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Note

3-Amino-5-*C*-phenyl-D-altrofuranose and 3-amino-5-*C*-[3-carboxy-4-(carboxymethyl)-2-oxo-3-cyclohexen-1-yl]-D-altrofuranose, possible intermediates for synthesis of the anthracycline antibiotic decilorubicin

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Decilorubicin (**1**) is an antitumor antibiotic produced by *Streptomyces virginiae*[1] whose structure was determined by a combination of chemical conversions, degradations and spectral interpretation[2]. Herein we describe the synthesis of 3-amino-5-*C*-phenyl-D-altrofuranose and 3-amino-5-*C*-[3-carboxy-4-(carboxymethyl)-2-oxo-3-cyclohexen-1-yl]-D-altrofuranose (or L-galactofuranose), possible intermediates for the synthesis of the chromophore of decilorubicin† having the 4-amino-2,6-epoxybenz[*g*]oxocane ring (DEF) system‡.

The key stage in the synthetic approach to the DEF ring is the highly stereospecific reaction of 3-benzamido-3,6-dideoxy-1,2-*O*-isopropylidene-β-D-*arabino*-hexofurano-5-sulose (**8**) with organometallic reagents derived from the D- or CD-ring synthon. The synthesis of **8** began with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**2**), readily available from D-glucose[7]. The successful *trans*-diaxial ring opening of oxirane in **2** to 3-azido-3-deoxy-α-D-altropyranoside (**3**) was achieved by treatment with sodium azide and ammonium chloride in a refluxing mixture of 2-methoxyethanol and water in 82% yield[8]. Compound **3** was converted into the corresponding 4-benzoate bromide **4** by Hanessian's procedure[9] in 96% yield. Generation of the alkene **5** from **4** was best achieved by refluxing with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene in 87% yield. The ^{1}H-n.m.r. spectrum of **5** clearly indicates a conformational flip from $^4C_1$ (D) to $^1C_4$ (D). Selective hydrogenation of the azido group without saturation of the double bond in **5** proved troublesome until we discovered that catalytic hydrogenation with sodim hydrogentelluride (NaTeH)[10], generated *in situ* from tellurium and sodium borohydride in ethanol, gave the desired reduction accompanied by migration of the benzoyl group to afford the amino-protect-

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† For an enantiocontrolled synthesis of the ABCD ring see ref. 3. For the synthesis of a new nitro-branched sugar (decironitrose) and 4-*O*-succinyl-L-digsnose, see ref. 4.
‡ For partial solutions to this synthesis, see ref. 5. For the total synthesis of nogalamycin congeners, see ref. 6.

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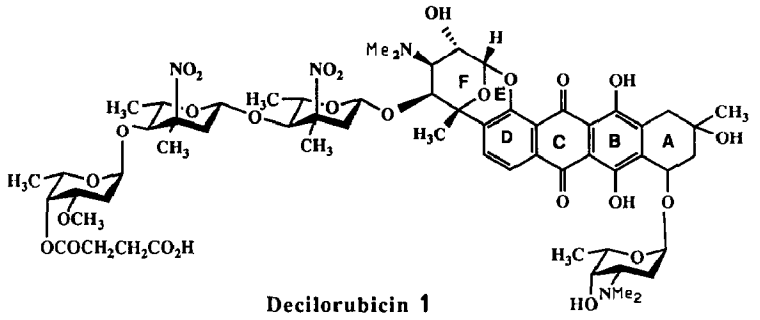
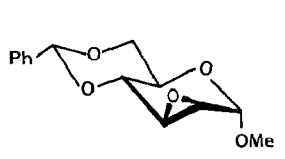
ed product **6** in 89% yield. Formation of hexofurano-5-sulose **7** was accomplished *via* recyclization from the pyranose to the furanose ring by hydrolysis of **6** [Amberlyst 15 (H^+), *N*,*N*-dimethylformamide–H_2O, 95%][11]. Subsequent acetonation of **7** afforded **8** in 92% yield.

The stereocontrolled construction of the C-5 asymmetric center was examined by nucleophilic addition with organometallic reagents generated from methoxymethyl



Decilorubicin **1**



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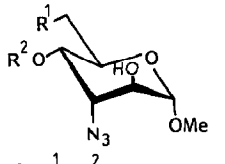
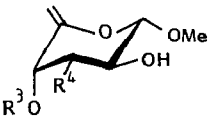


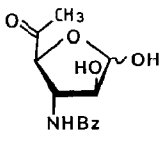
3 R^1, R^2= -OCH(Ph)-

4 R^1= Br, R^2= Bz



5 R^3= Bz, R^4= N_3

6 R^3= H, R^4= NHBz



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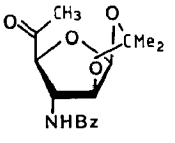

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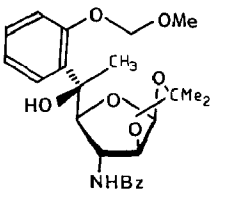

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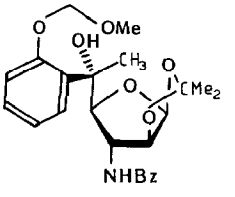

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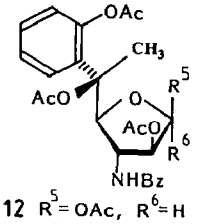
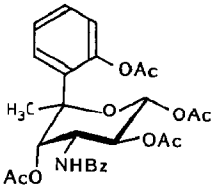


12 R^5= OAc, R^6= H

13 R^5= H, R^6= OAc

14 R^5= OMe, R^6= H



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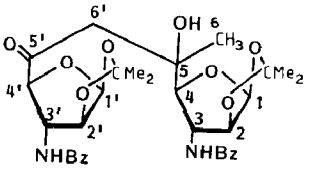

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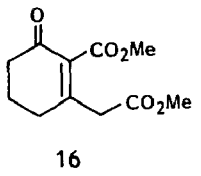

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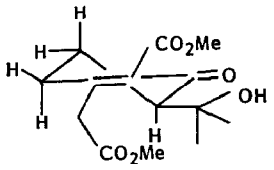

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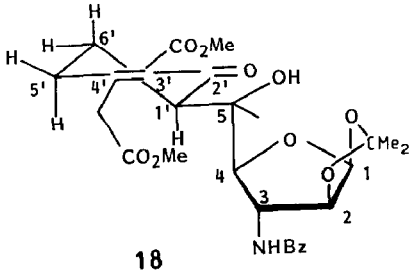

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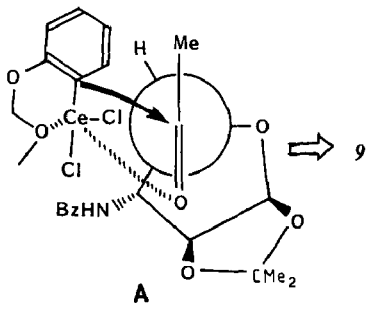

A

phenyl ether[12]. Addition of the aryllithium [$LiC_6H_4OCH_2OCH_3$; $C_6H_5OCH_2OCH_3$, BuLi–TMEDA–hexane, −78°] to **8** in THF afforded the tertiary carbinol epimers **9** and **10** in 1:1 ratio and 27% combined yield. On the other hand, Grignard reaction of **8** with 2-(methoxymethoxy)phenylmagnesium bromide was unsuccessful and afforded a single diastereomer **11** as a self-condensation product in 82% yield. Strikingly, nucleophilic addition of the arylcerium chloride[13] [$CeCl_2C_6H_4OCH_2OCH_3$; $LiC_6H_4OCH_2OCH_3$, $CeCl_3$, THF, −78°] to **8** improved both the stereoselectivity and chemical yield, giving **9** and **10** in 8.5:1 ratio and 95% yield. However, in the Grignard reaction with cerium chloride, the result was the same as without cerium chloride, suggesting that no metal exchange between magnesium and cerium took place. The absolute stereochemistry at C-5 of the major product **9** was established as (*S*) by X-ray crystallographic analysis*. The nucleophilic addition reaction seems to proceed stereospecifically in accordance with Cram's rule[14] through a transition state corresponding to the Felkin–Anh[15,†] model (A). Based on these findings, the nucleophilic addition of the dianion of methyl (2-methoxycarbonyl-3-oxo-1-cyclohexene)acetate[17] (**16**) was examined for a synthetic approach to the CDEF-ring system. In a model experiment, addition of the dianion of **16** (2 eq LDA, 2 eq HMPA, THF, −78°) to acetone, high regioselectivity was observed leading to **17** as the sole product in 44% yield. Interestingly, nucleophilic addition of the dianion of **16** (2 eq BuLi, 2 eq HMPA, THF, −78°) to **8** also exhibited high diastereoselectivity, and gave the diastereomer **18** as the major product, along with the three other

* The X-ray crystallographic analysis was carried out by Prof. Y. Iitaka and Dr. H. Nakamura, Laboratory of Biophysics, School of Pharmaceutical Sciences, Teikyo University, Sagamiko-machi, Tsukui-gun, Kanagawa 199-01, Japan.

† The same selectivity of nucleophilic additon to the ketone between the aryllithium and the arylcerium was observed, and an analogous reaction mechanism has been discussed; see ref. 16.

diastereomers in 6:1.5:1.5:1 ratio and in quantitative yield. The ^{1}H-n.m.r. spectrum of **18** clearly indicates an axial hydrogen at C-1′. The absolute stereochemistry at C-5 of **18** could not be rigorously determined. The condensation should proceed with similar stereospecificity as just described.

Preliminary attempts to cyclize the adduct **9** under protic conditions using acid hydrolysis followed by acetylation[5c] gave, instead of the desired epoxyoxocane, two acetyl furanosides **12** and **13**, a methyl furanoside **14** and an acetyl pyranoside **15** in 54, 26, 5.5, and 3% yields, respectively. Further synthetic studies on the CDEF ring-system are in progress.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto apparatus and are uncorrected. I.r. spectra were determined on Hitachi Model 260-10 and Jasco A-3 spectrophotometers. Optical rotations were measured with Perkin–Elmer Model 241 and Jasco DPI-140 polarimeters. The ^{1}H-n.m.r. spectra were recorded with Jeol GX-400 and Jeol GX-500 spectrometers. Chemical shifts are expressed in p.p.m. with Me_4Si as the internal standard. Proton-noise-decoupled f.t. ^{13}C-n.m.r. spectra were taken at 100.4 MHz with a Jeol GX-400 spectrometer using Me_4Si as the reference. The mass spectra were taken by a Hitachi RMU-6M mass spectrometer for electron-impact (e.i.) ionization, M-80 for field-desorption (F.d.), and RMU-7M for secondary ionization (s.i.).

Methyl 3-azido-4,6-O-benzylidene-3-deoxy-α-D-altropyranoside (**3**). — A solution of **2** (16.5 g, 625 mmol), NaN_3 (16.3 g, 0.25 mol) and NH_4Cl (6.7 g, 125 mmol) in a mixture of 2-methoxyethanol (165 mL) and water (110 mL) was refluxed for 3 h. After evaporation of the 2-methoxyethanol, the resulting precipitate was filtered off and the filtrate was extracted with CH_2Cl_2. The combined extracts were washed with water and saturated aq. NaCl, dried over $MgSO_4$, and filtered. Evaporation of the solvent gave an oil, which crystallized from a mixture of EtOH–hexane to give colorless crystals of **3** (15.7 g, 82%); m.p. 131–132°, $[\alpha]_D^{22}$ +39° (*c* 0.88, $CHCl_3$); ν_{max} 3480, 3080, 3060, 3040, 2980, 2950, 2880, 2840, 1265, and 1135 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 2.09 (d, 1 H, $J_{OH,2}$ 6 Hz), 3.34 (s, 3 H, OCH_3), 3.81 (t, 1 H, $J_{6ax,6eq}$, $J_{6ax,5}$ 10 Hz, H-6_{ax}), 3.97 (dd, 1 H, $J_{2,3}$ 3, $J_{2,OH}$ 6 Hz, H-2), 4.09 (t, 1 H, $J_{2,3}$, $J_{3,4}$ 3 Hz, H-3), 4.15 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.28 (m, 1 H, H-5), 4.33 (dd, 1 H, $J_{6eq,5}$ 5 Hz, H-6_{eq}), 4.60 (s, 1 H, H-1), 5.62 (s, 1 H, C*H*Ph) and 7.3–7.6 (m, 5H, phenyl); s.i.-m.s.: *m/z* 374 (M^+ + 1), 308, 282, 250, 132, 75, 57, and 45.

Anal. Calc. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.73; H, 5.39; N, 13.45.

Methyl 3-azido-4-O-benzoyl-6-bromo-3,6-dideoxy-α-D-altropyranoside (**4**). — To a suspension of **3** (23.2 g, 76 mmol) and $BaCO_3$ (67.2 g, 0.34 mol) in 1,2-dichloroethane (250 mL) was added *N*-bromosuccinimide (14.8 g, 83 mmol), and the mixture was stirred for 4.5 h at 90°. The insoluble material was filtered off, and washed with CH_2Cl_2.

The filtrate and washings were combined, washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over $MgSO_4$, and filtered. The filtrate was passed through a short column of Florisil, and evaporated to give a solid that crystallized from ether to afford colorless crystals of **4** (9.2 g, 96%); m.p. 112–113°, $[\alpha]_D^{22}$ −6.1° (*c* 0.92, $CHCl_3$): ν_{max} 3500, 3160, 3110, 2940, 2840, 2120, 1730, 1285, 1270, 1265, and 1255 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 2.49 (d, 1 H, $J_{OH,2}$ 5 Hz, OH-2), 3.53 (s, 3 H, OCH_3), 3.56 (dd, 1 H, $J_{6,6'}$ 11, 6-H), 3.62 (dd, 1 H, H-6'), 4.05 (broad td, 1 H, $J_{2,3}$, $J_{2,OH}$ ~4 Hz, H-2), 4.17 (t, 1 H, $J_{3,4}$ 4 Hz, H-3), 4.41 (ddd, 1 H, $J_{5,6}$ 7, $J_{5,6'}$ 3 Hz, H-5), 4.72 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 5.47 (dd, 1 H, $J_{4,5}$ 8.5 Hz, H-4), and 7.44, 7.61 and 8.30 (each m, total 5 H, Ph); s.i.-m.s.: *m/z* 386 (M^+) 360, 328, 132, 75, 57, and 45.

Anal. Calc. for $C_{14}H_{16}BrN_3O_5$: C, 43.54; H, 4.18; Br, 20.69; N, 10.88. Found: C, 43.97; H, 3.90; Br, 20.39; N, 10.89.

*Methyl 3-azido-4-*O*-benzoyl-3,6-dideoxy-*α*-*D*-*arabino*-hex-5-enopyranoside* (**5**). — To a solution of **4** (7.3 g, 0.019 mol) in benzene (57 mL) was added dropwise DBU (3.4 mL, 23 mmol), and the stirred mixture was gently boiled under reflux. The mixture was diluted with ether, and the solution was refrigerated. The resulting crystals were filtered off, and washed with ether. The filtrate and washings were combined, washed with saturated aq. NH_4Cl and saturated aq. NaCl, dried over $MgSO_4$, and filtered. The filtrate was passed through a short column of Florisil, and evaporated to afford a solid that crystallized from a mixture of ether–hexane to give colorless crystals of **5** (5 g, 87%); m.p. 113–114°, $[\alpha]_D^{22}$ −7.8° (*c* 1.0, $CHCl_3$); ν_{max} 3460, 2120, 1710, and 1275 cm^{-1}; ^{1}H-n.m.r. (500 MHz, $CDCl_3$): δ 2.51 (d, 1 H, OH-2), 3.65 (s, 3H, OCH_3), 3.70 (dd, 1 H, $J_{3,4}$ 3.7 Hz, H-3), 4.13 (ddd, 1 H, $J_{2,OH}$ 3.1, $J_{2,3}$ 9.8 Hz, H-2), 4.42 (d, 1 H, $J_{1,2}$ 6.7 Hz, H-1), 4.89 and 4.92 (each s, 2 H, H-6), 5.82 (d, 1 H, H-4), 7.45 (t, 2 H, *J* 7.9 Hz, Ph), 7.58 (t, 1 H, *J* 7.9 Hz, Ph), and 8.05 (d, 2 H, *J* 7.9 Hz, Ph); f.d.-m.s.: *m/z* 305 (M^+), 105.

Anal. Calc. for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 55.03; H, 4.70; N, 13.66.

*Methyl 3-benzamido-3,6-dideoxy-*α*-*D*-*arabino*-hex-5-enopyranoside* (**6**). — To a suspension of tellurium powder (8.0 g, 0.063 mol) in EtOH (100 mL) was added $NaBH_4$ 5.7 g, 0.15 mol). The mixture was refluxed with stirring under argon for 1.5 h, and then stirred overnight at room temperature. To the resulting purple solution was added dropwise a solution of **5** (7.6 g, 25 mmol) in EtOH (25 mL) with stirring during 25 min, and the mixture was stirred overnight at room temperature. After dilution with water (50 mL), the mixture was stirred under air until the purple color disappeared. The resulting insoluble material was filtered off, and the filtrate was extracted with CH_2Cl_2. The extracts were washed with water and saturated aq. NaCl, dried over $MgSO_4$, and filtered. The filtrate was passed through a short column of Florisil, and the product was eluted with a mixture of CH_2Cl_2–EtOAc. The eluate, evaporated to low volume, afforded colorless crystals of **6** (6.2 g, 89%); m.p. 129.5–130.5°, $[\alpha]_D^{22}$ +64.8° (*c* 1.0, 1:1, $CHCl_3$–MeOH); ν_{max} 3400, 2940, 1665, 1630, 1650, 1585, and 1555 cm^{-1}; ^{1}H-n.m.r. (500 MHz, $CDCl_3$): δ 3.20 (d, 1 H, OH-4), 5.51 (broad s, 1 H, H, OH-2), 3.98 (broad s, 1 H, H-2), 4.44 (dt, 1 H, $J_{3,4}$ 3.7, $J_{2,3}$ 4.3, $J_{3,NH}$ 7.9 Hz, H-3), 4.56 (broad dd, 1 H, $J_{4,OH}$ 6.1 Hz, H-4), 4.76 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.78 and 4.84 (each s, 2 H, H-6), 7.22 (broad d, 1 H,

NHCO), 7.46 (t, 2 H, *J* 7.6 Hz, Ph), 7.54 (t, 1 H, Ph), and 7.79 (d, 2 H, Ph); f.d.-m.s.: *m/z* 279 (M^+), 118.

Anal. Calc. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.51; H, 6.02; N, 5.44.

3-Benzamido-3,6-dideoxy-D-arabino-*hexofuranos-5-ulose* (**7**). — A solution of **6** (6.2 g, 22 mmol) in a mixture of *N,N*-dimethylformamide (33 mL) and water (33 mL) was stirred in the presence of Amberlyst 15 (H^+) resin (6.2 g) for 5 h. The resin was filtered off and the filtrate was evaporated to an oil that crystallized from EtOAc to afford colorless crystals of **7** (5.6 g, 95%).

3-Benzamido-3,6-dideoxy-1,2-O-*isopropylidene-β*-D-arabino-*hexofuranos-5-ulose* (**8**). — A solution of **7** (5.6 g, 21 mmol) in acetone (91 mL) was stirred in the presence of anhydrous $CuSO_4$ (5.8 g, 36 mmol) and *p*-toluenesulfonic acid (0.46 g, 18 mmol) overnight at room temperature. After filtration of insoluble matter, the filtrate was further stirred in the presence of an equal amount of anhydrous $CuSO_4$ under the same conditions overnight. After filtration of insoluble matter, to the filtrate was added Et_3N (0.2 mL). Evaporation of the solvent gave a solid, which was dissolved in CH_2Cl_2. The solution was washed successively with water, saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over $MgSO_4$, and filtered. The filtrate was passed through a short column of Florisil, and the product was eluted with 1:1 CH_2Cl_2–ether. The eluate was evaporated to give a solid, which was crystallized from ether to afford colorless crystals of **8** (6 g, 92%); m.p. 145–146°, $[\alpha]_D^{22}$ −19° (*c* 0.87, $CHCl_3$); ν_{max} 3360, 3040, 3020, 1730, 1660, and 1550 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.27 and 1.33 (each s, 3 H, CMe_2); 2.35 (s, 3 H, CH_3-6), 4.47 (d, 1 H, $J_{4,3}$ 2.4 Hz, H-4), 4.75 (dd, 1 H, $J_{2,1}$ 3.9, $J_{2,3}$ ~0.5 Hz, H-2), 4.79 (dd, 1 H, $J_{3,4}$ 2.4, $J_{3,NH}$ 7.0 Hz, H-3), 6.08 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 6.71 (d, 1 H, $J_{NH,3}$ 7.0 Hz, NHCO), and 7.42, 7.51 and 7.76 (each m, total 5 H, Ph); s.i.-m.s.: *m/z* 306 ($M^+ + 1$), 277, 248, 185, 132, 122, and 105.

Anal. Calc. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.12; H, 6.07; N, 4.57.

3-Benzamido-3,6-dideoxy-1,2-O-*isopropylidene-5*-C-*[2-(methoxymethoxy)phenyl]-β*-D-*altrofuranose* (**9**) *and 3-benzamido-3,6-dideoxy-1,2*-O-*isopropylidene-5*-C-*[2-(methoxymethoxy)phenyl]-β*-L-*galacto-furanose* (**10**). — To an ice-cold solution of BuLi in hexane (1.6M; 3.7 mL, 6 mmol) was added successively *N,N,N′,N′*-tetramethylethylenediamine (0.915 mL, 6 mmol) and methoxymethyl phenyl ether (0.846 g, 6 mmol), and the mixture was stirred for 45 min under argon[12]. This solution was added dropwise to a suspension of anhydrous cerium chloride (1.63 g, 6.6 mmol) in tetrahydrofuran (13 mL) with vigorous stirring during 10 min at −78° under argon, and the mixture was stirred for 50 min. To the resulting solution was added dropwise a solution of **8** in tetrahydrofuran (4 mL) under the same conditions during 15 min, and then the mixture was stirred for a further 5 h. After quenching with water, the mixture was extracted with CH_2Cl_2. The extract was washed successively with saturated aq. NH_4Cl, saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with 3:1 ether–hexane gave **9** as a solid (0.375 g, 85%) and **10** as a

foam (0.044 g, 10%). The solid **9** was crystallized from ether–hexane to afford colorless crystals.

Compound **9** had m.p. 114–115°, $[\alpha]_D^{22}$ −40° (*c* 0.31, $CHCl_3$); ν_{max} 3500, 3275, 3000, 2960, 1650, 1550, and 1500 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.35 and 1.65 (each s, 3 H, CMe_2), 1.74 (s, 3 H, CH_3-5), 3.06 (s, 1 H, OH-5), 3.20 (s, 3 H, OCH_3), 3.62 (td, 1 H, $J_{3,4}$, $J_{3,NH}$ 7.0 Hz, H-3), 4.79 and 4.86 (ABq, 2 H, *J* 6.9 Hz, OCH_2O), 5.05 (dd, 1 H, $J_{2,3}$ 1.9 Hz, H-2), 5.09 (d, 1 H, H-4), 5.62 (d, 1 H, NHCO), 6.15 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 6.91 (dd, 1 H, *J* 1.0, 8.5 Hz, pH), 7.08 (dd, 1 H, Ph), 7.23 (ddd, 1 H, *J* 2.0, 7.5, 8.5 Hz, Ph), 7.86 (dd, 1 H, Ph) and 7.1–7.6 (m, total 5 H, Bz); s.i.-m.s.: *m/z* 444 (M^+ + 1), 386, 306, 247, 146, 105; e.i.-m.s.: *m/z* 428 (M^+ -CH_3), 385, 307, 262, 204, 146, 105. The absolute stereochemistry was determined by X-ray crystallographic analysis (see footnote, p. 139).

Anal. Calc. for $C_{24}H_{29}NO_7$: C, 64.50; H, 6.59; N, 3.16. Found: C, 64.83; H, 6.47; N, 3.03.

Compound **10** had $[\alpha]_D^{22}$ −20.5° (*c* 1.0, $CHCl_3$); ν_{max} 3475, 3320, 3070, 3000, 2940, 1640 (sh), 1540 (sh), and 1490 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.34 and 1.59 (each s, 3 H, CMe_2), 1.67 (s, 3 H, CH_3-5), 3.36 (s, 3 H, OCH_3), 4.08 (td, 1 H, $J_{3,4}$, $J_{3,NH}$ 7.0 Hz, H-3), 4.19 (s, 1 H, OH-5), 4.89 (d, 1 H, H-4), 4.91 (dd, 1 H, $J_{2,3}$ 1.8 Hz, H-2), 5.09 and 5.14 (ABq, 2 H, *J* 6.8 Hz, OCH_2O), 5.97 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 6.17 (d, 1 H, NHCO), 7.04 and 7.06 (ABq, (?), 2 H, *J* ~8 Hz, Ph), 7.23 (td, 1 H, *J* 1.8, 8.0 Hz, Ph), 7.4–7.62 (m, total 6 H, protons of Ph and Bz); f.d.-m.s.: *m/z* 444 (M^+), 262, 181, 136, 45.

Anal. Calc. for $C_{24}H_{29}NO_7$: C, 64.50; H, 6.59; N, 3.16. Found: C, 64.90; H, 6.56; N, 3.25.

Undeculo-dialdose derivative **11**. — To a suspension of Mg turnings (29.2 mg, 12 mmol) in tetrahydrofuran (0.5 mL) was added a trace amount of I_2 and a solution of 2-(methoxymethoxy)phenyl bromide (217 mg, 1 mmol) in tetrahydrofuran (1.5 mL) under argon at room temperature, and the mixture was stirred for 1 h. To the Grignard reagent thus generated was added dropwise a solution of **8** (61.1 mg, 0.2 mmol) in tetrahydrofuran (0.75 mL) at −78° under argon, and the mixture was stirred for 5.5 h. After quenching with saturated aq. NH_4Cl, the mixture was extracted with CH_2Cl_2. The extract was washed with water and saturated aq. NaCl, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave a solid that was subjected to preparative t.l.c. on silica gel, developing with 1:1 ether–CH_2Cl_2 to give **11** as a colorless solid (50 mg, 82%); ^{1}H-n.m.r. (400 MHz, $(CD_3)_2CO$): δ 1.22, 1.28, 1.36, 1.39 and 1.51 (each s, 3 H, 2 × CMe_2 and CH_3-5), 3.04 and 3.10 (ABq, 2 H, *J* 16 Hz, H-6′), 3.78 (s, 1 H, OH-5), 4.23 (d, 1 H, H-4), 4.52 (d, 1 H, H-4′), 4.54 (ddd, 1 H, $J_{3,4}$ 7, $J_{3,NH}$ 8 Hz, H-3), 4.69 (d, 1 H, H-2′), 4.80 (dd, 1 H, $J_{2,3}$ 1.8 Hz, H-2), 4.89 (dd, 1 H, $J_{3',4'}$ 2, $J_{3',NH}$ 7.6 Hz, H-3′), 5.88 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 6.00 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1′), 7.2–7.9 (m, 10 H, 2 × Bz), 8.14 (d, 1 H, $J_{3',NH}$ 7.6 Hz, 3′-CONH) and 8.25 (d, 1 H; 3-CONH); ^{13}C-n.m.r. [100 MHz, $(CD_3)_2CO$]: δ 24.4 (C-6), 26.1, 26.4, 27.2 and 28.1 (4 × CH_3 of CMe_2), 47.3 (C-3), 56.0 (C-3′), 57.8 (C-6′), 72.1 (C-5), 86.1 [C-2′(?)], 88.3 [C-2(?)], 88.4 [C-4(?)], 90.8 [C-4′(?)], 105.5 [C-1(?)], 107.3 [C-1′(?)], 112.9 and 114.3 (2 × CMe_2), 128.0, 128.2, 129.12, 129.17, 132.2, 132.3, 135.1, 135.2 (2 × Ph), 167.6 and 167.6 (2 × NHCO), and 207.0 (C-5′).

1,2,5-Tri-O-acetyl-3-benzamido-3,6-dideoxy-5-C-(2-acetoxyphenyl)-β-D-altrofuranose (**12**), *1,2,5-tri-O-acetyl-3-benzamido-3,6-dideoxy-5-C-(2-acetoxyphenyl)-α-D-altrofuranose* (**13**), *methyl 2,5-di-O-acetyl-3-benzamido-3,6-dideoxy-5-C-(2-acetoxyphenyl)-β-D-altrofuranoside* (**14**) *and 1,2,4-tri-O-acetyl-3-benzamido-3,6-dideoxy-5-C-(2-acetoxyphenyl)-β-L-altropyranose* (**15**). — A solution of **9** (522 mg) in a mixture of MeOH (3 mL) and water (1.5 mL) was stirred in the presence of Amberlyst 15 (H^+) resin (522 mg) overnight. The resin was filtered off, and the filtrate was evaporated to give an oil. A solution of the oil in 9:1 $CHCl_3$–MeOH was passed through a short column of Florisil, and the products were eluted with the same solvent mixture. Evaporation of the eluate gave an oil, which was dissolved in CH_2Cl_2 (6 mL). To the ice-cooled solution was added pyridine (1.14 mL) and Ac_2O (0.89 mL), and the mixture was stirred overnight at room temperature. After quenching with a large excess of water, the mixture was extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a solid, which was subjected to column chromatography on silica gel. Elution with 1:2 ether–hexane and evaporation gave **12** as a foam (336 mg, 54%), **13** as a foam (162 mg, 26%), crystals of **14** (33 mg, 5.5%), and crystals of **15** (19 mg, 3%).

Compound **12** had m.p. 101–103° (foam), $[\alpha]_D^{25}$ −52° (*c* 0.2, $CHCl_3$); ν_{max} 1760, 1680 (sh), 1665 (sh), 1505, 1460 (sh), and 1390 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 2.04 (s, 3 H, CH_3-5), 2.05, 2.07, 2.15 and 2.33 (each s, 3 H, 4 × OAc), 4.32 (d, 1 H, $J_{3,4}$ 9 Hz, H-4), 5.16 (q, 1 H, $J_{3,2}$, $J_{3,NH}$ 9 Hz, H-3), 5.29 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 6.16 (d, 1 H, NHCO), 6.33 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 6.83 (d with a small coupling, 1 H, *J* 16 Hz, Ph), 6.99 (t with a small coupling, 1 H, Ph), 7.06 (t, 1 H, Ph), 7.43 (t, 1 H, Ph), and 7.25–7.55 (m, 5 H, benzyl); s.i.-m.s.: *m/z* 528 (M^+ + 1), 468, 408, 366, 245, 145, 105, 77, 57, and 43.

Anal. Calc. for $C_{27}H_{29}NO_{10}$: C, 61.47; H, 5.54; N, 2.66. Found: C, 61.10; H, 5.55; N, 2.52.

Compound **13** had m.p. 83–84° (foam), $[\alpha]_D^{25}$ +31.3° (*c* 0.2, $CHCl_3$); ν_{max} 1760 (sh), 1680 (sh), 1550 (sh), 1500, 1460, (sh), and 1190 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 2.03 (s, 3 H, CH_3-5), 2.04, 2.07, 2.14 and 2.31 (each s, 3 H, 4 × OAc), 4.69 (d, 1 H, H-4), 4.87 (ddd, 1 H, $J_{3,4}$ 6.4 Hz, H-3), 5.05 (d, 1 H, $J_{2,3}$ 1.8 Hz, H-2), 6.18 (s, 1 H, $J_{1/2h} \sim 1$ Hz, H-1), 6.32 (d, 1 H, $J_{NH,3}$ 8 Hz, NHCO), 6.96 (dd, 1 H, J_2, 7.5 Hz, Ph), 7.14–7.24 (m, 2 H, Ph), 7.49 (t with a small coupling, 1 H, Ph) and 7.35–7.65 (m, 5 H, Bz); s.i.-m.s.: *m/z* 528 (M^+ + 1), 468, 408, 366, 348, 287, 245, 145, 105, 75, 57, and 43.

Anal. Calc. for $C_{27}H_{29}NO_{10}$: C, 61.47; H, 5.54; N, 2.66. Found: C, 61.17; H, 5.53; N, 2.45.

Compound **14** had m.p. 184–185°, $[\alpha]_D^{25}$ − 88.6° (*c* 0.75, $CHCl_3$); ν_{max} 1780, 1750, 1660, 1570 (sh), 1500 (sh), 1460, and 1385 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 2.05 [s, 3 H, 5-CH_3(?)], 2.06, 2.09 and 2.33 (each s, 3 H, 3 × OAc), 4.32 (d, 1 H, $J_{3,4}$ 8.5 Hz, H-4), 5.04 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 5.05 (q, 1 H, $J_{3,NH}$ 8.5 Hz, H-3), 5.13 (dd, 1 H, $J_{1,2}$ 3.9, $J_{2,3}$ 8.5 Hz, H-2), 6.15 (d, 1 H, $J_{NH,3}$ 8.5 Hz, NHCO), 6.83 (dd, 1 H, J_2, 7 Hz, Ph), 7.02 (dt, 1 H, Ph), 7.06 (dt, 1 H, Ph), 7.42 (t with a small coupling, 1 H, *J* 7 Hz, Ph) and 7.2–7.6 (m, 5 H, Bz); s.i.-m.s.: *m/z* 500 (M^+ + 1), 440, 408, 380, 306, 245, 132, 75, 57, and 45.

Anal. Calc. for $C_{26}H_{29}NO_9$: C, 62.51; H, 5.85; N, 2.80. Found: C, 62.28; H, 5.42; N, 2.50.

Compound **15** had m.p. 231–232°, $[\alpha]_D^{25}$ −10.5° (*c* 0.75, $CHCl_3$); ν_{max} 3400, 3380, 3020, 2960, 1780, 1755, 1680, 1540, 1500, 1460, and 1390 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.38 (s, 3 H, CH_3-5), 1.99, 2.19, 2.24 and 2.41 (s, 3 H, 4 × OAc), 4.43 (ddd, 1 H, $J_{3,4}$ 2.2, $J_{3,NH}$ 7.3, $J_{2,3}$ 11.3 Hz, H-3), 5.31 (dd, 1 H, H-2), 6.04 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 6.47 (d, 1 H, $J_{NH,3}$ 7.3 Hz, NHCO), 6.74 (broad s, 1 H, $J_{1/2h}$ 2.2 Hz, H-4), and 7.1–8.1 (m, 9 H, Ph and Bz); n.o.e. was observed between a proton at C-3 and a proton at C-1, between a proton at C-3 and a proton at C-4, and between methyl protons at C-5 and a proton at C-4; s.i.-m.s.: *m/z* 528 (M^+ + 1), 468, 426, 418, 386, 376, 213, 203, 105, 75, 57, 45, and 43.

Anal. Calc. for $C_{27}H_{29}NO_{10}$: C, 61.47; H, 5.54; N, 2.66. Found: C, 61.69; H, 5.55; N, 2.52.

Methyl [4-(1-hydroxy-1-methylethyl)-2-methoxycarbonyl-3-oxo-1-cyclohexene]acetate (**17**). — To a solution of lithium diisopropylamide, prepared from diisopropylamine (0.059 mL) and a hexane solution of BuLi (1.55M; 0.271 mL) at −78°, in tetrahydrofuran (0.5 mL) was added dropwise a solution of **16** (45.2 mg) in tetrahydrofuran (0.4 mL) and hexamethylphosphoric triamide (0.073 mL) at −78°, and the mixture was stirred for 1 h. Acetone (0.022 mL) was added dropwise to the mixture at −78°, and the mixture was stirred for 1 h. After quenching with 2M HCl (1 mL), the mixture was extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$, and filtered. Evaporation of the filtrate afforded a residue that was subjected to preparative t.l.c. on silica gel developed with 9:1 CH_2Cl_2–ether to give **17** as an oil (24.9 mg, 44%); ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 2.42 (s, 6 H, 2 × CH_3), 1.83 (tdd, 1 H, $J_{5ax,5eq}$, $J_{5ax,6}$ 14, $J_{5ax,4ax}$ 10, $J_{5ax,4eq}$ 5.8 Hz, Hax-5), 2.14 (dq, 1 H, $J_{5eq,4eq}$, $J_{5eq,4ax}$, $J_{5eq,6}$ 4.2 Hz, Heq-5), 2.47 (dd, 1 H, H-6), 4.15–4.25 (m, 2 H, H-4), 3.30 and 3.36 (ABq, 2 H, *J* 15.6 Hz, CH_2CO_2), 3.73 and 3.83 (each s, 3 H, 2 × CO_2CH_3); ^{13}C-n.m.r. ($CDCl_3$): δ 24.5 (C-5), 24.9 and 28.2 [$H_3CC(OH)CH_3$] 30.9 (C-4), 40.5 (-CH_2-), 52.4 and 52.5 (2 × OCH_3), 55.2 (C-6), 72.3 [C(OH)], 135.0 (C-2), 156.1 (C-3), 166.0 and 168.8 (2 × -CO_2-), and 199.0 (C-1).

*3-Benzamido-3,6-dideoxy-1,2-O-isopropylidene-5-C-[3-methoxycarbonyl-4-(methoxycarbonylmethyl)-2-oxo-3-cyclohexen-1-yl)]-β-*D*-altrofuranose (or -β-*L*-galactofuranose)* (**18**). — The reaction of **8** with **16** was similar to the procedure used for the preparation of **17** just described; the yields of a major diastereomer and the other diastereomers of **18** were 60, 15, 15, and 10%, respectively: ^{1}H-n.m.r. data of the major isomer (400 MHz, $CDCl_3$): δ 1.25 and 1.37 (each s, 3 H, CMe_2), 1.64 (s, 3 H, CH_3-5), 1.85 (tdd, 1 H, $J_{6'ax,6'eq}$, $J_{6'ax,5'ax}$ 10, $J_{6'ax,5'eq}$ 6 Hz, H*ax*-6'), 2.26 (dq, 1 H, $J_{6'eq,5'eq}$, $J_{6'eq,5'ax}$ 4.2 Hz, H*eq*-6'), 2.5–2.8 (m, 2 H, H-5'), 2.96 (dd, 1 H, $J_{1',6'ax}$ 13, $J_{1',6'eq}$ 4.2 Hz, H-1'), 3.28 and 3.34 (ABq, 2 H, *J* 15 Hz, CH_2-CO_2), 3.72 and 3.82 (each s, 3 H, 3 × CO_2CH_3), 4.23 (d, 1 H, $J_{4,3}$ 7.2 Hz, H-4), 4.33 (dt, 1 H, $J_{3,4}$, $J_{3,NH}$ 7.2 Hz, H-3), 4.94 (dd, 1 H, $J_{2,3}$ 1.8 Hz, H-2), 6.01 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 6.98 (d, 1 H, NHCO), and 7.35–7.85 (m, 5 H, Ph).

Anal. Calc. for $C_{25}H_{33}NO_{10}$; C, 59.16; H, 6.55; N, 2.76. Found: C, 59.55; H, 6.20; N, 2.47.

in the molecule, vicinal to the furanone system, on the stereochemical course of the hydrogenation, we applied the sequence of β-elimination–hydrogenation to the lactonic disaccharide 2,3,5-tri-*O*-benzoyl-6-*O*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)-D-galactono-1,4-lactone (**7**). Interestingly, the glycosylfuranone **8**, resulting from the double elimination of benzoic acid from **7**, may be considered as an analog derivative of ranunculine[5], a natural glycosyl-α,β-unsaturated-1,4-lactone precursor of the vesicant substance protoanemonin. On the basis of the results obtained for the hydrogenation of the glycosylbutenolide **8**, an approach for the resolution of a conveniently derivatized, racemic 3,5-dideoxyaldohexono-1,4-lactone, was developed.

RESULTS AND DISCUSSION

Benzoylation of D-galactono- (**1a**), D-glucono- (**2a**), or D-mannono-1,4-lactones (**3a**) with an excess of benzoyl chloride and pyridine for 16 h at room temperature afforded the same product: 2,6-dibenzoyloxy-2,4-hexadien-4-olide (**4**), as the result of the elimination of two molecules of benzoic acid. A single isomer of **4** crystallized from the mixture upon addition of ether in 44, 43, and 11% yield, respectively. The configuration of the exocyclic double bond was identified as *Z* (see later). The yield of butenolide **4** was improved by treating the perbenzoylated derivatives of the aldonolactones (**1b**, **2b**, and **3b**) with 20% triethylamine in dichloromethane, for 2 h at room temperature. For the three lactone derivatives the yields of **4** were >70%. However, under these conditions, a mixture of **4**-*E* and **4**-*Z* was obtained, as determined by the spectral data of the product. Thus, its ^{1}H-n.m.r. spectrum showed two double doublets for H-5, and two doublets for H-6 and H-6′. Also, in the ^{13}C-n.m.r. spectrum, all of the signals of the furanone system appeared duplicated, because of the mixture of isomers. The configuration of the double bond was assigned by comparison of the relative chemical shifts of H-5, H-6,6′ and C-3, C-4 for each isomer with those of similar compounds of known configuration[6,7]. An additional confirmation for the structure was obtained from the long-range allylic coupling constant values ($^4J_{3,5}$) of **4**-*E* ($\sim$1 Hz) and **4**-*Z* (not observed), as a transoid disposition for H-3 and H-4 gives a larger $^4J_{3,5}$ value[8].

The fact that the butenolide **4** is obtained in similar yields from perbenzoylated aldonolactones having *cis* or *trans* relationships for H-2 and the benzoyloxy group of C-3 indicates that the formation of **4** is not influenced by the relative orientation of substituents and supports the E1cB mechanism proposed for the elimination[3]. Thus, removal of H-2 by a base should lead to a resonance-stabilized carbanion, which rearranges with *syn* or *anti* elimination of the benzoyloxy group at C-3. This first elimination favors the removal of H-4, being the resulting carbanion stabilized by conjugation with an α,β-unsaturated carbonyl group, and also a E1cB mechanism would operate for the second elimination.

Catalytic hydrogenation of the mixture **4**-*E*,*Z* gave a racemic 3,5-dideoxyaldono-1,4-lactone (**5**, 78% yield) as a single diastereoisomer, according to its ^{13}C-n.m.r. spectrum. The ring-proton coupling constants from the ^{1}H-n.m.r. spectrum of **5** indicated a *threo* relationship for its chiral centers[2]. As observed for other diunsaturated