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[2 + 2] CYCLOADDITION OF TRICHLOROACETYL ISOCYANATE TO GLYCALS*

MAREK CHMIELEWSKI† AND ZBIGNIEW KAŁUZA
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw (Poland)

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ABSTRACT

Cycloaddition of trichloroacetyl isocyanate to 1,5-anhydro-2-deoxy-D-*erythro*- and -L-*threo*-pent-1-enitols, and 1,5-anhydro-2-deoxy-D- and -L-*arabino*-hex-1-enitols having benzyl, methyl, *tert*-butyldimethylsilyl, and trimethylsilyl substituents on hydroxyl groups proceeds satisfactorily, under normal pressure at room temperature, to give a mixture of [2 + 2] and [4 + 2] cycloadducts. The isocyanate enters the glycal molecule stereospecifically *anti* with respect to the C-3 substituent. Bicyclic adducts slowly rearrange to the respective α,β-unsaturated amides. *N*-Deprotection of the trichloroacetyl substituent in [2 + 2] cycloadducts produces stable β-lactams. Further deprotection gives crystalline, water-soluble 2-carboxy-2-deoxypento- and -hexo-pyranosylaminolactams having a unique bicyclic sugar structure.

INTRODUCTION

Several attempts[1–5] have been made to carry out the reaction of tosyl, trichloroethoxysulfonyl, trichloroethylsulfonyl, trichloroacetyl, and trifluoroacetyl isocyanates **1–5** with 3,4-dihydro-2*H*-pyran (**6**), but the corresponding β-lactams were obtained in only a few cases. Cycloaddition of tosyl isocyanate to dihydropyran **6** at low temperature (~0°) leads to formation[1] of the bicyclic β-lactam **7**. Elevation of the temperature of cycloaddition causes rearrangement of the four-membered ring[1] to open-chain amide **11**. The more-active sulfonyl isocyanates **2** and **3** react with **6** to give substituted 1,5-anhydro-2-carbamoyl-2-deoxy-pent- and -hex-1-enitols (**12** and **13**, respectively), no β-lactams being formed[2]. Similar results were reported by Chan and Hall[3] for the addition of tosyl isocyanate to 2,6-disubstituted dihydropyrans.

On the other hand, acyl isocyanates react with **6** in a more complex way. The reaction of trichloroacetyl isocyanate (**4**) with dihydropyran **6** produces[4] amide **14**

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†To whom correspondence should be addressed.

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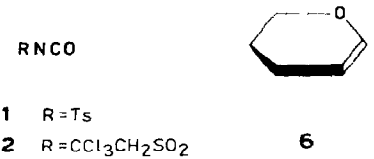
via intermediary formation of unstable β-lactam **8** and [4 + 2] adduct **16**; by-products **8** and **16** were both detected (in a n.m.r. test-tube only). Being more reactive than its trichloroacetyl analog, trifluoroacetyl isocyanate (**5**), under the same conditions, affords the open-chain amide **15**, without formation of bicyclic compounds[2,5]. Only 5-methyl- and 5-benzyl-3,4-dihydro-2*H*-pyran react with isocyanate **5**, to give the expected β-lactams **9** and **10**, respectively, obtained after removal of the trifluoroacetyl group with silica gel[2]. Less reactive isocyanates, such as benzoyl isocyanate, do not react with **6** in boiling benzene[4].



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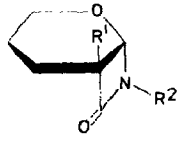

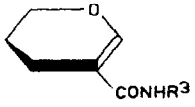

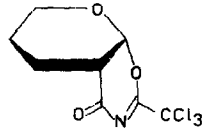

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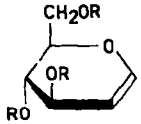
Attempts to add sulfonyl isocyanates to tri-*O*-acetyl-D-glucal (**17**) failed to give addition products[6,7]; isocyanate acts only as a Lewis acid, causing decomposition of the sugar substrate. According to our earlier results, application of a pressure of 1 GPa (1000 MPa) enables [2 + 2] cycloaddition of active isocyanates **1** and **4** to glycals **17, 22,** and **26** to occur, affording unstable β-lactams that, on heating, or even standing at room temperature, undergo retro-addition[8–10]. Our preliminary experiments on [2 + 2] cycloaddition of tosyl (**1**), trichloroethoxysulfonyl (**3**), and trichloroacetyl isocyanate (**4**) to glycals **18**–**20**, **23**, and **24** showed that the reaction proceeds under normal pressure at room temperature if the glycals bear non-polar blocking groups[11]. In the present work, the list of glycals used was extended, and trichloroacetyl isocyanate (**4**) was used exclusively. The latter offers easy access to stable, bicyclic β-lactams having the azetidinone ring fused to the sugar residue.



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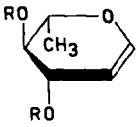
18 R=Me_3Si
19 R=$(Me_3C)Me_2Si$
20 R=Me
21 R=Bn



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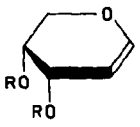
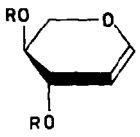
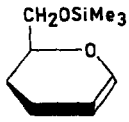
23 R=Me_3Si



24 R=Me_3Si
25 R=$(Me_3C)Me_2Si$



26 R=Ac
27 R=Me_3Si
28 R=$(Me_3C)Me_2Si$



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RESULTS AND DISCUSSION

The reactions of trichloroacetyl isocyanate (**4**) with compounds **6**, **18–21**, **23–25**, and **27–29** were conducted in absolute chloroform or acetonitrile at room temperature, 2 mol. equiv. of isocyanate being used. For an isocyanate:glycal ratio of 1:1, the conversion of the sugar substrate was only 40–60%, even after prolongation of the reaction time. The progress of all reactions was monitored by ^{1}H-n.m.r. spectroscopy (see Table I). The isocyanate **4** reacted with glycals **18–21**, **23–25**, and **27–29** more slowly than sulfonyl isocyanates[11] **1** and **3**. Reactions performed in chloroform solution were completed within ~50 h, whereas, in acetonitrile, the starting glycal disappeared after 22 h (see Table I). Dihydropyran **29** was more reactive than these; when the reaction was conducted in acetonitrile, a mixture of β-lactams **57** and **58**, [4 + 2] cycloadducts **59** and **60**, and unsaturated amide **61** was formed within ~10–20 min. Owing to overlapping of signals, the ratios of **57:58:59:60:61** could not be determined.

Isocyanate **4** added stereospecifically to glycals **18–21**, **23–25**, **27**, and **28** in a position *anti* to the C-3 substituent, to give the *cis*-fused bicyclic systems **30–37**, **42–47**, and **51–54**. Except for glycal **19**, the initially formed proportion of (2 + 2) and (4 + 2) adducts changes slowly to afford a prepondance of six-membered ones. Glycal **19** favored formation of β-lactam **31**; in chloroform solution, after 50 h, **31** became the main component of the reaction mixture, whereas, in acetonitrile, the [4 + 2] adducts **35** was not formed. In all cases, both [2 + 2] and [4 + 2] bicyclic intermediates slowly rearranged to α,β-unsaturated amide. The ratios of β-lactam: [4 + 2] adduct:amide depended on the reaction time and the glycal used (see Table

TABLE I

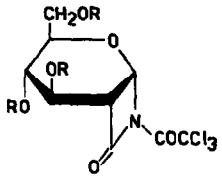
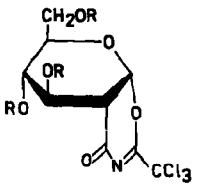
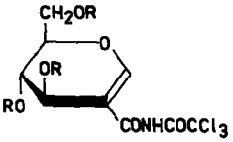
APPROXIMATE COMPOSITION (%) OF THE REACTION MIXTURE, INCLUDING THE SUBSTRATE, CYCLIC INTERMEDIATES, AND α,β-UNSATURATED AMIDE

Glycal	*Products*	*Time (h)*							
		2		*6*		*22*		*50*	
		$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN
	30	10	44	25	46	35	43	35	
18	**34**	15	45	40	54	65	57	65	
	38	[a]	[a]	[a]	[a]	[a]	[a]	[a]	
	31	2	10	12	30	28	40	50	
19	**35**	3	[a]	18	[a]	26	[a]	18	
	39	[a]	[a]	[a]	30	25	60	32	
	32	10[b]		25[b]		19		19	
20	**36**					47		74	
	40	[a]		[a]		[a]		7	
	33	10[b]	13	25[b]	30	60[b]	30		
21	**37**		12		30		20		
	41								
	42	8		23		23		10	
23	**45**	18		51		70		85	
	48	[a]		[a]		7		5	
	51	27	36	42		20	[a]	7	
24	**53**	31	44	50		76	78	88	
	55	[a]	21	[a]		4	22	5	
	52	31	38	43	39	26		16	20
25	**54**	31	42	43	40	51		63	50
	56	[a]	10	[a]	13	11		21	30
	43	5[b]	25	10[b]	31	19	37	21	15
27	**46**		21		26	25	34	36	38
	49	[a]	18	[a]	23	6	29	11	47
	44	7[b]	10[b]			12	17		
28	**47**					23	17		
	50	[a]	[a]			14	35		

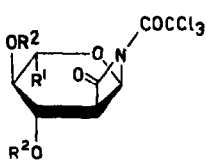
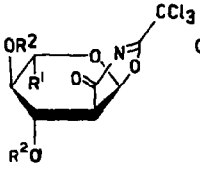
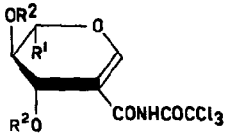
[a]Not detected. [b]Representing a mixture of the two cyclic intermediates.

I). The behavior of isocyanate **4** with glycals **18–21**, **23–25**, and **27–29** resembled, in general, that reported by Martin *et al.*[4] for addition of **4** to dihydropyran **6**.

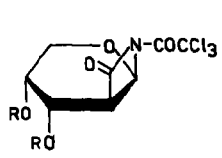
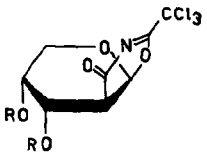
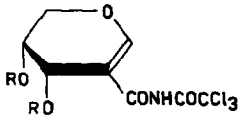
Acyl or sulfonyl substituents attached to the isocyanate group, required for cycloaddition, are responsible for the low stability of azetidinone rings. The electron-withdrawing Z-substituent stabilizes the partial negative charge at the nitrogen atom, whereas the partial positive charge at the anomeric carbon atom is stabilized by the pyranoid-ring oxygen atom. Attempts to isolate cycloadducts from the reaction mixture failed, owing to their high reactivity. Therefore, *N*-deprotection was necessary, prior to isolation or chemical transformation of β-lactams. Thus far, we have not succeeded in splitting sulfonyl substituents without opening of the four-membered azetidinone ring[11].

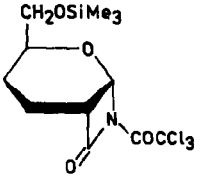
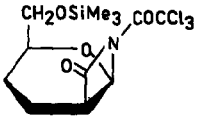
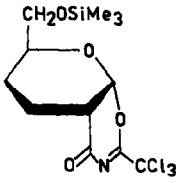
R = Me_3Si	**30**	**34**	**38**
R = $(Me_3C)Me_2Si$	**31**	**35**	**39**
R = Me	**32**	**36**	**40**
R = Bn	**33**	**37**	**41**

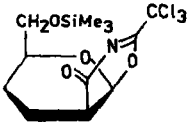
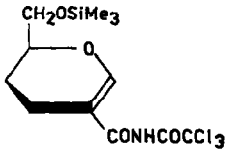
$R^1 = CH_3, R^2 = Me_3Si$	**42**	**45**	**48**
$R^1 = H, R^2 = Me_3Si$	**43**	**46**	**49**
$R^1 = H, R^2 = (Me_3C)Me_2Si$	**44**	**47**	**50**

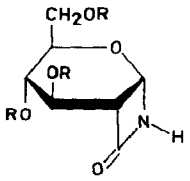
R = Me_3Si	**51**	**53**	**55**
R = $(Me_3C)Me_2Si$	**52**	**54**	**56**

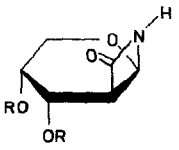
57 **58** **59**

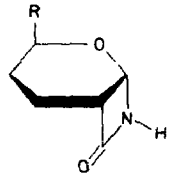
60 **61**



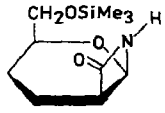
62 R=Me_3Si
63 R=$(Me_3C)Me_2Si$
64 R=Bn
65 R=H



66 R=Me_3Si
67 R=H



68 R=H
69 R=CH_2OSiMe_3



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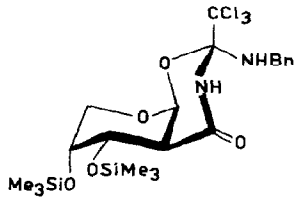

71

On the other hand, *N*-deprotection of the trichloroacetyl substituent proceeded satisfactorily in the presence of benzylamine, affording the stable, bicyclic β-lactams **63–65, 67, 69,** and **70**. The optimal time for addition of benzylamine, being specific for each reaction, was determined by a ^{1}H-n.m.r. monitoring experiment. Benzylamine is added to the C=N double bond of [4 + 2] cycloadducts, yielding unstable, bicyclic compounds. One of them, *i.e.*, the adduct **71**, obtained by addition of benzylamine to **53**, was isolated by chromatography, and its structure was proved by n.m.r. and m.s. data. β-Lactams **62–64, 66,** and **68–70** were isolated from the respective post-reaction mixtures by extraction with hexane and chromatographic separation. Further deprotection of compounds **62** and **66** with methanol gave crystalline, stable, water-soluble β-lactams **65** and **67** having a unique, bicyclic structure.

Owing to the stereospecificity of cycloaddition, the configuration of the starting glycal offers stereocontrol of formation of an appropriate configuration at the carbon atom attached to the nitrogen and oxygen atoms. This configuration is crucial for the biological activity of β-lactam antibiotics.

Our earlier experiments performed under high and normal pressure[8–11], and other findings involving simple dihydropyran derivatives[1–5], clearly point to the reversibility of cycloaddition. Such isocyanates as phenyl isocyanate or methyl isocyanatoacetate are unreactive towards glycals and dihydropyrans, even under high pressure. Benzoyl isocyanate is reactive only under at least 1000-MPa pressure[12]. On the other hand, very reactive isocyanates, such as trichloroethoxysulfonyl or trifluoroacetyl isocyanate, cause low stability of cycloadducts, and promote either rapid rearrangement to α,β-unsaturated amide or retro-addition. This is evident if the reactivity of *N*-tosyl β-lactams is compared with that of *N*-(tri-

chloroethoxy)sulfonyl compounds. Our preliminary experiments using trifluoroacetyl isocyanate and rhamnal **23** showed that, even after 20 h, there were still ~60% of the substrate and ~40% of unsaturated amide, with no cycloadducts present[7]. These data indicate that the rate of rearrangement is higher than that of cycloaddition. Thermodynamic and kinetic aspects of cycloaddition help in selection of the most effective isocyanate. In view of the present results, trichloroacetyl isocyanate seems to be the most suitable isocyanate that promotes cycloaddition, provides relative stability of cycloadducts, and offers a trichloroacetyl substituent readily removable under mild conditions.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 spectropolarimeter. I.r. spectra were recorded with a Beckman 4240 spectrophotometer. Column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). ^{1}H-N.m.r. spectra were recorded with a Varian EM 360 and a Bruker 300-MHz spectrometer. ^{13}C-N.m.r. spectra were recorded with a Varian CFT 20 spectrometer.

Glycals **18–21, 23–25**, and **27–29** were obtained from the respective hydroxy compounds by standard silylation or alkylation procedures; **18, 23, 24, 27,** and **29** by silylation with chlorotrimethylsilane and pyridine; **19, 25,** and **28** by silylation with *tert*-butylchlorodimethylsilane and imidazole in DMF; **20** by methylation with dimethyl sulfate and KOH in Me_2SO; and **21** by benzylation with benzyl bromide and KOH in Me_2SO.

The experiments performed in a n.m.r. test-tube were as follows. A solution of an appropriate glycal (0.5 mmol) in $CDCl_3$ or CD_3CN (~0.5 mL) was placed in a n.m.r. test-tube, and trichloroacetyl isocyanate (1.0 mmol) was added. The spectra were recorded at 0, 2, 6, 22, and 50 h after mixing of the substrates. Bicyclic products **30–37, 42–47, 51–54**, and **57–60** were characterized by chemical shifts and coupling constants for H-1 and H-2, whereas amides **38–41, 48–50, 55, 56,** and **61** were characterized by chemical shifts of H-1. The data are collected in Table II. The compositions of the reaction mixtures were determined approximately by integration of appropriate signals of H-1, and are recorded in Table I.

General procedure for cycloaddition. — To a glycal (15 mmol) dissolved in acetonitrile (15 mL) was added trichloroacetyl isocyanate (5.7 g, 30 mmol). After disappearance of the substrate (^{1}H-n.m.r. pilot experiment performed in a test-tube), the mixture was cooled to −30°, and benzylamine (5.3 g, 48 mmol) in acetonitrile (5 mL) was added. Subsequently, the temperature of the mixture was allowed to rise to room temperature, and it was evaporated to dryness and treated with hexane. The crystalline precipitate was removed by filtration. The filtrate was evaporated, and the oily residue was isolated on a column of silica gel by flash chromatography, to give the respective β-lactams (the more-polar fraction).

*2-Carboxy-2-deoxy-3,4,6-tri-*O*-(trimethylsilyl)-α-*D*-glucopyranosylaminolac-*

tam (**62**). — From the glucal **18**; 30%; m.p. 50–54°, $[\alpha]_D$ +61.5° (*c* 1, CH_2Cl_2); ν_{max}^{film} 3340 and 1760 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.18 (m, 1 H, H-2), 3.63–3.78 (m, 3 H, H-4,6,6'), 3.99 (dt, 1 H, *J* 6.7, 6.5, 2.9 Hz, H-5), 4.17 (t, 1 H, ΣJ 6.3 Hz, H-3), and 5.42 (d, 1 H, *J* 4.6 Hz, H-1).

Anal. Calc. for $C_{16}H_{35}NO_5Si_3$: C, 47.4; H, 8.7; N, 3.4. Found: C, 46.5; H, 8.7; N, 3.5.

*2-Carboxy-2-deoxy-3,4,6-tri-*O*-(tert-butyldimethylsilyl)-α-*D*-glucopyranosylaminolactam* (**63**). — From the glucal **19**; 50%; m.p. 74–76°; $[\alpha]_D$ −5.7° (*c* 1, CH_2Cl_2); $\nu_{max}^{CDCl_3}$ 3410 and 1775 cm^{-1}; ^{1}H-n.m.r. (CCl_4): δ 3.20 (m, 1 H, H-2), 3.3–4.0 (m, 4 H, H-4,5,6,6'), 4.15 (m, 1 H, H-3), and 5.40 (d, 1 H, *J* 4.6 Hz, H-1).

Anal. Calc. for $C_{25}H_{53}NO_5Si_3$: C, 56.4; H, 10.0; N, 2.6. Found: C, 56.1; H, 10.1; N, 2.6.

TABLE II

SELECTED SPECTRAL DATA FOR CYCLIC INTERMEDIATES AND α,β-UNSATURATED AMIDES

Compound	*Solvent*	*^{1}H-N.m.r. data*
30	$CDCl_3$	6.02 (d, 1 H, >*J* 5.5 Hz, H-1), 3.47 (dd, 1 H, *J* 3.0 Hz, H-2)
34	$CDCl_3$	6.15 (d, 1 H, *J* 3.7 Hz, H-1), 2.49 (dd, 1 H, *J* 9.0 Hz, H-2)
38[a]		
31	$CDCl_3$	6.03 (d, 1 H, *J* 6.2 Hz, H-1), 3.48 (dd, 1 H, *J* 2.8 Hz, H-2)
35	$CDCl_3$	6.17 (d, 1 H, *J* 6.5 Hz, H-1), 3.12 (dd, 1 H, *J* 3.2 Hz, H-2)
39	$CDCl_3$	7.52 (s, 1 H, H-1)
32	$CDCl_3$	6.08 (d, 1 H, *J* 5.0 Hz, H-1)
36	$CDCl_3$	6.10 (d, 1 H, *J* 3.3 Hz, H-1)
40	$CDCl_3$	7.80 (s, 1 H, H-1)
33	CD_3CN	6.07 (d, 1 H, *J* 5.8 Hz, H-1)
37	CD_3CN	6.18 (d, 1 H, *J* 3.8 Hz, H-1)
41	CD_3CN	[b]
42	$CDCl_3$	6.02 (d, 1 H, *J* 6.4 Hz, H-1)
45	$CDCl_3$	6.05 (d, 1 H, *J* 3.5 Hz, H-1), 2.98 (dd, 1 H, *J* 10.4 Hz, H-2)
48	$CDCl_3$	7.72 (s, 1 H, H-1)
43	CD_3CN	5.92 (d, 1 H, *J* 6.2 Hz, H-1)
46	CD_3CN	6.10 (d, 1 H, *J* 3.8 Hz, H-1), 2.85 (m, 1 H, H-2)
49	CD_3CN	7.60 (s, 1 H, H-1)
44	CD_3CN	5.88 (d, 1 H, *J* 4.5 Hz, H-1)
47	CD_3CN	6.02 (d, 1 H, *J* 5.7 Hz, H-1)
50	CD_3CN	7.60 (s, 1 H, H-1)
51	$CDCl_3$	5.82 (d, 1 H, *J* 5.4 Hz, H-1), 3.37 (t, 1 H, *J* 5.5 Hz, H-2)
53	$CDCl_3$	6.12 (d, 1 H, *J* 3.3 Hz, H-1), 3.15 (dd, 1 H, *J* 7.3 Hz, H-2)
55	$CDCl_3$	7.60 (s, 1 H, H-1)
52	$CDCl_3$	5.90 (d, 1 H, *J* 5.5 Hz, H-1), 3.52 (t, 1 H, *J* 5.0 Hz, H-2)
54	$CDCl_3$	6.10 (d, 1 H, *J* 3.2 Hz, H-1), 3.22 (dd, 1 H, *J* 7.3 Hz, H-2)
56	$CDCl_3$	7.50 (s, 1 H, H-1)
57	CD_3CN	5.95 (d, 1 H, *J* 5.7 Hz, H-1)
58	CD_3CN	5.80 (d, 1 H, *J* 5.2 Hz, H-1)
59	CD_3CN	6.18 (d, 1 H, *J* 3.5 Hz, H-1)
60	CD_3CN	6.21 (m, 1 H, H-1)
61	CD_3CN	7.70 (s, 1 H, H-1)

[a]Not detected. [b]Overlapped by absorption caused by aromatic protons.

2-Carboxy-2-deoxy-3,4,6-tri-O-benzyl-α-D-glucopyranosylaminolactam (**64**). — From **21**; 24%; colorless syrup; $[\alpha]_D$ +23.2° (*c* 1, CH_2Cl_2); $\nu_{max}^{CHCl_3}$ 3400 and 1770 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.25 (m, 1 H, H-2), 3.3–4.2 (m, 4 H, H-3,4,5,5′), 4.2–4.9 (m, 6 H, benzyl), 5.35 (d, 1 H, *J* 4.2 Hz, H-1), and 7.2 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{28}H_{29}NO_5$: C, 73.2; H, 6.4; N, 3.0. Found: C, 72.5; H, 6.1; N, 3.0.

2-Carboxy-2-deoxy-α-D-glucopyranosylaminolactam (**65**). — To a solution of compound **62** (0.1 g, 0.25 mmol) in methanol (10 mL) was added Dowex 50-W X-8 resin (0.05 g). The mixture was stirred for 1 h, filtered, and the filtrate evaporated to dryness, yielding **65** (0.045 g, 95%); m.p. 179–180°, $[\alpha]_D$ +65.4° (*c* 1, H_2O); ν_{max}^{Nujol} 3320 and 1715 cm^{-1}; ^{1}H-n.m.r. (Me_2SO-d_6): δ 3.20 (m, 1 H, H-2), 3.3–4.0 (m, 5 H, H-3,4,5,6,6′), and 5.50 (d, 1 H, *J* 4.0 Hz, H-1); ^{13}C-n.m.r., (Me_2SO-d_6): δ 56.72 (C-2), 61.22 (C-6), 69.44, 70.64, 71.71 (C-3,4,5), and 168.12 (C=O).

Anal. Calc. for $C_7H_{11}NO_5$: C, 44.4; H, 5.9; N, 7.4. Found: C, 44.6; H, 6.0; N, 7.4.

2-Carboxy-2-deoxy-3,4-di-O-(trimethylsilyl)-α-D-arabinopyranosylaminolactam (**66**). — From **24** according to the general procedure; 40%; m.p. 53–57°, $[\alpha]_D$ −53.5° (*c* 1, CH_2Cl_2); $\nu_{max}^{CHCl_3}$ 3410 and 1775 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.26 (m, 1 H, H-2), 3.74 (dd, 1 H, *J* 11.2, 5.9 Hz, H-5), 3.78 (dd, 1 H, *J* 3.7 Hz, H-5′), 3.91 (m, 1 H, H-4), 4.11 (dd, 1 H, *J* 4.6, 2.9 Hz, H-3), and 5.37 (d, 1 H, *J* 4.7 Hz, H-1).

Anal. Calc. for $C_{12}H_{25}NO_4Si_2$: C, 47.6; H, 8.3; N, 4.6. Found: C, 47.1; H, 8.3; N, 4.8.

2-Carboxy-2-deoxy-β-D-arabinopyranosylaminolactam (**67**). — A solution of compound **66** (0.1 g, 0.33 mmol) in methanol (2 mL) was boiled for 0.5 h, and cooled. The precipitate was filtered off, to give **67** (0.045 g, 85%); m.p. 172–173°, $[\alpha]_D$ −112.4° (*c* 1, H_2O); ν_{max}^{Nujol} 3380, 3240, and 1750 cm^{-1}; ^{1}H-n.m.r. (Me_2SO-d_6): δ 3.05 (dt, 1 H, *J* 4.3, 4.4, 3.0 Hz, H-2), 3.5–3.7 (m, 3 H, H-3,5,5′), 3.83 (m, 1 H, H-4), and 5.19 (d, 1 H, *J* 4.3 Hz, H-1); ^{13}C-n.m.r. (Me_2SO-d_6): δ 54.86 (C-2), 63.50, 64.31, 65.38 (C-3,4,5), 73.86 (C-1), and 168.38 (C=O).

Anal. Calc. for $C_6H_9NO_4$: C, 45.3; H, 5.7; N, 8.8. Found: C, 45.8; H, 5.9; N, 8.8.

8-Aza-2-oxabicyclo[4.2.0]octan-7-one (**68**). — From dihydropyran **6** according to the general procedure described; 25%; colorless syrup solidifying in a refrigerator; $\nu_{max}^{CHCl_3}$ 3420 and 1775 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.4–2.3 (m, 4 H, H-4,5,4′,5′), 3.30 (m, 1 H, H-6), 3.5–4.3 (m, 2 H, H-3,3′), and 5.40 (d, 1 H, *J* 4.2 Hz, H-1); ^{13}C-n.m.r. [$(CD_3)_2CO$]: δ 18.67, 20.74 (C-4,5), 47.90 (C-6), 60.05 (C-3), 75.30 (C-1), and 170.34 (C=O).

Anal. Calc. for $C_6H_9NO_2$: C, 56.7; H, 7.1; N, 11.0. Found: C, 56.4; H, 7.1; N, 11.5.

trans- *and* cis-*8-Aza-3-(trimethylsilyloxymethyl)-2-oxabicyclo[4.2.0]octan-7-one* (**69** *and* **70**). — From **29** according to the procedure described; 36% for a mixture of the two compounds. The mixture of **69** and **70** was not separated into pure compounds; $\nu_{max}^{CDCl_3}$ 3410 and 1770 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.4–2.4 (m, 4

H, H-4,5,4′,5′), 3.18 (m, 1 H, H-6), 3.3–4.2 (m, 3 H, H-3, CH_2O–), 5.18 (d, 0.4 H, *J* 4.2 Hz, H-1 *cis*), and 5.27 (d, 0.6 H, *J* 5.0 Hz, H-1 *trans*); ^{13}C-n.m.r. [$(CD_3)_2CO$] for the mixture of **69** and **70** (the assignments of lines to diastereoisomers are based on ^{13}C line-intensities and should be considered tentative); **69**: δ 18.57, 23.33 (C-4,5), 47.79 (C-6), 63.97 (–CH_2–), 66.23 (C-3), 75.71 (C-1), and 170.39 (C=O); **70**: δ 15.58, 22.44 (C-4,5), 50.24 (C-6), 67.39 (–CH_2–), 69.34 (C-3), 75.08 (C-1), and (C=O).

The mixture of **69** and **70** gave inconsistent elemental analyses.

(1S,3R,6S,7S,8R)-4-Aza-3-(benzylamino)-3-(trichloromethyl)-2,10-dioxa-7,8-di(trimethylsilyloxy)bicyclo[4.2.0]decan-5-one (**71**). — To a solution of **24** (3.9 g, 48 mmol). After 0.5 h, the mixture was cooled to −30°, and benzylamine (5.3 g) in acetonitrile (5 mL) was slowly added. The temperature of the mixture was allowed to rise to room temperature, the mixture was evaporated, and the oily residue was separated on a column of silica gel by using 9:1 (v/v) hexane–Et_2O as the eluant (flash chromatography), affording unstable, impure **71** (1.25 g, 15%); $\nu_{max}^{CHCl_3}$ 3400 and 1700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.05 (t, 1 H, H-6), 3.3–4.2 (m, 6 H, H-7,8,9,9′, CH_2Ph), 4.55 (m, 1 H, H-8), and 5.50 (d, 1 H, *J* 2.8 Hz, H-1); ^{13}C-n.m.r. ($CDCl_3$): δ 46.1, 46.9 (C-6, CH_2Ph), 64.6, 65.9, 69.5 (C-7,8,9), 93.5 (C-1), 100.8 (C-3), 106 (CCl_3), 127.3, 128.1, 128.5, 139.8 (phenyl), and 168.2 (C=O); *m/z*: M$^+$, 554. Subsequent washing of the column with methanol afforded **67** (0.8 g, 30%).

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