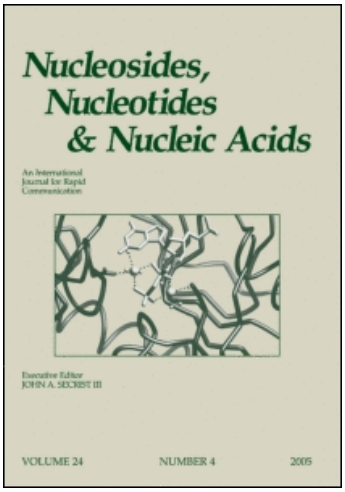


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# Synthesis of Novel α-l-Arabinopyranosides of β-Lactams with Potential Antimicrobial Activity

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# SYNTHESIS OF NOVEL α-L-ARABINOPYRANOSIDES OF β-LACTAMS WITH POTENTIAL ANTIMICROBIAL ACTIVITY

**Nasser S. A. M. Khalil** ▫ *Central Laboratory for Food and Feed, Agricultural Research Center, Giza, Egypt*

▫ *Synthetic routes toward the synthesis of some novel 1-(2,3,4-tri-O-acetyl-α-L-arabinopyranosyl)-azetidin-2-ones are described. Antimicrobial screening of three selected compounds revealed their activity against Bacillus subtilis and Escherichia coli.*

**Keywords** Synthesis, α-L-Arabinopyranosides, Monocyclic β-Lactams, Azetidin-2-Ones, Antimicrobial Activity



## INTRODUCTION

β-Lactams in general and monocyclic β-lactams in particular are the focus of much interest in medicinal chemistry. β-Lactam antibiotics have been successfully used in the treatment of infectious diseases for many years.[1,2] Despite a large number of compounds containing a β-lactam moiety that have already been synthesized and tested, there is still a need of this kind[3] due to the increasing resistance of bacterial strains to certain types of antibiotics.[4] Monocyclic β-lactams, which include compounds such as nocardicins, aztreonam, and carmonam, have been described for their chemotherapeutic importance as antibiotics.[5–9] Recently, some new biologically active monocyclic β-lactams displaying activities other than the usual antibiotic one, such as thrombin,[10] prostate specific antigen,[11] human cytomegalovirus protease,[12] and cholesterol absorption inhibition,[13] have been discovered. Keeping all the previous facts in mind and in continuation of our program of research on the synthesis of some biologically active compounds,[14–20] we have pursued the synthesis of new α-L-arabinopyranosides of some monocyclic β-lactams. Of these new nucleosides, compounds **5** and **10b,c** were tested against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida*

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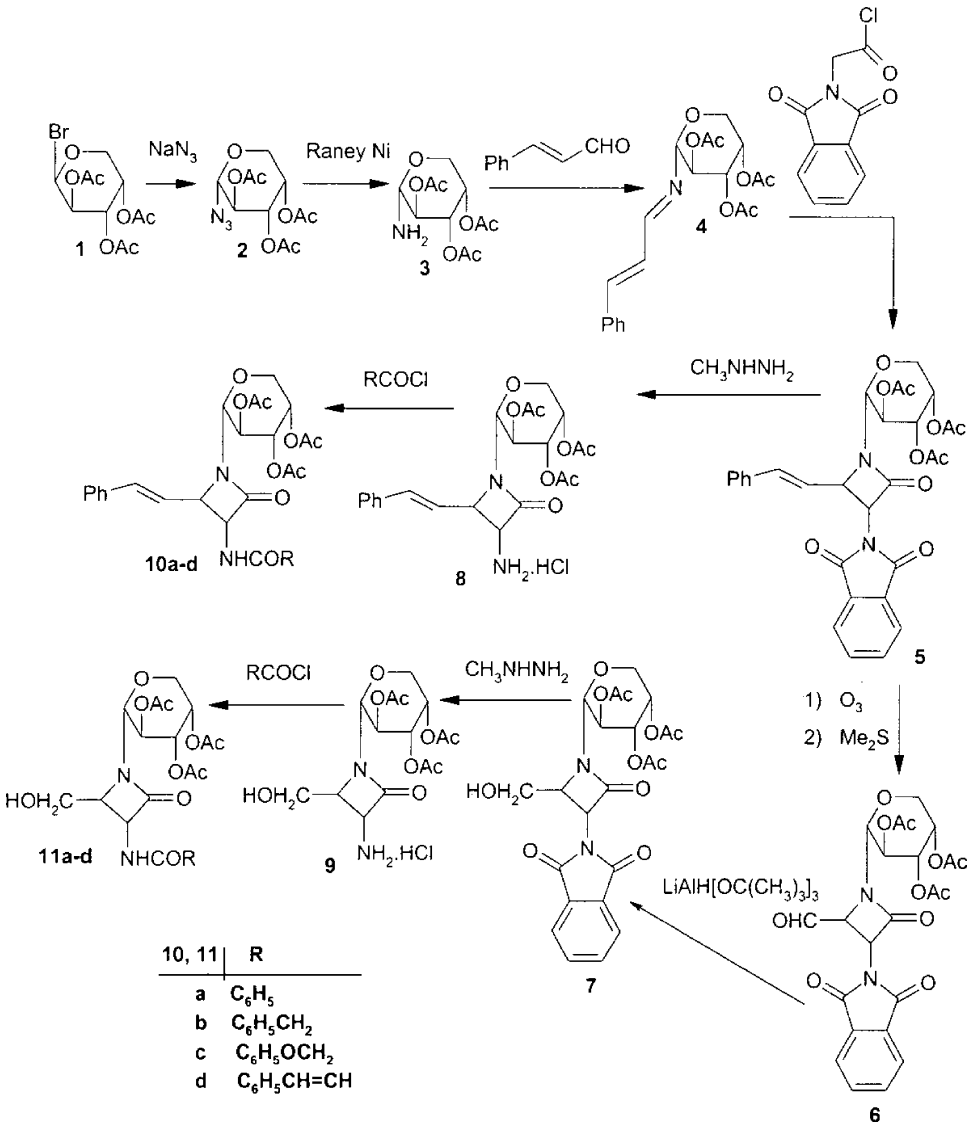
*albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Escherichia coli.*

## RESULTS AND DISCUSSION

Treatment of 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide **(1)** with sodium azide gave 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl azide **(2)** (Scheme 1). The structure of **2** was established based on its $^1$H NMR data. Thus, the position of




**SCHEME 1**

**TABLE 1** Antimicrobial Activity of **5, 10b,c** Compared to Standard Antimicrobial Agents

| | Compounds | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | | | 10b | | | 10c | | | St. | | |
| | Concentration (mg/mL) | | | | | | | | | | | |
| Test organisms | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 |
| Aspergillus fumigatus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | +++ | +++ | ++ |
| Penicillium italicum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | +++ | +++ | ++ |
| Syncephalastrum racemosum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | +++ | +++ | +++ |
| Candida albicans | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ | ++ | ++ |
| Staphylococcus aureus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ | ++ | ++ |
| Pseudomonas aeruginosa | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | +++ | ++ | ++ |
| Bacillus subtilis | ++ | ++ | ++ | + | + | + | + | + | + | ++ | ++ | ++ |
| Escherichia coli | +++ | ++ | ++ | ++ | + | + | + | + | + | +++ | ++ | ++ |

St. = Reference standard; Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent. The test was done using the diffusion agar technique.

Well diameter: 0.6 cm (100 μL of each conc. was tested).

Inhibition values = 0.1–0.5 cm beyond control = +.

Inhibition values = 0.61–1.0 cm beyond control = ++.

Inhibition values = 1.0–1.5 cm beyond control = +++.

0 = Not detected.



the anomeric proton at δ 6.02 with a coupling constant value of 9.2 Hz consistent with similar reported data[14–20] proves that the anomeric proton is in a *trans* position with respect to the proton on position 2 of the L-arabinopyranosyl ring, a fact that assigns its α-configuration. Similar inversion was reported when 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide was treated with sodium azide to yield 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide.[21]

Heteogeneous reduction of the azide group of **2** with Raney nickel in ethyl acetate afforded 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosylamine **(3)**. The $^1$H NMR data of the latter compound revealed its amino group at δ 4.50.

Condensation of **3** with cinnamaldehyde gave almost quantitatively α-L-arabinopyranosylamino-(*N*-cinnamylidene)-2,3,4-tri-*O*-acetate **(4)**. The $^1$H NMR data of **4** not only showed the absence of the amino group at δ 4.50, but also revealed the presence of N = CH proton at δ 7.52.

[2 + 2] Cycloaddition of **4** with phthalimidoacetyl chloride in dichloromethane in the presence of triethylamine yielded 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phthalimido-4-styryl-azetidin-2-one **(5)**. The IR spectrum of the later compound showed the lactam carbonyl function at 1781 cm-1 and the phthalimido carbonyl function at 1762 $cm^{-1}$ and 1735 $cm^{-1}$ consistent with similar reported data.[21]

Ozonolysis of the styryl group of 5 at −78°C in dichloromethane afforded 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phthalimido-4-formyl-azetidin-2-one **(6)**. The $^1$H NMR spectrum of 6 revealed its formyl proton at δ 10.12 (d, $J$ = 5.5 Hz).

Reduction of **6** using lithium tri-*tert*-butoxyaluminum hydride in dry THF at 0°C gave 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phthalimido-4-hydroxymethyl-azetidin-2-one (**7**). The $^1$H NMR data of the later compound showed the absence of

the formyl proton δ 10.12 and the appearance of the $D_2O$ exchangeable $CH_2OH$ proton at δ 3.75.

Dephthaloylation of **5** and **7** with ethanolic methylhydrazine yielded the corresponding 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-3-amino-4-styryl or hydroxymethyl-azetidin-2-one hydrochloride salt **(8)** and **(9)**.

Acylation of **8**, **9** afforded the corresponding 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-3-acylamino-azetidin-2-ones (**10a d**) and (**11a d**), respectively.

## BIOLOGICAL EVALUATION

The antimicrobial activity (in vitro) of **5, 10b,c** was tested against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Escherichia coli*. From data presented in Table 1, it is clear that **5, 10b,c** are active against *Bacillus subtilis* and *Escherichia coli*. Compound 5 showed high activity against *Bacillus subtilis* and *Escherichia coli* at all tested concentrations (5, 2.5, 1 mg/mL). Compounds **10b,c** showed moderate activity against the same organisms at the same concentrations.

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 spectrometer. $^1$H NMR spectra were recorded at 200 MHz with a Varian GEMINI 200 spectrometer. Elemental analyses were carried out at the Micro Analytical Center, Cairo University, Giza, Egypt. Antimicrobial screening of **5, 10b,c** was carried out at the Medical Mycology Lab, The regional center for Mycology and Biotechnology, Al Azhar University, Cairo, Egypt. The starting 2,3,4-tri-*O*-acetyl-β-L-Arabinopyranosyl bromide **(1)** was prepared as reported.[22]



**2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl azide (2).** To a solution **1** (3.39 g, 10 mmol) in 9:1 acetone/water (40 mL) was added sodium azide (0.65 g, 10 mmol) and the reaction mixture was heated at reflux temperature for 24 h, then stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the formed residue was dissolved in dichloromethane (50 mL), washed with water (3 × 50 mL), dried ($Na_2SO_4$), and filtered. After evaporation of the solvent under reduced pressure, the formed solid was recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give colorless crystals of **2** (2.22 g, 74%); mp 145–146°C; IR (KBr) 2141 ($N_3$), 1747 (CO acetate) cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 6.02 (d, 1H, $J$ = 9.2 Hz, H-1′), 5.96 (t, 1H, $J$ = 9.6 Hz, H-2′), 5.42 (d, 1H, $J$ = 3.4 Hz, H-4′), 5.28 (dd, 1H, $J$ = 3.4, 10.1 Hz, H-3′), 4.16 (dd, 1H, $J$ = 1.6, 13.4 Hz, H-5′), 3.92 (d, 1H, $J$ = 13.4 Hz, H-5″), 2.26, 2.06, 2.00 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{11}H_{15}N_3O_7$ (301.3): C, 43.86; H, 5.02; N, 13.95. Found: C, 43.78; H, 4.96; N, 14.04.

**2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosylamine (3).** To a solution of **2** (3.01 g, 10 mmol) in ethyl acetate (30 mL) was added Raney nickel (3.73 g) and

the reaction mixture was heated at reflux temperature for 3 h. The resulting solid was collected by filtration, washed with ether (50 mL), and recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give pale yellow crystals of **3** (2.34 g, 85%); mp 170–172°C; IR (KBr) 3410, 3336 ($NH_2$), 1742 (CO acetate) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.05 (d, 1H, *J* = 9.4 Hz, H-1′), 5.95 (t, 1H, *J* = 9.5 Hz, H-2′), 5.42 (d, 1H, *J* = 3.4 Hz, H-4′), 5.28 (dd, 1H, *J* = 3.4, 10.3 Hz, H-3′), 4.50 (brs, 2H, $D_2O$ exchangeable $NH_2$), 4.16 (dd, 1H, *J* = 1.7, 13.7 Hz, H-5′), 3.92 (d, 1H, *J* = 13.7 Hz, H-5″), 2.25, 2.05, 2.02 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{11}H_{17}NO_7$ (275.3): C, 48.00; H, 6.23; N, 5.09. Found: C, 48.15; H, 6.12; N, 5.04.

**α-L-Arabinopyranosylamino-(N-cinnamylidene)-2,3,4-tri-*O*-acetate (4).** A mixture of **3** (2,75 g, 10 mmol), cinnamaldehyde (1.32 g, 10 mmol), and sodium sulfate (15 g) in dry dichloromethane (50 mL) was heated at reflux temperature for 5 h. After cooling, the mixture was filtered and the filtrate was washed with water (3 × 50 mL), dried ($Na_2SO_4$), and filtered. The solvent was evaporated under reduced pressure and the formed solid was recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give yellow crystals of **4** (2.92 g, 75%); mp 153–154°C; IR (KBr) 1743 (CO acetate) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.52 (d, 1H, *J* = 8.3 Hz, N = CH), 7.15–7.29 (m, 5H, ArH), 6.62 (d, 1H, *J* = 16.4 Hz, PhC<u>H</u> = CH), 6.05 (d, 1H, *J* = 9.0 Hz, H-1′), 5.94 (t, 1H, *J* = 9.5 Hz, H-2′), 5.64 (dd, 1H, *J* = 8.3, 16.4 Hz, PhCH = C<u>H</u>), 5.41 (d, 1H, *J* = 3.4 Hz, H-4′), 5.28 (dd, 1H, *J* = 3.4, 10.0 Hz, H-3′), 4.16 (dd, 1H, *J* = 1.5, 13.2 Hz, H-5′), 3.92 (d, 1H, *J* = 13.2 Hz, H-5″), 2.25, 2.07, 2.00 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{20}H_{23}NO_7$ (389.4): C, 61.69; H, 5.95; N, 3.60. Found: C, 61.84; H, 5.98; N, 3.71.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phthalimido-4-styryl-azetidin-2-one (5).** To a cold solution (−10°C) of **4** (3.89 g, 10 mmol) in dry dichloromethane (100 mL) and triethylamine (1.21 g, 12 mmol) was added dropwise while stirring phthalimidoacetyl chloride (8.94 g, 40 mmol). The solution was stirred at room temperature for 24 h then washed with brine (100 mL) and saturated $NaHCO_3$ solution (2 × 100 mL) and water (30 × 100 mL). The combined aqueous phase was reextracted with dichloromethane and the combined organic phase was dried ($Na_2SO_4$) and filtered. After evaporation of the solvent under reduced pressure, the formed solid was recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give pale crystals of **5** (4.10 g, 71%); 141–142°C; IR (KBr) 1781 (β-lactam CO), 1762, 1735 (phthalimido CO), 1742 (CO acetate) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.0–7.58 (m, 4H, $C_6H_4(CO)_2N$), 7.27–7.08 (m, 5H, Ph), 6.41 (d, 1H, *J* = 16.4 Hz, PhC<u>H</u> = CH), 6.22 (dd, 1H, *J* = 8.0, 16.4 Hz, PhCH = C<u>H</u>), 6.05 (d, 1H, *J* = 9.2 Hz, H-1′), 5.96 (t, 1H, *J* = 9.6 Hz, H-2′), 5.42 (d, 1H, *J* = 3.4 Hz, H-4′), 5.27 (dd, 1H, *J* = 3.4, 10.1 Hz, H-3′), 4.89 (d, 1H, *J* = 5.1 Hz, CH-$N(CO)_2$), 4.52 (dd, 1H, *J* = 5.1, 8.0 Hz, PhCH = CH–C<u>H</u>), 4.16 (dd, 1H, *J* = 1.6, 13.3 Hz, H-5′), 3.92 (d, 1H, *J* = 13.3 Hz, H-5″), 2.25, 2.05, 2.03 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{30}H_{28}N2O_{10}$ (576.6): C, 62.50; H, 4.90; N, 4.86. Found: C, 62.68; H, 4.99; N, 5.10.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phthalimido-4-formyl-azetidin-2-one (6).** A solution of **5** (3.46 g, 6 mmol) in dry dichloromethane (100 mL) was cooled to −78°C. Ozone gas was passed through the reaction mixture until a pale blue coloration was observed and then it was purged with nitrogen. A solution of dimethyl sulfide (6 mL) in dichloromethane (20 mL) was added dropwise while stirring and cooling (−78°C). After complete addition, the cooling bath was removed and the solution was stirred at room temperature for 1 h. The reaction mixture was washed with brine (3 × 100 mL) and water (3 × 100 mL). The combined aqueous phase was reextracted with dichloromethane and the combined organic phase was dried ($Na_2SO_4$) and filtered. After evaporation of the solvent under reduced pressure, the obtained oily residue was column chromatographed [petroleum ether (bp 40–60°C) → 60% dichloromethane/petroleum ether (bp 40–60°C)] then recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give pale crystals of **6** (2.56 g, 85%); $R_f$ 0.84; mp 128–130°C; IR (KBr) 1780 (β-lactam CO), 1760, 1732 (phthalimido CO), 1750 (CHO), 1743 (CO acetate) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 10.12 (d, 1H, *J* = 5.5 Hz, CHO), 7.96–7.61 (m, 4H, $C_6H_4(CO)_2N$), 6.05 (d, 1H, *J* = 9.1 Hz, H-1′), 5.95 (t, 1H, *J* = 9.5 Hz, H-2′), 5.42 (d, 1H, *J* = 3.4 Hz, H-4′), 5.28 (dd, 1H, *J* = 3.4, 10.0 Hz, H-3′), 4.91 (d, 1H, *J* = 5.0 Hz, CH-N$(CO)_2$), 4.69 (dd, 1H, *J* = 5.0, 5.5 Hz, C<u>H</u>CHO), 4.17 (dd, 1H, *J* = 1.7, 13.7 Hz, H-5′), 3.94 (d, 1H, *J* = 13.7 Hz, H-5″), 2.26, 2.07, 2.05 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{23}H_{22}N_2O_{11}$ (502.4): C, 54.98; H, 4.41; N, 5.58. Found: C, 55.14; H, 4.57; N, 5.63.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phthalimido-4-hydroxymethyl-azetidin-2-one (7).** To **6** (2.51 g, 5 mmol) in dry tetrahydrofuran (130 mL) was added lithium tri-*tert*-butoxyaluminum hydride (2.54 g, 10 mmol). The reaction mixture was stirred under nitrogen for 3 h, acidified with 2% hydrochloric acid to pH 5, then 2 g silica gel was added and the suspension was stirred for 20 min. The later suspension was filtered and the solvent was evaporated under reduced pressure. The residue obtained was dissolved in dichloromethane (100 mL), washed with brine (3 × 50 mL) and water (3 × 100 mL). The combined aqueous phase was reextracted with dichloromethane and the combined organic phase was dried ($Na_2SO_4$) and filtered. The solvent was evaporated under reduced pressure and the obtained oily residue was recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give pale crystals of 7 (2.14 g, 85%); mp 133–135°C; IR (KBr) 3560–3252 (OH), 1781 (β-lactam CO), 1760, 1730 (phthalimido CO), 1743 (CO acetate) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.95–7.57 (m, 4H, $C_6H_4(CO)_2N$), 6.12 (d, 1H, *J* = 9.2 Hz, H-1′), 5.95 (t, 1H, 9.6 Hz, H-2′), 5.41 (d, 1H, *J* = 3.4 Hz, H-4′), 5.27 (dd, 1H, *J* = 3.4, 10.3 Hz, H-3′), 4.94 (d, 1H, *J* = 5.2 Hz, CH–N$(CO)_2$), 4.59 (dd, 1H, *J* = 5.2, 6.00 Hz, C<u>H</u>$CH_2OH$), 4.48 (brs, 1H, $D_2O$ exchangeable OH), 4.17 (dd, 1H, *J* = 1.7, 13.7 Hz, H-5′), 3.75 (m, 2H, C<u>H</u>$_2$OH), 3.94 (d, 1H, *J* = 13.7 Hz, H-5″), 2.25, 2.07, 2.03 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{23}H_{24}N_2O_{11}$ (504.4) C, 54.76; H, 4.80; N, 5.55. Found: C, 54.84; H, 4.78; N, 5.42.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-amino-4-styryl or hydroxymethyl-azetidin-2-one hydrochloride salt (8) and (9).** General procedure: To a solution of **5** (5.77 g, 10 mmol) or **7** (5.04 g, 10 mmol) in ethanol (30 mL) was added methylhydrazine (0.46 g, 10 mmol) and the reaction mixture was heated at reflux temperature for 3 h then stirred overnight at room temperature. The excess ethanol and methylhydrazine were evaporated under reduced pressure and to the residue obtained was added 5N HCl (25 mL). The mixture was stirred for 3 h at room temperature and filtered (to get rid of undesired methylphthalylhydrazide). To the filtrate was added 3 mL concentrated HCl and the aqueous solution was eavaporated under reduced pressure to give **8** and **9**.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-amino-4-styryl-azetidin-2-one hydrochloride salt (8).** Using the general procedure, **5** gave **8** (3.48 g, 72%); mp 141–142°C; IR (KBr) 3300, 3215 ($NH_2$), 1782 (β-lactam CO), 1742 (CO acetate) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.25–7.12 (m, 5H, Ph), 6.40 (d, 1H, $J$ = 16.2 Hz, PhCH = CH), 6.25 (dd, 1H, $J$ = 8.4, 16.2 Hz, PhCH = CH), 6.10 (d, 1H, $J$ = 9.4 Hz, H-1′), 5.96 (t, 1H, $J$ = 9.5 Hz, H-2′), 5.41 (d, 1H, $J$ = 3.5 Hz, H-4′), 5.28 (dd, 1H, $J$ = 3.5, 10.1 Hz, H-3′), 4.92 (d, 1H, $J$ = 5.2 Hz, $CHNH_2$), 4.70 (br, 2H, $D_2O$ exchangeable $NH_2$), 4.52 (dd, 1H, $J$ = 5.3, 8.4 Hz, PhCH = CH–CH), 4.16 (dd, 1H, $J$ = 1.6, 13.4 Hz, H-5′), 3.92 (d, 1H, $J$ = 13.4 Hz, H-5″), 2.26, 2.05, 2.02 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{22}H_{26}N_2O_8$.HCl (482.9): C, 54.72; H, 5.64; N, 5.80. Found: C, 54.65; H, 5.56; N, 5.97.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-3-amino-4-hydroxy-methyl-azetidin-2-one hydrochloride salt (9).** Using the general procedure, **7** gave **9** (3.45 g, 84%); mp 158–160°C; IR (KBr) 3500–3200 ($NH_2$, OH), 1780 (β-lactam CO), 1743 (CO acetate) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.08 (d, 1H, $J$ = 9.5 Hz, H-1′), 5.94 (t, 1H, $J$ = 9.5 Hz, H-2′), 5.43 (d, 1H, $J$ = 3.3 Hz, H-4′), 5.28 (dd, 1H, $J$ = 3.3, 10.1 Hz, H-3′), 4.94 (d, 1H, $J$ = 5.0 Hz $CHNH_2$), 4.62 (dd, 1H, $J$ = 5.0, 6.2 Hz, $CHCH_2OH$), 4.73 (br, 2H, $D_2O$ exchangeable $NH_2$), 4.47 (br, 1H, $D_2O$ exchangeable OH), 4.18 (dd, 1H, $J$ = 1.5, 13.0 Hz, H-5′), 3.92 (d, 1H, $J$ = 13.0 Hz, H-5″), 3.74 (m, 2H, $CHH_2OH$) 2.25, 2.05, 2.01 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{15}H_{22}N_2O_9$.HC1 (410.8): C, 43.86; H, 5.64; N, 6.82. Found: C, 43.91; H, 5.83; N, 6.82.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-acylamino-4-styryl or hydroxymethyl-azetidin-2-one (10a–d) or (11a–d).** General procedure: To a solution of **8** (2.41 g, 5 mmol) or **9** (2.05 g, 5 mmol) in dichloromethane (50 mL) was added pyridine (0.39 g, 5 mmol) followed by dropwise addition of a solution of the corresponding acid chloride (5 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 3 h then it was washed with 10% hydrochloric acid (50 mL) and 10% $NaHCO_3$ solution (50 mL) and water (2 × 50 mL). The combined aqueous phase was

reextracted with dichloromethane and the combined organic phase was dried ($Na_2SO_4$) and filtered. After evaporation of the solvent under reduced pressure, the residue obtained was recrystallised from dichloromethane/petroleum ether (bp 40–60°C) to give yellow crystals of **10a–d, 11d** and colorless crystals of **11a–c**.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-benzamido-4-styryl-azetidin-2-one (10a).** Using the general procedure, **8** and benzoyl chloride (0.70 g) gave **10a** (1.92 g, 70%); mp 118–120°C; IR (KBr) 3412 (NH), 1779 (β-lactam CO), 1740 (CO acetate), 1684 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.33–7.05 (m, 10H, 2Ph), 6.65 (d, 1H, $J$ = 8.4 Hz, $D_2O$ exchangeable NH), 6.43 (d, 1H, $J$ = 16.0 Hz, PhC<u>H</u> = CH), 6.22 (dd, 1H, $J$ = 8.1, 16.0 Hz, PhCH = C<u>H</u>), 6.04 (d, 1H, $J$ = 9.3 Hz, H-1′), 5.93 (t, 1H, $J$ = 9.5 Hz, H-2′), 5.43 (d, 1H, $J$ = 3.4 Hz, H-4′), 5.26 (dd, 1H, $J$ = 3.4, 10.1 Hz, H-3′), 4.90 (dd, 1H, $J$ = 5.1, 8.4 Hz, C<u>H</u>NH), 4.54 (dd, 1H, $J$ = 5.4, 8.0 Hz, PhCH = CH–C<u>H</u>), 4.16 (dd, 1H, $J$ = 1.7, 13.1 Hz, H-5′), 3.92 (d, 1H, $J$ = 13.1 Hz, H-5″), 2.26, 2.03, 2.01 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{29}H_{30}N_2O_9$ (550.6): C, 63.27; H, 5.49; N, 5.09. Found: C, 63.42; H, 5.41; N, 5.28.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phenylacetamido-4-styryl-azetidin-2-one (10b).** Using the general procedure, **8** and phenylacetyl chloride (0.77 g) gave **10b** (1.91 g, 68%); mp 110–112°C; IR (KBr) 3413 (NH), 1775 (β-lactam CO), 1743 (CO acetate), 1683 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.28–7.00 (m, 10H, 2Ph), 6.62 (d, 1H, $J$ = 8.0 Hz, $D_2O$ exchangeable NH), 6.40 (d, 1H, $J$ = 16.2 Hz, PhC<u>H</u> = CH), 6.24 (dd, 1H, $J$ = 8.3, 16.2 Hz, PhCH = C<u>H</u>), 6.08 (d, 1H, $J$ = 9.0 Hz, H-1′), 5.95 (t, 1H, $J$ = 9.3 Hz, H-2′), 5.40 (d, 1H, $J$ = 3.4 Hz, H-4′), 5.28 (dd, 1H, $J$ = 3.4, 10.4 Hz, H-3′), 4.92 (dd, 1H, $J$ = 5.1, 8.0 Hz, C<u>H</u>NH), 4.51 (dd, 1H, $J$ = 5.1, 8.3 Hz, PhCH = CH–C<u>H</u>), 4.15 (dd, 1H, $J$ = 1.5, 13.3 Hz, H-5′), 3.94 (d, 1H, $J$ = 13.4 Hz, H-5″), 3.42 (s, 2H, PhC<u>H</u>$_2$CO), 2.25, 2.04, 2.00 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{30}H_{32}N_2O_9$ (564.6): C, 63.82; H, 5.71; N, 4.96. Found: C, 63.84; H, 5.89; N, 4.82.

**1-(2,3,4-Tri-*O*-acetyl-α-l-arabinopyranosyl)-3-phenoxyacetamido-4-styryl-azetidin-2-one (10c).** Using the general procedure, **8** and phenoxyacetyl chloride (0.85 g) gave **10c** (2.14 g, 74%); mp 128°C; IR (KBr) 3410 (NH), 1772 (β-lactam CO), 1741 (CO acetate), 1681 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.31–7.01 (m, 10H, 2Ph), 6.65 (d, 1H, $J$ = 8.4 Hz, $D_2O$ exchangeable NH), 6.43 (d, 1H, $J$ = 16.0 Hz, PhC<u>H</u> = CH), 6.25 (dd, 1H, $J$ = 8.1, 16.0 Hz, PhCH = C<u>H</u>), 6.12 (d, 1H, $J$ = 9.4 Hz, H-1′), 5.85 (s, 2H, PhOC<u>H</u>$_2$), 5.92 (t, 1H, $J$ = 9.5 Hz, H-2′), 5.42 (d, 1H, $J$ = 3.1 Hz, H-4′), 5.26 (dd, 1H, $J$ = 3.1, 10.2 Hz, H-3′), 4.90 (dd, 1H, $J$ = 5.0, 8.4 Hz, C<u>H</u>NH), 4.49 (dd, 1H, $J$ = 5.2, 8.1 Hz, PhCH = CH–C<u>H</u>), 4.17 (dd, 1H, $J$ = 1.7, 13.1 Hz, H-5′), 3.96 (d, 1H, $J$ = 13.1 Hz, H-5″), 2.26, 2.03, 2.01 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{30}H_{32}N_2O_{10}$ (580.6): C, 62.06; H, 5.56; N, 4.82. Found: C, 652.14; H, 5.49; N, 5.09.

**1-(2,3;4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-cinnamoylamino-4-styryl-azetidin-2-one (10d).** Using the general procedure, **8** and cinnamoyl chloride (0.83 g) gave **10d** (2.07 g, 72%); mp 141–142°C; IR (KBr) 3412 (NH), 1778 (β-lactam CO), 1740 (CO acetate), 1685 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.67, 6.84 (2d, 2H, *J* = 16.4 Hz, PhCH = CH–CO), 7.35–7.00 (m, 10H, Ph), 6.65 (d, 1H, *J* = 8.0 Hz, $D_2O$ exchangeable NH), 6.44 (d, 1H, *J* = 16.0 Hz, PhC<u>H</u> = CHCH), 6.22 (dd, 1H, *J* = 8.2, 16.0 Hz, PhCH = C<u>H</u>CH), 6.04 (d, 1H, *J* = 9.4 Hz, H-1′), 5.94 (t, 1H, *J* = 9.5 Hz, H-2′), 5.41 (d, 1H, *J* = 3.5 Hz, H-4′), 5.28 (dd, 1H, *J* = 3.5, 10.1 Hz, H-3′), 4.92 (dd, 1H, *J* = 5.1, 8.0 Hz, C<u>H</u>NH), 4.54 (dd, 1H, *J* = 5.2, 8.2 Hz, PhCH = CH–C<u>H</u>), 4.16 (dd, 1H, *J* = 1.6, 13.4 Hz, H-5′), 3.95 (d, 1H, *J* = 13.4 Hz, H-5″), 2.26, 2.03, 2.01 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{31}H_{32}N_2O_9$ (576.6): C, 64.58; H, 5.59; N, 4.86. Found: C, 64.63; H, 5.88; N, 4.74.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-benzamido-4-hydroxymethyl-azetidin-2-one (11a).** Using the general procedure, **9** and benzoyl chloride (0.70 g) gave **11a** (1.62 g, 68%); mp 115–116°C; IR (KBr) 3500–3200 (OH, NH), 1780 (β-lactam CO), 1741 (CO acetate), 1680 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.37–7.02 (m, 5H, Ph), 6.61 (d, 1H, *J* = 8.0 Hz, $D_2O$ exchangeable NH), 6.14 (d, 1H, *J* = 9.0 Hz, H-1′), 5.95 (t, 1H, *J* = 9.4 Hz, H-2′), 5.44 (d, 1H, *J* = 3.1 Hz, H-4′), 5.26 (dd, 1H, *J* = 3.1, 10.2 Hz, H-3′), 4.94 (dd, 1H, *J* = 5.0, 8.0 Hz, C<u>H</u>NH), 4.67 (dd, 1H, *J* = 5.0, 6.2 Hz, C<u>H</u>$CH_2OH$), 4.45 (br, 1H, $D_2O$ exchangeable OH), 4.18 (dd, 1H, *J* = 1.5, 13.3 Hz, H-5′), 3.92 (d, 1H, *J* = 13.3 Hz, H-5″), 3.72 (m, 2H, C<u>H</u>$_2$OH), 2.26, 2.05, 2.00 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{22}H_{26}N_2O_{10}$ (478.5); C, 55.23; H, 5.48; N, 5.85. Found: C, 55.19; H, 5.37; N, 5.98.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phenylacetamido-4-hydroxymethyl-azetidin-2-one (11b).** Using the general procedure, **9** and phenylacetyl chloride (0.77 g) gave **11b** (1.77 g, 72%); mp 121–123°C; IR (KBr) 3411 (NH), 1774 (β-lactam CO), 1743 (CO acetate), 1685 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.29–7.02 (m, 5H, Ph), 6.64 (d, 1H, *J* = 8.4 Hz, $D_2O$ exchangeable NH), 6.07 (d, 1H, *J* = 9.1 Hz, H-1′), 5.92 (t, 1H, *J* = 9.3 Hz, H-2′), 5.41 (d, 1H, *J* = 3.5 Hz, H-4′), 5.27 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3′), 4.66 (dd, 1H, *J* = 5.1, 6.3 Hz, C<u>H</u>$CH_2OH$), 4.90 (dd, 1H, *J* = 5.3, 8.4 Hz, C<u>H</u>NH), 4.43 (br, 1H, $D_2O$ exchangeable OH), 4.16 (dd, 1H, *J* = 1.6, 13.4 Hz, H-5′), 3.96 (d, 1H, *J* = 13.4 Hz, H-5″), 3.74 (m, 2H, C<u>H</u>$_2$OH), 3.45 (s, 2H, PhC<u>H</u>$_2$CO), 2.26, 2.04, 2.02 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{23}H_{28}N_2O_{10}$ (492.5): C, 56.09; H, 5.73; N, 5.69. Found: C, 55.99; H, 5.74; N, 5.71.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-phenoxyacetamido-4-hydroxymethyl-azetidin-2-one (11c).** Using the general procedure, **9** and phenoxyacetyl chloride (0.85 g) gave **11c** (1.75 g, 69%); mp 133–134°C; IR (KBr) 3411 (NH), 1771 (β-lactam CO), 1740 (CO acetate), 1680 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.33–7.04 (m, 5H, Ph), 6.65 (d, 1H, *J* = 8.1 Hz,

$D_2O$ exchangeable NH), 6.09 (d, 1H, $J$ = 9.0 Hz, H-1′), 5.83 (s, 2H, PhOC$\underline{H}_2$), 5.93 (t, 1H, $J$ = 9.3 Hz, H-2′), 5.44 (d, 1H, $J$ = 3.3 Hz, H-4′), 5.27 (dd, 1H, $J$ = 3.3, 10.0 Hz, H-3′), 4.95 (dd, 1H, $J$ = 5.2, 8.1 Hz, C$\underline{H}$NH), 4.61 (dd, 1H, $J$ = 5.0, 6.0 Hz, C$\underline{H}$C$H_2$OH), 4.45 (br, 1H, $D_2O$ exchangeable OH), 4.16 (dd, 1H, $J$ = 1.6, 13.2 Hz, H-5′), 3.94 (d, 1H, $J$ = 13.2 Hz, H-5″), 3.71 (m, 2H, C$\underline{H}_2$OH), 2.26, 2.04, 2.02 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{23}H_{28}N_2O_{11}$ (508.5): C, 54.33; H, 5.55; N, 5.51. Found: C, 54.27; H, 5.44; N, 5.64.

**1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl)-3-cinnamoylamino-4-hydroxymethyl-azetidin-2-one (11d).** Using the general procedure, **9** and cinnamoyl chloride (0.83 g) gave **11d** (1.91 g, 76%); mp 137°C; IR (KBr) 3411 (NH), 1774 (β-lactam CO), 1742 (CO acetate), 1682 (CO amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.63, 6.88 (2d, 2H, $J$ = 16.0 Hz, PhCH = CH–CO), 7.33–7.02 (m, 5H, Ph), 6.62 (d, 1H, $J$ = 8.2 Hz, $D_2O$ exchangeable NH), 6.09 (d, 1H, $J$ = 9.3 Hz, H-1′), 5.96 (t, 1H, $J$ = 9.4 Hz, H-2′), 5.40 (d, 1H, $J$ = 3.4 Hz, H-4′), 5.29 (dd, 1H, $J$ = 3.4, 10.1 Hz, H-3′), 4.93 (dd, 1H,, $J$ = 5.0, 8.2 Hz, C$\underline{H}$NH), 4.65 (dd, 1H, $J$ = 5.1, 6.3 Hz, C$\underline{H}$C$H_2$OH), 4.42 (br, 1H, $D_2O$ exchangeable OH), 4.14 (dd, 1H, $J$ = 1.7, 13.5 Hz, H-5′), 3.92 (d, 1H, $J$ = 13.5 Hz, H-5″), 3.73 (m, 2H, C$\underline{H}_2$OH), 2.25, 2.04, 2.00 (3s, 9H, $CH_3CO$). Anal. Calcd. for $C_{24}H_{28}N_2O_{10}$ (504.5): C, 57.14; H, 5.59; N, 5.55. Found: C, 57.32; H, 5.47; N, 5.57.

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