acid of the two epimeric nitriles (40 h for 2*R* and 2.5 h for 2*S*) gave two 2-deoxy-2-hydroxymethyl-2-*p*-toluidino-D-hexaono-1,4-lactones (90% yield for 2*R* and 15.9% total yield from fructosyl-*p*-tolylamine for 2*S*). The formation of an isopropylidene acetal (15) proved the configuration at C-2 for the 2*S*-epimer (10), while the 2*R*-epimer (11) afforded a bisisopropylidene acetal (16) under the same conditions (acetone, H_2SO_4).

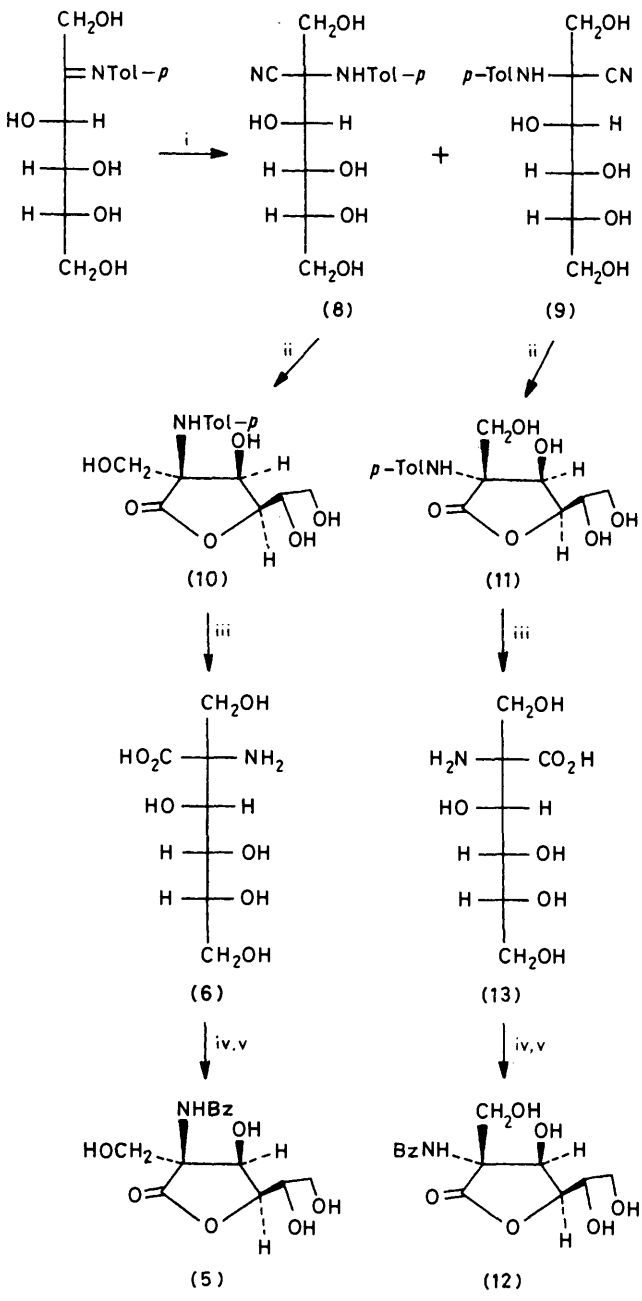
Interruption of the acetalization of (11) after a suitable time gave the isopropylidene acetal (17) as the main product together with small amounts of the isomeric mono-acetal and the bis-acetal (16). The configuration at C-2 of the two epimers (10) and (11) was also confirmed by a comparison of their ^{13}C n.m.r. spectra, where some sterically induced upfield shifts were noted.

Hydrogenolysis (Pd/C, 1M-HCl) of 2-deoxy-2-hydroxymethyl-2-*p*-toluidino-D-mannono-1,4-lactone (10) and of the glucono-1,4-lactone (11) gave, respectively, 2-amino-2-deoxy-2-hydroxymethyl-D-mannonic acid (6) and 2-amino-2-deoxy-2-hydroxymethyl-D-gluconic acid (13) in 90% yield. Attempts to effect selective *N*-benzoylation or acetylation of these amino-acids with a conventional Schotten-Baumann reaction [11] or its modifications [12] gave very poor results; similar attempts using reagents designed for the selective *N*-acylation [12] of amino-alcohols were unsuccessful.

The best synthesis of 2-benzoylamino-2-deoxy-2-hydroxymethyl-D-mannono-1,4-lactone (5) (60% yield) and of the



Scheme 1.



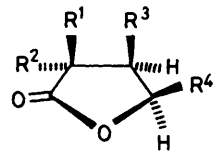
Scheme 2. *Reagents:* i, HCN; ii, HCl; iii, H_2/Pd; iv, BzCl; v, NEt_3, MeOH

perbenzoylation with an excess of benzoyl chloride in pyridine of the amino-acids (6) and (13) followed by methanolysis of the products in the presence of a catalytic amount of triethylamine.

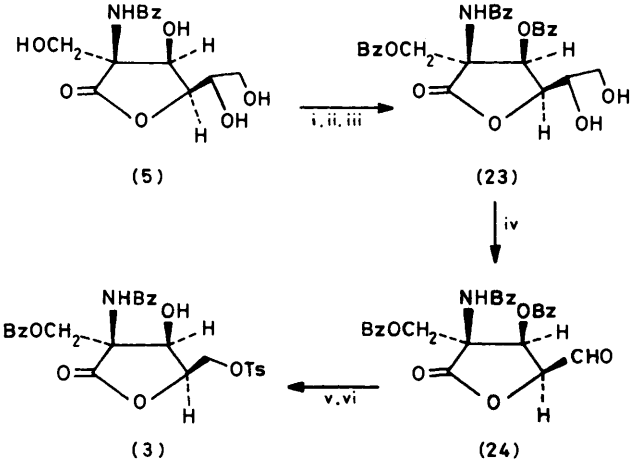
Sodium periodate oxidation of the lactone (5) gave the hemiacetal dimer (25) (98% yield); this was characterized by the absence of both an aldehyde carbonyl group (i.r.) and an aldehyde proton (n.m.r.), and the presence of a $2M - 3$ H_2O peak in its mass spectrum. This structure (25) was assigned in analogy with the work of Hecht [13] on the structure of the species resulting from oxidation of 2-acetamido-2-deoxy-D-mannono-1,4-lactone.

Therefore it was necessary to transform compound (5) into corresponding glucono-1,4-lactone (12) (70% yield) was the the tribenzoylated vicinal diol (23) according to the following sequence (Scheme 3): treatment with acetone and sulphuric acid to afford the isopropylidene acetal (18) (90% yield), esterification with benzoyl chloride in pyridine to give (19) (90% yield), and hydrolysis of the isopropylidene acetal with acetic acid in THF–H_2O (90% yield). Sodium periodate oxidation of the diol (23) gave the perbenzoylated aldehyde (24) in 100% yield.

A bis(isopropylidene) acetal (20) resulted when the glucono-1,4-lactone (12) was treated with acetone and sulphuric acid. The use of milder acetalization conditions gave the mono-isopropylidene acetal (21) as the main product, together with small amounts of the isomeric mono-acetal and the bis-acetal (20). With the aid of this selective acetalization, the glucono



(14): R^1 – NHBz; R^2 = CH_2OBz; R^3 = OBz; R^4 = CH_2CHO
(15): R^1 = NHTol-*p*; R^2 = CH_2OH; R^3 = OH;
R^4 = O·CMe_2·O·CH_2·CH
(16): R^2 = NHTol-*p*; R^1,R^3 = CH_2O·CMe_2·O;
R^4 = O·CMe_2·O·CH_2·CH
(17): R^1 = CH_2OH; R^2 = NHTol-*p*; R^3 = OH;
R^4 = O·CMe_2·O·CH_2·CH
(18): R^1 = NHBz; R^2 = CH_2OH; R^3 = OH;
R^4 = O·CMe_2·O·CH_2·CH
(19): R^1 = NHBz; R^2 = CH_2OBz; R^3 = OBz;
R^4 = O·CMe_2·O·CH_2·CH
(20): R^2 = NHBz; R^1,R^3 = CH_2O·CMe_2·O;
R^4 = O·CMe_2·O·CH_2·CH
(21): R^1 = CH_2OH; R^2 = NHBz; R^3 = OH;
R^4 = O·CMe_2·O·CH_2·CH
(22): R^1 = NHBz; R^2 = CH_2OBz; R^3 = OBz; R^4 = CH_2OH



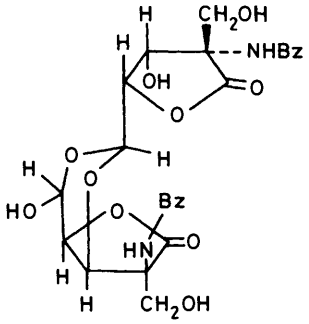
Scheme 3. *Reagents:* i, Me_2CO,H_2SO_4; ii, BzCl,Py; iii, H_3O^+; iv, $NaIO_4$; v, $NaB(CN)H_3$; vi, TsCl.

epimers of the above mentioned compounds (18), (19), (23), and (24) could be easily achieved.

The aldehyde (24) is not a very stable compound being decomposed during silica gel chromatography and transformed by methanol–silica gel into the corresponding methyl acetal. Furthermore, all attempts to react the aldehyde (24) with organolithium derivatives or phosphorus ylides failed giving only complex reaction mixtures. Also, the homologous aldehyde (14), which was obtained by OsO_4–$NaIO_4$ degradation on benzoylated anhydrothermozymocidin (2), proved to be very unstable, and was converted back into (2), by reaction with a suitable lithium phosphonic bis(dimethyl)amide obtained from (27) [8] only in very poor yield.

It was therefore necessary to reduce the aldehyde carbonyl group ($NaBH_3CN$,[14] THF, 100% yield) and to transform the alcohol (22) into the tosylate (3) (toluene-*p*-sulphonyl chloride, 4-dimethylaminopyridine,[15] triethylamine in methylene chloride at −20 °C, 95% yield).

The tosylate (3) was subjected to model studies using the



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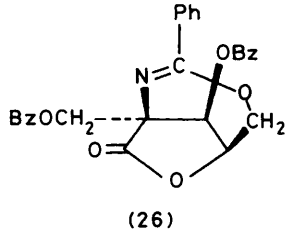

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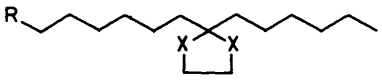
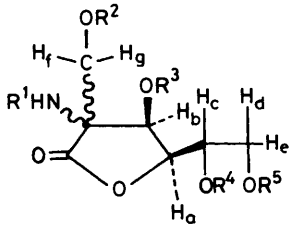


(27) R = $CH_2PO(NMe_2)_2$; X = O
(28) R = C≡CH; X = O
(29) R = C≡CH; X = S



(30)

vinyl alanate [16] obtained from oct-1-yne (DIBAH, Bu^nLi). Reaction in THF–HMPT gave a single major product, the structure of which was tentatively assigned as (26). This behaviour is probably due to the presence of some unchanged vinylalane which, like a Lewis acid, induces the formation of the carbocation, and therefore favours the intramolecular substitution of the tosylate.

In contrast, coupling of the tosylate (3) with the lithium divinylcuprate derived from (*E*)-1-iodo-oct-1-ene [17] (Bu^tLi, CuBr–Me_2S) gave the desired adduct in 30% yield. Thus, the (*E*)-lithium divinylcuprate suitable for the synthesis of thermozymocidin was synthesized. The alkynes (28) and (29) were converted into the corresponding vinyl iodides (DIBAH, I_2).[17] This reaction gave very poor yields in the case of (28) because of the presence of the acetal,[18] which was extensively reduced by DIBAH.[19] This problem was solved using the thioacetal (29) which gave quite good results.

The vinyl iodide was then treated with 2 equivalents of Bu^tLi[20] and with CuBr–Me_2S to give the (*E*)-lithium divinylcuprate. Coupling of the tosylate with this cuprate under standard conditions [7] gave, after hydrolysis of the thioacetal protecting the carbonyl group of the side-chain [MeI, acetone–H_2O (9 : 1)],[21] benzoylated anhydrothermozymocidin (2) in moderate yield (28%); this was converted (1M-NaOH, 65% yield) into natural (+)-thermozymocidin (1).

Experimental

^1H N.m.r. and ^{13}C n.m.r. spectra were recorded with Varian XL-100 or Bruker WP-80 instruments, using tetramethylsilane as internal standard. I.r. spectra were recorded with a Perkin-Elmer 681 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Mass spectra were recorded with a Varian MAT 112 spectrometer. Elemental

analyses were performed with a Perkin-Elmer 240 instrument. Kieselgel 60 F_{254} (Merck) was used for t.l.c.; 70—230 mesh or 270—400 mesh (for flash chromatography) [22] silica gel (Merck) were used for column chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. Physical and spectroscopic data for compounds (18)—(21), (23), (27)—(29), are available as a Supplementary Publication [SUP No. 23585 (5 pp.)].* For numbering of protons in the ^1H n.m.r. spectra see the general formula (30).

Hydrocyanation Reaction of 2-*Deoxy*-2-p-*toluidino*-D-*fructose*.—2-Deoxy-2-*p*-toluidino-D-fructose[9] (25 g, 93 mmol) was dissolved with warming to 60 °C in EtOH–water (1 : 0.74) (265 ml). Anhydrous HCN (29 ml), prepared following the Ziegler's procedure,[23] was added to the above solution, which had previously been rapidly cooled to 20 °C. The mixture was then stirred for several minutes. After 2 days at 0 °C the precipitate was filtered off and washed with cold ether to give compound (9) (17.1 g, 62.3%), m.p. 138 °C (decomp.), $[\alpha]_D^{20}$ +15.0° (pyridine, *c* 0.2) (Found: C, 56.15; H, 6.65; N, 9.2. $C_{14}H_{20}N_2O_5$ requires C, 56.75; H, 6.80; N, 9.46%). The mother liquors were evaporated at low temperature and pressure (0 °C, 0.1 mmHg) to give a mixture of 2-deoxy-2-*p*-toluidino-D-fructose, (8) and (9).

Hydrolysis of (9) *to* 2-*Deoxy*-2-*hydroxymethyl*-2-p-*toluidino*-D-*glucono*-1,4-*lactone* (11).—Compound (9) (14.7 g, 49.6 mmol) was dissolved in concentrated HCl (20 ml) and stirred at room temperature under nitrogen for 40 h. The mixture was then diluted with water, neutralized to pH 7—8 with $NaHCO_3$, and evaporated to give a residue which was taken up in methanol and filtered through silica gel. The crude product was then chromatographed on silica gel (CH_2Cl_2–MeOH, 9 : 1) to give compound (11) (13.3 g, 90%), m.p. 161—162 °C (decomp.) (MeOH–CH_2Cl_2), $[\alpha]_D^{20}$ +55.6° (MeOH, *c* 1); $\nu_{max.}$ (KBr) 1750 cm^{-1}; δ(CD_3OD) 6.80—7.00 (4 H, m, ArH), 3.30—5.20 (7 H, m, CHO and CH_2O), and 2.18 (3 H, s, CH_3) (Found: C, 55.95; H, 6.25; N, 4.6. $C_{14}H_{19}NO_6$ requires C, 56.56; H, 6.45; N, 4.71%).

Hydrolysis of the Mother Liquors to 2-*Deoxy*-2-*hydroxymethyl*-2-p-*toluidino*-D-*mannono*-1,4-*lactone* (10).—The crude mixture obtained from the mother liquors was treated with concentrated HCl (48 ml) at room temperature under nitrogen for 2.5 h. The resulting solution was worked up as described above for the glucono-lactone, to give, after silica gel chromatography, compound (10) (4.4 g, 15.9% total yield from 2-deoxy-2-*p*-toluidino-D-fructose), m.p. 57—60 °C (decomp.), $[\alpha]_D^{20}$ +68.8° (MeOH *c* 1), $\nu_{max.}$ (KBr) 1 770 cm^{-1}; δ(CD_3OD) 6.80—7.00 (4 H, m, ArH), 3.30—5.20 (7 H, m, CHO and CH_2O), and 2.21 (3 H, s, CH_3) (Found: C, 54.95; H, 6.3; N, 4.55. $C_{14}H_{19}NO_6$ requires C, 56.56; H, 6.45; N, 4.71%).

2-*Deoxy*-2-*hydroxymethyl*-2-p-*toluidino*-5,6,O-(1-*methylethylidene*)-D-*mannono*-1,4-*lactone* (15).—A solution of (10) (150 mg, 0.505 mmol) in dry acetone (2 ml) was treated with concentrated H_2SO_4 (0.07 ml), and stirred at room temperature for 1 h. The mixture was then treated with Et_3N (pH 9) and evaporated to give a crude product which was purified by silica gel chromatography (CH_2Cl_2–MeOH, 96 : 4) to give compound (15) (118 mg, 69%), $\nu_{max.}$ ($CHCl_3$) 1 770, 1 380, and 1 370 cm^{-1}; δ($CDCl_3$) 6.60—7.05 (4 H, m, ArH), 3.70–4.50 (8 H, m, NH, CHO and CH_2O), 2.20 (3 H, s, $ArCH_3$), 1.40 and 1.32 (6 H, 2 s, CH_3CO) (Found: C, 59.75; H, 6.75; N, 3.9. $C_{17}H_{23}NO_6$ requires C, 60.52; H, 6.87; N, 4.15%).

2-*Deoxy*-2-*hydroxymethyl*-2-p-*toluidino*-3,7:5,6-*di*-O-(1-*methylethylidene*)-D-*glucono*-1,4-*lactone* (16).—A solution of (11) (100 mg, 0.336 mmol) in dry acetone (2 ml) was treated with concentrated H_2SO_4 (0.07 ml) and then stirred at room temperature for 4 h. The mixture was treated with Et_3N (pH 9), evaporated and purified by silica gel chromatography (CH_2Cl_2–MeOH, 98 : 2) to give compound (16) (100 mg, 79%), $\nu_{max.}$ ($CHCl_3$) 1 785, 1 382, and 1 375 cm^{-1}; δ($CDCl_3$) 6.72—7.04 (4 H, m, ArH), 4.68 (1 H, dd, H_a, J_{ab} 3.2 Hz, J_{ac} 6.4 Hz), 4.48 (1 H, d, H_b), 4.38 (1 H, m, H_c), 4.13 (2 H, d, H_c and H_d, $J_{cd} = J_{ce}$ = 6 Hz), 4.04 (2 H, AB system, H_f and H_g, J_{fg} 12 Hz), 3.47 (1 H, s, NH), 2.19 (3 H, s, Ar CH_3), and 1.38, 1.35, 1.29, and 1.28 (12 H, 4 s, CH_3CO) (Found: C, 63.1; H, 7.3; N, 3.65. $C_{20}H_{27}NO_6$ requires C, 63.65; H, 7.21; N, 3.71%).

2-*Deoxy*-2-*hydroxymethyl*-2-p-*toluidino*-5,6-O-(1-*methylethylidene*)-D-*glucono*-1,4-*lactone* (17).—A solution of (11) (300 mg, 1.008 mmol) in dry acetone (6 ml) was treated with concentrated H_2SO_4 (0.06 ml) and then stirred at room temperature for 40 min. The mixture was treated with Et_3N (pH 9), evaporated, and purified by silica gel chromatography (CH_2Cl_2–MeOH, 96 : 4) to give compound (17) (136 mg, 40%), m.p. 143 °C (decomp.) (n-hexane–AcOEt), $[\alpha]_D^{20}$ +68.5° (MeOH, *c* 0.5), $\nu_{max.}$ (Nujol) 1 752, 1 375, and 1 367 cm^{-1}; δ($CDCl_3$) 6.70—7.10 (4 H, m, ArH), 3.27—5.20 (8 H, m, NH, CHO, and CH_2O), 2.22 (3 H, s, $ArCH_3$), 1.42 and 1.36 (6 H, 2 s, CH_3CO) (Found: C, 60.65; H, 6.9; N, 4.25. $C_{17}H_{23}NO_6$ requires C, 60.52; H, 6.87; N, 4.15%).

^{13}C *N.m.r. Spectra of Compounds* (10), (11), and (17).—Mannono-1,4-lactone (10): δ(CD_3OD) 177.7 (C=O), 142.6, 130.4, 130.1, and 118.1 (C=C), 81.5 (CH–O), 73.0 (CH–O), 70.0 (CH–O) 69.1 (N-*C*-C=O), 64.4 ($CHOHCH_2OH$), 62.5 ($NCCH_2$-OH), and 20.5 (CH_3). Glucono-1,4-lactone (11): δ(CD_3OD) 176.6 (C=O), 143.7, 130.2, 119.4 (*C*=C), 81.0 (CH–O), 75.3 (CH–O), 69.8 (CH–O), 68.7 (N–*C*–C=O), 64.5 (CHOH–CH_2OH), 58.3 (N–C–CH_2–OH), and 20.6 (CH_3). Isopropylidene acetal (17): δ(CD_3OD) 176.0 (C=O), 143.0, 130.3, 127.4, 119.6 (C=C), 110.2 (O–C–O), 83.0 (CH–O), 75.0 (CH–O), 74.2 (CH–O), 68.7 (N–*C*–C=O), 67.2 (*C*H–O–C), 58.2 (N–C–CH_2–OH), 26.9, 25.5 (O–C–CH_3), and 20.6 (Ar-CH_3).

Note the 4.2 p.p.m. (from 62.5 to 58.3) upfield shift of the CH_2OH carbon α to the epimeric site, in the glucono isomer, due to steric congestion (γ effect). On the other hand, the CH–OH carbon α to the epimeric site shifts from 75.3 to 73.0 in the mannono isomer. The position of the isopropylidene acetal was confirmed to be as depicted in (17) by the downfield shifts of the CHO–CH_2O carbons (from 69.8 to 74.2 and from 64.5 to 67.2).

2-*Amino*-2-*deoxy*-2-*hydroxymethyl*-D-*mannonic Acid* (6).—A solution of (10) (1.41 g, 4.74 mmol) in 1M-HCl (75 ml) was hydrogenated at room temperature and pressure for 3 days in the presence of 10% Pd/C (3.18 g). The catalyst was filtered off and the solution was washed with diethyl ether (4 × 20 ml) and then passed through a column of Amberlite IR-45 (OH^-) resin (60 g). Removal of water by evaporation at reduced pressure gave the amino acid (6) as a white powder (0.95 g, 89%), m.p. 160 °C (decomp.); $[\alpha]_D^{20}$ −17.4° (H_2O, *c* 0.32); $\nu_{max.}$ (KBr) 1 620 and 1 604 cm^{-1} (Found: C, 34.25; H, 7.0; N, 5.85. $C_7H_{15}NO_7 \cdot H_2O$ requires C, 34.57; H, 7.04; N, 5.76%.

* For details of the Supplementary publications scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1.

2-Amino-2-deoxy-2-hydroxymethyl-D-gluconic Acid (13).—A solution of (11) (3 g, 10.09 mmol) in 1M-HCl (150 ml) was hydrogenated at room temperature and pressure for 1 day in the presence of 10% Pd/C (6 g). The catalyst was filtered off and the solution was washed with diethyl ether (4 × 40 ml) and then passed through a column of Amberlite IR-45 (OH^-) resin (100 g). Removal of water by evaporation at reduced pressure gave the amino acid (13) as a white powder (2.25 g, 99%), m.p. 207—208 °C (decomp.) (H_2O); $[\alpha]_D^{20}$ −25.5° (1M-HCl, *c* 1); $\nu_{max.}$ (KBr) 1 620 and 1 604 cm^{-1} (Found: C, 34.45; H, 7.0, N, 5.75. $C_7H_{15}NO_7 \cdot H_2O$ requires C, 34.57; H, 7.04; N, 5.76%).

2-Benzoylamino-2-deoxy-2-hydroxymethyl-D-glucono-1,4-lactone (12).—(i) *By a Schotten-Baumann reaction.* To a solution of (13) (424 mg, 1.88 mmol) in 5% aqueous NaOH (2 ml) benzoyl chloride (1 ml) was added at 0 °C in 0.1 ml portions during 1 h. The pH was kept in the range 8—10 by adding 0.3 ml portions of 5% NaOH. After 3 h the reaction mixture was treated with 1M-H_2SO_4 to pH 2—3, and evaporated. The residue was suspended in CH_2Cl_2 and filtered. The residue was washed with CH_2Cl_2 and then heated at 100 °C under reduced pressure (0.1 mmHg) in the presence of P_4O_{10} for 5 h to give a crude mixture which was chromatographed on silica gel (CH_2Cl_2–MeOH, 96 : 4) to give (12) (90 mg, 15.3%).

(ii) *Through perbenzoylation–methanolysis.* To a suspension of (13) (700 mg, 3.10 mmol) in dry pyridine (24 ml), benzoyl chloride (4.33 ml, 37.3 mmol) was added and the mixture was stirred for 1 day at room temperature. The reaction was quenched with water (20 ml) and the resulting mixture was evaporated. The residue was taken up in CH_2Cl_2, and the solution washed with 5% aqueous $NaHCO_3$ (5 × 10 ml) and then evaporated. Silica gel chromatography (CH_2Cl_2–MeOH, 97 : 3) gave 2-benzoylamino-2-benzoyloxymethyl-2-deoxy-3,5,6-tri-*O*-benzoyl-D-glucono-1,4-lactone (2.1 g, 93%), $\nu_{max.}$ ($CHCl_3$ 1 782, 1 720, and 1 660 cm^{-1}; δ($CDCl_3$) 7.10—8.20 (25 H, m, ArH), 6.50 (1 H, d, H_b, J_{ab} 5.6 Hz), 5.70—6.10 (2 H, m, H_a + H_c), 4.60—5.20 (4 H, m, H_d, H_e, H_f, and H_g). A solution of this compound (2.025 g, 2.785 mmol) in anhydrous methanol (150 ml) was treated with Et_3N (0.8 ml) and stirred at 60 °C for 15 h. The solution was then evaporated under reduced pressure and the residue was chromatographed on silica gel (CH_2Cl_2–MeOH, 99 : 1 to 80 : 20) to give (12) (646 mg, 75%), $\nu_{max.}$ (KBr) 1 760 and 1 640 cm^{-1}; δ(CD_3OD) 7.40—8.00 (5 H, m, ArH), 3.20—4.30 (7 H, m, CH–O and CH_2–O) (Found: C, 54.15; H, 5.55; N, 4.45. $C_{14}H_{17}NO_7$ requires C, 54.02; H, 5.50; N, 4.50%).

2-Benzoylamino-2-deoxy-2-hydroxymethyl-D-mannono-1,4-lactone (5).—This compound was synthesized starting from the amino acid (6) (809 mg, 3.595 mmol) with the perbenzoylation–methanolysis method above described. 2-Benzoylamino-2-benzoyloxymethyl-2-deoxy-3,5,6-tri-*O*-benzoyl-D-mannono-1,4-lactone (2.15 g, 82%) was characterized as follows: m.p. 94—96 °C $[\alpha]_D^{20}$ −42.7° ($CHCl_3$, *c* 0.17), $\nu_{max.}$ ($CHCl_3$) 1 785, 1 720, and 1 665 cm^{-1}; δ(CD_3COCD_3) 7.00—8.20 (25 H, m, ArH), 6.25 (1 H, d, H_b, J_{ab} 7.3 Hz), 6.10 (1 H, m, H_c), 5.55 (1 H, dd, H_a, J_{ac} 8.9 Hz), 4.90 (1 H, d, H_f or H_g, J_{fg} 10.6 Hz), 4.63 (1 H, d, H_f or H_g), and 4.51—5.02 (2 H, m, H_d and H_e); *m/z* (%) 727 (M^+) (0.10), 622 (0.73), 500 (4.74), 484 (5.17), 212 (14.22), and 105 (100) (Found: C, 69.5; H, 4.6; N, 2.0. $C_{42}H_{33}NO_{11}$ requires C, 69.32; H, 4.57; N, 1.92%). Et_3N catalysed methanolysis gave (5) (671 mg, 73%), m.p. 141 °C; $[\alpha]_D^{20}$ +31.9° (MeOH, *c* 0.5), $\nu_{max.}$ (Nujol) 1 770 and 1 645 cm^{-1}; δ (CD_3OD) 7.50—8.00 (5 H, m, ArH), and 3.80—4.25 (7 H, m, CH–O and CH_2–O); *m/z* (%) 263 (0.31), 218 (1.23), 203 (11.61), 185 (12.26), and 105 (100) (Found: C, 53.7; H, 5.6; N, 4.4. $C_{14}H_{17}NO_7$ requires C, 54.02; H, 5.50; N, 4.50%).

2-Benzoylamino-2-deoxy-2-hydroxymethyl-3,7:5,6-di-O-(1-methylethylidene)-D-glucono-1,4-lactone (20).—A solution of the glucono-1,4-lactone (12) (90 mg, 0.29 mmol) in dry acetone (2 ml) was treated with concentrated H_2SO_4 (0.07 ml) for 3 h at room temperature. The mixture was then worked up as described above and purified by silica gel chromatography (CH_2Cl_2–MeOH, 98 : 2) to give compound (20) (60 mg, 53%).

2-Benzoylamino-2-deoxy-2-hydroxymethyl-5,6-O-(1-methylethylidene)-D-glucono-1,4-lactone (21).—A solution of the glucono-1,4-lactone (12) (140 mg, 0.45 mmol) in dry acetone (30 ml) was treated at 0 °C with concentrated H_2SO_4 (0.01 ml). The mixture was stirred for 10 min at 0 °C and then worked up as described above. Purification of the crude product by silica gel chromatography (CH_2Cl_2–MeOH, 95 : 5) gave compound (21) (118 mg, 75%).

Sodium Periodate Oxidation of 2-Benzoylamino-2-deoxy-2-hydroxymethyl-D-mannono-1,4-lactone (5).—A solution of (5) (85 mg, 0.273 mmol) in methanol (1.5 ml) was treated with 0.2M-aqueous $NaIO_4$ (1.36 ml, 0.273 mmol) at 0 °C and the mixture was stirred in the dark for 50 min. The solvent was then evaporated and the residue was taken up in anhydrous ethanol and stored in the freezer (−20 °C) overnight. $NaIO_3$ was filtered off and the solution was evaporated to give a crude product, which, after chromatography on silica gel (CH_2Cl_2–MeOH, from 99 : 1 to 95 : 5) gave the hemiacetal dimer (25) (70 mg, 91%), m.p. 144 °C, $[\alpha]_D^{20}$ +36.4° (EtOH, *c* 0.5), $\nu_{max.}$ (Nujol) 3 600—3 200, 1 780, and 1 645 cm^{-1}; δ(CD_3OD) 7.30—8.00 (10 H, m, ArH), 4.40—5.15 (10 H, m, O-H and CH–O), 4.04 (4 H, s, CH_2OH); *m/z* (%) 504 (0.01), 279 (0.74), 207 (6.05), 202 (6.98), and 105 (100) (Found: C, 55.7; H, 4.7; N, 4.95. $C_{26}H_{26}N_2O_{12}$ requires C, 55.91; H, 4.69; N, 5.02%).

2-Benzoylamino-2-benzoyloxymethyl-2-deoxy-3-O-benzoyl-D-mannono-1,4-lactone (23).—A suspension of compound (5) (317 mg, 1.02 mmol) in dry acetone (7.4 ml) was treated with concentrated H_2SO_4 (0.025 ml). The resulting solution was stirred for 10 min and then worked up as described above. Silica gel chromatography (CH_2Cl_2–MeOH, 95 : 5) of the crude product gave 2-benzoylamino-2-deoxy-2-hydroxymethyl-5,6-*O*-(1-methylethylidene)-D-mannono-1,4-lactone (18) (321 mg, 90%). This compound (337 mg, 0.96 mmol) was suspended in dry pyridine (3 ml) and treated with benzoyl chloride (0.45 ml, 3.84 mmol). The resulting mixture was stirred at room temperature for 1 day and then quenched with water (3 ml). The resulting mixture was evaporated, the residue dissolved in $CHCl_3$ (10 ml), and the solution washed with 5% aqueous $NaHCO_3$ (2 × 3 ml) and then evaporated under reduced pressure. Silica gel chromatography (CH_2Cl_2–MeOH, from 99 : 1 to 80 : 20) gave 2-benzoylamino-2-benzoyloxymethyl-2-deoxy-3-*O*-benzoyl-5,6-*O*-(1-methylethylidene)-D-mannono-1,4-lactone (19) (480 mg, 90%). A solution of this compound (376 mg, 0.672 mmol) in AcOH–H_2O–THF (3 : 1 : 1; 13 ml) was stirred at 60 °C for 6 h. The solvent was then evaporated under reduced pressure and the crude mixture purified by silica gel chromatography (CH_2Cl_2–AcOEt, from 9 : 1 to 1 : 1) to give (23) (315 mg, 90%).

4-Benzoylamino-4-benzoyloxymethyl-4-deoxy-3-O-benzoyl-D-arabinurono-2,5-lactone (24).—A solution of (23) (150 mg, 0.289 mmol) in tetrahydrofuran (5.8 ml) was treated with 0.2M-aqueous $NaIO_4$ (5.07 ml, 1.01 mmol) and the mixture was stirred at room temperature in the dark for 6 h. After removal of the solvent under reduced pressure, the crude

product was taken up in CH_2Cl_2 and washed with water. The organic phase was then evaporated to give the aldehyde (24) as a white powder (140 mg, 99%). The latter, purified by crystallization (CH_2Cl_2–n-hexane), had m.p. 95 °C, $[\alpha]_D^{20}$ +31.2°, $\nu_{max.}$ ($CHCl_3$) 2 740, 1 800, 1 730—1 740, and 1 670 cm^{-1}; δ($CDCl_3$) 9.95 (1 H, d, CH=O, J_{ac} 1.85 Hz), 6.95—8.10 (16 H, m, ArH and NH), 5.98 (1 H, d, H_b, J_{ab} 8 Hz), 5.03 (1 H, dd, H_a), 4.90 (1 H, d, H_f or H_g, J_{fg} 11 Hz), and 4.70 (1 H, d, H_f or H_g); *m/z* (%) 414 (0.07), 380 (0.17), 336 (2.13), 199 (3.08), and 105 (100) (Found: C, 66.6; H, 4.45; N, 2.8. $C_{27}H_{21}NO_5$ requires C, 66.53; H, 4.34; N, 2.87%).

2-Benzylamino-2-benzoyloxymethyl-2,5-dideoxy-3-O-benzoyl-5-(E)-9-oxopentadec-1-enyl-D-lyxono-1,4-lactone (2) *from the Natural Product.*—A suspension of (1) (310 mg, 0.77 mmol) in pyridine (12 ml) was treated with benzoyl chloride (0.72 ml, 6.18 mmol) and stirred at room temperature for 1 day. The reaction was then quenched with water (10 ml) and the resulting mixture evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (20 ml), and the solution washed with 5% aqueous $NaHCO_3$ (5 × 5 ml), and then evaporated. Silica gel chromatography (CH_2Cl_2–AcOEt, from 99 : 1 to 9 : 1) gave (2) as an oil (316 mg, 59%) $[\alpha]_D^{20}$ +49.4° ($CHCl_3$, *c* 0.7), $\nu_{max.}$ ($CHCl_3$) 1 790, 1 735, 1 720, 1 680, and 975 cm^{-1}; δ($CDCl_3$) 7.00—8.10 (15 H, m, ArH), 6.86 (1 H, s, NH), 6.24 (1 H, d, H_b, J_{ab} 5.3 Hz), 5.30—5.60 (2 H, m, C*H*=CH), 5.00 (1 H, ddd, H_a), 4.97 (2 H, s, CH_2OCO), 2.20—2.80 (6 H, m, O–CH–CH_2–CH=CH and CH_2–C=O), 1.73—2.02 (2 H, m, CH_2–CH_2–CH=CH), 1.07—1.68 (16 H, m, C–CH_2–C), 0.85 (3 H, t, CH_3); *m/z* (%) 659 (M^+) (0.32), 625 (0.39), 573 (1.28), 424 (1.33), 216 (0.94), and 105 (100) (Found: C, 72.25; H, 7.1; N, 1.85. $C_{42}H_{49}NO_8$ requires C, 72.50; H, 7.10; N, 2.01%).

5-Benzoylamino-5-benzoyloxymethyl-2,5-dideoxy-4-O-benzoyl-D-mannurono-3,6-lactone (14).—Compound (2) (265 mg, 0.381 mmol) was treated with OsO_4 and then with $NaIO_4$ as previously reported with the orginal structure elucidation.[2] The crude aldehyde was obtained as a white powder and was purified by crystallization (pentane–diethyl ether) to give (14) (98 mg, 52%), m.p. 78 °C, $[\alpha]_D^{20}$ +42.7° ($CHCl_3$, *c* 0.5), $\nu_{max.}$ ($CHCl_3$) 2 740, 1 790, 1 720—1 740, and 1 675 cm^{-1}; δ($CDCl_3$) 9.87 (1 H, s, CH=O), 7.10—8.25 (15 H, m, ArH), 7.02 (1 H, s, NH), 6.21 (1 H, d, H_b, J_{ab} 6.4 Hz), 5.63 (1 H, dt H_a, J_{ac} = $J_{ac'}$ = 5.5 Hz), 5.06 (1 H, d, H_f or H_g, J_{fg} 11 Hz), 4.90 (1 H, d, H_f or H_g), and 3.33 (2 H, d, H_c and $H_{c'}$); *m/z* (%) 501 (M^+) (0.06), 472 (0.11), 396 (1.85), 335 (1.95), 244 (1.15), 122 (38.5), and 105 (100) (Found: C, 67.1; H, 4.5; N, 2.75. $C_{28}H_{23}NO_8$ requires C, 67.06; H, 4.62; N, 2.79%).

2-Benzoylamino-2-benzoyloxymethyl-2-deoxy-3-O-benzoyl-D-lyxono-1,4-lactone (22).—A solution of (24) (1.01 g, 2.06 mmol) in tetrahydrofuran (4 ml) was treated with $NaBH_3CN$ (130 mg, 2.13 mmol). After the addition of two drops of Methyl Orange, a solution of 1.5M-HCl in THF was dropped with stirring until the solution became persistently pink. The mixture was then stirred for 1 h, diluted with CH_2Cl_2 (5 ml), and the solution washed with 5% aqueous $NaHCO_3$ (2 × 2 ml) and saturated brine (2 × 2 ml); finally it was evaporated to give (22) as a white powder (1 g, 99%), m.p. 180 °C, $[\alpha]_D^{20}$ +41.8° ($CHCl_3$, *c* 1), $\nu_{max.}$ ($CHCl_3$) 1 785, 1 710—1 730, and 1 670 cm^{-1}; δ($CDCl_3$) 7.20—8.20 (15 H, m, ArH), 7.02 (1 H, s, NH), 6.25 (1 H, d, H_b, J_{ab} 6 Hz), 5.20 (1 H, q, H_a, J_{ac} = $J_{ac'}$ = 6 Hz), 5.05 (1 H, d, H_f or H_g, J_{fg} 10.5 Hz), 4.99 (1 H, d, H_f or H_g), 4.16 (1 H, dd, H_c, $J_{cc'}$ 12 Hz), 4.15 (1 H, dd, $H_{c'}$), and 3.70br (1 H, s, OH); *m/z* (%) 489 (M^+) (0.01), 472 (0.02), 384 (0.08), 262 (0.09), 177 (35.85), and 105 (100) (Found: C, 65.8; H, 4.8; N, 2.65. $C_{27}H_{23}NO_8$ requires C, 66.25; H, 4.74; N, 2.86%).

2-Benzoylamino-2-benzoyloxymethyl-2-deoxy-3-O-benzoyl-5-O-p-tolylsulphonyl)-D-lyxono-1,4-lactone (3).—A solution of (22) (230 mg, 0.47 mmol) in CH_2Cl_2 (0.5 ml) was treated, under nitrogen, at −10 °C with Et_3N (0.10 ml, 0.72 mmol), 4-(*N*,*N*-dimethylamino)pyridine (22 mg, 0.18 mmol), and tosyl chloride (120 mg, 0.63 mmol). After 1 h the reaction was quenched with water (1 ml) and the aqueous phase was extracted with CH_2Cl_2 (4 × 5 ml). The organic extracts were washed with 5% aqueous $NaHCO_3$ and water and then evaporated under reduced pressure. The crude product was chromatographed on silica gel (CH_2Cl_2–MeOH, 97 : 3) to give (3) (287 mg, 95%), m.p. 73—75 °C, $[\alpha]_D^{20}$ +57.4° ($CHCl_3$, *c* 1), $\nu_{max.}$ ($CHCl_3$) 1 785, 1 720, 1 665, 1 445, and 1 365 cm^{-1}; δ($CDCl_3$) 7.15—8.15 (19 H, m, ArH), 6.93 (1 H, s, NH), 6.15, 1 H, d, H_b, J_{ab} 6 Hz), 5.29 (1 H, q, H_a, J_{ac} = $J_{ac'}$ = 6 Hz), 5.01 (1 H, d, H_f or H_g, J_{fg} 12 Hz), 4.83 (1 H, d, H_f or H_g), 4.69 H, d, H_c and $H_{c'}$), and 2.42 (3 H, s, CH_3) (Found: C, 63.45; H, 4.6; N, 2.25. $C_{34}H_{29}NO_{10}S$ requires C, 63.44; H, 4.54; N, 2.18%).

Reaction of 2-Benzoylamino-2-benzoyloxymethyl-2-deoxy-3-O-benzoyl-5-O-(p-tolylsulphonyl)-D-lyxono-1,4-lactone (3) *with Octenylalanate.*—A solution of oct-1-yne (24 mg, 0.216 mmol) in n-hexane (0.3 ml) was treated at 0 °C, under nitrogen, with a solution of 1.9M-di-isobutylaluminium hydride in n-hexane (0.126 ml, 0.239 mmol), and then stirred at 55 °C for 4 h. The mixture was then cooled to room temperature, treated with a solution of 1.3M-n-butyl-lithium in n-hexane (0.184 ml, 0.239 mmol) and stirred for 1 h. A solution of (27) (107 mg, 0.166 mmol) in THF–HMPT (3 : 1; 1.3 ml) was then added, and the resulting solution stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the aqueous phase extracted with ethyl acetate. The organic extracts were evaporated and the crude product was purified by silica gel chromatography (n-hexane–ethyl acetate, 7 : 3) to give one main product which was characterized as (26) (40 mg, 50%), $\nu_{max.}$ ($CHCl_3$) 1 795, 1 715—1 735, and 1 640 cm^{-1}; δ($CDCl_3$) 7.30—8.20 (15 H, m, ArH), 6.07 (1 H, d, H_b, J_{ab} 6 Hz), 5.33 (1 H, dd, H_a, J_{ac} 3.5 Hz, $J_{ac'}$ < 1 Hz), 4.94 (2 H, s, H_f and H_g), 4.75 (1 H, dd, H_c, $J_{cc'}$ 12 Hz), 4.41 (1 H, d, $H_{c'}$) (Found: C, 69.1; H, 4.45; N, 2.8. $C_{28}H_{21}NO_7$ requires C, 69.56; H, 4.38; N, 2.90%).

Reaction of 2-Benzoylamino-2-benzoyloxymethyl-2-deoxy-3-O-benzoyl-5-O-(p-tolylsulphonyl)-D-lyxono-1,4-lactone (3) with *Bis-[(E)-9-(1,3-dithiolan-2-yl)pentadec-1-enyl]lithium Cuprate* (4).—A solution of (29) (1 g, 3.35 mmol) in n-hexane (3.12 ml) was treated at 0 °C, under nitrogen, with a solution of 1.0M-di-isobutyl aluminium hydride in n-hexane (3.69 ml, 3.69 mmol) and stirred for 4 h at 55 °C. After evaporation of the solvent under reduced pressure, the residue was taken up in THF (6.7 ml) and the solution was cooled to −50 °C. A solution of iodine (890.8 mg, 3.51 mmol) in THF (6.7 ml) was added. The mixture was stirred for 20 min and then allowed to warm to room temperature and quenched with an excess of pH 7 phosphate buffer. The resulting mixture was diluted with n-hexane and filtered through a Celite cake. The organic phase was separated, washed with aqueous $Na_2S_2O_3$ and water, and evaporated. The crude product was purified by 'flash chromatography' [22] (n-hexane–benzene, 96 : 4) to give a pale orange oil (1.07g, 75%) [δ($CDCl_3$) 6.51 (1 H, dt, C=C*H*–CH_2, *J* 15 and 7.3 Hz), 5.97 (1 H, d, I–CH=C, *J* 15 Hz), 3.25 (4 H, s, CH_2–S)], which was immediately used for the following reaction. A solution of the vinyl iodide (160 mg, 0.375 mmol) in diethyl ether (0.4 ml) was cooled to −78 °C and treated with a

solution of 2M-t-butyl-lithium in n-hexane (0.375 ml, 0.75 mmol), and stirred for 2 h at −78 °C. The temperature was then allowed to rise to −50 °C and a solution of $CuBr \cdot Me_2S$ complex (38.6 mg, 0.188 mmol) in diethyl ether–Me_2S (1 : 1; 0.6 ml) was added. After being stirred for 1 h at −50 °C the solution was treated with a solution of the tosylate (3) (60 mg, 0.093 mmol) in THF–HMPT (1.8 : 1; 1 ml), and the resulting mixture allowed to warm slowly to room temperature (3 h). The reaction was then quenched with saturated aqueous NH_4Cl (2 ml), and the mixture extracted with diethyl ether; and the organic extracts were evaporated. The crude product was treated with CH_3I (5.33 g, 37.5 mmol) in aqueous 90% acetone (7.5 ml) in the presence of $CaCO_3$ (0.94 mmol, 94 mg). The mixture was stirred and heated at reflux under nitrogen for 24 h, and then diluted with diethyl ether (30 ml), washed with saturated brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (CH_2Cl_2–AcOEt, from 99 : 1 to 9 : 1) to give (2) as an oil (18 mg, 28%), identical chromatographically and spectroscopically with the sample obtained from the natural product.

2-Amino-2,5-dideoxy-2-hydroxymethyl-5-(E)-9-oxopentadec-1-enyl-D-lyxonic Acid (*Thermozymocidin*) (1).—A solution of (2) (100 mg, 0.152 mmol) in aqueous 1M-NaOH (4 ml) was refluxed under nitrogen overnight. The mixture was cooled, neutralised with dilute HCl, and concentrated to a small volume. After 1 day at 5 °C the precipitate was collected by filtration, washed with acetone and ethyl acetate, and crystallized from EtOH–H_2O to give (1) (38.5 mg, 63%) chromatographically and spectroscopically identical with the natural product.[2]

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